Risk Factors Associated with Disease Severity and Clinical Outcomes for COVID-19 in Wuhan, China

Yun Liu (liuyun@njmu.edu.cn)
Department of medical informatics, School of biomedical engineering and informatics,Nanjing medical university

Hao Wu
Department of emergency, the first affiliated hospital of nanjing medical university.

Bei Zhu
department of geriatric, the first affiliated hospital of nanjing medical university

Yi Yang
center for global health, school of public health, nanjing medical university

Peng Cheng
department of geriatric, the first affiliated hospital of nanjing medical university

Chaolin Huang
dividion of tntensive care unit, wuhan jin yin-tan hosipital

Wenjuan Wu
dibidion of intensive care unit,wuhan jin yin-tan hospital

Weihong Zhao
department of geriatric, the first affiliated hospital of nanjing medical university

Jinsong Zhang
department of emergency, the first affiliated hospital of nanjing medical university

Research article

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Abstract

Background: A new type of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in Wuhan, China. However, the risk factors and characteristics related to the severity of the disease and its outcomes need to be further explored.

Methods: In this retrospective study, we evaluated COVID-19 patients with severe disease and those who were critically ill, as diagnosed at Jinyintan Hospital (Wuhan, China). The demographic information, clinical characteristics, complications, and laboratory results for the patients were evaluated. Multivariate logistic regression methods were used to analyze risk factors related to hospital deaths.

Results: The 235 COVID-19 patients included were divided into a severe group of 183 (78%) and a critical group of 52 (22%). Of these patients, 185 (79%) were discharged, and 50 (21%) died during hospitalization. In multivariate logistic analyses, age (OR=1.07, 95% CI 1.02-1.14, P=0.009), critical disease (OR=48.23, 95% CI 10.91-323.13, P<0.001), low lymphocyte counts (OR=15.48, 95% CI 1.98-176.49, P=0.015), elevated interleukin 6 (IL-6) (OR=9.11, 95% CI 1.69-67.75, P=0.017), and elevated aspartate aminotransferase (AST) (OR=8.46, 95% CI 2.16-42.60, P=0.004) were independent risk factors for adverse outcomes.

Conclusions: The results show that advanced age (> 64 years), critical illness, low lymphocyte levels, and elevated IL-6 and AST were factors for the risk of death for COVID-19 patients who had severe disease and those who were critically ill.

1. Instruction

In December 2019, a new type of pneumonia caused by coronavirus was observed in Wuhan, China. The coronavirus is named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. Infections with SARS-CoV-2 can cause a fatal respiratory syndrome [2]. The coronavirus, which is highly infectious, has rapidly become widespread in China and around the world [3]. To date, globally, 14 million people have been infected SARS-CoV-2, and 600,000 have died.

Li and co-workers compared the laboratory indicators of 54 coronavirus disease

2019 (COVID-19) patients with severe or critical cases. Of these, 31 patients with severe illness recovered. Of the 23 critically ill patients, 6 died and 17 recovered [4]. Among the 41 patients with COVID-19, 27 had contact history with a seafood market in South China, 13 were sent to ICU, and 6 died [5]. Another investigation found that of 36 patients who entered the ICU, 6 died [6]. In a retrospective case study in Italy, ICU mortality was 26% [7]. Patients with COVID-19 had a higher risk of death when they become severely ill. Therefore, it is important to evaluate changes in relevant indicators of severe and critical illness for the assessment of their condition and for prediction of the risk of death.

At present, research on the pathogenic mechanism, disease risk, and treatment measures for the coronavirus is being accomplished throughout the world. Several groups have analyzed factors influencing development of COVID-19 for patients, but the specific clinical features of the disease and effective measures for treatment are not yet established. The focus of the present research was on laboratory indicators and treatment methods that affect the risk of COVID-19 progressing from severe to critical disease and to death. Risk factors that lead to the death of COVID-19 patients were assessed, with the goal reducing the risk of death caused by SARS-CoV-2 infections.

2. Methods

2.1 Population

This retrospective study included 235 patients from Jinyintan Hospital who were diagnosed with SARS-CoV-2 infections according to World Health Organization (WHO) guidelines. Jinyintan Hospital was designated as a hospital for treatment of COVID-19 patients with serious disease. Those included were COVID-19 patients at Jinyintan Hospital from January 10, 2020 to March 30, 2020, these were patients admitted directly due to serious illness or transferred from other hospitals to Jinyintan Hospital due to the seriousness of their condition. The COVID-19 patients included had a definite outcome (non-survivor or survivor). The investigation was approved by the Ethics Commission of Jinyintan Hospital.

2.2 Data collection and processing

Demographic data, symptoms and signs, results of laboratory tests and radiologic assessments, treatments, and clinical outcomes were obtained from the electronic medical records of patients. All data were cross-checked to ensure their accuracy, and all information was entered into a computer for analysis. The standard for discharge was based on the guidelines for diagnosis and treatment of new coronavirus infections (trial version 7) issued by the National Health Commission of China. The patients were divided into severe and critical COVID-19 groups according to the guidelines.

2.3 Laboratory and radiological analyses

The patients were determined to be infected with COVID-19 by real-time Q-PCR. Results of positive throat swab samples were confirmed by the hospital and by the Center for Disease Control and Prevention. Laboratory tests included complete blood counts and assessments of liver function, kidney function, blood coagulation, serum myocardial enzymes, and interleukin 6 (IL-6). All patients underwent CT scans. Treatment measures included antiviral agents, antibiotics, and albumin. Pulmonary therapy included routine oxygen therapy, invasive mechanical ventilation, and non-invasive mechanical ventilation.

2.4 Definitions

Assessment of the severity of COVID-19 disease was based on the guidelines of the 7th trial version of the National Health Commission of China. Severe cases were defined as having any of the following conditions: shortness of breath, respiratory frequency ≥ 30 times/minute, finger oxygen saturation at rest ≤ 93%, or oxygenation index [PaO2/FiO2] ≤ 300 mmHg (1 mmHg = 0.133 kPa). Either of the following conditions was defined as critical cases: respiratory failure that required mechanical ventilation or shock combined with other organ failure that required intensive care and treatment. The discharge criteria were as follows: body temperature returned to normal for more than 3 days; substantially improved respiratory symptoms; lung imaging data showing improvement of acute exudative lesions; or two consecutive sputum, nasopharyngeal swabs, or other respiratory specimens testing negative for SARS-CoV-2 nucleic acid (sampling interval 24 hours).

2.5 Statistical analyses

Continuous variables were expressed as means (SD) or medians (interquartile range (IQR), as appropriate, and categorical variables were presented as counts and percentages. Continuous variables were compared by independent group t tests (normal distribution) and Mann-Whitney U tests (non-normal distribution). Categorical variables were compared by Chi-square or Fisher exact tests. Multivariate logistic regression models were used to analyze risk factors related to deaths. Data analysis was performed by using R, version 3.6.3.

3. Results

3.1 Demographic and clinical characteristics, as well as underlying medical conditions

In the present research, 235 COVID-19 patients at Jinyintan Hospital with severe or critical disease were included. The median age of patients was 64 years (IQR 51–70); there were 129 (55%) male patients and 106 (45%) female patients. The patients were divided into a severe group 183 (78%) and critical group 52 (22%) according to disease seriousness. The mean age of the critically ill group was higher than that of the severely ill group (median 65 vs 63, $P < 0.001$). According to clinical outcomes, 185 (79%) COVID-19 patients in the survivor group were discharged, and 50 (21%) died during hospitalization. Compared to the survivors, the mean age of non-survivors was higher (median 70 vs 61, $P < 0.001$) (Table 1).

Table 1
Demographic characteristics for COVID-19 patients

	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
Characteristics							
Age, years	64(51–70)	63(50–70)	65(59–73)	< 0.001	61(48–69)	70(63–78)	< 0.001
< 40	23/235(10%)	21/183(11%)	2/52(4%)	0.044	23/185(12%)	0/50(0%)	< 0.001
40–60	74/235(31%)	62/183(34%)	12/52(23%)		68/185(37%)	6/50(12%)	
> 60	138/235(59%)	100/183(55%)	38/52(73%)		94/185(51%)	44/50(88%)	
Sex							
Male	129/235(55%)	99/183(54%)	30/52(58%)	0.646	96/185(52%)	33/50(66%)	0.075
Female	106/235(45%)	84/183(46%)	22/52(42%)		89/185(48%)	17/50(34%)	
P < 0.05 was considered statistically significant.							

The prevalence of a respiratory rate of > 24 breaths per min for the critically ill group was higher than that for the severely ill group (46% vs 16%, P < 0.001) and, for the survivor group, was higher than for the non-survivor group (40% vs 18%, P = 0.001). The main clinical symptoms for hospitalization included fatigue 214 (91%), fever 192 (82%), cough 169 (72%), and shortness of breath 122 (52%). The prevalence of fever and shortness of breath for the critically ill group and the non-survivor group was higher than for the severely ill group and the survivor group (Table 2).

Table 2
Baseline clinical characteristics for COVID-19 patients

	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
Clinical characteristics							
Pulse ≥ 125 beats per min	6/235(3%)	5/183(3%)	1/52(2%)	1.000	5/185(3%)	1/50(2%)	1.000
Respiratory rate > 24 breaths per min	53/235(23%)	29/183(16%)	24/52(46%)	< 0.001	33/185(18%)	20/50(40%)	0.001
Systolic blood pressure ≥ 140 mm Hg	60/235(26%)	49/183(27%)	11/52(21%)	0.412	49/185(26%)	11/50(22%)	0.519
Symptoms reported at illness onset							
Fever (temperature ≥ 37.3℃)	192/235(82%)	143/183(78%)	49/52(94%)	0.008	146/185(80%)	46/50(92%)	0.034
Cough	169/235(72%)	132/183(72%)	37/52(71%)	0.890	134/185(72%)	35/50(70%)	0.734
Shortness of breath (dyspnea)	122/235(52%)	84/183(46%)	38/52(73%)	0.001	89/185(48%)	33/50(66%)	0.025
Fatigue	214/235(91%)	163/183(89%)	51/52(98%)	0.083	167/185(90%)	47/50(94%)	0.589
Diarrhea	12/235(5%)	1/52(2%)	11/183(6%)	0.410	10/185(5%)	2/50(4%)	0.969
Chest pain	7/235(3%)	6/183(3%)	1/52(2%)	0.964	6/185(3%)	1/50(2%)	1.000
P < 0.05 was considered statistically significant.							

In regard to underlying medical conditions, hypertension 82(35%) and diabetes 37(16%) were relatively common comorbidities for severe and critical COVID-19 patients. The prevalence of diabetes for critical patients was higher than that for severe patients (35% vs 10%, P < 0.001). Compared with patients for the survivor group, those for the non-survivor group had a higher prevalence of diabetes (28% vs 13%, P = 0.008). Also, the median time from illness onset to hospital admission was 7 days (IQR 2–11); this time was shorter for the critical and non-survivor groups (Table 3). The results show that age, fever, shortness of breath, and diabetes are notable factors of vulnerability.

Table 3
Underlying medical conditions for COVID-19 patients

	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
Underlying medical conditions							
Diabetes mellitus	37/233(16%)	19/181(10%)	18/52(35%)	< 0.001	23/183 (13%)	14/50(28%)	0.008
Hypertension	82/233(35%)	62/181(34%)	20/52(38%)	0.576	62/183 (34%)	20/50(40%)	0.422
Cardiac disease	26/233(11%)	19/181(10%)	7/52(13%)	0.550	17/183 (9%)	9/50(18%)	0.083
Cerebral infarction	8/233(3%)	5/181(3%)	3/52(6%)	0.537	5/183 (3%)	3/50(6%)	0.492
Chronic kidney disease	12/233(5%)	8/181(4%)	4/52(8%)	0.558	11/183 (6%)	1/50(2%)	0.438
Chronic obstructive lung	4/233(2%)	2/181(1%)	2/52(4%)	0.462	2/183 (1%)	2/50(4%)	0.431
Carcinoma	11/233(5%)	8/181(4%)	3/52(6%)	0.973	9/183 (5%)	2/50(4%)	1.000
Other	91/233(39%)	71/181(39%)	20/52(38%)	0.921	73/183 (40%)	18/50(36%)	0.617
Time from illness onset to hospital admission, days	7(2–11)	7(2–13)	5(1–9)	0.009	7(2–7)	6(3–10)	0.009

P < 0.05 was considered statistically significant.

3.2 Analysis of blood and inflammation indicators associated with disease severity and clinical outcomes

Compared to severe patients, critical patients presented with higher white blood cell counts (median 9.05 vs 6.07, P < 0.001) and neutrophil counts (median 8.08 vs 4.13, P < 0.001). The lymphocyte counts (median 0.62 vs 1.05, P < 0.001) and hemoglobin levels (median 115 vs 123, P = 0.002) for critical patients were lower than those for severe patients. Further, platelet counts were lower for the critical and non-survivor groups (Table 4).

Table 4
Blood values for COVID-19 patients

	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
White blood cell count, $\times 10^9$ per L	6.39(4.66–9.32)	6.07(4.49–8.48)	9.05(5.85–13.17)	< 0.001	6.09(4.56–8.70)	9.07(5.31–12.93)	< 0.001
No increase	185/235(78.7%)	155/183(84.7%)	30/52(57.7%)	< 0.001	154/185(83.2%)	31/50(62.0%)	0.001
Increased > 9.5	50/235(21.3%)	28/183(15.3%)	22/52(42.3%)		31/185(16.8%)	19/50(38.0%)	
Lymphocyte count, $\times 10^9$ per L	0.92(0.62–1.41)	1.05(0.72–1.53)	0.62(0.41–0.92)	< 0.001	1.06(0.71–1.53)	0.65(0.42–0.83)	< 0.001
No decrease	89/235(37.9%)	85/183(46.4%)	4/52(7.7%)	< 0.001	86/185(46.5%)	3/50(6.0%)	< 0.001
Decreased < 1.1	146/235(62.1%)	98/183(53.6%)	48/52(92.3%)		99/185(53.5%)	47/50(94.0%)	
Neutrophil count, $\times 10^9$ per L	4.54(3.05–7.78)	4.13(2.95–6.80)	8.08(4.74–11.41)	< 0.001	4.13(2.89–6.55)	8.06(4.59–11.24)	< 0.001
No increase	156/234(66.7%)	135/183(73.8%)	21/51(41.2%)	< 0.001	137/184(74.5%)	19/50(38.0%)	< 0.001
Increased > 6.3	78/234(33.3%)	48/183(26.2%)	30/51(58.8%)		47/184(25.5%)	31/50(62.0%)	
Hemoglobin, g/L	122(113–133)	123(115–135)	115(101–130)	0.002	123(114–134)	118(105–131)	0.072
No decrease	77/235(32.8%)	62/183(33.9%)	15/52(28.8%)	0.498	62/185(33.5%)	15/50(30.0%)	0.639
Decreased < 130	158/235(67.2%)	121/183(66.1%)	37/52(71.2%)		123/185(66.5%)	35/50(70.0%)	
Platelet count, $\times 10^9$ per L	194(151–260)	196(151–268)	192(155–236)	0.573	207(163–276)	169(121–223)	< 0.001
No increase	218/235(92.8%)	169/183(92.3%)	49/52(94.2%)	0.874	169/185(91.4%)	49/50(98.0%)	0.193
Increased > 350	17/235(7.2%)	14/183(7.7%)	3/52(5.8%)		16/185(8.6%)	1/50(2.0%)	

P < 0.05 was considered statistically significant. Hs-CRP: high-sensitive C-reactive protein. ESR: erythrocyte sedimentation rate. IL-6: interleukin 6.

Inflammation indicators, including high-sensitive C-reactive protein (Hs-CRP) (median 77.1 vs 18.2, P < 0.001) and erythrocyte sedimentation rate (ESR) (median 56 vs 40, P = 0.007), were higher for critically ill patients than for severely ill patients (Table 5). Compared with survivors, non-surviving COVID-19 patients also had similar results, except for hemoglobin (Table 4) and ESR (Table 5). In addition, the IL-6 levels for non-survivors were higher than those of survivors (median 9.47 vs 8.40, P = 0.027). For the group with elevated IL-6, there were more non-surviving patients than surviving patients (81.6% vs 61.9%, P = 0.010) (Table 5). In summary, elevated white blood cell counts, neutrophil counts, hS-CRP, and lymphocyte counts were risk factors associated with disease severity and clinical outcomes.

Table 5
Inflammation indexes for COVID-19 patients

	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
Hs-CRP, mg/L	35.8(5.3–99.2)	18.2(3.3–84.2)	77.1(38.1-137.9)	< 0.001	18.3(3.7–80.4)	89.0(43.5-156.7)	< 0.001
No increase	73/222(32.9%)	70/170(41.2%)	3/52(5.8%)	< 0.001	71/173(41.0%)	2/49(4.1%)	< 0.001
Increased > 10	149/222(67.1%)	100/170(58.8%)	49/52(94.2%)		102/173(59.0%)	47/49(95.9%)	
ESR, mm/H	44(22–64)	40(21–62)	56(32–72)	0.007	41(21–63)	50(29–65)	0.102
No increase	36/234(15.4%)	30/183(16.4%)	6/51(11.8%)	0.418	31/185(16.8%)	5/49(10.2%)	0.258
Increased > 15	198/234(84.6%)	153/183(83.6%)	45/51(88.2%)		154/185(83.2%)	44/49(89.8%)	
IL-6 (pg/mL)	8.76(6.34–12.30)	8.55(6.28–12.36)	9.06(6.78–12.24)	0.354	8.40(6.17–12.10)	9.47(7.62–13.68)	0.012
No increase	78/230(33.9%)	64/180(35.6%)	14/50(28.0%)	0.318	69/181(38.1%)	9/49(18.4%)	0.010
Increased ≥ 7.0	152/230(66.1%)	116/180(64.4%)	36/50(72.0%)		112/181(61.9%)	40/49(81.6%)	

P < 0.05 was considered statistically significant. Hs-CRP: high-sensitive C-reactive protein. ESR: erythrocyte sedimentation rate. IL-6: interleukin 6.

3.3 Analysis of COVID-19 patients' organ damage indexes associated with disease severity and clinical outcomes

In terms of indicators related to liver function, critical patients had higher levels of aspartate aminotransferase (AST) (median 41 vs 32, P = 0.002), lactate dehydrogenase (median 426 vs 261, P < 0.001), and globulin (median 35.0 vs 31.7, P = 0.007), as compared with those for severe patients. There were similar results when the non-surviving COVID-19 patients were compared with surviving patients. Thus, higher levels of AST, globulin, and lactate dehydrogenase were associated with COVID-19 disease severity and clinical outcomes (Table 6).

Table 6
Indexes of liver damage for patients with COVID-19

	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
ALT, U/L	30(20–56)	30(19–57)	35(23–53)	0.399	27(19–53)	40(24–60)	0.069
No increase	149/234(63.7%)	118/182(64.8%)	31/52(59.6%)	0.490	120/184(65.2%)	29/50(58.0%)	0.347
Increased > 41	85/234(36.3%)	64/182(35.2%)	21/52(40.4%)		64/184(34.8%)	21/50(42.0%)	
AST, U/L	33(25–50)	32(24–45)	41(30–60)	0.002	31(24–42)	51(35–71)	< 0.001
No increase	151/234(64.5%)	126/183(68.9%)	25/51(49.0%)	0.009	134/184(72.8%)	17/50(34.0%)	< 0.001
Increased > 40	83/234(35.5%)	57/183(31.1%)	26/51(51.0%)		50/184(27.2%)	33/50(66.0%)	
Lactate dehydrogenase, U/L	282(211–417)	261(197–343)	426(348–623)	< 0.001	261(197–340)	469(387–613)	< 0.001
No increase	73/234(31.2%)	70/183(38.3%)	3/51(5.9%)	< 0.001	71/184(38.6%)	2/50(4.0%)	< 0.001
Increased > 225	161/234(68.8%)	113/183(61.7%)	48/51(94.1%)		113/184(61.4%)	48/50(96.0%)	
Globulin, g/L	32.3(28.8–36.0)	31.7(28.5–35.5)	35.0(29.3–37.6)	0.007	31.8(28.6–35.5)	34.5(29.3–36.9)	0.038
No increase	159/232(68.5%)	133/183(72.7%)	26/49(53.1%)	0.009	132/182(72.5%)	27/50(54.0%)	0.012
Increased > 35	73/232(31.5%)	50/183(27.3%)	23/49(46.9%)		50/182(27.5%)	23/50(46.0%)	

P < 0.05 was considered statistically significant. ALT: alanine aminotransferase. AST: aspartate aminotransferase. eGFR: estimated glomerular filtration rate. hs-cTn: high-sensitivity cardiac troponin. Bnp: B-type natriuretic peptide.

Concerning renal function, compared to severe patients, critical patients showed elevated levels of urea (median 7.4 vs 4.7, P < 0.001). Non-survivors had higher levels of creatinine (median 73.6 vs 66.5, P = 0.006), urea (median 7.0 vs 4.7, P < 0.001), and creatine kinase (median 100 vs 75, P = 0.016); they had lower estimated glomerular filtration rates (eGFR) (median 97.9 vs 110.2, P < 0.001) and as compared with patients in the survivor group (Table 7).

Table 7
Indexes of kidney damage for patients with COVID-19

	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
eGFR, [ml/(min*1.73M^2)]	106.7 (86.60123.0)	109.0 (88.7-131.1)	102.9 (79.1-126.8)	0.346	110.2 (91.3–134.0)	97.9 (67.9-117.1)	0.006
No decrease	166/230(72.2%)	132/179(73.7%)	34/51(66.7%)	0.320	138/180(76.7%)	28/50(56.0%)	0.004
Decreased ≤ 90	64/230(27.8%)	47/179(26.3%)	17/51(33.3%)		42/180(23.3%)	22/50(44.0%)	
Creatinine, μmol/L	67.9(56.6–80.7)	66.9(56.1–80.2)	72.4(58.5–92.3)	0.237	66.5(54.9–78.2)	73.6(62.4-100.1)	0.006
No increase	210/235(89.4%)	166/183(90.7%)	44/52(84.6%)	0.208	170/185(91.9%)	40/50(80.0%)	0.016
Increased > 104	25/235(10.6%)	17/183(9.3%)	8/52(15.4%)		15/185(8.1%)	10/50(20.0%)	
Urea, mmol/L	4.9(3.8–7.2)	4.7(3.7–6.2)	7.4(4.4–9.6)	< 0.001	4.7(3.6–6.3)	7.0(4.6–10.6)	< 0.001
No increased	193/234(82.5%)	163/183(89.1%)	30/51(58.8%)	< 0.001	164/184(89.1%)	29/50(58.0%)	< 0.001
Increased > 8.3	41/234(17.5%)	20/183(10.9%)	21/51(41.2%)		20/184(10.8%)	21/50(42.0%)	
Creatine kinase, U/L	77(53–126)	76(53–123)	81(46–143)	0.855	75(50–117)	100(64–177)	0.016
No increase	201/233(86.3%)	157/183(85.8%)	44/50(88.0%)	0.688	161/183(88.0%)	40/50(80.0%)	0.146
Increased > 190	32/233(13.7%)	26/183(14.2%)	6/50(12.0%)		22/183(12.0%)	10/50(20.0%)	

P < 0.05 was considered statistically significant. ALT: alanine aminotransferase. AST: aspartate aminotransferase. eGFR: estimated glomerular filtration rate. hs-cTn: high-sensitivity cardiac troponin. Bnp: B-type natriuretic peptide.

Also, compared with patients in the survivor group, the blood glucose levels for non-survivors were higher (median 7.5 vs 5.8, P < 0.001). Compared to the severe patients, critical patients had the same outcome. In terms of indicators related to heart damage, levels of high-sensitivity cardiac troponin (hs-cTn) (median 23.1 vs 4.7, P < 0.001) and B-type natriuretic peptide (BNP) (median 62.0 vs 21.2, P < 0.001) were elevated for non-survivors compared with survivors (Table 8). Since, for critically ill patients and dying patients, there were more severe liver and kidney damage, the indicators of liver and kidney damage can be used as risk factors for disease deterioration and death.

Table 8
Indexes of heart damage and levels of blood glucose for patients with COVID-19

	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
Hs-cTn, pg/mL	6.4(2.4–16.2)	4.9(1.8–10.5)	19.0(8.5–54.6)	< 0.001	4.7(1.8–9.3)	23.1(11.1–88.6)	< 0.001
No increase	204/234(87.2%)	167/183(91.3%)	37/51(72.5%)	< 0.001	172/184(93.5%)	32/50(64.0%)	< 0.001
Increased > 34.2	30/234(12.8%)	16/183(8.7%)	14/51(27.5%)		12/184(6.5%)	18/50(36.0%)	
Bnp, pg/mL	30.8(10.0-78.6)	21.2(10.0–60.0)	62.0(33.0-149.4)	< 0.001	18.0(10.0-55.5)	78.5(38.7-180.2)	< 0.001
No increase	192/198(97.0%)	143/146(97.9%)	49/52(94.2%)	0.384	147/149(98.7%)	45/49(91.8%)	0.053
Increased ≥ 486	6/198(3.0%)	3/146(2.1%)	3/52(5.8%)		2/149(1.3%)	4/49(8.2%)	
Blood glucose, mmol/L	5.9(5.1–7.6)	5.8(5.0-6.8)	7.7(5.6–10.5)	< 0.001	5.8(5.0-6.9)	7.5(5.8–9.9)	< 0.001
No increase	130/234(55.6%)	112/183(61.2%)	18/51(35.3%)	0.001	111/184(60.3%)	19/50(38.0%)	0.005
Increased > 6.1	104/234(44.4%)	71/183(38.8%)	33/51(64.7%)		73/184(39.7%)	31/50(62.0%)	

P < 0.05 was considered statistically significant. ALT: alanine aminotransferase. AST: aspartate aminotransferase. eGFR: estimated glomerular filtration rate. hs-cTn: high-sensitivity cardiac troponin. Bnp: B-type natriuretic peptide.

3.4 Analysis of coagulation function and CT associated with disease severity and clinical outcomes

Abnormal coagulation function was associated with disease severity and clinical outcomes for COVID-19 patients. The values for prothrombin time (median 12.0 vs 11.2, P = 0.001), fibrinogen (median 4.6 vs 3.6, P = 0.009), and D-dimer (median 2.35 vs 0.79, P < 0.001) for critical patients were higher than those for severe patients. Higher prothrombin times (median 12.5 vs 11.2, P < 0.001) and levels of D-dimer (median 4.07 vs 0.79, P < 0.001) were evident for non-surviving COVID-19 patients. Elevated procalcitonin levels were more common for critical patients relative to severe patients (75.0% vs. 28.6%, P < 0.001) and for non-survivors relative to survivors (84.0% vs 26.6%, P < 0.001). Taken together, these results suggest that high prothrombin times and levels of d-dimer and procalcitonin were associated with the severity of the disease and clinical outcomes. Representative chest CTs for assessing ground-glass opacity and bilateral pulmonary infiltration were performed for COVID-19 patients on admission (Fig. 1A-B). Of the 234 patients with CT examinations, 62 (26.5%) showed ground-glass opacity; 216 (92.3%) had bilateral pulmonary infiltration (Table 9).

Table 9
Blood coagulation and electrolyte values for COVID-19 patients

	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
Prothrombin time, s	11.3(10.6–12.5)	11.2(10.4–12.2)	12.0(11.1–13.2)	0.001	11.2(10.4–12.0)	12.5(11.3–13.6)	< 0.001
No increase	222/234(94.9%)	176/182(96.7%)	46/52(88.5%)	0.043	179/184(97.3%)	43/50(86.0%)	< 0.001
Increased > 14.5	12/234(5.1%)	6/182(3.3%)	6/52(11.5%)		5/184(2.7%)	7/50(14.0%)	
Procalcitonin, ng/mL	–	–	–	–	–	–	–
No increase	143/234(61.1%)	130/182(71.4%)	13/52(25.0%)	< 0.001	135/184(73.4%)	8/50(16.0%)	< 0.001
Increased, > 0.05	91/234(38.9%)	52/182(28.6%)	39/52(75.0%)		49/184(26.6%)	42/50(84.0%)	
Fibrinogen, g/L	3.8(2.7–5.1)	3.6(2.6–4.9)	4.6(3.3–5.6)	0.009	3.7(2.6-5.0)	4.3(3.3–5.5)	0.061
No increase	133/233(56.6%)	111/182(61.0%)	22/51(43.1%)	0.023	110/183(60.1%)	23/50(46.0%)	0.074
Increased > 4	100/233(42.9%)	71/182(39.0%)	29/51(56.9%)		73/183(39.9%)	27/50(54.0%)	
D-dimer, μg/mL	0.96(0.43–2.87)	0.79(0.33–1.80)	2.35(1.25–13.48)	< 0.001	0.79(0.33–1.82)	4.07(1.23–23.82)	< 0.001
No increase	69/231(29.9%)	67/182(36.8%)	2/49(4.1%)	< 0.001	67/183(36.6%)	2/48(4.2%)	< 0.001
Increased > 0.5	162/231(70.1%)	115/182(63.2%)	47/49(95.9%)		116/183(63.4%)	46/48(95.8%)	
Imaging features							
Ground-glass opacity	62/234(26.5%)	54/182(29.7%)	22/52(42.3%)	0.086	54/185(29.2%)	16/49(32.7%)	0.977
Bilateral pulmonary infiltration	216/234(92.3%)	170/182(93.4%)	46/52(88.5%)	0.376	173/185(93.5%)	43/49(87.8%)	0.297

P < 0.05 was considered statistically significant. Some cases were not included due to missing clinical data.

3.5 Analysis of the effect of treatment methods associated with disease severity and clinical outcomes

Of the COVID-19 patients, 221 (94.0%) received antibiotic treatment; 203 (86.4%) received antiviral therapy. Further, 67 (28.5%) of patients were given corticosteroids, 82 (34.9%) were given human serum albumin, and 78 (33.2%) received intravenous immunoglobin. Of the patients, 210 (89.4%) received routine oxygen therapy, and 52 (22.1%) received high-flow oxygen therapy. Invasive mechanical ventilation was required for 39 (16.6%) patients and non-invasive mechanical ventilation for 20 (8.5%) patients. Compared with severe cases, more critical cases received human serum albumin (69.2% vs 25.1%, P < 0.001), corticosteroids (42.3% vs 24.6%, P = 0.013), and intravenous immunoglobin (51.9% vs 27.9%, P = 0.001). Similar results were found when non-surviving cases were compared with surviving cases. More non-survivors were administered extracorporeal membrane oxygenation (ECMO) (12.0% vs 1.6%, P < 0.003), renal replacement therapy (34.0% vs 2.7%, P < 0.001), and invasive mechanical ventilation (64.0% vs 3.8%, P < 0.001) as compared with survivors (Table 10).

Table 10
Treatments for COVID-19 patients

Treatment	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
Antibiotic treatment	221/235(94.0%)	169/183(92.3%)	52/52(100%)	0.044	171/185(92.4%)	50/50(100%)	0.045
Antiviral treatment	203/235(86.4%)	152/183(83.1%)	51/52(98.1%)	0.005	154/185(83.2%)	49/50(98.0%)	0.007
Corticosteroids	67/235(28.5%)	45/183(24.6%)	22/52(42.3%)	0.013	43/185(23.2%)	24/50(48.0%)	0.001
Human serum albumin	82/235(34.9%)	46/183(25.1%)	36/52(69.2%)	< 0.001	47/185(25.4%)	35/50(70.0%)	< 0.001
Intravenous immunoglobin	78/235(33.2%)	51/183(27.9%)	27/52(51.9%)	0.001	49/185(26.5%)	29/50(58.0%)	< 0.001
Tracheotomy	4/235(1.7%)	0/183(0%)	4/52(7.7%)	0.002	3/185(1.6%)	1/50(2.0%)	1.000
ECMO	9/235(3.8%)	0/183(0%)	9/52(17.3%)	< 0.001	3/185(1.6%)	6/50(12.0%)	0.003
Renal replacement therapy	22/235(9.4%)	1/183(0.5%)	21/52(40.4%)	< 0.001	5/185(2.7%)	17/50(34.0%)	< 0.001
Support treatment							
Routine oxygen therapy	210/235(89.4%)	158/183(86.3%)	52/52(100%)	0.002	161/185(87.0%)	49/50(98.0%)	0.026
High-flow oxygen therapy	52/235(22.1%)	19/183(10.4%)	33/52(63.5%)	< 0.001	15/185(8.1%)	37/50(74.0%)	< 0.001
Non-invasive mechanical ventilation	20/235(8.5%)	0/183(0%)	20/52(38.5%)	< 0.001	7/185(3.8%)	13/50(26.0%)	< 0.001
Invasive mechanical ventilation	39/235(16.6%)	0/183(0%)	39/52(75.0%)	< 0.001	7/185(3.8%)	32/50(64.0%)	< 0.001

P < 0.05 was considered statistically significant. ECMO: extracorporeal membrane oxygenation. ARDS: Acute respiratory distress syndrome.

Respiratory failure 60 (25.5%) was the most common complication, followed by heart failure 43 (18.3%), kidney failure 42 (17.9%), hypoxemia 25 (10.6%), and septic shock 20 (8.5%). The cases of respiratory failure (92.0% vs 7.6%, P < 0.001), kidney failure (78.0% vs 1.6%, P < 0.001), and heart failure (86.0% vs 0.0%, P < 0.001) for the non-survivors were more than those for the survivors. Similar findings were evident for the critical group compared with the severe group (Table 11).

Table 11
Outcomes for COVID-19 patients

Outcomes	Total (n = 235)	Disease severity			Clinical outcomes		
		Severe (n = 183)	Critical (n = 52)	*P* value	Survivor (n = 185)	Non-survivor (n = 50)	*P* value
Septic shock	20/235(8.5%)	5/183(2.7%)	15/52(28.8%)	< 0.001	0/185(0%)	20/50(40.0%)	< 0.001
Sepsis	19/235(8.1%)	5/183(2.7%)	14/52(26.9%)	< 0.001	1/185(0.5%)	18/50(36.0%)	< 0.001
Respiratory failure	60/235(25.5%)	22/183(12.0%)	38/52(73.1%)	< 0.001	14/185(7.6%)	46/50(92.0%)	< 0.001
Heart failure	43/235(18.3%)	12/183(6.6%)	31/52(59.6%)	< 0.001	0/185(0%)	43/50(86.0%)	< 0.001
Kidney failure	42/235(17.9%)	12/183(6.6%)	30/52(57.7%)	< 0.001	3/185(1.6%)	39/50(78.0%)	< 0.001
Cardiac injury	6/235(2.6%)	2/183(1.1%)	4/52(7.7%)	0.030	0/185(0%)	6/50(12.0%)	< 0.001
Coagulopathy	12/235(5.1%)	1/183(0.5%)	11/52(21.2%)	< 0.001	2/185(1.1%)	10/50(20.0%)	< 0.001
ARDS	19/235(8.1%)	0/183(0%)	19/52(36.5%)	< 0.001	4/185(2.2%)	15/50(30.0%)	< 0.001
Hypoproteinemia	15/235(6.4%)	10/183(5.5%)	5/52(9.6%)	0.448	10/185(5.4%)	5/50(10.0%)	0.394
Hypoxemia	25/235(10.6%)	10/183(5.5%)	15/52(28.8%)	< 0.001	9/185(4.9%)	16/50(32.0%)	< 0.001

P < 0.05 was considered statistically significant. ECMO: extracorporeal membrane oxygenation. ARDS: Acute respiratory distress syndrome.

3.6 Risk factors for clinical outcomes of severe and critical COVID-19 patients

The following classification factors were statistically related with the deaths of COVID-19 patients: age, disease severity, diabetes mellitus, white blood cell count, lymphocyte count, neutrophil count, hs-CRP, IL-6, AST, lactate dehydrogenase, globulin, eGFR, creatinine, urea, hs-cTn, prothrombin time, procalcitonin, and D-dimer. Included in the multivariable logistic regression analyses were 18 factors.

In multivariate logistic analysis, age (OR = 1.07, 95% CI 1.02–1.14, P = 0.009), critical illness (OR = 48.23, 95% CI 10.91-323.13, P < 0.001), low lymphocyte counts (OR = 15.48, 95% CI 1.98-176.49, P = 0.015), high IL-6 (OR = 9.11, 95% CI 1.69–67.75, P = 0.017), and elevated AST (OR = 8.46, 95% CI 2.16–42.60, P = 0.004) were independent risk factors for adverse outcomes (Fig. 2A). Kaplan-Meier analysis showed that patients in the critical group of COVID-19 had lower survival rates compared with those in the severe group. Further, compared with the age group of > 64 years (the median age was 64 years), the survival rate of the group of age < 64 years was higher (Figs. 2B-C).

4. Discussion

Several studies have established that, for infected patients, the inflammatory response induced by SARS-CoV-2 is the main cause of severe disease and death [8]. After SARS-CoV-2 infection, older macaques have more serious inflammatory reactions [9]. In the present study, non-surviving patients were older than surviving patients, and critical patients were older than severe patients, indicating that advanced age was associated with disease development and death risk. Consistent with the findings by Du et al., advanced age was a risk factor for death of COVID-19 patients [10]. Diabetics are more likely to acquire infectious diseases, which increases their risk of diabetes mortality [11, 12]. Chen et al. found that patients with diabetes accounted for 21% of non-surviving COVID-19 cases [13]. Diabetics are more likely to have disease progression after being infected with the SARS-CoV-2, and diabetes is a risk factor for death [14, 15]. Our results show that higher numbers of critical and non-surviving COVID-19 patients had diabetes. Further, the non-survivor group had higher levels of blood glucose than the survivor group. Therefore, diabetic patients should be concerned about development of COVID19 after SARS-CoV-2 infection.

For critical patients and non-surviving patients, the numbers of white blood cells were high, but most of the critical and dying patients had low lymphocyte counts, perhaps due to a “non-reactive” immune state [16]. The levels of hs-CRP and IL-6 were higher for patients in the non- surviving group, and more deaths occurred for patients with high levels of hs-CRP and IL-6. These results indicate that, for patients with SARS-CoV-2 infections, there was a strong inflammatory response. These results are consistent with previous reports [17, 18]. On cholangiocytes, angiotensin-converting enzyme 2 (ACE2) combines with SARS-CoV-2 virus, causing inflammation and liver damage [19]. After COVID-19 infection, patients have a high risk of acute kidney injury [20]. Our research found liver and kidney damage for critically ill COVID-19 patients and dying patients. Liver injury is manifested by high levels of lactate dehydrogenase and alanine aminotransferase (ALT); high levels of eGFR and urea are associated with reduced renal function. Heart damage is reported for dying COVID-19 patients [21]. We found that hs-cTn and BNP levels were higher for dying patients, indicating that heart injury was a morbidity feature for COVID-19. Abnormal blood coagulation is an indicator of critical illness and death for patients with SARS-CoV-2 infections [22]. In groups with elevated D-dimer, fibrinogen, and procalcitonin, the proportions of critically ill and dying patients were higher.

Since, for severe and critically ill patients, there is currently no definitive treatment, symptomatic supportive treatment has been adopted to reduce the risk of death. In the present study, most critically ill patients and non-surviving patients received antibiotic and antiviral treatment. Further, 42.3% of critically ill COVID-19 patients and 48.0% of the non-surviving patients received corticosteroids. The effects of these treatments need further evaluation. Most critical patients and non-surviving patients received invasive mechanical ventilation. Respiratory failure was the most common complication of non-surviving patients. This result is similar to previous research [23].

Early identification of severe and critical COVID-19 patients is necessary to reduce their risk of death. We found that advanced age, disease severity, low lymphocyte levels, and high levels of IL-6 and AST were related to the fatal outcomes of COVID-19 patients. Other reports show that advanced age, low lymphocyte counts, and elevated AST are risk factors for disease progression and death of COVID-19 patients [24, 25]. Survival analysis showed that the survival rate for critically ill and elderly patients is poor. Clinicians should pay special attention to changes in the conditions of elderly, critically ill patients.

In summary, this research explored factors related to severe and critically ill, surviving and non-surviving COVID-19 patients. The results showed that older age (> 64 years), critical illness, low lymphocyte levels, and elevated IL-6 and AST were factors in the risk of death.

Declarations

The authors declare that they have no competing financial interests.

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Figures

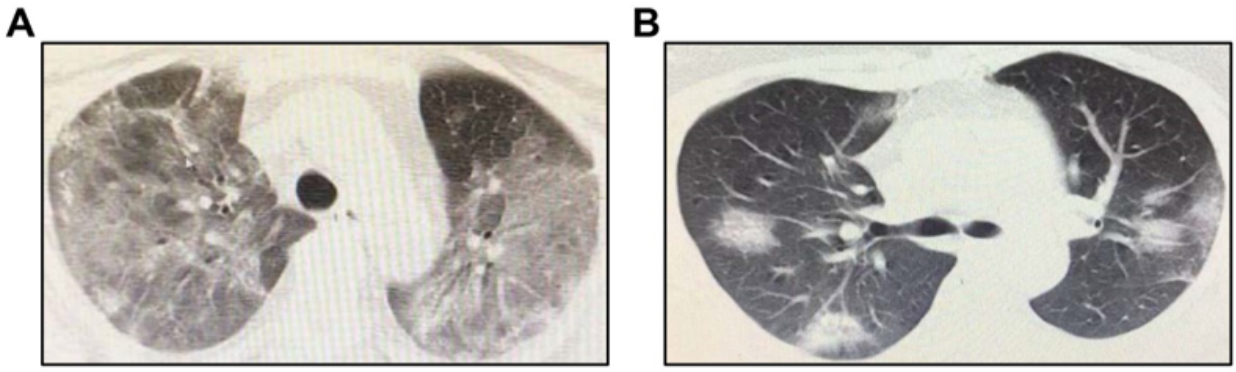

Figure 1

Representative chest CTs of COVID-19 patients. A. Chest CT showing ground-glass opacities in bilateral lungs. B. Chest CT showing bilateral pulmonary infiltration.

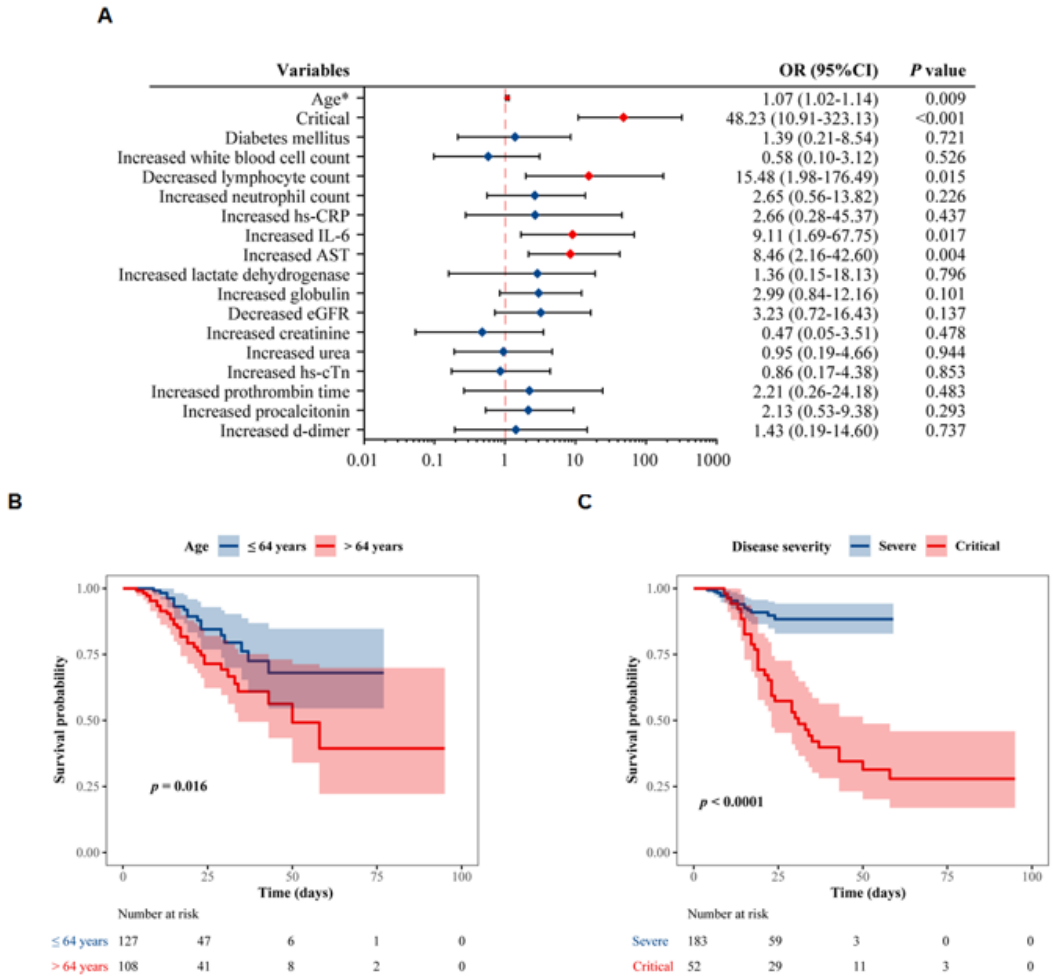

Figure 2

Multivariate regressions and Kaplan-Meier curves for survival. A. Logistic regressions were used to analyze factors related to clinical outcome. B. Kaplan-Meier curve demonstrating survival of COVID-19 patients by age group: ≤ 64 years and > 64 years. C. Kaplan-Meier curve demonstrating survival of COVID-19 patients by disease severity: severe and critical groups. *Per 1-unit increase.