Cardiac Troponin I Associated with Poor Prognosis and Death Risk in 726 Severe and Critical COVID-19 Patients: A Retrospective Cohort Study

Huilong Chen
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Xinjie Li
Peking University School of Basic Medical Sciences
Tuohutaerbieke Marmar
Peking University School of Basic Medical Sciences
Qiang Xu
Peking University School of Basic Medical Sciences
Jing Tu
Peking University School of Basic Medical Sciences
Tong Li
Peking University School of Basic Medical Sciences
Jun Han
National Institute for Viral Disease Control and Prevention
Dong Xu
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology
Tao Shen (taoshen@hsc.pku.edu.cn)
https://orcid.org/0000-0002-1365-9862

Research Article

Keywords: Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome coronavirus (SARS-CoV-2), Prognosis, Hypersensitive cardiac troponin I (hs-cTnI), Lactate dehydrogenase (LDH)

Posted Date: August 4th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-50051/v1

Abstract

Background: A few patients with coronavirus disease 2019 (COVID-19) may progress into irreparable outcomes. Early identification of patients with serious symptoms who may develop critical illness and even death is of considerable importance for personalizing treatment and balancing medical resources.

Methods: In this retrospective study, demographic, clinical characteristics and laboratory tests from 726 patients with serious COVID-19 from Tongji Hospital (Wuhan, China) were analyzed. The standards for the serious type are guided by the Chinese management guideline for COVID-19. Patients were classified into critical group (174 cases) and severe group (552 cases) based on whether the composite endpoint was reached, and the former group was divided into the survivors (47 cases) and non-survivors (127 cases). Univariable and multivariable logistic regression and receiver operating characteristic (ROC) curve analysis were performed to investigate the risk factors associated with poor prognosis and mortality outcomes.

Results: Male patients accounted for 62.1% and 51.6% in the critical group and severe group, with a median age of 68 and 65 years, respectively. Among critical cases there was a higher prevalence of chronic obstructive lung disease ($p = 0.029$) and chest distress ($p = 0.040$) than in severe cases. In the multivariable analysis, the risk factors associated with poor prognosis in severe cases were advanced age ($p = 0.002$), high respiratory rate (RR) ($p < 0.0001$), high lactate dehydrogenase (LDH) level ($p = 0.021$), high hypersensitive cardiac troponin I (hs-cTnI) level ($p < 0.0001$), and low platelet counts ($p = 0.005$) at admission. In the adjusted models, higher mortality outcomes in critical patients were associated with high hs-cTnI level ($p = 0.037$). By plotting ROC curves of different indices, hs-cTnI and LDH were found to be predictive factors for poor prognosis in patients with severe COVID-19.

Conclusions: For the risk assessment of serious COVID-19 patients on admission, advanced age, high level of RR, LDH, hs-cTnI, and low platelet counts, constitute important risk factors for poor prognosis in severe cases, and the hs-cTnI level can be helpful in predicting fatal outcomes in critically ill patients.

Introduction

Since the first case of COVID-19 was reported, this new type of virus has been sweeping the world at a terrible speed, plunging the world into extreme panic. As of June 28, 2020, the total number of confirmed cases of COVID-19 worldwide has exceeded 10 million with more than 500,000 deaths [1]. Owing to the diversity and complexity of the transmission path, population susceptibility and possibility of asymptomatic infections, the speed of the virus spread is far beyond imagination.

COVID-19 patients are often characterized as having fever, cough and fatigue, while patients with severe COVID-19 may rapidly progress into irreparable outcomes such as acute respiratory distress syndrome, septic shock, metabolic acidosis, blood coagulation dysfunction and multiple organ failure [2, 3]. Furthermore, updated studies have demonstrated that in addition to lung damage, patients with severe COVID-19 can also suffer varying degrees of damage to the heart, gastrointestinal tract, kidneys,

coagulation system and immune system, and it can even result in neurological impairment [4, 5]. An epidemiological survey of the largest case series containing 72314 patients showed that 81% of COVID-19 infections were mild, 14% were severe and 5% were critical. Despite the overall case fatality rate of only 2.3%, the fatality rate in critically ill patients was as high as 49% [6], which may be even higher in some countries and regions with poor medical conditions.

The latest clinical recommendations for the treatment of severe COVID-19 also state that patients with severe COVID-19 have a disproportionate risk of prolonged critical illness and death, urgently requiring early therapeutic interventions by clinicians [7]. However, as the ravages of COVID-19 remain unabated, numerous local medical resources are overwhelmed, optimizing the life-saving use of ventilators, renal replacement therapy equipment and intensive care facilities has been raised as a pressing issue. Therefore, it is highly desirable to expeditiously and efficaciously predict adverse outcomes in severe patients and mortality odds in critical patients to economize medical resources and rationalize healthcare staffing.

This retrospective study mainly focused on serious cases (including severe and critical cases) of COVID-19, in which the differences in demographic parameters and laboratory test results between severe and critical cases as well as survivors and non-survivors among critical cases were systematically compared. Aiming to screen out parameters associated with poor prognosis and death risk with positive predictive value, this research was conducted to provide clinicians with a reference for substantial risk assessment of severe and critical patients at the earliest opportunity for emergency monitoring and graded treatment, thus maximizing the life-saving potential for patients.

Methods

Study Participants

This was a retrospective cohort study in which we screened 1,396 patients with laboratory-confirmed COVID-19 from the Department and Institute of Infectious Disease, Tongji Hospital, Wuhan, China, who were admitted from January 27 to February 12, 2020, and were followed-up for a month. Wuhan Tongji Hospital is one of the first batches of "designated hospitals for treating severe and critical cases of COVID-19", and was also the designated hospital that treated the most critical patients during the epidemic. Patients with COVID-19 enrolled in this study were diagnosed according to World Health Organization interim guidance [8], and the diagnoses were confirmed by positive high-throughput sequencing of nasopharyngeal swab specimens or positive nucleic acid detection by real-time reverse transcription-polymerase chain reaction (RT-PCR). The inclusion criteria were age ≥ 18 years and disease severity assessed on admission according to the "Chinese management guideline for COVID-19 (version 7.0)" [9], excluding patients with significant incomplete information and those with mild or moderate disease. A total of 726 serious cases were eventually included in the study. Serious cases were separated into severe cases (552 cases) and critical cases (174 cases) based on whether the patients reached the

composite endpoint, and critical cases were grouped into survivors (47 cases) and non-survivors (127 cases) based on whether patients died.

The standard for the serious type is the presence of any of the following conditions based on clinical symptoms consistent with COVID-19: 1) respiratory distress with RR ≥ 30 times/min; 2) pulse oxygen saturation (SPO_2) ≤ 93% at rest; 3) arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 mmHg (1 mmHg = 0.133 kPa). Composite endpoints were defined as follows: 1) respiratory failure, requiring mechanical ventilation; 2) shock; 3) other organ failure, requiring intensive care unit (ICU) monitoring; or 4) death.

The study was approved by the National Health Commission of China and the Institutional Review Board of Tongji Hospital in Wuhan. The ethics committee of the designated hospital waived the informed consent requirement.

Data Collection

Data were collected from electronic medical records by medical professionals using standardized case reporting forms that included demographic characteristics (sex, age), time from illness onset to hospital admission, clinical symptoms (fever, cough, diarrhea, fatigue and chest distress), level of severity, comorbidities (hypertension, diabetes, coronary heart disease, chronic obstructive lung disease, chronic kidney disease, carcinoma and other diseases), treatments (antibiotics, antivirals, corticosteroids, high-flow nasal cannula oxygen therapy (HFNC), intravenous immunoglobulin (IVIG), invasive mechanical ventilation (IV), non-invasive mechanical ventilation (NIV), extracorporeal membrane oxygenation (ECMO), and renal replacement therapy (RRT)), and outcomes during the patient's hospitalization. Laboratory tests were conducted on admission, including heart rate, blood pressure, respiratory rate, oxygen saturation, and blood cell counts, blood chemistry analysis, assessment of coagulation, liver and kidney function, measures of electrolytes, markers of inflammation and markers of myocardial injury. Hs-cTnI testing was performed in the laboratory of Tongji Hospital using the Chemiluminescent microparticle immunoassay (CMIA) on the Abbott Architect i2000. The 99th % URL for this method is 28 pg/mL and the lower limit of detection is 1.9 pg/mL. All data were independently integrated and verified by two technicians to ensure the completeness and authenticity of the data.

Statistical Analysis

We compared the basic characteristics of patients with COVID-19 in the severe versus critical group and among the survivors versus non-survivors according to disease severity and differences in outcomes. All categorical variables were compared using the χ^2 test or Fisher's exact test and were expressed as counts and percentages; for continuous variables, comparisons were performed using the Mann-Whitney U test and were expressed as the median and inter-quartile range (IQR) as the data did not conform to a normal distribution. For variables with missing data, we did not perform valuation interpolation. We performed a univariable logistic regression analysis of 40 variables related to demographics and post-graded parameters of laboratory testing. After this analysis, selected variables with $p < 0.1$ were included in a

multivariable stepwise logistic regression model with calculated OR values and 95% conference interval (CI) to explore the risk factors associated with poor prognosis in hospitalized severe cases and death in critically ill patients. We performed four different logistic models that included hs-cTnI: model 1 was unadjusted and only included hs-cTnI, model 2 included hs-cTnI with the additional covariate of age, model 3 included hs-cTnI with the additional covariates of age and sex, model 4 included comorbidities based on model 3. We also plotted ROC curves for the variables of interest and calculated the area under the curve (AUC) and used the Youden index method to obtain the best cutoff point. All analyses were two-sided, and p values < 0.05 were considered statistically significant. In all cases, the statistical analysis was performed using SPSS version 26.0 (IBM).

Results

Comparison of demographic and clinical characteristics of patients with severe and critical COVID-19

In this retrospective study, we collected data on 1,396 inpatients with laboratory-confirmed COVID-19 positivity between January 27, 2020 and February 12, 2020, who were admitted to Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China. After excluding 4 cases with age less than 18 years old, 26 cases with grossly inadequate information as well as 640 cases with mild or moderate symptoms of COVID-19, 726 patients with serious disease were ultimately enrolled in this study, including 552 severe patients and 174 critical patients who reached the composite endpoint. Of the critical cases, only 47 patients survived, while the other 127 patients died eventually. The patient recruitment process is shown in Fig. 1.

Among the 726 severe cases included in this analysis, male patients accounted for the majority (54.1%), and the proportion of male was considerably higher in the critical group than in the severe group (62.1% vs. 51.6%, p = 0.016). Patients over 50 years of age predominated, whereas the age in the critical group was significantly higher than that in the severe group (IQR 68 [58, 77] vs. 65 [55, 71], p < 0.0001). The most common symptoms included fever (85.6% vs. 86.8%), followed by cough (78.2% vs. 78.3%) and chest distress (63.2% vs. 54.3%), while fatigue (37.9% vs. 40.2%) and diarrhea (13.8% vs. 18.3%) were relatively infrequent. Chest distress was more likely to be observed in critical patients in contrast with severe patients (p = 0.04), with no noticeable difference in other symptoms. Hypertension was the most common comorbidity (46.6% vs. 41.1%), while critical patients suffered from chronic obstructive lung disease (COLD) (8.6% vs. 4.3%, p = 0.029) and other diseases (24.1% vs. 17.4%, p = 0.048) (including a history of surgery, hepatitis, thyroid disease, Parkinson's disease, gout, prostatic hyperplasia, etc.) at higher rates than severe patients. Treatment also varied from group to group. Antibiotics (94.3% vs. 76.6%) and antiviral treatment (90.8% vs. 95.7%) were the most widely used therapies, and critical patients tended to require more antibiotics (p < 0.0001), IVIG (p < 0.0001), HFNC (p < 0.0001), IV (p < 0.0001), NIV (p < 0.0001), ECMO (p = 0.003), RRT (p < 0.0001) than severe patients, while the proportion of

severe patients on antiviral treatment was relatively higher than that among critical patients ($p = 0.015$) (Table 1).

Table 1
Demographic and clinical characteristics of patients diagnosed with severe and critical COVID-19 on admission

Variables	Critical patients (n = 174)	Severe patients (n = 552)	p value
Sex, n (%)			
Male	108 (62.1)	285 (51.6)	0.016
Age (yrs), median (IQR) or n (%)	68 (58, 77)	65 (55, 71)	< 0.0001
> 50	162 (93.1)	454 (82.2)	< 0.0001
Time from illness onset to hospital admission (days), median (IQR)	10 (7, 15)	10 (7, 14)	*0.958*
Symptom, n (%)			
Fever (temperature ≥ 37.3 °C)	149 (85.6)	479 (86.8)	*0.700*
Diarrhea	24 (13.8)	101 (18.3)	*0.170*
Cough	136 (78.2)	432 (78.3)	*0.729*
Fatigue	66 (37.9)	222 (40.2)	*0.591*
Chest distress	110 (63.2)	300 (54.3)	0.040
Treatment, n (%)			
Antibiotics	164 (94.3)	423 (76.6)	< 0.0001
Antiviral treatment	158 (90.8)	528 (95.7)	0.015
Corticosteroids	139 (79.9)	240 (43.5)	< 0.0001
IVIG	86 (49.4)	123 (22.3)	< 0.0001
HFNC	29 (16.7)	26 (4.7)	< 0.0001

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with the available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO_2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Variables	Critical patients (n = 174)	Severe patients (n = 552)	p value
NIV	75 (43.1)	24 (4.3)	< 0.0001
IV	75 (43.1)	2 (0.4)	< 0.0001
ECMO	4 (2.3)	1 (0.2)	0.003
RRT	9 (6.0)	1 (0.3)	< 0.0001
Comorbidity, n (%)			
Hypertension	81 (46.6)	227 (41.1)	*0.206*
Diabetes	40 (23.0)	100 (18.1)	*0.155*
COLD	15 (8.6)	24 (4.3)	0.029
CHD	16 (9.2)	55 (10.0)	*0.766*
CKD	5 (2.9)	8 (1.4)	*0.217*
Carcinoma	7 (4.0)	19 (3.4)	*0.719*
Other disease	42 (24.1)	96 (17.4)	0.048
Physiological parameter, median (IQR) or n/N (%)			
Heart rate, per min	95 (81, 108)	88 (80, 102)	0.003
< 60	0/173 (0)	10/552 (1.8)	0.001
60–100	104/173 (60.1)	395/552 (71.6)	
> 100	69/173 (39.9)	147/552 (26.6)	
Systolic pressure	132 (120, 150)	129 (119, 141)	0.010
> 120	128/172 (74.4)	381/552 (69.0)	*0.176*
Diastolic pressure	80 (72, 90)	79 (70, 88)	*0.107*
≤ 80	88/172 (51.2)	309/552 (56.0)	*0.268*

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with the available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO_2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Variables	Critical patients (n = 174)	Severe patients (n = 552)	p value
RR, breaths per min	22 (20, 26)	20 (20, 22)	< 0.0001
> 24	56/171 (32.7)	58/552 (10.5)	< 0.0001
SPO_2	92 (83, 97)	95 (92, 97)	< 0.0001
≤ 95	88/138 (63.8)	277/523 (53.0)	0.023
Biological parameters, median (IQR) or n/N (%)			
WBC, $\times 10^9$/L	7.3 (5.4, 10.9)	5.7 (4.5, 7.5)	< 0.0001
< 4	17/174 (9.8)	98 /551 (17.8)	< 0.0001
4–10	106/174 (60.9)	392/551 (71.1)	
> 10	51/174 (29.3)	61/551 (11.1)	
Neutrophil, $\times 10^9$/L	6.1 (4.0, 9.6)	4.0 (2.9, 5.7)	< 0.0001
< 1.8	4/174 (2.3)	36/551 (6.5)	< 0.0001
1.8–6.3	86/174 (49.4)	402/551 (73.0)	
> 6.3	84/174 (48.3)	113/551 (20.5)	
Lymphocyte, $\times 10^9$/L	0.70(0.50, 0.95)	0.95 (0.66, 1.35)	< 0.0001
≤ 0.8	113/174 (64.9)	223/551 (40.5)	< 0.0001
Hemoglobin, g/L	129 (117, 141)	128 (117, 139)	*0.378*
< 110	23/174 (13.2)	72/551 (13.1)	*0.157*
110–150	132/174 (75.9)	443/551 (80.4)	

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with the available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO_2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Variables	Critical patients (n = 174)	Severe patients (n = 552)	p value
> 150	19/174 (10.9)	36/551 (6.5)	
Platelet, $\times 10^9$/L	172.5 (121.7, 242.7)	219.0 (160.0, 294.0)	< 0.0001
≤ 100	27/174 (15.5)	21/550 (3.8)	< 0.0001
Albumin, g/L	31.3 (28.8, 34.5)	33.5 (30.6, 36.6)	< 0.0001
< 35	136/173 (78.6)	339/551 (61.5)	< 0.0001
35–55	36/173 (20.8)	212/551 (38.5)	
> 55	1/173 (0.6)	0/551 (0)	
LDH, U/L	459.0 (314.0, 588.5)	302.0 (247.0, 413.0)	< 0.0001
> 220	163/173 (94.2)	464/550 (84.5)	0.001
$NaHCO_3$, mmol/L	22.9 (20.7, 25.2)	23.8 (21.9, 25.1)	0.006
< 22	69/174 (39.7)	142/551 (25.8)	0.001
22–27	86/174 (49.4)	360/551 (65.3)	
> 27	19/174 (10.9)	49/551 (8.9)	
Urea, mmol/L	5.8 (4.6, 8.3)	4.6 (3.6, 6.3)	< 0.0001
> 7.5	58/174 (33.3)	82/551 (14.9)	< 0.0001
Creatinine, μmol/L	78.0 (60.0, 97.3)	71.0 (58.0, 87.0)	0.003
> 133	16/174 (9.2)	26/551 (4.7)	0.028

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with the available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO_2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Variables	Critical patients (n = 174)	Severe patients (n = 552)	p value
Creatine kinase, U/L	99.5 (46.8, 236.3)	66.0 (43.0, 139.0)	*0.053*
> 185	26/86 (30.2)	33/199 (16.6)	0.009
CRP, mg/L	87.3 (39.3, 142.7)	43.0 (11.0, 91.6)	< 0.0001
< 10	14/166 (8.4)	123/535 (23.0)	< 0.0001
10–50	37/166 (22.3)	167/535 (31.2)	
> 50	115/166 (69.3)	245/535 (45.8)	
PCT, ng/mL	0.16 (0.08, 0.37)	0.07 (0.04, 0.15)	< 0.0001
< 0.5	115/138 (83.3)	378/406 (93.1)	0.001
0.5–2	15/138 (10.9)	22/406 (5.4)	
> 2	8/138 (5.8)	6/406 (1.5)	
SF, μg/L	1130.9 (606.0, 1645.7)	801.6 (480.1, 1415.0)	0.014
> 300	73/79 (92.4)	166/192 (86.5)	*0.168*
Fibrinogen, g/L	5.1 (3.9, 6.5)	5.4 (4.4, 6.3)	*0.168*
< 2	8/148 (5.4)	6/436 (1.4)	0.004
2–4	33/148 (22.3)	72/436 (16.5)	
> 4	107/148 (72.3)	358/436 (82.1)	
hs-cTnI, pg/mL	18.8 (7.1, 54.9)	6.2 (3.1, 13.8)	< 0.0001
> 28	55/147 (37.4)	44/422 (10.4)	< 0.0001

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with the available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO_2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Variables	Critical patients (n = 174)	Severe patients (n = 552)	p value
IL-2R, U/mL	1051.5 (617.0, 1447.7)	806.0 (609.5, 1106.0)	0.007
< 220	1/84(1.2)	6/228 (2.6)	*0.259*
220–710	24/84 (28.6)	84/228 (36.8)	
> 710	59/84 (70.2)	138/228 (60.5)	
IL-6, pg/mL	43.4 (18.3, 82.3)	22.8 (7.3, 53.6)	< 0.0001
> 7	71/83 (85.5)	75/232 (75.4)	*0.056*
IL-8, pg/mL	21.7 (12.8, 32.7)	17.3 (10.1, 28.1)	0.037
> 62	10/84 (11.9)	16/228 (7.0)	*0.166*
IL-10, pg/mL	7.7 (5.3, 12.0)	5.5 (5.0, 9.2)	0.001
> 9	33/83 (39.8)	59/228 (25.9)	0.018
NT-proBNP, pg/mL	455.5 (168.2, 1269.0)	178.5 (68.7, 449.5)	< 0.0001
< 500	69/136 (50.7)	292/370 (78.9)	< 0.0001
500–1000	29/136 (21.3)	45/370 (12.2)	
> 1000	38/136 (27.9)	33/370 (8.9)	
D-Dimer, μg/mL	2.5 (0.91, 21.0)	1.0 (5.2, 2.1)	< 0.0001
< 0.5	17/162 (10.5)	118/504 (23.4)	< 0.0001
0.5–1	28/162 (17.3)	136/504 (27.0)	
> 1	117/162 (72.2)	250/504 (49.6)	

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with the available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO_2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

There were also statistically significant differences in various laboratory test parameters between patients in the critical group and severe group. Compared with severe group, heart rate ($p = 0.003$), systolic pressure ($p = 0.010$), RR ($p < 0.0001$), WBC ($p < 0.0001$), neutrophil ($p < 0.0001$), LDH ($p < 0.0001$), urea ($p < 0.0001$), creatinine ($p = 0.003$), C-reactive protein (CRP) ($p < 0.0001$), PCT ($p < 0.0001$), serum ferritin ($p = 0.014$), hs-cTnI ($p < 0.0001$), IL-2R ($p = 0.007$), IL-6 ($p < 0.0001$), IL-8 ($p = 0.037$), IL-10 ($p = 0.001$), NT-proBNP ($p < 0.0001$) and D-Dimer ($p < 0.0001$) levels were found to be dramatically increased in critical group, whereas lymphocyte ($p < 0.0001$), platelet ($p < 0.0001$), albumin ($p < 0.0001$), and $NaHCO_3$ ($p = 0.006$) levels were obviously decreased in the critical group. Interestingly, after grading the indicators, we found that the proportion of patients with creatine kinase > 185 U/L was notably higher in the critical group than in the severe group ($p = 0.009$), while the proportion of patients with fibrinogen > 4 g/L was much lower than that in the severe group ($p = 0.004$) (Table 1).

Comparison of demographic and clinical characteristics of survivors and non-survivors among critical COVID-19 patients

After dividing critical patients into survivors and non-survivors and comparing them, we found a similar distribution of survivors and non-survivors in terms of gender ($p = 0.726$) and age ($p = 0.171$). Notably, the survivor group appeared to have relatively more pronounced clinical signs as there were higher proportions of patients with cough (89.4% vs. 74%, $p = 0.038$) and hypertension (59.6% vs. 41.7%, $p = 0.041$) than in the non-survivor group. Among the laboratory parameters, the hs-cTnI level was considerably higher in deceased than in surviving patients ($p = 0.047$), which persisted even after grading the indicator ($p = 0.031$). In addition, the proportion of patients with creatinine > 133 μmol/L was larger in the non-survivors than in the survivors ($p = 0.050$) (Table 2).

Table 2
Demographic and clinical characteristics of survivors and non-survivors among critical COVID-19 patients on admission

Variables	Non-survivors (n = 127)	Survivors (n = 47)	p value
Sex, n (%)			
Male	80 (63.0)	28 (59.6)	*0.726*
Age (yrs), median (IQR) or n (%)	68 (59, 77)	66 (57, 74)	*0.171*
> 50	119 (93.7)	43 (91.5)	*0.609*
Time from illness onset to hospital admission (days), median (IQR)	10 (7, 15)	12 (9, 14)	*0.477*
Symptom, n (%)			
Fever (temperature ≥ 37.3 °C)	107 (84.3)	42 (89.4)	*0.473*
Diarrhea	18 (14.2)	6 (12.8)	*1.000*
Cough	94 (74)	42 (89.4)	0.038
Fatigue	47 (37)	19 (40.4)	*0.726*
Chest distress	79 (62.2)	31 (66)	*0.725*
Treatment, n (%)			
Antibiotics	120 (94.5)	44 (93.6)	*1.000*
Antiviral treatment	113 (89)	45 (95.7)	*0.241*
Corticosteroids	104 (81.9)	35 (74.5)	*0.292*
IVIG	61 (48)	25 (53.2)	*0.610*
HFNC	17 (13.4)	12 (22.5)	*0.068*
NIV	58 (45.7)	17 (36.2)	*0.303*
IV	58 (45.7)	17 (36.2)	*0.303*
ECMO	3 (2.4)	1 (2.1)	*1.000*

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Variables	Non-survivors (n = 127)	Survivors (n = 47)	p value
RRT	5 (4.7)	4 (9.1)	*0.449*
Comorbidity, n (%)			
Hypertension	53 (41.7)	28 (59.6)	0.041
Diabetes	29 (22.8)	11 (23.4)	*1.000*
COLD	12 (9.4)	3 (6.4)	*0.762*
CHD	12 (9.4)	4 (8.5)	*1.000*
CKD	5 (3.9)	0 (0)	*0.325*
Carcinoma	6 (4.7)	1 (2.1)	*0.676*
Other disease	33 (26)	9 (19.1)	*0.427*
Physiological parameter, median (IQR) or n/N (%)			
Heart rate, per min	95 (82, 108)	95 (81, 108)	*0.879*
60–100	73/126 (57.9)	31/47 (66.0)	*0.338*
> 100	53/126 (42.1)	16/47 (34.0)	
Systolic pressure	132 (120, 146)	134 (120, 151)	*0.617*
> 120	94/126 (74.6)	34/46 (73.9)	*0.927*
Diastolic pressure	79 (72, 90)	83 (75, 92)	*0.246*
≤ 80	69/126 (54.8)	19/46 (41.3)	*0.118*
RR, breaths per min	21 (20, 27)	22 (20, 26)	*0.857*
> 24	41/125 (32.8)	15/46 (32.6)	*0.981*
SPO2	90.5 (81.8, 97.0)	94.5 (86.3, 97.0)	*0.171*
≤ 95	64/98 (65.3)	24/40 (60.0)	*0.556*
Biological parameters, median (IQR) or n/N (%)			

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Variables	Non-survivors (n = 127)	Survivors (n = 47)	p value
WBC, $\times 10^9$/L	7.7 (5.7, 11.3)	7.3 (4.6, 9.5)	*0.241*
< 4	10/127 (7.9)	7/47 (14.9)	*0.198*
4–10	76/127 (59.8)	30/47 (63.8)	
> 10	41/127 (32.3)	10/47 (21.3)	
Neutrophil, $\times 10^9$/L	6.4(4.2, 10.0)	6.0 (3.5, 8.0)	*0.233*
< 1.8	1/127 (0.8)	3/47 (6.4)	*0.076*
1.8–6.3	62/127 (48.8)	24/47 (51.1)	
> 6.3	64/127 (50.4)	20/47 (42.6)	
Lymphocyte, $\times 10^9$/L	0.67 (0.47, 0.90)	0.73 (0.53, 1.00)	*0.109*
≤ 0.8	87/127 (68.5)	26/47 (55.3)	*0.106*
Hemoglobin, g/L	129 (117, 141)	128 (117, 141)	*0.634*
< 110	18/127 (14.2)	5/47 (10.6)	*0.819*
110–150	95/127 (74.8)	37/47 (78.7)	
> 150	14/127 (11.0)	5/47 (10.6)	
Platelet, $\times 10^9$/L	167 (120, 248)	174 (122, 240)	*0.708*
≤ 100	20/127 (15.7)	7/47 (14.9)	*0.890*
Albumin, g/L	31.3 (28.3, 34.6)	31.5 (30.0, 34.4)	*0.186*
< 35	100/126 (79.4)	36/47 (76.6)	*0.257*
35–55	26/126 (20.6)	10/47 (21.3)	
> 55	0/126 (0)	1/47 (2.1)	
LDH, U/L	459.0 (323.2, 574.0)	445.0 (281.0, 609.0)	*0.816*

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Variables	Non-survivors (n = 127)	Survivors (n = 47)	p value
> 220	118/126 (93.7)	45/47 (95.7)	*0.600*
$NaHCO_3$, mmol/L	22.6 (20.5, 25.0)	23.2 (20.7, 25.6)	*0.394*
< 22	52/127 (40.9)	17/47 (36.2)	*0.805*
22–27	62/127 (48.8)	24/47 (51.1)	
> 27	13/127 (10.2)	6/47 (12.8)	
Urea, mmol/L	5.9 (4.7, 9.0)	5.6 (3.9, 7.7)	*0.178*
> 7.5	46/127 (36.2)	12/47 (25.5)	*0.184*
Creatinine, μmol/L	77.0 (60.0, 97.0)	79.0 (58.0, 101.0)	*0.926*
> 133	15/127 (11.8)	1/47 (2.1)	0.050
Creatine kinase, U/L	106.0 (48.0, 246.0)	73.0 (44.5, 231.0)	*0.775*
> 185	18/61 (29.5)	8/25 (32.0)	*0.819*
CRP, mg/L	92.4 (39.8, 152.8)	66.4 (33.1, 117.2)	*0.089*
< 10	10/120 (8.3)	4/45 (8.9)	*0.903*
10–50	26/120 (21.5)	11/45 (24.4)	
> 50	85120 (70.2)	30 /45 (66.7)	
PCT, ng/mL	0.16 (0.09, 0.41)	0.16 (0.07, 0.29)	*0.162*
< 0.5	81/100 (81.0)	34/38 (89.5)	*0.194*
0.5–2	11/100 (11.0)	4 /38 (10.5)	
> 2	8/100 (8.0)	0 /38 (0)	
SF, μg/L	1162.5 (637.8, 1728.7)	893.6 (549.3, 142.0)	*0.274*

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Variables	Non-survivors (n = 127)	Survivors (n = 47)	p value
> 300	54/57 (94.7)	19/22 (86.4)	*0.208*
Fibrinogen, g/L	5.4 (4.0, 6.7)	5.1 (3.7, 5.9)	*0.554*
< 2	7/103 (6.8)	1/45 (2.2)	*0.276*
2–4	20/103 (19.4)	13/45 (28.9)	
> 4	76/103 (73.8)	31/45 (68.9)	
hs-cTnI, pg/mL	22.5 (7.6, 64.0)	11.8 (4.2, 26.1)	0.047
> 28	46/108 (42.6)	9 /39 (23.1)	0.031
IL-2R, U/mL	1094.5 (642.0, 1534.0)	1009.5(608.2, 1165.5)	*0.289*
< 220	1/60 (1.7)	0/24 (0)	*0.444*
220–710	15/60 (25)	9/24 (37.5)	
> 710	44/60 (73.3)	15/24 (62.5)	
IL-6, pg/mL	51.4 (18.3, 119.6)	35.6 (15.2, 48.1)	*0.062*
> 7	52/59 (88.1)	19/24 (79.2)	*0.292*
IL-8, pg/mL	22.9 (13.4, 38.9)	17.1 (10.4, 28.0)	*0.148*
> 62	8/60 (13.3)	2/24 (8.3)	*0.523*
IL-10, pg/mL	8.3 (5.4, 10.8)	6.7 (5.0, 15.8)	*0.868*
> 9	23/59 (39.0)	10/24 (41.7)	*0.821*
NT-proBNP, pg/mL	565.0 (186.7, 1338.5)	311.0 (121.0, 799.5)	*0.092*
< 500	48/104 (46.2)	21/32 (65.6)	*0.142*
500–1000	25/104 (24.0)	4/32 (12.5)	
> 1000	31/104 (29.8)	7/32 (21.9)	

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Variables	Non-survivors (n = 127)	Survivors (n = 47)	p value
D-Dimer, μg/mL	3.1 (0.94, 21.0)	1.7 (0.66, 21.0)	*0.251*
< 0.5	10/120 (8.3)	7/42 (16.7)	*0.314*
0.5–1	21/120 (17.5)	7/42 (16.7)	
> 1	89/120 (74.2)	28/42 (66.7)	

Data are shown as the median (IQR), n (%), or n/N (%), where N is the total number with available data. IQR, Interquartile range; IVIG, Intravenous immunoglobin; HFNC, High-flow nasal cannula oxygen therapy; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; RRT, Renal replacement therapy; COLD, Chronic obstructive lung disease; CHD, Coronary heart disease; CKD, Chronic kidney disease; ECMO, Extracorporeal membrane oxygenation; RR, Respiratory rate; SpO2, Pulse oxygen saturation; SF, Serum ferritin; hs-cTnI, Hypersensitive cardiac troponin I; WBC, White blood cell count; NT-proBNP, N terminal pro B type natriuretic peptide; PCT, Procalcitonin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.

Risk factors for poor prognosis in patients with severe COVID-19

To explore the risk factors associated with critical outcomes or contributing to a poor prognosis in severe patients, univariable logistic regression (**Supplementary Table 1**) and multivariable logistic regression models were established, and the variables that were finally included in the model were six parameters: age (per year) (OR, 1.029; 95% CI, 1.011–1.048, p = 0.002), RR (> 24 times/min) (OR, 4.146; 95% CI, 2.457–6.993, p < 0.0001), lymphocyte count (< 0.8×10^9/L) (OR, 1.519; 95% CI, 0.976–2.364, p = 0.064), platelet count (< 100×10^9/L) (OR, 3.083; 95% CI, 1.412–6.731, p = 0.005), LDH (> 220 U/L) (OR, 2.848; 95% CI, 1.167–6.949, p = 0.021), hs-cTnI (> 28 pg/mL) (OR, 2.899; 95% CI, 1.743–4.822, p < 0.0001) (Table 3). The evidence suggests that advanced age, RR > 24 breaths per min, lymphocyte count < 0.8×10^9/L, platelet count < 100×10^9/L, LDH > 220 U/L, and hs-cTnI > 28 pg/mL are independent risk factors for poor prognosis and conversion to critical outcomes in severe patients.

Table 3
Multivariable logistic regression model for predicting the risk of critical outcomes among severe COVID-19 patients.

Variables	Odds ratio	95% CI	p value
Age, year	1.029	1.011–1.048	0.002
RR, breaths per min (> 24 vs ≤ 24)	4.146	2.457–6.993	< 0.0001
Lymphocyte count, × 10^9/L (< 0.8 vs ≥ 0.8)	1.519	0.976–2.364	*0.064*
Platelet count, × 10^9/L (< 100 vs ≥ 100)	3.083	1.412–6.731	0.005
LDH, U/L (> 220 vs ≤ 220)	2.848	1.167–6.949	0.021
Hs-cTnI, pg/mL (> 28 vs ≤ 28)	2.899	1.743–4.822	< 0.0001
Constant	0.009	-	< 0.0001

RR, Respiratory rate; LDH, Lactate dehydrogenase; hs-cTnI, Hypersensitive cardiac troponin I; CI, Confidence interval.

Risk factors associated with mortality outcomes in patients with critical COVID-19

To further investigating the possible risk factors for death in critical patients, we performed univariable and multivariable logistic regression analyses in both survivors and non-survivors, and found that hs-cTnI level could be an independent risk factor for mortality outcomes in critical patients (**Supplementary Table 2, 3**). Moreover, with elevated hs-cTnI levels, there seems to be a trend of increasing rates of poor prognosis and mortality among serious patients (**Supplementary Fig. 1**). We developed four different models to observe the effect of hs-cTnI levels on the risk of death in critical patients (Table 4). In the unadjusted hs-cTnI- only logistic regression model (model 1), the risk of death in critical patients with a high hs-cTnI level (> 28 pg/mL) was 2.473 times that among patients with low levels (95% CI, 1.071–5.711, p = 0.034). In the model that included age, sex, and comorbidity effects, critical patients with high hs-cTnI level were still 2.637 times more likely to die than those with low levels (95% CI,1.058–6.570, p = 0.037), which indicates that hs-cTnI levels may be useful in assessing mortality risk in critical patients with COVID-19. In addition, among all serious patients, therapeutic measures, such as corticosteroids (p < 0.0001), IVIG (p = 0.003), IV (p < 0.0001) and NIV (p = 0.008), were needed more often patients who had high hs-cTnI level than in patients with low hs-cTnI level. Furthermore, comorbidities such as hypertension (p = 0.038) and cardiac disease (p = 0.01) were also more frequent in serious patients with high hs-cTnI level (Fig. 3).

Table 4
Relationship between hs-cTnI levels and risk of death among critical COVID-19 patients.

Model	Odds ratio (> 28 vs ≤ 28 pg/mL)	95% CI	p value
Model 1	2.473	1.071–5.711	0.034
Model 2	2.210	0.944–5.177	*0.068*
Model 3	2.284	0.969–5.384	*0.059*
Model 4	2.637	1.058–6.570	0.037

Model 1 is the unadjusted hypersensitive troponin I -only model. Model 2 includes hypersensitive troponin I with the additional covariate of age. Model 3 includes hypersensitive troponin I with the additional covariates of age and sex. Model 4 includes hypertension, diabetes, chronic obstructive lung disease, coronary heart disease, chronic kidney disease, carcinoma and other disease based on model 3. hs-cTnI, Hypersensitive cardiac troponin I; CI, Confidence interval.

Indicators predicting poor prognosis in severe patients and mortality outcomes in critical patients with ROC curve

By plotting ROC curves of different indices, hs-cTnI and LDH showed inspiring predictive value for predicting poor prognosis in patients with severe COVID-19. Using a cut-off of 17.45 pg/ml, the ROC curve of hs-cTnI (AUC, 71.5%; 95% CI, 66.5%-76.5%) yielded a sensitivity of 54.4% and a specificity of 82.5%, while the ROC curve of LDH (AUC, 71.6%; 95% CI, 67.1–76.2%) yielded a sensitivity of 50.3% and a specificity of 84.0% at a cut-off of 458.50 U/L. While predicting mortality outcomes in critically ill patients, in addition to hs-cTnI (AUC, 73.0%; 95% CI, 67.5–78.6%) and LDH (AUC, 70.9%; 95% CI, 65.8–75.9%), PCT (AUC, 70.6%; 95% CI, 65.1–76.1%) and D-Dimer (AUC, 70.1%; 95% CI, 64.7–75.4%) also possess promising potential (Fig. 2). In addition to those indicators with an AUC > 70% mentioned above, there were numerous indicators with AUC values between 60% and 70% that may also hold potential value for risk prediction (**Supplementary Table 3, 4**). The combination of detection and analysis of different indicators can assist physicians in evaluating the risk of poor prognosis and death at an early stage to a certain extent when patients with serious COVID-19 are admitted to the hospital, thus enabling them to take appropriate treatment measures in a timely manner.

Discussion

For patients who have been diagnosed with serious COVID-19 on admission, the rapid progression of the disease, the extremely difficult process of treatment, and coupled with the risk of criticality or even death at any time, have important significance for closely monitoring the progression of the disease and taking appropriate treatment measures in a timely manner. To uncover key factors for evaluating the risk of critical progression and mortality outcomes in serious patients, we comprehensively compared the differences across various indicators of admission between severe and critical cases and between survivors and non-survivors among critical patients. In this study, by multivariable logistic regression

analysis, we found that advanced age, a high level of respiratory rate, LDH and hs-cTnI, and lymphopenia and thrombocytopenia at admission were strongly associated with the incidence of poor prognosis in patients with severe COVID-19. In addition, our results also reveal that hs-cTnI levels are substantially associated with mortality outcomes in critical patients, as a high hs-cTnI level acts as a crucial risk factor for death in critical patients, both in models that included and excluded age, gender, and disease history. Moreover, it was observed that LDH and hs-cTnI were sound diagnostic markers when distinguishing between severe and critical cases, whereas PCT and D-dimer levels, along with the above two markers, were also of value when predicting mortality outcome among all patients with serious COVID-19.

In the research cohort, males accounted for a large proportion of patients admitted for severe COVID-19, and the proportion of males in the critical group was significantly higher than that in the severe group, suggesting that males appear to be more susceptible to COVID-19 and are more likely to develop into clinically severe COVID-19. Previous analysis of epidemiological characteristics also showed that the prevalence and mortality among males with COVID-19 were obviously higher than those among females [10, 11]. Possible explanations are the effects of different hormones and the fact that smoking, which is much more prevalent in the male population than in the female population, leads to an upregulation expression of angiotensin-converting enzyme 2 (ACE2), which may serve as a potential invasion receptor for SARS-CoV-2 [12–14]. The results showed that patients in severe conditions were overwhelmingly older than 50 years and that critical patients were notably older than those with severe conditions, indicating that older patients are at a higher risk of requiring critical care, which is consistent with the current study's findings [15]. Critical patients were more likely to feel chest distress than severe patients, which means they are prone to breathlessness and require additional respiratory assistance support [16]. The higher incidence of COLD and other diseases in critical patients can be explained by the fact that patients with comorbidities are comparatively more immunocompromised and less resistant to viruses, as previous studies have indicated that a history of underlying disease acts as an influential factor in the death of critical patients with COVID-19 [17]. In this study, we did not identify a clear distinction between the severe and critical groups within regard to carcinoma and coronary heart disease, presumably owing to the relatively limited number of patients with the corresponding diseases. Thus, this needs to be examined further in a larger relevant population.

Among a range of indicators that differed sharply from severe to critical cases, we identified that in addition to advanced age, elevated RR, LDH, and hs-cTnI, as well as decreased lymphocyte and platelet counts, constitute important risk factors for poor prognosis in severe patients, while the ROC curve also demonstrated that LDH and hs-cTnI are valuable predictors of critical progression in severe cases. Critical patients are more likely than severe patients to suffer from shortness of breath and dyspnea, leading to acute respiratory distress syndrome (ARDS) and even respiratory failure, as rapid breathing often indicates ventilatory dysfunction [18]. Therefore, intensely and promptly monitoring changes in respiratory rate could satisfy the auxiliary ventilation needs in severe patients and, reduce the perilous risk. lymphocyte and platelet counts are often indicative of viral infection in patients. Likewise, studies have shown that lymphopenia exists in the majority of patients with severe COVID-19 [19, 20], and sustained low levels may further exacerbate the risk of poor prognosis and death in severe cases. LDH

and hs-cTnI, as sensitizing markers of myocardial injury, provide an early indicator of to the extent of cardiac damage in patients [21]. However, the differences between the severe and critical groups suggest that patients with severe COVID-19 may have sustained varying degrees of cardiac damage as the disease progresses. Recent studies have also indicated that multiple serious sequelae persisted in patients who recovered from severe COVID-19 disease, including massive heart impairment [22, 23]. Furthermore, some other parameters with distinct differences in elevated levels such as D-dimer, cytokines (IL-2R, IL-6, IL-8, IL-10) and of inflammatory factors (CRP, PCT) also imply, to some extent, that the probability of adverse prognosis progression in severe patients, as other scholars elucidated in early research [24, 25].

Surprisingly, hs-cTnI also play a pivotal role among the risk factors affecting mortality outcomes in critically ill patients, since patients with higher hs-cTnI levels tend to experience greater severity and mortality rates among all serious cases, they are also more likely to necessitate aggressive therapeutic measures such as invasive and noninvasive mechanical ventilation and corticosteroids therapy. Hs-cTnI, compared to LDH, displays superior sensitivity and specificity in diagnosing the myocardial injury. In most clinical situations, elevated hs-cTnI is suggestive of myocardial injury with necrosis and associated with adverse clinical outcomes [26]. Given that only 10.8% of serious patients in this study had a heart-related disease, and elevated hs-cTnI levels as shown in patients with severe and critical COVID-19 are more likely to be attributed to the primary myocardial injury caused by SARS-CoV-2. A newly research has also shown that SARS-CoV-2 can infect heart cells in petri dishes of laboratory, suggesting that the heart cells in COVID-19 patients may be directly infected by the virus, resulting in heart muscle damage and heart-related complications [27]. Previous studies have reported an increased risk of death in COVID-19 patients with elevated hs-cTnI levels [28–29], moreover, our findings suggest that even when adjusted for influences such as sex, age and disease history, hs-cTnI levels continued to work in predicting the progression of prognosis and the outcome of death in serious cases. As a result, early monitoring of cardiac injury-related markers, including hs-cTnI, can play a significant role in reducing the risk of death in serious condition.

Unavoidably, several limitations in our study are worth noting. First, as this study was retrospective, and the outbreak of the disease imposed a tight time frame for patient resuscitation, which resulted in inadequate data for some items, thus, further validation of the specific findings is required in a prospective cohort study. In addition, the classification of indicators was based more on the healthy individuals, and more specific and detailed classification references should be established for COVID-19 patients. Finally, most of the data from this study were derived from the patient's examination results at admission, which is more applicable to the future assessment of the diagnosis and treatment of COVID-19 patients on admission, for long-term monitoring during hospitalization, subsequent follow-up data are required foe support. At present, research on patients with severe COVID-19 remains sparse and is mostly derived from single-source cases, in particular, there is a lack of appropriate pharmaceuticals and methodological support for minimizing or reducing the risk of poor prognosis and death in severe as well as critical patients. Therefore, larger, and wider case-source cohorts are called for in future studies to further explore effective treatment measures for patients with serious COVID-19.

Conclusions

In general, our study focused on adverse clinical prognosis and mortality outcomes in patients with serious COVID-19, and risk prediction models of selected valuable indicators were developed by comparing the differences in various demographic and laboratory tests among severe and critical cases as well as survivors and non-survivors among critical cases. In this way, it provides clinicians with a practical reference for risk assessment among serious patients on admission, early graded care and rational allocation of medical resources, which can be helpful in realizing efficient and individualized resuscitation.

Abbreviations

COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus; RT-PCR: reverse transcription-polymerase chain reaction; ICU: intensive care unit; PaO2: partial pressure of oxygen; FiO2: fraction of inspiration oxygen; ECMO: extracorporeal membrane oxygenation; CMIA: chemiluminescent microparticle immunoassay; IQR: interquartile range; CI: confidence interval; ROC: receiver operating characteristic; AUC: area under curve; OR: odds ratio; ACE2: angiotensin-converting enzyme 2; COLD: chronic obstructive lung disease; HFNC: high-flow nasal cannula oxygen therapy; IVIG: Intravenous immunoglobin; IV: Invasive mechanical ventilation; NIV: non-invasive mechanical ventilation; RRT: renal replacement therapy; WBC: white blood cell count; Hs-cTnI: hypersensitive cardiac troponin I; LDH: Lactate dehydrogenase; CPR: C-reactive protein; PCT: procalcitonin; ARDS: acute respiratory distress syndrome.

Declarations

Acknowledgments

We would like to thank all participants recruited in this study.

Authors' contributions

TS, JH and DX designed the study and wrote the study plans. HLC contributed to data collection and supervised the laboratory testing results. XJL undertook the data management and analysis. TS and XJL took the lead in drafting and interpreting the manuscript. THMM, QX, JT, TL were participated in the development and revision of statistical methods. All authors reviewed and approved the manuscript for publication.

Funding

The study was supported by the National Science and Technology Major Project of China (2017ZX10202101-003, 2018ZX10731101-001-005 and 2018ZX09739002-003). The research was

designed, conducted, analyzed, and interpreted by the authors entirely independently of the funding sources.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-C20200101). Owing to the rapid emergence of this infectious disease, written informed consent was waived.

Consent for publication

Not applicable.

Competing Interests

The authors have declared that no competing interest exists.

References

1. Worldometer. COVID-19 CORONAVIRUS PANDEMIC. https://www.worldometers.info/coronavirus/. Accessed June 29, 2020.
2. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):811-818. https://doi.org/10.1001/jamacardio.2020.1017.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
4. Bian X-W, the C-PT. Autopsy of COVID-19 victims in China. National Science Review. 2020. https://doi.org/10.1093/nsr/nwaa123.
5. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5:428-30.
6. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020. https://doi.org/10.1001/jama.2020.2648.
7. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med. 2020. https://doi.org/10.1056/NEJMcp2009575.
8. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance. https://apps.who.int/iris/handle/10665/331446. Accessed March 25,

2020.

9. National Health Commission of the People's Republic of China. Chinese management guideline for COVID-19 (version 7.0). http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml. Accessed at March 03, 2020.
10. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020. https://doi.org/10.1001/jama.2020.5394.
11. Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, Morton CE, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv. 2020:2020.05.06.20092999. https://doi.org/10.1101/2020.05.06.20092999.
12. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol. 2020;20:442-7.
13. Cai G. Bulk and single-cell transcriptomics identify tobacco-use disparity in lung gene expression of ACE2, the receptor of 2019-nCov. medRxiv. 2020:2020.02.05.20020107. https://doi.org/10.1101/2020.02.05.20020107.
14. Cai H. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med. 2020;8:e20.
15. Clark A, Jit M, Warren-Gash C, Guthrie B, Wang HHX, Mercer SW, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. Lancet Glob Health. 2020. https://doi.org/10.1016/S2214-109X(20)30264-3.
16. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med. 2020;382:2012-22.
17. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475-81.
18. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016;315:788-800.
19. Yan L, Zhang H-T, Goncalves J, Xiao Y, Wang M, Guo Y, et al. An interpretable mortality prediction model for COVID-19 patients. Nat Mach Intell. 2020;2:283-8.
20. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323(20):2052-2059. https://doi.org/10.1001/jama.2020.6775.
21. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72:2231-64.

22. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-810. https://doi.org/10.1001/jamacardio.2020.0950.
23. Marinho PM, Marcos AAA, Romano AC, Nascimento H, Belfort R, Jr. Retinal findings in patients with COVID-19. Lancet. 2020;395:1610.
24. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.
25. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med. 2020. https://doi.org/10.1001/jamainternmed.2020.2033.
26. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J. 2012;33:2252-7.
27. Sharma A, Garcia G, Arumugaswami V, Svendsen CN. Human iPSC-Derived Cardiomyocytes are Susceptible to SARS-CoV-2 Infection. bioRxiv. 2020.04.21.051912. https://doi.org/10.1101/2020.04.21.051912.
28. Franks CE, Scott MG, Farnsworth CW. Elevated Cardiac Troponin I Is Associated with Poor Outcomes in COVID-19 Patients at an Academic Medical Center in Midwestern USA. J Appl Lab Med. 2020. https://doi.org/10.1093/jalm/jfaa092.
29. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection. J Am Coll Cardiol. 2020. https://doi.org/10.1016/j.jacc.2020.06.007.

Figures

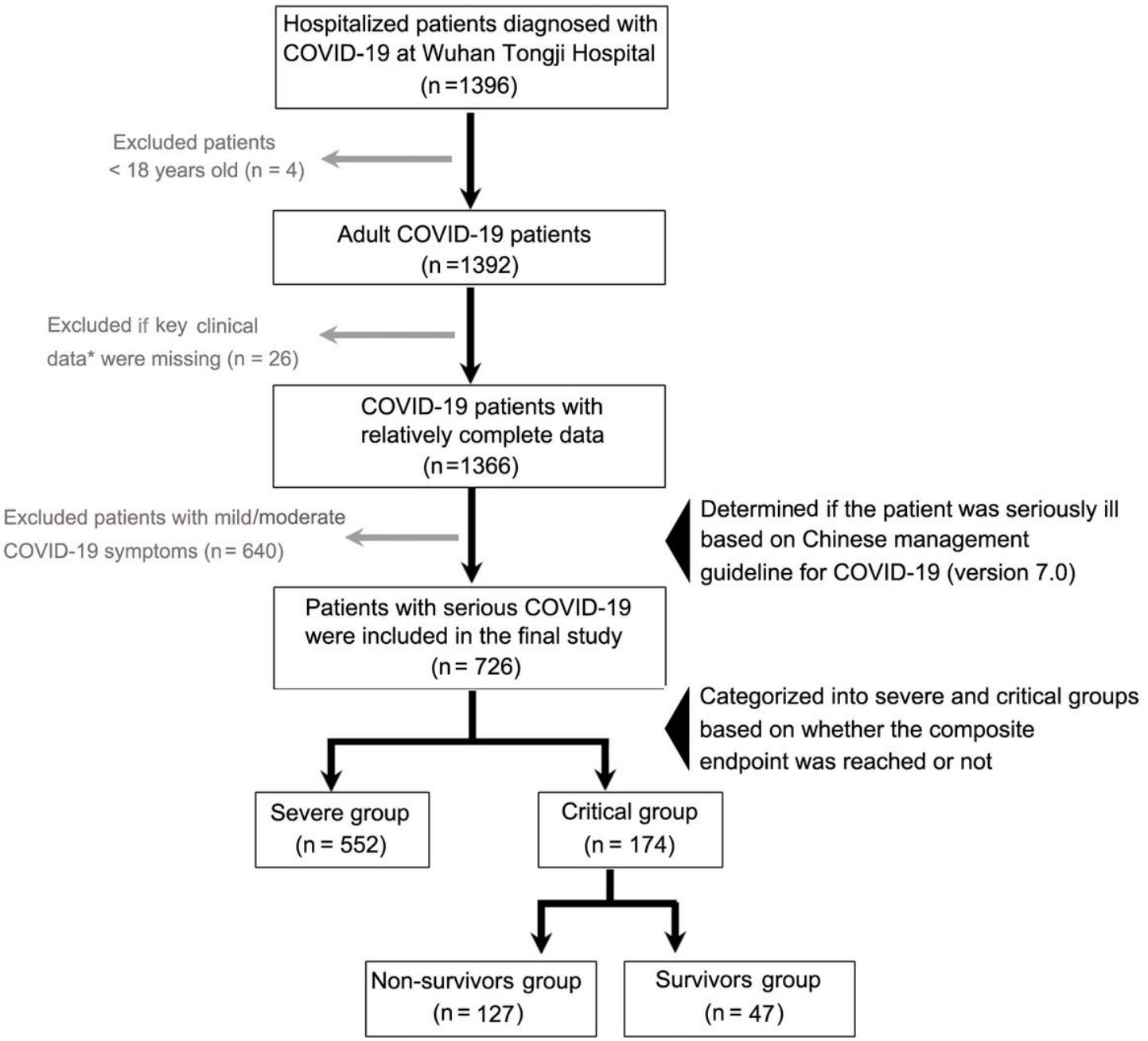

Figure 1

A flow diagram for COVID-19 patient recruitment in this study. *Key clinical data mainly refer to the time from illness onset to hospital admission, treatment options and comorbidity details. COVID-19, Coronavirus disease 2019.

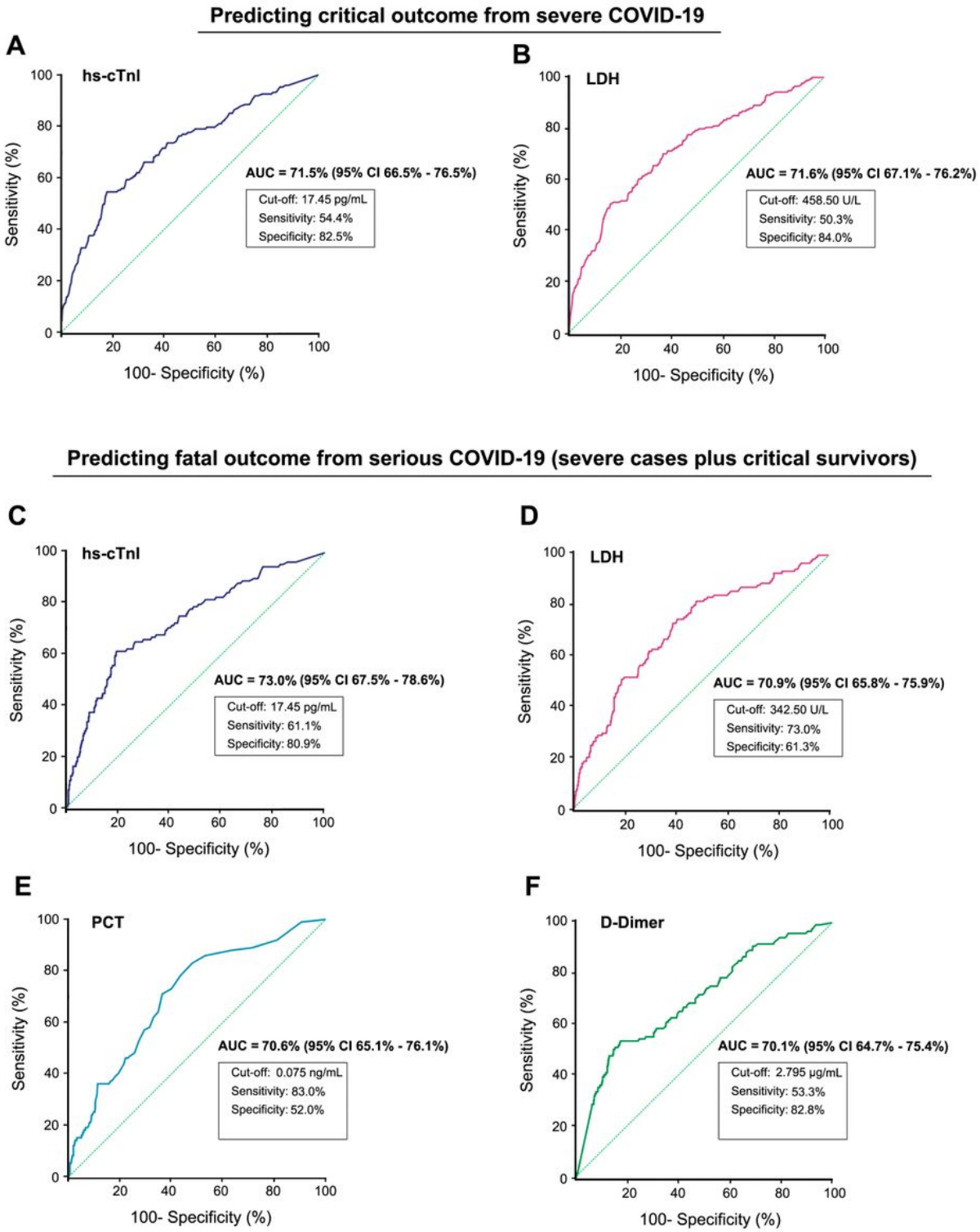

Figure 2

The diagnostic value of some clinical chemistry parameters for predicting critical outcomes from severe COVID-19 or fatal outcomes from serious COVID-19 were analyzed using ROC curves (only parameters with an AUC higher than 70% are listed). A-B The ROC curve of hs-cTnI and LDH for predicting critical illness from severe cases respectively. C-F The ROC curve for predicting fatal outcomes from serious

COVID-19 (severe cases and critical survivors). ROC, Receiver operating characteristic; AUC, Area under curve; hs-cTnI, Hypersensitive cardiac troponin I; LDH, Lactate dehydrogenase; PCT, Procalcitonin.

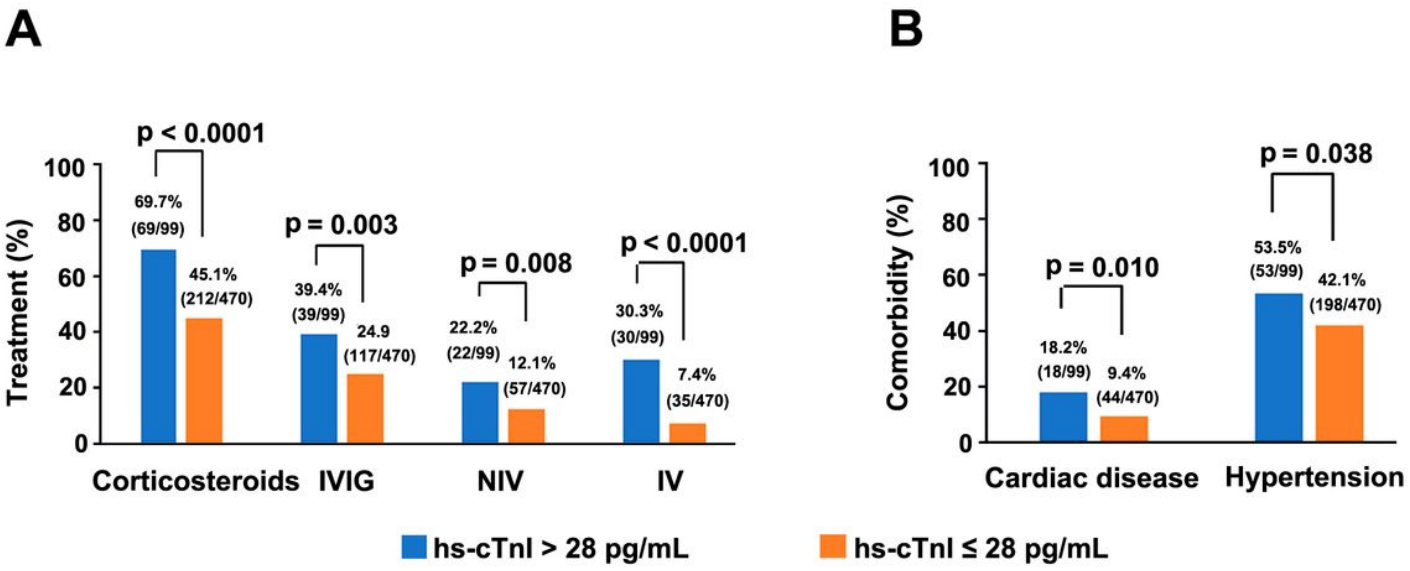

Figure 3

Comparison of the main therapeutic methods (A) and comorbidities (B) between serious COVID-19 patients with initial hs-cTnI concentrations on admission > 28 pg/mL and ≤ 28 pg/mL. Of cardiac diseases, there were 4 patients suffered from cardiac diseases that were not coronary heart disease. 2 patients had bradycardia after cardiac pacemaker surgery (1 patient with hs-cTnI > 28 pg/mL and another with hs-cTnI ≤ 28 pg/mL), 1 patient had heart failure (hs-cTnI > 28 pg/mL) and 1 patient suffered from heart valve insufficiency (hs-cTnI > 28 pg/mL). COVID-19, Corona virus disease 2019; IVIG, Intravenous immunoglobin; NIV, Non-invasive mechanical ventilation; IV, Invasive mechanical ventilation; hs-cTnI, Hypersensitive cardiac troponin I.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarydata.doc