ORIGINAL RESEARCH ARTICLE

Risk factors for myocardial injury in patients with coronavirus disease 2019 in China

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Abstract

Aims   In patients with coronavirus disease 2019 (COVID-19), the involvement of the cardiovascular system significantly relates to poor prognosis. However, the risk factors for acute myocardial injury have not been sufficiently studied. Thus, we aimed to determine the characteristics of myocardial injury and define the association between routine blood markers and cardiac troponin I, in order to perform a predictive model.

Methods and results   This retrospective cohort study included patients with confirmed COVID-19 from Wuhan Tongji Hospital (Wuhan, China). Data were compared between those with and without myocardial injury. Kaplan–Meier analysis and Cox regression models were used to describe the association between myocardial injury and poor prognosis. Simple correlation analyses were used to find factors associated with high-sensitivity cardiac troponin I levels. Univariate and multivariate logistic regression methods were used to explore the risk factors associated with myocardial injury. The area under the receiver operating characteristic curve was used to determine the predictive value of the model. Of 353 patients included in the study, 79 presented myocardial injury. Patients with myocardial injury had higher levels of inflammation markers, poorer liver and kidney function, and more complications compared with patients without myocardial injury. High-sensitivity cardiac troponin I levels were significantly associated with neutrophil/lymphocyte ratio, creatinine, D-dimer, lactate dehydrogenase, and inflammatory cytokines and negatively associated with oxygen saturation. It was significantly associated with poor prognosis after adjusting for age, sex, and complications. Multivariate regression showed that myocardial injury was associated with a high neutrophil/lymphocyte ratio (odds ratio 2.30, 95% CI 1.11–4.75, per standard deviation increase, $P = 0.02$), creatinine (3.58, 1.35–8.06, $P = 0.01$), and lactate dehydrogenase (3.39, 1.42–8.06, $P = 0.01$) levels. Using a predictive model, the area under the receiver operating characteristic curve was 0.92 (0.88–0.96).

Conclusions   In patients with COVID-19, neutrophil/lymphocyte ratio, creatinine, and lactate dehydrogenase are blood markers that could help identify patients with a high risk of myocardial injury at an early stage.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has spread globally since December 2019.[1] The clinical spectrum of COVID-19 appears to be wide, ranging from an asymptomatic infection, mild upper respiratory tract illness, or varying degrees of viral pneumonia to respiratory failure, multiple organ dysfunction, and death.[2–4] Identification and early

management of risk factors for complications is key to improving survival in COVID-19.

Like other respiratory tract infections, COVID-19 can worsen underlying cardiovascular disease and even precipitate *de novo* cardiac complications.[5,6] Recent studies demonstrate that patients with COVID-19 who suffer acute myocardial injury have increased death rates compared with those without myocardial injury.[7,8] Acute myocardial injury has been shown to be a strong negative prognostic marker in patients with COVID-19.[9]

Taking this into consideration, it would be imperative to risk stratify patients in order to identify those at highest risk who may require further tests as well as more intensive surveillance and support. Early recognition of high-risk patients would aid in the clinical decision-making process allowing prompt specific treatment. However, risk factors for myocardial injury in COVID-19 remain unclear, as limited studies have been conducted to this purpose. Here, we aimed to determine the prevalence and characteristics of myocardial injury in patients with COVID-19 in Wuhan, China, and investigated the association between routine blood markers and cardiac troponin I (cTNI) in order to perform a predictive model.

Methods

Study design and participants

This retrospective cohort study included patients diagnosed with COVID-19 from 10 February to 5 March 2020, at Tongji Hospital (Wuhan, Hubei Province, China). Clinical diagnosis criteria were as follows: (i) fever or respiratory symptoms; (ii) leukopenia or lymphopenia; and (iii) a computerized tomography scan showing imaging features of viral pneumonia with characteristic changes.[10,11] Those with ≥2 clinical criteria and a positive result of either next-generation sequencing or real-time polymerase chain reaction assays were diagnosed with COVID-19.[12]

This study complied with the edicts of the 1975 Declaration of Helsinki[13] and was approved by the research ethics commission of Ruijin Hospital (Shanghai, China). Written informed consent was obtained from patients or patients' next of kin.

Data collection

Epidemiological, demographic, clinical, laboratory, treatment, complication, and outcome data were extracted from electronic medical records. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was detected in Wuhan Tongji Hospital laboratory using next-generation sequencing or real-time PCR methods, according to World Health Organization interim guidance.[14] Throat-swab specimens were obtained after clinical remission of symptoms such as fever, cough, and dyspnoea.

Routine laboratory examinations consisted of complete blood count (Sysmex XN-2000 and its original reagent, Kobe, Japan), renal and liver function tests (creatinine, alanine transaminase, and albumin) (Roche cobas 8000 and its original reagent, Basel, Switzerland), myocardial enzymes, coagulation profile (Stago STA-R and its original reagent, Paris, France), lactate dehydrogenase (LDH) (Roche cobas 8000 and its original reagent, Basel, Switzerland), and inflammatory cytokines including high-sensitivity C-reactive protein (hsCRP) and several interleukins (Roche cobas e602 and its original reagent, Basel, Switzerland). hsCRP was tested using CRP-LATEX X2 kit (612755, Denka Seiken Co., Tokyo, Japan), and high-sensitivity cTNI was tested using STAT High Sensitive Troponin-I Reagent Kit (3P25-77, Abbott, Dublin, Ireland). The normal upper limits of cTNI in men and women were 34.2 and 15.6 pg/mL, respectively. Other reference intervals were specifically shown in Supporting Information, *Table S1*. Chest computed tomography scans were performed in all patients. A trained team of physicians reviewed all the data.

Definitions

Fever was defined as axillary temperature ≥37.3°C. Myocardial injury was diagnosed if serum levels of cTNI were above the 99th percentile upper reference limit.[3] The severity of COVID-19 was classified according to the Chinese guidelines for management of COVID-19 (Version 7.0).[15,16] Severe cases were defined when at least one of the following was present: (i) respiratory rate >30 breaths per minute; (ii) oxygen saturation (SpO_2) ≤93%; and (iii) PaO_2/FiO_2 ratio ≤300 mmHg. Critical cases were defined as those including at least one of the following: (i) respiratory failure requiring mechanical ventilation; (ii) shock; (iii) presence of other organ damage apart from respiratory; and (iv) admission to intensive care unit. Kidney injury was diagnosed according to the KDIGO clinical practice guidelines.[17] Acute respiratory distress syndrome was diagnosed according to the Berlin Definition.[18] Coagulopathy was defined as a 3 s extension of prothrombin time or a 5 s extension of activated partial thromboplastin time.

Statistical analysis

Continuous variables were log transformed to obtain a normal distribution and were presented as mean values ± standard deviation. Categorical variables were presented as number of individuals, with percentages within parentheses. Student's *t*-test, χ^2 test, and Fisher's exact test were used to compare differences between patients with and without myocardial injury when appropriate. Kaplan–Meier analysis was used to

Table 1 Demographic, clinical, and laboratory findings of patients with and without myocardial injury on admission

	Total (*n* = 353)	Without myocardial injury (*n* = 274)	With myocardial injury (*n* = 79)	*P* value
Demographic and clinical characteristics				
Age (years)	60.47 ± 10.05	57.65 ± 14.68	70.25 ± 11.96	<0.01
Sex, male (%)	186 (52.7)	136 (49.6)	50 (63.3)	0.03
Exposure history (%)	218 (61.8)	165 (60.2)	53 (67.1)	0.27
Co-morbidity				
Hypertension (%)	129 (36.5)	87 (31.8)	42 (53.2)	<0.01
Diabetes (%)	67 (19.0)	49 (17.9)	18 (22.8)	0.33
Coronary heart disease (%)	40 (11.3)	24 (8.8)	16 (20.3)	0.01
Chronic obstructive lung disease (%)	26 (7.4)	18 (6.6)	8 (10.1)	0.29
Chronic kidney disease (%)	13 (3.7)	3 (1.1)	10 (12.7)	<0.01
Carcinoma (%)	11 (3.1)	9 (3.3)	2 (2.5)	0.73
Stroke (%)	13 (3.7)	10 (3.6)	3 (3.8)	0.95
Symptom				
Fever (temperature ≥37.3°C) (%)	271 (76.8)	211 (77.0)	60 (75.9)	0.84
Cough (%)	288 (81.6)	219 (79.9)	69 (87.3)	0.13
Sputum (%)	185 (52.4)	141 (51.5)	44 (55.7)	0.51
Dyspnoea (%)	129 (36.5)	90 (32.8)	39 (49.4)	0.01
Pharyngalgia (%)	45 (12.7)	32 (11.7)	13 (16.5)	0.26
Headache (%)	51 (14.4)	40 (14.6)	11 (13.9)	0.88
Myalgia (%)	71 (20.1)	53 (19.3)	18 (22.8)	0.5
Fatigue (%)	135 (38.2)	104 (38.0)	31 (39.2)	0.84
Chest pain (%)	63 (17.8)	44 (16.1)	19 (24.1)	0.1
Chest distress (%)	144 (40.8)	102 (37.2)	42 (53.2)	0.01
Diarrhoea (%)	81 (22.9)	58 (21.2)	23 (29.1)	0.14
Nausea or vomiting (%)	49 (13.9)	37 (13.5)	12 (15.2)	0.7
CURB-65 score				<0.01
0–1 (%)	220 (62.3)	205 (74.8)	15 (19.0)	
2 (%)	77 (21.8)	58 (21.2)	19 (24.1)	
3–5 (%)	56 (15.9)	11 (4.0)	45 (56.9)	
Disease severity status				<0.01
General (%)	247 (70.0)	229 (83.6)	18 (22.8)	
Severe (%)	56 (15.9)	40 (14.6)	16 (20.3)	
Critical (%)	50 (14.1)	5 (1.8)	45 (57.0)	
Physical examination				
Systolic blood pressure (mmHg)	130.86 ± 18.55	129.86 ± 17.97	134.32 ± 20.17	0.06
Diastolic blood pressure (mmHg)	79.11 ± 12.24	78.85 ± 11.77	79.99 ± 13.77	0.47
Heart rate (b.p.m.)	88.19 ± 14.29	86.76 ± 14.19	93.16 ± 13.61	<0.01
Respiratory rate (breaths per minute)	20.96 ± 4.62	20.60 ± 4.31	22.20 ± 5.40	0.02
Temperature (°C)	36.80 ± 0.74	36.75 ± 0.71	36.96 ± 0.81	0.04
Minimum SpO$_2$ (%)	90.39 ± 12.09	93.99 ± 5.86	77.78 ± 18.34	<0.01
Laboratory findings				
White blood cell count (× 10^9/L)	6.40 ± 3.04	5.79 ± 1.99	8.56 ± 4.69	<0.01
Lymphocyte count (× 10^9/L)	1.30 ± 0.57	1.42 ± 0.52	0.85 ± 0.49	<0.01
Neutrophil count (× 10^9/L)	4.50 ± 3.08	3.75 ± 1.85	7.12 ± 4.71	<0.01
Minimum lymphocyte count (× 10^9/L)	1.18 ± 0.55	1.33 ± 0.48	0.66 ± 0.44	<0.01
Maximum neutrophil/lymphocyte	8.48 ± 15.38	3.75 ± 3.58	25.12 ± 25.96	<0.01
Monocyte count (× 10^9/L)	0.62 ± 1.11	0.62 ± 1.15	0.62 ± 1.00	0.99
Haemoglobin (g/L)	126.59 ± 17.22	126.96 ± 15.31	125.29 ± 22.78	0.54
Platelet count (× 10^9/L)	250.89 ± 100.25	265.54 ± 91.74	199.32 ± 111.96	<0.01
Albumin (g/L)	36.33 ± 5.22	37.56 ± 4.53	32.08 ± 5.22	<0.01
Alanine transaminase (U/L)	55.73 ± 239.14	34.89 ± 34.44	127.87 ± 496.77	<0.01
Creatinine (μmol/L)	90.07 ± 78.18	71.16 ± 18.79	155.42 ± 143.86	<0.01
Lactate dehydrogenase (U/L)	338.54 ± 296.87	243.72 ± 84.14	655.05 ± 480.10	<0.01
High-sensitivity cardiac troponin I (pg/mL)	329.33 ± 3041.59	4.91 ± 4.12	1428.02 ± 6278.61	<0.01
Myoglobin (ng/mL)	123.40 ± 246.35	43.30 ± 41.79	396.18 ± 408.17	<0.01
Creatine phosphokinase-MB (ng/mL)	1.87 ± 4.74	0.76 ± 0.78	5.62 ± 8.91	<0.01
N-terminal pro-brain natriuretic peptide (pg/mL)	1727.72 ± 6878.03	125.24 ± 136.62	6913.51 ± 12914.95	<0.01
Prothrombin time (s)	14.50 ± 5.26	13.59 ± 0.80	17.51 ± 10.35	<0.01
D-dimer (μg/mL)	3.80 ± 7.38	1.73 ± 5.07	10.80 ± 9.43	<0.01
High-sensitivity C-reactive protein (mg/L)	43.62 ± 68.14	21.50 ± 37.54	120.22 ± 91.32	<0.01
IL-1β (pg/mL)	13.74 ± 69.43	8.31 ± 19.07	29.83 ± 133.89	0.01
IL-2R (U/mL)	767.02 ± 788.73	490.81 ± 260.34	1585.79 ± 1176.23	<0.01
IL-6 (pg/mL)	189.38 ± 781.30	8.69 ± 20.74	728.22 ± 1438.00	<0.01
IL-8 (pg/mL)	102.87 ± 501.07	14.59 ± 28.17	364.57 ± 955.62	<0.01
TNF-α (pg/mL)	14.54 ± 36.95	7.76 ± 5.00	34.63 ± 69.73	<0.01

IL, interleukin; SpO$_2$, oxygen saturation; TNF, tumour necrosis factor.

compare the mortality rate in patients with and without myocardial injury. Univariate and multivariate Cox regression models were analysed to describe the association between cTNI and poor prognosis. Simple correlation analyses were used to explore the relationship between cTNI and other variables. Univariate and multivariate logistic regression models were used to explore risk factors associated with myocardial injury, and an area under the receiver operating characteristic curve was applied to determine the predictive value of the model. A two-sided α of less than 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS software (Version 20.0).

Results

Baseline characteristics

A total of 475 cases of suspected COVID-19 were identified, of which 122 were excluded either because they lacked SARS-CoV-2 confirmation by RNA detection or because they were still hospitalized by 5 March. Therefore, 353 patients were included in the final analysis. *Table 1* shows the clinical features of patients with confirmed COVID-19. The mean age of these patients was 60.47 ± 10.05, ranging from 18 to 89 years. Co-morbidities were present in nearly half of

patients, with hypertension being the most prevalent condition, followed by diabetes and coronary heart disease. On admission, the most common symptoms were cough and fever; sputum, chest distress, fatigue, and dyspnoea also occurred in over 25% of the patients. Regarding laboratory findings, mean levels of alanine transaminase, LDH, myocardial enzymes, D-dimer, and inflammatory cytokines were all significantly increased compared with normal levels. Lymphocytopenia ($<0.8 \times 10^9$/L) occurred in 98 (27.8%) patients.

Clinical features and laboratory characteristics in patients with and without myocardial injury

Cardiac injury occurred in 79 (22.4%) patents with COVID-19. Compared with those without myocardial injury, these patients were predominantly male, had an older age, and presented a higher prevalence of hypertension and coronary artery disease. Although symptoms of COVID-19 did not differ between the two groups, patients with myocardial injury exhibited more severe forms of the disease. Moreover, patients with myocardial injury demonstrated higher leucocyte and neutrophil counts and lower lymphocyte and platelet counts. Elevations in alanine transaminase, creatinine, and LDH were more frequent in patients with myocardial injury, as well as coagulation pathway abnormalities, including high

Figure 1 Temporal changes in laboratory markers from illness onset in patients with coronavirus disease 2019, with and without myocardial injury. Temporal changes in high-sensitivity C-reactive protein (A), white blood cell count (B), neutrophil count (C), lymphocyte count (D), neutrophil/lymphocyte ratio (E), monocyte count (F), haemoglobin levels (G), and platelet count (H). Differences between patients with and without myocardial injury were significant for all time points shown, except for monocyte count at all time points and haemoglobin at Day 2.
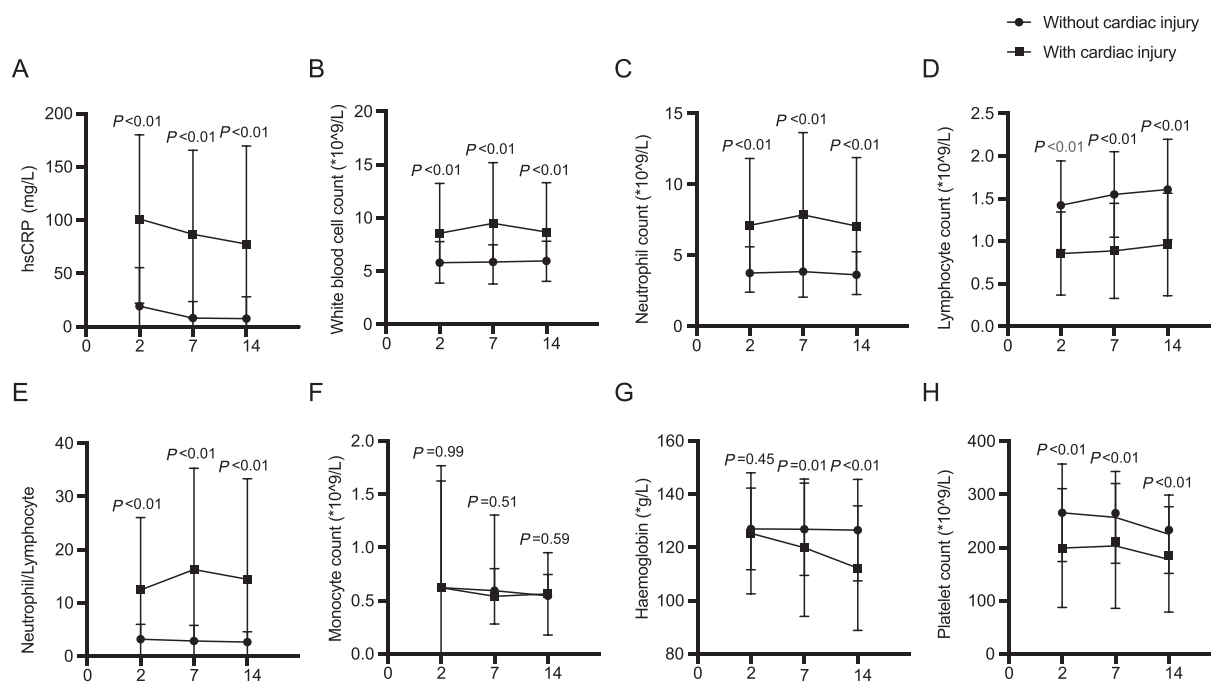
D-dimer and prolonged prothrombin time. Inflammatory cytokines including hsCRP, interleukin (IL)-1β, IL-2R, IL-6, IL-8, and tumour necrosis factor-α were also significantly higher in this group of patients (*Table 1*).

Focusing on blood results at Day 2 of hospitalization, patients who developed myocardial injury had higher levels of hsCRP, higher leucocyte and neutrophil counts, and lower lymphocyte and platelet counts than patients who did not develop this complication. The monocyte count and haemoglobin level were similar between the two groups (*Figure 1*). In patients without myocardial injury, leucocyte count and neutrophil/lymphocyte ratio were highest on Day 7 and later improved, whereas these remained unchanged in those with myocardial injury. Moreover, the haemoglobin level gradually decreased in patients with myocardial injury.

Treatment and outcome

Following current guidelines, 325 (92.1%) patients received antivirals including umifenovir, oseltamivir, ribavirin, and lopinavir/ritonavir; 271 (76.8%) received antibiotics; and 256 (72.5%) were treated with Chinese medicine. Corticosteroids, intravenous immunoglobulin, oxygen therapy, and mechanical ventilation were also used as appropriate (*Table 2*).

Liver damage was the most frequent complication, followed by myocardial injury, respiratory failure, and kidney injury. The frequency of complications was significantly higher in patients with myocardial injury than in those without it (*Table 2*). Overall, 49 patients (13.9%) died during hospitalization and 267 (75.6%) recovered. Mortality rates were markedly higher in the group with myocardial injury (*Figure 2*). Myocardial injury, as determined by cTNI levels, was significantly associated with mortality after adjusting for age, sex, and complications including respiratory failure, liver damage, kidney injury, coagulopathy, and septic shock, as well as the specific values of multiorgan function (*Table 3*).

The predictive model of myocardial injury

In all patients with COVID-19, cTNI levels were strictly correlated with age; minimum SpO$_2$; CURB-65 score; liver, kidney, and coagulation functions; lymphocytopenia; neutrophil/lymphocyte ratio; LDH; N-terminal pro-brain natriuretic peptide; and inflammatory markers such as hsCRP, IL-6, and several cytokines (Supporting Information, *Table S2*).

In univariate analysis, myocardial injury was significantly more frequent in older patients with hypertension or coronary heart disease. In addition, myocardial injury was associated with low albumin levels and SpO$_2$; an increased respiratory rate; a high neutrophil/lymphocyte ratio; and elevated levels of ALT, creatinine, LDH, D-dimer, prothrombin time, and inflammatory markers (*Table 4*).

In multivariate logistic regression models, variables were first adjusted for age and sex, then adjusted for age, sex, and co-morbidities (including hypertension, diabetes,

Table 2 Treatments, complications, and outcomes of patients with and without myocardial injury

	Total (n = 353)	Without myocardial injury (n = 274)	With myocardial injury (n = 79)	P value
Treatments				
Antiviral treatment	325 (92.1)	260 (94.9)	65 (82.3)	<0.01
Antibiotics	271 (76.8)	198 (72.3)	73 (92.4)	<0.01
Corticosteroids	62 (17.6)	24 (8.8)	38 (48.1)	<0.01
Intravenous immunoglobulin	44 (12.5)	18 (6.6)	26 (32.9)	<0.01
Chinese medicine	256 (72.5)	218 (79.6)	38 (48.1)	<0.01
Nasal cannula oxygen therapy	240 (68.0)	188 (68.6)	52 (65.8)	0.64
Mask oxygen inhalation	36 (10.2)	16 (5.8)	20 (25.3)	<0.01
High-flow nasal cannula oxygen therapy	14 (4.0)	2 (0.7)	12 (15.2)	<0.01
Non-invasive mechanical ventilation	29 (8.2)	3 (1.1)	26 (32.9)	<0.01
Invasive mechanical ventilation	26 (7.4)	2 (0.7)	24 (30.4)	<0.01
Circulatory support	11 (3.1)	0 (0.0)	11 (13.9)	<0.01
Renal replacement therapy	11 (3.1)	0 (0.0)	11 (13.9)	<0.01
Complications				
Respiratory failure	57 (16.1)	8 (2.9)	49 (62.0)	<0.01
Acute liver damage	92 (26.1)	51 (18.6)	41 (51.9)	<0.01
Acute kidney injury	53 (15.0)	14 (5.1)	39 (49.4)	<0.01
Septic shock	20 (5.7)	2 (0.7)	18 (22.8)	<0.01
MODS	46 (13.0)	0 (0.0)	46 (58.2)	<0.01
Coagulopathy	18 (5.1)	5 (1.8)	13 (16.5)	<0.01
Outcomes				<0.01
Recovery	267 (75.6)	239 (87.2)	28 (35.4)	
Improvement	35 (9.9)	31 (11.3)	4 (5.1)	
Stabilization	1 (0.3)	0 (0.0)	1 (1.3)	
Aggravation	1 (0.3)	0 (0.0)	1 (1.3)	
Death	49 (13.9)	4 (1.5)	45 (57.0)	

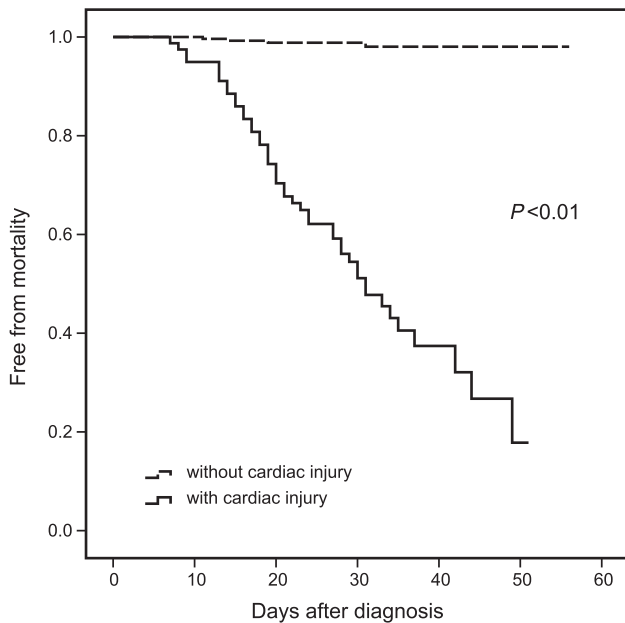ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome.

Table 3 Univariate and multivariate Cox proportional hazard models for cTNI as a predictor of mortality

Log cTNI per SD	HR (95% CI)	P value
Univariable	2.75 (2.30–3.29)	<0.01
Adjusted for Model 1	2.57 (2.10–3.13)	<0.01
Adjusted for Model 2	2.29 (1.81–2.89)	<0.01
Adjusted for Model 3	1.65 (1.17–2.34)	<0.01

CI, confidence interval; cTNI, cardiac troponin I; HR, hazard ratio; SD, standard deviation; SpO_2, oxygen saturation.
Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, respiratory failure, liver damage, kidney injury, coagulopathy, and septic shock. Model 3: adjusted for age, sex, log alanine transaminase, log creatinine, log prothrombin time, and SpO_2.

coronary heart disease, and chronic obstructive lung disease), and further analysed in a model that included all variables. Notably, we found that creatinine, LDH, and neutrophil/lymphocyte ratio were independently associated with increased odds of myocardial injury (*Table 4*).

We further analysed the predictive value of this model using an area under the receiver operating characteristic curve derived from multivariate analysis. The area under the receiver operating characteristic curve was 0.92 (0.88–0.96), and the sensitivity and specificity of the cut-off predictive value were 0.75 and 0.96, respectively (*Figure 3*). The recommended reference cut-off value of each parameter was 7.32 for maximum neutrophil/lymphocyte, 87.5 μmol/L for serum creatinine, and 278.5 U/L for serum LDH. Moreover, this model could predict the presence of myocardial injury in both patients with and without other organ dysfunction (Supporting Information, *Table S3*).

Discussion

This retrospective cohort study identified several risk factors and performed a predictive model for myocardial injury in hospitalized patients with COVID-19 in Wuhan, China. Notably, a high neutrophil/lymphocyte ratio and elevated levels of creatinine and LDH were associated with higher odds of myocardial injury. In addition, older age, lower SpO_2, and elevated levels of ALT, D-dimer, and inflammatory cytokines were significantly correlated with increased levels of cTNI. As expected, patients with myocardial injury suffered from more complications during hospitalization and had a poorer prognosis than those without myocardial injury.

Risk factors of cardiac events after pneumonia include older age, pre-existing cardiovascular diseases, and greater severity of disease.[19,20] To date, the aetiology of cardiac disease in patients with COVID-19 is likely to be multifactorial, and mechanisms underlying myocardial injury during the course of COVID-19 infection remain unknown.[21]

Severe acute respiratory syndrome coronavirus 2 may exert direct cytopathic effects on cardiac tissue, leading to the increase of cTNI levels. It has been shown that both SARS-CoV and SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE2), which is highly expressed in the heart and vasculature, as a cell entry receptor.[22,23] Previous studies indicated that SARS-CoV is detectable and ACE2 expression is down-regulated in the heart of infected patients, leading to the activation of renin–angiotensin–aldosterone system and further exacerbating myocardial injury.[24] SARS-CoV-2 may as well bind to ACE2 expressed in the heart and induces ACE2 down-regulation as well as renin–angiotensin–aldosterone system dysfunction, leading to cardiac dysfunction and pneumonia progression. Interstitial inflammatory cell infiltrates in heart tissue have also been documented in fatal cases of COVID-19, supporting the possibility of direct myocardial infection.[25]

The elevation of cTNI levels and the presence of myocardial injury may also be due to the indirect, infection-related pathogenesis on myocardium. Associations between cTNI elevation and other features of the disease need to be systematically examined, with further analyses aiming to stratify patients with high risk of cardiovascular complications in COVID-19.[26] The present study indicated the significant predictive value of neutrophil/lymphocyte ratio, creatinine, and LDH.

Many conclusions can be drawn from these results. First, this study confirmed that high levels of inflammation are associated with myocardial injury in patients with COVID-19. cTNI levels were strictly correlated to levels of hsCRP and

Table 4 Risk factors associated with cardiac injury

	Univariable OR (95% CI)	P value	Adjusted for Model 1 OR (95% CI)	P value	Adjusted for Model 2 OR (95% CI)	P value	Adjusted for Model 3 OR (95% CI)	P value
Demographic and clinical characteristics								
Log age per SD	3.84 (2.34–6.29)	<0.01	✓	✓	✓	✓	✓	✓
Male sex (vs. female)	1.75 (1.05–2.93)	0.03	✓	✓	✓	✓	✓	✓
Co-morbidity present (vs. not present)								
Hypertension	2.44 (1.47–4.06)	<0.01	—	—	✓	✓	✓	✓
Diabetes	1.36 (0.74–2.49)	0.33	—	—	✓	✓	✓	✓
Coronary heart disease	2.65 (1.33–5.28)	0.01	—	—	✓	✓	✓	✓
Chronic obstructive lung disease	1.60 (0.67–3.84)	0.29	—	—	✓	✓	✓	✓
Respiratory rate (breaths per minute)								
≤24	1 (ref)		1 (ref)				—	—
>24	2.41 (1.24–4.68)	0.01	1.99 (0.98–4.05)	0.06	—	—	—	—
Min SpO₂ (%)								
>93	1 (ref)		1 (ref)		1 (ref)		—	—
≤93	8.15 (4.62–14.35)	<0.01	5.93 (3.28–10.73)	<0.01	5.77 (3.15–10.55)	<0.01	—	—
Laboratory findings								
Log maximum neutrophil/lymphocyte per SD	6.84 (4.47–10.46)	<0.01	6.32 (4.02–9.93)	<0.01	6.09 (3.92–9.45)	<0.01	2.30 (1.11–4.75)	0.02
Log alanine transaminase per SD	1.80 (1.38–2.33)	<0.01	1.90 (1.41–2.56)	<0.01	1.92 (1.42–2.60)	<0.01	—	—
Log creatinine per SD	5.25 (3.30–8.35)	<0.01	6.79 (3.77–12.23)	<0.01	6.66 (3.71–11.97)	<0.01	3.58 (1.35–9.54)	0.01
Log lactate dehydrogenase per SD	8.32 (4.87–14.21)	<0.01	8.27 (4.62–14.82)	<0.01	8.22 (4.52–14.91)	<0.01	3.39 (1.42–8.06)	0.01
Log albumin per SD	0.30 (0.22–0.41)	<0.01	0.37 (0.26–0.53)	<0.01	0.34 (0.24–0.49)	<0.01	—	—
Log D-dimer per SD	4.76 (3.37–6.74)	<0.01	4.55 (3.10–6.69)	<0.01	4.41 (3.05–6.37)	<0.01	—	—
Log prothrombin time per SD	6.79 (3.66–12.60)	<0.01	4.52 (2.45–8.36)	<0.01	4.51 (2.36–8.60)	<0.01	—	—
Log hsCRP per SD	6.82 (4.22–11.01)	<0.01	5.82 (3.57–9.48)	<0.01	5.50 (3.42–8.84)	<0.01	—	—
Log IL-1β per SD	1.66 (1.19–2.31)	<0.01	1.97 (1.34–2.88)	<0.01	1.93 (1.33–2.80)	<0.01	—	—
Log IL-2R per SD	6.81 (3.90–11.88)	<0.01	5.28 (2.97–9.40)	<0.01	5.28 (2.97–9.40)	<0.01	—	—
Log IL-6 per SD	6.68 (4.00–11.15)	<0.01	5.45 (3.17–9.36)	<0.01	5.34 (3.13–9.11)	<0.01	—	—
Log IL-8 per SD	5.75 (3.36–9.84)	<0.01	4.35 (2.52–7.51)	<0.01	4.17 (2.39–7.27)	<0.01	—	—
Log TNF-α per SD	7.23 (4.00–13.06)	<0.01	5.69 (3.09–10.45)	<0.01	5.59 (3.03–10.32)	<0.01	—	—
Antiviral treatment	0.25 (0.11–0.55)	<0.01	0.30 (0.13–0.73)	0.01	0.30 (0.13–0.73)	<0.01	—	—

CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; OR, odds ratio; SD, standard deviation; SpO₂, oxygen saturation; TNF, tumour necrosis factor; /, divide; neutrophil/lymphocyte, neutrophil/lymphocyte ratio.
Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, and conventional risk factors for cardiac injury including hypertension, diabetes, and coronary heart disease. Model 3: adjusted for all factors included in the univariable analysis.
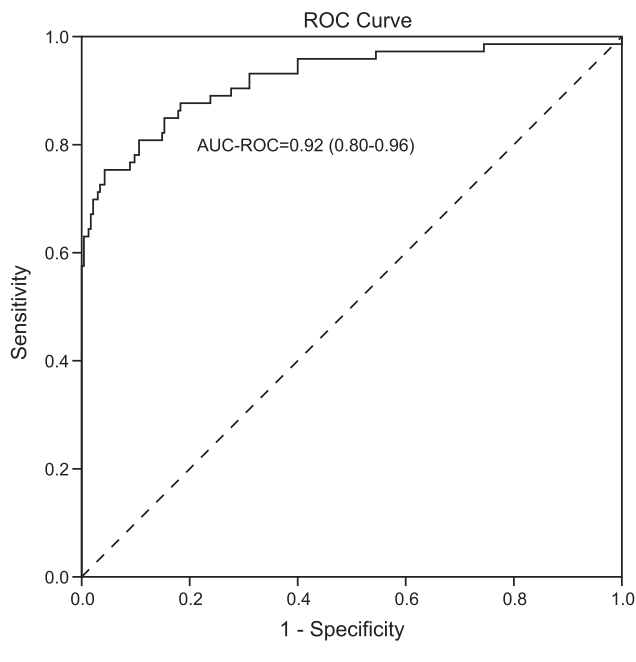
several cytokines, suggesting that the heart is affected by the systemic immune activation and cytokine storm. After the respiratory tract, immune organs are the second most affected system in COVID-19. Research has revealed that, in severe cases with multiorgan involvement (including myocardial injury), peripheral blood lymphopenia is related to a significant reduction in the number of spleen and lymph node lymphocytes.[3,27] Additionally, in our study, the neutrophil count was positively associated with cTNI levels and occurrence of myocardial injury. Considering that neutrophil counts may increase in secondary infections, the neutrophil/lymphocyte ratio may not only be indicative of the degree of immune damage in COVID-19 but may as well point to sepsis, which exerts its own inflammatory and immune negative effects.[28] Development of the uncontrolled overactivation of the immune system may partly account for the severe cardiovascular injury. Autopsy analysis of hearts from COVID-19 patients also demonstrated the potential involvement of systematic inflammation in heart injury.[25]

Second, increased creatinine levels predicted the occurrence of myocardial injury. Recent studies have observed a high prevalence of renal dysfunction in hospitalized patients with COVID-19, and the presence of kidney disease was associated with a higher mortality and poorer outcome.[4,29] Renal injury may be indicative of overall disease severity: patients with higher creatinine level are likely to present multiple organ impairment, including cardiovascular damage. However, renal dysfunction is an independent risk factor for myocardial injury; it has been reported that a loss of glomerular filtration rate, either in acute or chronic kidney disease, independently accelerates the progression of cardiovascular disease. In patients with COVID-19 and kidney injury, the accumulation of toxic metabolites, activation of inflammatory response, metabolic and nutritional changes, and altered haemodynamic, acid–base, or fluid status may altogether take a toll on the heart, leading to the occurrence and/or aggravation of myocardial injury.[30]

Third, our study found that increased LDH levels were an important independent predictor of myocardial injury. To date, many studies have revealed that almost all hospitalized COVID-19 patients show increased serum levels of LDH, a feature significantly associated with disease severity.[3,26] This may be due to the severity of systemic inflammation and tissue necrosis, thus leading to multiorgan dysfunction including the heart.[31] Moreover, LDH level was associated with hypoxia, which may be one of the causes of cardiac damage. We also found that minimum SpO_2 was a risk factor for elevated cTNI and myocardial injury after adjusting for age, sex, and co-morbidities. Both acute respiratory compromise and increased cardiometabolic oxygen demand may impair myocardial oxygen supply, leading to injury.

Fourth, in our study, elevated D-dimer levels were positively correlated to cTNI. As a feature of disseminated intravascular coagulation, elevated D-dimer levels are highly prevalent in COVID-19, especially in severe/critical patients.[32] This is in accordance with the finding that coagulation abnormalities cause organ injury and are associated with a poor prognosis.[19]

Fifth, although previous studies with unadjusted analyses suggested that hypertension was associated with severe forms of the disease, analyses adjusting for other risk factors revealed that hypertensive patients have no increased susceptibility to complications of COVID-19.[26,33] In accordance with the latter statement, our study found that hypertension was not an independent risk factor of myocardial injury.

Finally, because COVID-19 is a major global health and economic burden, strategies are urgently required to minimize unwarranted downstream diagnostic/therapeutic procedures and alleviate the strain on the healthcare system. Our present study found that the neutrophil/lymphocyte ratio and blood levels of creatinine and LDH could significantly predict the occurrence of myocardial injury, with good specificity and sensitivity. Because these are widely available tests, our model could serve as a quick risk stratification tool that helps reserve specific assays (such as cardiac biomarkers) for circumstances in which they would meaningfully contribute to management. Additionally, this model may help identify patients with high risk of myocardial injury who require early interventional therapies to prevent deterioration.

The present study has several limitations. Some patients were transferred to our hospital late in the course of their illness; in these cases, inadequate standard supportive therapy and late antiviral therapy might have contributed to myocardial injury and poor outcomes. Furthermore, although multivariate analysis was adjusted for many confounders, unknown or unmeasured variables might have contributed to myocardial injury. Further studies should be conducted to confirm these results and validate the prognostic utility of our model. Follow-up data after hospital discharge were not available for analysis; therefore, the long-term outcome of patients with myocardial injury was unknown. In addition, the precise impact of COVID-19 on cardiac structure and function was not assessed in this study.

In conclusion, the prevalence of myocardial injury in hospitalized patients with COVID-19 in Wuhan, China, was high. Blood cTNI levels were significantly associated with immune response, multiple organ dysfunction, and poor outcomes. After adjustment for confounders, the neutrophil/lymphocyte ratio, creatinine, and LDH emerged as independent predictors of myocardial injury. We consider that these variables may be useful for early detection and risk stratification of myocardial injury in hospitalized patients with COVID-19.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. The specific kits and reference intervals of clinical measurements.
Table S2. The correlation between high-sensitivity cardiac troponin I and clinical characteristics as well as laboratory findings.
Table S3. The area under the receiver operating characteristic (AUC-ROC) derived from multivariate analysis in table 4 in subgroup patients.

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