Original Article

Cardiology Discovery

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Non-Ischemic, Non-Hypoxic Myocardial Injury, and Long-Term Mortality in Patients with Coronavirus Disease 2019: A Retrospective Cohort Study

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Abstract

Objective: Cardiac damage is commonly reported in patients with coronavirus disease 2019 (COVID-19) but its prevalence and impact on the long-term survival of patients remain uncertain. This study aimed to explore the prevalence of myocardial injury and assess its prognostic value in patients with COVID-19.

Methods: A single-center, retrospective cohort study was performed at the Affiliated Hospital of Jianghan University. Data from 766 patients with confirmed COVID-19 who were hospitalized from December 27, 2019 to April 25, 2020 were collected. Demographic, clinical, laboratory, electrocardiogram, treatment data and all-cause mortality during follow-up were collected and analyzed.

Results: Of the 766 patients with moderate to critically ill COVID-19, 86 (11.2%) died after a mean follow-up of 72.8 days. Myocardial injury occurred in 94 (12.3%) patients. The mortality rate was 64.9% (61/94) and 3.7% (25/672) in patients with and without myocardial injury, respectively. Cox regression showed that myocardial injury was an independent risk factor for mortality (hazard ratio: 8.76, 95% confidence interval: 4.76–16.11, $P < 0.001$). Of the 90 patients with myocardial injury with electrocardiogram results, sinus tachycardia was present in 29, bundle branch block in 26, low voltage in 10, and abnormal T-wave in 53.

Conclusions: COVID-19 not only involves pneumonia but also cardiac damage. Myocardial injury is a common complication and an independent risk factor for mortality in COVID-19 patients.

Keywords: Coronavirus; COVID-19; Mortality; Myocardial injury

CLINICAL PERSPECTIVE

WHAT IS NEW?

- In this single-center, retrospective cohort study of 766 coronavirus disease 2019 (COVID-19) patients with a mean follow-up of 72.8 days, the myocardial injury occurred in 94 (12.3%) patients.
- Myocardial injury was a common complication and an independent risk factor for mortality in COVID-19 patients.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Considering the high risk of myocardial injury in COVID-19 patients, regular monitoring of myocardial injury in COVID-19 patients should be performed.
- Myocardial injury was associated with a higher risk of mortality among COVID-19 patients. Therefore, intensive care was recommended for COVID-19 patients with myocardial injury.

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Introduction

Coronavirus disease 2019 (COVID-19) is a public health emergency of international concern caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] According to the COVID-19 situation report released by the World Health Organization on August 3, 2020, COVID-19 had already affected 17,918,582 people from over 200 countries/territories/areas worldwide.[2] COVID-19 is a potentially fatal disease. Thousands of people died worldwide.[3–6] Although great efforts have been made globally, patients with severe illness may quickly progress to acute respiratory distress syndrome, end-organ failure, or even death. Studies have shown that age, sex, and comorbidities may be risk factors for a poor prognosis.[4,5] However, these studies were mainly focused on lung injury and had a short follow-up duration; the long-term impacts and causes of myocardial injury are unclear.

Cardiac troponin is a constituent of the myocardium and is specifically released during myocardial damage and is then detectable in the blood.[7] Non-ischemic myocardial injury may occur secondary to cardiac conditions such as myocarditis, with a dynamic rise and/or fall in cardiac troponin, or it may occur secondary to systemic conditions such as sepsis, renal failure, heart failure, and pulmonary embolism. Acute myocardial injury has been reported to occur in 7.2% to 23% of COVID-19 patients.[4,8–10] The variation may be the result of relatively small sample sizes or myocardial injury not rigorously assessed in some clinical settings. Additionally, it was unknown whether the myocardial injury can predict the mortality of patients with COVID-19, hampering accurate prognostic stratification globally. In this large and long-term study, we explored the prevalence of myocardial injury and its prognostic value in patients with COVID-19.

Methods

Study overview

This single-center, retrospective cohort study of hospitalized patients with confirmed COVID-19 was designed by researchers at the Affiliated Hospital of Jianghan University (Wuhan, China). Consecutive patients with COVID-19 who were admitted to the hospital between December 27, 2019 and April 25, 2020 were enrolled. COVID-19 was diagnosed according to the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (5th edition) published by the National Health Commission of the People's Republic of China.[11] A confirmed diagnosis of COVID-19 was based on clinical characteristics, chest imaging, a positive result on high-throughput sequencing or reverse transcription-polymerase chain reaction assay of nasal and pharyngeal swab specimens, and the ruling out of common bacterial and viral pathogens that cause pneumonia.[12] Only moderate, severe, and critically ill COVID-19 patients were admitted to the hospital and enrolled in this study.[11] The severity of COVID-19 (moderate, severe, or critically ill) was defined based on the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (5th edition).[11]Asymptomatic and mild cases were admitted to mobile cabin hospitals and were not included in the analysis.

This study was approved by the National Health Commission of China and the Ethics Commission of the Affiliated Hospital of Jianghan University (WHSHIRB-K-2020008). Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

Laboratory data

A venous blood sample was obtained within 1 day after hospital admission. The blood samples were centrifuged at 800 *g* for 5 minutes at 4°C and the serum was obtained. Blood biochemical examination including alanine aminotransferase (ALT), total bilirubin (TBIL), creatinine, creatine kinase (CK)-MB, D-dimer, and N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) were measured in the core laboratories of the hospital. Arterial blood gas analysis was performed within 1 day after admission. High-sensitivity cardiac troponin (hs-cTnI) concentration was assessed by ADVIA Centaur® TnI-Ultra® assay (Siemens Healthcare Diagnostics Inc., Malvern, Pennsylvania, USA) on an ADVIA Centaur XP Immunoassay System (Siemens Healthcare GmbH, Erlangen, Germany).

Myocardial injury assessment

Myocardial injury was defined as a hs-cTnI concentration above 0.1 ng/mL. Heart failure, myocarditis, cardiogenic shock, and pulmonary embolism were identified based on clinical manifestations, laboratory test results (including coagulation profile), clinical diagnosis, and clinical guidelines. All patients' data were independently analyzed by 2 groups of consultants, and the cause of myocardial injury was independently determined by each group. If the inferred cause of myocardial injury was not the same between the 2 groups, recommendations provided by 2 senior physicians, who specialized in cardiology, respiratory, or critical care medicine, were taken. Electrocardiograms (ECGs) of each patient were independently reviewed by 2 experienced cardiologists. ECGs were analyzed for rhythm, conduction pattern, and repolarization abnormalities in all myocardial injury patients.

Data sources

Medical records and compiled data were obtained from the Affiliated Hospital of Jianghan University. Demographics, medical history, clinical symptoms or signs, laboratory results, ECGs, and clinical outcomes were ascertained by carefully reviewing the medical records. Repeated hs-cTnI and ECG results were also collected for further analysis.

Treatment

COVID-19 patients were treated following the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (5th edition)[11]: (1) isolation on admission; (2) general treatment: close monitoring of vital signs, effective oxygen therapy (including nasal catheter, oxygen mask, high-flow nasal cannula oxygen therapy, or noninvasive ventilation, to maintain the peripheral oxygen saturation (SpO_2) at a normal or almost normal level), and tracheal intubation and invasive mechanical ventilation in a timely manner if the patient's condition was not rapidly improved or deteriorated; (3) anti-viral treatment; (4) antibiotics for the prevention and treatment of double infection, when necessary; (5) active treatment of underlying diseases and prevention of complications; and (6) drugs to improve myocardial energy metabolism (such as phosphocreatine and

coenzyme Q10) and cardiac function (trimetazidine) for patients with myocardial injury, with careful control of the volume and speed of infusion.

Follow-up

Based on follow-up data, survival time was calculated from the date of admission to the date of death or date of study termination (April 25, 2020), which formed the primary endpoint.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or median (Q1, Q3). Categorical data are expressed as frequency and percentage. Groups were compared using Student *t* test, the Mann-Whitney *U* test, or the χ^2 test, as necessary. Survival curves were plotted using the Kaplan-Meier method and compared between patients with or without myocardial injury using the logrank test. Cox proportional hazard models were used to identify the risk factors for mortality during hospitalization. All variables that were significantly related to mortality ($P < 0.05$) in the univariate Cox regression models were included in the multivariate Cox regression model. In the regression analyses, age was divided into tertiles: ≤55, 56–67, and ≥68 years. Missing data (3 cases for D-dimer and 22 for NT-proBNP) were replaced by the mean. In the Cox regression analyses, hazard ratios (HRs) for mortality along with 95% confidence intervals (CIs) were calculated. Data were analyzed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA). Two-tailed *P* value of less than 0.05 was considered significant.

Results

Patient characteristics

Of the 2417 suspected COVID-19 patients examined, 1651 were excluded because the diagnosis of COVID-19 was not confirmed, the COVID-19 was asymptomatic or mild, severe renal failure necessitated dialysis, hs-cTnI test results were missing, or the patient was lost to follow-up. This study therefore included 766 patients hospitalized with confirmed COVID-19 [Figure 1]; 86 patients (11.2%) died and 680 (88.8%) were discharged or still alive in hospital at the end of the study [Table 1].

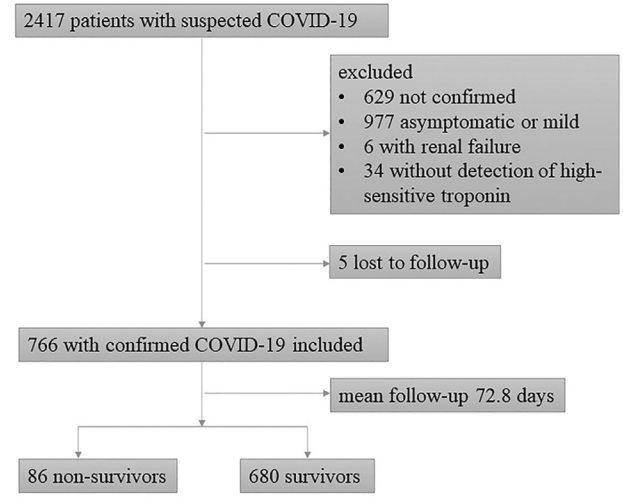

Figure 1: Flowchart of COVID-19 patient enrollment. COVID-19: Coronavirus disease 2019.

Comparison of baseline characteristics between survivors and non-survivors

After a mean follow-up of 72.8 days (from 1 to 120 days), 86 (11.2%) COVID-19 patients died. The myocardial injury occurred in 94 (12.3%) patients, and a higher prevalence was observed in non-survivors compared to survivors (70.9% *vs.*

Table 1

Demographics, clinical characteristics, and laboratory findings of COVID-19 patients.

Characteristic/laboratory finding	All (*n* = 766)	Survivors (*n* = 680)	Non-survivors (*n* = 86)	*P*
Male, *n* (%)	364 (47.5)	299 (44.0)	65 (75.6)	<0.001
Age (years), *n* (%)				<0.001
≤55	257 (33.6)	255 (37.5)	2 (2.3)	
56–67	267 (34.9)	239 (35.1)	28 (32.6)	
≥68	242 (31.6)	186 (27.4)	56 (65.1)	
Myocardial injury, *n* (%)	94 (12.3)	33 (4.9)	61 (70.9)	<0.001
Severity, *n* (%)				<0.001
Moderate/severe	625 (81.6)	592 (87.1)	33 (38.4)	
Critically ill	141 (18.4)	88 (12.9)	53 (61.6)	
Hypertension, *n* (%)	253 (33.0)	213 (31.3)	40 (46.5)	0.005
Cardiovascular disease, *n* (%)	49 (6.4)	39 (5.7)	10 (11.6)	0.035
Diabetes mellitus, *n* (%)	93 (12.1)	78 (11.5)	15 (17.4)	0.110
Creatinine (μmol/L), median (Q1, Q3)	68.7 (56.3, 85.6)	67.3 (54.8, 82.1)	89.0 (71.2, 119.1)	<0.001
ALT (U/L), median (Q1, Q3)	25.6 (17.4, 40.0)	25.0 (17.3, 39.6)	28.7 (19.5, 44.0)	0.091
TBIL (μmol/L), median (Q1, Q3)	9.9 (7.5, 13.0)	9.6 (7.4, 12.7)	12.1 (8.8, 15.7)	<0.001
D-dimer (mg/L), median (Q1, Q3)	0.4 (0.3, 0.7)	0.4 (0.3, 0.6)	0.8 (0.5, 2.7)	<0.001
CK-MB (U/L), median (Q1, Q3)	11.0 (7.8, 14.8)	10.6 (7.8, 13.9)	15.1 (11.1, 26.2)	<0.001
NT-proBNP (pg/mL), median (Q1, Q3)	341.9 (109.0, 693.7)	276.4 (95.9, 600.9)	1264.3 (631.5, 4034.2)	<0.001

ALT: Alanine aminotransferase; CK-MB: Creatine kinase MB; COVID-19: Coronavirus disease 2019; NT-proBNP: N-terminal fragment of pro-brain natriuretic peptide; TBIL: Total bilirubin.

4.9%, $P < 0.001$). Compared to survivors, patients who died were older, were more likely to be male, were more likely to have hypertension, and had higher laboratory test results (including creatine, TBIL, D-dimer, CK-MB, and NT-proBNP) (all $P < 0.001$) [Table 1].

Survival of COVID-19 patients with myocardial injury

All-cause mortality was 64.9% (61/94) and 3.7% (25/672) in patients with and without myocardial injury, respectively. Kaplan-Meier curves for patients with and without myocardial injury are shown in Figure 2. Patients with myocardial injury had a significantly lower survival probability than those without myocardial injury (log-rank test $P < 0.0001$). HRs for mortality were calculated by Cox regression. After adjustment for demographic and clinical characteristics, patients with myocardial injury had an approximately 8 times greater hazard of mortality than those without myocardial injury (HR: 8.76, 95% CI: 4.76–16.11, $P < 0.0001$). In addition, multivariate Cox regression showed that male (HR = 2.69, 95% CI: 1.57–4.63, $P < 0.001$), older age (HR = 8.67, 95% CI: 2.03–37.14, $P = 0.004$ for 56–67 *vs.* ≤ 55 years; HR = 7.23, 95% CI: 1.66–31.42, $P = 0.008$ for ≥68 *vs.* ≤55 years), critically ill (HR = 3.21, 95% CI: 1.20–8.55, $P = 0.020$ for critically ill *vs.* moderate), and log (NT-proBNP) (HR = 1.28, 95% CI: 1.07–1.53, $P = 0.008$) were all independently associated with mortality [Table 2].

ECG characteristics of COVID-19 patients with myocardial injury

In the 94 COVID-19 patients with myocardial injury, the ECG quality for 4 patients was too poor to be analyzed. Of the remaining 90 patients [Table 3], 29 had sinus tachycardia, 7 had atrial fibrillation, 26 had right bundle branch block (RBBB) or indeterminate BBB, 10 had low voltage, and 53 had abnormal T-wave. Summarizing the opinion provided by 2 independent groups of consultants, 3 patients were diagnosed with ST-segment elevation myocardial infarction. Typical ECG changes are shown in Supplementary Figure 1 (http://links.lww.com/CD9/A17).

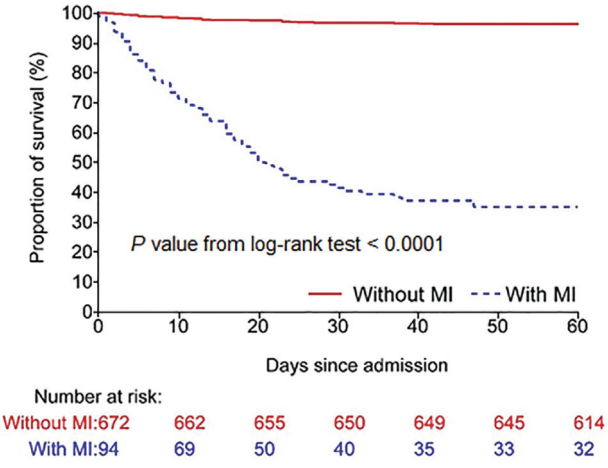

Figure 2: Kaplan-Meier curves of COVID-19 patients with and without myocardial injury. After a mean follow-up of 72.8 days, Kaplan-Meier curves showed that the survival in patients with myocardial injury was significantly lower than those without myocardial injury (hazard ratio: 8.76; 95% confidence interval: 4.76–16.11). COVID-19: Coronavirus disease 2019; MI: Myocardial injury.

Discussion

The purpose of this study was to determine the prevalence of myocardial injury in patients with COVID-19, and to assess the impact of the myocardial injury on all-cause mortality in a retrospective cohort study. An important discovery in this study is that COVID-19 not only involves pneumonia but can also damage the heart. Our results also demonstrate that (1) myocardial injury was a common complication (12.3%) in moderate to critically ill COVID-19 patients; (2) all-cause mortality was significantly higher for patients with myocardial injury compared to those without myocardial injury; and (3) sinus tachycardia, RBBB, indeterminate BBB, and low voltage were the most common abnormal ECG results.

Table 2

Predictors of in-hospital mortality in patients with COVID-19: Cox regression analyses.

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Male	3.68 (2.25–6.01)	<0.001	2.69 (1.57–4.63)	<0.001
Age (years)				
56–67 (*vs.* ≤55)	0.90 (0.58–1.42)	0.657	8.67 (2.03–37.14)	0.004
≥68 (*vs.* ≤55)	4.43 (2.84–6.90)	<0.001	7.23 (1.66–31.42)	0.008
Myocardial injury	26.53 (16.59–42.44)	<0.001	8.76 (4.76–16.11)	<0.001
Severity				
Severe (*vs.* moderate)	0.38 (0.24–0.59)	<0.001	1.04 (0.38–2.83)	0.943
Critically ill (*vs.* moderate)	8.85 (5.73–13.68)	<0.001	3.21 (1.20–8.55)	0.020
Hypertension	1.84 (1.21–2.81)	0.005	0.78 (0.49–1.23)	0.281
Creatinine	1.01 (1.01–1.01)	<0.001	1.00 (1.00–1.01)	0.261
ALT	1.01 (1.00–1.01)	0.010	1.00 (1.00–1.01)	0.299
TBIL	1.03 (1.02–1.04)	<0.001	1.00 (0.98–1.02)	0.896
D-dimer	1.08 (1.06–1.11)	<0.001	0.99 (0.95–1.02)	0.394
CK-MB	1.01 (1.00–1.01)	<0.001	1.00 (1.00–1.00)	0.446
Log (NT-proBNP)	2.13 (1.87–2.43)	<0.001	1.28 (1.07–1.53)	0.008

ALT: Alanine aminotransferase; CI: Confidence interval; CK-MB: Creatine kinase MB; COVID-19: Coronavirus disease 2019; HR: Hazard ratio; NT-proBNP: N-terminal fragment of pro-brain natriuretic peptide; TBIL: Total bilirubin.

Table 3

Electrocardiographic characteristics of COVID-19 patients with myocardial injury ($n = 90$).

Characteristic	Number of patients, *n* (%)
Arrhythmia	
Sinus tachycardia	29 (32.2)
Atrial fibrillation	7 (8.5)
Supraventricular premature beats	8 (8.9)
Ventricular premature beats	6 (6.7)
Conduction pattern	
RBBB	9 (10.0)
Indeterminate BBB	17 (18.9)
Low voltage	10 (11.1)
Repolarization abnormalities	
ST-segment elevation	3 (3.3)
ST-segment depression	7 (7.8)
T-wave abnormal	53 (58.9)

BBB: Bundle branch block; COVID-19: Coronavirus disease 2019; RBBB: Right bundle branch block.

COVID-19 is a contagious disease involving multiple systems, especially the respiratory system. A novel β coronavirus has been confirmed to be the pathogen underlying COVID-19.[13] Although severe respiratory distress syndrome was considered the most common cause of COVID-19 deaths, more and more studies have shown the importance of myocardial injury in patients' risk of mortality.[3,9,14] Zhou et al[15] reported that cardiac complications were common in COVID-19, especially in patients who died.

A meta-analysis also demonstrated that cTnI values were increased to a greater extent in COVID-19 patients with severe disease than those without.[3] Recently, Shi et al[16] reported that 82 (19.7%) out of 416 COVID-19 patients had a cardiac injury, reflecting that cardiac injury is common among hospitalized patients with COVID-19. Our study shows that 12.3% of hospitalized patients with moderate to critically ill COVID-19 had a myocardial injury, which is consistent with previous research.

Myocardial injury has been observed after the development of a variety of cardiovascular diseases, such as myocarditis, coronary artery disease, and congestive heart failure.[7,17] We found that myocardial injury was a common complication and an independent risk factor for mortality in COVID-19 patients. Usually, lung infections impair blood oxygenation. The systolic pressure and cardiac output are increased with right-side heart overload, simultaneously increasing the oxygen demand. Small coronary arteries dilate during initial hypoxemia but rapidly become exhausted and blood flow is then limited. Systematic impaired oxygen balance combined with local coronary artery diseases leads to myocardial ischemia and causes myocardial injury. However, of the 94 patients in our study with myocardial injury, only 3 had ST-elevated myocardial infarction (ischemic myocardial injury), and the remaining 87 patients had a nonischemic myocardial injury on ECG.

All the patients were given standardized treatment including effective oxygen therapy immediately after hospital admission to improve oxygen saturation and reduce the risk of myocardial injury induced by hypoxemia. The arterial blood gas analysis showed that there was no significant difference in pH or SpO_2 between survivors and non-survivors with myocardial injury, which suggests that the most likely cause of non-ischemic myocardial injury may be acute myocarditis.[18] When myocardial injury, ischemic or non-ischemic, is detected in COVID-19 patients, comprehensive intensive treatment should be emphasized in clinical practice.

Acute myocarditis is a potentially lethal disease, and the etiological agents include enteroviruses (such as coxsackieviruses), adenoviruses, parvoviruses, hepatitis C virus, human immunodeficiency virus, and influenza virus. [19] Ukimura et al[18] reported that the influenza A virus may cause acute viral myocarditis, myocyte degeneration with lymphocyte infiltration (based on endomyocardial biopsy), and interstitial edema. Recently, through autopsy, Xu et al[20] found interstitial mononuclear inflammatory cell infiltrates in the cardiac tissue of COVID-19 patients, which indicates viral myocarditis. More pathological studies are needed to confirm viral myocarditis. Furthermore, the outcome is worse for patients with myocardial injury. This suggests that myocardial injury could be caused by compromised pulmonary alveoli epithelium function and subsequent hypoxemia, as well as inflammatory and tissue damage and the following cytokine storm, chemotaxis, and proinflammatory immune cell infiltration.[15,16,21] In addition, severe COVID-19 patients with dehydration and immobilization may develop intracoronary microvascular thrombosis. The above causes of myocardial injury in COVID-19 patients might be some of the underlying reasons for the more severe clinical characteristics in these COVID-19 patients. However, the exact mechanisms of myocardial injury in COVID-19 still need to be determined.

The ECG analysis also showed multiple abnormalities including arrhythmia, conduction pattern, low voltage, and repolarization abnormalities. Sinus tachycardia, conduction delay, ST-T changes, and low voltage on ECG may be the typical alterations of myocarditis. Although sinus tachycardia, RBBB, indeterminate BBB, and low voltage were the most common abnormalities in the COVID-19 patients with myocardial injury, the overall ECG changes were still non-specific and diverse, similar to the report by Ukena et al.[21] In clinical practice, medical staff should be alert for diverse ECG changes in patients with COVID-19 and ensure relevant timely monitoring of such patients.

Studies have shown that increased concentration of cardiac troponin was a strong predictor of long-term mortality in patients with myocardial infarction, unstable angina pectoris, pulmonary embolism, and end-stage renal disease.[22,23] Recently, Shi et al[16] reported that the mortality rate reached 51.2% in COVID-19 patients with cardiac injury, much higher than those without myocardial injury, but this study had a follow-up time of just 2 weeks. In contrast, our study had a mean follow-up time of 72.8 days, making it possible to assess the long-term effect of myocardial injury on all-cause mortality. The results indicate that when treating patients with COVID-19, great attention should be paid to patients with myocardial injury. Effective oxygen therapy should be started as early as possible to avoid hypoxemia induced myocardial injury. Drugs that improve myocardial energy metabolism could be considered. Glucocorticoids and immunoglobulins might be considered to suppress the excessive immune responses. When necessary, blood oxygen saturation, D-dimer assessment, ultrasound for thrombosis in lower limb deep veins, and even computed tomography pulmonary angiography could be used to exclude acute pulmonary embolism. The use of extracorporeal membrane oxygenation should be considered as early as possible for critically ill patients with myocardial injury.

Limitations

This study has several limitations. Firstly, the results might be limited by the retrospective nature of the data. Not all laboratory

tests were conducted for all patients and some missing data were unavoidable. Secondly, only moderate to critically ill patients were included, and the association between myocardial injury and survival in asymptomatic or mild COVID-19 patients still needs to be explored. Thirdly, as the duration between when COVID-19 manifested and the first hs-cTnI concentration assessment varied among patients, it was not possible to establish the interval between COVID-19 manifestation and myocardial injury, which could be related to mortality.

Conclusions

In summary, this study indicates that myocardial injury was a common complication in patients with COVID-19, and the mechanism may be related to myocarditis rather than hypoxia.

COVID-19 patients with myocardial injury had a significantly higher mortality rate than those without. During hospitalization, the co-existence of COVID-19 and myocarditis needs urgent attention from clinicians. Monitoring of myocardial injury markers should be strengthened, and comprehensive intensive treatment of COVID-19 patients with myocardial injury should be emphasized.

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Author Contributions

Xiqi Xu, Chenghong Li, and Shuyang Zhang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Shuyang Zhang, Chenghong Li, Min Liu.

Acquisition, analysis, or interpretation of data: Fajiu Li, Xiqi Xu, Duolao Wang, Ziyang Zhu, Shi Chen, Xiaoyan Gao, Yalin Xu, Bo Zhang, Wei Yu.

Drafting of the manuscript: Xiqi Xu, Fajiu Li, Xijie Zhu.

Critical revision of the manuscript for important intellectual content: Xiqi Xu, Zhuang Tian, Duolao Wang, Yinjian Yang, Shuyang Zhang.

Statistical analysis: Duolao Wang, Xiqi Xu.

Administrative, technical, or material support: Fajiu Li, Xiqi Xu, Shi Chen, Xiaoyan Gao, Yalin Xu, Bo Zhang, Wei Yu.

Supervision: Xiqi Xu, Chenghong Li, Shuyang Zhang.

Conflicts of interest

None.

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