Cardiac Biomarker Abnormalities Are Closely Related to Prognosis in Patients with COVID-19

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Summary
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is erupting and spreading globally. Cardiovascular complications secondary to the infection have caught notice. This study aims to delineate the relationship of cardiac biomarkers and outcomes in severe cases of coronavirus disease 2019 (COVID-19). One hundred forty-eight critically ill adult patients with COVID-19 were enrolled. From these patients, the demographic data, symptoms, cardiac biomarkers, treatments, and clinical outcomes were collected. Data were compared between survivors and non-survivors. Four patients in the non-survivor group were selected, and their cardiac biomarkers were collected and analyzed. Among the 148 patients, the incidence of cardiovascular complications was 19 (12.8%). Five of them were survivors (5.2%), and 14 of them were non-survivors (26.9%). Compared with the survivors, the non-survivors had higher levels of high-sensitivity cardiac troponin I, creatine kinase isoenzyme-MB, myoglobin, and N-terminal pro-brain natriuretic peptide (P < 0.05). The occurrence of cardiovascular events began at 11-15 days after the onset of the disease and reached a peak at 14-20 days. COVID-19 not only is a respiratory disease but also causes damage to the cardiovascular system. Cardiac biomarkers have the potential for early warning and prognostic evaluation in patients with COVID-19. It is recommended that cardiac biomarker monitoring in patients with COVID-19 should be initiated at least from the 11th day of the disease course.

Key words: SARS-CoV-2, Hs-cTnI, Nt-proBNP, Cardiovascular complication

Since mid-December 2019, corona virus disease 2019 (COVID-19) has broken out in Wuhan, and it has spread rapidly throughout the country and many other countries around the world. As the number of cases increase, the number of critically ill patients and deaths continue to rise, and the mortality rate remains high. As of 08:00 on February 26, 2020, China reported 8,752 critical cases of SARS-CoV-2 infection and registered 2,718 deaths. In the published literature, SARS-CoV-2 reported mortality rates of 4.3%, 11.0%, and 14.6%, respectively, with a higher proportion in Wuhan. Scholars have suggested that the occurrence of cardiovascular complication is related to the high mortality of patients with SARS-CoV-2; however, complete data on cardiovascular events in patients with SARS-CoV-2 have not been published. High-sensitivity cardiac troponin I (hs-cTnI), creatine kinase isoenzyme-MB (CK-MB), myoglobin (MB), and N-terminal pro-brain natriuretic peptide (Nt-proBNP) are markers for the diagnosis of acute cardiovascular complications and have predictive value for patients’ long-term prognosis and the occurrence of death events. Remin Hospital of Wuhan University, the first hospital battlefield for treating SARS-CoV-2 critically ill patients, analyzed cardiac biomarkers of patients with SARS-CoV-2 with known prognosis (discharge or death) in the hospital, to better understand the differences between the survivors and the non-survivors and then provide a reference for future diagnosis and treatment.

Methods
Patients with severe and critical SARS-CoV-2 who were admitted to Remin Hospital of Wuhan University (Wuhan, China) from February 1, 2020, to February 26, 2020, with a clear prognosis outcome (discharge or death) were selected as the research subjects. The cases without cardiac biomarkers were excluded. The monitoring of clinical results ended at 18:00 on February 26, 2020. Patient’s informed consent was waived because of the rapid emergence of this infectious disease. CT scan, 2019nCoV...
nucleocapsid protein gene, 2019nCoV open reading coding frame 1ab, Nt-proBNP, hs-cTnI, CK-MB, MB, electrocardiogram, cardiac ultrasound, blood pressure, arterial oxygen pressure, treatment, and prognosis were collected from the electronic medical record system. Statistical tables were formulated from this information. This study was approved by the Ethics Committee of Renmin Hospital of Wuhan University (WDRY2020-K096).

**Evaluation and judgment standard:** The diagnostic and classification criteria are based on a new diagnosis and treatment plan for guidelines for the diagnosis and treatment of novel coronavirus (2019-ncov) infection by Chinese national health commission (trial version 5).19

**Diagnosis:** Confirmed cases need to satisfy one of the following two conditions: (1) Detection of SARS-CoV-2 nucleic acid positive by real-time fluorescence or (2) viral gene sequencing highly homologous with known SARS-CoV-2. There are four classifications of the diagnosis. 1) Mild type is characterized by slight clinical symptoms and no pneumonia on imaging. 2) Ordinary type is manifested by fever, respiratory tract symptoms, and pneumonia on imaging. 3) Severe type meets any of the following: 1. shortness of breath with RR ≥ 30 cycles per minute; 2. oxygen saturation of < 93% in resting state; 3. arterial blood oxygen partial pressure (PaO2)/oxygen concentration (FiO2) < 300 mmHg (mmHg = 0.133 kPa), and at high altitudes (above 1000 m), PaO2/FiO2 should be corrected according to the following formula: PaO2/FiO2 × [atmospheric pressure (mmHg)/760]; 4. pulmonary imaging showed significant progression of lesions within 24-48 hours. 4) Critical meets one of the following conditions: (1) Respiratory failure occurs and requires mechanical ventilation; (2) shock occurs; and (3) ICU monitoring and treatment are required for combined organ failure. This study examined whether SARS-CoV-2 would result in cardiovascular complications, which included tachycardia, bradycardia, hypotension, cardiac arrhythmias, cardiomegaly, and decreased urine output. Cardiovascular complications was defined as levels of cardiac biomarker abnormalities (hs-cTnI or Nt-proBNP) above the 99th-percentile upper reference limit, regardless of new abnormalities in electrocardiography and echocardiography. The normal reference values of myocardial enzymes in the central laboratory of Renmin Hospital of Wuhan University are Nt-proBNP, 0-450 pg/mL; hs-cTnI, 0-0.04 ng/mL; CK-MB, 0-5 ng/mL; and MB, 0-110 μg/L. Hs-cTnI > 0.04 ng/mL indicates myocardial injury, and dynamic observation is recommended; > 0.78 ng/mL indicates a higher possibility of myocardial infarction or myocarditis.

**Statistical analysis:** Continuous data were expressed as mean (SD) or median (interquartile range [IQR]) values. The Shapiro-Wilk test was performed to determine if the continuous variables were normally distributed. Normally distributed continuous variables were compared using t-tests. Otherwise, continuous variables were compared using a Mann-Whitney U-test. Enumeration data were presented as frequency and ratios n (%). A chi-square test was used to analyze differences between the two groups. The data were analyzed by using the Statistical Package for the Social Sciences version 17.0 (SPSS, Inc., Chicago, USA). The P-value < 0.05 was considered statistically significant.

**Results**

By 18:00 on February 26, 1,253 patients with severe SARS-CoV-2 were admitted to our hospital. Nine hundred fifty patients were being treated in hospitals, of which 303 patients had known short-term prognoses. One hundred sixteen patients died, with a mortality rate of 9.26%; 187 patients (15.0%) were cured and discharged from hospital. One hundred fifty patients with missing core results of laboratory examination (hs-cTnI, CK-MB, MB, and Nt-proBNP) were excluded. A total of 148 patients with SARS-CoV-2, who had a known short-term prognosis and had complete clinical and laboratory data required for this study, were included in this study. There were 81 women (54.7%) and 67 men (45.3%). The male-to-female ratio was 1:1.2. There were 96 cases (64.9%) of survivors and 52 cases (35.1%) of non-survivors. The average age was 57.2 ± 17.7 years. The average age of survivors was 51.4 ± 16.1 years. The average age of non-survivors was 68.6 ± 14.8 years. Comparing the two groups, they were statistically significant (P < 0.001). Among them, 99 (66.9%) patients had chronic diseases such as hypertension, diabetes, anemia, hepatic and renal insufficiency, chronic lung conditions, cardio-cerebrovascular disease, cancer, and recent surgery. Among the 148 patients, incidence of cardiovascular complications was 19 (12.8%); the survivors were 5 (5.2%), and the non-survivors were 14 (26.9%), which is shown in Table I.

Dynamic cardiac biomarkers were detected in all enrolled patients. The peak data available during hospitalization were selected. The Nt-proBNP, hs-cTnI, MB, and CK-MB levels in survivors were (median [IQR], 81.15 [50.62-309.40] pg/mL), (median [IQR], 0.000 [0.000-0.019] pg/mL), (median [IQR], 0.67 [0.48-1.27] pg/mL), and (median [IQR], 26.86 [24.97-32.47] μg/L). The Nt-proBNP, hs-cTnI, MB, and CK-MB levels in non-survivors were (median [IQR], 1035.46 [578.37-1653.50] pg/mL), (median [IQR], 0.116 [0.029-0.409] pg/mL), and (median [IQR], 2.62 [1.43-4.47] μg/L), and (median [IQR], 101.83 [26.86-370.65] μg/L), as shown in Table II.

Among the non-survivors, four critically ill patients had serious cardiovascular complications during hospitalization. According to the Chinese Society of Cardiology expert consensus statement on the diagnosis and treatment of adult fulminant myocarditis, the diagnosis of fulminant myocarditis was made.6 The Figure shows the dynamic changes in cardiac biomarkers of four patients during treatment. The ordinate is CK-MB (ng/mL), Hs-cTnI (ng/mL), MB (μg/L), and Nt-proBNP (pg/mL); the abscissa is the time from onset to the blood test. Case 1 was hospitalized for 13 days with a survival time of 18 days. On the third day after admission, the patient felt chest tightness and shortness of breath and became hypothermic at rest. Dopamine was given to maintain normal blood pressure. On the 17th day, the patient lost consciousness and had decreased urine output. Electrocardiogram showed 3rd degree heart block. The level of cardiac biomarkers was measured on the first, third, and fifth days after admission. CK-MB (ng/mL) was 4.0, 13.3, and 15.7; Hs-cTnI
and 3340. Case 4 was hospitalized for 13 days and sur-
727.7; and Nt-proBNP (pg/mL) was 31, 504, 894, 3478,
0.25; MB (μg/L) was 69.0, 203.7, 894.3, 390.0, and
ured on the first, fourth, fifth, sixth, and seventh days af-
achycardia. The level of cardiac biomarkers was meas-
cardiographic monitoring showed paroxysmal ventricular
output occurred on the sixth day after admission. Electro-
hospital 8 days after onset, and the survival time was 16
was 2415, 1967, and 4645. Case 3 was admitted to the
L) was 14.0, 191.2, and 101.8; and Nt-proBNP (pg/mL)
3.5; Hs-cTnI (ng/mL) was 0.70, 0.25, and 1.04; MB (μg/
was 2.4, 2.0, and 3.4; Hs-cTnI (ng/mL) was 0.05, 0.19,
and 0.0.25; MB (μg/L) was 117.2, 95.8, and 135.2; and
Nt-proBNP (pg/mL) was 31, 504, 894, 3478, and 3340. Case 4 was hospitalized for 13 days and sur-
ricular disease 23 (15.2) 8 (8.1) * 15 (28.8) 0.001
Cancer 4 (2.6) 1 (1.0) 3 (5.8) 0.118
Recent surgery 12 (7.9) 7 (7.1) 5 (9.6) 0.583
Symptoms, n (%) Fever 107 (75.9) 66 (69.5) 41 (89.1) 0.011
Cough 92 (65.7) 58 (59.8) 34 (79.1) 0.027
Wheezeing 60 (42.3) 34 (35.1) 26 (57.8) 0.111
Chest tightness 56 (41.2) 34 (35.1) 22 (56.4) 0.022
Weakness 74 (54.0) 48 (49.5) 26 (56.0) 0.098
Nausea 10 (6.7) 5 (5.2) 5 (9.6) 0.300
Vomiting 5 (3.4) 2 (2.1) 3 (5.8) 0.343
Diarrhea 11 (7.4) 6 (6.2) 5 (9.6) 0.445
Cardiovascular complication 19 (12.8) 5 (5.2) 14 (26.9) 0.182
Cardiac arrhythmias 17 (11.5) 3 (2.7) * 14 (26.9) < 0.001
Hypotension 16 (10.8) 2 (2.1) * 14 (26.9) < 0.001
Oliguria 10 (6.7) 2 (2.1) * 8 (15.4) 0.004
Cardiomegaly 5 (2.4) 1 (1.0) 4 (7.7) 0.056

Compared with the survivors, the average age in non-survivors is older. *P < 0.001; the rates of underlying hypertension and cardio-cerebrovascular disease were higher.

Table II. The Highest Levels of Cardiac Biomarkers in the Two Groups during Hospitalization

| Variables     | Normal range | Survivors (n = 97) | Non-survivors (n = 49) | P values |
|---------------|--------------|--------------------|------------------------|----------|
| NT-proBNP (pg/mL) | < 450        | 81.15 (50.62–309.40) * | 1035.46 (578.37–1653.50) | < 0.001  |
| CTnI (ng/mL)   | < 0.04       | 0.000 (0.000–0.019) * | 0.131 (0.034–0.758)     | 0.035    |
| CK-MB (ng/mL)  | < 5          | 0.67 (0.48–1.27) *   | 2.62 (1.43–4.47)         | < 0.001  |
| Mb (μg/L)      | < 110        | 26.86 (24.97–32.47) * | 101.83 (26.86–370.65)    | < 0.001  |

Compared with the survivors, levels of the NT-proBNP, hs-cTnI, MB, and CK-Mb in non-survivors were higher. *P < 0.005

SARS-CoV-2 is a highly infectious viral outbreak in Wuhan, China. In the early days of the epidemic, people were unaware of the dangers of SARS-CoV-2, leading to a high proportion of critically ill patients. Medical personnel focus on monitoring patients’ respiratory status and oxygen saturation. They paid little attention to the occurrence of cardiovascular events. Because of the severe shortage of treatment resources, unfortunately, not every patient received a cardiac ultrasound examination or car-

Discussion

SARS-CoV-2 is a highly infectious viral outbreak in Wuhan, China. In the early days of the epidemic, people were unaware of the dangers of SARS-CoV-2, leading to a high proportion of critically ill patients. Medical personnel focus on monitoring patients’ respiratory status and oxygen saturation. They paid little attention to the occurrence of cardiovascular events. Because of the severe shortage of treatment resources, unfortunately, not every patient received a cardiac ultrasound examination or car-
Cardiac magnetic resonance imaging, so it is difficult to collect relevant data in this regard. Cardiac biomarkers, blood pressure, and the assessment of circulatory status are the primary indicators in detecting cardiovascular events. At present, in some articles, the author also mentioned the significance of measuring cardiac biomarkers in patients with COVID-19, but each article has a different focus. Among the 148 patients with SARS-CoV-2 included in our study, non-survivors showed higher levels of Nt-proBNP, hs-cTnI, CK-MB, and MB. This indicates that the level of cardiac biomarkers is correlated with the prognosis of patients with SARS-CoV-2. In this study, four cases of SARS-CoV-2 infections had severe cardiovascular complications, with death in 48 hours. This was manifested by hypotension, decreased urine output, subsequent disturbance of consciousness, and decreased heart rate. The biomarker levels also peaked during this period; therefore, it is speculated that SARS-CoV-2 not only is a simple respiratory disease but also involves damage to the cardiovascular system.

CK-MB in Case 1 was normal on the 13th day of the course of disease and began to rise on the 15th day, reaching its peak on the 17th day. The other three indicators (Nt-proBNP, hs-cTnI, MB) had changed from the starting point of monitoring on the 13th day, and then gradually increased, reaching the peak on the 17th day. CK-MB in Case 2 was normal during the whole monitoring process. MB changed on the 17th day and reached the peak on the 20th day. Nt-proBNP, hs-cTnI rose on the 14th day of monitoring and gradually increased, reaching the peak on the 20th day. CK-MB in Case 3 showed no significant change during the whole monitoring process. The other three indicators (Nt-proBNP, hs-cTnI, MB) changed on the 11th day, and reached the peak on the 14th day.

| Variables | Sex | Age (years) | Previous history | Time from onset to admission (days) | Survivors time (days) | Gag nucleocapsid gene of 2019nCoV | Open reading frames 1ab of 2019nCoV |
|-----------|-----|-------------|------------------|------------------------------------|----------------------|-----------------------------------|-----------------------------------|
| Case 1    | Female | 81 | Hypertension and diabetes | 13                          | 18                  | +++                              | +++                               |
| Case 2    | Male | 83 | Coronary heart disease     | 14                          | 21                  | +++                              | +++                               |
| Case 3    | Male | 56 | Hypertension               | 8                           | 16                  | +++                              | +++                               |
| Case 4    | Male | 47 | Healthy                    | 13                          | 19                  | +++                              | +++                               |

Figure. Dynamic profile of cardiac biomarker abnormalities that had severe cardiovascular complications.
There was no significant change in CK-MB in Case 4, while the other three indicators (Nt-proBNP, hs-cTnI, MB) changed on the 13th day and peaked on the 17th day. In the four cases, abnormal cardiac biomarkers occurred between 11 and 15 days after onset, with the peak occurring between 14 and 20 days. It is recommended that the monitoring of cardiac biomarkers for patients with SARS-CoV-2 should be initiated on day 11 of the course of the disease, with particular attention to changes in Nt-proBNP and hs-cTnI.

Faverio, et al. proposed that an acute pulmonary infection can affect the cardiovascular system through a variety of mechanisms, directly causing or aggravating cardiovascular complications, such as heart failure, acute coronary syndrome, arrhythmias, and stroke. Our study confirmed that SARS-CoV-2 can also cause cardiovascular events, though the mechanism remains unclear. In previous studies, the mechanism is mainly the direct damage of myocardium caused by viruses and the immune damage caused by inflammatory storm. Abnormal immune system activation, excessive polarization of macrophages, and indirect damage caused by aggregation in tissues and organs are important pathophysiological mechanisms leading to the rapid deterioration of patients’ conditions. Cameron, et al. proposed that 14% of pneumonia inpatients and 1.4% of pneumonia outpatients could develop heart failure, and patients with high-risk pneumonia (such as those admitted to the ICU) had a higher incidence of heart failure (24%). Once heart failure occurs, it can quickly cause hemodynamic compromise and lead to death, and its mechanism is related to the continuous inflammatory state. We speculate that SARS-CoV-2 infection may also cause myocardial immune impairment.

Conclusions

Although this is a single-center study and the sample size is small, the current study shows that cardiovascular events are more frequent in critically ill patients with SARS-CoV-2, and fulminant myocarditis is a common cause of death. Progressive elevation of cardiac biomarkers may have the potential for early warning and prognostic evaluation.

Acknowledgment

We would like to thank our researchers for their hard work and reviewers for their valuable advice.

Disclosure

Conflicts of interest: The authors have no conflicts of interest to declare.

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