Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019

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Aims
To investigate the characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019 (COVID-19).

Methods and results
We enrolled 671 eligible hospitalized patients with severe COVID-19 from 1 January to 23 February 2020, with a median age of 63 years. Clinical, laboratory, and treatment data were collected and compared between patients who died and survivors. Risk factors of death and myocardial injury were analysed using multivariable regression models. A total of 62 patients (9.2%) died, who more often had myocardial injury (75.8% vs. 9.7%; P < 0.001) than survivors. The area under the receiver operating characteristic curve of initial cardiac troponin I (cTnI) for predicting in-hospital mortality was 0.92 [95% confidence interval (CI), 0.87–0.96; sensitivity, 0.86; specificity, 0.86; P < 0.001]. The single cut-off point and high level of cTnI predicted risk of in-hospital death, hazard ratio (HR) was 4.56 (95% CI, 1.28–16.28; P = 0.019) and 1.25 (95% CI, 1.07–1.46; P = 0.004), respectively. In multivariable logistic regression, senior age, comorbidities (e.g. hypertension, coronary heart disease, chronic renal failure, and chronic obstructive pulmonary disease), and high level of C-reactive protein were predictors of myocardial injury.

Conclusion
The risk of in-hospital death among patients with severe COVID-19 can be predicted by markers of myocardial injury, and was significantly associated with senior age, inflammatory response, and cardiovascular comorbidities.

Keywords
Coronavirus disease 2019 • Mortality • Myocardial injury • Risk

Introduction
Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains pandemic with considerable morbidity and mortality. Similar to SARS in 2003, acute respiratory distress syndrome (ARDS) is usually considered to be an acute process confined to the lungs and results in a high mortality rate in COVID-19 patients. However, accumulating evidence points to myocardial injury as a COVID-19-related complication with an incidence ranging from 7.2% to 12%.1,2 Notably, an American College of Cardiology clinical bulletin has highlighted the cardiac implications of COVID-19. It suggests that patients with underlying cardiovascular disease face higher risks and recommends them to be triaged and treated with priority.3 However, according to

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limited information on cardiac complication of COVID-19, characteristics and clinical significance of myocardial injury for risk of death remain unclear. In this study, we determined the predictive value of myocardial indicators on in-hospital death, and investigated the features and potential causes of myocardial injury in cases of severe COVID-19.

Methods

Participants

All consecutive patients admitted to Renmin Hospital of Wuhan University with laboratory-confirmed COVID-19 were included in the present retrospective study. Renmin Hospital of Wuhan University, located in Wuhan, Hubei Province, was assigned responsibility for the treatment of patients with severe COVID-19 by the Wuhan government.

The patients with severe COVID-19 enrolled in this study were diagnosed according to the guidelines for diagnosis and treatment of COVID-19 (trial sixth edition) published by the Chinese National Health Commission on 18 February 2020. The cases in this study included severe and critically ill disease, which was defined by the presence of any of the following: respiratory rate >30/min; oxygen saturation <93%; PaO2/FiO2 ratio < 300 mmHg; respiratory failure requiring mechanical ventilation; shock; or respiratory failure combined with other organ failure requiring ICU treatment. The cases under 18 years of age and missing cardiac biomarkers, including levels of cardiac troponin I (cTnl), were excluded. The clinical outcomes (i.e. discharges, mortality, and length of stay) of all included patients were monitored up to 23 February 2020, the final date of follow-up.

This study was approved by the National Health Commission of China and the institutional review board at Renmin Hospital of Wuhan University (Wuhan, China). Written informed consent was waived by the Ethics Commission of the designated hospital for emerging infectious diseases.

Data collection

The demographic characteristics (age and gender), clinical data (comorbidities, laboratory findings, treatments, complications, and outcomes), laboratory findings and results of cardiac examinations (cardiac biomarkers) for patients during hospitalization were extracted from electronic medical records by two investigators. All the data were independently reviewed and entered into a computer database by a trained team of physicians. Patients were grouped according to whether they died (death group) or survived (survivors group). The study outcome was rate of in-hospital death, and clinical outcomes were determined based on the information of our hospital’s real-time medical records system.

Myocardial injury was defined as blood levels of cardiac biomarkers cTnl increased above the 99th percentile upper reference limit.4 ARDS was defined according to the Berlin Definition.5 The date of disease onset was defined as the day when the symptom was noticed.

The detection principle of creatinine kinase-myocardial band (CK-MB), myoglobin (MYO), and cTnl is the double-antibody sandwich method of chemiluminescence immunotechnology, the detection instrument is Siemens ADVIA Centaur XP Immunoassay System, and the reagent is an original matching kit from Siemens. The normal reference range of CK-MB is 0–5 ng/mL; the normal reference range of MYO is 0–110 ug/L; the normal reference range of cTnl is 0–0.04 ng/mL, and the minimum detectable concentration (analytical sensitivity) is 0.006 ng/mL.

in our hospital. The detection method of N-terminal pro-B-type natriuretic peptide (NT-proBNP) is based on a double-antibody clip one-step enzyme immunoassay based on the heart detection principle. The detection instrument is a Dimension EXL with LM automatic biochemical analysis system. The reagent is a Siemens Dimension EXL with LM kit. The normal reference range is 0–900 pg/mL.

To confirm COVID-19, the Viral Nucleic Acid Kit (Health, Ningbo, China) was used to extract nucleic acids from clinical samples according to manufacturer’s instructions. A 2019-nCoV detection kit (Bioperfectus, Taizhou, China) was used to detect the ORF1ab gene (nCovORF1ab) and the N gene (nCov-NP) according to the manufacturer’s instructions using real-time RT-PCR.6 An infection was considered as laboratory-confirmed if both the nCovORF1ab and nCov-NP showed positive results.

Statistical analysis

Descriptive statistics were obtained for all study variables. Continuous data are expressed as median (interquartile range, IQR). Categorical data are expressed as proportions. All categorical variables were compared for the study outcome by using the Fisher’s exact test or Chi-square test, and continuous variables were compared using the Student t-test or the Mann–Whitney U test, if appropriate. A receiver operating characteristic (ROC) curve analysis was performed to establish a single cut-off point. Multivariable Cox regression models using all covariates available were performed to determine the risk factors for in-hospital mortality, with a time from admission to the end of follow-up. Logistic regression analysis was performed to determine the predictors of myocardial injury. The cases missing biomarker data were excluded listwise with statistics software. Data were analysed using SPSS 25.0 (IBM, Chicago, IL). Statistical charts were generated using Prism 5 (GraphPad), Minitab (Version 18), and Python. For all statistical analyses, P < 0.05 was considered significant.

Results

Patient characteristics and treatment

A total of 2253 cases with confirmed COVID-19 were screened initially, from 1 January to 23 February 2020, in a tertiary teaching hospital with two integrated hospital districts and a cabin hospital. Figure 1 depicts the flowchart for participant selection. Briefly, after excluding cases with mild COVID-19 (1095), duplicated cases (156), and cases without available core medical information (331), 761 cases (death, 62; survivors, 699) with severe COVID-19 were enrolled in final analysis. In these patients, the median age was 63 years (IQR, 50–72 years), 48% of patients were male, and the median time from symptom and admission to end of follow-up was 23 days and 17 days, respectively. The most common main comorbidity was hypertension (29.7%), followed by diabetes (14.5%), coronary heart disease (8.9%), chronic renal disease (4.2%), chronic obstructive pulmonary disease (3.4%), cancer (3.4%), chronic heart failure (3.3%), cerebrovascular disease (3.3%), and atrial fibrillation (1.0%). During hospitalization, 95.5% of patients were given oxygen treatment; however, use of extracorporeal membrane oxygenation and continuous renal replacement therapy was rare. The proportion of antiviral treatment use was 96.4% in included patients, and 59.5%, 56.5%, and 54.2% of patients, respectively, were treated with intravenous immunoglobulin, glucocorticoids, and antibiotics, Table 1.
Comparison of clinical characteristics between death and survivors groups

The patients who died were older, more often male than the survivors (all \( P < 0.001 \), Table 1). Prevalence of hypertension, diabetes, coronary heart disease, chronic renal failure, chronic heart disease, and cerebrovascular disease was higher among the patients who died (all \( P < 0.01 \), Table 1); however, frequencies of other comorbidities including chronic obstructive pulmonary disease, cancer, and atrial fibrillation were similarly distributed between groups (all \( P > 0.05 \), Table 1). Compared with survivors, patients who died had more often received mechanical ventilation, extracorporeal membrane oxygenation, and continuous renal replacement therapy (all \( P < 0.001 \), Table 1). The proportion of antiviral treatment use was similarly distributed between groups; however, the usage of intravenous immunoglobulin, glucocorticoids, and antibiotics was higher among the patients who died (all \( P < 0.001 \), Table 1).

On admission, most patients who died presented abnormal laboratory results, such as higher leucocyte counts, neutrophil rate, and levels of aspartic transaminase, creatinine, C-reactive protein, and procalcitonin (PCT). Moreover, non-survivors had significantly higher levels of all cardiac indices than survivors, including CK-MB, MYO, cTnI, and NT-proBNP (all \( P < 0.001 \), Table 2). However, lymphocyte rate, platelet counts, albumin level, and creatinine

**Table 1  Baseline characteristics**

| Characteristics                               | All patients \((n = 671)\) | Death \((n = 62)\) | Survivors \((n = 609)\) | \(P\)-value |
|-----------------------------------------------|-----------------------------|-------------------|-------------------------|-------------|
| Age (years), median (IQR)                    | 63 (50–72)                  | 74 (66–81)        | 61 (49–70)              | \(< 0.001\) |
| Gender (male), n (%)                         | 322 (48.0)                  | 35 (56.5)         | 287 (47.1)              | \(< 0.001\) |
| Time from symptom, days (IQR)                | 23 (17–28)                  | 15 (10–18)        | 24 (17–28)              | \(< 0.001\) |
| Time from admission, days (IQR)              | 17 (8–18)                   | 4 (3–7)           | 17 (9–19)               | \(< 0.001\) |
| **Comorbidities, n (%)**                     |                             |                   |                         |             |
| Hypertension                                 | 199 (29.7)                  | 37 (59.7)         | 162 (26.6)              | \(< 0.001\) |
| Diabetes                                     | 97 (14.5)                   | 17 (27.4)         | 80 (13.1)               | 0.004       |
| Coronary heart disease                       | 60 (8.9)                    | 21 (33.9)         | 39 (6.4)                | \(< 0.001\) |
| Chronic renal disease                        | 28 (4.2)                    | 12 (19.4)         | 16 (2.6)                | \(< 0.001\) |
| Chronic obstructive pulmonary disease        | 23 (3.4)                    | 2 (3.2)           | 21 (3.4)                | 1.000       |
| Cancer                                       | 23 (3.4)                    | 4 (6.5)           | 19 (3.1)                | 0.154       |
| Chronic heart failure                        | 22 (3.3)                    | 13 (21.0)         | 9 (1.5)                 | \(< 0.001\) |
| Cerebrovascular disease                      | 22 (3.3)                    | 8 (12.9)          | 14 (2.3)                | \(< 0.001\) |
| Atrial fibrillation                          | 7 (1.0)                     | 2 (3.2)           | 5 (0.8)                 | 0.130       |
| **Treatment, n (%)**                         |                             |                   |                         |             |
| Oxygen inhalation                            | 527 (78.5)                  | 16 (25.8)         | 511 (83.9)              | \(< 0.001\) |
| Non-invasive ventilation                     | 76 (11.3)                   | 17 (27.4)         | 59 (9.7)                | \(< 0.001\) |
| Invasive mechanical ventilation              | 36 (5.4)                    | 29 (46.8)         | 7 (1.1)                 | \(< 0.001\) |
| Extracorporeal membrane oxygenation          | 2 (0.3)                     | 2 (3.2)           | 0 (0.0)                 | 0.008       |
| Continuous renal replacement therapy         | 4 (0.6)                     | 4 (6.5)           | 0 (0.0)                 | \(< 0.001\) |
| Antiviral                                    | 647 (96.4)                  | 58 (93.5)         | 589 (96.7)              | 0.267       |
| Immunoglobulin                               | 399 (59.5)                  | 55 (88.7)         | 344 (56.5)              | \(< 0.001\) |
| Glucocorticoids                              | 379 (56.5)                  | 53 (85.5)         | 326 (53.5)              | \(< 0.001\) |
| Antibiotic                                   | 364 (54.2)                  | 49 (79.0)         | 315 (51.7)              | \(< 0.001\) |

IQR, interquartile range.
Table 2  Laboratory findings

| Characteristics          | Normal range | All patients (n = 671) | Death (n = 62) | Survivors (n = 609) | P-value |
|--------------------------|--------------|------------------------|---------------|---------------------|---------|
| Leucocyte counts         | 3.5–9.5 × 10^9/L | 5.8 (4.3–8.2)          | 9.6 (7.8–14.0) | 5.2 (3.7–7.0)       | <0.001  |
| Neutrophil rate          | 40–75 %      | 72 (62–84)             | 91 (86–93)    | 68 (59–76)          | <0.001  |
| Lymphocyte rate          | 20–50 %      | 19 (10–26)             | 6 (4–10)      | 26 (16–28)          | <0.001  |
| Platelet count           | 125–350 × 10^5/L | 210 (155–270)          | 153 (75–204)  | 215 (172–284)       | <0.001  |
| Erythrocyte count        | 3.8–5.1 × 10^12/L | 4.1 (3.6–4.5)          | 4.0 (3.4–4.4) | 4.1 (3.8–4.5)       | 0.050   |
| Haemoglobin              | 115–150 g/L | 124 (111–135)          | 128 (103–140) | 125 (118–135)       | 0.545   |
| Alkaline aminotransferase| 7–40 U/L     | 27 (18–44)             | 26 (19–39)    | 22 (15–35)          | 0.823   |
| Aspartic transaminase     | 7–40 U/L     | 29 (21–40)             | 42 (29–64)    | 25 (20–32)          | <0.001  |
| Albumin                  | 40–55 g/L    | 36 (33–38)             | 33 (30–35)    | 37 (35–39)          | <0.001  |
| Creatinine               | 41–73 µmol/L | 58 (48–70)             | 87 (59–160)   | 55 (48–63)          | <0.001  |
| Creatinine clearance     | > 90 mL/min  | 97 (88–97)             | 67 (35–94)    | 99 (92–107)         | <0.001  |
| C-reactive protein       | < 10 mg/L    | 41 (12–81)             | 111 (64–191)  | 30 (8–59)           | <0.001  |
| Procalcitonin            | < 0.1 ng/mL  | 0.06 (0.04–0.13)       | 0.46 (0.14–1.58) | 0.05 (0.03–0.09) | <0.001  |
| CK-MB                    | 0–5 ng/mL    | 0.96 (0.63–1.82)       | 3.6 (2.4–6.9) | 0.8 (0.6–1.2)       | <0.001  |
| MYO                      | 0–110 µg/L   | 42 (27–85)             | 268 (92–768)  | 32 (24–63)          | <0.001  |
| cTnI*                    | 0–0.04 ng/mL | 0.006 (0.006–0.016)    | 0.235 (0.042–1.996) | 0.006 (0.006–0.011) | <0.001  |
| NT-proBNP                | 0–900 pg/mL  | 189 (67–494)           | 1819 (759–5164) | 132 (58–237)       | <0.001  |

CK-MB, creatinine kinase-myocardial band; MYO, myoglobin; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*indicated that the proportion of patients with cTnI levels >0.04 ng/mL in all included patients, dead patients, and survivors was 15.8%, 75.8%, and 9.7% on admission, respectively.

Table 3  Cause of death in included patients

| Complications                     | No. (%) |
|-----------------------------------|---------|
| Acute respiratory distress syndrome | 61 (98.4) |
| Acute respiratory failure         | 56 (90.3) |
| Acute myocardial injury           | 20 (30.6) |
| Acute heart failure               | 12 (19.4) |
| Multiple organ failure syndrome   | 6 (9.7) |
| Shock                             | 4 (6.5) |
| Sudden death                      | 1 (1.6) |

Table 3 summarized the distribution of death-related complications in included patients, including ARDS (98.4%), acute respiratory failure (90.3%), acute myocardial injury (30.6%), acute heart failure (19.4%), multiple organ failure syndrome (9.7%), shock (6.5%), and sudden death (1.6%).

The rapid deterioration of the respiratory function was the main cause of death, followed by cardiovascular complications. Table 3 summarized the distribution of death-related complications in included patients, including ARDS (98.4%), acute respiratory failure (90.3%), acute myocardial injury (30.6%), acute heart failure (19.4%), multiple organ failure syndrome (9.7%), shock (6.5%), and sudden death (1.6%).

Predictive value of cardiac indicators for in-hospital mortality

ROC curve analysis was performed to determine the value of CK-MB, MYO, and cTnI for predicting mortality during the time from admission to the end of follow-up in patients with severe COVID-19. As shown in Figure 2, the area under the ROC curve (AUC) for the outcome of mortality was 0.87 (95% CI, 0.81–0.93), 0.88 (95% CI, 0.83–0.93), and 0.92 (95% CI, 0.87–0.96), all with significant sensitivity and specificity (all P < 0.001). The single cut-off concentrations of CK-MB, MYO, and cTnI were 2.2 ng/mL, 73 µg/L, and 0.026 ng/mL, respectively.

On Kaplan–Meier analysis, baseline CK-MB [49/117 (41.9%) vs. 13/554 (2.3%); P < 0.001], MYO [53/182 (29.1%) vs. 9/489 (1.8%); P < 0.001], and cTnI [51/133 (38.3%) vs. 11/538 (2.0%); P < 0.001] above these cut-offs were associated with markedly higher hospitalized death (Figure 3A). We performed a contour plot to determine the relationship between levels of cardiac biomarkers, age, and mortality. The results showed that the higher initial levels of CK-MB, MYO, and cTnI were consistently associated with higher mortality, which was pronounced in patients with senior age (Figure 3B).

To analyse the risk factors for in-hospital mortality by multivariable Cox regression, the values of these biomarkers were transformed into categorical variables according to ROC cut-off points (CK-MB, MYO, and cTnI) and the 99th percentile upper reference limit. We performed a contour plot to determine the relationship between levels of cardiac biomarkers, age, and mortality. The results showed that the higher initial levels of CK-MB, MYO, and cTnI were consistently associated with higher mortality, which was pronounced in patients with senior age (Figure 3B).

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MYO (HR, 1.00; 95% CI, 1.00–1.01; P < 0.001), cTnI (HR, 1.25; 95% CI, 1.07–1.46; P = 0.004), and NT-proBNP (HR, 1.00; 95% CI, 1.00–1.00; P = 0.045) were risk factors for death, Figure 4B.

After these continuous variables were ln-transformed, the results of multivariable Cox regression model 2 showed PCT (HR, 1.72; 95% CI, 1.20–2.45) and cTnI (HR, 1.90; 95% CI, 1.44–2.49) were significantly associated with in-hospital mortality, but the other factors were no longer significant, including age, C-reactive protein, MYO, and NT-proBNP. In order to avoid the influence of collinearity among CK-MB, MYO, and cTnI, we excluded CK-MB and MYO in two multivariable Cox models, the results displayed that cTnI was still a significant factor in both the models, with 11.18 (95% CI, 3.23–38.75) and 1.27 (95% CI, 1.10–1.46) of HR in model 1 and model 2, respectively. Moreover, coronary heart disease (HR, 2.25; 95% CI, 1.04–4.87) became a new significant factor in model 1, and chronic heart disease (HR, 3.37; 95% CI, 1.24–9.18) was significant in model 2, respectively.

### Incidence and predictors of myocardial injury

A total of 106 patients (15.8%) had myocardial injury in all included patients on admission. Patients with myocardial injury had older age, more comorbidities, and more abnormalities in laboratory findings than those patients without myocardial injury (Table 4). Patients who died had suffered more often from myocardial injury during hospitalization compared with survivors (75.8% vs. 9.7%; P < 0.001). A contour plot for the distribution characteristics of myocardial indicators showed that these biomarkers were higher among patients who died (Figure 5A). During the period from admission to death, cardiac indicators showed a dynamic change in the death group, especially in the

| Variables | AUC   | 95% CI | Sensitivity | Specificity | P-value |
|-----------|-------|--------|-------------|-------------|---------|
| CK-MB     | 0.87  | 0.81–0.93 | 0.81        | 0.87        | <0.001  |
| MYO       | 0.88  | 0.83–0.93 | 0.85        | 0.76        | <0.001  |
| cTnI      | 0.92  | 0.87–0.96 | 0.86        | 0.86        | <0.001  |

Figure 2 Receiver operating characteristic analysis of the clinical prediction model. Prediction of in-hospital mortality by levels of CK-MB, MYO, and cTnI; the area under the curve was 0.87, 0.88, and 0.92, respectively. All P < 0.001. AUC, area under the receiver operating characteristic curve; CI, confidence interval; CK-MB, creatinine kinase-myocardial band; MYO, myoglobin; cTnI, cardiac troponin I.

A

![Figure A](https://academic.oup.com/eurheartj/article-abstract/41/22/2070/5835730)

B

![Figure B](https://academic.oup.com/eurheartj/article-abstract/41/22/2070/5835730)
Figure 4  Multivariable Cox regression analysis of clinical indicators of in-hospital mortality in patients with severe COVID-19. (A) In multivariable model 1, CK-MB > 2.2 ng/mL, cTnI > 0.026 ng/mL, and NT-proBNP > 900 pg/mL were risk factors; these cardiac indicators were transformed into categorical variables according to the cut-off points, and procalcitonin, C-reactive protein, and NT-proBNP were transformed into categorical variables according to the 99th percentile upper reference limit. (B) In multivariable model 2, senior age, C-reactive protein, MYO, cTnI, and NT-proBNP were risk factors; these biomarkers were performed as continuous variables. HR, hazard ratio; CI, confidence interval; CK-MB, creatinine kinase-myocardial band; MYO, myoglobin; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 4  Baseline characteristics in patients with and without myocardial injury

| Characteristics                           | Myocardial injury (n = 106) | Without myocardial injury (n = 565) | P-value |
|-------------------------------------------|----------------------------|-------------------------------------|---------|
| Age (years), median (IQR)                 | 73 (66–80)                 | 57 (43–70)                          | <0.001  |
| Gender (male), n (%)                      | 58 (54.7)                  | 264 (46.7)                          | 0.139   |
| Comorbidities, n (%)                      |                            |                                     |         |
| Hypertension                              | 63 (59.4)                  | 136 (24.1)                          | <0.001  |
| Diabetes                                  | 25 (23.6)                  | 72 (12.7)                           | 0.006   |
| Coronary heart disease                    | 29 (27.4)                  | 31 (5.5)                            | <0.001  |
| Chronic renal disease                     | 17 (16.0)                  | 11 (1.9)                            | <0.001  |
| Chronic obstructive pulmonary disease     | 10 (9.4)                   | 13 (2.3)                            | 0.001   |
| Cancer                                    | 8 (7.5)                    | 15 (2.7)                            | 0.019   |
| Chronic heart failure                     | 13 (12.3)                  | 9 (1.6)                             | <0.001  |
| Cerebrovascular disease                   | 11 (10.4)                  | 11 (1.9)                            | <0.001  |
| Atrial fibrillation                       | 1 (0.9)                    | 6 (1.1)                             | 1.000   |
| Laboratory findings, median (IQR)         |                            |                                     |         |
| Leucocyte count, × 10^9/L                 | 9.0 (6.2–13.3)             | 5.3 (4.0–7.3)                       | <0.001  |
| Neutrophil rate, %                        | 88 (82–92)                 | 68 (59–79)                          | <0.001  |
| Lymphocyte rate, %                        | 8 (4–12)                   | 21 (14–28)                          | <0.001  |
| Alanine aminotransferase, U/L             | 29 (18–43)                 | 23 (16–36)                          | 0.527   |
| Aspartic transaminase, U/L                | 36 (27–52)                 | 26 (20–34)                          | <0.001  |
| Creatinine, μmol/L                        | 67 (57–117)                | 55 (48–65)                          | <0.001  |
| C-reactive protein, mg/L                  | 88 (60–147)                | 29 (8–64)                           | <0.001  |
| Procalcitonin, ng/mL                      | 0.23 (0.09–0.69)           | 0.05 (0.03–0.09)                    | <0.001  |
| CK-MB, ng/mL                              | 2.81 (1.45–5.72)           | 0.85 (0.58–1.21)                    | <0.001  |
| MYO, μg/L                                 | 125 (66–343)               | 34 (24–62)                          | <0.001  |
| cTnI, ng/mL                               | 0.159 (0.075–0.695)        | 0.006 (0.006–0.007)                 | <0.001  |
| NT-proBNP, pg/mL                          | 1346 (474–3018)            | 133 (50–265)                        | <0.001  |

IQR, interquartile range; CK-MB, creatinine kinase-myocardial band; MYO, myoglobin; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
levels of CK-MB and cTnl, Figure 5B. Because most patients were not continuously monitored during hospitalization, the serial biomarker results were based on a very small subcohort. In univariable logistic regression analysis, male, senior age, hypertension, diabetes, coronary heart disease, chronic renal failure, chronic heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, and high levels of PCT and C-reactive protein were risk factors for myocardial injury (Table 5). In multivariable logistic regression analysis, male, diabetes, chronic heart failure, cerebrovascular disease, and PCT were no longer predictors (Table 5).

**Discussion**

The major findings of the present study are as follows: (i) myocardial injury is not uncommon among patients with severe COVID-19, especially among those who die; (ii) elevated levels of myocardial markers predict risk for in-hospital death; and (iii) senior age, inflammatory response, and underlying cardiovascular-related comorbidities are associated with myocardial injury in patients with COVID-19.

COVID-19 has managed to supersede the death toll of SARS and MERS. Severe respiratory distress is usually considered as a leading cause of coronavirus-induced death. In a recent study on the largest clinical sample in China, severe pneumonia was independently associated with admission to ICU, mechanical ventilation, or death. Other complications also were associated with higher risk of in-hospital death. Cheng et al. documented a 3.2% prevalence of kidney impairment in hospitalized COVID-19 patients in association with higher risk of mortality. Although information on cardiac complications is limited among COVID-19 patients, cardiac impairment has been demonstrated as a direct or underlying cause of death in 27% of pneumonia-associated deaths. Even after adjustment for baseline risk, cardiac complications are associated with a 60% increase in pneumonia-associated short-term mortality. However, there was insufficient evidence to suggest that patients with cardiovascular...
Myocardial injury in patients with severe COVID-19

Table 5  Univariate and multivariate predictors of myocardial injury

| Characteristics                          | No. | Univariate |     |      |     |     | Multivariate |     |      |     |
|------------------------------------------|-----|------------|-----|------|-----|-----|--------------|-----|------|-----|
|                                         |     | OR         | 95% CI | P-value | OR        | 95% CI | P-value |
| Male                                     | 322 | 1.81       | 1.21–2.70 | 0.004 | 1.74 | 0.97–3.13 | 0.064 |
| Age (per 10-year increase)               | 671 | 2.23       | 1.84–2.69 | <0.001 | 1.64 | 1.28–2.10 | <0.001 |
| Hypertension                             | 199 | 5.74       | 3.77–8.74 | <0.001 | 3.30 | 1.77–6.14 | <0.001 |
| Diabetes                                 | 97  | 2.00       | 1.21–3.28 | 0.006 | 0.63 | 0.29–1.34 | 0.231 |
| Coronary heart disease                   | 60  | 6.79       | 3.90–11.83 | <0.001 | 2.92 | 1.32–6.48 | 0.008 |
| Chronic renal disease                    | 28  | 11.33      | 4.98–25.75 | <0.001 | 9.03 | 2.43–33.59 | 0.001 |
| Chronic heart failure                    | 22  | 7.32       | 3.05–17.55 | <0.001 | 2.19 | 0.54–8.92 | 0.276 |
| Atrial fibrillation                      | 7   | 1.85       | 0.36–9.66 | 0.465 | 0.10 | 0.01–1.48 | 0.093 |
| Cerebrovascular disease                  | 22  | 4.95       | 2.10–11.72 | <0.001 | 1.35 | 0.35–5.21 | 0.663 |
| Chronic obstructive pulmonary disease    | 23  | 4.08       | 1.72–9.69 | 0.001 | 4.01 | 1.28–12.61 | 0.018 |
| Procalcitonin (ng/mL)                    | 671 | 1.28       | 1.08–1.52 | 0.005 | 0.99 | 0.79–1.23 | 0.900 |
| C-reactive protein (mg/L)                | 671 | 1.02       | 1.01–1.02 | <0.001 | 1.01 | 1.01–1.02 | <0.001 |

OR, odds ratio; CI, confidence interval.
presentation.\textsuperscript{18,19} Nonetheless, about one third of transient cardiac complications occur in patients without a history of cardiac disease.\textsuperscript{20} A study in SARS also found that reversible left ventricular impairment appears common even among those without underlying cardiac disease.\textsuperscript{21} However, sufficient evidence is needed to clarify whether the effects of COVID-19 and SARS on the myocardium are different. In the present study, patients who died had higher proportions of both myocardial injury and cardiovascular-related comorbidities, suggesting that cardiac complications with underlying cardiovascular disease or risk usually co-exist and develop to irreversible outcome. Alternatively, the systemic inflammatory response to pneumonia can also increase the inflammatory activity within coronary atherosclerotic plaques, rendering them unstable and prone to rupture.\textsuperscript{22} Therefore, the presence of pre-existing cardiovascular disease or related risk factors may aggravate myocardial injury, which therefore cannot be ignored in management of COVID-19. In general, patients with COVID-19 and myocardial injury are not actively recommended for emergency intervention strategies due to existing risk of cross-infection, and in most mid/moderate myocardial injury, the standard process of comprehensive management is generally based on risk stratification and patient classification.\textsuperscript{23}

Limitations

Although this study included a large number of patients, it has several limitations. First, some data (such as echocardiography and dynamic measurements of myocardial markers) were lacking from clinical examinations of patients in isolation ward or ICU because of the logistical restriction at the onset of these emerging infections in Wuhan. Second, due to the existence of either unmeasured or unknown confounders, the causes of death or myocardial injury could be underestimated by analysis of multivariable regression. Third, because the clinical observation of patients is still ongoing at the time of manuscript submission, most patients have not reached the clinical endpoint. Finally, for the total number of 2 350 000 patients with COVID-19 worldwide, the current sample size is still small. In order to avoid statistical bias as much as possible, data from multiple centres and larger samples are warranted to further confirm the results of the present study.

Conclusion

Myocardial injury is not an uncommon complication among patients with severe COVID-19, especially among those who die. cTnI and CK-MB levels predict risk for in-hospital death, and myocardial injury is associated with senior age, inflammatory response, and cardiovascular-related comorbidities.

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