The peak levels of highly sensitive troponin I predicts in-hospital mortality in COVID-19 patients with cardiac injury: a retrospective study

Yaxin Wang†, Huaqing Shu†, Hong Liu†, Xia Li‡, Xing Zhou‡, Xiaojing Zou†, Shangwen Pan†, Qijian Xu†, Dan Xu†, Xin Zhao†, Xiaobo Yang†, Yuan Yu†, Yin Yuan†, Hong Qi†, Qiongya Wang‡, and You Shang†*

1Department of Critical Care Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1277, Jiefang Ave, Wuhan, 430022 Hubei, China; and 2Research Center for Translational Medicine, Jinyintan Hospital, No. 1, Yintan Ave, Wuhan, 430012 Hubei, China

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Aims
To investigate the association between levels of highly sensitive troponin I (hs-troponin I) and mortality in novel coronavirus disease 2019 (COVID-19) patients with cardiac injury.

Methods and results
We retrospectively reviewed the medical records of all COVID-19 patients with increased levels of hs-troponin I from two hospitals in Wuhan, China. Demographic information, laboratory test results, cardiac ultrasonographic findings, and electrocardiograms were collected, and their predictive value on in-hospital mortality was explored using multivariable logistic regression. Of 1500 patients screened, 242 COVID-19 patients were enrolled in our study. Their median age was 68 years, and (48.8%) had underlying cardiovascular diseases. One hundred and seventy-six (72.7%) patients died during hospitalization. Multivariable logistic regression showed that C-reactive protein (>75.5 mg/L), D-dimer (>1.5 μg/mL), and acute respiratory distress syndrome were risk factors of mortality, and the peak hs-troponin I levels (>259.4 pg/mL) instead of the hs-troponin I levels at admission was predictor of death. The area under the receiver operating characteristic curve of the peak levels of hs-troponin I for predicting in-hospital mortality was 0.79 (95% confidence interval, 0.73–0.86; sensitivity, 0.80; specificity, 0.72; P < 0.0001).

Conclusion
Our results demonstrated that the risk of in-hospital death among COVID-19 patients with cardiac injury can be predicted by the peak levels of hs-troponin I during hospitalization and was significantly associated with oxygen supply-demand mismatch, inflammation, and coagulation.

Keywords
COVID-19  •  Cardiac injury  •  Peak levels of troponin I  •  Levels of troponin I at admission  •  Mortality

Introduction
The ongoing outbreak of novel coronavirus disease 2019 (COVID-19) has become a global plague, which was first identified in Wuhan, Hubei province, China since December 2019. As of 11 August 2020, there are more than 20 million confirmed cases in the world. COVID-19 is caused by a new virus which was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as it is similar to bat-derived severe acute respiratory syndrome-like coronaviruses.1 The high infectivity and rapid progression make the prevention and treatment is more difficult.

The spectrum of COVID-19 in humans is not yet been fully understood. Although pneumonia is the main manifestation of SARS-CoV-2 infection, lung is not the only organs involved in COVID-19.

* Corresponding author. Tel: +86 027 85751606, Fax: +86 027 85751607, Email: you_shanghust@163.com and Tel: +86 27 8550 9068, Fax: +86 27 85509002, Email: 243276106@qq.com
†These authors contributed equally to the study.
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Accumulating evidence demonstrated that cardiac injury is one of the COVID-19-related complications with high mortality, especially in critically ill patients. Currently, although cardiac injury in COVID-19 has been widely reported, large scale clinical data on cardiac injury of patients with SARS-CoV-2 infection during hospitalization is still limited, but of great importance in the acknowledge of COVID-19. The purpose of this retrospective study is to assess the relationship between levels of highly sensitive troponin I (hs-troponin I) and mortality in COVID-19 patients with cardiac injury.

**Methods**

**Study participants**

During the period from 1 January 2020 to 28 February 2020, we identified 1500 adult individuals who were confirmed COVID-19 in Wuhan Jinyintan Hospital and west branch of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology union hospital. The two hospitals are designated hospitals for the treatment of patients with COVID-19 patients.

The patients with COVID-19 enrolled in this study were diagnosed with COVID-19 according to guidelines released by National Health Commission of the People’s Republic of China and had a definite outcome (discharge or dead) during the treatment. The patients whose hs-troponin I levels were greater than the upper limit of reference range during hospitalization were enrolled in the study.

This study was approved by the Research Ethics Commission of Jinyintan Hospital the central co-ordinating centre and the informed consent was waived.

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

**Data collection**

The data including demographic characteristics (age and gender), clinical data (underlying diseases, laboratory results, treatments, complications, and outcomes), laboratory findings, and cardiac biomarkers for patients during hospitalization were collected from electronic medical records by one investigator. All the data were independently reviewed and entered into the computer by two analysts.

**Definitions**

Cardiac injury was defined as the serum levels of hs-troponin I above 28 pg/mL, the upper limit of reference range. Acute respiratory distress syndrome (ARDS) was defined according to Berlin definition. Bacterial pneumonia was diagnosed when patients exhibited clinical symptoms or signs of pneumonia or bacteraemia and a positive culture of a new pathogen was obtained from lower respiratory tract specimens after admission. Liver dysfunction was diagnosed if serum alanine aminotransferase >50 U/L or aspartate aminotransferase (AST) >40 U/L during disease progression. Acute kidney injury (AKI) was identified according to the >50 U/L or aspartate aminotransferase (AST) >40 U/L during disease progression. Acute kidney injury (AKI) was identified according to the

**Statistical analysis**

Categorical data are expressed as count (percentage), and continuous data as mean (standard deviation) and median [interquartile range (IQR)]. To explore the differences between survivors and non-survivors, categorical data were compared using the Fisher’s exact test, and continuous data were compared using the Student’s t-test or the Mann–Whitney U test, including hs-troponin I. To further explore the association between hs-troponin I and mortality, firstly, patients were categorized into early elevation group or late elevation group based on whether the level of hs-troponin I was elevated at hospital admission, then multiple logistic regression was conducted; secondly, patients were categorized into severe elevation group and mild elevation group based on whether the peak level of hs-troponin I was above or below the median peak level of all patients, then multiple logistic regression was also conducted; thirdly, receiver operating characteristic (ROC) curve was used to depict the predictive value of in-hospital mortality. All data were analysed using SPSS version 22.0 (IBM), \( P < 0.05 \) was considered statistically significant.

**Results**

**Patients’ characteristics**

A total of 1500 adult patients confirmed with COVID-19 between 1 January 2020 and 28 February 2020 were screened, and 242 patients were included. As shown in Table 1, their median age was 68 years (IQR, 61–75 years), and male patients occupied a large proportion (62.4%). The median time from illness onset to admission and the length of hospitalization were both 10 days. Of 242 patients, 71.1% patients had underlying diseases. The most common comorbidity was cardiovascular diseases (48.8%), including hypertension and coronary heart disease. Fever (86.4%) was the most common symptom among these patients.

One hundred and seventy-six patients died during hospitalization. No significant differences in age, duration from symptom onset to admission, prevalence of comorbidities, or symptoms were identified between survivors and non-survivors. However, compared with survivors, non-survivors were with more men (47.9% vs. 14.5%, \( P = 0.046 \)), and the duration from symptom onset to admission was almost the same in the two groups.

There were no significant differences in blood pressure, heart rate, or body temperature at admission between the two groups. Respirator rate was significantly higher in non-survivors [median (IQR), 23 (20–30) vs. 21 (20–24), \( P = 0.019 \)].

**Laboratory findings**

As shown in Table 2, patients in non-survivor group presented higher white blood cell (WBC) and neutrophilic percentage. Lymphocyte counts, lymphocyte percentage, and platelets were lower compared with that of survivor group. Moreover, patients in non-survivor group also had higher levels of prothrombin time, D-dimer, AST, glucose, urea nitrogen, but a lower level of albumin and calcium. The inflammatory biomarkers, including C-reactive protein (CRP) and procalcitonin (PCT), were significantly higher in deceased patients.

**Treatments and outcomes**

During hospitalization, patients in non-survivor group developed more frequent severe complications (Table 3), including bacterial pneumonia [55 (31.3%) vs. 4 (6.1%)], AKI [107 (60.8%) vs. 2 (3.1%)], heart failure [47 (26.9%) vs. 3 (4.5%)], sepsis shock [41 (23.3%) vs. 0], acute liver dysfunction [50 (28.4%) vs. 1 (1.5%)], ARDS [166 (94.3%) vs. 2 (3.1%)].

| Table 2 | Table 3 |
vs. 5 (7.6%)], and pneumothorax [15 (8.5%) vs. 0]. Acute myocardial infarction [6 (2.5%)] and pulmonary embolism [1 (0.4%)] occurred in several patients, but there was no significant difference between the two groups. Meanwhile, there was no significant difference in the incidence of cerebrovascular accident between the two groups.

Compared with survivors, more patients in non-survivors received glucocorticoid, anticoagulant, vasoconstrictor, and life-supporting treatments including invasive mechanical ventilation, continuous renal replacement therapy, prone position ventilation, and extracorporeal membrane oxygenation.

Electrocardiogram examination was performed in 183 patients (Supplementary material online, Table 1S). Abnormal changes were more often observed in non-survivor group [113 (82.5%) vs. 31 (67.4%)]. Except axis deviation, there were no significant difference between the survivor group and non-survivor group. Besides, 62 patients

| Table 1  | Demographics and clinical characteristics |
|----------|------------------------------------------|
|          | Total | Survivor | Non-survivor | P-value |
| Number of patients | 242   | 66       | 176         | None    |
| Male      | 151 (62.4%) | 35 (14.5%) | 116 (47.9%) | 0.046   |
| Age (years) | 68 (61–75) | 66 (56–73) | 69 (62–75) | 0.055   |
| Hospitalization (days) | 10.0 (6.0–15.0) | 13.5 (8.8–19.0) | 9.0 (5.0–14.0) | <0.0001 |
| Duration from onset to admission (days) | 10.0 (7.0–14.0) | 10.0 (8.0–14.0) | 10.0 (7.0–13.0) | 0.265   |
| Comorbidty | 172 (71.1%) | 48 (72.7%) | 124 (70.5%) | 0.43    |
| Cardiovascular diseases | 118 (48.8%) | 30 (45.5%) | 88 (50%) | 0.31    |
| Diabetes  | 48 (19.8%) | 14 (21.1%) | 34 (19.3%) | 0.43    |
| Malignant neoplasm | 14 (5.8%) | 4 (6.1%) | 10 (5.7%) | 0.56    |
| Chronic kidney disease | 7 (2.9%) | 3 (4.5%) | 4 (2.3%) | 0.29    |
| Cerebrovascular disease | 16 (6.6%) | 2 (3.0%) | 14 (8.0%) | 0.14    |
| Hyperlipidaemia | 5 (2.1%) | 0 | 5 (2.8%) | 0.38    |
| Smoking   | 1 (0.4%) | 0 | 1 (0.6%) | 0.73    |
| Drinking  | 2 (0.8%) | 0 | 2 (1.1%) | 0.53    |
| COPD      | 9 (3.7%) | 1 (1.5%) | 8 (4.5%) | 0.24    |
| Rheumatic immune disease | 10 (4.1%) | 3 (4.5%) | 7 (4.0%) | 0.54    |
| Asthma    | 2 (0.8%) | 1 (1.5%) | 1 (0.6%) | 0.47    |

Sign and symptoms at admission

| Fever          | 209 (86.4%) | 53 (80.3%) | 156 (88.6%) | 0.07   |
| Cough          | 176 (72.7%) | 51 (77.3%) | 125 (71.0%) | 0.21   |
| Fatigue        | 49 (20.2%)  | 14 (21.2%) | 35 (19.9%) | 0.47   |
| Sore throat    | 14 (5.8%)   | 1 (1.5%)   | 13 (7.4%)   | 0.14   |
| Sputum         | 44 (18.2%)  | 9 (13.6%)  | 35 (19.9%) | 0.18   |
| Runny          | 12 (5.0%)   | 3 (1.5%)   | 9 (5.2%)   | 0.38   |
| Gasp           | 9 (3.7%)    | 2 (3.0%)   | 7 (4.0%)   | 0.11   |
| Shortness of breath | 9 (3.7%) | 2 (3.0%) | 7 (4.0%) | 0.08   |
| Chest pain     | 3 (1.2%)    | 1 (0.4%)   | 2 (1.2%)   | 0.38   |
| Chest tightness| 68 (28.1%)  | 16 (27.3%) | 52 (28.4%) | 0.5    |
| Palpitations   | 9 (3.7%)    | 3 (4.5%)   | 6 (3.4%)   | 0.46   |
| Chill          | 47 (19.4%)  | 11 (16.7%) | 36 (20.0%) | 0.52   |
| Difficulty breathing | 25 (10.3%) | 7 (10.6%) | 18 (10.2%) | 0.55   |
| Muscle ache    | 9 (3.7%)    | 2 (3.0%)   | 7 (4.0%)   | 0.24   |
| Headache       | 6 (2.5%)    | 2 (3.0%)   | 4 (2.3%)   | 0.52   |
| Nausea         | 1 (0.4%)    | 0 | 1 (0.6%) | 0.73   |
| Vomiting       | 1 (0.4%)    | 0 | 1 (0.6%) | 0.73   |
| Diarrhoea      | 1 (0.4%)    | 0 | 1 (0.6%) | 0.73   |
| Joint pain     | 2 (0.8%)    | 1 (1.5%)   | 1 (0.6%)   | 0.47   |
| Respiratory rate| 22 (22–26)  | 21 (20–24) | 23 (20–30) | 0.019  |
| Pulse          | 89 (82–102) | 88 (82–97) | 90 (81.5–102) | 0.442 |
| Systolic blood pressure | 128 (117.8–140) | 126 (119–137.5) | 129 (116–143) | 0.179 |
| Body temperature | 36.6 (36.4–36.9) | 36.6 (36.4–37) | 36.6 (36.4–36.8) | 0.915 |

COPD, chronic obstructive pulmonary disease.
received echocardiography examination during hospitalization (Supplementary material online, Table 2S). There was no difference in left ventricular systolic dysfunction in both survivors and non-survivors. The value of E/A, an important index reflecting diastolic function, was higher than 1 in most of the patients with fatal outcomes.

**The dynamic changes of hs-troponin I**

In terms of cardiac indices at admission, compared with survivors, non-survivors had a similar level of hs-troponin I [median (IQR), 33.9 (13.2–130.0) vs. 37.5 (29.7–75.1)] and higher levels of creatinine kinase [CK, median (IQR), 118.5 (66.8–285.5) vs. 96.0 (54.0–171.0)], creatinine kinase-myocardial band [CK-MB, median (IQR), 44.0 (3.0–61.0) vs. 36.5 (27.0–46.3)], lactate dehydrogenase [LDH, median (IQR), 532.5 (425.5–690.0) vs. 371.0 (277.0–439.0)], and myoglobin [median (IQR), 19.5 (15.0–27.0) vs. 13.0 (11.0–18.0)] (Table 4). Non-survivors had shorter duration of hospitalization [median (IQR), 9.0 (5.0–14.0) vs. 13.5 (8.8–19.0); P < 0.0001]. Moreover, the results showed that there were 86 (35.5%) patients with normal hs-troponin I at admission (Supplementary material online, Figure 1S).

In terms of peak levels of cardiac indices during hospitalization, compared with survivors, non-survivors had a higher levels of hs-troponin I [median (IQR), 474.2 (102.1–2406.1) vs. 59.1 (36.6–211.9), P < 0.0001]. The peak levels of CK, CK-MB, LDH and myoglobin were not different between the two groups. Non-survival patients had a shorter hospitalization days [median (IQR), 9.0 (5.0–14.0) vs. 13.5 (8.8–19.0); P < 0.0001], but there was no significant difference in the time for hs-troponin I reached the peak value [median (IQR), 3.0 (1.0–8.0) vs. 1.0 (1.0–6.0); P = 0.083] between the two groups. There was a significant increase in hs-troponin I levels in non-survival patients compared with the hs-troponin I levels in survival groups during hospitalization, indicating a more serious cardiac injury happened in these patients (Supplementary material online, Figure 2S, A). Moreover, the dynamic changes of CRP and D-dimer tracked with the changes of hs-troponin I (Supplementary material online, Figure 2S, B and C).

**Survival curve analysis**

Figure 1A showed the total survival rate in these patients. The mean survival time was 14.6 days and the mortality rate was 72.3%. In order to investigate the impact of high hs-troponin I on mortality during hospitalization, we divided the patients into two groups (normal hs-troponin I group and high hs-troponin I group) according to hs-troponin I levels at admission. It was found that there was no significant difference between the two groups in the in-hospital mortality (Figure 1B).

| Characteristic       | Total (n = 242) | Survival (n = 66) | Non-survival (n = 176) | P-value |
|----------------------|----------------|------------------|----------------------|---------|
| White blood cell     | 8.2 (5.3–12.3) | 5.6 (3.9–7.9)    | 9.0 (6.5–13.9)       | <0.0001 |
| Neutrophil%          | 88.2 (81.1–92.2)| 78.8 (67.7–86.9) | 89.9 (84.7–93.0)     | <0.0001 |
| Lymphocyte           | 0.63 (0.46–0.91) | 0.81 (0.55–1.13) | 0.57 (0.43–0.84)     | <0.0001 |
| Lymphocyte%          | 7.5 (4.3–13.2) | 13.2 (7.6–22.4)  | 6.6 (3.7–10.0)       | <0.0001 |
| Platelets            | 166.0 (1140–2200) | 197.0 (1435–2545) | 161.0 (1093–208)     | 0.001   |
| Haemoglobin          | 123.0 (19.8) | 118.4 (19.9)     | 123.7 (19.8)         | 0.700   |
| Coagulation profiles |               |                  |                      |         |
| Prothrombin time     | 12.0 (11.1–13.3) | 11.5 (10.7–12.7) | 12.3 (11.2–13.7)     | 0.003   |
| APTT                 | 27.7 (23.3–32.0) | 27.0 (23.0–31.5) | 27.9 (23.5–32.4)     | 0.477   |
| D-dimer              | 2.7 (0.9–18.8) | 1.1 (0.7–3.0)    | 5.6 (1.1–27.0)       | <0.0001 |
| Liver function       |               |                  |                      |         |
| Total bilirubin      | 14.0 (10.5–20.3) | 12.0 (9.1–16.0)  | 15.3 (10.9–22.4)     | 0.290   |
| ALT                  | 36.0 (22.0–56.0) | 32.0 (16.8–55.8) | 38.0 (24.0–56.0)     | 0.090   |
| AST                  | 44.0 (33.0–61.0) | 36.5 (27.0–46.3) | 50.0 (36.0–67.0)     | <0.0001 |
| Albumin              | 28.9 (26.3–31.5) | 29.4 (27.5–32.5) | 28.7 (25.7–30.9)     | 0.010   |
| Glucose              | 7.1 (5.7–9.4) | 6.0 (5.3–8.0)    | 7.6 (6.1–9.7)        | <0.0001 |
| Renal function       |               |                  |                      |         |
| Creatinine           | 76.7 (65.3–100.8) | 76.1 (62.3–95.3) | 77.5 (65.7–104.5)    | 0.423   |
| Urea nitrogen        | 6.9 (5.2–10.1) | 5.5 (4.4–7.7)    | 7.3 (5.4–10.5)       | <0.0001 |
| Potassium            | 4.1 (3.7–4.7) | 4.2 (3.7–4.7)    | 4.1 (3.6–4.6)        | 0.960   |
| Calcium              | 1.96 (1.87–2.05) | 1.99 (1.91–2.08) | 1.95 (1.86–2.04)     | 0.023   |
| Inflammatory biomarkers |          |                  |                      |         |
| CRP                  | 75.5 (29.6–118.2) | 28.8 (6.48–66.8) | 93.9 (48.5–128.8)    | <0.0001 |
| Procalcitonin        | 0.19 (0.09–0.43) | 0.10 (0.06–0.20) | 0.23 (0.12–0.52)     | <0.0001 |
| IL-6                 | 9.38 (7.0–13.7) | 8.7 (6.8–11.6)   | 9.6 (7.3–13.9)       | 0.133   |

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CRP, C-reactive protein; IL-6, interleukin-6.
Next, the whole patients were grouped into another two groups (low hs-troponin I and high hs-troponin I) according to the median of the peak value of hs-troponin I (259.4 pg/mL) during hospitalization. The mortality rate was higher among patients with high hs-troponin I level vs. low hs-troponin I level [108 (89.3%) vs. 67 (55.3%), \( P < 0.0001 \), Figure 1C]. Moreover, the survival curve was calculated in these patients according to the hs-troponin I level >259.4 ng/mL at admission. The result showed the patients who presented high hs-troponin I levels (>259.4 ng/mL) at admission developed severe COVID-19 and with a very high mortality (nearly 0, Figure 1D).

The role of hs-troponin I in predicting in-hospital mortality

The causes of cardiac injury are diverse, including non-specific cardiac injury, myocarditis, pulmonary embolism, myocardial infarction, impaired renal function, and so on. Therefore, we chose WBC, lymphocyte, creatine, CRP, interleukin-6 (IL-6), PCT, and D-dimer to use as risk factors for COX analysis.

D-dimer and CRP were dichotomized at medians, and PCT, hs-troponin I, CK-MB, and myoglobin at the upper limit of reference range. In univariable analysis, we found a significantly higher risk of death in patients with ARDS, abnormal WBC numbers, D-dimer >1.5 mg/mL, CRP >75 mg/L, IL-6 >7 pg/mL, PCT >0.5 ng/mL, CK-MB >24 U/L, and myoglobin >146.9 ng/mL. The multivariable Cox model demonstrated ARDS [odds ratio (OR), 12.21; 95% confidence interval (CI), 2.34–63.82; \( P = 0.003 \)], D-dimer (OR, 3.89; 95% CI, 1.47–10.26; \( P = 0.006 \)), and CRP (OR, 3.72; 95% CI, 1.92–7.22; \( P < 0.0001 \)) were risk factors for death (Table 5).

As a part of patients presented a normal hs-troponin I level on admission, the initial troponin I level can’t reflect the actual degree of cardiac injury, we transformed the peak hs-troponin I into categorical variables according to the median (259.4 pg/mL). Sex, age, 

| Table 3 | Treatments and outcomes |
|---------|-------------------------|
|         | Total (\( n = 242 \)) | Survivor (\( n = 66 \)) | Non-survivor (\( n = 176 \)) | \( P \)-value |
| **Treatments** | | | | |
| Antivirus | 130 (53.7%) | 40 (60.6%) | 90 (51.1%) | 0.200 |
| Glucocorticoid | 129 (53.3%) | 26 (39.4%) | 103 (58.5%) | 0.009 |
| Anticoagulant | 78 (32.2%) | 9 (13.6%) | 69 (39.2%) | <0.0001 |
| Antiarrhythmic drugs | 22 (9.1%) | 4 (6.1%) | 18 (10.2%) | 0.452 |
| Cardiotoxic | 18 (7.4%) | 2 (3.0%) | 16 (9.1%) | 0.167 |
| Vasoconstrictor | 70 (28.9%) | 1 (1.5%) | 69 (39.2%) | <0.0001 |
| Oxygen inhalation | 93 (38.4%) | 60 (90.9%) | 33 (18.8%) | <0.0001 |
| Nasal high flow oxygen inhalation | 110 (45.5%) | 8 (12.1%) | 102 (58.0%) | <0.0001 |
| Non-invasive ventilation | 99 (40.9%) | 4 (6.1%) | 95 (54.0%) | <0.0001 |
| Invasive mechanical ventilation | 92 (38.0%) | 2 (3.0%) | 90 (58.0%) | <0.0001 |
| CRRT | 49 (20.2%) | 2 (3.0%) | 47 (26.7%) | <0.0001 |
| Prone position ventilation | 19 (7.9%) | 0 | 19 (10.9%) | 0.002 |
| ECMO | 12 (5.0%) | 0 | 12 (6.8%) | 0.04 |
| Blood transfusion | 32 (13.2%) | 2 (3.0%) | 30 (17.0%) | 0.003 |
| **Complications** | | | | |
| Bacterial pneumonia | 59 (24.4%) | 4 (6.1%) | 55 (31.3%) | <0.0001 |
| AKI | 109 (45.2%) | 2 (3.1%) | 107 (60.8%) | <0.0001 |
| Heart failure | 50 (20.7%) | 3 (4.5%) | 47 (26.9%) | <0.0001 |
| Sepsis shock | 41 (16.9%) | 0 | 41 (23.3%) | <0.0001 |
| Liver dysfunction | 51 (21.1%) | 1 (1.5%) | 50 (28.4%) | <0.0001 |
| Coagulation dysfunction | 34 (14%) | 2 (3.0%) | 32 (18.2%) | 0.002 |
| Arrhythmia | 51 (21.1%) | 7 (10.6%) | 44 (25.0%) | 0.014 |
| ARDS | 171 (70.7%) | 5 (7.6%) | 166 (94.3%) | <0.0001 |
| Pneumothorax | 15 (6.2%) | 0 | 15 (8.5%) | 0.013 |
| Thrombocytopenia | 66 (27.3%) | 1 (1.5%) | 65 (36.9%) | <0.0001 |
| Cerebrovascular accident | 4 (1.7%) | 1 (1.5%) | 3 (1.7%) | 0.700 |
| Acute myocardial infarction | 6 (2.5%) | 0 | 6 (3.4%) | 0.129 |
| Pulmonary embolism | 1 (0.4%) | 0 | 1 (0.6%) | 0.539 |

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.
cardiovascular diseases, diabetes, cerebrovascular disease, ARDS, and hs-troponin I were analysed by using multivariable Cox model analysis (Figure 2). The result demonstrated ARDS (OR, 9.98; 95% CI, 3.23–30.54; \( P < 0.0001 \)) and hs-troponin I (OR, 5.92; 95% CI, 2.88–12.20; \( P < 0.0001 \)) were risk factors for death.

In order to investigate the value of risk factors for predicting mortality in hospital, ROC curve analysis was performed by using the screening risk factors (hs-troponin I, CRP, D-dimer, myoglobin, and CK-MB), respectively. The result demonstrated that the peak levels of hs-troponin I instead of that at admission predict the in-hospital mortality (Supplementary material online, Figure 3S). Moreover, the levels of D-dimer, CK-MB, and myoglobin were associated with higher mortality (Supplementary material online, Figure 3S). Area under the curve for the highest value of hs-troponin I (0.79; 95% CI 0.73–0.86) was greater than that in D-dimer, CK-MB, respectively. The result demonstrated that the peak levels of hs-TNI instead of CRP and D-dimer were independent risk factors of in-hospital death. It maybe postulated that possibly an activated inflammation/coagulation system is a principal driver of hs-troponin I release in the disease. Although there were six patients met the criteria for acute myocardial infarction according to the electrocardiogram and echocardiography changes, the fact that type 2 myocardial ischaemia rather than type 1 infarction (an obstructive coronary event) should be responsible for cardiac damage in this pneumonia patients.

Nearly half of the patients combined with cardiovascular diseases (48.8%). The mortality of these patients was approximative with the previous report that the mortality of patients with elevated troponin T levels and underlying cardiovascular diseases was 69.44%.

The mechanisms of cardiac injury are various, including a direct injury by SARS-CoV-2, hypoxia-induced cardiac injury, inflammatory response-mediated cardiac damage, and microvascular damage. In the current study, we found CRP and D-dimer were elevated significantly in these patients and ARDS at admission, CRP, and D-dimer were independent risk factors of in-hospital death. It maybe postulated that possibly an activated inflammation/coagulation system is a principal driver of hs-troponin I release in the disease. Although there were six patients met the criteria for acute myocardial infarction according to the electrocardiogram and echocardiography changes, the fact that type 2 myocardial ischaemia rather than type 1 infarction (an obstructive coronary event) should be responsible for cardiac damage in this pneumonia patients.

In addition, it has been reported that direct viral infection is a possible causal pathway of cardiac damage. Another study analysed 187 COVID-19 patients and found 27.8% patients presented cardiac injury with a high mortality (59.6%). In our study, the overall prevalence of cardiac injury was 16.1%, but the mortality rate in the patients with cardiac injury was higher than the other two investigations (72.7%). First, the enrolled patients were older than the previous studies (the median age was 68). While the median age was 58.5 and 64 as Guo et al. and Shi et al. reported, respectively. It has been confirmed that increased age was associated with death in COVID-19 patients. Second, cardiovascular diseases was an common comorbidity and an indicator of poor prognosis in COVID-19. Nearly half of the patients combined with cardiovascular diseases was 69.44%.

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In addition, it has been reported that direct viral infection is a possible causal pathway of cardiac damage. In the current study, we also observed one patients with fulminant myocarditis. Although we

### Table 4 The changes of cardiac indicators

| Factors          | Total                  | Survivor                | Non-survivor              | \( P \)-value |
|------------------|------------------------|-------------------------|---------------------------|--------------|
|                  |                        |                         |                           |              |
| On admission     |                        |                         |                           |              |
| hs-troponin I    | 36.0 (15.9–97.4)       | 37.5 (29.7–75.1)        | 33.9 (13.2–130.0)         | 0.665        |
| CK               | 110.0 (64.0–261.0)     | 96.0 (54.0–171.0)       | 118.5 (66.8–285.5)        | 0.045        |
| CK-MB            | 18.0 (13.0–24.0)       | 13.0 (11.0–18.0)        | 19.5 (15.0–27.0)          | <0.0001      |
| LDH              | 464.0 (355.0–630.5)    | 371.0 (277.0–439.0)     | 532.5 (425.5–690.0)       | <0.0001      |
| Myoglobin        | 102.7 (61.3–184.5)     | 73.2 (44.7–120.6)       | 111.8 (67.9–194.5)        | <0.0001      |
| BNP              | 89.8 (48.2–205.4)      | 67.2 (33.0–183.3)       | 97.4 (50.1–527.0)         | 0.111        |
| Hospitalization  | 10.0 (6.0–15.0)        | 13.5 (8.8–19.0)         | 9.0 (5.0–14.0)            | <0.0001      |

The time point when hs-troponin I reached peak levels

| Factors          | Total                  | Survivor                | Non-survivor              | \( P \)-value |
|------------------|------------------------|-------------------------|---------------------------|--------------|
|                  |                        |                         |                           |              |
| hs-troponin I    | 259.4 (60.8–1250.3)    | 59.1 (36.6–211.9)       | 474.2 (102.1–2406.1)      | <0.0001      |
| CK               | 212.0 (99.0–554.0)     | 192.0 (76.0–498.0)      | 176.5 (94.3–506.5)        | 0.810        |
| CK-MB            | 25.0 (16.0–47.0)       | 32.0 (17.0–70.0)        | 23.0 (15.0–38.5)          | 0.096        |
| LDH              | 634.0 (428.0–925.0)    | 638.0 (474.0–992.0)     | 578.5 (389.3–861.8)       | 0.144        |
| Myoglobin        | 169.5 (79.0–403.8)     | 169.0 (67.0–423.0)      | 170.5 (93.5–386.2)        | 0.758        |
| BNP              | 290.3 (59.6–1026.8)    | 189.7 (56.4–200.4)      | 1609.5 (60.7–3507.1)      | 0.056        |
| Days after admission | 2.5 (1.0–7.0)     | 1.0 (1.0–6.0)          | 3.0 (1.0–8.0)             | 0.521        |

BNP, B-type natriuretic peptide; CK, creatinine kinase; CK-MB, creatinine kinase-myocardial band; hs-TNI, highly sensitive troponin I; LDH, lactate dehydrogenase.
could not provide more evidence of myocarditis except by using the levels of troponin I, electrocardiogram, and echocardiography change, it was possible that the cardiac injury in some patients was developed from acute myocarditis.13 Notably, we found the increase of hs-troponin I levels at admission was not a risk factor of in-hospital mortality by multi-Cox analysis and it can’t predict in-hospital mortality well. This might be explained by the following facts. First, the severity of COVID-19 in enrolled patients was different and our study was conducted in a clinical domain that only including the COVID-19 patients with cardiac injury during hospitalization. The other studies enrolled all these COVID-19 patients no matter with or without cardiac injury at admission. Second, the initial hs-troponin I levels were generally present at relatively low levels in COVID-19 patients with cardiac injury but were significantly associated with death.17 In the current study, nearly one-third of these patients presented normal levels of hs-troponin I at admission, but the mortality rate was very high. Therefore, this would reduce the weight of cardiac injury in predicting death. All these indicated that the level of hs-troponin I at admission was not suitable to use as a time-dependent predictor of death.

Meanwhile, we found a more serious cardiac injury occurred in non-survivors during hospitalization, as there was a significant difference in the overall hs-troponin I levels in survival group and non-survival group. The result showed the peak levels of hs-troponin I seemed to emerged in the early stage of the hospitalization (the median days: 3 days). This was accordance with the hs-troponin I release pattern in community-acquired pneumonia.18 Whether an effective respiratory supporting and antiviral therapy contribute the overall decline of the peak hs-troponin I values in these patients is still needed more investigations.

The ROC curve demonstrated the peak level of hs-troponin I was the most reliable predictor of in-hospital mortality in COVID-19 patients with cardiac injury. A possible explanation for this was that the hs-troponin I increased significantly in the days preceding the death in a portion of patients,19,20 but not all. In our study, there was about one-third of the patients presented the peak hs-troponin I levels at admission. Moreover, we found the mortality rate was very high if the level of hs-troponin I exceed 259.4 pg/mL, which was nearly 10 folds of the upper limit of the normal range. This magnitude of hs-troponin I elevation is similar with that in patients with severe sepsis and septic shock.22 Moreover, it has been reported that the peak hs-troponin I was significantly higher in the right ventricular dysfunction patients with sepsis and septic shock.22 In our study, the echocardiography results also demonstrated right ventricular dysfunction (E/
Whether there was a connection between hs-troponin I and right ventricular dysfunction in COVID-19 patients is still needed more investigations. Therefore, it is necessary to observe the dynamic changes of hs-troponin I in COVID-19 patients no matter with or without cardiac injury at admission, especially in the patients with diabetes, high CRP, and D-dimer levels. A significant elevation of hs-troponin I (>259.4 pg/mL) portends a poor prognosis in COVID-19 patients and the clinicians should pay more attention to these patients with a high hs-troponin I level (hs-troponin I > 259.4 pg/mL).

**Limitations**

The study has several limitations. First, some clinical data (such as oxygenation index) were lacking. Therefore, their role in cardiac injury might be underestimated. Second, a large proportion of severely patients were transferred from other hospitals. The severity of the disease and lack of effective treatment due to a poor clinical outcomes. Thirdly, there may be some statistical bias due to the small sample size. Therefore, more studies were still needed to a better understanding of the disease.

| Factor       | OR (95% CI) | P-value | OR (95% CI) | P-value |
|--------------|-------------|---------|-------------|---------|
| Sex          | 0.58 (0.33–1.04) | 0.067   | 0.64 (0.25–1.67) | 0.364   |
| Cardiovascular disease | 1.20 (0.68–2.12) | 0.529   | 1.14 (0.48–2.71) | 0.761   |
| Diabetes     | 1.14 (0.56–2.26) | 0.742   | 3.28 (1.20–8.98) | 0.021   |
| ARDS         | 9.85 (3.43–28.31) | <0.0001 | 12.21 (2.34–63.88) | 0.003   |
| WBC 4–10     | 1 (ref)     | 1 (ref) | 1 (ref)     | 1 (ref) |
| WBC <4       | 0.34 (0.16–0.74) | 0.007   | 0.67 (0.22–2.05) | 0.672   |
| WBC >10      | 3.23 (1.50–6.93) | 0.003   | 1.33 (0.43–4.10) | 0.619   |
| Lymphocyte   | 0.89 (0.75–1.05) | 0.166   | 0.88 (0.66–1.17) | 0.391   |
| Creatinine   | 1.12 (0.63–1.97) | 0.701   | 1.35 (0.54–3.33) | 0.521   |
| D-dimer      | 3.49 (1.90–6.41) | <0.0001 | 3.04 (1.22–7.58) | 0.017   |
| CRP          | 4.47 (2.63–7.60) | <0.0001 | 4.15 (2.19–7.90) | <0.0001 |
| hs-TNI       | 3.08 (1.56–6.08) | 0.001   | 1.67 (0.68–4.10) | 0.260   |
| IL-6         | 2.11 (0.97–4.57) | 0.058   | 3.86 (1.70–8.78) | 0.001   |
| Procalcitonin| 3.19 (1.36–7.48) | 0.008   | 2.53 (1.26–5.09) | 0.009   |

ARDS, acute respiratory distress syndrome; CI, confidence interval; CRP, C-reactive protein; hs-TNI, highly sensitive troponin I; IL-6, interleukin-6; OR, odds ratio; WBC, white blood cell.
Conflict of interest: none declared.

Supplementary material

Supplementary material is available at European Heart Journal: Acute Cardiovascular Care online.

Conflicts of interest: none declared.

References

1. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med 2020;26:450–452.
2. Bozkirin M, Hillami A, Moroni F, Annabi MS, Addad F, Ribeiro MFl, Mansour S, Zhao X, Yaarra LF, Abbate A, Vila LM, Azzalin L. Cardiovascular implications of the COVID-19 pandemic: a global perspective. Con J Cardiol 2020;36:1068–1080.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang R, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie J, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
4. Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, Zhou T, Yuan Y, Qi H, Fu S, Liu H, Xiao J, Xu Z, Yu Y, Li R, Ouyang Y, Wang R, Ren L, Hu Y, Xu D, Zhao X, Yuan S, Zheng D, Shang C. Clinical course and predictors of 60-day mortality in 231 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. Crit Care 2020;24:394.
5. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307:2526–2533.
6. van Vught LA, Klein Klouwenberg PMC, Spitoni C, Sciscia MA, Wiewel MA, Horn J, Schulz MJ, Nurmberg P, Bonten MJ, Cremer OL, van der Poll T. For the MARS Consortium. Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis. JAMA 2016;315:1469–1479.
7. Zhang C, Shi L, Wang F. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5:428–430.
8. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012;120:e179–e184.
9. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5:802–810.
10. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:811–818.
11. Guan W-J, Ni Z-y, Hu Y, Liang W-h, Ou C-Q, He J-x, Liu M, Shan H, Lei C-L, Hui DSC, Du B, Li L-j, Zeng G, Yuen K-Y, Chen R-C, Tang C-L, Wang T, Chen P-Y, Xiang J, Li S-y, Wang J-L, Liang Z-J, Peng Y-X, Wei L, Liu Y, Hu T-h, Peng P, Wang J-M, Liu J-y, Chen Z, Li G, Zheng Z-J, Qiu S-Q, Luo J, Ye C-J, Zhu S-Y, Zhong N-S. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–1720.
12. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.
13. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259–260.
14. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burkhoff D, Kumaraiah D, Rabbani LRoy, Schwartz A, Unel N. COVID-19 and cardiovascular disease. Circulation 2020;141:1648–1655.
15. Kim I-C, Kim JY, Kim HA, Han S. COVID-19-related myocarditis in a 21-year-old female patient. Eur Heart J 2020;41:1859–1859.
16. Inciardi RM, Lupo L, Zaccone G, Italia L, Raffo M, Tomasini D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adorno M, Ammirati E, Sinagra G, Lombardi CM, Metra M. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:819–816.
17. Lata A, Johnson KW, Januzi JL, Russak AJ, Panarese I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A, Chaudhry F, De Freitas JK, Fayad ZA, Pinney SP, Levin M, Charney A, Bagella E, Narula J, Glickberg BS, Nadkarni G, Mancini DM, Fuster V. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. J Am Coll Cardiol 2020;76:533–546.
18. Franken JF, van Baal L, Kappen TH, Donker DW, Horn J, van der Poll T, van Klei WA, Bonten MJ, Cremer OL, de Beer FM, Bos LDJ, Glas Gj, van
Hooijdonk RTM, Schouten LRA, Straat M, Witteveen E, Wieske L, van Vught LA, Wiewel M, Hoogendijk AJ, Huson MA, Scicluna B, Schultz MJ, Ong DSY, Klein Klouwenberg PMC, van de Groep K, Verboom D, Koster-Brouwer ME. Myocardial injury in critically ill patients with community-acquired pneumonia. A cohort study. *Ann Am Thorac Soc* 2019;16:606–612.

19. Doyen D, Moceri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. *Lancet* 2020;395:1516.

20. Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, Cheng Y, Yan J, Ping H, Zhou Q. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. *Int J Cardiol* 2020;311:116–121.

21. Klouche K, Pommet S, Amigues L, Bargnoux AS, Dupuy AM, Machado S, Serveaux-Delouis M, Morena M, Jonquet O, Cristol JP. Plasma brain natriuretic peptide and troponin levels in severe sepsis and septic shock: relationships with systolic myocardial dysfunction and intensive care unit mortality. *J Intensive Care Med* 2014;29:229–237.

22. Kim J-S, Kim M, Kim Y-J, Ryoo SM, Sohn CH, Ahn S, Kim WY. Troponin testing for assessing sepsis-induced myocardial dysfunction in patients with septic shock. *J Clin Med* 2019;8:239.