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

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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.

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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.[2–4] 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.[5] 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.[6] Liver dysfunction was diagnosed if serum alanine aminotransferase >50 U/L or aspartate aminotransferase (AST) >40 U/L during disease progression.[7] Acute kidney injury (AKI) was identified according to the Kidney Disease: Improving Global Outcomes definition.[8] Sepsis and sepsis shock were diagnosed by the 2016 Third International Consensus definition for Sepsis and Septic shock.

Electrocardiogram was performed if there was evidence of cardiac injury or arrhythmia. Whether transthoracic echocardiography was done depending on the judgement of clinicians.

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 syndrome 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%)

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
Comorbidity	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	3 (1.2%)	0	3 (1.7%)	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	3 (1.2%)	0	3 (1.7%)	0.38
Sputum	44 (18.2%)	9 (13.6%)	35 (19.9%)	0.18
Runny	3 (1.2%)	0	3 (1.2%)	0.38
Gasp	55 (22.7%)	11 (16.7%)	44 (25.0%)	0.11
Shortness of breath	49 (20.2%)	9 (13.6%)	40 (22.7%)	0.08
Chest pain	3 (1.2%)	0	3 (1.7%)	0.38
Chest tightness	68 (28.1%)	18 (27.3%)	50 (28.4%)	0.5
Palpitations	9 (3.7%)	3 (4.5%)	6 (3.4%)	0.46
Chill	17 (7.0%)	5 (7.6%)	12 (6.8%)	0.52
Difficulty breathing	25 (10.3%)	7 (10.6%)	18 (10.2%)	0.55
Muscle ache	9 (3.7%)	1 (1.5%)	8 (4.5%)	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)	89 (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.

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 differences 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 during hospitalization (Supplementary material online, *Table 1S*). Abnormal changes were more often observed in non-survivor group compared with 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 2 Laboratory results at admission

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 (114.0–220.0)	197.0 (143.5–254.5)	161.0 (109.3–208)	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.

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), 19.5 (15.0–27.0) vs. 13.0 (11.0–18.0)], lactate dehydrogenase [LDH, median (IQR), 532.5 (425.5–690.0) vs. 371.0 (277.0–439.0)], and myoglobulin [median (IQR), 111.8 (67.9–194.5) vs. 73.2 (44.7–120.6)] (*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 term 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 myoglobulin 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*).

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
Cardiotonic	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 (38.0%)	<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.

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 pg/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 μg/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 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 (days)	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				
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.

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 (*Figure 3*). 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, and myoglobin. Therefore, the peak value of hs-troponin I most accurately predicted a higher risk of in-hospital mortality.

Discussion

In this study, we systematically analysed the characters and outcomes of patients who developed cardiac injury during hospitalization. The observation showed that: (i) the disease progressed rapidly in COVID-19 patients with cardiac injury and the overall mortality was very high; (ii) diabetes, ARDS, CRP, and D-dimer are independent risk factors of mortality. Besides, the peak levels of hs-TNI instead of the hs-troponin I levels at admission predicted in-hospital death.

Cardiac injury, manifesting as an increased hs-troponin I level in serum, has been reported in COVID-19 patients, and mortality has been associated with the elevation in hs-troponin I levels >99th percentile of the upper limit of normal. In one single-centre cohort studies, cardiac lesion was present in 19.7% patients and the in-hospital mortality rate was 51.2%, compared with those without cardiac injury.[9] Another study analysed 187 COVID-19 patients and found 27.8% patients presented cardiac injury with a high mortality (59.6%).[10] 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.*[9] and Shi *et al.*[10] reported, respectively. It has been confirmed that increased age was associated with death in COVID-19 patients.[11,12] Second, cardiovascular diseases was an common comorbidity and an indicator of poor prognosis in COVID-19.[13] 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.[14] 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.[15,16] In the current study, we also observed one patients with fulminant myocarditis. Although we

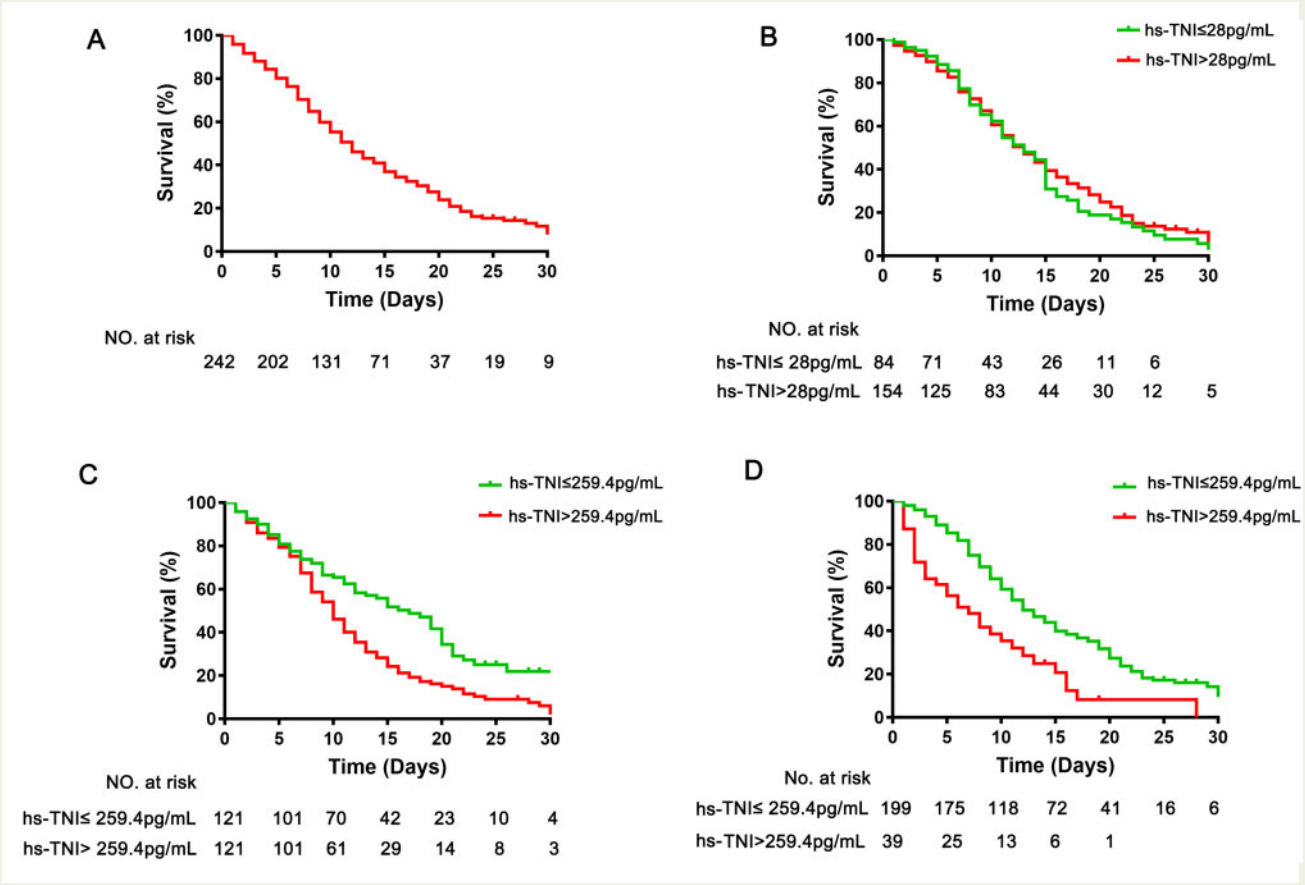


Figure 1 Kaplan–Meier analysis of survival rates in COVID-19 patients with cardiac injury. (*A*) The overall survival rate in COVID-19 patients with cardiac injury. (*B*) The survival rate in patients with hs-troponin I >28 pg/mL and hs-TNI ≤28 pg/mL at admission. (*C*) Survival rate in patients with peak hs-TNI >259.4 pg/mL and the peak hs-troponin I≤259.4 pg/mL, $P < 0.0001$ by log-rank test. (*D*) Survival rate in patients with the hs-troponin I level >259.4 pg/mL and the hs-troponin I level ≤259.4 pg/mL at admission, $P < 0.0001$ by log-rank test. hs-TNI, highly sensitive troponin I.

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.[21] Moreover, it has been reported that the peak hs-troponin I was significantly higher in the right ventricular dysfunction patients with sepsis and sepsis shock.[22] In our study, the echocardiography results also demonstrated right ventricular dysfunction (*E*/

Table 5 Risk factors associated with in-hospital death

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)	
<4	0.34 (0.16–0.74)	0.007	0.67 (0.22–2.05)	0.672
>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		
Procalcitonin	3.86 (1.70–8.78)	0.001		
CK-MB	3.19 (1.36–7.48)	0.008		
Myoglobin	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.

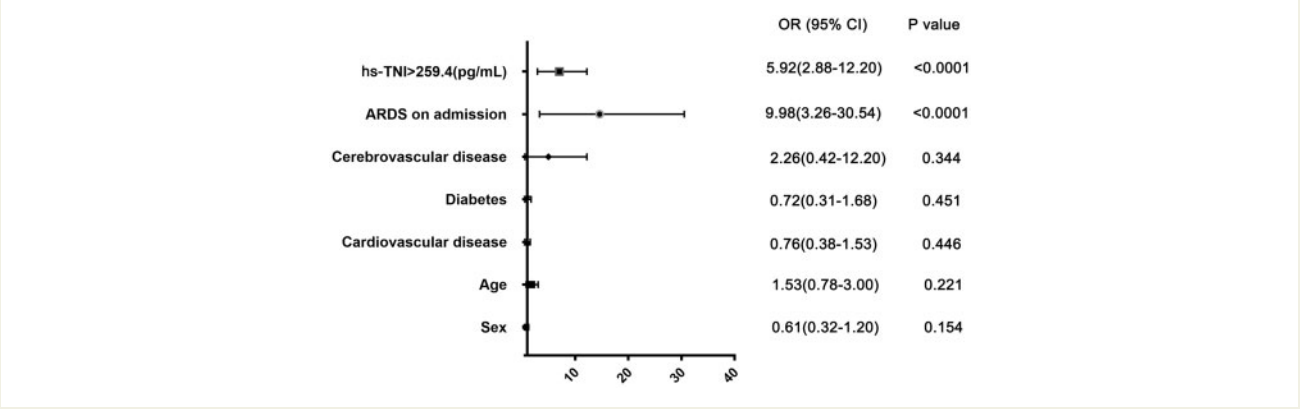
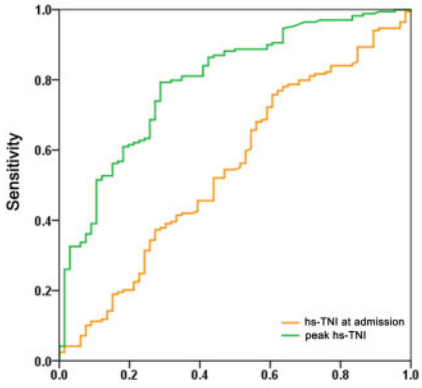


Figure 2 Multivariable Cox regression analysis of clinical indicators of in-hospital mortality in COVID-19 patients with cardiac injury. The peak hs-troponin I level >259.4 pg/mL and ARDS were risk factors. The peak hs-troponin I levels were transformed into categorical variables according to cut-off point (259.4 pg/mL). ARDS, acute respiratory distress syndrome; hs-troponin I, highly sensitive troponin I.

A < 1) in the non-survivor patients. 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.



Variables	AUC	95%CI	Sentivity	Specifivity	P value
hs-TNI at admission	0.552	0.468-0.635	0.783	0.652	0.213
peak hs-TNI	0.793	0.726-0.86	0.796	0.717	<0.0001

Figure 3 Receiver operating characteristic analysis of the clinical prediction mode. Prediction of in-hospital mortality by the peak hs-troponin I levels during hospitalization and the initial hs-troponin I levels at admission. hs-troponin I, highly sensitive troponin I.

Conclusion

Cardiac injury in COVID-19 patients is associated with a high mortality and it can be happened in any stage of the disease. Therefore, initial hs-troponin I levels cannot indicate the outcomes. COVID-19 patients with a high hs-troponin I level (>259.4 pg/mL) have a high risk of death and should be paid more attention in clinical work. Moreover, diabetes, ARDS, D-dimer, and CRP are effective predictors for in-hospital mortality in these patients.

Supplementary material

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

Conflict of interest: none declared.

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