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Original Article

Cardiac biomarkers and COVID-19: A systematic review and meta-analysis

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Objective: To systematically investigate the relationship between cardiac biomarkers and COVID-19 severity and mortality.

Methods: We performed a literature search using PubMed, Web of Science, and Google Scholar. The standardized mean difference (SMD) and 95% confidence interval (CI) were applied to estimate the combined results of 67 studies. A meta-analysis of cardiac biomarkers was used to evaluate disease mortality and severity in COVID-19 patients.

Results: A meta-analysis of 7812 patients revealed that patients with high levels of cardiac troponin I (SMD = 0.81 U/L, 95% CI = 0.14–1.48, P = 0.017), cardiac troponin T (SMD = 0.78 U/L, 95% CI = 0.07–1.49, P = 0.032), high-sensitive cardiac troponin I (SMD = 0.56 pg/mL, 95% CI = 0.51–0.81, P < 0.001), high-sensitive cardiac troponin T (SMD = 0.93 U/L, 95% CI = 0.21–1.65, P = 0.012), creatine kinase-MB (SMD = 0.54 U/L, 95% CI = 0.39–0.69, P < 0.001), and myoglobin (SMD = 0.80 U/L, 95% CI = 0.57–1.03, P < 0.001) were associated with prominent disease severity in COVID-19 infection. Moreover, 9532 patients with a higher serum level of cardiac troponin I (SMD = 0.51 U/L, 95% CI = 0.37–0.64, P < 0.001), high-sensitive cardiac troponin (SMD = 0.51 ng/mL, 95% CI = 0.29–0.73, P < 0.001), high-sensitive cardiac troponin I (SMD = 0.51 pg/mL, 95% CI = 0.38–0.63, P < 0.001), high-sensitive cardiac troponin T (SMD = 0.85 U/L, 95% CI = 0.63–1.07, P < 0.001), creatine kinase-MB (SMD = 0.48 U/L, 95% CI = 0.32–0.65, P < 0.001), and myoglobin (SMD = 0.55 U/L, 95% CI = 0.45–0.65, P < 0.001) exhibited a prominent level of mortality from COVID-19 infection.

Conclusion: Cardiac biomarkers (cardiac troponin I, cardiac troponin T, high-sensitive cardiac troponin, high-sensitive cardiac troponin I, high-sensitive cardiac troponin T, creatine kinase-MB, and myoglobin) should be more frequently applied in identifying high-risk COVID-19 patients so that timely treatment can be implemented to reduce severity and mortality in COVID-19 patients.

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Introduction

In December 2019, a novel coronavirus pneumonia (coronavirus disease 2019, COVID-19) outbreak was reported in Wuhan, China, and developed into a global pandemic. SARS-CoV-2 infection is induced by a combination of the spike protein of the virus and an angiotensin-converting enzyme 2 (ACE2), which is strongly expressed in the heart and lungs [1]; it primarily invades alveolar epithelial cells and causes respiratory symptoms. ACE2 is not only expressed in the lung, but also in the heart and blood vessels. Therefore, SARS-CoV-2 may cause acute myocardial injury and chronic cardiovascular injury [2]. Myocardial injury, as shown by increased cardiac biomarkers, was identified among the first 41 patients with COVID-19 in Wuhan [3].

Increases in lactate dehydrogenase (LDH), creatine kinase (CK), and aspartate aminotransferase (AST) can serve as markers of myocardial damage, as well as damage to the lungs, liver, kidneys, or other organs. In contrast, myoglobin (Mb), an oxygen binding protein, is mainly distributed in the cytoplasm of skeletal muscle and in the myocardium. Mb is a marker that can be detected...
early after myocardial injury. Creatine kinase-MB (CK-MB), cardiac troponin I (cTnI), and cardiac troponin T (cTnT) are also myocardial-specific isoenzymes and proteins. Increases in CK-MB, cTnl, cTnT, and hs-cTnl have high specificity in the diagnosis of myocardial injury. High-sensitive cardiac troponin I (hs-cTnI) has high sensitivity as a marker of early myocardial injury [4]. Some studies in patients with COVID-19 reported that levels of specific myocardial biomarkers including CK-MB, Mb, and cTnl were higher in patients treated in an intensive care unit (ICU) than in patients who did not require ICU care [5–7]. In this regard, identification of cardiac-specific biomarkers may reflect the severity of COVID-19 and improve outcomes by assisting with the management of COVID-19 patients.

The purpose of the present research was to investigate the relationships between cardiac-specific biomarkers (cTnl, cTnT, hs-cTn, hs-cTnl, hs-cTnT, CK-MB, and Mb) and COVID-19 severity and mortality through a meta-analysis.

**Methods**

**Search strategy**

This meta-analysis and systematic review is reported in accordance with the Preferred Reporting Items and Meta-Analyses (PRISMA) guidelines. Two researchers (An, Wang) screened the literature and chose the relevant studies using the Web of Science, PubMed, and Google Scholar for publications as of May 9, 2021, published in either English or Chinese. The following terms were used for the study search: (“SARS-CoV-2” or “COVID-19” or “Novel coronavirus 2019” or “coronavirus disease 2019”) and (“Cardiac injury” or “Cardiac biomarkers” or “Heart” or “Myoglobin” or “Cardiac troponin I” or “cTnI” or “Cardiac troponin T” or “cTnT” or “Creatine Kinase-MB” or “CK-MB” or “High-sensitive cardiac troponin I” or “hs-cTnI” or “High-sensitive cardiac troponin T” or “hs-cTnT” or “High-sensitive cardiac troponin Mb” or “hs-cTnl”). Studies in the reference list of related papers were also included in the study. IRB approval was not required.

**Selection criteria**

The inclusion criteria were as follows: (a) types of studies: observational, retrospective, prospective, case-control, or descriptive studies of cardiac biomarkers including cTnI, cTnT, hs-cTn, hs-cTnl, hs-cTnT, CK-MB, and Mb in COVID-19 patients at admission; (b) subjects: patients diagnosed with COVID-19; (c) exposure/intervention: including at least one outcome of ICU vs. non-ICU, severe vs. non-severe, or survived vs. deceased; and (d) outcome measurements: mean and standard deviation or IQR for each laboratory experiment and total sample size for events. Editorial materials, reviews, summaries of discussions, and conference abstracts were excluded.

**Definition of endpoints**

The end point of the severity of this study was the diagnosis of severe or critical cases at admission (including other cases requiring ICU care). Severe cases meet any of the following criteria: (1) increased respiratory rate (≥30 beats/min), dyspnea or cyanosis of lips; (2) decreased blood oxygen saturation ≤93% after inhalation; (3) Arterial partial pressure of oxygen (PaO2) / oxygen concentration (FiO2) ≤300 mmHg (1 mmHg = 0.133 kPa). Critical cases meet one of the following conditions: (1) respiratory failure requiring mechanical ventilation; (2) shock; or (3) complicated with organ failure requiring ICU monitoring and treatment. Or the severity in accordance with the cap guidelines of the American Thoracic Soci-
Table 1

Characteristics of the studies in the meta-analysis.

| Study (years) | Country | Mean age, year | Sample size | Severity (%) | Mortality (%) | Reported biomarkers |
|---------------|---------|----------------|-------------|--------------|---------------|---------------------|
| Du et al. [8] | China   | 57.6           | –           | 179 (12)     | cTnI          |                     |
| Shi et al. [9]| China   | 63            | –           | 671 (9)      | cTnI          |                     |
| Lanza et al. [10]| China   | 65.9           | –           | 324 (14)     | cTnI          |                     |
| Pan et al. [11]| China   | 65            | –           | 124 (72)     | cTnI          |                     |
| Zhao et al. [12]| China   | 64            | –           | 83 (59)      | cTnI          |                     |
| Ozdemir et al. [13]| Turkey   | 76            | –           | 350 (16)     | cTnI          |                     |
| Chen et al. [14]| China   | 65            | –           | 681 (15)     | cTnI          |                     |
| Luo et al. [15]| China   | 67            | –           | 146 (34)     | cTnI, Mb      |                     |
| Peiro et al. [16]| China   | 67.5          | –           | 196 (19)     | cTnI          |                     |
| Guo et al. [17]| China   | 61            | –           | 74 (62)      | cTnI, CK-MB, Mb|                     |
| Zhang et al. [18]| Turkey   | 54            | –           | 432 (95)     | cTnI, CK-MB, Mb|                     |
| Zhu et al. [19]| China   | 68            | –           | 64 (63)      | cTnI, CK-MB, Mb|                     |
| Rodriguez-Raya et al. [20]| USA | 68            | –           | 313 (32)     | hs-cTnI       |                     |
| Bemfour et al. [21]| Algeria | 62.3          | –           | 120 (31)     | hs-cTnI       |                     |
| Kocyigit et al. [22]| Turkey   | 69.6          | –           | 103 (50)     | hs-cTnI, CK-MB|                     |
| Barman et al. [23]| Turkey   | 68.5          | –           | 607 (17)     | hs-cTnI, hs-cTnI, CK-MB| |
| Luo et al. [24]| China   | 56            | –           | 403 (25)     | hs-cTnI       |                     |
| Chen et al. [25]| China   | 62            | –           | 274 (41)     | hs-cTnI       |                     |
| Chio et al. [26]| Italy    | 68.6          | –           | 405 (31)     | hs-cTnI       |                     |
| Zhang et al. [27]| China   | 64.03         | –           | 48 (35)      | hs-cTnI       |                     |
| Li et al. [28]| China   | 57            | –           | 102 (15)     | hs-cTnI       |                     |
| Viana-Llamas et al. [29]| Spain | 71            | –           | 609 (21)     | hs-cTnI       |                     |
| Shi et al. [30]| Turkey   | 57.4          | –           | 205 (31)     | hs-cTnI, CK-MB|                     |
| Wang et al. [31]| China   | 64            | –           | 344 (39)     | hs-cTnI, CK-MB|                     |
| Zhou et al. [32]| China   | 56            | –           | 191 (28)     | hs-cTnI       |                     |
| Hu et al. [33]| China   | 62            | –           | 50 (32)      | hs-cTnI       |                     |
| Cao et al. [34]| China   | 56.8          | –           | 101 (35)     | hs-cTnI, Mb   |                     |
| Primmaz et al. [35]| Switzerland | 64         | –           | 129 (19)     | hs-cTnI       |                     |
| Zhou et al. [36]| China   | 59.5          | –           | 220 (24)     | hs-cTnI       |                     |
| Larcher et al. [37]| France | 67            | –           | 32 (29)      | hs-cTnT       |                     |
| Li et al. [38]| China   | 66            | –           | 74 (19)      | CK-MB         |                     |
| Wu et al. [39]| China   | 51            | –           | 84 (52)      | CK-MB         |                     |
| Vassiliou et al. [40]| Greece | 62            | –           | 38 (26)      | CK-MB         |                     |
| Cortes-Telles et al. [41]| Mexico | 55            | –           | 200 (39)     | CK-MB         |                     |
| Aladag et al. [42]| Turkey   | 68            | –           | 50 (30)      | CK-MB         |                     |
| Ruan et al. [43]| China   | –             | –           | 150 (45)     | Mb            |                     |
| Wang et al. [44]| China   | 63            | –           | 202 (16)     | Mb            |                     |
| Deng et al. [45]| China   | 64.5          | –           | 262 (20)     | Mb            |                     |
| Wang et al. [46]| China   | 59.2          | –           | 293 (40)     | Mb            |                     |
| Zhao et al. [47]| China   | 52            | 77 (26)     | 77 (53)      | CK-MB, Mb     |                     |
| Li et al. [47]| China   | 63            | 1539 (20)  | 305 (33)     | CK-MB         |                     |
| Cao et al. [48]| China   | 50.1          | 175 (10)    | –           | cTnI          |                     |
| Li et al. [49]| China   | 50.2          | 299 (8)     | –           | cTnI          |                     |
| Chen et al. [50]| China   | 126 (16)      | –           | –           | cTnI          |                     |
| Liaqat et al. [51]| Pakistan | 144 (28)      | –           | –           | –             |                     |
| Lano et al. [52]| France  | 73.5          | 122 (37)    | –           | cTnT          |                     |
| Vial et al. [53]| Chile   | 37            | 88 (20)     | –           | cTnT          |                     |
| Han et al. [54]| China   | 63            | 59 (45)     | –           | cTnI, CK-MB   |                     |
| Deng et al. [55]| China   | 65            | 45 (60)     | –           | cTnI, CK-MB   |                     |
| Peng et al. [56]| China   | 61            | 208 (15)    | –           | cTnI, CK-MB   |                     |
| Peng et al. [57]| China   | 62            | 96 (14)     | –           | cTnI, CK-MB   |                     |
| He et al. [58]| China   | 63            | 1031 (49)  | –           | hs-cTnI       |                     |
| Taghaloo et al. [59]| Iran | 62            | 61 (36)     | –           | hs-cTnI       |                     |
| Wang et al. [60]| China   | 56            | 138 (26)    | –           | hs-cTnI, CK-MB|                     |
| Zhang et al. [60]| China   | 55            | 221 (25)    | –           | hs-cTnI, CK-MB|                     |
| Rivinus et al. [61]| Germany | 58.6         | 21 (38)     | –           | hs-cTnI       |                     |
| Xiong et al. [62]| China   | 58.5          | 116 (47)    | –           | hs-cTnI, CK-MB, Mb| |
| Ma et al. [63]| China   | 48            | 84 (24)     | –           | CK-MB         |                     |
| Wang et al. [64]| China   | 45            | 242 (15)    | –           | CK-MB         |                     |
| Gong et al. [65]| China   | 49            | 177 (15)    | –           | CK-MB         |                     |
| Wu et al. [66]| China   | 43.12         | 280 (30)    | –           | CK-MB         |                     |
| Abohmarr et al. [67]| Saudi Arabia | 46.36      | 768 (46)    | –           | CK-MB         |                     |
| Saleh et al. [68]| Germany | 67            | 40 (33)     | –           | CK-MB         |                     |
| Zeng et al. [69]| China   | 64            | 416 (8)     | –           | CK-MB, Mb     |                     |
| Zheng et al. [70]| China   | 49.4          | 88 (35)     | –           | Mb            |                     |
| Li et al. [71]| China   | 57            | 193 (34)    | –           | Mb            |                     |
| Yang et al. [72]| China   | 56            | 136 (24)    | –           | Mb            |                     |

*Serum levels of cardiac troponin I, cardiac troponin T, high-sensitive cardiac troponin I, high-sensitive cardiac troponin T, creatine kinase-MB, and myoglobin and severity of COVID-19 infection.*

*Disease severity based on the guidelines for diagnosis and management of COVID-19 by the National Health Commission of China and the World Health Organization interim guidance for COVID-19. cTnI: cardiac troponin I; cTnT: cardiac troponin T; hs-cTnI: high-sensitive cardiac troponin I; hs-cTnT: high-sensitive cardiac troponin T; CK-MB: creatine kinase-MB; Mb: myoglobin.*
95% CI = 0.51–0.81, P < 0.001), hs-cTnT (SMD = 0.93 U/L, 95% CI = 0.21–1.65, P = 0.012), CK-MB (SMD = 0.54 U/L, 95% CI = 0.39–0.69, P < 0.001), and Mb (SMD = 0.80 U/L, 95% CI = 0.57–1.03, P < 0.001) levels were significantly associated with severe COVID-19 infection. Forest plots of the severity are listed in Fig. 2.

Serum levels of cardiac troponin I, high-sensitive cardiac troponin, high-sensitive cardiac troponin I, high-sensitive cardiac troponin T, creatine kinase-MB, myoglobin, and mortality of COVID-19 infection.

In forty-one (cTnI: 12; hs-cTnI: 4; hs-cTnT: 3; CK-MB: 15; Mb: 11) studies with mortality information, 9532 patients with COVID-19 infection (deceased = 2858, survived = 6674) were analyzed. High levels of cTnl (SMD = 0.51 U/L, 95% CI = 0.37–0.64, P < 0.001), hs-cTnI (SMD = 0.51 ng/L, 95% CI = 0.29–0.73, P < 0.001), hs-cTnT (SMD = 0.51 pg/ml, 95% CI = 0.38–0.63, P < 0.001), hs-cTnT (SMD = 0.85 U/L, 95% CI = 0.63–1.07, P < 0.001), CK-MB (SMD = 0.48 U/L, 95% CI = 0.32–0.65, P < 0.001), and Mb (SMD = 0.55 U/L, 95% CI = 0.45–0.65, P < 0.001) were associated with a remarkable increase in mortality from COVID-19 infection. The forest plots of the mortality are listed in Fig. 3.

**Discussion**

Based on a comprehensive analysis of a large number of studies, this meta-analysis identified cardiac biomarkers at admission (cTnI, cTnT, hs-cTnI, hs-cTnT, CK-MB, and Mb) related to COVID-19 and analyzed their impact on the disease. One study showed that elevated serum myoglobin was associated with increased hospitalization mortality in patients, while elevated creatine kinase-MB and cardiac troponin I were not [73]. However, this study suggests that an increase in serum cTnI, hs-cTnI, hs-cTnT, CK-MB, and Mb except for cTnT is directly related to COVID-19 mortality, while a raise in serum cTnI, cTnT, hs-cTnI, hs-cTnT, CK-MB, or Mb except for hs-cTnI is directly related to the severity of COVID-19. Our meta-analysis of 16,791 samples suggests that increased cardiac biomarkers at admission in patients with COVID-19 infection are related to increased risk of disease and death. The present study’s findings of increase in mortality and severity risk among COVID-19 patients with cardiac abnormality biomarkers test are consistent with previous narrative reviews [9,74–76].

In COVID-19 infection patients, in addition to the typical clinical manifestations of the respiratory system, there is also a certain proportion of patients with cardiac involvement in whom myocardial injury is more common [77]. Published studies showed that 7.2–19.7% of COVID-19 patients [6,9,78,32] had acute heart injury, defined as cardiac troponin I above the 99th percentile. Studies also revealed that patients with heart injuries had a higher mortality rate [9,79].

There are several possible mechanisms of COVID-19-induced myocardial injury: 1. Myocardial injury that is caused by an imbal-

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**Fig. 2.** Severity of (a) cTnI, (b) cTnT, (c) hs-cTnI, (d) hs-cTnT, (e) CK-MB, and (f) Mb. SMD: standardized mean difference; CI: confidence interval; cTnI: cardiac troponin I; cTnT: cardiac troponin T; hs-cTnI: high-sensitive cardiac troponin I; hs-cTnT: high-sensitive cardiac troponin T; CK-MB: creatine kinase-MB; Mb: myoglobin.

**Publication bias and sensitivity analysis**

The results of the sensitivity analysis (I² > 50%) and publication bias (n ≥ 10) showed that overall estimates were not dependent on a single publication (Supplement Figs. S1–S15). The source of heterogeneity and publication bias were mainly due to the different measurement methods within the group.
ance of oxygen supply and demand. Severe clinical symptoms such as arrhythmia, severe tachycardia, anaemia, and respiratory failure in patients with COVID-19 are related to increased cTnI due to myocardial injury [80]; 2. Myocardial injury that is directly caused by viral invasion. The SARS-CoV-2 virus enters human cells by binding with angiotensin-converting enzyme 2 (ACE2) receptors, which is expressed in the heart and lungs. The binding of the SARS-CoV-2 virus to ACE2 receptors may be the cause of acute myocardial and lung injury [1]; 3. Excessive immune response further damages the heart, leading to ischemia and hypoxia of the heart tissue, and this overload of the heart maintains a high output and low resistance state. This leads to further ischemic injury and changes in laboratory cardiac markers, such as CK-MB, troponin I, and N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) increases [5]. Myocardial injury resulting in an excessive immune response mechanism can increase the severity of the disease and mortality.

Evidence suggested that five (12%) of 41 COVID-19 cases had virus-related myocardial injury that mainly manifested as increased high-sensitive cardiac troponin I (hs-cTnI) (>28 pg/mL) [3] and changes in laboratory cardiac biomarkers, such as increased creatine kinase-MB and cardiac troponin I, which can reflect ischemic damage of the heart [5]. There can also be progressive myocardial injury in COVID-19 patients. Clinical evidence from Wuhan showed that most of the 112 COVID-19 patients had normal troponin level at admission but then showed a gradual increase with clinical deterioration and systemic inflammation. The data displayed an increase in 42 (37.5%) patients during hospitalization and a significant increase in cardiac troponin I level in the week before death [55]. Another study reported that, four days after the onset of symptoms, the high-sensitive cardiac troponin I (hs-cTnI) level was 8.8 pg/mL in non-survivors and 2.5 pg/mL in survivors [81]. An elevated level of serum myoglobin (>306.5 μg/L) was related to greater in-hospital mortality among non-survivors [73]. Elevated hs-cTnI is also associated with increased utilization of non-invasive and invasive mechanical ventilation as well as acute respiratory distress syndrome (ARDS) [82]. However, cardiac biomarker levels at admission are also related to the mortality of COVID-19 patients. High levels of high-sensitive cardiac troponin I (hs-cTnI) (>6.126 pg/mL) and creatine kinase-MB at admission were associated with increased mortality [83]. Furthermore, creatine kinase-MB and cardiac troponin I have prognostic value in the prognosis of COVID-19 [84]. Elevated cTnT levels are common in patients with ARDS without electrocardiographic evidence of myocardial ischemia. Therefore, potential myocardial injury can be detected earlier by observing these biomarker levels at admission and comparing them to those during hospitalization. Once abnormal changes in myocardial markers are detected in COVID-19 patients at admission, the attending doctor can administer timely treatment to reduce the risk of serious disease and improve the prognosis of patients.

**Limitations**

A limitation of this study could be the source region of the sample. Although samples from different countries were included, Chinese samples were predominant in this study. Some cardiac biomarkers (hs-cTnI, hs-cTnT, and cTnI) were involved in only a limited number of studies, which may have led to some bias in
the results. For the comparison of cardiac markers and ECG, there was no valid meta-analysis due to the lack of original study data. Despite these limitations, we believe that the large sample from various publications can somewhat attenuate the limitations.

Conclusion

The meta-analysis showed a clinically meaningful relationship between serum levels of cardiac markers and the severity and mortality of COVID-19 infection. The results suggest that the cardiac biomarkers of cTnI, cTnT, hs-cTnI, hs-cTnT, CK-MB, and MB have the potential to predict poor prognosis of COVID-19, especially in critically ill patients. In conclusion, detection of elevated serum cardiac biomarkers at admission and during hospitalization is invaluable for reducing mortality and severity in COVID-19 patients.

Contributorship statement

Wen An and Quiyang Wang designed the model and the computational framework, and analyzed the data. Ju-seop Kang was involved in planning and supervised the work. Tae-Eun Kim discussed the results and commented on the manuscript.

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Competing interests

None declared.

Ethical approval

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2021.07.016.

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