Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Infection and Public Health 14 (2021) 1191–1197

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Original Article

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

Wen An [a], Ju-Seop Kang [a,*], Qiuyang Wang [b], Tae-Eun Kim [c]

[a] Department of Pharmacology & Clinical Pharmacology, College of Medicine, Hanyang University, Seoul, Republic of Korea
[b] Department of Central China Research Institute of Health, Xinxiang Medical University, Xinxiang, China
[c] Department of Clinical Pharmacology, Konkuk University Hospital, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 15 October 2020
Received in revised form 8 July 2021
Accepted 26 July 2021

Keywords:
COVID-19
Cardiac biomarkers
Meta-analysis
Severity
Mortality

ABSTRACT

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 = 0.66 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/L, 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.

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 lactose 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

Abbreviations: hs-cTnI, high-sensitive cardiac troponin I; hs-cTnT, high-sensitive cardiac troponin T; hs-cTn, high-sensitive cardiac troponin; cTnI, cardiac troponin I; cTnT, cardiac troponin T; Mb, myoglobin; CK-MB, creatine kinase-MB.

* Corresponding author.
E-mail addresses: anwen@hanyang.ac.kr (W. An), jskang@hanyang.ac.kr (J.-S. Kang), 202034@xxmu.edu.cn (Q. Wang), tekim@kuh.ac.kr (T.-E. Kim).

https://doi.org/10.1016/j.jiph.2021.07.016

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, cTnI, cTnT, and hs-cTnT 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 cTnI 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 (cTnI, cTnT, hs-cTn, hs-cTnI, 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" or "hs-cTn"). 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-cTnI, 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 ($\geq$30 beats/min), dyspnea or cyanosis of lips; (2) decreased blood oxygen saturation $\leq$ 93% after inhalation; (3) Arterial partial pressure of oxygen (PaO2) / oxygen concentration (FiO2) $\leq$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 Society (ATS). The mortality rate was determined by death regardless of other causes.

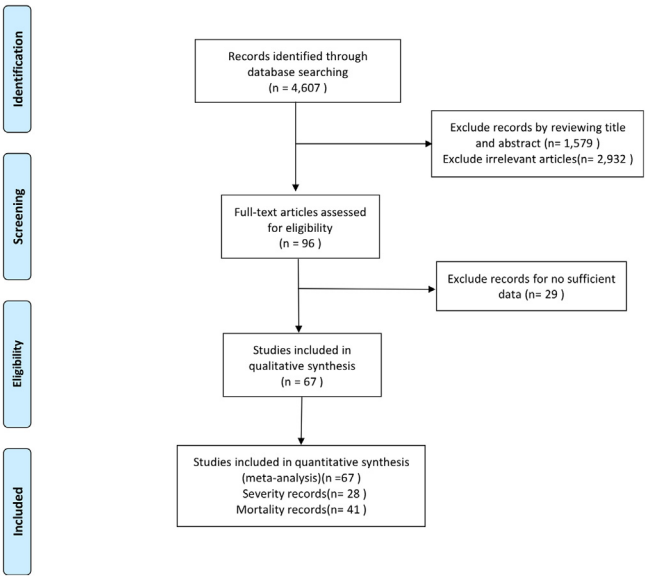

Fig. 1. Flow chart of the study selection process.

Data abstraction

Data were extracted using a pre-designed excel worksheet. Any differences were resolved by a third investigator. The following data were extracted from the studies: first author; sample size; study design; age of patients; serum levels of cTnI, cTnT, hs-cTn, hs-cTnI, hs-cTnT, CK-MB, and Mb at admission; mortality; and severity.

Statistical analysis

Standardized mean difference (SMD) and 95% confidence interval (CI) for serum levels of cTnI, cTnT, hs-cTn, hs-cTnI, hs-cTnT, CK-MB, and Mb at admission were used to estimate the pooled results. We used fixed effects to evaluate the studies. Publication bias was estimated using a funnel plot. Sensitivity analyses were conducted to assess the impact of each study on the pooled effect. A P value <0.05 was considered statistically significant. All statistical analyses were carried out using Stata version 15.1 (StataCorp, USA).

Results

Study selection and characteristics

A total of 4607 articles were retrieved based on the keywords. After screening the abstracts and titles of the studies, 96 were selected for full-text evaluation. Among them, 29 were excluded owing to the lack of sufficient data such as median (IQR) or mean (SD). The final 67 studies were included in the meta-analysis and comprised 28 articles comparing the performance of severe vs. non-severe patients, and forty-one studies conducted to compare the performance of survivors vs. non-survivors (Fig. 1). The characteristics of the included studies are listed in Table 1.

In the 28 (cTnI:8; cTnT:2; hs-cTnI:5; hs-cTnT:2; CK-MB:17; Mb:6) studies comprising 7812 COVID-19-infected patients (severe = 2225 non-severe = 5587) with severity information, increased cTnI (SMD = 0.81 U/L, 95% CI = 0.14–1.48, P = 0.017), cTnT (SMD = 0.78 U/L, 95% CI = 0.07–1.49, P = 0.032), hs-cTnI (SMD = 0.66 pg/mL,

Table 1
Characteristics of the studies in the meta-analysis.

Study (years)	Country	Mean age, year	Sample size		Reported biomarkers
			Severity (%)	Mortality (%)	
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
Tuo 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-Nava et al. [20]	USA	68	–	313 (32)	hs-cTn
Bennouar et al. [21]	Algeria	62.3	–	120 (31)	hs-cTn
Kocayigit et al. [22]	Turkey	69.6	–	103 (50)	hs-cTn, CK-MB
Barman et al. [23]	Turkey	68.5	–	607 (17)	hs-cTn, hs-cTnI, CK-MB
Luo et al. [24]	China	56	–	403 (25)	hs-cTnI
Chen et al. [25]	China	62	–	274 (41)	hs-cTnI
Ghio 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
Sit 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	56.6	–	101 (35)	hs-cTnI, Mb
Primmaz et al. [35]	Switzerland	64	–	129 (19)	hs-cTnT
Zhou et al. [36]	China	59.5	–	220 (24)	hs-cTnT
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. [7]	China	52	77 (26)	77 (53)	CK-MB, Mb
			2068 (23)	476 (38)	hs-cTnI
Li et al. [47]	China	63	1539 (20)	305 (33)	CK-MB
			–	311 (33)	Mb
Cao et al. [48]	China	50.1	175 (10)	–	cTnI
Li et al. [49]	China	50.1	299 (8)	–	cTnI
Chen et al. [50]	China	–	126 (16)	–	cTnI
Liaqat et al. [51]	Pakistan	44.6	144 (28)	–	cTnI
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
Taghiloo et al. [59]	Iran	62	61 (36)	–	hs-cTnI
Wang et al. [6]	China	56	138 (26)	–	hs-cTnI, CK-MB
Zhang et al. [60]	China	55	221 (25)	–	hs-cTnI, CK-MB
Rivinius et al. [61]	Germany	58.6	21 (38)	–	hs-cTnT
Xiong et al. [62]	China	58.5	116 (47)	–	hs-cTnT, 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
Abohamr 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

*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-cTn: high-sensitive cardiac troponin; hs-cTnI: high-sensitive cardiac troponin I; hs-cTnT: high-sensitive cardiac troponin T; CK-MB:creatine kinase-MB; Mb: myoglobin.
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.

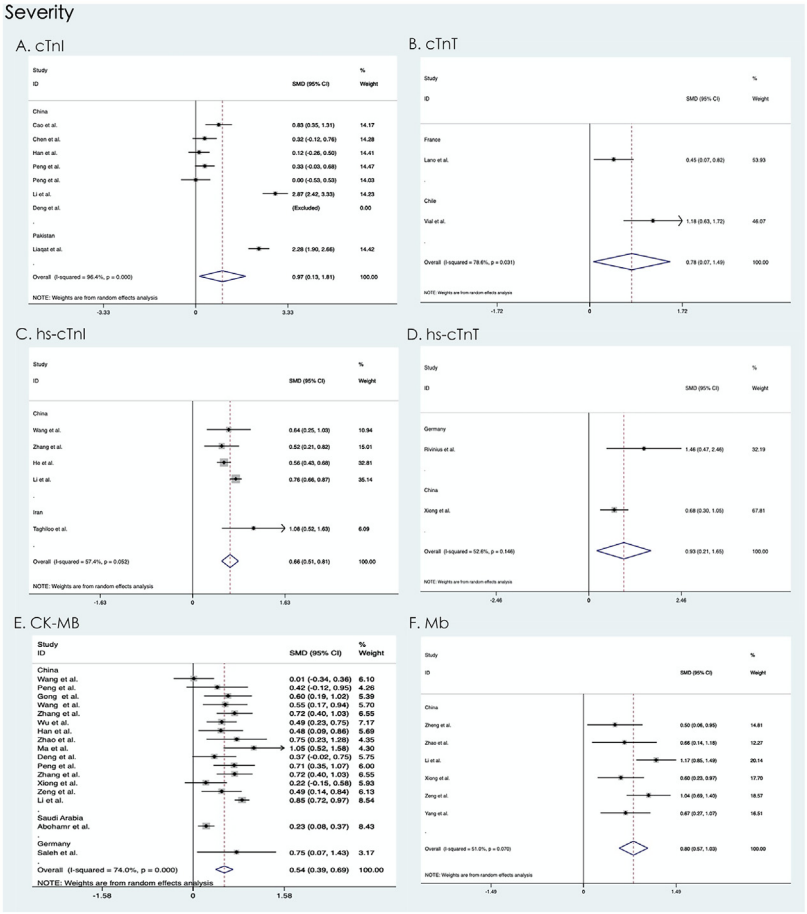

Fig. 2. Severity of (a) cTnI, (b) cTnT, (c) hs-cTnI, (d) hs-cTnT, (e) CK-MB, and (f) Mb. SMD: standardized mean difference; CI: confidence interval; cTnI: cardiac troponin I; cTnT: cardiac troponin T; hs-cTnI: high-sensitive cardiac troponin I; hs-cTnT: high-sensitive cardiac troponin T; CK-MB:creatine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

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-cTn:4; hs-cTnI:13; 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 cTnI (SMD = 0.51 U/L, 95% CI = 0.37–0.64, P < 0.001), hs-cTn (SMD = 0.51 ng/L, 95% CI = 0.29–0.73, P < 0.001), hs-cTnI (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.

Publication bias and sensitivity analysis

The results of the sensitivity analysis (I^2 > 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.

Discussion

Based on a comprehensive analysis of a large number of studies, this meta-analysis identified cardiac biomarkers at admission (cTnI, cTnT, hs-cTn, 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-cTn, 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-cTn 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-

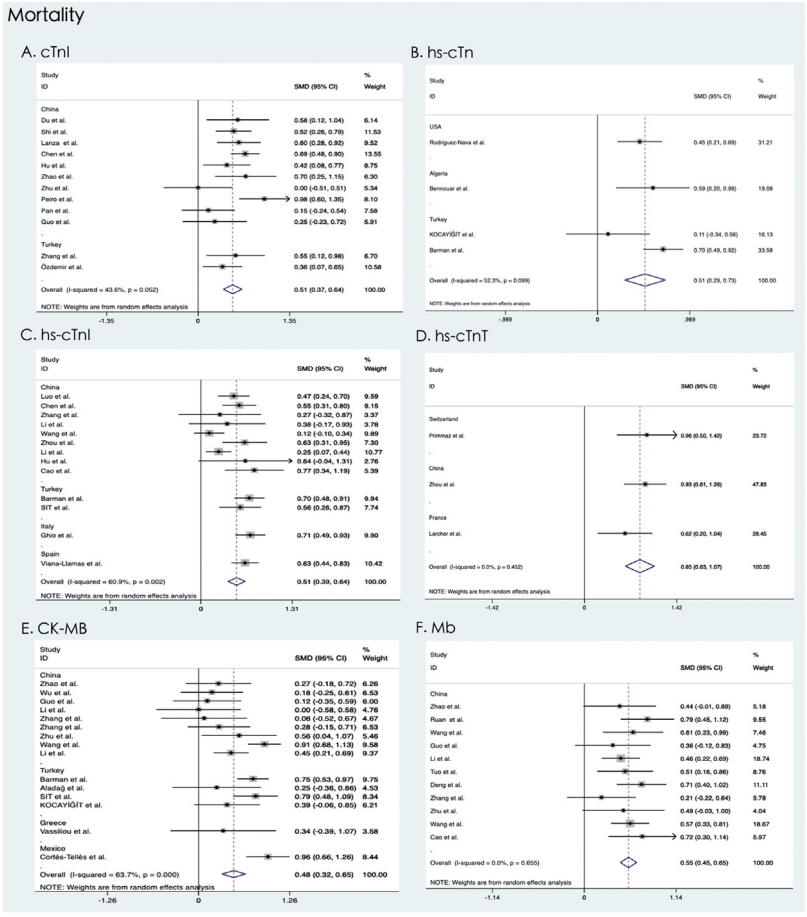

Fig. 3. The mortality of (a) cTnI, (b) hs-cTn, (c) hs-cTnI, (d) hs-cTnT, (e) CK-MB, (f) Mb. SMD: standardized mean difference; CI: confidence interval; cTnI: cardiac troponin I; hs-cTn: high-sensitive cardiac troponin; hs-cTnI: high-sensitive cardiac troponin I; hs-cTnT: high-sensitive cardiac troponin T; CK-MB: creatine kinase-MB; Mb: myoglobin.

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-cTn, hs-cTnT, and cTnT) 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-cTn, 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 Qiuyang 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.

Funding

No funding sources.

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.

References

[1] Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci 2004;25(6):291–4.
[2] Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17(5):259–60.
[3] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506.
[4] Boeddinghaus J, Nestelberger T, Koechlin L, Wussler D, Lopez-Ayala P, Walter JE, et al. Early diagnosis of myocardial infarction with point-of-care high-sensitivity cardiac troponin I. J Am Coll Cardiol 2020;75(10):1111–24.
[5] Li L, Zhou Q, Xu J. Changes of laboratory cardiac markers and mechanisms of cardiac injury in coronavirus disease 2019. Biomed Res Int 2020;2020:7413673.
[6] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323(11):1061–9.
[7] Zhao W, Zha X, Wang N, Li D, Li A, Yu S. Clinical characteristics and durations of hospitalized patients with COVID-19 in Beijing: a retrospective cohort study. medRxiv 2021, 2020.2003.2013.20035436.
[8] Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020;55(5).
[9] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5(7):802–10.
[10] Lanza GA, De Vita A, Ravenna SE, D'Aiello A, Covino M, Franceschi F, et al. Electrocardiographic findings at presentation and clinical outcome in patients with SARS-CoV-2 infection. Europace 2021;23(1):123–9.
[11] Pan F, Yang L, Li Y, Liang B, Li L, Ye T, et al. Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): a case-control study. Int J Med Sci 2020;17(9):1281–92.
[12] Zhao S, Lin Y, Zhou C, Wang L, Chen X, Clifford SP, et al. Short-term outcomes of patients with COVID-19 undergoing invasive mechanical ventilation: a retrospective observational study from Wuhan, China. Front Med (Lausanne) 2020;7:571542.
[13] Ozdemir IH, Ozlek B, Cetin N. Permanent atrial fibrillation portends poor outcomes in hospitalized patients with COVID-19: a retrospective observational study. J Electrocardiol 2021;65:113–20.
[14] Chen FF, Zhong M, Liu Y, Zhang Y, Zhang K, Su DZ, et al. The characteristics and outcomes of 681 severe cases with COVID-19 in China. J Crit Care 2020;60:32–7.
[15] Tuo H, Li W, Tang L, He B, Yao B, Mao P, et al. Cardiac biomarker abnormalities are closely related to prognosis in patients with COVID-19. Int Heart J 2021;62(1):148–52.
[16] Peiro OM, Carrasquer A, Sanchez-Gimenez R, Lal-Trehan N, Del-Moral-Ronda V, Bonet G, et al. Biomarkers and short-term prognosis in COVID-19. Biomarkers 2021;26(2):119–26.
[17] Guo H, Shen Y, Wu N, Sun X. Myocardial injury in severe and critical coronavirus disease 2019 patients. J Card Surg 2021;36(1):82–8.
[18] Zhang XB, Hu L, Ming Q, Wei XJ, Zhang ZY, Chen LD, et al. Risk factors for mortality of coronavirus disease-2019 (COVID-19) patients in two centers of Hubei province, China: a retrospective analysis. PLoS One 2021;16(1):e0246030.
[19] Zhu Q, Zhang W, Wang Q, Liu JH, Wu CH, Luo T, et al. Clinical characteristics and outcome of 64 patients with severe COVID-19. Zhonghua Jie He He Hu Xi Za Zhi 2020;43(8):659–64.
[20] Rodriguez-Nava G, Yanez-Bello MA, Trelles-Garcia DP, Chung CW, Chaudry S, Khan AS, et al. Clinical characteristics and risk factors for death of hospitalized patients with COVID-19 in a community hospital: a retrospective cohort study. Mayo Clin Proc Innov Qual Outcomes 2021;5(1):1–10.
[21] Bennouar S, Cherif AB, Kessira A, Bennouar DE, Abdi S. Vitamin D deficiency and low serum calcium as predictors of poor prognosis in patients with severe COVID-19. J Am Coll Nutr 2021;40(2):104–10.
[22] Kocayigit H, Ozmen Suner K, Tomak Y, Demir G, Kocayigit I, Yaylaci S, et al. Characteristics and outcomes of critically ill patients with covid-19 in Sakarya, Turkey: a single centre cohort study. Turk J Med Sci 2021;51(2):440–7.
[23] Barman HA, Atici A, Sahin I, Alici G, Aktas Teki E, Baycan OF, et al. Prognostic significance of cardiac injury in COVID-19 patients with and without coronary artery disease. Coron Artery Dis 2020.
[24] Luo X, Xia H, Yang W, Wang B, Guo T, Xiong J, et al. Characteristics of patients with COVID-19 during epidemic ongoing outbreak in Wuhan, China. medRxiv 2020, 2020.2003.2019.20033175.
[25] Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.
[26] Ghio S, Baldi E, Vicentini A, Lenti MV, Di Sabatino A, Di Matteo A, et al. Cardiac involvement at presentation in patients hospitalized with COVID-19 and their outcome in a tertiary referral hospital in Northern Italy. Intern Emerg Med 2020;15(8):1457–65.
[27] Zhang F, Yang D, Li J, Gao P, Chen T, Cheng Z, et al. Myocardial injury is associated with in-hospital mortality of confirmed or suspected COVID-19 in Wuhan, China: a single center retrospective cohort study. medRxiv 2020, 2020.2003.2021.20040121.
[28] Li K, Chen D, Chen S, Feng Y, Chang C, Wang Z, et al. Radiographic findings and other predictors in adults with Covid-19. medRxiv 2020, 2020.2003.2023.20041673.
[29] Viana-Llamas MC, Arroyo-Espliguero R, Silva-Obregon JA, Uribe-Heredia G, Nunez-Gil I, Garcia-Magallon B, et al. Hypoalbuminemia on admission in COVID-19 infection: an early predictor of mortality and adverse events. A retrospective observational study. Med Clin (Barc) 2021;156(9):428–36.
[30] Sit O, Oksen D, Atici A, Barman HA, Alici G, Pala AS, et al. Prognostic significance of Tp-e interval and Tp-e/QTc ratio in patients with COVID-19. Eur Rev Med Pharmacol Sci 2021;25(8):3272–8.
[31] Wang Y, Lu X, Li Y, Chen H, Chen T, Su N, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med 2020;201(11):1430–4.
[32] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62.
[33] Hu B, Wang D, Hu C, Hu M, Zhu F, Xiang H, et al. Clinical features of critically ill patients with COVID-19 infection in China. Res Square 2020.
[34] Cao Y, Han X, Gu J, Li Y, Liu J, Alwalid O, et al. Prognostic value of baseline clinical and HRCT findings in 101 patients with severe COVID-19 in Wuhan, China. Sci Rep 2020;10(1):17543.
[35] Primmaz S, Le Terrier C, Suh N, Ventura F, Boroli F, Bendjelid K, et al. Preparedness and reorganization of care for coronavirus disease 2019 patients in a Swiss ICU: characteristics and outcomes of 129 patients. Crit Care Explor 2020;2(8):e0173.
[36] Zhou S, Mi S, Luo S, Wang Y, Ren B, Cai L, et al. Risk factors for mortality in 220 patients with COVID-19 in Wuhan, China: a single-center, retrospective study. Ear Nose Throat J 2021;100(2_suppl):140S–7S.
[37] Larcher R, Besnard N, Akouz A, Rabier E, Teule L, Vandercamere T, et al. Admission high-sensitive cardiac troponin t level increase is independently associated with higher mortality in critically ill patients with COVID-19: a multicenter study. J Clin Med 2021;10(8).

[38] Li J, Xu G, Yu H, Peng X, Luo Y, Cao C. Clinical characteristics and outcomes of 74 patients with severe or critical COVID-19. Am J Med Sci 2020;360(3):229–35.
[39] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180(7):934–43.
[40] Vassiliou AG, Keskinidou C, Jahaj E, Gallos P, Dimopoulou I, Kotanidou A, et al. ICU admission levels of endothelial biomarkers as predictors of mortality in critically ill COVID-19 patients. Cells 2021;10(1).
[41] Cortes-Telles A, Lopez-Romero S, Mancilla-Ceballos R, Ortiz-Farias DL, Nunez-Caamal N, Figueroa-Hurtado E. Risk factors for mortality in hospitalized patients with COVID-19: an overview in a mexican population. Tuberc Respir Dis (Seoul) 2020;83(Suppl. 1):S46–54.
[42] Aladag N, Atabey RD. The role of concomitant cardiovascular diseases and cardiac biomarkers for predicting mortality in critical COVID-19 patients. Acta Cardiol 2021;76(2):132–9.
[43] Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to: clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46(6):1294–7.
[44] Wang L, He WB, Yu XM, Liu HF, Zhou WJ, Jiang H. Prognostic value of myocardial injury in patients with COVID-19. Zhonghua Yan Ke Za Zhi 2020;56(0):E009.
[45] Deng P, Ke Z, Ying B, Qiao B, Yuan L. The diagnostic and prognostic role of myocardial injury biomarkers in hospitalized patients with COVID-19. Clin Chim Acta 2020;510:186–90.
[46] Wang Z, Ye D, Wang M, Zhao M, Li D, Ye J, et al. Clinical features of COVID-19 patients with different outcomes in Wuhan: a retrospective observational study. Biomed Res Int 2020;2020:2138387.
[47] Li C, Jiang J, Wang F, Zhou N, Veronese G, Moslehi JJ, et al. Longitudinal correlation of biomarkers of cardiac injury, inflammation, and coagulation to outcome in hospitalized COVID-19 patients. J Mol Cell Cardiol 2020;147:74–87.
[48] Cao M, Zhang D, Wang Y, Lu Y, Zhu X, Li Y, et al. Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai, China. medRxiv 2020.
[49] Ling Y, Zhang J, Li W, Zhang X, Jin Y, et al. Clinical characteristics of SARS-CoV-2 infections involving 325 hospitalized patients outside Wuhan. Res Square 2020.
[50] Chen C, Chen C, Yan JT, Zhou N, Zhao JP, Wang DW. Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19. Zhonghua Xin Xue Guan Bing Za Zhi 2020;48(7):567–71.
[51] Liaqat A, Ali-Khan RS, Asad M, Rafique Z. Evaluation of myocardial injury patterns and ST changes among critical and non-critical patients with coronavirus-19 disease. Sci Rep 2021;11(1):4828.
[52] Lano G, Braconnier A, Bataille S, Cavaille G, Moussi-Frances J, Gondouin B, et al. Risk factors for severity of COVID-19 in chronic dialysis patients from a multicentre French cohort. Clin Kidney J 2020;13(5):878–88.
[53] Vial MR, Peters A, Perez I, Spencer-Sandino M, Barbe M, Porte L, et al. Covid-19 in South America: clinical and epidemiological characteristics among 381 patients during the early phase of the pandemic in Santiago, Chile. BMC Infect Dis 2020;20(1):955.
[54] Han Y, Zhang H, Mu S, Wei W, Jin C, Tong C, et al. Lactate dehydrogenase, an independent risk factor of severe COVID-19 patients: a retrospective and observational study. Aging (Albany NY) 2020;12(12):11245–58.
[55] Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol 2020;311:116–21.
[56] Peng Y, Meng K, He M, Zhu R, Guan H, Ke Z, et al. Clinical characteristics and prognosis of 244 cardiovascular patients suffering from coronavirus disease in Wuhan, China. J Am Heart Assoc 2020;9(19):e016796.
[57] Peng Y, M KK, Guan H, Leng L, Zhu R, Wang B, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Chin J Cardiol 2020;48:450–5.
[58] He X, Wang L, Wang H, Xie Y, Yu Y, Sun J, et al. Factors associated with acute cardiac injury and their effects on mortality in patients with COVID-19. Sci Rep 2020;10(1):20452.
[59] Taghiloo S, Aliyali M, Abedi S, Mehravaran H, Sharifpour A, Zaboli E, et al. Apoptosis and immunophenotyping of peripheral blood lymphocytes in Iranian COVID-19 patients: clinical and laboratory characteristics. J Med Virol 2021;93(3):1589–98.
[60] Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol 2020;127:104364.
[61] Rivinius R, Kaya Z, Schramm R, Boeken U, Provaznik Z, Heim C, et al. COVID-19 among heart transplant recipients in Germany: a multicenter survey. Clin Res Cardiol 2020;109(12):1531–9.
[62] Xiong S, Liu L, Lin F, Shi J, Han L, Liu H, et al. Clinical characteristics of 116 hospitalized patients with COVID-19 in Wuhan, China: a single-centered, retrospective, observational study. BMC Infect Dis 2020;20(1):787.
[63] Ma K-L, Liu Z-H, Cao C-F, Liu M-K, Liao J, Zou J-B, et al. COVID-19 myocarditis and severity factors: an adult cohort study. medRxiv 2020, 2020.2003.2019.20034124.
[64] Wang G, Wu C, Zhang Q, Wu F, Yu B, Lv J, et al. Epidemiological and clinical features of corona virus disease 2019 (COVID-19) in Changsha, China. Lancet 2020.
[65] Gong J, Ou J, Qiu X, Jie Y, Chen Y, Yuan L, et al. Multicenter development and validation of a novel risk nomogram for early prediction of severe 2019-novel coronavirus pneumonia. Lancet 2020.
[66] Wu J, Li W, Shi X, Chen Z, Jiang B, Liu J, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). J Intern Med 2020;288(1):128–38.
[67] Abohamr SI, Abazid RM, Aldossari MA, Amer HA, Badhawi OS, Aljunaidi OM, et al. Clinical characteristics and in-hospital mortality of COVID-19 adult patients in Saudi Arabia. Saudi Med J 2020;41(11):1217–26.
[68] Saleh A, Matsumori A, Abdelrazek S, Eltaweel S, Salous A, Neumann FJ, et al. Myocardial involvement in coronavirus disease 19. Herz 2020;45(8):719–25.
[69] Zeng JH, Wu WB, Qu JX, Wang Y, Dong CF, Luo YF, et al. Cardiac manifestations of COVID-19 in Shenzhen, China. Infection 2020;48(6):861–70.
[70] Zheng Y, Xu H, Yang M, Zeng Y, Chen H, Liu R, et al. Epidemiological characteristics and clinical features of 32 critical and 67 noncritical cases of COVID-19 in Chengdu. J Clin Virol 2020;127:104366.
[71] Li Z, Wu M, Yao J, Guo J, Liao X, Song S, et al. Caution on kidney dysfunctions of COVID-19 patients. medRxiv 2020, 2020.2002.2008.20021212.
[72] Yang Q, Xie L, Zhang W, Zhao L, Wu H, Jiang J, et al. Analysis of the clinical characteristics, drug treatments and prognoses of 136 patients with coronavirus disease 2019. J Clin Pharm Ther 2020;45(4):609–16.
[73] Su M, Wang Y, Peng J, Wu MJ, Deng W, Yang YS. Elevated cardiac biomarkers are associated with increased mortality for inpatients with COVID-19: a retrospective case-control study. J Clin Anesth 2020;65:109894.
[74] Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J 2020;41(22):2070–9.
[75] Qiang Z, Wang B, Garrett BC, Rainey RP, Superko HR. Coronavirus disease 2019: a comprehensive review and meta-analysis on cardiovascular biomarkers. Curr Opin Cardiol 2021;36(3):367–73.
[76] Dy LF, Lintao RCV, Cordero CP, Cabaluna ITG, Dans LF. Prevalence and prognostic associations of cardiac abnormalities among hospitalized patients with COVID-19: a systematic review and meta-analysis. Sci Rep 2021;11(1):8449.
[77] Madjid M, Solomon S, Vardeny O. ACC clinical bulletin cardiac implications of novel coronavirus (COVID-19). Am Coll Cardiol Extended Learn Suppl Tape 2020.
[78] Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020;92(7):797–806.
[79] Li L, Zhang S, He B, Chen X, Zhao Q. Retrospective study of risk factors for myocardial damage in patients with critical coronavirus disease 2019 in Wuhan. J Am Heart Assoc 2020;9(15):e016706.
[80] Sarkisian L, Saaby L, Poulsen TS, Gerke O, Hosbond S, Jangaard N, et al. Prognostic impact of myocardial injury related to various cardiac and noncardiac conditions. Am J Med 2016;129(5), 506–514 e501.
[81] B KA, Chaudhuri D. A review of acute myocardial injury in coronavirus disease 2019. Cureus 2020;12(6):e8426.
[82] Gordon JS, Drazner MH. Biomarkers of cardiac stress and cytokine release syndrome in COVID-19: a review. Curr Heart Fail Rep 2021:1–6.
[83] Wu C, Hu X, Song J, Du C, Xu J, Yang D, et al. Heart injury signs are associated with higher and earlier mortality in coronavirus disease 2019 (COVID-19). medRxiv 2020, 2020.2002.2026.20028589.
[84] Aboughdir M, Kirwin T, Abdul Khader A, Wang B. Prognostic value of cardiovascular biomarkers in COVID-19: a review. Viruses 2020;12(5).