

Cardiac injury is associated with severe outcome and death in patients with Coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of observational studies

Mohammad Parohan¹, Sajad Yaghoubi² and Asal Seraji³

Abstract

Coronavirus disease 2019 (COVID-19) is a global pandemic impacting 213 countries/territories and more than 5,934,936 patients worldwide. Cardiac injury has been reported to occur in severe and death cases. This meta-analysis was done to summarize available findings on the association between cardiac injury and severity of COVID-19 infection. Online databases including Scopus, PubMed, Web of Science, Cochrane Library and Google Scholar were searched to detect relevant publications up to 20 May 2020, using relevant keywords. To pool data, a fixed- or random-effects model was used depending on the heterogeneity between studies. In total, 22 studies with 3684 COVID-19 infected patients (severe cases=1095 and death cases=365) were included in this study. Higher serum levels of lactate dehydrogenase (weighted mean difference (WMD) =108.86 U/L, 95% confidence interval (CI)=75.93–141.79, $p<0.001$) and creatine kinase-MB (WMD=2.60 U/L, 95% CI=1.32–3.88, $p<0.001$) were associated with a significant increase in the severity of COVID-19 infection. Furthermore, higher serum levels of lactate dehydrogenase (WMD=213.44 U/L, 95% CI=129.97–296.92, $p<0.001$), cardiac troponin I (WMD=26.35 pg/mL, 95% CI=14.54–38.15, $p<0.001$), creatine kinase (WMD=48.10 U/L, 95% CI=0.27–95.94, $p = 0.049$) and myoglobin (WMD=159.77 ng/mL, 95% CI=99.54–220.01, $p<0.001$) were associated with a significant increase in the mortality of COVID-19 infection. Cardiac injury, as assessed by serum analysis (lactate dehydrogenase, cardiac troponin I, creatine kinase (-MB) and myoglobin), was associated with severe outcome and death from COVID-19 infection.

Keywords

COVID-19, heart injury, meta-analysis, systematic review

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Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic impacting 213 countries and territories around the world. As of 31 May 2020, a total of 5,934,936 COVID-19 confirmed cases and 367,166 deaths have been reported worldwide.¹ Full-genome sequencing indicated that the novel coronavirus belongs to the β genus of coronavirus, which also includes severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).²

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COVID-19 infection is caused by binding of the viral spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor following activation of the viral spike protein by transmembrane protease serine 2.³ ACE2 is highly expressed in the lung, vascular endothelium, intestinal epithelium, liver and the kidneys, providing a mechanism for the multi-organ failure that can be seen with COVID-19 infection.^{4,5} ACE2 is also expressed in the heart, counteracting the effects of angiotensin II in states with intense activation of the renin–angiotensin system such as congestive heart failure, hypertension and atherosclerosis.⁴

Several studies have reported the clinical and laboratory findings associated with cardiovascular disease in patients with COVID-19 infection.^{6–27} We are aware of no systematic review and meta-analysis that summarized available findings in this regard. Thus, in the present study, the laboratory findings and mechanism of cardiac dysfunction caused by COVID-19 infection were summarized.

Methods

Study protocol

A systematic literature search and a quantitative meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.²⁸

Search strategy

We conducted a literature search using the online databases of Scopus, PubMed, Web of Science, Cochrane Library and Google Scholar for relevant publications up to 20 May 2020. The following medical subject headings (MeSH) and non-MeSH keywords were used: ('Severe acute respiratory syndrome Coronavirus 2' OR 'SARS-CoV-2' OR 'COVID-19' OR 'Novel Coronavirus' OR '2019-nCoV') AND ('Cardiovascular Disease' OR 'Heart' OR 'Troponin I' OR 'Creatine Kinase' OR 'Creatine Kinase, MB Form' OR 'Myoglobin' OR 'Lactate Dehydrogenase'). The literature search was performed by two independent researchers (MP and AS). We also searched the reference lists of the relevant articles to identify missed studies. No restriction was applied to language and time of publication. To facilitate the screening process of articles, all search results were downloaded into an EndNote library (version X8, Thomson Reuters, Philadelphia, USA). The search strategies and keywords are presented in detail in Supplementary Material Table 1 online.

Eligibility criteria

Studies were included in this review if they met the following inclusion criteria: (1) observational studies with retrospective or prospective design; (2) all articles assessing the association between serum levels of cardiac troponin I,

creatinine kinase, creatine kinase-MB, myoglobin, lactate dehydrogenase and severe outcome or death from COVID-19 infection as the major outcomes of interest and reported median (interquartile range; IQR) or mean (SD) for serum levels of these biomarkers. Review studies, books, expert opinion articles and theses were excluded.

Data extraction and assessment for study quality

Two independent researchers (MP and SY) extracted the following data from the studies: time of publication, first author's name, age and gender of patients, sample size, study design, serum levels of cardiac troponin I, creatine kinase, creatine kinase-MB, myoglobin and lactate dehydrogenase and outcome assessment methods.

The Newcastle–Ottawa Scale was used for quality assessment of included articles.²⁹ Based on these criteria, a maximum of nine points can be awarded to each study. In this systematic review and meta-analysis, studies with the Newcastle–Ottawa Scale score of ≥ 5 were considered as high quality studies.

Statistical analysis

Median (IQR) or mean (SD) for serum levels of cardiac troponin I, creatine kinase, creatine kinase-MB, myoglobin and lactate dehydrogenase were used to estimate the effect size. The fixed- or random-effect model was used based on the heterogeneity between studies. Heterogeneity of the studies was assessed using the Cochrane Q test and I^2 statistics.³⁰ The publication bias was evaluated by the Egger's regression tests and visual inspection of funnel plot.³¹ The sensitivity analysis was performed to evaluate the effect of each study on the pooled effect size. All statistical analyses were done using the Stata 14 software package (Stata Corp., College Station, Texas, USA).

Results

Search results

Overall, 239 publications were identified in our literature search. Of these, 54 duplicates, 24 non-English, 15 reviews and 110 publications that did not fulfill our eligibility criteria were excluded, leaving 36 articles for further assessment. Out of remaining 36 articles, 14 were excluded because of the following reason: did not report median (IQR) or mean (SD). Finally, we included 22 articles in the present systematic review and meta-analysis (Figure 1).

Study characteristics

All studies were conducted in China. Twenty studies used retrospective design^{6,7,9–18,20–27} and two studies used

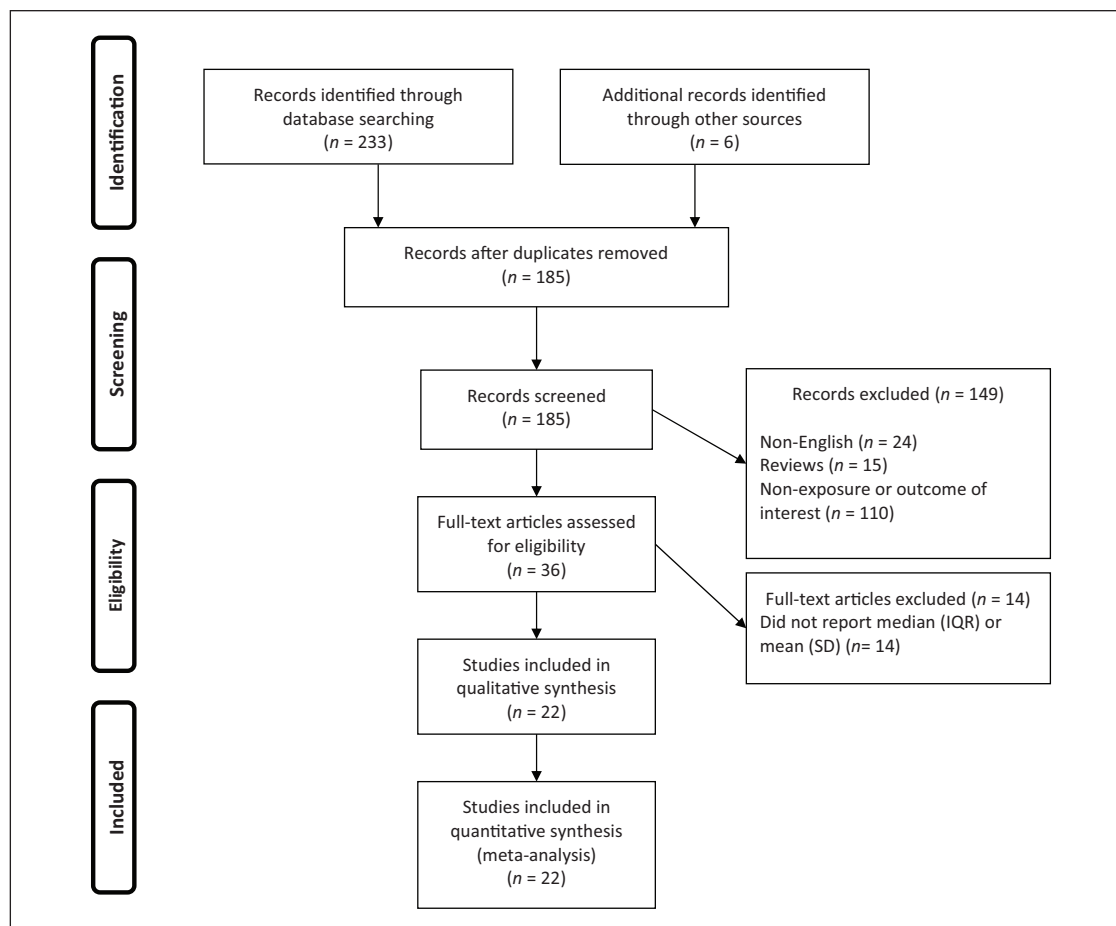


Figure 1. Flow chart of study selection.
IQR: interquartile range

prospective design.^{8,19} The sample size of studies ranged from 10 to 645 patients (mean age in severe patients: 60.95 years, mean age in non-severe patients: 46.95 years). All studies used real-time reverse transcriptase–polymerase chain reaction to confirm COVID-19 infection. The characteristics of the included studies are presented in Table 1.

Serum levels of lactate dehydrogenase, creatine kinase-MB, creatine kinase, cardiac troponin I, myoglobin and severity of COVID-19 infection

In the pooled estimate of 17 studies^{6,8–16,18,20–22,24–26} with 2467 COVID-19 infected patients (severe patients = 1095 and non-severe patients = 1372), it was shown that higher serum levels of lactate dehydrogenase (weighted mean difference = 108.86 U/L, 95% confidence interval (CI) = 75.93 to 141.79, $p < 0.001$, $I^2 = 85.4\%$, $p_{\text{heterogeneity}} < 0.001$) (Figure 2) and creatine kinase-MB (weighted mean difference = 2.60 U/L, 95% CI = 1.32 to 3.88, $p < 0.001$, $I^2 = 0.0\%$, $p_{\text{heterogeneity}} = 0.517$) (Figure 3) were associated with a significant increase in the severity of COVID-19

infection. Combined results showed that serum levels of creatine kinase (weighted mean difference = 15.10 U/L, 95% CI = -0.93 to 31.12, $p = 0.065$, $I^2 = 46.9\%$, $p_{\text{heterogeneity}} = 0.058$) (Figure 4), cardiac troponin I (weighted mean difference = 4.05 pg/mL, 95% CI = -0.20 to 8.30, $p = 0.062$, $I^2 = 0.0\%$, $p_{\text{heterogeneity}} = 0.591$) (Figure 5) and myoglobin (weighted mean difference = 21.40 ng/mL, 95% CI = -0.22 to 43.02, $p = 0.052$, $I^2 = 29.3\%$, $p_{\text{heterogeneity}} = 0.243$) (Figure 6) had no significant association with severity of the disease.

Serum levels of lactate dehydrogenase, creatine kinase-MB, creatine kinase, cardiac troponin I, myoglobin and mortality from COVID-19 infection

Six studies^{7,14,17,19,23,27} including a total of 1217 patients with COVID-19 infection (non-survivor = 365 and survivor = 852) reported mortality as an outcome measure. Combined results showed that higher serum levels of lactate dehydrogenase (weighted mean difference = 213.44 U/L, 95% CI = 129.97 to 296.92, $p < 0.001$, $I^2 = 90.4\%$,

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

Authors (year)	Design of study	Country	Mean age, years	Sample size	Sex	Pre-existing CVDs, n (%)	COVID-19 detection	Disease severity criteria	Serum levels in severe cases, mean±SD	Serum levels in mild cases, mean±SD	The time interval between laboratory tests and disease severity
Chen G et al. (2020)	Retrospective	China	56.5	21	F/M	Not reported	Real-time RT-PCR	The guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China	LDH: 537.0±202.1	LDH: 224.0±38.1	Laboratory tests and disease severity were assessed at the same time on admission
				11		CK: 214.0±177.1	CK: 64.0±19.2				
				10							
Chen T et al. (2020)	Retrospective	China	59.5	274	F/M	Death cases: 16 (14%) Recovered cases: 7 (4%)	Real-time RT-PCR	The guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China	LDH: 564.5±210.9	LDH: 268.0±75.7	Laboratory tests and disease severity were assessed at the same time on admission
				113		cTnI: 40.8±106	cTnI: 3.3±3.8				
				161		CK: 189±207.4	CK: 84.0±66.3				
Du RH et al. (2020) (a)	Retrospective	China	70.7	109	F/M	Severe cases: 15 (29.4%) Mild cases: 22 (37.9%)	Real-time RT-PCR	The patients were diagnosed according to the World Health Organization interim guidance for COVID-19	Myo: 71.4±86.4	Myo: 68.1±72.7	Laboratory tests and disease severity were assessed at the same time on admission
				51							
				58							
Du RH et al. (2020) (b)	Prospective	China	57.6	179	F/M	Death cases: 12 (57.1%) Recovered cases: 17 (10.8%)	Real-time RT-PCR	The patients were diagnosed according to the World Health Organization interim guidance for COVID-19	Myo: 162.0±218.0	Myo: 32.3±33.2	Laboratory tests and disease severity were assessed at the same time on admission
				21							
				158							
Han H et al. (2020)	Retrospective	China	49.0	213	F/M	Not reported	Real-time RT-PCR	The patients were diagnosed according to the World Health Organization interim guidance for COVID-19	cTnI: 10.0±14.8	cTnI: 10.0±7.4	Laboratory tests and disease severity were assessed at the same time on admission
				15		Myo: 75.3±66.1	Myo: 34.7±20.8				
				198							
Huang C et al. (2020)	Prospective	China	49.0	41	F/M	Severe cases: 3 (23%) Mild cases: 3 (11%)	Real-time RT-PCR	The diagnosis of pneumonia was based on clinical characteristics, chest imaging, and the ruling out of common bacterial and viral pathogens that cause pneumonia	LDH: 400.0±188.9	LDH: 281.0±91.8	Laboratory tests and disease severity were assessed at the same time on admission
				13		cTnI: 3.3±118.5	cTnI: 3.5±3.4				
				28		CK: 132.0±304.4	CK: 133.0±94.8				
Ji D et al. (2020)	Retrospective	China	44.0	208	F/M	Not reported	Real-time RT-PCR	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	LDH: 304.0±105.2	LDH: 224.0±48.9	Laboratory tests and disease severity were assessed at the same time on admission
				40							
				168							

Table 1. (Continued)

Authors (year)	Design of study	Country	Mean age, years	Sample size	Sex	Pre-existing CVDs, n (%)	COVID-19 detection	Disease severity criteria	Serum levels in severe cases, mean±SD	Serum levels in mild cases, mean±SD	The time interval between laboratory tests and disease severity
Lo IL et al. (2020)	Retrospective	China	54.0	10 Severe cases: 4 Mild cases: 6	F/M	Not reported	Real-time RT-PCR	<i>The guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China</i>	LDH: 238.0±52.0	LDH: 183.0±61.0	Laboratory tests and disease severity were assessed at the same time on admission
Mo P et al. (2020)	Retrospective	China	53.5	155 Severe cases: 85 Mild cases: 70	F/M	Severe cases: 14 (16.5%) Mild cases: 0	Real-time RT-PCR	The diagnosis of pneumonia was based on clinical characteristics and chest imaging	LDH: 293.0±178.5 CK: 89.0±59.2	LDH: 241.0±103.7 CK: 100.0±63.7	Laboratory tests and disease severity were assessed at the same time on admission
Qu R et al. (2020)	Retrospective	China	54.7	30 Severe cases: 3 Mild cases: 27	F/M	Not reported	Real-time RT-PCR	<i>The guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China</i>	LDH: 772.3±292.3	LDH: 528.1±188.6	Laboratory tests and disease severity were assessed at the same time on admission
Ruan Q et al. (2020)	Retrospective	China	58.5	150 Severe cases: 68 Mild cases: 82	F/M	Death cases: 13 (19%) Recovered cases: 0	Real-time RT-PCR	The diagnosis of pneumonia was based on clinical characteristics and chest imaging	cTnI: 30.3±151.0 Myo: 258.9±307.6	cTnI: 3.5±6.2 Myo: 77.7±136.1	Not reported
Wan S et al. (2020)	Retrospective	China	50.0	135 Severe cases: 40 Mild cases: 95	F/M	Severe cases: 6 (15%) Mild cases: 1 (1%)	Real-time RT-PCR	The patients were diagnosed according to the World Health Organization interim guidance for COVID-19	LDH: 309.0±114.4 CK: 82.0±66.6	LDH: 212.0±58.9 CK: 57.0±37.0	Laboratory tests and disease severity were assessed at the same time on admission
Wang D et al. (2020)	Retrospective	China	58.5	138 Severe cases: 36 Mild cases: 102	F/M	Severe cases: 9 (25%) Mild cases: 11 (10.8%)	Real-time RT-PCR	The patients were diagnosed according to the World Health Organization interim guidance for COVID-19	LDH: 435.0±217.8 cTnI: 11.0±15.4 CK: 102.0±140.7 CKMB: 13.0±2.9 18.0±17.0	LDH: 212.0±89.6 cTnI: 5.1±5.7 CK: 87.0±49.6 CKMB: 13.0±2.9	Laboratory tests were done on admission. The median time from admission to developing severe outcome was one day (IQR, 0–3 days)
Wang L et al. (2020)	Retrospective	China	69.0	339 Death cases: 65 Recovered cases: 274	F/M	Death cases: 21 (32.8%) Recovered cases: 32 (11.7%)	Real-time RT-PCR	<i>The guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China and the World Health Organization interim guidance for COVID-19</i>	LDH: 439.0±209.6 CK: 84.0±127.4	LDH: 286.0±100.0 CK: 60.0±42.2	Laboratory tests and disease severity were assessed at the same time on admission

(Continued)

Table 1. (Continued)

Authors (year)	Design of study	Country	Mean age, years	Sample size	Sex	Pre-existing CVDs, n (%)	COVID-19 detection	Disease severity criteria	Serum levels in severe cases, mean \pm SD	Serum levels in mild cases, mean \pm SD	The time interval between laboratory tests and disease severity
Wang Z et al. (2020)	Retrospective	China	53.7	69 Severe cases: 14 Mild cases: 55	F/M	Severe cases: 5 (36%) Mild cases: 3 (5%)	Real-time RT-PCR	<i>The guidelines for diagnosis and management of COVID-19 (3rd edition, in Chinese) by the National Health Commission of China</i>	LDH: 517.5 \pm 208.9	LDH: 207.0 \pm 68.9	Laboratory tests were done on admission. The median time from admission to developing severe outcome was one day (IQR, 0–2 days).
Wu C et al. (2020)	Retrospective	China	53.2	201 Severe cases: 84 Mild cases: 117	F/M	Severe cases: 5 (6%) Mild cases: 3 (2.6%) Death cases: 4 (9.1%) Recovered cases: 4 (10%)	Real-time RT-PCR	<i>The patients were diagnosed according to the World Health Organization interim guidance for COVID-19</i>	LDH: 396.0 \pm 148.9 CKMB: 17.0 \pm 5.5 Death cases: LDH: 484.0 \pm 161.1 CKMB: 17.0 \pm 5.2	LDH: 257.0 \pm 81.1 CKMB: 15.0 \pm 5.2 Recovered cases: LDH: 349.5 \pm 90.7 CKMB: 16.0 \pm 5.7	Laboratory tests were done on admission. The median time from admission to developing severe outcome was one day (IQR, 0–2 days). Laboratory tests were done on admission. The median time from admission to developing severe outcome was two days (IQR, 1–4 days)
Wu J et al. (2020)	Retrospective	China	43.1	280 Severe cases: 83 Mild cases: 197	F/M	Severe cases: 43 (51.8%) Mild cases: 14 (7.1%)	Real-time RT-PCR	<i>The patients were diagnosed according to the World Health Organization interim guidance for COVID-19</i>	LDH: 235.0 \pm 137.0 CK: 76.0 \pm 168.1 CKMB: 13.0 \pm 12.5	LDH: 184.0 \pm 79.2 CK: 67.0 \pm 38.5 CKMB: 9.0 \pm 5.2	Laboratory tests and disease severity were assessed at the same time on admission
Zhang X et al. (2020)	Retrospective	China	40.7	645 Severe cases: 573 Mild cases: 72	F/M	Severe cases: 5 (1%) Mild cases: 0	Real-time RT-PCR	<i>The guidelines for diagnosis and management of COVID-19 (5th edition, in Chinese) by the National Health Commission of China and the World Health Organization interim guidance for COVID-19</i>	LDH: 213.0 \pm 70.4 CK: 73.0 \pm 46.7	LDH: 174.5 \pm 64.8 CK: 62.5 \pm 27.2	Laboratory tests were done on admission. The time from onset to COVID-19 infection confirmation was 5.0 (2.5–7.0) days among patients with severe outcome
Zheng F et al. (2020)	Retrospective	China	45.0	161 Severe cases: 30 Mild cases: 131	F/M	Severe cases: 2 (6.7%) Mild cases: 2 (1.5%)	Real-time RT-PCR	<i>The guidelines for diagnosis and management of COVID-19 (5th edition, in Chinese) by the National Health Commission of China</i>	LDH: 226.2 \pm 90.1 CK: 100.3 \pm 249.8	LDH: 162.0 \pm 55.4 CK: 68.7 \pm 50.4	Laboratory tests and disease severity were assessed at the same time on admission

Table 1. (Continued)

Authors (year)	Design of study	Country	Mean age, years	Sample size	Sex	Pre-existing CVDs, n (%)	COVID-19 detection	Disease severity criteria	Serum levels in severe cases, mean±SD	Serum levels in mild cases, mean±SD	The time interval between laboratory tests and disease severity
Zhou B et al. (2020)	Retrospective	China	65	34 Severe cases: 8 Mild cases: 26	F/M	Not reported	Real-time RT-PCR	<i>The guidelines for diagnosis and management of COVID-19</i> (4th edition, in Chinese) by the National Health Commission of China	LDH: 513.0±168.1 cTnI: 46.8±196.7 CK: 199.0±154.1 CKMB: 13.0±11.1 Myo: 101.7±113.3	LDH: 287.0±62.9 cTnI: 4.8±4.4 CK: 88.0±59.2 CKMB:	Laboratory tests and disease severity were assessed at the same time on admission
Zhou F et al. (2020)	Retrospective	China	60.5	191 Severe cases: 54 Mild cases: 137	F/M	Death cases: 13 (24%) Recovered cases: 2 (1%)	Real-time RT-PCR	<i>The guidelines for diagnosis and management of COVID-19</i> (6th edition, in Chinese) by the National Health Commission of China and the World Health Organization interim guidance for COVID-19	LDH: 521.0±226.7 cTnI: 22.2±57.4 CK: 39.0±97.4	LDH: 253.5±73.3 cTnI: 3.0±3.2 CK: 18.0±29.3	Laboratory tests and disease severity were assessed at the same time on admission
Zhou Y et al. (2020)	Retrospective	China	41.8	17 Severe cases: 5 Mild cases: 12	F/M	Not reported	Real-time RT-PCR	<i>The guidelines for diagnosis and management of COVID-19</i> (5th edition, in Chinese) by the National Health Commission of China	LDH: 157.0±72.6	LDH: 180.0±135.5	Laboratory tests and disease severity were assessed at the same time on admission

COVID-19; coronavirus disease 2019; F: female; M: male; CVD: cardiovascular disease; RT-PCR: reverse transcriptase–polymerase chain reaction; LDH: lactate dehydrogenase; CK: creatine kinase; cTnI: cardiac troponin I; Myo: myoglobin; CKMB: creatine kinase-MB; IQR: interquartile range

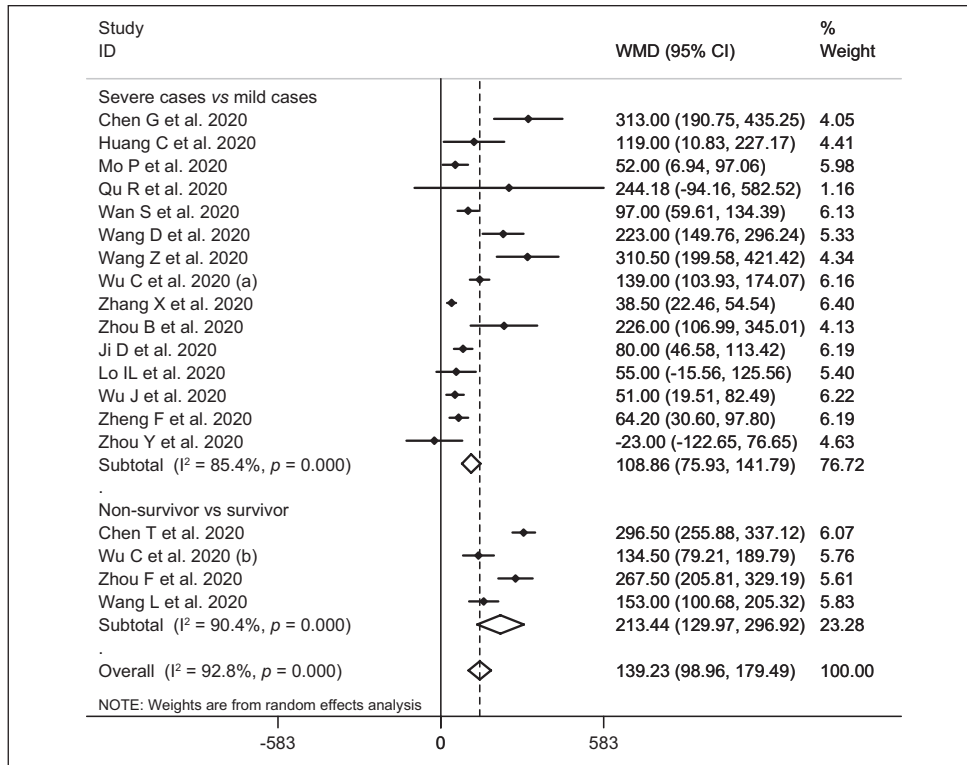


Figure 2. Forest plot for the association between serum levels of lactate dehydrogenase and severe outcome or death from COVID-19 infection using random-effects model. WMD: weighted mean difference; CI: confidence interval

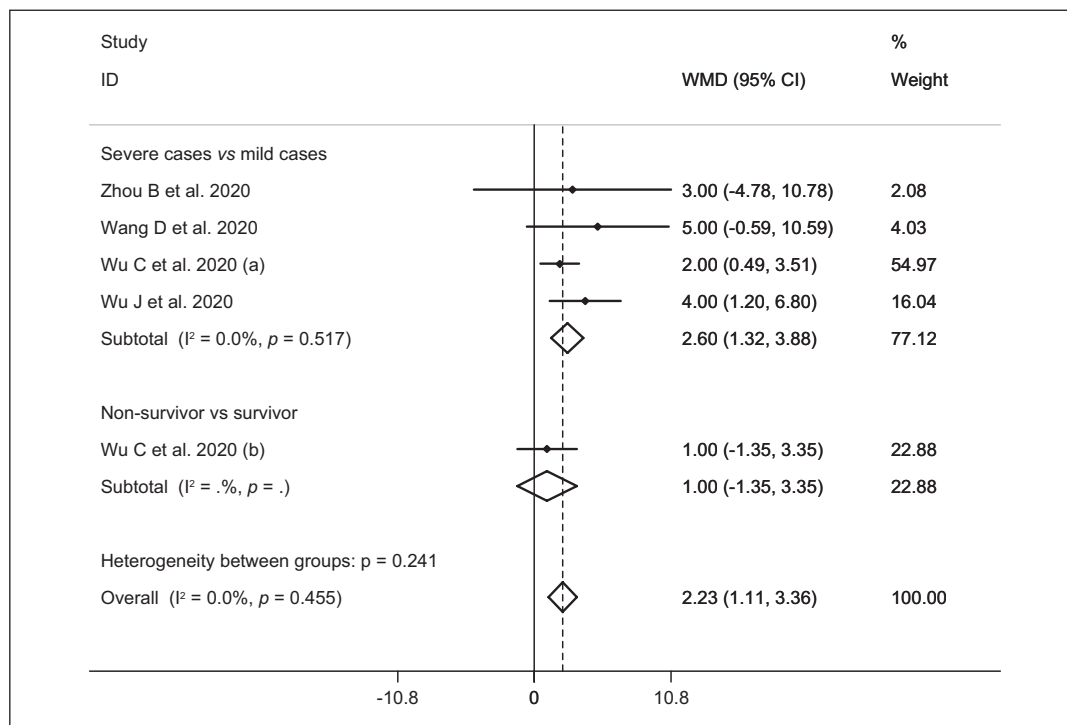


Figure 3. Forest plot for the association between serum levels of creatine kinase-MB and severe outcome or death from COVID-19 infection using fixed-effects model. WMD: weighted mean difference; CI: confidence interval

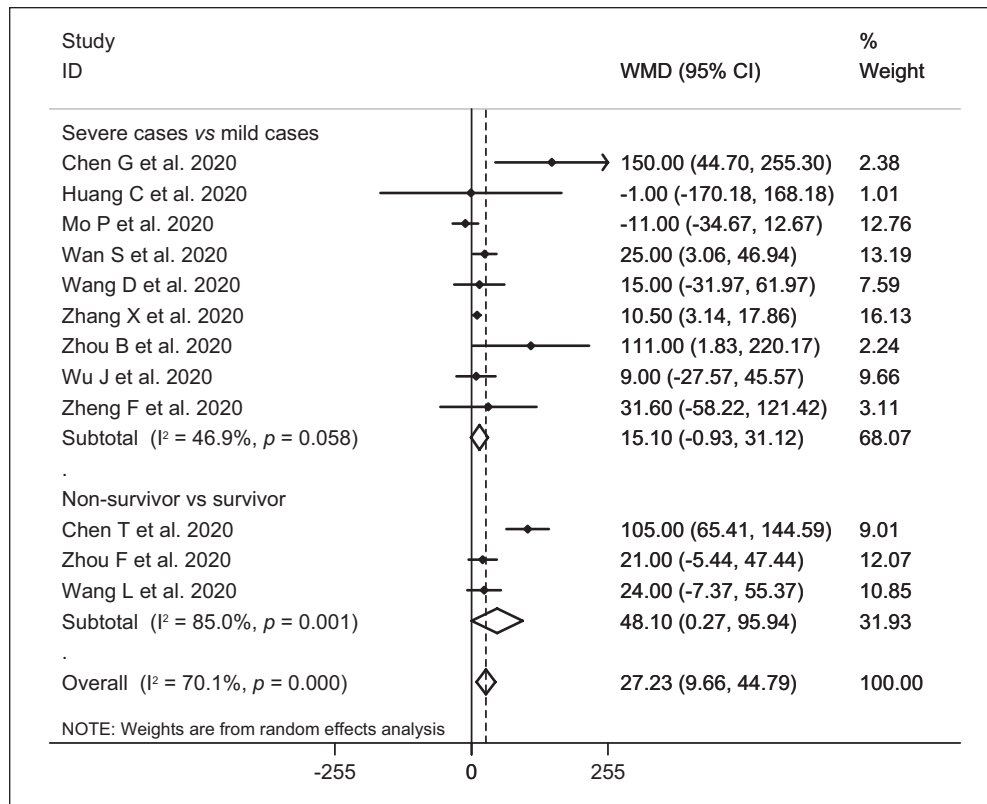


Figure 4. Forest plot for the association between serum levels of creatine kinase and severe outcome or death from COVID-19 infection using random-effects model. WMD: weighted mean difference; CI: confidence interval

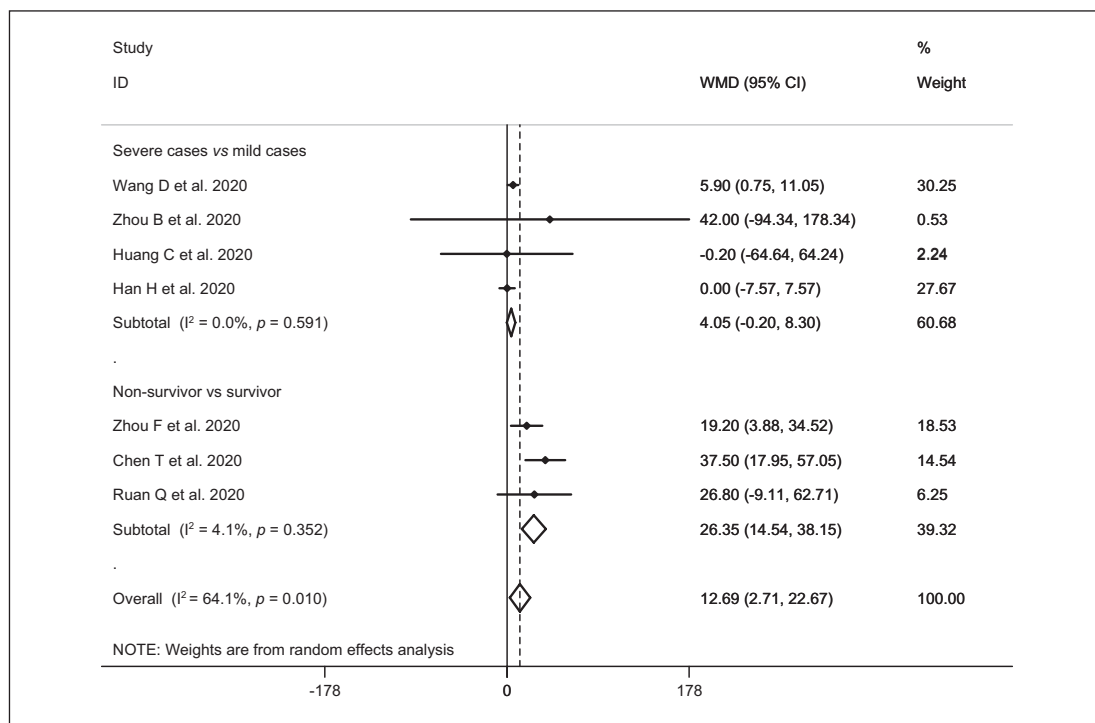


Figure 5. Forest plot for the association between serum levels of cardiac troponin I and severe outcome or death from COVID-19 infection using random-effects model. WMD: weighted mean difference; CI: confidence interval

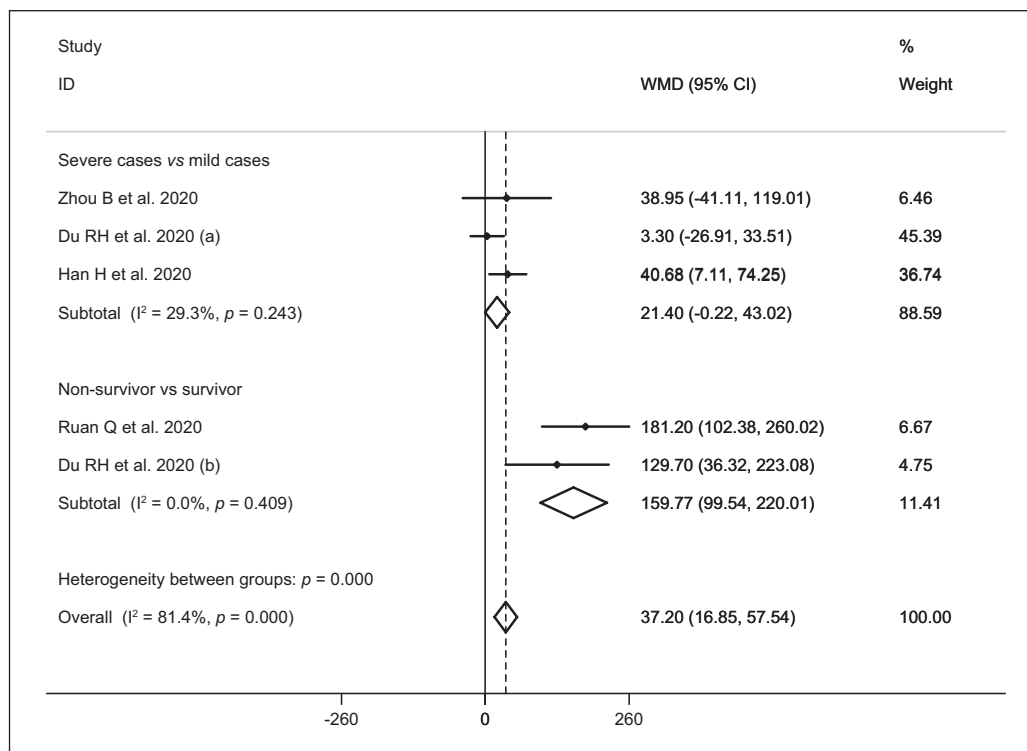


Figure 6. Forest plot for the association between serum levels of myoglobin and severe outcome or death from COVID-19 infection using fixed-effects model.

WMD: weighted mean difference; CI: confidence interval

$p_{\text{heterogeneity}} < 0.001$) (Figure 2), creatine kinase (weighted mean difference = 48.10 U/L, 95% CI = 0.27 to 95.94, $p = 0.049$, $I^2 = 85.0\%$, $p_{\text{heterogeneity}} = 0.001$) (Figure 4), cardiac troponin I (weighted mean difference = 26.35 pg/mL, 95% CI = 14.54 to 38.15, $p < 0.001$, $I^2 = 4.1\%$, $p_{\text{heterogeneity}} = 0.352$) (Figure 5) and myoglobin (weighted mean difference = 159.77 ng/mL, 95% CI = 99.54 to 220.01, $p < 0.001$, $I^2 = 0.0\%$, $p_{\text{heterogeneity}} = 0.409$) (Figure 6) were associated with a significant increase in the mortality of COVID-19 infection.

Publication bias and sensitivity analysis

Based on the results of Egger's test, we found no evidence of publication bias for lactate dehydrogenase ($p=0.454$), creatine kinase-MB ($p=0.367$), creatine kinase ($p=0.220$), cardiac troponin I ($p=0.961$) and myoglobin ($p=0.748$). Furthermore, findings from sensitivity analysis indicated that overall estimates did not depend on a single publication (Supplementary Figures 1–5).

Discussion

Findings from this review supported the hypothesis that heart injury is associated with severe outcome and death in patients with COVID-19 infection. To our knowledge, this

study is the first meta-analysis to assess the association between serum levels of cardiac biomarkers and severity of COVID-19 infection.

Our results are partially in line with previous narrative reviews.^{32–36} Previously, cardiac lesion has been reported as a risk factor for severe outcome and death in SARS and MERS.^{37–40}

Older age (≥ 65 years), male gender and presence of comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease and cancer are known to be the major risk factors for COVID-19 mortality.⁴¹ Presence of myocarditis and cardiac injury (defined by elevated cardiac troponin I levels greater than the 99th percentile upper limit) are other independent risk factors associated with mortality.^{27,42}

COVID-19 may either exacerbate underlying cardiovascular diseases and/or induce new cardiac pathologies. Previous studies have shown that the incidence of acute cardiac injury in severe COVID-19 patients and death cases ranged from 5% to 31% and 59% to 77%, respectively.^{7,8,11,17} Contributory mechanisms include hemodynamic changes, induction of pro-coagulant factors and systemic inflammatory responses that are mediators of atherosclerosis directly contributing to plaque rupture through local inflammation, which predispose to thrombosis and ischemia.^{43–45}

In addition, ACE2, the receptor for COVID-19, is expressed on vascular endothelial cells and myocytes,^{46,47} so there is at least theoretical potential possibility of direct

cardiovascular involvement by the virus. In theory this could have a potential impact on patients taking angiotensin-converting enzyme inhibitors, resulting in greater risk of acquiring COVID-19 infection and increased severity of the disease.³³

Other suggested mechanisms of COVID-19 related heart injury include cytokine storm, mediated by increased pro-inflammatory cytokine production by innate immunity after COVID-19 infection, and hypoxia induced excessive intracellular calcium leading to myocyte apoptosis.^{17,36}

COVID-19 appears to affect the myocardium and cause myocarditis.⁴⁸ Interstitial mononuclear inflammatory infiltrates in myocardium has been documented in death cases of COVID-19.⁴⁸ Furthermore, cases of myocarditis with reduced systolic function have been reported after COVID-19 infection.³² Cardiac injury is likely associated with ischemia and/or infection-related myocarditis and is an important prognostic factor in patients with COVID-19 infection.

Cardiac biomarker studies suggest a high prevalence of heart injury in death cases of COVID-19 infection.^{48,42} Mortality was significantly higher in patients with high serum levels of lactate dehydrogenase, cardiac troponin I, creatine kinase and myoglobin. The mechanism of cardiac biomarker elevation in COVID-19 infection is not fully understood. The underlying pathophysiology is suggestive of a cardio-inflammatory response as many severe COVID-19 infected patients demonstrate concomitant elevations in cardiac biomarkers and acute phase reactants such as C-reactive protein.³³ The rise in cardiac biomarkers with other inflammatory biomarkers raises the possibility that this reflects cytokine storm and may present clinically as fulminant myocarditis.³³

Until effective and specific antiviral therapies against COVID-19 become available, the treatment of COVID-19 infection will be primarily based on the treatment of complications and supportive care. Treatment of cardiovascular complications should be based on optimal use of guideline-based therapies. As with other triggers for cardiovascular events, the use of β -blockers, statins and antiplatelet agents are recommended per practice guidelines.

The present study has some limitations. First, interpretation of findings might be limited by the small sample size. Second, this study did not include data such as body weight, body mass index and smoking history, which are potential risk factors for disease severity.

Conclusion

In this meta-analysis of 3534 patients with confirmed COVID-19, cardiac injury as assessed by serum analysis (lactate dehydrogenase, cardiac troponin I, creatine kinase (-MB) and myoglobin) was associated with severe outcome and death from COVID-19 infection. With the fast-moving development of COVID-19 across the globe and with better

understanding of the mechanisms of cardiac involvement in patients with COVID-19 infection, cardiac biomarkers can be utilized as an indicator of improving response due to cardioprotective intervention or as a metric of a worsening clinical scenario.

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Conflict of interest

The authors have no conflicts of interest to declare.

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