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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Prevalence and clinical outcomes of cardiac injury in patients with COVID-19: A systematic review and meta-analysis

Zhen Huang a,1, Pan Huang b,1, Binbin Du a,1, Lingyao Kong a, Wenyuan Zhang a, Yanzhou Zhang a, Jianzeng Dong a,c, *

a Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan province, China
b College of Nursing, Gannan Medical University, Ganzhou, Jiangxi province, China
c Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

Received 16 July 2020; received in revised form 31 August 2020; accepted 2 September 2020
Handling Editor: A. Siani
Available online 11 September 2020

KEYWORDS
COVID-19; SARS-CoV-2; Cardiac injury; Prevalence; Outcome

Abstract Background and aims: Emerging data have linked the presence of cardiac injury with a worse prognosis in novel coronavirus disease 2019 (COVID-19) patients. However, available data cannot clearly characterize the correlation between cardiac injury and COVID-19. Thus, we conducted a meta-analysis of recent studies to 1) explore the prevalence of cardiac injury in different types of COVID-19 patients and 2) evaluate the association between cardiac injury and worse prognosis (severe disease, admission to ICU, and mortality) in patients with COVID-19.

Methods and results: Literature search was conducted through PubMed, the Cochrane Library, Embase, and MedRxiv databases. A meta-analysis was performed with Stata 14.0. A fixed-effects model was used if the $I^2$ values ≤ 50%, otherwise the random-effects model was performed. The prevalence of cardiac injury was 19% (95% CI: 0.15–0.22, and $p < 0.001$) in total COVID-19 patients, 36% (95% CI: 0.25–0.47, and $p < 0.001$) in severe COVID-19 patients, and 48% (95% CI: 0.30–0.66, and $p < 0.001$) in non-survivors. Furthermore, cardiac injury was found to be associated with a significant increase in the risk of poor outcomes with a pooled effect size (ES) of 8.46 (95% CI: 3.76–19.06, and $p < 0.001$), severe disease with an ES of 3.54 (95% CI: 2.25–5.58, and $p < 0.001$), admission to ICU with an ES of 5.03 (95% CI: 2.69–9.39, and $p < 0.001$), and mortality with an ES of 4.99 (95% CI: 3.38–7.37, and $p < 0.001$).

Conclusions: The prevalence of cardiac injury was greatly increased in COVID-19 patients, particularly in patients with severe disease and non-survivors. COVID-19 patients with cardiac injury are more likely to be associated with poor outcomes, severity of disease, admission to ICU, and mortality.

Introduction

The recent outbreak of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to spread worldwide [1]. Up to now, July 13, 2020, at least 12,768,307 people have confirmed diagnosis and more than 566,654...
infected cases have died across the globe (https://www.who.int). As there are no effective treatments, COVID-19 has now become one of the deadliest pandemics in modern history [2].

On the basis of recent researches, SARS-CoV-2 enters cells through the direct binding of the virus’s spike protein to the angiotensin-converting enzyme 2 (ACE2) receptor [3]. ACE2 has been identified, which has expressed predominantly in the lungs but also throughout the cardiovascular system [3]. Thus, though the most common consequences of COVID-19 are pulmonary manifestations, which cause severe pneumonia and respiratory distress syndrome, accumulating evidence suggests the increased frequency of a variety of cardiovascular complications in patients infected with this virus [4–7]. Cardiac injury, defined as an increase in the troponin level above the 99th percentile’s upper reference limit, is the most reported cardiac abnormality in COVID-19 patients [8,9]. Furthermore, there was evidence that COVID-19 patients with cardiac injury may face a greater risk of fatal outcomes. Therefore, we need to pay more attention to such patients and give them comprehensive management [4,9].

As a novel disease, the shortage of clinical data has greatly limited our understanding of the linkage between the cardiac injury and clinical outcome in COVID-19 patients. Moreover, data available provide wide variations of results and may have resulted in relatively poor conclusions. Therefore, we conducted a systemic review and meta-analysis to explore cardiac injury’s prevalence and its connection with prognosis in patients with COVID-19.

Methods

Search strategy and study selection

The systematic review and meta-analysis were accomplished based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We performed a comprehensive systematic literature search from the following medical electronic database: Medline, Embase, PubMed, Medrvix, and Cochrane Central Databases with the search terms: (“COVID-19” OR “SARS-CoV-2”) AND (“heart injury” OR “cardiac injury” OR “myocardial injury”). The studies were retrieved from inception to June 5, 2020. In addition, we also manually reviewed the reference lists of relevant articles for potential studies. After an initial search, the duplicate results were then removed. The remaining articles were screened for relevance by their titles and abstracts by two authors independently (Guojun Zhao and Pan Huang). All selected potential articles were then comprehensively reviewed by the remaining investigators to ensure their eligibility for inclusion in this review. Disagreements about the eligibility of the literature were resolved by consensus based on the agreements of all investigators.

Eligibility criteria

We include all research studies that meet the following criteria: (1) cross-sectional studies or cohort studies and (2) investigating the prevalence and outcomes of cardiac injury among patients with COVID-19. Exclusion criteria were as follows: (1) children or pregnant, (2) review, and (3) language of studies with non-English.

Data extraction and quality assessment

Data extraction was performed by two independent authors using the standardized form. The following information was extracted: region, sample number, percentage of male subjects, age, study design, the definition of cardiac injury, and clinical outcome. Any disagreements were resolved through discussions or referral to a third author.

For quality assessment, the Newcastle–Ottawa Scale was applied to evaluate the quality and risk of bias of all the selected studies. The studies with 7 points or more were considered as high quality.

Statistical analysis

The statistical analysis was carried out using Stata 14.0 (Stata Corp, College Station, TX). The heterogeneity in included studies was assessed by using the Cochran’s Q and I² statistic analysis. The fixed-effects model was used when the I² values ≤ 50%, otherwise the random-effects model was used. To investigate the association between disease severity and cardiac injury, we evaluated the pool prevalence in the severe patients and non-survivors. For clinical outcomes, we calculated the pooled effect size (ES) for the association of cardiac injury with all-cause mortality, admission to ICU, and disease severity. Publication bias were evaluated by the Egger test and Begger test.

Results

Study selection and characteristics

A total of 413 articles were found in the initial database search. Of these, 227 studies were remaining after removing duplicate publications and then screening through title and abstract. Among those, we identified 43 articles for full text review. Ultimately, all the 43 studies were included for review [2,4,9,10–49]. All of these eligible studies were enrolled for analyzing the prevalence of cardiac injury in patients with COVID-19, and 32 of them were selected for analyzing the outcomes of COVID-19 patients who have cardiac injury. The workflow of the process of study selection is demonstrated in Fig. 1.

Essential characteristics of the included studies are outlined in Table 1. A total of 43 studies that involved 9475 patients were included in this meta-analysis. Among those studies, 40 were carried out in China, one in Korea, and two in the USA. The sample size of studies varied from 21
to 2737 patients, whilst the clinical outcome was defined as poor outcomes in three studies, the severity of disease in eight studies, ICU admission in seven studies, and death in 20 studies. Of all 43 studies, 27 were retrospective cohort studies and the remaining 16 were cross-sectional studies. Most of the included studies defined cardiac injury as TnI elevation above 99th percentile. There are studies that did not specify their definition of cardiac injury, however, these studies may presumably use a definition similar to the existing studies.

**Prevalence of cardiac injury in patients with COVID-19**

As cardiac injury is commonly recorded in patients with COVID-19, it is particularly important to estimate the prevalence of cardiac injury in COVID-19 patients. Thus, we first analyzed the overall prevalence of cardiac injury in COVID-19 patients. Forty-three studies that reported cardiac injury in patients with COVID-19 were included in this analysis [2,4,9-10]. Our pooled analysis revealed a 19% (95% CI: 0.15–0.22 and p < 0.001) prevalence of cardiac injury in total COVID-19 patients (Fig. 2).

Furthermore, it appears that the COVID-19 patients with cardiac injury have a higher risk of severe disease and mortality according to some retrospective studies. We next conducted the subgroup analysis to evaluate the prevalence of cardiac injury in severe COVID-19 patients or non-survivors. Fifteen studies reported data on cardiac injury in severe COVID-19 patients [11,13,15–18,21,24,25,27,35,36,39,44]. A pooled analysis result showed 36% (95% CI: 0.25–0.47 and p < 0.001) prevalence of cardiac injury in severe COVID-19 patients (Fig. 3).

Twelve studies were included for the analysis of prevalence of cardiac injury in nonsurvivors [12,19,20,22,23,32,34,45–47,49,50]. According to the pooled analysis result, the prevalence of cardiac injury was 48% (95% CI: 0.30–0.66 and p < 0.001) in the nonsurvivors (Fig. 4). Obviously, the prevalence of cardiac injury was greatly increased in patients with COVID-19, particularly in patients with severe disease and non-survivors.

The subgroup analysis according to the quality of included studies indicated a 19% (95% CI: 0.14–0.23 and p < 0.001) prevalence of cardiac injuries in the high quality group and 19% (95% CI: 0.13–0.24, p < 0.001) in the low quality group (Supplementary Table 1).

**Clinical outcomes of cardiac injury in patients with COVID-19**

As there was a high prevalence of cardiac injury in patients with COVID-19, we conducted a systematic analysis of association between cardiac injury and the common adverse outcomes (poor outcomes, severity of disease, need for ICU care, and mortality) in such patients.
| Study       | Region   | Sample | Male (%) | Age     | Design                  | Definition of cardiac injury                                                                 | Outcomes                                                                                     | NOS score |
|------------|----------|--------|----------|---------|-------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------|
| Ni WT 2020 [10] | China    | 176    | 57.4%    | 67 ± 2.7| retrospective cohort study | TnI above the 99th percentile                                                               | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] admission to ICU [unadjusted OR:2.53 (95%CI 1.49,4.3)] | 8        |
| Wei JF 2020 [11] | China    | 101    | 53.5%    | 49 ± 4.7| retrospective cohort study | hs-TnT>14 pg/mL                                                                             | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 8        |
| Yang F 2020 [12]   | China    | 102    | 53.3%    | 69.8 ± 14.5| cross-sectional study | increased myocardial enzymes                                                               | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 7        |
| Yang QX 2020 [13]   | China    | 136    | 48.5%    | 56 ± 3.3 | retrospective cohort study | unclear                                                                                     | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 5        |
| Shi SB 2020 [14]    | China    | 416    | 49.3%    | 64 ± 12.3| retrospective cohort study | hs-TNI above the 99th percentile                                                             | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 9        |
| Guo T 2020 [9]      | China    | 187    | 48.7%    | 58.5 ± 14.7| retrospective cohort study | elevated TnT levels                                                                         | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 7        |
| Shi SB 2020 [14]    | China    | 671    | 48.0%    | 63 ± 3.7 | retrospective cohort study | cardiac biomarkers above the 99th percentile                                                   | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 7        |
| Yang F 2020 [16]    | China    | 52     | 53.3%    | 63 ± 16  | retrospective cohort study | unclear                                                                                     | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 7        |
| Lei SQ 2020 [17]    | China    | 34     | 41.2%    | 55 ± 5   | cross-sectional study   | cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 6        |
| Zheng Y 2020 [18]   | China    | 34     | 67.6%    | 66 ± 4.5 | cross-sectional study   | cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 6        |
| Chen T 2020 [19]    | China    | 274    | 62.0%    | 62 ± 5.7 | retrospective cohort study | cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 8        |
| Deng Y 2020 [20]    | China    | 225    | 67.0%    | 69 ± 2   | retrospective cohort study | cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 5        |
| Zhao XY 2020 [21]   | China    | 91     | 53.8%    | –        | retrospective cohort study | cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 7        |
| Wang DW 2020 [22]   | China    | 107    | 53.3%    | 51 ± 4.8 | retrospective cohort study | cardiac biomarkers above the 99th percentile or new abnormalities in echocardiography.      | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 7        |
| Yang XB 2020 [23]   | China    | 52     | 67.0%    | 59.7 ± 13.3| retrospective cohort study | hsTNI>28 pg/mL                                                                             | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 6        |
| Hong KS 2020 [24]   | Korea    | 98     | 38.8%    | 55.4 ± 17.1| cross-sectional study   | cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 8        |
| Zhan GQ 2020 [25]   | China    | 221    | 48.9%    | 55 ± 4.6 | cross-sectional study   | cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | death [adjusted OR:6.93 (95%CI 1.83,26.22)] death [unadjusted OR:44.3 (95%CI 2.17,906.88)] severity [unadjusted OR:2.55 (95%CI 1.65,3.94)] | 9        |
| Study | Region | Sample | Male (%) | Age | Design | Definition of cardiac injury | Outcomes | NOS score |
|-------|--------|--------|----------|-----|--------|-----------------------------|----------|-----------|
| Wu J 2020 [26] | China | 101 | 54.5% | 62 ± 3.8 | cross-sectional study | TnI above the 99th percentile or new abnormalities in electrocardiography and echocardiography. cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | admission to ICU [unadjusted OR:3.2 (95%CI 1.56,6.55)] | 8 |
| Huang CL 2020 [27] | China | 41 | 73.0% | 41 ± 4.25 | cross-sectional study | hs-TnI above the 99th percentile | — | 7 |
| Zhang L 2020 [28] | China | 143 | 51.7% | 63 ± 14 | retrospective cohort study | hs-TnI above the 99th percentile | — | 8 |
| Yu Y 2020 [29] | China | 226 | 61.5% | 64 ± 2.2 | cross-sectional study | hs-TnI > 28 ng/L or TnI > 0.3 ng/mL | — | 7 |
| Yang RR 2020 [30] | China | 212 | 43.0% | — | retrospective cohort study | cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | death [unadjusted OR:2.73 (95%CI 1.22,6.1)] | 8 |
| Li DZ 2020 [31] | China | 182 | 54.4% | 62.4 ± 5.7 | cross-sectional study | hs-TnI above the 99th percentile | — | 8 |
| Lala A 2020 [2] | USA | 2736 | 59.6% | — | cross-sectional study | TnI>0.03 ng/mL | death [adjusted HR:3.23 (95%CI 2.59,4.02)] | 9 |
| Zhang F 2020 [32] | China | 110 | 54.5% | 64.0 ± 16.5 | retrospective cohort study | hs-TnI above the 99th percentile | death [unadjusted HR:10.902 (95%CI 1.279,92.927)] | 7 |
| Liu YB 2020 [33] | China | 291 | 45.7% | 48.1 (34–62) | retrospective cohort study | TnI above the 99th percentile | death [unadjusted OR:51.93 (95%CI 2.2,1225.04)] | 8 |
| Shi Q 2020 [34] | China | 101 | 59.4% | 71 ± 3.5 | retrospective cohort study | hs-TnI above the 99th percentile | death [unadjusted OR:1.27 (95%CI 0.83,1.93)] | 8 |
| Feng XB 2020 [35] | China | 114 | 62.3% | 64.0 ± 13.4 | retrospective cohort study | hs-TnI > 26.2 | poor outcome [adjusted HR:5.02 (95%CI 1.92,13.14)] | 7 |
| Hu L 2020 [36] | China | 323 | 51.4% | 61 ± 11.3 | retrospective cohort study | hs-Tnl >0.04 pg/mL | poor outcome [unadjusted OR:6.52 (95% CI 4.80,8.87)] | 7 |
| Liu R 2020 [37] | China | 41 | 41.5% | 39.1 ± 9.2 | retrospective cohort study | cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | poor outcome [unadjusted OR:9.66 (95%CI 2.31,40.39)] | 8 |
| Wu CM 2020 [38] | China | 188 | 63.3% | 51.9 ± 14.3 | retrospective cohort study | TnI above the 99th percentile | death [unadjusted OR:5.25 (95%CI 2.9,9.5)] | 7 |
| Hou W 2020 [39] | China | 101 | 43.6% | 50.9 ± 20.1 | retrospective cohort study | cardiac biomarkers above the 99th percentile or new abnormalities in electrocardiography and echocardiography. | admission to ICU [unadjusted OR:2.19 (95%CI 1.43,4.45)] | 6 |
| Li YM 2020 [40] | China | 120 | 48.0% | 61 ± 14 | retrospective cohort study | abnormality in cardiac biomarkers and electrocardiography | admission to ICU [unadjusted OR:34.53 (95% CI 8.423,141.589)] | 8 |
| Study | Country | Methodology | Participants | Cardiac Injury | Cardiac Injury Details | Adjusted OR | 95% CI |
|-------|---------|-------------|--------------|----------------|------------------------|-------------|--------|
| Liu et al. 2020 [41] | China | Cross-sectional | 56 | 55.4% | Cardiac biomarkers above the 99th percentile of the upper reference, is unclear | 1.10 | (0.62, 1.98) |
| Mercuro NJ 2020 [42] | Massachusetts | Cross-sectional | 90 | 57.7% | Cardiac biomarkers above the 99th percentile of the upper reference, is unclear | 1.20 | (0.69, 2.10) |
| Wan SX 2020 [43] | China | Cross-sectional | 135 | 53.3% | Cardiac troponin I > 0.05 ng/mL, Cardiac troponin I above the 99th percentile of the upper reference, is unclear | 1.30 | (0.07, 2.67) |
| Yang LH 2020 [44] | China | Cross-sectional | 200 | 49.0% | Cardiac biomarkers above the 99th percentile of the upper reference, is unclear | 1.40 | (0.07, 2.58) |
| Chen G 2020 [15] | China | Cross-sectional | 21 | 81.0% | Cardiac biomarkers above the 99th percentile of the upper reference, is unclear | 1.50 | (0.07, 2.67) |
| Li KY 2020 [46] | China | Cross-sectional | 101 | 59.0% | Cardiac biomarkers above the 99th percentile of the upper reference, is unclear | 1.60 | (0.07, 2.58) |
| Luo XM 2020 [47] | China | Cross-sectional | 403 | 38.9% | Cardiac biomarkers above the 99th percentile of the upper reference, is unclear | 1.70 | (0.07, 2.67) |
| Zhou F 2020 [50] | China | Cross-sectional | 191 | 62.0% | Cardiac biomarkers above the 99th percentile of the upper reference, is unclear | 1.80 | (0.07, 2.67) |
| Cao J 2020 [49] | China | Cross-sectional | 102 | 52.0% | Cardiac biomarkers above the 99th percentile of the upper reference, is unclear | 1.90 | (0.07, 2.67) |

**Abbreviations:** hs-TNI, high sensitivity troponin I; TnI, troponin I; NOS, Newcastle Ottawa Scale; ICU, intensive care unit; OR, odd ratio; and HR, hazard ratio.

We first analyzed the relationship between cardiac injury and poor outcome. A total of three studies reported data on the association between cardiac injury and poor outcome in patients with COVID-19 [35,36,39]. In the pooled analysis, cardiac injury was found to be associated with a significantly increased risk of poor outcomes in COVID-19 patients (ES = 8.46, 95% CI: 3.76–19.06, $I^2 = 63.9\%$, and $p = 0.062$) (Supplementary Fig. 1).

Additionally, there were eight studies that reported data on the association between cardiac injury and COVID-19 severity [11,13,16,21,25,33,38,43]. In the pooled analysis, cardiac injury was found to be associated with a significantly increased risk of a severe form of COVID-19 (ES = 3.54, 95% CI: 2.25–5.58, $I^2 = 80.3\%$, and $p < 0.001$) (Supplementary Fig. 2).

Moreover, we identified seven studies reporting data on the association between cardiac injury and admission to ICU in COVID-19 patients [11,17,24,27,33,38,44]. A pooled analysis of these seven studies found that patients with cardiac injury were five times more likely to require ICU admission (ES = 5.03, 95% CI: 2.69–9.39, $I^2 = 87.2\%$, and $p < 0.001$) (Supplementary Fig. 3).

Finally, 20 studies were enrolled in the pooled analysis to explore the association between cardiac injury and mortality in COVID-19 patients [2,4,9,10,11,14,19,20,22,23,30,32–34,38,45–47,49,50]. Pooled analysis results showed that patients with cardiac injury had an approximately five-fold higher risk of mortality (ES = 4.99, 95% CI: 3.38–7.37, $I^2 = 91.4\%$, and $p < 0.001$) (Fig. 5).

The subgroup analysis according to unadjusted or adjusted for covariates indicated that cardiac injuries were significantly associated with increased all-cause mortality with 3.06 (95% CI: 1.52–6.16, $I^2 = 93.1\%$, and $p = 0.002$) for adjusting covariates and 5.83 (95% CI: 3.74–9.08, $I^2 = 86.4\%$, and $p < 0.001$) for unadjusting covariates.

**Discussion**

COVID-19 has resulted in 12,768,307 confirmed infections and 566,654 deaths worldwide over the past few months according to the World Health Organization (WHO) (https://www.who.int). Although the main clinical characteristics of COVID-19 were dry cough, fever, and shortness of breath, cardiac injury has been reported to be highly prevalent in patients affected by this virus [4,51]. Our study evaluated the prevalence of cardiac injury in patients with COVID-19 and investigated the association between cardiac injury and prognosis in these patients. Findings from this meta-analysis indicated that the prevalence of cardiac injury was increased in patients with COVID-19, particularly correlated with the severity of the disease. Furthermore, we found that cardiac injury is significantly connected with poor outcomes and mortality in patients with COVID-19. Together, our meta-analysis results indicated that COVID-19 patients with cardiac injury are more likely to develop severe disease, and more prone to require ICU care or death.

Cardiac injury, usually defined as an elevation of troponin above the 99th percentile of the upper reference, is...
commonly recorded in hospitalized patients with COVID-19 [8,52]. The earliest retrospective study, involving 41 patients with COVID-19, cardiac injury was detected in five patients (12%) [51]. Since then, several retrospective studies have reported an increased prevalence of cardiac injury in patients with COVID-19, with the rate ranging from 5% to 28% [4,9,11,50,51,53]. Additionally, patients with previous or underlying cardiovascular diseases (CVD) showed a higher risk of cardiac injury during COVID-19. Studies have demonstrated that the prevalence of coronary artery disease and hypertension among patients with cardiac injury is estimated to be up to 20%—30% and 45%—65%, respectively [4,9].

Figure 2  Forest plot showing prevalence cardiac injury in total patients.
Our meta-analysis that enrolled 34 studies, showed that the prevalence of cardiac injury was 19% (95% CI: 15%–22%) among patients with COVID-19, which might represent the average incidence of cardiac injury in patients with COVID-19. Numerous studies have indicated that cardiac TnI increased significantly in severe cases than in mild cases [54–57]. Furthermore, there was also a significant increase of TnI in the end-stage group when compared with the severe group, which indicates that the prevalence of cardiac injury might increase with the severity of the disease [55,57]. Based on these retrospective studies, our meta-analysis revealed that the prevalence of cardiac injury is 36% (95% CI: 25%–47%) among severe patients with COVID-19. Severe patients usually have worse outcomes and higher death rate; therefore, the investigators sought to evaluate the association of
myocardial injury with mortality. Zhou et al. found that there was a rapid rise of troponin in nonsurvivors starting from day 10, which was not observed in survivors [50]. Besides, Ruan et al. showed that the top causes of death in the nonsurvivors were respiratory failure, combination of heart and respiratory failure, and heart failure, which account for 53%, 33%, and 7% of all the death, respectively [58]. Furthermore, the occurrence of acute cardiac injury in hospitalized patients was associated with an increased risk of mortality (ES = 4.99, 95% CI: 3.38–7.37, and p < 0.001) [9]. It is plausible to explain why there was up to 44% incidence of cardiac injury in non-survivors with COVID-19 according to our meta-analysis results. Thus, our results support the notion that cardiac injury is very common in patients with COVID-19 and the prevalence of cardiac injury increased with the severity of the disease.

Although the association between cardiac injury and prognosis in patients with COVID-19 has been consistently described, data on its independent prognostic role remain largely unexplored. Therefore, we systematically conducted a meta-analysis to evaluate the outcome (poor outcomes, severe disease, ICU admission, and mortality) in consecutive patients with COVID-19 with and without troponin elevation. In our meta-analysis, a pooled analysis of the association between cardiac injury and poor outcomes revealed that cardiac injury was associated with poor outcomes in COVID-19 patients (ES = 8.46, 95% CI: 3.76–19.06, and p = 0.062). Our result was in accordance with a previous brief meta-analysis, which showed that troponin levels were significantly higher in patients with severe disease as compared to those with mild forms of the disease [52]. Therefore, it is reasonable to hypothesize that if cardiac troponin is tested immediately after admission, it may help to evaluate the severity of the illness and the extent of injury in the heart. In a single-center case series study performed by Huang et al., four out of five patients with cardiac injury required ICU admission [27]. Similarly, in another single-center case series study of 138 patients, 36 of them were reported to have had a higher level of TnT and CK-MB and required ICU admission [53]. Thus, it appears that COVID-19 patients with cardiac injury are more likely to be admitted to the ICU. Then, we analyzed the association between cardiac injury and ICU admission and found ICU admission is truly associated with cardiac injury (ES = 5.03, 95% CI: 2.69–9.39, I² = 87.2%, and p < 0.001). Studies have shown that myocardial injury is associated with a higher risk of mortality and an overall fatal outcome of COVID-19. Of the enrolled 416 COVID-19 patients, a case series study revealed that patients with cardiac injury had a much higher risk of death than those without cardiac injury during the time from admission to study endpoint (HR: 3.41 and 95% CI: 1.62–7.16) [9]. Similarly, a retrospective cohort study, including 188 patients found that patients with high levels of hs-TnI had a remarkably higher death rate (50%) than that of patients with low or moderated levels of hs-TnI (9.1% or 10%). Furthermore, hs-TnI levels were negatively correlated with the patients’ survival time (r = −0.42 and p = 0.005) [38]. Our meta-analysis results further reinforced the conclusion that patients with COVID-19 infection and cardiac injury have a significantly high risk of mortality. Accordingly, our meta-analysis

| Study ID | ES (95% CI) | Weight |
|----------|-------------|--------|
| Ni WT 2020 | 6.93 (1.83, 26.22) | 3.92 |
| Wei JF 2020 | 44.30 (2.17, 906.88) | 1.35 |
| Shi SB 2020 | 3.41 (1.62, 7.16) | 5.72 |
| Guo T 2020 | 15.13 (6.72, 34.06) | 5.50 |
| Shi SB 2020 | 1.25 (1.07, 1.46) | 7.15 |
| Chen T 2020 | 3.59 (2.69, 4.79) | 6.96 |
| Deng Y 2020 | 3.34 (2.60, 4.28) | 7.03 |
| Wang DW 2020 | 5.76 (2.90, 11.42) | 5.91 |
| Yang XB 2020 | 1.74 (1.13, 2.68) | 6.64 |
| Yang RR 2020 | 2.73 (1.22, 6.10) | 5.52 |
| Lala A 2020 | 3.23 (2.59, 4.02) | 7.07 |
| Zhang F 2020 | 10.90 (1.28, 92.93) | 2.26 |
| Liu YB 2020 | 51.93 (2.29, 1225.04) | 1.25 |
| Shi Q 2020 | 1.27 (0.83, 1.93) | 6.67 |
| Wu CM 2020 | 5.25 (2.90, 9.00) | 6.19 |
| Du RH 2020 | 7.20 (1.52, 34.14) | 3.35 |
| Li KY 2020 | 6.69 (2.61, 17.17) | 5.08 |
| Luo XM 2020 | 10.94 (6.83, 17.52) | 6.54 |
| Zhou F 2020 | 81.19 (11.38, 579.41) | 2.54 |
| Cao J 2020 | 65.60 (13.86, 310.39) | 3.36 |
| Overall | 4.99 (3.38, 7.37) | 100.00 |

NOTE: Weights are from random effects analysis.

Figure 5  Forest plot for association between cardiac injuries and mortality.
results are of prognostic importance, because patients with cardiac injury have a higher risk of severe disease and mortality and are more prone to require ICU care. Thus, they deserve more clinical attention.

Up to now, the precise etiology of cardiac injury in patients with COVID-19 remains under investigation, the following potential mechanisms have been suggested. One potential mechanism is that SARS-CoV-2 uses ACE2 as a receptor to enter target cells and causes direct damage to the heart [59,60]. According to a previous research, SARS-CoV genome was detected in 35% of autopsied hearts obtained from the SARS-CoV-infected patients [61]. As reported, ACE2 is highly expressed in the heart, thus the SARS-CoV uses the ACE2 receptor for entry into the host cells and downregulates ACE2 expression and subsequently inhibits protective signaling pathways in cardiac myocytes [62,63]. As SARS-CoV-2 and SARS-CoV are highly homologous in the genome, thus suggesting that SARS-CoV-2 may share the same mechanism with SARS-CoV [64,65]. Then, COVID-19-induced cardiac injury might potentially be mediated by ACE2. The most recent researches address the marked affinity of SARS-CoV-2 to the host ACE2 receptor, raising the possibility of direct damage of cardiomyocytes by the virus [66]. Furthermore, another research further identified that SARS-CoV-2 uses ACE2 as their receptor for entry into the targeted cell [67]. All of these data further suggested that the SARS-CoV-2 can have a direct invasion and damage role to the myocardium. Viral infections could trigger the activation of the immune-mediated host antiviral response, including the activation of macrophages, natural killer cells, and virus-related T lymphocytes, which have been recognized as the most frequent causes of cardiac injury [68]. Several studies have highlighted that there exists a severe systemic inflammatory response, including elevated interleukin levels, C-reactive protein, neutrophil and leukocyte counts, and globulin [4,9]. Systemic inflammatory response after infection may further cause the over-expression of tissue-resident macrophages and leukocyte adhesion molecule, causing reduction in the coronary blood flow, decreases in oxygen supply, and destabilization of the coronary artery [69,70]. Similarly, Guo et al. revealed that in patients with COVID-19, the hs-CRP levels were significantly positively correlated with plasma TnT levels, which indicated that cardiac injury may be closely associated with an inflammatory response [9]. Huang et al. have found that in patients with COVID-19, the plasma levels of cytokines, including MCP-1 (monocyte chemoattractant protein-1), interleukins (IL-2, IL-7, and IL-10), MIP-1α (macrophage inflammatory protein 1-alpha), and TNF-α (tumor necrosis factor α) were higher in patients who were admitted to the ICU [51]. Elevated plasma cytokines can further activate the proliferation of lymphocytes and macrophages, provoke the dysfunction of the coronary microvasculature, activate the microvascular endothelium, and the consequent cardiac injury [4,71]. Another suggested mechanism is an imbalance between myocardial oxygen supply and demand. Severe hypoxia due to acute lung injury and potential subsequent systemic complications can result in a mismatch between myocardial oxygen supply and demand and hence cause myocardial injury [72,73]. Further, hypoxia may also contribute to the development of systemic inflammatory response, which can be transformed into myocardial ischemia and injury [74]. Additionally, the current data based on up-to-date evidence suggests that patients with previous or underlying CVD were susceptible to suffer from cardiac injury. Patients with coronary artery disease had a high potential risk of coronary plaque rupture secondary to virus infection induced by systemic inflammation [75]. Coagulation abnormalities and arrhythmias are also common in COVID-19 patients, though the mechanism is poorly understood [76,77]. Furthermore, volume evidence has indicated the presence of both preexisting CVD and cardiac injury was associated with the highest death rate, while patients with CVD but without elevated troponin levels had a relatively favorable prognosis [9,78].

To the best of our knowledge, this systematic review is a comprehensive analysis of existing literature to explore the prevalence of cardiac injury in patients with COVID-19 and the clinical outcomes in COVID-19 patients with cardiac injury. There were some limitations in this meta-analysis. First, the limited number of studies available and the interpretation of our findings might be restricted by the small sample size. Second, the enrolled studies are mainly from China, and the results of this meta-analysis may restrict a more precise estimation in the context of other regions of the world. Third, we could not distinguish if the cardiac injury in COVID-19 patients was preexisting or caused by a virus infection. Four, there existed a large heterogeneity in our included studies. Fifth, there were significant differences in adjusting confoundings in studies investigating the association of cardiac injury with clinical outcomes, which may weaken the reliability of our result. Fortunately, the results from subgroup analysis according to studies with unadjusting or adjusting for covariates, cardiac injuries were significantly associated with increased all-cause mortality.

It is concluded that COVID-19 has been associated with an increased prevalence of cardiac injury, even more so in patients with severe disease. The presence of cardiac injury may act as a marker of adverse outcomes or a risk of mortality in patients with COVID-19. Further studies are warranted to elucidate the predominant etiology of cardiac injury in patients with COVID-19 and thus to promote targeted treatment programs and preventive strategies to improve patients’ prognosis.

Acknowledgment

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Clinical features and treatment of COVID-19 patients in northeast China:

Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. J Med Virol 2020;92:797–806.

Yang L, Liu J, Zhang R, Li M, Li Z, Zhou X, et al. J Clin Virol: Off Publ Pan Am Soc Clin Virol 2020;129:104475.

Du R-H, Liang L-R, Yang C-Q, Wang W, Cao T-Z, 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.e1801.

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. https://doi.org/10.1101/2020.03.19.20033175.

Qi X, Liu Y, Fallowfield JA, Wang J, Wang J, Li X, et al. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicenter cohort study. medRxiv 2020. https://doi.org/10.1101/2020.02.14.20021666.

Cao J, Tu W-J, Cheng W, Yu L, Liu Y-K, Hu X, et al. Clinical features and short-term outcomes of 102 patients with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis: Off Publ Infect Dis Soc Am 2020.

Zhou F, Yu T, Du R, Fan G, Li 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;395:1054–62.

Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China. 2019. N Engl J Med 2020;382:727–33.

Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients infected with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. Progress in cardiovascular diseases. 2020.

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. J Am Med Assoc 2020;323:1061–9.

He XW, Lai JS, Cheng J, Wang MW, Liu YJ, Xiao ZC, et al. Impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients. Zhonghua Xinxiu guanbing Za Zhi 2020;48: E008-E.

Zhou B, She J, Wang Y, Ma X. The clinical characteristics of myocardial injury in severe and very severe patients with 2019 novel coronavirus disease. J Infect 2020;81:147–78.

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 Xinxiu guanbing Za Zhi 2020;48: E008-E.

Han H, Xie L, Liu R, Yang J, Liu F, Wu K, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. J Med Virol 2020;92:189–23.

Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846–8.

Tan W, Abouhoms J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. Int J Cardiol 2020;309:70–7.

Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. COVID-19 and cardiovascular disease. Circulation 2020;141:1648–55.

Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Pennington JM, et al. SARS-CoV-2 coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest 2009;39:618–25.

Aliano M, Alipano F, Forzeg P, Ianneli A. Renin-angiotensin system at the heart of COVID-19 pandemic. Biochimie 2020;174:30–3.

Wu L, O’Kane AM, Peng H, Bi Y, Motrikes-Smith D, Ren J. SARS-CoV-2 and cardiovascular complications: from molecular mechanisms to pharmaceutical management. Biochem Pharmacol 2020;114114.

Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020;63:457–60.

Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Scicuti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 congenital shock. Eur J Heart Fail 2020;22:911–5.

Yang C, Jin Z. An acute respiratory infection runs into the most common noncommunicable epidemic-COVID-19 and cardiovascular diseases. JAMA cardiology 2020.

Hoffmann M, Klein-Weber H, Schroeder S, Krueger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;180:271.

Fung G, Luo H, Qiu Y, Yang D, McManus B. Myocarditis. Circulation Research 2016;118:496–514.

Bonow RO, Fonarow GC, O’Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA cardiology 2020.

Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China (vol 395, pg 497, 2020). Lancet 2020;395:496.

Libby P. The heart in COVID19: primary target or secondary bystander? JACC Basic Translat Sci 2020.

Madjid M, Safavi-Naeni P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA cardiology 2020.

Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259–60.

Wilcox I, Chan KH, Lattimore J-D. Hypoxia and inflammation. N Engl J Med 2011;364:1976–7.

Xiong T-Y, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. Eur Heart J 2020;41:1798–800.

Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol. 2020;7: E438–40.

Kochav SM, Coromilas E, Nalbandian A, Ranard LS, Gupta A, Chung MK, et al. Cardiac arrhythmias in COVID-19 infection. Circ Arrhythmia Electrophysiol 2020;13. e008719-e.

Cosyns B, Lochy S, Luchian ML, Gimelli A, Sciutti F, Bottazzi A, et al. The role of cardiovascular imaging for myocardial injury in hospitalized COVID-19 patients. Eur Heart J Cardiovasc Imaging 2020;21:709–14.