Letter to the Editor

Myocardial injury is associated with higher mortality in patients with coronavirus disease 2019: a meta-analysis

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In December 2019, coronavirus disease 2019 (COVID-19) caused by a novel coronavirus (SARS-CoV-2) broke out in Wuhan, China, and has spread widely all over the world, reaching the pandemic level.[1] According to the latest WHO report, 693,224 cases of COVID-19 were confirmed globally as of March 30, 2020, with more than 33,000 deaths.[2] Because COVID-19 is highly contagious and harmful, it is crucial to determine the predictors of severe infection and death for risk stratification and guiding clinical treatment and intervention.

Respiratory symptoms are the most prevalent manifestations of COVID-19. However, studies have shown that acute cardiac injury is a common complication in COVID-19 patients.[3,4] Indeed, a study in the early stage of the disease outbreak showed that 12% of 41 patients diagnosed with COVID-19 had acute myocardial injury, which was characterized by a significant increase in the level of hypersensitive troponin I (hs-cTnI).[5] The heart autopsy results of three COVID-19 cases revealed pathological changes of cardiomyocyte hypertrophy, partial cardiomyocyte degeneration and necrosis, mild interstitial congestion and edema, accompanied by a small number of lymphocytes, monocytes and neutrophil infiltration.[6] Additionally, a meta-analysis showed that hs-cTnI was significantly increased in patients with severe COVID-19 compared with mild forms.[7] Therefore, myocardial injury is likely to be an important prognostic factor for COVID-19. Here, we summarize the current literature to explore the correlation between myocardial injury and mortality in patients with COVID-19.

PubMed, the Web of Science, MedRxiv and COVID-19 academic research communication platforms (articles in Chinese, http://medjournals.cn/2019NCP/index.do) were used to search articles published until March 30, 2020 without language restriction application. The following keywords were used: (“coronavirus disease 2019” or “COVID-19” or “novel coronavirus pneumonia” or “2019-nCoV” or “SARS-CoV-2”) and (“heart injury” or “cardiac injury” or “myocardial injury”) and (“death” or “mortality” or “non-survivor” or “deceased”) alone and in combination. The title, abstract and full text of all documents identified using the search criteria were assessed, and those reporting the mortality rate in COVID-19 patients with and without myocardial injury were included in this meta-analysis. The reference lists of all studies were also analyzed to identify additional eligible studies.

A meta-analysis was performed on retrievable data, including estimation of the odds ratio (OR) and its 95% confidence interval (CI) of mortality in patients with or without myocardial injury. All statistical analyses were conducted with RevMan 5.3 software (Chichester, The UK Centre, The Cochrane Collaboration). The Mantel-Haenszel (statistical method) and fixed effect (analysis model) models were employed to assess outcomes. Forest plots were utilized to visually illustrate effect estimates of the included studies. Funnel plots were used to examine publication bias. We used the Newcastle-Ottawa Scale (NOS) to further evaluate the quality of the observational studies, with NOS score > 7 considered good quality.[8]

Overall, 134 studies were originally detected based on our electronic and reference search; after screening by title, abstract and full text, 125 studies were excluded [as not specifically related to COVID-19 (n = 52), review articles (n = 18), did not provide relevant data (n = 20), editorials (n = 21), and compared patients by severity but not by mortality (n = 14)]. Ultimately, 9 studies involving a total of 1470 patients were enrolled.[9–17]
The characteristics of the included studies are described in Table 1, and the treatment and clinical outcome of the patients are described in Table 2. All articles included in the meta-analysis had high quality according to the NOS. The mortality rate with or without myocardial injury in patients with COVID-19 are depicted in Figure 1A. In our study, the overall mortality rate was 23.5%. The mortality rate of patients without myocardial injury was considerably lower than that of patients with myocardial injury (11.2% vs. 67.1%, \( P < 0.001 \)), and myocardial injury was significantly associated with increased mortality in patients with COVID-19 (OR = 13.68, 95% CI: 9.81–19.08, \( P < 0.001 \)). Heterogeneity among the studies was borderline significant (\( I^2 = 52\% \), \( P = 0.03 \)). A funnel plot showed symmetry, indicating a low risk of publication bias (Figure 1B).

SARS-CoV-2 causes myocardial injury through direct and indirect pathogenic pathways. Single-cell data analysis identified that human myocardial cells express angiotensin-converting enzyme 2 (ACE2) and that higher expression is present in patients with heart failure.\(^{[18]}\) SARS-CoV-2 may invade cells by binding to ACE2, causing direct damage to cardiomyocytes. However, the autopsy results of COVID-19 cases failed to detect SARS-CoV-2 virus components in myocardial tissue by electron microscope observation, immunohistochemical staining or PCR.\(^{[19]}\) SARS-CoV-2 infection may also cause myocardial injury through overactivation of the immune system, with the release of a large number of cytokines and cytokine storms.\(^{[19,20]}\) In addition, pulmonary infection-induced hypoxemia, respiratory failure and shock might lead to insufficient myocardial oxygen supply; after infection, the burden of the heart increases, and the imbalance between oxygen supply and demand leads to myocardial injury.\(^{[21]}\) Overall, more studies are necessary to clarify the mechanism of SARS-CoV-2-induced myocardial injury.

The overall mortality rate was 23.5% in our meta-analysis, which is much higher than the value of 2.3% of 44,672 confirmed cases reported in the study of the Chinese Centers for Disease Control and Prevention.\(^{[22]}\) A possible reason is that these involved studies included a high proportion of critically ill patients. This large sample size report also showed that the case fatality rate was associated with disease severity, as all death cases were among critical patients. Our meta-analysis showed that COVID-19 patients with

| Study | Study period | Location | NOS score | Number of patients* | Age, yrs | Male | Hyper-tension | Diabetes | COPD | CVD | CKD | Cancer |
|-------|--------------|----------|-----------|--------------------|---------|------|---------------|----------|------|-----|-----|-------|
| He, et al\(^{[9]}\) | 2020.2.4–2020.4.23 | The Sino-French New City Branch of Tongji Hospital | 8 | 54 | 68.0 (59.8–74.3) | 34 | 24 (44.4%) | 13 (24.1%) | 2 (3.7%) | 8 (14.8%) | NA | 2 (3.7%) |
| Xu, et al\(^{[20]}\) | 2020.12–2020.2.14 | West China Hospital | 7 | 53 | 78.5 (60.5–81.8) | 28 | 8 (15.1%) | 8 (15.1%) | 8 (15.1%) | 6 (11.3%) | NA | NA |
| Yang, et al\(^{[21]}\) | 2019.12.24–2020.1.6 | Wuhan Jiny-Tan Hospital | 8 | 52 | 59.7 ± 13.3 | 35 | NA | 9 (17.0%) | 4 (8.0%) | 5 (10.0%) | NA | 2 (4.0%) |
| Zhou, et al\(^{[12]}\) | 2019.12.29–2020.1.31 | Wuhan Jiny-Tan Hospital and Pulmonary Hospital | 8 | 191 | 56.0 (46–67) | 119 | 58 (30.0%) | 36 (19.0%) | 15 (3.0%) | 2 (1.0%) | 2 (1.0%) |
| Liu, et al\(^{[13]}\) | 2020.1.10–2020.2.24 | Guangzhou Eighth People’s Hospital | 7 | 291 | 48.0 (34–62) | 133 | 54 (18.5%) | 22 (7.6%) | NA | 15 (5.1%) | NA | NA |
| Zhang, et al\(^{[14]}\) | 2019.12.25–2020.2.15 | Wuhan Hospital of Traditional Chinese & Western Medicine | 8 | 48 | 70.6 ± 13.4 | 33 | 32 (68.7%) | 32 (66.7%) | 10 (20.8%) | NA | 13 (27.1%) | 5 (10.4%) | NA |
| Shi, et al\(^{[15]}\) | 2020.1.20–2020.2.10 | Renmin Hospital of Wuhan University | 8 | 416 | 64.0 (21–95) | 211 | 127 (50.7%) | 60 (30.5%) | 12 (4.4%) | 6 (14.7%) | 14 (3.4%) | 9 (2.2%) |
| Guo, et al\(^{[16]}\) | 2020.1.23–2020.2.23 | Seventh Hospital of Wuhan | 8 | 187 | 58.5 ± 14.7 | 91 | 61 (48.7%) | 28 (32.6%) | 4 (15.0%) | 29 (15.5%) | 6 (3.2%) | NA |
| Chen, et al\(^{[17]}\) | 2020.1.13–2020.2.28 | Tongji Hospital | 8 | 274 | 62.0 (44–70) | 171 | 93 (34.0%) | 47 (17.0%) | 24 (7.0%) | 24 (9.0%) | 4 (1.0%) | 7 (3.0%) |

Data are presented as means ± SD, n (%) or median (interquartile range). *Refer to number of COVID-19 confirmed patients. COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; CVD: cardiovascular disease; NA: data not available; NOS: the Newcastle-Ottawa Scale.

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myocardial injury have a higher mortality rate. A previous meta-analysis also reported a significant increase in cTnI in patients with severe SARS-CoV-2 infection, indicating that myocardial injury might be related to COVID-19 severity.\[^7\] Therefore, the existence of myocardial injury should be regarded as an important index in the risk stratification of disease severity and death for COVID-19. Continuous monitoring of myocardial injury markers and cardiac function during hospitalization should be strengthened. For patients with myocardial injury, we believe that doctors should conduct comprehensive treatment, including correcting hypoxemia and improving myocardial oxygen supplementation, applying immunoglobulins to inhibit the excessive immune response, improving myocardial energy metabolism, and maintaining water-electrolyte balance, to improve the prognosis of COVID-19 patients.

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**Table 2. Treatment and clinical outcome of patients with COVID-19 in the meta-analysis.**

| Study          | CSR | CFR | Main Symptom at admission | Treatment                | MI definition                                           |
|----------------|-----|-----|---------------------------|--------------------------|--------------------------------------------------------|
| He, et al\[^9\] | 54  | 26  | Fever                     | 51 (94.4%)               | Three times higher serum cTnI                           |
|                |     |     | Cough                     | 35 (64.8%)               | hs-TNI above the 99th-percentile upper reference limit (≥ 28 pg/mL) |
|                |     |     | Dyspnea                   | NA                       | hs-TNI above the 99th-percentile upper reference limit (≥ 28 pg/mL) |
|                |     |     | Myalgia                   | 20 (37.1%)               | hs-TNI above the 99th-percentile upper reference limit (≥ 28 pg/mL) |
|                |     |     | Diarrhea                  | 2 (3.7%)                 | hs-TNI above the 99th-percentile upper reference limit (≥ 28 pg/mL) |
|                | 51  | 35  | Antiviral treatment       | 2 (3.7%)                 | hs-TNI above the 99th-percentile upper reference limit (≥ 28 pg/mL) |
|                |     |     | Glucocorticoids           | 30 (55.6%)               | hs-TNI above the 99th-percentile upper reference limit (≥ 28 pg/mL) |
|                |     |     | Oxygen inhalation         | 20 (37.1%)               | hs-TNI above the 99th-percentile upper reference limit (≥ 28 pg/mL) |
|                |     |     | NIV                        | 2 (3.7%)                 | hs-TNI above the 99th-percentile upper reference limit (≥ 28 pg/mL) |
|                |     |     | IMV                        | 10 (18.5%)               | hs-TNI above the 99th-percentile upper reference limit (≥ 28 pg/mL) |
|                |     |     | ECMO                       | 8 (14.8%)                | hs-TNI above the 99th-percentile upper reference limit (≥ 28 pg/mL) |

Data are presented as n (%). CFR: case fatality rate; COVID-19: coronavirus disease 2019; CSR: case severity rate; cTnI: cardiac troponin; ECMO: extracorporeal membrane oxygenation; hs-TNI: high-sensitivity troponin I; IMV: invasive mechanical ventilation; MI: myocardial injury; NA: data not available; NIA: non-invasive ventilation.
Figure 1. Meta-analysis for mortality in COVID-19 patients with or without myocardial injury. (A): Forest plot of demonstrating association of myocardial injury and mortality in patients with COVID-19; and (B): funnel plot for the assessment of publication bias. CI: confidence interval; COVID-19: coronavirus disease 2019; MI: myocardial injury; OR: odds ratio.

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