The Impact of Cardiac Injury on COVID-19 Patients Mortality: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Cardiovascular system was the second most common organ system affected by COVID-19 and many cases of COVID-19 reported cardiac injury. The goal of this study was to explore the correlation of cardiac injury with mortality in patients with COVID-19.

Objectives: This study aimed to explore the incidence of cardiac injury in patients with COVID-19, analyze the correlation between cardiac injury, represented by cardiac biomarker elevation, and mortality in COVID-19 patients, and search the feasible mechanism of cardiac injury in COVID-19 patients.

Methods: We performed a systematic review and meta-analysis study. The relevant studies were identified through scientific electronic databases such as PubMed, Cochrane, and ScienceDirect up to August 2020. The study quality assessment was conducted using the GRADE approach. The pooled odds ratio (OR) and 95% confidence interval (CI) were estimated using the random-effects model.

Results: A total of 10 studies involving 2619 patients were included in the meta-analysis. The incidence of cardiac injury in COVID-19 patients was 28.5%. All-cause mortality was significantly higher in patients with cardiac injury (52.8% vs. 13.1%; OR = 13.78; 95% CI = 7.22-26.32; I^2 = 88%; Z = 7.95; P < 0.00001).

Conclusion: In COVID-19 patients, heart failure is associated with higher mortality. As a major aspect in the risk stratification for COVID-19 mortality, cardiac damage should be considered.

1. Introduction

COVID-19 has been an emerging global health issue. The numbers of COVID-19 patients continue to increase, with 25 million confirmed cases from January to August 2020.1 In Indonesia, over 170 thousand confirmed cases were reported at the end of August 2020. The case fatality rate in Indonesia was 4.2%, higher than the global average case fatality rate, which is 3.4%.2,3 On August 31, 2020, Indonesia was the runner-up for the mortality rate caused by COVID-19 in Southeast Asia, under the Philippines. The mortality rate in Indonesia was 28 per million, while the Philippines was 33.9 per million.4 Due to its high mortality rate, the identification of predictors of progression towards fatal disease is urgently needed, as we are still encountering difficulties in how to identify patients at risk for severe disease early in the course of COVID-19.4

Progression of COVID-19 consists of three stages: early infection, pulmonary, and severe hyperinflammation.5 Virus infiltrates and proliferates during the early infection phase, induce activation of monocytes and macrophages. Pulmonary damage induces hypoxemia and cardiovascular stress as secondary organ damage. The cardiovascular system was the second most common organ system affected by COVID-19 after the lungs. Among deceased COVID-19 confirmed cases in Indonesia, 7.6% of patients had cardiovascular disease.1 Several manifestations of cardiac injury in COVID-19 are arrhythmias, acute coronary syndrome, heart failure, cardiogenic shock, and thromboembolism.6,7 Elevation of cardiac troponin is a surrogate of myocardial injury. The goal of this systematic review and meta-analysis was to investigate the association of heart injury with mortality in patients with COVID-19.

2. Methods

2.1. Search strategy

In this systematic review and meta-analysis study, we collected relevant studies from the electronic scientific databases such as PubMed, Cochrane, and ScienceDirect up to August 10, 2020. The keywords were "myocardial damage" or "myocardial injury" or "cardiac injury" or "myocarditis" or "myocardium" and "coronavirus" or "COVID" or "COVID-19" or "SARS-CoV2" or "mortality" or "death." We carried article searching without date or language restriction.
2.2. Selection criteria

Cohort studies, case-control studies or case series that examined the effects of heart injury on mortality were screened. Inclusion criteria were: (1) cohort, case-control, or case series study; (2) study included all patients with confirmed COVID-19 using PCR; (3) available data of the presence of cardiac injury, which was defined as an increased troponin level; (4) available data of mortality in cardiac injury patients compared to mortality in non-cardiac injury patients. We exclude papers that only include severe COVID-19 patients, no data of increased cardiac marker, unpublished studies, and duplicate articles. We conducted a study quality assessment using the GRADE approach.8

2.3. Data collection

Papers were evaluated by two authors separately. Standardized types were created, including authors, year of study, design of study, cut-off point for high sensitivity cardiac troponin I (hs-cTn), cut-off point for troponin, cardiac injury, and mortality. The cardiac injury was defined as the elevation of hs-cTn or troponin level of more than its 99th percentile above the upper reference limit, disregarding the electrocardiography and echocardiography variables. The primary outcome was all-cause mortality.

2.4. Statistical analysis

With the random effects model, the odds ratio and 95 percent confidence interval (CI) were calculated and heterogeneity was tested with RevMan 5.44 using the I2 test.9 The findings of the I2 statistics were interpreted as 25%, 50% and 75%, reflecting low, moderate and high heterogeneity. Funnel plots and the Harbord test was used to test publication bias. Funnel plot asymmetry indicates the presence of publication bias, and the Harbord test p-value < 0.05 indicates a small-study effect, which suggests the presence of publication bias.

3. Results

We identified 818 papers, and 814 remained after the removal of duplicates. We screened the title or abstracts then excluded 755 papers. Sixty-one papers were evaluated for eligibility criteria. We excluded 51 papers because of several reasons: 1) only included severe COVID-19 patients (n=10), 2) no data of increased cardiac marker (n=7), 3) no data of cardiac injury mortality (n=14), 4) unpublished studies (n=9), 5) included not only confirmed case but also probable case (n=10), 6) used myoglobin as biomarker assessment (n=1), 7) included patients with significant comorbidities (n=10). Finally, we included 10 studies in this meta-analysis (Figure 1).

Table 1 displays the baseline features of the included studies. All the studies used were observational cohort studies. Ten studies from Turkey, China, the United States, and Spain with 2038 patients were included in this meta-analysis. The incidence of cardiac injury in COVID-19 patients was 28.5%. The all-cause mortality was significantly higher in patients with cardiac injury (52.8% vs. 13.1%; OR = 13.78; 95% CI = 7.22-26.32; I² = 88%; Z = 7.95; P < 0.00001) as shown in figure 2. The presence of significant heterogeneity was revealed by I2 value of 81%. The existence of publication bias was indicated by the asymmetric funnel plot (Figure 3) and the Harbord test result (p = 0.031) (Supplementary figure 1).
Table 1. Baseline characteristics of included studies

| Authors       | Study Design                  | Subject                                                                 | Definition of Myocardial Injury                                                                 | Patient with Cardiac Injury | Patient without Cardiac Injury | Enrollment period                  | Outcome                                                                 |
|---------------|-------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------|--------------------------------|-----------------------------------|------------------------------------------------------------------------|
| Shi S et al, 2020 | Retrospective cohort, single center | Inpatients with laboratory-confirmed COVID-19                          | Serum high-sensitivity cardiac troponin I above the 99th percentile upper reference limit       | 82                         | 334                            | January 20, 2020 to February 10, 2020 | Mortality                                                                 |
| Zhou F et al, 2020 | Retrospective cohort, multicenter | All adult inpatients with laboratory confirmed COVID-19               | High-sensitivity cardiac troponin I >28 pg/mL                                                   | 33                         | 158                            | December 29, 2019 to January 31, 2020 | Mortality                                                                 |
| Guo T et al, 2020 | Retrospective, single center case series | 187 patients confirmed with COVID-19                                    | Elevated troponin T level                                                                      | 52                         | 135                            | January 23, 2020 to February 23, 2020 | Mortality                                                                 |
| Wang D et al, 2020 | Retrospective case series, multi center | All the discharged (alive at home and dead) patients with confirmed COVID-19 | Highly sensitive troponin I >26.2 pg/mL                                                        | 6                          | 101                            | Up to February 10, 2020            | Mortality                                                                 |
| Cao J et al, 2020 | Retrospective cohort study, single center | All patients with COVID-19 admitted to Hospital                        | Hyper-sensitive troponin I >26 pg/mL                                                             | 15                         | 87                             | January 3, 2020 to February 15, 2020 | Mortality                                                                 |
| Wang L et al, 2020 | Single center, retrospective | All patients admitted to Wuhan University People's Hospital from January 31 to February 5 and were diagnosed with COVID-19. | Serum high-sensitivity cardiac troponin I level >0.04 μg/L.                                      | 27                         | 175                            | January 31, 2020 to March 11, 2020  | Mortality                                                                 |
| Harmouch F et al | Cohort retrospective, single center | A total of 563 confirmed COVID-19 case were admitted to St Luke's hospital during the period of interest. | Elevated troponin (> 0.05 ng/mL)                                                                | 97                         | 385                            | March 1, 2020 to April 15, 2020     | Mortality, mechanical ventilation, Intensive care unit admission disease severity, admission to intensive care unit, need for mechanical ventilation or vasoactive agents, and death |
| Wei JP et al, 2020 | Prospective, multi-centered | Confirmed with COVID-19                                                 | High-sensitivity troponin I value greater than the institutional upper limit of normal (14 pg/mL) | 16                         | 85                             | January 16, 2020 to March 10, 2020  | Disease severity, admission to intensive care unit, need for mechanical ventilation or vasoactive agents, and death |
| Ros et al, 2020 | Retrospective, single center | Confirmed with COVID-19                                                 | High-sensitivity cardiac troponin I >14 ng/L                                                    | 112                        | 112                            | March 18, 2020 to April 23, 2020    | Acute respiratory distress syndrome, non-invasive ventilation, intensive care unit admission, hospital stay, mortality |
| Barman et al, 2020 | Multi-center retrospective | Confirmed COVID-19 patients who were hospitalized                      | Increase in high-sensitivity troponin I. The upper reference limit (99th percentile) ranges with an upper reference range of 14 pg/ml for patients. | 150                        | 457                            | March 20, 2020 to April 20, 2020    | Length of stay, development of Acute respiratory distress syndrome, intensive care unit treatment, acute kidney injury, and mortality |
4. Discussion

This meta-analysis revealed that the incidence of cardiac injury among COVID-19 patients was very high (28.5%). Cardiac injury, proven by the elevated troponin levels, is significantly associated with higher all-cause mortality. COVID-19 is caused by the infection of SARS-CoV-2, the virus that infects the host via ACE2 receptors. The ACE2 receptors can be found in type II pneumocyte lung epithelium, myocardium, endothelium, gastrointestinal tract, bone marrow, kidney, and spleen. There are three stages in COVID-19 infection: stage I (initial viral infection), stage II (acute respiratory distress syndrome), and stage III (hyperinflammatory state).\textsuperscript{10} Besides causing severe acute respiratory syndrome, SARS-CoV-2 can also induce cardiac injury. The pathogenic mechanism of cardiac injury in COVID-19 is still unclear. Several possible mechanisms of cardiac injury in COVID-19 patients are: 1) direct myocardial injury; 2) microvascular injury; 3) systemic inflammation; 4) oxygen demand and supply mismatch in myocardium due to lung damage; and 5) acute coronary event due to plaque rupture induced by inflammation.\textsuperscript{10,11}

Direct myocardial injury can occur because of fulminant myocarditis mediated by the ACE2 receptors on the myocardium.\textsuperscript{19} The minimally invasive autopsy was performed on patients who died from COVID-19 in China. The results showed that the nucleic acid of SARS-CoV-2 was found not only in the lungs but also in the heart, blood vessels, liver, and other organs.\textsuperscript{12} Microvascular injury is caused by
coagulation and fibrinolytic disruption. More than 70% of patients who died from COVID-19 met the DIC criteria. Infection and sepsis are associated with immune complexes that lead to a hypercoagulable state, similar to DIC. Hypercoagulable state causes microthrombus formation and microvascular dysfunction, which is thought to cause cardiac injury.

The COVID-19 infection causes the elevation in inflammatory biomarkers and cytokines level, including IL-6, CRP, TNF-alpha, IL-2R, and ferritin, resulting in the systemic inflammatory response. The patient who reaches stage III has severe COVID-19 manifestation due to cytokine storm. In this stage, patients have various clinical presentation form of multi-organ dysfunction to death. The increased cytokine level can also activate inflammatory cells in atherosclerotic plaques. When activated, intraplaque inflammatory cells will up-regulate host response proteins, including metalloproteinases and peptidases. This condition may lead to oxidative stress and extracellular matrix component degradation, contributing to plaque destabilization. The plaque will be more prone to rupture, exposing the thrombogenic components in the subendothelial layer, leading to acute thrombus formation. Severe COVID-19 infection can reduce oxygen delivery to the myocardium through systemic hypoxemia and vasoconstriction mechanism. Severe infection also increases oxygen demand. The oxygen demand and supply mismatch can induce myocardial ischemia in patients with underlying coronary artery disease.

Abnormal electrocardiography in COVID-19 patients may vary, including tachycardia, atrioventricular or interventricular block, ST-T changes, QT-interval prolongation, and malignant arrhythmias. Viral infection causes cytokine storm, hypoxemia, and hypercoagulability state, leading to hypoxemia, myocardial tissue damage, and arrhythmias. Arrhythmias can also occur secondary to COVID-19 medical therapy. Fever may increase sympathetic tone and leads to tachyarrhythmias in COVID-19 patients without heart disease. Fever may induce ventricular fibrillation in COVID-19 patients with underlying heart disease.

The limitation of this study was the presence of heterogeneity because COVID-19 is a relatively new disease. The treatment strategies were widely varied among several centers. There was also publication bias indicated by the asymmetric funnel plot and the Harbord test result. The included studies in our meta-analysis also did not specify whether the elevation in troponin level was due to myocarditis, myocardial infarction, or other mechanisms. Therefore, the elevated troponin levels indicated cardiac injury but did not define the specific mechanism.

5. Conclusion

Cardiac injury is associated with a higher mortality rate in COVID-19 patients. Therefore, cardiac injury should be considered as an important variable in the risk stratification for mortality in COVID-19. Elevated troponin, which represents cardiac injury, might be the potential marker of poor prognosis in COVID-19.

6. Declarations

6.1. Ethics Approval and Consent to participate

This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

6.2. Consent for publication

Not applicable.

6.3. Availability of data and materials

Data used in our study were presented in the main text.

6.4. Competing interests

Not applicable.

6.5. Funding source

Not applicable.

6.6. Authors contributions

Idea/concept: NAN. Design: NAN. Control/supervision: MDHQ. Data collection/processing: MDHQ. Extraction/Analysis/interpretation: NAN, MDHQ. Writing the article: NAN. Critical review: NAN, MDHQ. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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