# Meta-analysis Comparing Outcomes in Patients With and Without Cardiac Injury and Coronavirus Disease 2019 (COVID 19)

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**Current evidence is limited to small studies describing the association between cardiac injury and outcomes in patients with coronavirus disease 2019 (COVID-19). To address this, we performed a comprehensive meta-analysis of studies in COVID-19 patients to evaluate the association between cardiac injury and all-cause mortality, intensive care unit (ICU) admission, mechanical ventilation, acute respiratory distress syndrome, acute kidney injury and coagulopathy. Further, studies comparing cardiac biomarker levels in survivors versus nonsurvivors were included. A total of 14 studies (3,175 patients) were utilized for the final analysis. Cardiac injury in patients with COVID-19 was associated with higher risk of mortality (risk ratio [RR]:7.79; 95% confidence interval [CI]: 4.69 to 13.01; $I^2$=58%), ICU admission (RR: 4.06; 95% CI: 1.50 to 10.97; $I^2$ = 61%), mechanical ventilation (RR: 5.53; 95% CI: 3.09 to 9.91; $I^2$ = 0%), and developing coagulopathy (RR: 3.86; 95% CI:2.81 to 5.32; $I^2$ = 0%). However, cardiac injury was not associated with increased risk of acute respiratory distress syndrome (RR:3.22; 95% CI:0.72 to 14.47; $I^2$ = 73%) or acute kidney injury (RR: 11.52, 95% CI:0.03 to 4,159.80; $I^2$ = 0%). The levels of hs-cTnI (MD:34.54 pg/ml;95% CI: 24.67 to 44.40 pg/ml; $I^2$ = 88%), myoglobin (MD:186.81 ng/ml; 95% CI: 121.52 to 252.10 ng/ml; $I^2$ = 88%), NT-pro BNP (MD:1183.55 pg/ml; 95% CI: 520.19 to 1846.91 pg/ml: $I^2$ = 96%) and CK-MB (MD:2.49 ng/ml;95% CI: 1.86 to 3.12 ng/ml; $I^2$ = 90%) were significantly elevated in nonsurvivors compared with survivors with COVID-19 infection. The results of this meta-analysis suggest that cardiac injury is associated with higher mortality, ICU admission, mechanical ventilation and coagulopathy in patients with COVID-19.**  **(Am J Cardiol 2021;141:140−146)**

The 2019 novel coronavirus (2019-nCoV) and/or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or coronavirus disease 2019 (COVID-19), was declared as a global pandemic on March 11, 2020.[1] As of June 17, 2020, COVID-19 has infected more than 8 million individuals with over 416,000 fatalities worldwide.[2] It has been reported that in up to 5% of infected patients, the disease may progress to a critical form manifesting as hypoxic respiratory failure, multiorgan dysfunction or shock, and approximately 2.5% of infected individuals have died from the infection.[3] Acute cardiac injury in patients infected with COVID-19 has been associated with increased risk of all-cause mortality, intensive care unit (ICU) admission, and developing severe COVID-19 infection.[4−6] However, most studies of outcomes in patients with cardiac injury and COVID-19 have been small, and limited in scope. Further delineation of outcomes with cardiac injury via pooled analysis may be important, as laboratory predictors of clinical deterioration can help stratify risk and assist in appropriate triaging and resource utilization. We therefore systematically reviewed the current scientific literature to perform a meta-analysis determining the association between acute cardiac injury and mortality, ICU admission, acute respiratory distress syndrome (ARDS), mechanical ventilation, acute kidney injury (AKI) and coagulopathy in patients with COVID-19.

## Methods

We carried out an electronic systematic search in Medline (PubMed), Embase, Google Scholar, Cochrane database and medRxiv databases using the keywords "Coronavirus 2019" OR "COVID 19" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" AND "acute cardiac injury" OR "cardiovascular disease" OR "cardiac biomarkers" OR "troponin" or "high-sensitivity cardiac troponins" or "hs-cTnI" or "creatine kinase" or "CK-MB" OR "BNP" OR "NT-pro BNP" OR "myoglobin" between 2019 and June 17, 2020.

The study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines (Figure 1). After removing duplicates, the title and abstracts were independently screened by 2 authors (AB and RPP). We included the studies reporting cardiac injury associated outcomes defined as either all-

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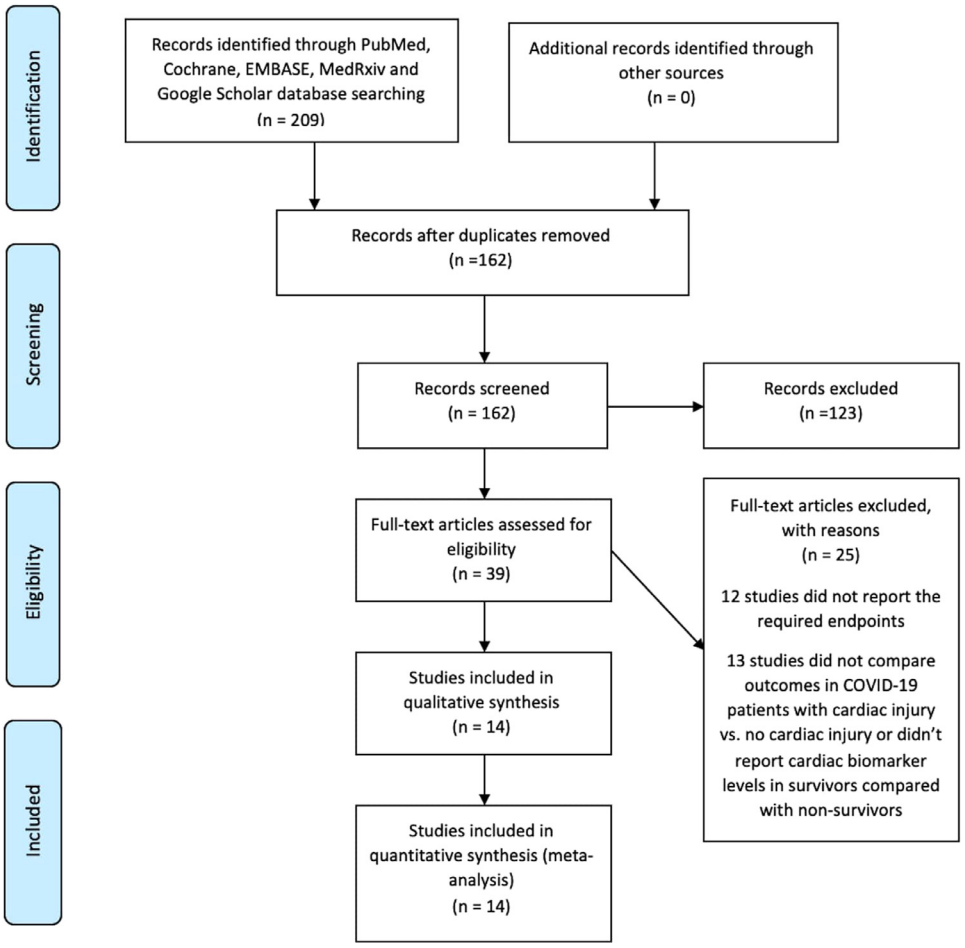


Figure 1. PRISMA diagram describing the selection of studies for our meta-analysis. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

cause mortality, ICU admission, ARDS, mechanical ventilation, AKI or coagulopathy, studies with information on cardiac biomarkers (hs-cTnI, myoglobin, CK-MB, NT-pro BNP) in survivors compared with non-survivors of COVID-19 infection. Articles other than original research (i.e., review articles, case reports, letter to editor, editorial, or commentaries), duplicate publications and non-English publications were excluded from the analysis. Full texts of the included studies were then reviewed independently by 2 authors (AB and AK) and data were extracted. Any discrepancies were resolved by the consensus of the authors. To ensure that no potentially important studies were missed, the reference lists from the retrieved articles were also checked.

The following data were collected from each study: author name, year published, country where the study was performed, study design, age, definition of cardiac injury, mean and/or median cardiac biomarker levels in survivors versus non survivors, following event rates in COVID-19 patients with cardiac injury compared with patients without cardiac injury, all-cause mortality, ICU admission, ARDS, mechanical ventilation, AKI and coagulopathy. The definition of cardiac injury was as per individual studies included. In the studies included, ARDS was defined according to the Berlin definition and AKI was defined according to the Kidney disease: Improving Global Outcomes definition.[7,8]

We used inverse variance method with Paule-Mandel estimator of tau2 and Hartung-Knapp-Sidik-Jonkmanthe adjustment to calculate risk ratio (RR) with 95% confidence interval (CI), and inverse variance method with DerSimonian-Laird method to calculate mean difference (MD) with 95% CI. When the study did not report mean and the standard deviation, the same were extrapolated from the sample size, median and interquartile range (Q1 to Q3) as per Hozo et al.[9] $I^2$ statistic was used to assess the heterogeneity between studies. Funnel plot was used to assess publication bias. All statistical analysis was carried out using R version 3.6.3.

## Results

Our systematic electronic search retrieved 39 publications after the initial screening of titles and abstracts. Subsequently, 25 studies were excluded, yielding 14 studies[4,10–22] that met the inclusion criteria for studies comparing outcomes in COVID-19 patients with cardiac injury or studies comparing levels of cardiac biomarkers in survivors and non-survivors In total, 8 studies [4,11–16,20] were included for the association of cardiac injury with mortality, 4 studies

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

| First author, country | Hs-c-TnI cut-off (pg/mL) | Sample size (cases/controls) | Median age (years) (cases vs. controls) | hs-c-TnI (pg/ml) (cases vs. controls) | NT-pro BNP (pg/ml) (cases vs. controls) | CK-MB (ng/ml) (cases vs. controls) | Myoglobin (ug/L) (cases vs. controls) |
|---|---|---|---|---|---|---|---|
| Zhou F 2020,[16] Wuhan, China | 28 | 191 (54/137) | 69 vs. 52 | 22.2 vs. 3 | - | - | - |
| Chen T 2020,[15] Wuhan, China | 15.6 | 274 (113/161) | 68 vs. 51 | 40.8 vs. 3.3 | 800 vs. 72 | - | - |
| Shi S 2020,[4] Wuhan, China | 40 | 671 (62/609) | 74 vs. 61 | 235 vs. 6 | 1819 vs. 132 | 3.6 vs. 0.8 | 268 vs. 32 |
| Li K 2020,[12] Wuhan, China | 34.2 | 32 (11/21) | 69 vs. 51 | 24.2 vs. 4.3 | 817.5 vs. 92.5 | - | 817.5 vs. 92.5 |
| Ruan Q 2020,[19] Wuhan, China | 28 | 150 (68/82) | 67 vs. 50 | 30.3 vs. 3.5 | - | - | 258.9 vs. 77.7 |
| Zhang F 2020,[21] Wuhan, China | 26 | 48 (17/31) | 79 vs. 66 | 34 vs. 6 | - | 9.5 vs. 9 | - |
| Wang Y 2020,[17] Wuhan, China | - | 344 (133/211) | 70 vs. 57 | 46.7 vs. 3.4 | - | 2.5 vs. 0.4 | 179 vs. 31 |
| Wu C 2020,[14] Wuhan, China | 6.126 | 188 | - | | | | |
| Luo X 2020,[13] Wuhan, China | 40 | 403 (100/303) | 71 vs. 49 | 35 vs. 6 | - | - | - |
| Guo T 2020,[20] Wuhan, China | - | 187 (43/144) | - | - | - | - | - |
| Hu B 2020,[11] China | 26.2 | 36 (16/20) | 56 vs. 66 | 30 vs. 11.9 | - | - | - |
| Cao 2020,[22] Shangai, China | 40 | 194 (19/175) | 64 vs. 48 | 39 vs. 19 | - | - | - |
| Huang 2020,[10] Wuhan, China | 28 | 41 (13/28) | 49 vs. 49 | 3.3 vs. 3.5 | - | - | - |
| Shi S 2020,[18] Wuhan, China | - | 416 | | - | - | - | - |

for ICU admission[3,10,14,22] 2 studies for mechanical ventilation,[18,20] 3 studies for ARDS [14,18,20] and 2 studies each for AKI[18,20] and coagulopathy.[18,20] With respect to cardiac biomarkers in survivors versus non survivors, 9 studies[11–13,15–19,21] were included for hs-cTnI and 3 studies each for myoglobin,[17–19] NT-pro BNP[12,15,18] and CK-MB.[17,18,21] Table 1 elucidates the characteristics of the included studies. The present meta-analysis included a total of 3175 patients from 14 studies.

After pooled analysis, cardiac injury in COVID-19 patients was associated with higher risk of all-cause mortality (RR:7.79; 95% CI:4.69 to 13.01: $I^2 = 58\%$) (Figure 2). The levels of hs-cTnI (MD:34.54 pg/ml; 95% CI: 24.67 to 44.40 pg/ml; $I^2 = 88\%$), myoglobin (MD:186.81 ng/ml; 95% CI: 121.52 to 252.10 ng/ml; $I^2 = 88\%$), NT-pro BNP (MD:1183.55 pg/ml; 95% CI: 520.19 to 1846.91 pg/ml: $I^2 = 96\%$) and CK-MB (MD:2.49 ng/ml; 95% CI: 1.86 to 3.12 ng/ml; $I^2 = 90\%$) were significantly elevated in nonsurvivors compared with survivors with COVID-19 infection (Figure 3).

Cardiac injury in patients with COVID-19 was likewise associated with higher risk of ICU admission (RR: 4.06; 95% CI: 1.50 to 10.97; $I^2 = 61\%$), mechanical ventilation (RR: 5.53; 95%CI: 3.09 to 9.91; $I^2 = 0\%$), and developing coagulopathy (RR: 3.86; 95% CI: 2.81 to 5.32; $I^2 = 0\%$). However, cardiac injury was not associated with a risk of ARDS (RR:3.22; 95%CI:0.72 to 14.47; $I^2 = 73\%$) or AKI (RR: 11.52, 95%CI:0.03 to 4159.80; $I^2 = 0\%$) (Figure 4).

A funnel plot assessing publication bias of studies reporting all-cause mortality associated with cardiac injury in COVID patient, indicated that there was no publication bias in our results (Figure 5).

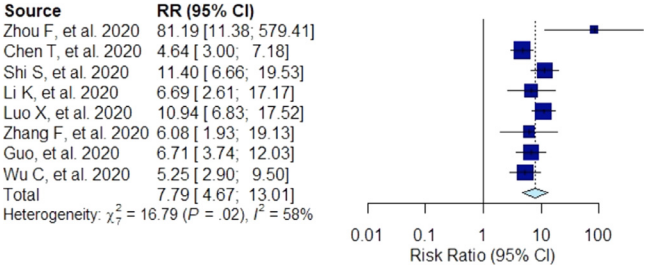


Figure 2. Forest plot for all-cause mortality in COVID-19 patients with cardiac injury compared with patients without cardiac injury. CI = confidence interval; RR = risk ratio.

## Discussion

In the present meta-analysis, acute cardiac injury in patients with COVID-19 infection was associated with increased risk of all-cause mortality, ICU admission, need for mechanical ventilation and development of coagulopathy. In addition, the levels of cardiac biomarkers (hs-cTnI, myoglobin, NT-pro BNP, and CK-MB) were significantly elevated in COVID 19 nonsurvivors compared with survivors. Cardiac injury was however not associated with an increased risk of ARDS or AKI.

There are several plausible mechanisms for myocardial injury in COVID-19 patients. First, it is postulated that human SARS-CoV can infect the myocardium directly by binding to the angiotensin converting enzyme-2 receptors leading to myocardial inflammation and damage. Further, the downregulation of ACE-2 by SARS-CoV infection can impair the cardioprotective effects of angiotensin 1 to 7, resulting in enhanced production of inflammatory cytokines TNF-a that can cause indirect myocardial injury.[23,24] Guo et al in their study reported that higher cardiac biomarker levels in COVID-19 patients were associated with higher levels of inflammatory markers, thus suggesting the possibility of indirect myocardial injury due to inflammatory state.[20] Additionally, SARS-CoV can also activate the TGF-b signaling and induce myocardial injury.[25] Similarly, type 2 myocardial infarction can occur in critically ill patients because of demand-supply inequity in patients with stable coronary artery disease. To this point, patients with severe COVID-19 infection often have other co-morbidities (such as but not limited to chronic renal insufficiency and congestive heart failure), which can predispose to type 2 myocardial infarction as a cause of cardiac biomarkers.

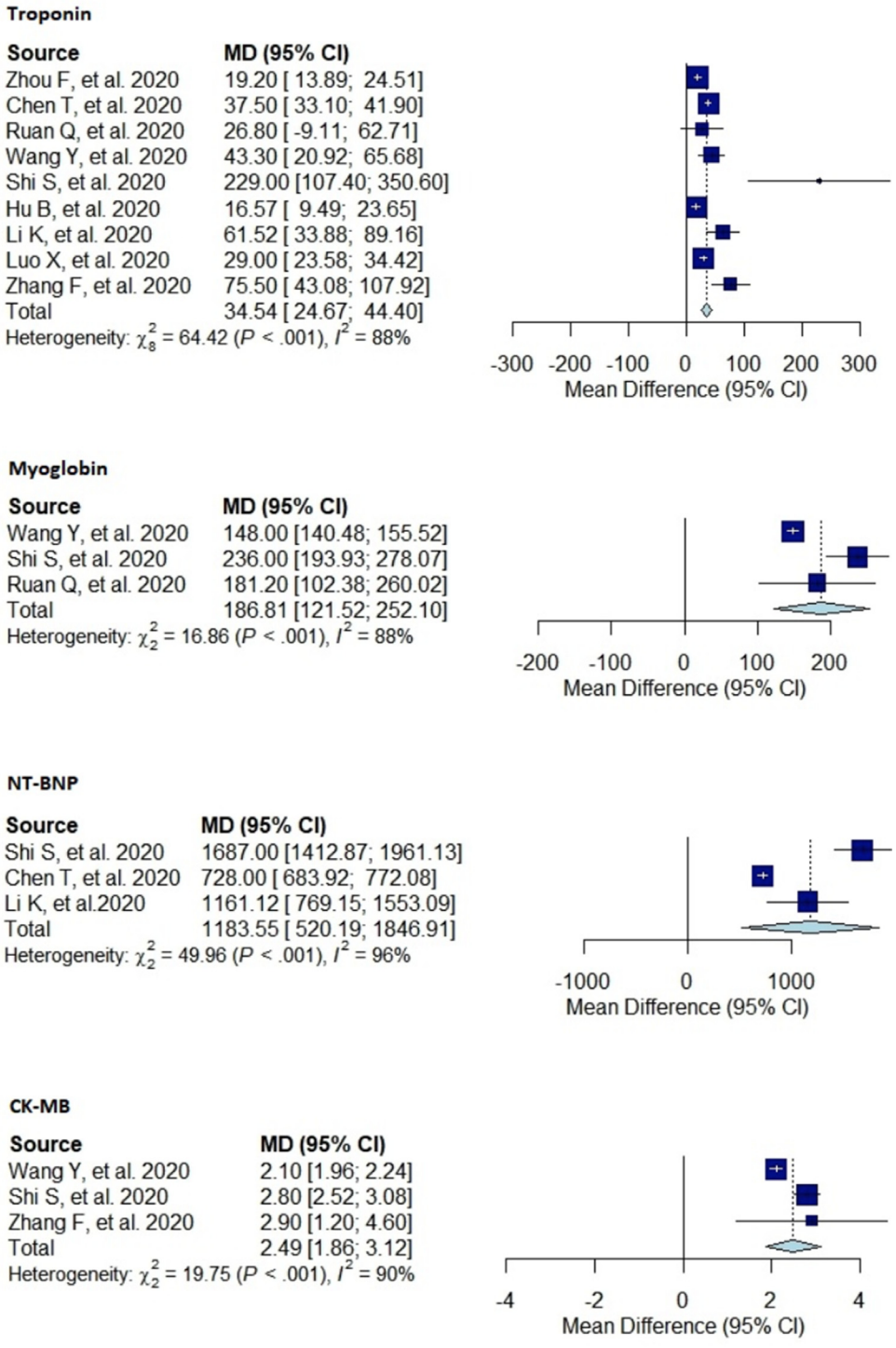


Figure 3. Forest plot for cardiac troponins, myoglobin, NT-pro BNP and CK-MB in non survivors compared with survivors, among COVID-19 infected patients. CI = confidence interval; MD = mean difference.

Further, intense inflammation and cytokine stimulation from COVID-19 infection can lead to plaque destabilization and rupture resulting in a type 1 myocardial infarction. It has been well established that patients with a history of cardiovascular disease are at an increased risk of developing complications from severe coronavirus infection, which may in part be explained by these reasons.

This meta-analysis has certain limitations. All of the studies were retrospective in design, were from a single country (China), and few studies were from preprint servers. Also, there was a significant heterogeneity in the reported results likely due to the varied definitions of cardiac injury among the included studies. As such, we were unable to determine whether there is a threshold value for

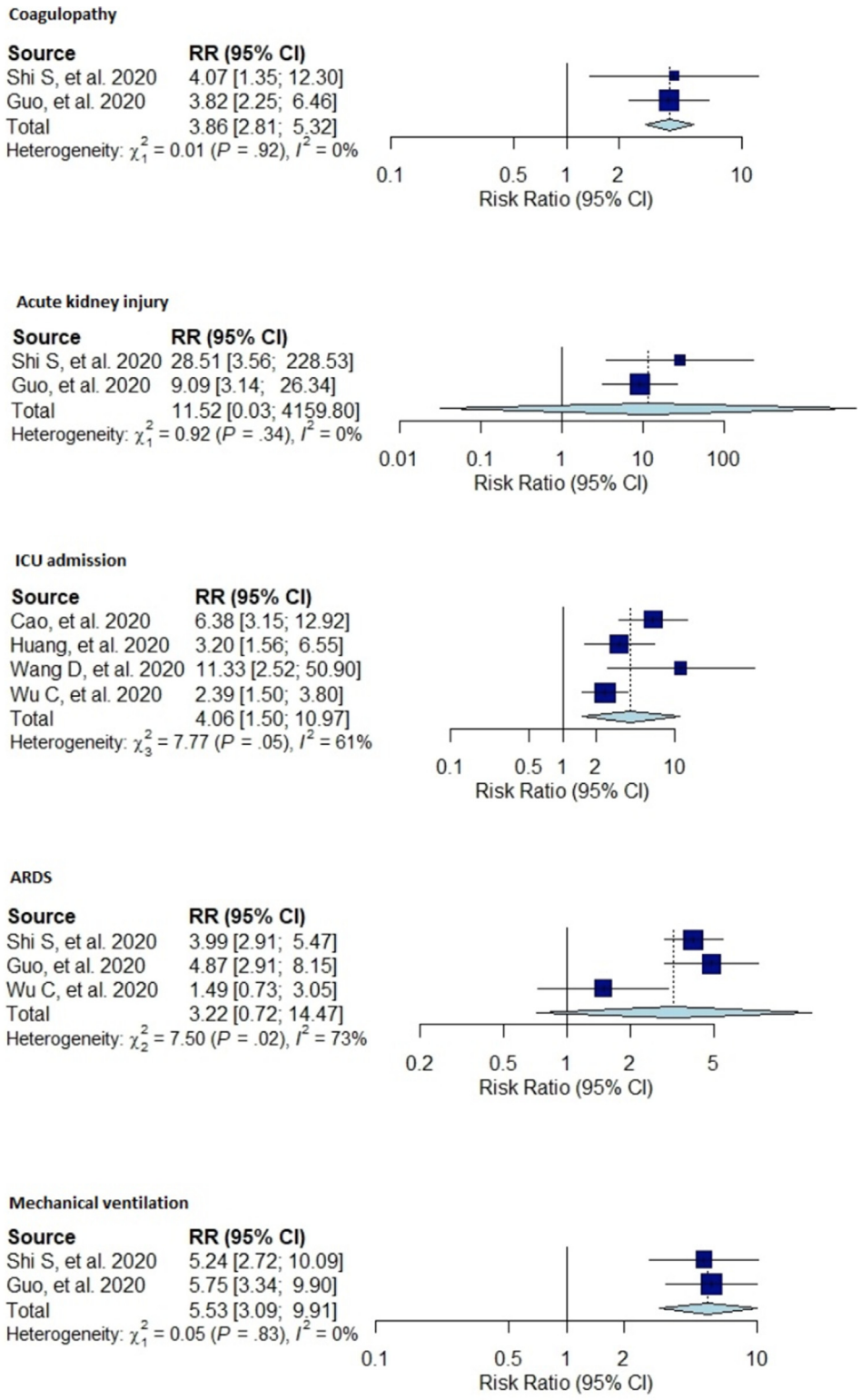


Figure 4. Forest plot for coagulopathy, acute kidney injury, ICU admission, ARDS and mechanical ventilation in COVID-19 patients with cardiac injury compared with patients without cardiac injury. CI = confidence interval; RR = risk ratio.

individual cardiac biomarker levels which could be used to predict outcomes.

In conclusion, the results of this meta-analysis suggest that cardiac biomarkers hs-cTnI, myoglobin, NT-pro BNP and CK-MB are more likely to be significantly elevated in patients who die from COVID-19. Further, the presence of cardiac injury was associated with higher risk of mortality and other adverse outcomes. The initial measurement of

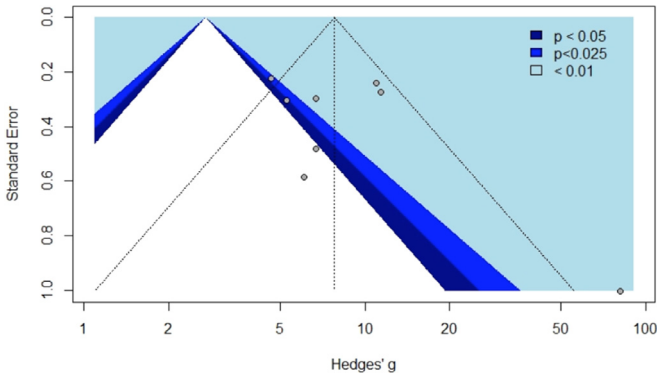


Figure 5. Funnel-plot analysis assessing publication bias of studies reporting all-cause mortality in COVID-19 patients with cardiac injury compared with patients without cardiac injury.

cardiac biomarkers along with their continuous monitoring during hospitalization can aid in the early identification of patients with severe COVID-19 infection, and thus be an indication to escalate care as appropriate. Further studies are required to assess if routine monitoring of cardiac biomarker levels may lead to improved patient outcomes in patients hospitalized with COVID-19.

## Authors' Contribution

Bansal, Agam: Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Wiring − Original Draft, Writing − Review & Editing, Visualization; Kumar, Asish: Formal Analysis, Data Curation, Writing − Review & Editing, Visualization; Patel, Divyang: Formal Analysis, Data Curation, Writing − Review & Editing, Visualization; Puri, Rishi: Formal Analysis, Data Curation, Writing − Review & Editing, Visualization; Kalra, Ankur: Conceptualization, Methodology, Formal Analysis, Data Curation, Writing − Review & Editing, Visualization; Kapadia, Samir: Conceptualization, Methodology, Writing − Review & Editing, Visualization; Reed, Grant: Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Wiring − Original Draft, Writing − Review & Editing, Visualization, Supervision, Project administration.

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.


1. Anon. Coronavirus Disease (COVID-19) Situation Reports. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed September 26, 2020.
2. Anon. COVID-19 Map - Johns Hopkins Coronavirus Resource Center. Available at: https://coronavirus.jhu.edu/map.html. Accessed September 26, 2020.
3. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus −infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061–1069. https://doi.org/10.1001/jama.2020.1585.
4. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020;5:802–810. Available at: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631382631. Accessed September 26, 2020.
5. Santoso A, Pranata R, Wibowo A, Al-Farabi MJ, Huang I, Antariksa B. Cardiac injury is associated with mortality and critically ill pneumonia in COVID-19: a meta-analysis. *Am J Emerg Med* 2020.
6. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. *Prog Cardiovasc Dis* 2020;63:390–391. Available at: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L2005225026. Accessed September 26, 2020.
7. Force* TADT. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307:2526–2533. https://doi.org/10.1001/jama.2012.5669.
8. Kellum JA, Lameire N, Group KAKIGW. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013;17:204.. Available at: https://pubmed.ncbi.nlm.nih.gov/23394211. Accessed September 26, 2020.
9. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13. https://doi.org/10.1186/1471-2288-5-13.
10. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)* 2020;395:497–506.
11. Hu B, Wang D, Hu C, Hu M, Zhu F, Xiang H, Zhao B, Zhang X, Kashani K, Peng Z. Clinical features of critically ill patients with COVID-19 infection in China. 2020. Available at: https://www.researchsquare.com/article/rs-16250/v1. Accessed September 26, 2020.
12. Li K, Chen D, Chen S, Feng Y, Chang C, Wang Z, Wang N, Zhen G. Radiographic findings and other predictors in adults with covid-19. *medRxiv* 2020;2020. Available at: http://medrxiv.org/content/early/2020/03/27/2020.03.23.20041673.abstract. Accessed September 26, 2020.
13. Luo X, Xia H, Yang W, Wang B, Guo T, Xiong J, Jiang Z, Liu Y, Yan X, Zhou W, Ye L, Zhang B. Characteristics of patients with COVID-19 during epidemic ongoing outbreak in Wuhan, China. *medRxiv* 2020;2020. Available at: http://medrxiv.org/content/early/2020/03/23/2020.03.19.20033175.abstract. Accessed September 26, 2020.
14. Wu C, Hu X, Song J, Du C, Xu J, Yang D, Chen D, Zhong M, Jiang J, Xiong W, Lang K, Zhang Y, Shi G, Xu L, Song Y, Zhou X, Wei M, Zheng J. Heart injury signs are associated with higher and earlier mortality in coronavirus disease 2019 (COVID-19). *medRxiv* 2020;2020.02.26.20028589. Available at: http://medrxiv.org/content/early/2020/02/29/2020.02.26.20028589.abstract. Accessed September 26, 2020.
15. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, Ma K, Xu D, Yu H, Wang H, Wang T, Guo W, Chen J, Ding C, Zhang X, Huang J, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020;368. m1091−m1091.
16. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H,

Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England)* 2020;395:1054–1062.
17. Wang Y, Lu X, Li Y, Chen H, Chen T, Su N, Huang F, Zhou J, Zhang B, Yan F, Wang J. Clinical course and outcomes of 344 intensive care patients with COVID-19. *Am J Respir Crit Care Med* 2020;201:1430–1434. https://doi.org/10.1164/rccm.202003-0736LE.
18. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, Cao S, Liu X, Xiang Y, Zhao Q, Huang H, Yang B, Huang C. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J* 2020;41:2070–2079. https://doi.org/10.1093/eurheartj/ehaa408.
19. 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;46:846–848. https://pubmed.ncbi.nlm.nih.gov/32125452. Accessed September 26, 2020.
20. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1–8. Available at http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631345247. Accessed September 26, 2020.
21. Zhang F, Yang D, Li J, Gao P, Chen T, Cheng Z, Cheng K, Fang Q, Pan W, Yi C, Fan H, Wu Y, Li L, Fang Y, Liu J, Tian G, He L. Myocardial injury is associated with in-hospital mortality of confirmed or suspected COVID-19 in Wuhan, China: a single center retrospective cohort study. *medRxiv* 2020;2020. 03.21.20040121Available at: http://medrxiv.org/content/early/2020/03/24/2020.03.21.20040121.abstract. Accessed September 26, 2020.
22. Cao M, Zhang D, Wang Y, Lu Y, Zhu X, Li Y, Xue H, Lin Y, Zhang M, Sun Y, Yang Z, Shi J, Wang Y, Zhou C, Dong Y, Liu P, Dudek SM, Xiao Z, Lu H, Peng L. Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai, China. *medRxiv* 2020;2020. 03.04.20030395Available at: http://medrxiv.org/content/early/2020/03/06/2020.03.04.20030395.abstract. Accessed September 26, 2020.
23. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong J-C, Turner AJ, Raizada MK, Grant MB, Oudit GY. Angiotensin converting enzyme 2: SARS-CoV-2 receptor and regulator of the Renin-Angiotensin system. *Circ Res* 2020;126:1456–1474.
24. Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: possible mechanisms. *Life Sci* 2020;253:117723. Available at: http://www.sciencedirect.com/science/article/pii/S0024320520304719. Accessed September 26, 2020.
25. Zhao X, Nicholls JM, Chen Y-G. Severe acute respiratory syndrome-associated coronavirus nucleocapsid protein interacts with Smad3 and modulates transforming growth Factor-$\beta$ signaling. *J Biol Chem* 2008;283:3272–3280. Available at: http://www.jbc.org/content/283/6/3272.abstract. Accessed September 26, 2020.