

Incidence of Cardiac Injury and Associated Poor Outcomes in Hospitalized Patients with COVID-19: A Systematic Review and Meta-Analysis

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Systematic Review

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Abstract

Background: Increasing number of studies have indicated a link between coronavirus disease 2019 (COVID-19) and acute cardiac injury. However, there is currently no consensus on the incidence of cardiac injury and its associated prognosis in COVID-19 patients.

Methods: We searched PubMed and Embase for studies that evaluated cardiac injury in hospitalized COVID-19 patients. Demographic information, co-morbidities, and relevant laboratory values were extracted and a meta-analysis was performed.

Results: Ten studies with 1637 patients were included in this meta-analysis. The overall incidence of cardiac injury was 23.2% (380/1637) in hospitalized COVID-19 patients. The incidence was higher (58.5%) in patients who were critically ill, admitted to the intensive care unit (ICU) or died. The composite mortality rate of patients with cardiac injury was 75.1% (251/334). Cardiac injury was significantly associated with increased mortality (OR=21.71, 95% CI 9.16-51.46) in those patients. When combining death with ICU admission and patients who were critically ill, patients with cardiac injury was again strongly associated with worse outcomes (OR=22.18, 95% CI 11.68-42.10). In subgroup analyses, hospitalized COVID-19 patients who were older and had history of hypertension, coronary artery disease, chronic obstructive respiratory disease, and diabetes were associated with increased risk of developing cardiac injury.

Conclusion: Cardiac injury is common in hospitalized COVID-19 patients and is significantly associated with poor outcomes. Patients who are older and have hypertension, diabetes, coronary artery diseases and chronic obstructive pulmonary diseases are prone to develop cardiac injury. When appropriate, early screening, triage and cardiac monitoring are needed for these patients.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is the most recently discovered member of the coronavirus family. Since late December 2019, COVID-19 has caused initially a local epidemic in Wuhan, China and subsequently a global pandemic involving 212 countries, areas or territories. As of April 11, 2020, more than 160,000 cases have been confirmed and 99,000 lives lost[1]. As we gradually came to understand that this virus is not simply one that causes respiratory symptoms, more and more cases and reports have shown alarming complications in the cardiovascular system. Recent works by Huang et al[2] and Guo et al[3] not only demonstrated that a considerable number of hospitalized patients diagnosed with COVID-19 exhibited cardiac injury (represented by elevation of cardiac biomarkers such as troponin), but that those who developed cardiac injury had a significantly higher mortality than those without. Moreover, Shi et al[4] performed a multivariate analysis of 416 patients and found that cardiac injury was independently associated with an increased risk of mortality in patients with COVID-19. Despite these illuminating results, few other studies directly looked into the association of cardiac injury with prognosis and co-

morbidities. As a result, the authors have decided to perform a systematic review and meta-analysis to further investigate the correlation between cardiac injury and outcomes in COVID-19 patients.

Methods

1. Data Source and Searches

We performed a systematic literature search in PubMed and Embase. We used the search term “coronavirus”. The search was limited to Chinese and English and all articles from Jan 1, 2020 to April 5, 2020 were reviewed.

2. Study Selection, Data Extraction and Definitions

Original studies that reported cardiac injury, troponin or creatine kinase MB (CKMB) were included. Review articles, meta-analysis and case reports were excluded. The extracted data included the number of patients enrolled in each study, age, gender, co-morbidities (coronary artery disease [CAD], diabetes [DM], hypertension [HTN], and chronic obstructive pulmonary diseases [COPD]), laboratory values (C-reactive protein [CRP], procalcitonin, and NT-pro brain natriuretic peptide [NT-proBNP]), and mortality. Definitions of cardiac injury for each article were reviewed and all studies defined cardiac injury as troponin above the 99th percentile upper limit of the reference range.

In studies that did not directly report mortality in patients with or without cardiac injury, the mortality of patients with cardiac injury was calculated as the ratio of deceased patients with cardiac injury over all patients with cardiac injury. Poor outcomes were defined as a composite of death, intensive care unit (ICU) admission and those reported as “critically ill” by the original authors (Chen C. et al and Zhou B. et al) per the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia 6th Edition, National Health Commission of the People’s Republic of China (abbreviated as the 6th edition)[5]. It was defined as patients who fit into any one of the following: 1) respiratory failure in need of mechanical ventilation; 2) shock; or 3) other organ dysfunction needing ICU admission[5].

3. Statistical analysis

Review Manager 5.3 (Cochrane, London, UK) was used to perform data analysis. Continuous data were extracted and median with interquartile range was converted to mean with standard deviation using the equations delineated by Hozo et al[6]. Dichotomous variables were analyzed using the Mantel-Haenszel method and the random effects model. A 95% confidence interval was selected and the results were expressed as odds ratio. P value of less than 0.05 was considered statistically significant. Statistical heterogeneity was evaluated using the I^2 statistic. Publication bias was evaluated using funnel plots.

Results

1. Study characteristics

A total of 2413 abstracts resulted with the search term as of April 5, 2020. Each abstract was reviewed by the authors and 48 studies that reported troponin and CKMB were reviewed in full. Figure 1 shows the literature search and selection process. Since most early data originated from Wuhan, China, several original articles included patients from the same hospitals during the same period of time. Only the ones with more patients were included in the analysis to minimize duplication and maximize study effect. He et al[7] had a different definition of cardiac injury (>3 times the reference value of troponin) and was not included in the final analysis. The study by Du et al[8] was an observational study that only reported fatal cases and was also not included. As a result, 10 studies were included in the analysis and these studies were summarized in Table 1.

2. Incidence, mortality and poor outcomes of hospitalized COVID-19 patients with cardiac injury

The pooled overall incidence of cardiac injury in hospitalized COVID-19 patients was 23.2% (380/1637). We separately calculated the incidence of cardiac injury in hospitalized COVID-19 patients who were in the poor outcomes category defined above. The incidence of cardiac injury for those patients was 58.5% (286/489). In contrast, the incidence of cardiac injury in patients who were not in the poor outcomes group was only 8.3% (95/1148). Supplemental Table 1 compiles the incidence of cardiac injury in hospitalized COVID-19 patients.

The overall mortality rate of hospitalized COVID-19 patients with cardiac injury was 75.1% (251/334). Compared to patients without cardiac injury, these patients had significantly higher risk for mortality (OR = 21.71, 95% CI 9.16–51.46, $I^2 = 75%$, $Z = 6.99$, $P < 0.00001$) as shown in Figure 2A.

The overall rate of poor outcomes in hospitalized COVID-19 patients with cardiac injury was 75.3% (286/380). A comparison of poor outcomes between patients with or without cardiac injury also revealed significantly higher odds of poor outcomes in those with cardiac injury (OR = 22.18, 95% CI 11.68–42.10, $I^2 = 61%$, $Z = 9.48$, $P < 0.00001$) as shown in Figure 2B. Funnel plots in Supplemental Figure 1 showed symmetrical distribution of effect sizes in the studies included in the mortality and poor outcomes analysis.

3. Demographics/Co-morbidities and Cardiac Injury

Combining data from the two papers that directly compared patients with or without cardiac injury, we found that patients with cardiac injury were of older age (mean difference = 15.98 years, 95% CI 11.80–20.15, $I^2 = 74%$, $Z = 7.50$, $P < 0.00001$) and consisted of fewer females (OR = 0.58, 95% CI 0.28–1.18, $I^2 = 67%$, $Z = 1.50$, $P = 0.13$). However, the gender discrepancy was not statistically significant (Figure 4A-B).

Hospitalized COVID-19 patients who had a history of HTN (OR = 5.13, 95% CI 3.41–7.72, $I^2 = 0\%$, $Z = 7.84$, $P < 0.00001$), CAD (OR = 8.94, 95% CI 3.83–20.87, $I^2 = 44\%$, $Z = 5.07$, $P < 0.00001$), DM (OR = 3.07, 95% CI 1.64–5.75, $I^2 = 35\%$, $Z = 3.51$, $P = 0.0004$) and COPD (OR = 6.33, 95% CI 1.44–27.85, $I^2 = 23\%$, $Z = 2.44$, $P = 0.01$) all had significantly increased risk of developing cardiac injury during hospitalization (Figure 4C-F).

4. Cardiac Injury and lab values

Last but not least, we looked into the correlation of important laboratory parameters and cardiac injury (Figure 5A-C). Hospitalized COVID-19 patients with cardiac injury had significantly higher CRP (mean difference = 6.00, 95% CI 4.95–7.06, $I^2 = 85\%$, $Z = 11.15$, $P < 0.00001$), procalcitonin (mean difference = 0.18, 95% CI 0.13–0.23, $I^2 = 76\%$, $Z = 7.33$, $P < 0.00001$) and NT-proBNP (mean difference = 1113.44, 95% CI 256.94–1969.95, $I^2 = 99\%$, $Z = 2.55$, $P = 0.01$) levels.

Discussion

Our meta-analysis of the currently published data has demonstrated that: 1) a considerable amount of hospitalized COVID-19 patients developed cardiac injury (23.2%) and the incidence was significantly higher in patients who were sicker (58.5%); 2) hospitalized COVID-19 who developed cardiac injury exhibited significantly higher rates of mortality (75.1%) and poor outcomes (75.3%) compared to those without; and 3) hospitalized COVID-19 patients who were older and had co-morbidities including HTN, CAD, DM and COPD demonstrated increased risk of developing cardiac injury.

1. Incidence of cardiac injury in COVID-19 patients

Since the outbreak in China, increasing spotlight has been brought up on cardiac injury in COVID-19 patients who needed inpatient care. Hu et al[9] described a 37 year-old male patient in Wuhan positive for COVID-19 who developed fulminant myocarditis after three days of chest pain and shortness of breath. He presented with hemodynamic instability, severely elevated cardiac biomarkers (Troponin T [TnT] $> 10,000$ ng/L and NT-BNP $> 21,000$ ng/L) and depressed ventricular systolic function (LVEF 27%). In Europe, Inciardi et al[10] reported an otherwise healthy 53 year-old female positive for COVID-19 who developed acute myopericarditis. Similarly, she had elevated cardiac biomarkers as well as radiographic evidence of biventricular myocardial interstitial edema and diffuse late gadolinium enhancement on cardiac magnetic resonance imaging. Fortunately, both patients stabilized after undergoing aggressive treatment. These case reports should ring a bell on the potential involvement of the cardiovascular system in a wider range of COVID-19 patients worldwide.

More than a dozen studies have reported incidence of cardiac injury in hospitalized COVID-19 patients, ranging from 7% to 44%[2–4,11–17]. However, there is no consensus on the overall incidence of cardiac

injury in these patients. Li et al[18] performed a meta-analysis and attempted to determine the incidence of cardiac injury. However, they only analyzed two studies (179 patients) and presented the overall incidence of cardiac injury at 8% (15/179). Although two other studies with more patients were included, these studies only reported elevated creatine kinase levels, which was not specific for cardiac injury and hence could not represent true incidence.

With more evidence available, we included all of the current studies that reported cardiac injury and determined its incidence in hospitalized COVID-19 patients was 23.2% from a total of 1637 patients (380/1637). Moreover, we performed subgroup analyses and discovered a significantly higher incidence of cardiac injury (58.5%, 286/489) in patient with poor outcomes (death, ICU admission or critically ill). Although not included in our pooled analysis, Du et al's[8] investigation of 85 fatal cases reported that the incidence of cardiac injury in patient who died from COVID-19 was 44.7% (38/85). This was in stark contrast with patients who were not in the poor outcomes group as their incidence of cardiac injury was only 8.3% (95/1148). Although it can be expected that the incidence of cardiac injury would be higher in patients who were sicker, this marked difference requires more attention in our current battle with COVID-19. We believe the overall incidence rate presented in this pooled analysis is more representative due to the larger number of patients included.

2. Demographics and co-morbidities associated with cardiac injury

Age is perhaps the most talked about indicators of patient outcomes in this current COVID-19 outbreak as the general public often has the notion that this is a disease of the elderly. Whether there is a connection between age and the development of cardiac injury was also studied. Here, our pooled analysis was consistent with other studies that COVID-19 patients who developed cardiac injury were significantly older (mean difference = 15.98 years, 95% CI 11.80–20.15, $P < 0.00001$). Besides age, the male gender has also been associated with poor outcomes in COVID-19 patients. A pre-print meta-analysis of 77,932 patients by Wei et al[19] revealed that the male gender had significantly higher risks of developing severe cases (OR = 1.63, 95% CI 1.28–2.06) and death (OR = 1.71, 95% CI 1.51–1.93). However, although both Shi et al and Guo et al reported more male patients in the cardiac injury group[3,4], our pooled analysis of these two studies did not achieve statistical significance. Thus, whether male patients are more likely to develop cardiac injury still needs more evidence.

Several studies have looked into cardiovascular co-morbidities in COVID-19 patients. In Li et al's meta-analysis of 6 studies[18], the incidence of HTN, DM and cardio-cerebral vascular diseases were 17.1%, 9.7% and 16.4%. Chen T. et al[11] reported that hospitalized COVID-19 patients with cardiovascular co-morbidities were more likely to develop cardiac complications. In the multivariate analysis carried out by Wang L. et al [20], a history of cardiovascular disease was an independent predictor for death. This was consistent with another multivariate analysis from Chen C. et al [17]. On the other end of the spectrum, Guo et al [3] pointed out that a significant number of patient with these co-morbidities did not progress to

cardiac injury and had relatively favorable outcomes. According to China CDC Weekly in February[21], 80.9% of all COVID-19 patients (hospitalized and non-hospitalized) with cardiovascular co-morbidities had only mild symptoms with no mortality, 13.8% severe symptoms and only 4.7% critically ill among 44,672 confirmed cases. To determine whether having cardiovascular co-morbidities affected the risk of developing cardiac injury, we looked at the combined effects of 603 patients in Guo et al and Shi et al. Consistent with previous reports, hospitalized COVID-19 patients with history of HTN (OR = 5.13, 95% CI 3.41–7.72, $P < 0.00001$), CAD (OR = 8.94, 95% CI 3.83–20.87, $P < 0.00001$), DM (OR = 3.07, 95% CI 1.64–5.75, $P = 0.0004$) and COPD (OR = 6.33, 95% CI 1.44–27.85, $P = 0.01$) were more likely to develop cardiac injury.

In addition to demographics and co-morbidities, we also observed substantially elevated levels of NT-proBNP in patients who developed cardiac injury (mean difference = 1113.44, 95% CI 256.94–1969.96, $P = 0.01$) during their hospitalization. This pointed to one possible explanation of the high mortality rate in patients with cardiac injury: acute decompensated heart failure. In the two case reports mentioned above, both patients developed heart failure and required inotropic support[9,10]. Zhou F. et al[14] reported that 23% of hospitalized COVID-19 patients (44/191) developed heart failure symptoms. This ratio increased to 52% in those who died (28/54). Guo et al[3] not only reported a positive correlation of TnT levels in COVID-19 patients with NT-proBNP ($\beta = 0.613$, $P < 0.001$), but also showed a dynamic increase of NT-proBNP during the hospital course exclusively in patients who eventually died. Together with our analysis, these data proposed a new area of investigation of whether COVID-19 patients with cardiac injury died from heart failure.

3. Cardiac injury in hospitalized COVID-19 patients predicts poor outcomes and death

Not only is it important to know the association of cardiac injury with co-morbidities, whether it predicts prognosis is of more value. Some studies included in our review reported positive correlation of elevated cardiac biomarkers in patients who had poor outcomes. Both Shi et al[4] and Chen C. et al[17] performed multivariate regression analysis and both reported that cardiac injury was an independent predictor of mortality. However, in the multivariate analysis performed by Wang L et al[20], cardiac injury was only predictive of fatal outcomes in univariate analysis but failed to achieve significance in multivariate analysis. Lippi et al conducted a preliminary meta-analysis of troponin levels in COVID-19 patients and found that it was increased in COVID-19 patients with severe disease than in those without[22].

In our analysis, we integrated 10 studies to better look into how cardiac injury affected outcomes in hospitalized COVID-19 patients. We discovered that hospitalized COVID-19 patients with cardiac injury had a significantly increased mortality rate compared to those without, with an OR of 21.71. The mortality rate of hospitalized COVID-19 patients with cardiac injury was found to be 75.1% (251/334). This mortality rate was significantly higher than any mortality rates reported so far. Guo et al[3] described a mortality rate of 69.44% (25/36) for patients who developed cardiac injury and also had underlying

cardiovascular diseases and 37.50% (6/16) for those with cardiac injury but without cardiovascular comorbidities. Shi et al[4] reported a mortality rate of 51.2% (42/82) in patients with cardiac injury. This extremely high rate of mortality among patients with cardiac injury is alarming. Revisiting the studies included in our analysis, we discovered that in two studies by Zhou F. et al[14] and Deng et al[12], death rate among patients with cardiac injury were particularly high: 97.0% (32/33) and 98.5% (65/66) respectively. These extreme rates may have skewed the overall mortality rate higher and needed to be considered with caution.

Since only 6 studies associated cardiac injury with mortality, we combined death, ICU admission and those who were critically ill as poor outcomes and investigated whether cardiac injury predicted overall poor prognosis in COVID-19 patients. With the rate of poor outcomes as high as 75.3% (286/380), patients with cardiac injury again had significantly elevated risk of being critically ill, needing ICU admission or even death compared to those without (OR = 22.18, 95% CI 11.68–42.10, $P < 0.00001$). It is important to note that these high rates of mortality and poor outcomes were only associated with COVID-19 patients who were hospitalized and cannot be applied to those who do not require hospitalization.

4. Possible etiology of cardiac injury in COVID-19 patients

Currently several editorials and review articles have elaborated on the possible etiologies of cardiac injury. The mainstream hypotheses include 1) damage caused by cytokine storm triggered by the virus[18], 2) Type II demand ischemia due to hypoxemia caused by the dominating respiratory failure[23], and 3) direct myocardial injury by viral infiltration[24]. As of now, no evidence was available to substantiate direct viral infiltration of cardiomyocytes. Only a few autopsy reports were available that described pathological involvement of the heart. Xu et al.[25] observed the presence of interstitial mononuclear inflammatory infiltrates in the heart but no substantial tissue damage. Another Chinese pathology report by Yao et al[26] described three patients who died of COVID-19 in Chongqing, China. They observed enlarged and necrotic cardiomyocytes with infiltrative phagocytes and rare CD4+ T cells in all three patients. Again, no virus was detected in the heart. More autopsy results are needed. Although Type II demand ischemia should always be kept in mind in patients with respiratory distress, there is hardly direct evidence pointing towards hypoxemia as the sole cause of cardiac injury. Moreover, in Inciardi et al's [10] case report, the previously healthy 53 year-old female COVID-19 patient did not exhibit any signs and symptoms of pneumonia and had normal chest radiographic findings. It seemed like in her case, cardiac involvement was the only complication from her SARS-CoV-2 infection. This potentially reasoned against hypoxemia and Type II demand ischemia as the main cause of cardiac injury. Currently, the most convincing hypothesis of cardiac injury involves cytokine storm. This has been solidified by Huang et al[2], whose study revealed higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNF α in COVID-19 patients admitted to the ICU. Our analyses also agreed with this hypothesis by showing significantly elevated inflammatory markers including CRP (mean difference = 6.00, 95% CI 4.95–7.06, $P < 0.00001$) and procalcitonin (mean difference = 0.18, 95% CI 0.13–0.23, $P < 0.00001$) in

patients with cardiac injury compared to those without. In order to further elucidate the cytokine storm hypothesis, more studies are needed to compare inflammatory marker between COVID–19 patients with or without cardiac injury.

5. Recommendations for managing hospitalized COVID–19 patients with cardiac injury

Given the high risk of mortality in hospitalized COVID–19 patients with cardiac injury, the authors recommend early screening with cardiac biomarkers, electrocardiograms, and echocardiograms in patients who are at higher risk of developing cardiac injury. These patients are older and often have history of HTN, DM, CAD, and COPD. We hope early detection with appropriate triage and support would help reduce the incidence of cardiac injury in hospitalized COVID–19 patients and the dangerously high rate of mortality and poor outcomes.

Limitations

This study is limited in several ways. First, limited number of studies reported cardiac injury in COVID–19 patients. Second, only two studies directly compared hospitalized COVID–19 patients with or without cardiac injury. Moreover, a small number of studies did not define or had different diagnostic criteria of cardiac injury and therefore could not be included in the analysis. Third, most studies reported their continuous variables as median with interquartile range. In order to analyze some of these continuous variables, conversion to median with standard deviation was necessary, which might introduce bias in our results.

Conclusion

Our meta-analysis revealed that cardiac injury was common in hospitalized COVID–19 patients and its incidence was higher in those who had poor outcomes. The overall mortality of patients with cardiac injury was alarmingly high. Cardiac injury was significantly associated with older age and co-morbidities including HTN, DM, CAD and COPD. Hopefully, early screening, triage and support could help reduce the incidence of cardiac injury in hospitalized COVID–19 and its associated poor outcomes.

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Table 1

Table 1 Summary of Studies Included

Authors	Year	Hospital	Type	COVID-19 Patient Selection	Number of Patients	Number of Cardiac Injury	Death
Chen T. et al ¹¹	2020	Tongji Hospital Wuhan	Retrospective	1/13/2020 to 2/12/2020; all deceased or discharged patients	274	89	113
Deng et al ¹²	2020	Hankou and Caidian branch of Tongji Hospital (and) Hankou branch of Central Hospital of Wuhan	Retrospective	1/1/2020 to 2/21/2020; all deceased or discharged patients	225	66	109
Yang et al ¹³	2020	Jin Yin-Tan Hospital Wuhan	Retrospective	12/24/2019 to 1/26/2020; All critically ill patients	52	12	32
Zhou F. et al ¹⁴	2020	Jin Yin-Tan Hospital Wuhan (and) Wuhan Pulmonary Hospital	Retrospective	12/29/2019 to 1/31/2020; all discharged or deceased patients	191	33	54
Guo et al ³	2020	Seventh Hospital of Wuhan City	Retrospective	1/23/2020 to 2/23/2020 all patients	187	52	43
Shi et al ⁴	2020	Renmin Hospital of Wuhan University	Retrospective	1/20/2020 to 2/10/2020; all patients	416	82	57
Huang et al ²	2020	Jin Yin-Tan Hospital Wuhan	Prospective	12/16/2019 to 1/2/2020; all patients	41	5	6
Wang et al ¹⁶	2020	Zhongnan Hospital of Wuhan University	Retrospective	1/1/2020 to 1/28/2020; all patients	138	10	6
Chen C. et al ¹⁷	2020	Hankou, Zhongfa Xin Cheng and Guang Gu branches of Tongji Hospital	Retrospective	1/2020 to 2/2020; all patients	150	22*	11
Zhou B. et al ¹⁵	2020	West District of Union Hospital of Tongji Medical College	Retrospective	2/5/2020 to 2/13 2020, all patients	34	9*	Not reported

*Reported as elevated CTnI (cardiac troponin I). Defined as value >99th percentile of normal reference value, which is the same definition of cardiac injury in other studies

Figures

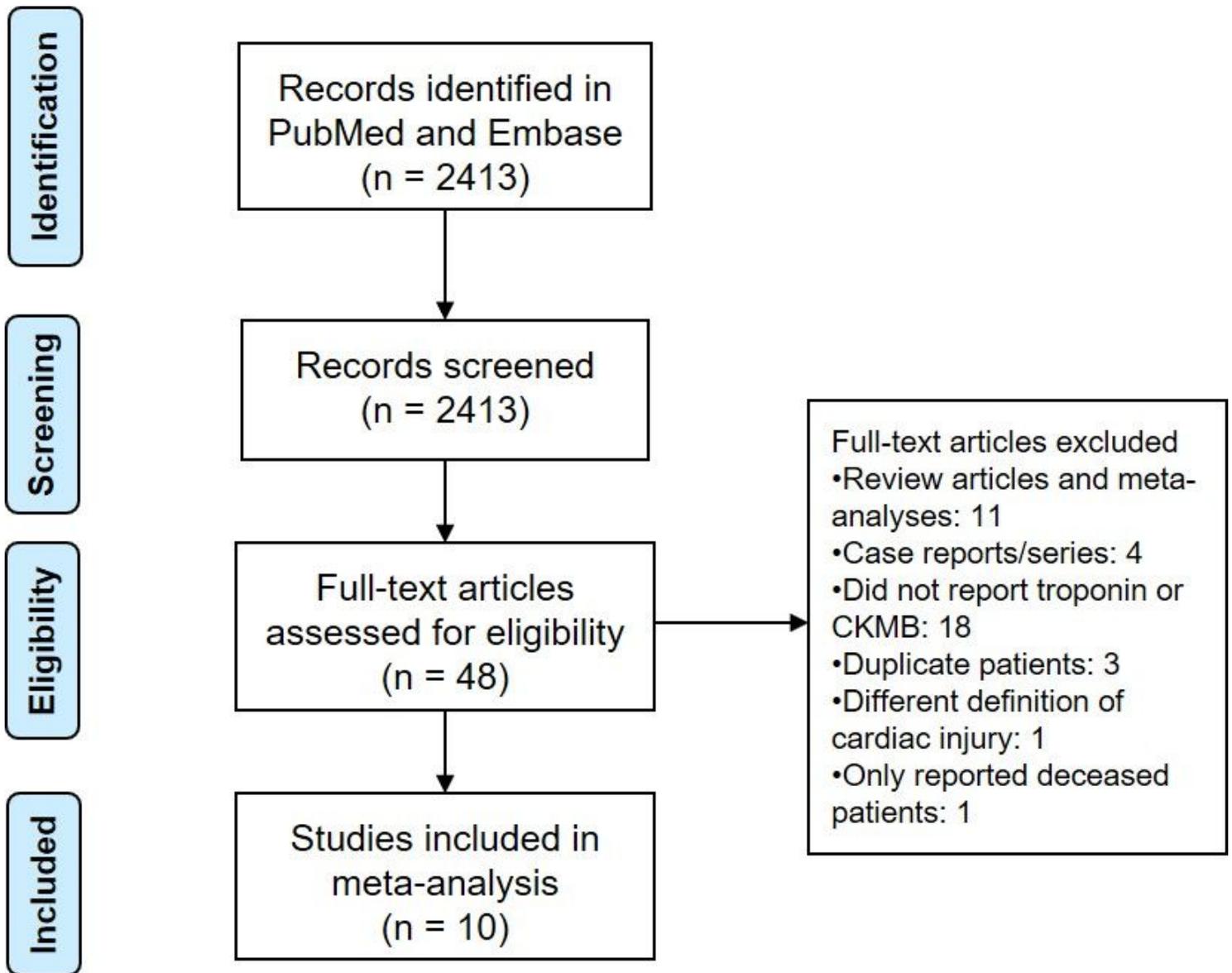


Figure 1

Flowchart of Study Selection Process

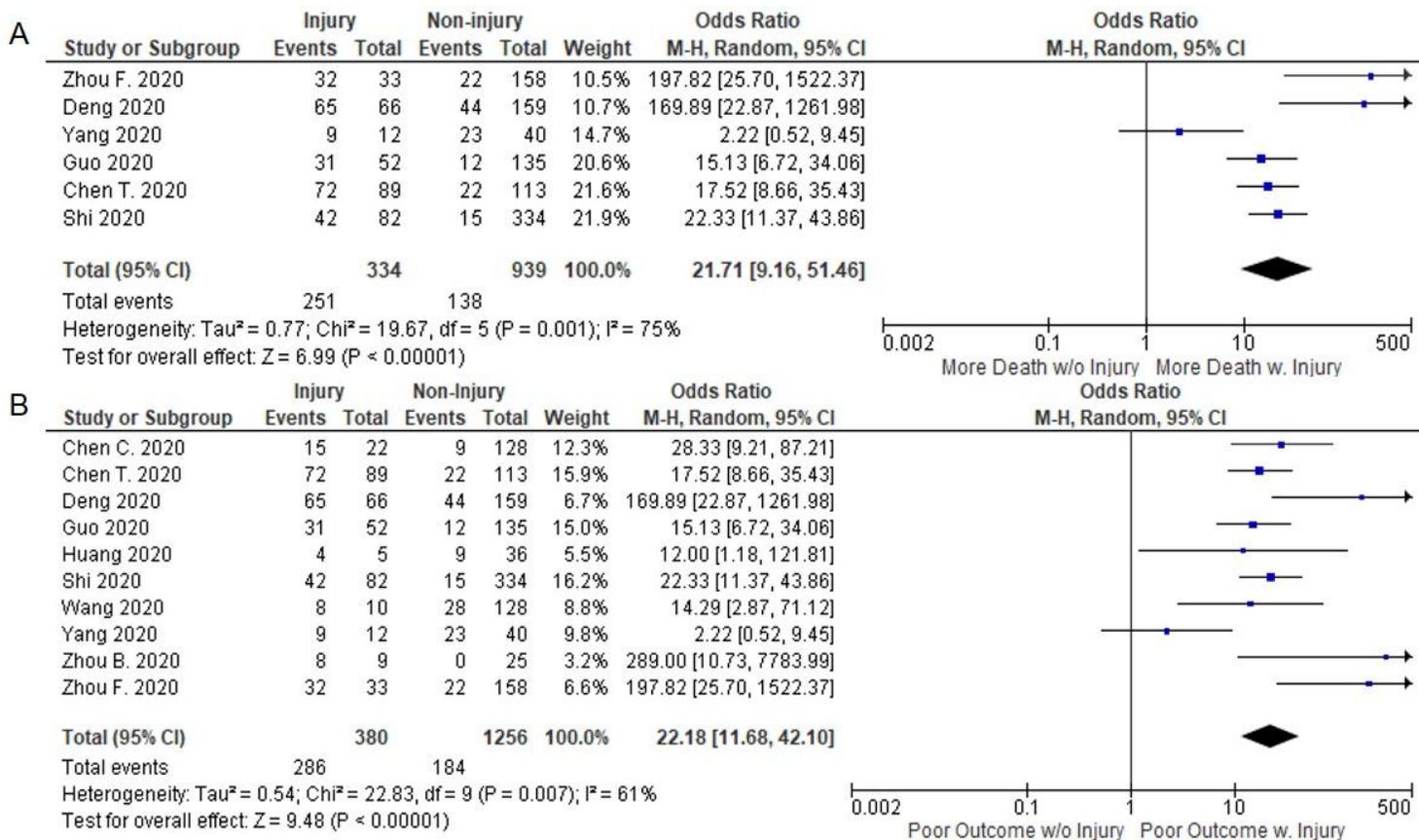


Figure 2

Comparison of Mortality and Poor Outcomes in Hospitalized COVID-19 Patients With or Without Cardiac Injury. A) Cardiac injury and mortality; B) Cardiac injury and poor outcomes (combined death, ICU admission and critically ill). Hospitalized COVID-19 patient with cardiac injury had significantly higher rates of mortality and poor outcomes compared to those without

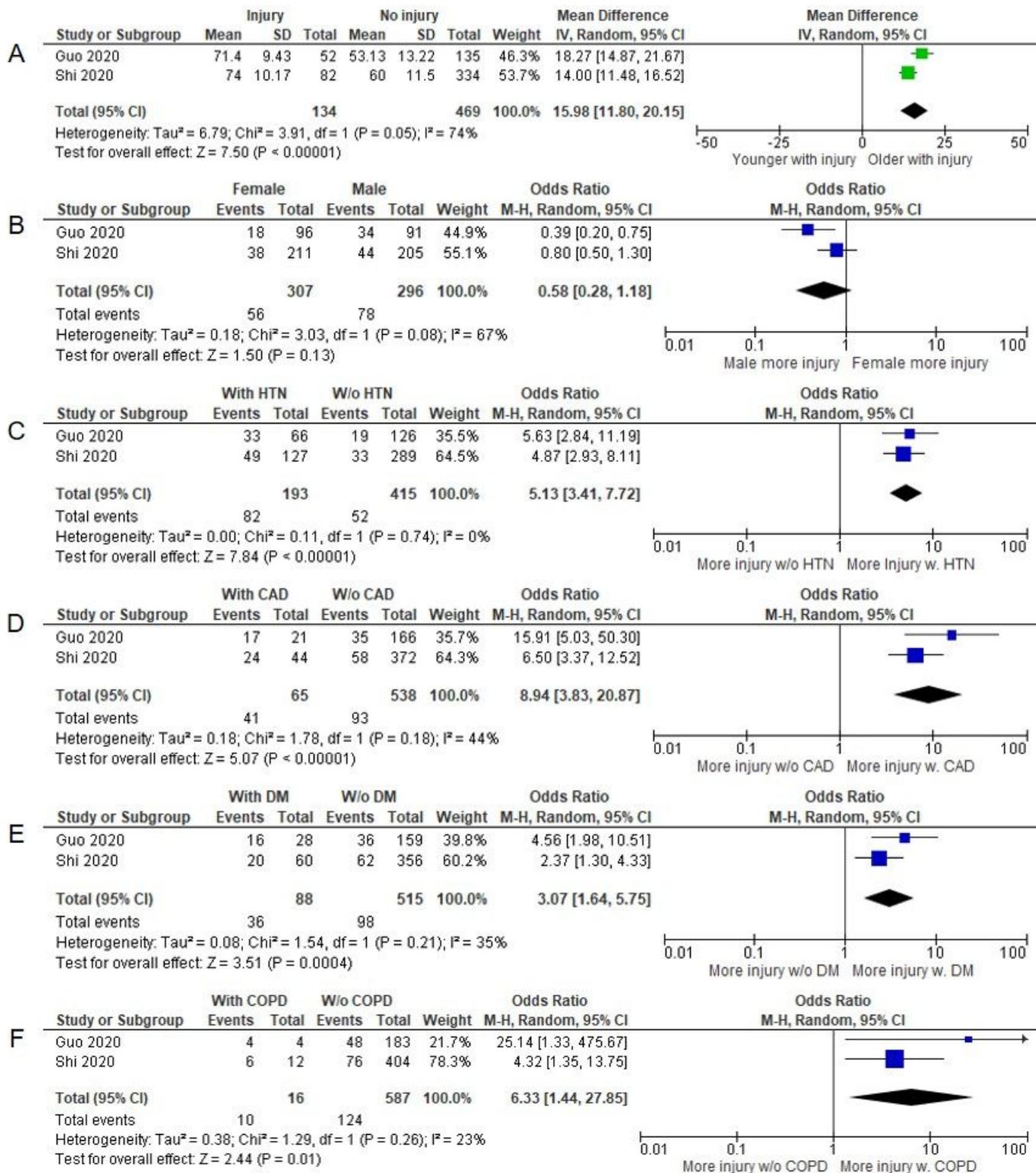


Figure 3

Comparison of Demographics and Co-morbidities in Hospitalized COVID-19 Patients With or Without Cardiac Injury. A) Age; B) Gender; C) Hypertension (HTN); D) Coronary artery disease (CAD); E) Diabetes (DM); F) Chronic Obstructive Pulmonary Diseases (COPD). COVID-19 patients who were older and had history of HTN, CAD, DM and COPD exhibited increased odds of developing cardiac injury during hospitalization. The effect of gender on cardiac injury did not reach statistical significance

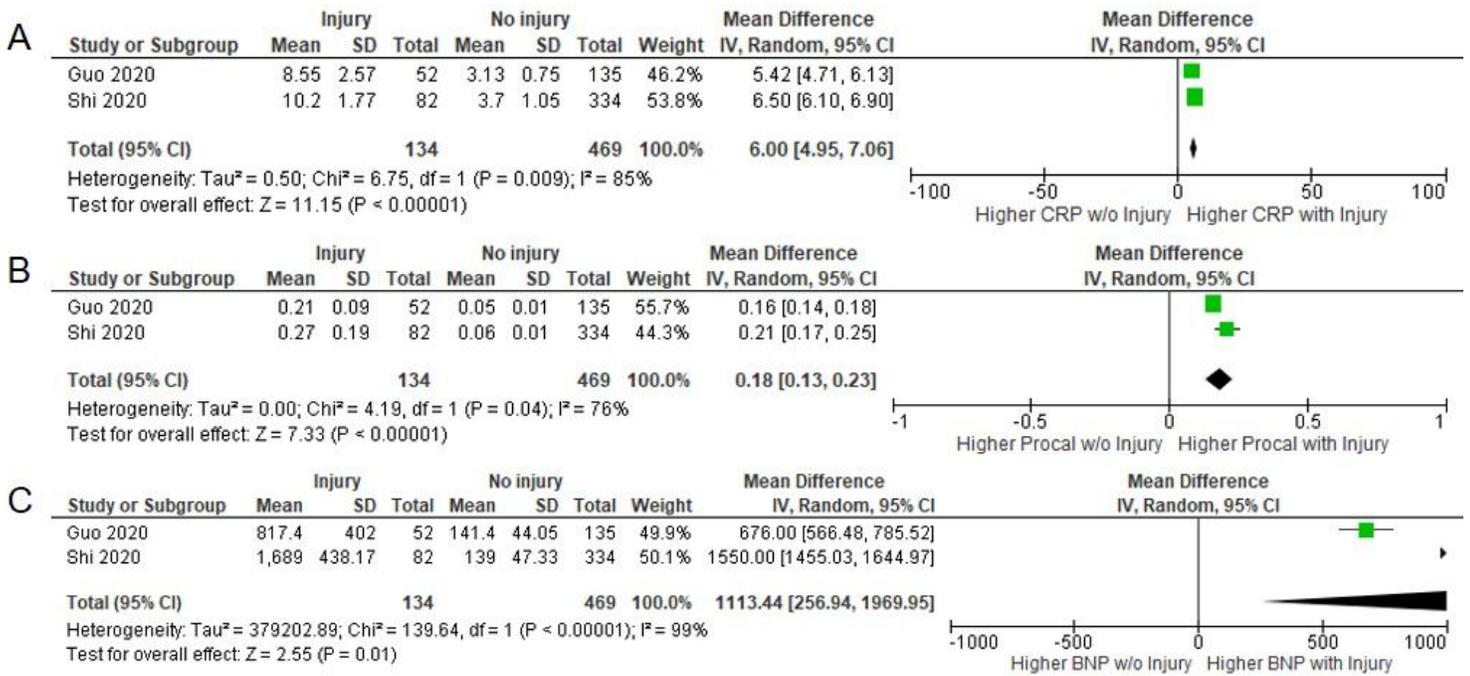


Figure 4

Comparison of Laboratory Values in Hospitalized COVID-19 Patients With or Without Cardiac Injury. A) C-reactive protein (CRP); B) Procalcitonin (Procal); C) NT-pro brain natriuretic peptide (NT-proBNP). Hospitalized COVID-19 patients with cardiac injury had significantly increased CRP, procalcitonin and NT-proBNP compared to those without

Supplementary Files

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- [SupplementalInformation.docx](#)