Elevated cardiac troponin I as a predictor of outcomes in COVID-19 hospitalizations: a meta-analysis

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SUMMARY

Globally, coronavirus is causing more social, economic and healthcare disruption than expected. The emerging literature has reported the complications of coronavirus, and the mortality and risk factors involved, including cardiac injury and multisystem organ failure. In this meta-analysis, we aim to evaluate the association of elevated troponin I levels with outcomes in COVID-19 hospitalized patients. Observational studies describing troponin I levels and outcomes of COVID-19 hospitalized patients from 1 December 2019 to 15 August 2020 were identified. Data were extracted following PRISMA guidelines with a consensus of two independent reviewers. Adverse outcomes were defined as admission to intensive care units (ICUs), oxygen saturation <90%, invasive mechanical ventilation (IMV), and in-hospital mortality. The odds ratio (OR) and 95% confidence interval (95% CI) were obtained and forest plots were created using random-effects models. Ten studies with 3982 confirmed COVID-19 patients were included. In patients with poor outcomes, the prevalence of elevated troponin I levels was 51% (690/1341). In meta-analysis, patients with elevated troponin I levels had higher odds of poor outcomes compared to better outcomes with pooled OR of 7.92 (95% CI: 3.70-16.97; p<0.00001) with 70% heterogeneity (p=0.0005). Our meta-analysis suggests that COVID-19 patients with elevated troponin I levels had a higher risk of poor outcomes. Hence, evaluating the troponin I levels might be helpful in preventing risk of cardiac complications and other organ dysfunction.

Keywords: COVID-19, Coronavirus, cardiac injury, troponin I, outcomes, mechanical ventilation, ICU.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging outbreak from Wuhan City, China caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the World Health Organization (WHO), COVID-19 has spread rapidly in roughly 215 countries/territories/areas, causing over 30.6 million confirmed cases and 950,000 deaths as of 20 September 2020 [1]. Considering the global threat, the WHO has declared COVID-19 a public health emergency of international concern. COVID-19 is currently suspected to originate from an animal host (zoonotic origin) followed by human-to-human transmission. The virus is also known to have a relatively low pathogenicity but higher transmissibility, which is evident from the continuously increasing number of confirmed cases globally. The clinical course of COVID-19 is complicated by the onset of severe interstitial pneumonia which may then progress towards acute respiratory distress syndrome (ARDS) and/or multi-organ failure and death in about 15% of patients [2]. Currently, due to the lack of vaccines against SARS-CoV-2 or

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specific therapeutic drugs, potential therapeutic strategies being evaluated stem from previous experience with treating SARS-CoV, MERS-CoV, and other emerging viral diseases [3].
Globally, COVID-19 has caused striking damage to the health care and economy. Emerging literature has reported that 7-28% of COVID-19 patients had developed acute cardiac injury eventually causing more complications and mortality [4-7]. A few reasons for this acute cardiac injury include acute myocardial infarction, viral myocarditis, and inflammation and oxidative stress-induced myocardial damage [6]. Hence, it is important to identify risk stratifying tools to triage these patients, with minimal utilization of resources. In this meta-analysis, we aimed to evaluate the association of elevated Troponin I levels with outcomes in COVID-19 hospitalized patients.

MATERIALS AND METHODS

Endpoint
The aim of the study was to evaluate the role of the elevated cardiac troponin I in predicting outcomes in COVID-19 hospitalized patients. COVID-19 confirmation was evaluated by combined findings of reverse transcription PCR, serology, symptoms and MRI chest in all the studies.
Composite poor outcomes were defined by intensive care unit (ICU) admission, oxygen saturation<90%, invasive mechanical ventilation (IMV) utilization, severe disease, and in-hospital mortality.

Search strategy and selection criteria
A systematic search was conducted on published studies using PRISMA guidelines and followed the MOOSE checklist from December 1, 2019 to August 15, 2020 [8, 9]. We searched PubMed, Web of Science, Scopus, and medRxiv for observational studies that described BMI or comorbidities and outcomes of COVID-19 patients following keyword/MESH terms: (COVID-19) OR coronavirus OR SARS-CoV-2 OR 2019-nCoV. Studies were included in this meta-analysis if they had elevated troponin I levels and outcomes of COVID-19 hospitalized patients. Literature other than observational studies, non-English literature, non-full text, and animal studies were excluded. Flow diagram of the literature search and study selection process is described in Figure 1.

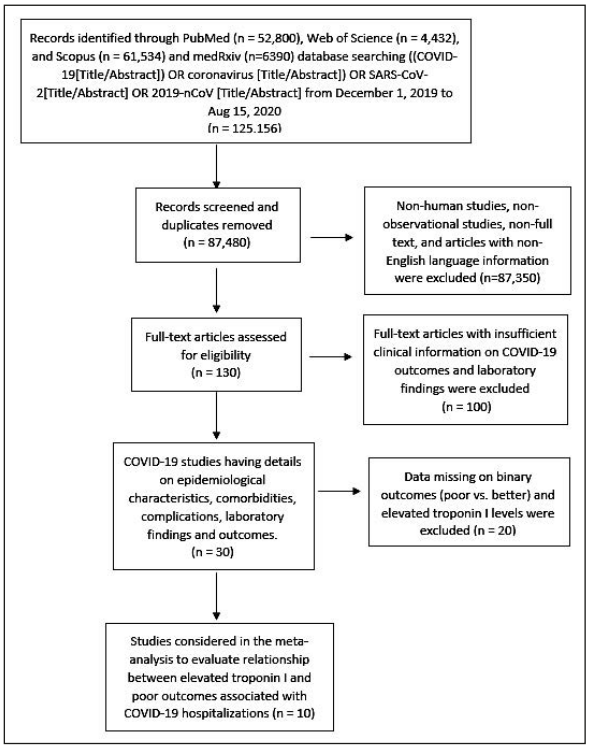


Figure 1 - Flow diagram of literature search and study selection process of COVID-19 outcomes and elevated troponin I.

Study selection
Abstracts were reviewed, and articles were retrieved and reviewed for availability of data on elevated cardiac troponin I and outcomes of COVID-19 patients. Studies which gave details on outcomes were selected for quantitative analysis. PM and UP independently screened all identified studies and assessed full-texts to decide eligibility. Any disagreement was resolved through consensus with NP.

Data collection
From the included studies, we extracted elevated cardiac troponin I and outcomes. Details on binary outcomes like ICU vs. non-ICU admission, severe vs non-severe disease, IMV vs no-IMV use, oxygen saturation <90% vs >90%, in-hospital mortality vs discharged alive and survivors were collected using prespecified data collection forms by two authors (PM and UP) with a consensus with NP.
We have presented the study characteristics like the first authors last name, publication month and

year, country of origin, sample size, study design, outcomes and cut-off range for elevated cardiac troponin I in that individual study Table 1.

Statistical analysis

Data analysis was performed using Review Manager version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). If the study has more than one outcome comparison, then we have used data from the most severe outcome in the analysis to minimise the overall selection bias of our study. The Maentel-Haenszel formula was used to calculate dichotomous variables to obtain odds ratios (ORs) along with its 95% confidence intervals (95% CI) to describe the relationship of elevated cardiac troponin I and outcomes of COVID-19 patients in each study. Random-effects models were used regardless of heterogeneity to estimate the combined effect and its precision, to give a more conservative estimate of the ORs and 95% CI. $p<0.05$ was considered significant. The I^2 statistic was used to assess statistical heterogeneity and value >50% was considered significant heterogeneity. Publication bias was assessed visually using funnel plots and risk of bias of included studies using the Newcastle-Ottawa Scale (NOS) described in (Table2) respectively. NOS was used to assess the quality and bias in the included studies, which rates selection, comparability and outcome. All studies were assessed to be of moderate quality. Sensitivity analysis was performed to assess the effect of publication bias and heterogeneity by excluding outlying studies on the funnel plot. The pooled-OR and 95% CI are represented in the form of forest plots. Each square on the chart area

Table 1 - Study characteristics, outcomes and cardiac troponin I values.

Study	*Country*	*Sample size (no.)*	*Study design*	*Outcomes*	*Elevated hypersensitive cardiac troponin I*
Huang et al., Jan 2020 [21]	China	41	Retrospective Single center	ICU vs. Non-ICU	>28 pg/ml
Zhou et al., Mar 2020 [22]	China	191	Retrospective multi-center	Non-Survivor vs. Survivor	>28 pg/ml
Goyal et al., April 2020 [23]	USA	393	Retrospective multi-center	Invasive Mechanical ventilation vs. Non-Invasive Mechanical Ventilation	>0.5 ng/ml
Huang et al., May 2020 [24]	China	202	Retrospective multi-center	Severe vs. non severe*	No value only increased
Zhao et al., Apr 2020 [25]	China	91	Retrospective single-center	Severe vs. mild*	>0.01 µg/l
Du et al., May 2020 [26]	China	179	Prospective single-center	Deceased vs. Survivors	>0.05 ng/ml
Mikami et al., Jun 2020 [27]	USA	6493	Retrospective multi-center	Non-Survivors vs. survivors	>0.03 ng/dl
Suleyman et al., Jun 2020 [28]	USA	463	Retrospective multi-center	Hospitalized vs. Discharged	>99th percentile
Ferguson et al., Aug 2020 [29]	USA	72	Retrospective multi-center	ICU vs. Non-ICU	>0.055 ng/ml
Yang et al., Aug 2020 [30]	China	136	Retrospective single-center	Moderate vs. Severe+critical	No value only increased
Total		8261			

*World Health Organization and the National Health Commission of China interim guidelines defined disease severity and improvement as follows: Mild cases: The mild clinical symptoms and no pneumonia in imaging. Moderate cases: symptoms like fever and respiratory tract symptoms, etc., and pneumonia can be seen in imaging. Severe cases: Meeting any of the following - respiratory distress, respiratory rate ≥30 breaths/min; SpO_2 ≤93% at rest; and PaO_2/FIO_2 ≤300. Patients with >50% lesion progression within 24 to 48 hours. Critical/extremely severe cases: if they have one of the following: respiratory failure requiring mechanical ventilation, shock, and other organ failure requiring ICU treatment.

Table 2 - Risk of bias of included studies.

Study	*Newcastle-Ottawa Scale*			*Overall risk of bias*
	Selection	*Comparability*	*Exposure*	
Huang et al., Jan 2020	***	*	**	Moderate
Zhou et al., Mar 2020	**	*	*	High
Goyal et al., Apr 2020	***	*	*	Low
Huang et al., May 2020	**	*	*	High
Zhao et al., Apr 2020	***	*	**	Low
Du et al., May 2020	***	*	**	Low
Mikami et al., Jun 2020	****	*	*	Moderate
Suleyman et al., Jun 2020	**	*	*	High
Ferguson et al., Aug 2020	**	*	**	Low
Yang et al., Aug 2020	****	*	*	Moderate

represents individual study, and the area of each square is equivalent to the weight of the study, which is the inverse of the study variance. The diamond represents the summary measures and the width corresponds to the 95% CI.

RESULTS

Review of the databases identified 125,156 articles, out of which 130 full text articles assessed for eligibility after removing duplicated articles, non-human studies, non-observational studies and articles with non-English language. During the second round, 100 articles with insufficient clinical information on COVID-19 outcomes and elevated cardiac troponin I were excluded, and 30 articles on epidemiological characteristics, comorbidities, complications, laboratory findings and outcomes were extracted for final evaluation. 20 articles with missing data on binary outcomes (poor vs non-poor) and elevated cardiac troponin I were excluded. After detailed assessment and considering strict inclusion and exclusion criteria, as of 15 August 2020, we included 10 observational studies with 8261 confirmed cases of COVID-19 patients detailing elevated cardiac troponin I and outcomes. Meta-analysis random-effects models quantified the study level impact of elevated cardiac troponin I on outcomes in COVID-19 patients.

A total of 10 studies with data reported on elevated cardiac troponin I and outcomes of COVID-19 patients, including 3982 confirmed COVID-19 patients. In patients with poor outcomes, the prevalence of elevated troponin I levels was 51% (690/1341). In meta-analysis, patients with elevated troponin I levels had approximately 8 times higher odds of poor outcomes compared to better outcomes (aOR:7.92; 95%CI:3.70-16.97; p<0.00001) with 70% heterogeneity (p=0.0005)

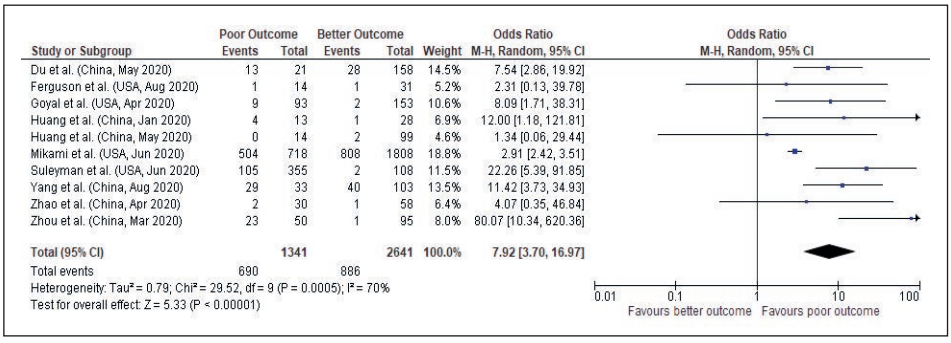


Figure 2 - Forest plot of elevated troponin I with outcomes in COVID-19 hospitalizations.

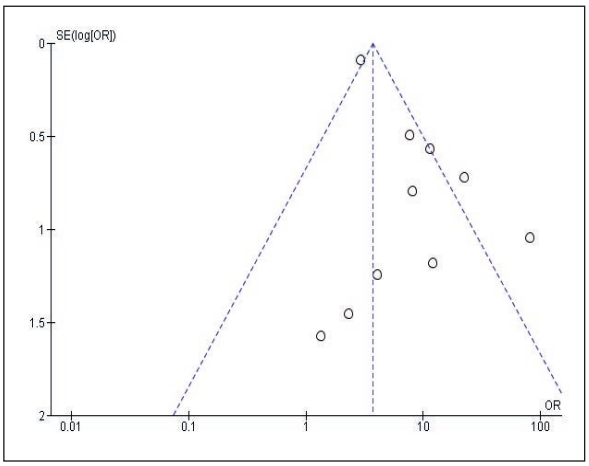


Figure 3 - Funnel plot of elevated troponin I with outcomes in COVID-19 hospitalizations.

(Figure 2). In order to account for heterogeneity between studies, we performed a sensitivity analysis by eliminating the 2 outlying studies (Suleyman et al. and Zhou et al.) on funnel plot **(**Figure 3). Results after sensitivity analysis also showed significant pooled OR of 5.14 (95%CI:2.84-9.28; p<0.00001) with 41% heterogeneity in the data (p=0.10) (Figure 4).

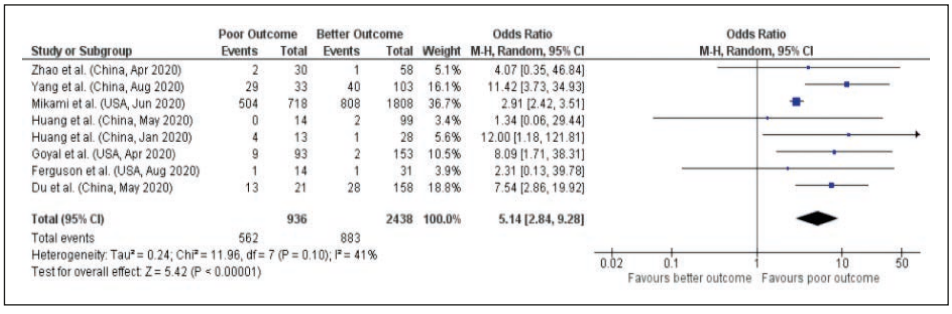
DISCUSSION

Our meta-analysis suggests that COVID-19 patients with elevated Troponin I levels had higher risk of poor outcomes. These findings are consistent with other studies [5, 6]. Analyzing the first reports from China, 12-28% of patients presented elevated cardiac troponin levels [10]. Those with elevated troponin levels were older and had significantly higher rates of comorbidities including diabetes, hypertension and coronary artery disease (CAD [5]. Notably, patients with higher troponin levels were more likely to be admitted to the intensive care unit and showed higher in-hospital mortality [4-6, 11]. Elevated troponin I levels in COVID-19 patients may signify an increased inflammatory response, coronary vascular ischemia, or direct viral myocarditis [5, 6, 12].

An increased inflammatory response is presumed to cause an elevation in troponin 1 levels through the down-regulation of angiotensin-converting enzyme 2 (ACE2), which also serves as the entry receptor for SARS-CoV-2. Consequently, this down-regulation leads to a decrease in Ang1-7, which normally act to limit the synthesis of proinflammatory and profibrotic cytokines and mediate protective cardiovascular effects [3, 13]. ACE2 is also highly expressed in pericytes of adult human hearts [14]. Oudit et al., found that SARS-CoV-2 can mediate myocardial inflammation (myocarditis) and damage through the downregulation of ACE2, which could be responsible for adverse outcomes in patients with SARS [15]. On autopsy of patients who died from SARS, it was found that 35% of heart samples presented with viral RNA in the myocardium were associated with reduced ACE2 protein expression. Therefore, because SARS and SARS-CoV-2 are highly homologous in genome, it can be presumed that SARS-CoV-2 may share the same mechanism of myocardial damage. Guo et al. found a positive linear correlation between plasma troponin levels and plasma C-reactive protein levels indicating that the upregulation of cytokines can potentially lead to myocardial injury [5]. Additionally, it is known that cytokines play a role in heart failure through their role in inflammatory modulation, myocyte injury and apoptosis, fibroblast activation and extracellular remodeling [16].

Release of cytokines can also explain the mech-

Figure 4 - Sensitivity analysis: forest plot of elevated troponin I with outcomes in COVID-19 hospitalizations.



anism by which coronary vascular ischemia occurs. In epidemiologic studies done on influenza patients, it was found that patients with pre-existing coronary artery disease (CAD) and with risk factors for atherosclerotic cardiovascular disease (CVD) were at increased risk of developing acute coronary syndrome during acute infections and other inflammatory conditions [17, 18]. A type 1 MI, which is caused by a plaque rupture with thrombus formation could be precipitated by COVID-19 as a result of atherosclerotic plaque instability and rupture due to circulating cytokines [19]. Additionally, COVID-19 can cause hypoxic respiratory failure, which leads to reduced oxygen supply and consequently, an imbalance between oxygen supply and demand in the acute setting [20]. This could therefore lead to an increase in troponin level secondary to a type 2 myocardial infarction (MI), which typically occurs in the absence of underlying CAD. In all, high sensitivity troponin I testing may be useful in assessing the extent of myocardial injury and organ dysfunction in COVID-19 patients. These results may complement clinical practice because evaluating the levels of troponin I and other cardiac biomarkers could help triage severe COVID-19 patients with injury risk and allow for prompt treatment to improve their prognosis. Additionally, this can aid in expediting cardiac consultation and consequently help mitigate the burden of COVID-19.

The main limitation of this meta-analysis is the heterogeneity of the included studies. Furthermore, the different definitions of the severity of the COVID-19 disease and discrepancy in the cut off values for cardiac troponin I might be explanations for the heterogeneity. Despite these limitations, this meta-analysis of 3982 confirmed COVID-19 patients suggests that elevated cardiac troponin I reflects disease progression to severity and carries a significant prognostic value. This may help in early stratification of high-risk patients and prevent the fatal cardiac complications. In conclusion, our meta-analysis results showed that elevated Troponin I levels had higher risk of poor outcomes in COVID-19 patients. Hence, evaluating the troponin I levels in high risk patients will be helpful in triaging patients to prevent risk of cardiac complication and other organ dysfunction. However, future studies are required to validate whether testing cardiac biomarkers improves triage, aids in treatment decisions, and modifies outcomes. Additionally, future studies are required to study the usefulness in cardiac biomarkers in predicting other complications associated with acute cardiac injury like arrhythmias, cardiogenic shock, and ischemic stroke.

Conflict of interest

The authors declare no conflict of interest.

Funding

The study had no internal or external funding source.

Authors contributions

Conceptualization: PM; Methodology: PM, UP; Acquisition of data: PM, UP; Formal analysis and investigation: PM; Writing-original draft preparation: PM, UP, NP SS, Writing - review, critical feedback, and editing: JS; Funding acquisition: None; Resources: None; Supervision: JS.

Ethical approval

Though this article does not contain any studies with direct involvement of human participants or animals performed by any of the authors, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

The data used in this study is deidentified and collected from the studies published online thus informed consent or IRB approval was not needed for this study.

Availability of data and material

The data is collected from the studies published online, publicly available, and specific details related to data and/or analysis will be made available upon request.

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