Cardiac troponins predict mortality in patients with COVID-19: A meta-analysis of adjusted risk estimates

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Letter to the Editor

Cardiac troponins predict mortality in patients with COVID-19: A meta-analysis of adjusted risk estimates ☆

Dear Editor,

Critical illness and sepsis are often associated with a troponin rise.[1,2] Therefore, troponin, in daily clinical practice, is frequently used as a marker of disease severity and as a predictor of future unfavourable outcomes.[1] Recently, several studies including a recent paper in this Journal by Zheng and colleagues, investigated the prognostic role of biomarkers of myocardial injury (i.e. troponins) with mortality in hospitalized patients with coronavirus disease 2019 (COVID-19).[3–5] Of note, those meta-analyses included studies that reported primarily unadjusted effect estimates of increased in-hospital mortality with higher troponin levels. Compared to patients with normal troponin levels, those with elevated troponins and consequently worse outcome were older and had higher rates of comorbidities including coronary artery disease, hypertension, chronic kidney disease, and diabetes.[3–5] As a consequence, the final results of those studies showed a significant heterogeneity and markedly different risk estimates of mortality (risk ratios were 43.24, 3.85, and 7.95, and I^2 were 34%, 90% and 65% for the studies of Zheng et al., Li et al., and Santoso et al. respectively).[3–5] Therefore, the crucial question is whether cardiac injury is an independent prognostic marker in COVID-19 or it is simply related to the burden of concomitant cardiovascular disease .

Although we clearly know that troponin levels are higher in non-survivors of COVID-19, and that a significant percentage of hospitalised patients are presented with elevated cardiac troponins, the data on its independent prognostic role beyond accompanying cardiovascular comorbidities are still missing.[6]

Therefore, we (MV, AVP) systematically searched Medline and Scopus (using the search terms “troponin” AND “coronavirus 2019″ OR “2019-nCoV” OR “SARS-CoV-2″ OR “COVID-19″) to identify all observational cohort studies published between Jan 1, 2020 and Apr 30, 2020, that compared outcome (in-hospital mortality) in consecutive patients hospitalized with COVID-19 with and without troponin elevation. High-sensitivity cardiac troponin I was reported in the included studies and tests were performed within 48 h after the admission. Cardiac injury was defined if the serum troponin level was above the 99th percentile upper reference limit. A meta-analysis of studies that reported adjusted effect estimates was conducted using the generic inverse variance method, and heterogeneity between studies was investigated using the Cochrane's Q test and I^2 statistic. Publication bias was assessed graphically using a funnel plot. Analyses were conducted using statistical software MedCalc Version 19.1.5.

Overall, 36 documents were initially identified based on our search criteria, and four studies were included in the final analysis[7–10] including a total of 982 patients (Table 1). Median age of the population was 67 years (range 58 to 71 years), 51% were males (range 49% to 69%), 36% had hypertension, and 20% had cardiovascular or cerebrovascular comorbidities. Three studies were retrospective[7–9] and one was prospective in nature.[10]

A total of 160 (16%) patients died during in-hospital stay. Elevated (positive) cardiac troponin was present in 21% of patients with COVID-19, and ranged between 20% and 27%. Meta-analysis of studies that reported adjusted hazard ratios (HR, fixed effects model), showed a significant association between elevated troponin values and mortality (HR = 2.48; 95% CI 1.50–4.11) (Fig. 1A), without significant heterogeneity between studies ($I^2 = 52\%$, Cochran $Q = 4.17$, $p = 0.12$), and no publication bias was detected (Fig. 1B).

The predictive value of troponin in COVID-19 could be the result of several potential mechanisms: (1) myocarditis caused by the virus, (2) cytokine mediated myocardial injury (cytokine storm), (3) coronary small-vessel disease (microangiopathy) due to pro-thrombotic state and endothelial dysfunction associated with COVID-19, and (4) associated (previously silent) coronary artery disease with subsequent type 2 myocardial infarction (i.e. supply-demand mismatch), which altogether may contribute to poor prognosis.[3–5]

In conclusion, troponin positivity is common in hospitalised COVID-19 patients, and may serve as an additional risk stratification tool in everyday clinical setting. These results are of prognostic importance, since patients with elevated troponins have higher risk of in-hospital mortality, are more prone to deterioration during hospital stay and so deserve more focused clinical attention.

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Table 1
Characteristics of studies included in meta-analysis.

Author, year	Country	Patients (n)	Age (years)	Male (%)	HTN (%)	DM (%)	CVD (%)	Study design	Mortality (%)	Troponin positive (%)	Adjusted effect estimate (95% CI)	Confounders
Wang L, 2020	China	339	71	49	41	16	22	R	19.2	20.6	HR 1.55 (0.75–3.19)	Age, acute kidney injury, arrhythmia, ARDS, heart failure, bacterial infection
Shi S, 2020	China	416	64	49	31	14	16	R	13.7	19.7	HR 3.41 (1.62–7.16)	Age, hypertension, diabetes, CVD, heart failure, chronic obstructive pulmonary disease, renal failure, cancer, ARDS
Zhang F, 2020	China	48	71	69	67	21	50	R	35.4	27.1	HR 10.90 (1.28–92.93)	Age, creatinine, D-dimer, oxygen saturation
Du RH, 2020	China	179	58	54	32	18	16	P	11.7	23.0	OR 4.08 (1.17–14.25)	Age, CVD, CD3+CD8+ *T* cells

ARDS, acute respiratory distress syndrome; CI, confidence interval; CVD, cardiovascular or cerebrovascular disease; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; OR, odds ratio; P, prospective; R, retrospective.

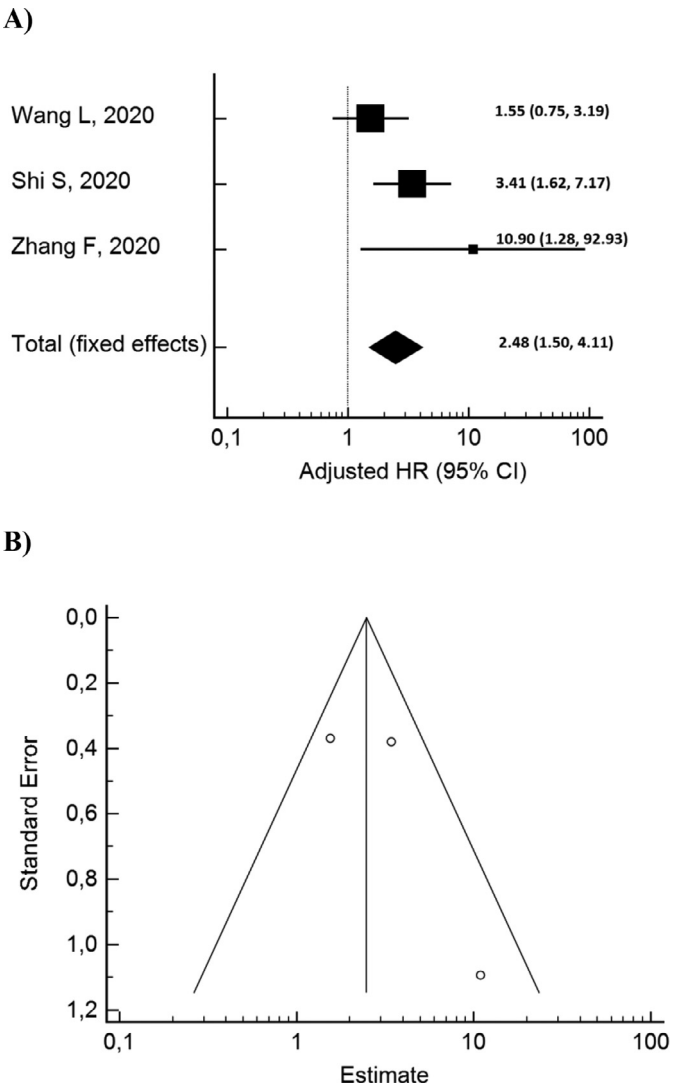

Fig. 1. **(A)** Forest plot of hazard ratios (HRs) for high-sensitivity cardiac troponin to predict in-hospital mortality in patients with coronavirus disease 2019 (COVID-19). **(B)** Funnel plot of HRs showing no publication bias.
The meta-analysis was conducted using the generic inverse variance method, and pooled HR was reported with 95% confidence interval (CI). There was no significant heterogeneity observed across studies.

Conflict of Interest

The authors declare no competing interests.

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