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Impact of myocardial injury on mortality in patients with COVID-19: a meta-analysis

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Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is causing a dramatic pandemic, affecting 12,847,293 patients worldwide as of July 12, 2020. COVID-19 clinical course is extremely heterogeneous, ranging from no symptoms to death. Therefore, data to improve the risk stratification based on clinical and laboratory parameters are urgently needed. The fatal clinical course of COVID-19 patients has been largely attributed to acute respiratory distress syndrome.[1,2] However, myocardial involvement has been observed in patients with COVID-19 and has been associated with worse clinical outcomes.[3–8] We aimed to provide a comprehensive and quantitative assessment of evidence about the impact of myocardial injury on mortality in patients with COVID-19.

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines. On July 8, 2020, we searched PubMed using the following terms: “COVID,” “troponin,” “cardiovascular,” “myocardial infarction,” “STEMI,” “NSTEMI,” “ACS,” “ck,” and “hs-tn.” Eligible studies had to satisfy the following criteria: 1) study population including patients with COVID-19 and 2) studies including patients with myocardial injury. We excluded studies not reporting myocardial injury, case reports, and animal studies. The primary outcome measure was the risk of all-cause mortality. Methodological quality of included studies was assessed using the Risk of Bias In Non-randomized Studies of Interventions assessment Tool from Cochrane handbook (ROBINS-I). Myocardial injury was assessed according to the definition used in each study. Odds ratios (ORs) with 95% confidence intervals (CIs) were used as the metric of choice for treatment effects with random effects models. A sensitivity analysis by calculating hazard ratio (HR), using the random effects inverse variance model with the DerSimonian-Laird estimate of tau was performed, including all studies reporting HR and 95% CI. The I^2 index was used to assess heterogeneity across studies. Analyses were performed using the Stata version 13.1 (Stata Corp., College Station, Texas).

Out of 1783 articles screened, 1769 articles did not meet the inclusion criteria and were excluded. A total of 14 studies including 6,462 patients with confirmed COVID-19 were included. Key clinical characteristics of patients included are reported in Table 1. The overall risk of bias, calculated with the ROBINS-I tool, was critical for all the included studies.

Effect estimates are summarized in Fig. 1. Patients with COVID-19 and myocardial injury were associated with a higher risk of all-cause mortality as compared to patients with COVID-19 without myocardial injury (OR 9.16; 95% CI 5.30–15.83; p<0.001, and I^2 = 88.8%). This result was largely attenuated by the sensitivity analysis, using the adjusted HR from the multivariable analysis as effect estimates (HR 1.62; 95% CI 1.35–1.94; p = 0.016, and I^2 = 70.9%) that were available in four studies.[8–11]

This comprehensive and quantitative analysis of available evidence on patients with COVID-19, shows a dramatic increase in the risk of all-cause mortality when myocardial injury occurs. Our findings are in line with previous studies that have shown a strong link between myocardial injury and the risk of death in patients with COVID-19.[8–11] Shi et al found that cardiac injury was associated with a higher unadjusted risk of inhospital death (HR 4.26, 95% CI 1.92– 9.49, and p<0.001).[10] Guo et al also reported a higher crude mortality in patients with myocardial injury than in patients without myocardial injury (59.6% vs 8.9%).[3] Recently, Ferrante et al have reported a strong correlation between myocardial injury and the adjusted risk of death in 332 COVID-19 patients from a European cohort (HR 2.25, 95% CI 1.27–3.96, and P = 0.005).[8]

Multiple mechanisms of myocardial injury have been proposed in patients with COVID-19, such as myocarditis, direct vascular infection, prolonged hypoxemia due to acute respiratory distress syndrome, cytokine storm, increased sympathetic stimulation, and type-1 myocardial infarction.[12] While patients with a known history of cardiovascular disease are more likely to experience myocardial injury after SARS-CoV-2 infection, it is of particular interest that myocardial injury has also proven to increase the risk of death in the absence of known cardiovascular disease.[3] Our findings strongly suggest that cardiac biomarkers (i.e., troponin) determination should be routinely assessed in all patients with COVID-19, to improve risk stratification and to promptly implement a more aggressive treatment strategy in the case of evidence of myocardial involvement.

The key limitation of this meta-analysis is the lack of patient-level data, which did not allow to assess the impact of baseline clinical and procedural variables on treatment effects. Moreover, an overestimation of treatment effects might exist due to publication bias. Finally, we acknowledge additional limitations because of

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Table 1
Key clinical characteristics of patients included in the meta-analysis

Study	No. of patients	Age (years)	Male (%)	Diabetes (%)	Hypertension (%)	Known CAD (%)	Fever (%)	Cough (%)
Chen et al.[13]	203	62	62	17	34	8*	91	68
Du et al.[14]	179	58	54	18	32	16#	99	82
Ferrante et al.[8]	332	67	71	21	54	15	–	–
Franks et al.[15]	128	64	57	–	–	–	–	
Guo et al.[3]	187	59	49	15	33	11	–	–
Hingwei et al.[16]	54	68	–	15	24	6	–	–
Lorente-Ros et al.[9]	224	67	57	25	75	–	–	–
Mikami et al.[17]	2820	59	54	18	25	–	20§	–
Pan et al.[18]	124	68	69	20	50	15#	86	69
Shi et al.[10]	671	63	48	15	30	9	–	–
Si et al.[11]	1159	§§	§§	§§	§§	§§	§§	§§
Wan et al.[19]	135	47	53	9	10	5	89	77
Wei et al.[20]	101	49	54	14	21	5	73	–
Zhou et al.[5]	145	56	62	19	30	8	94	79
Overall	6462	60.3	55.2	17.7	30.8	10.3	36.7	74.9

CAD = coronary artery disease.
* Reported as cardiovascular disease.
# Reported as cardiovascular or cerebrovascular disease.
§ Reported as temperature ≥ 39°C.
§§ Data provided only for patients with elevated troponin.

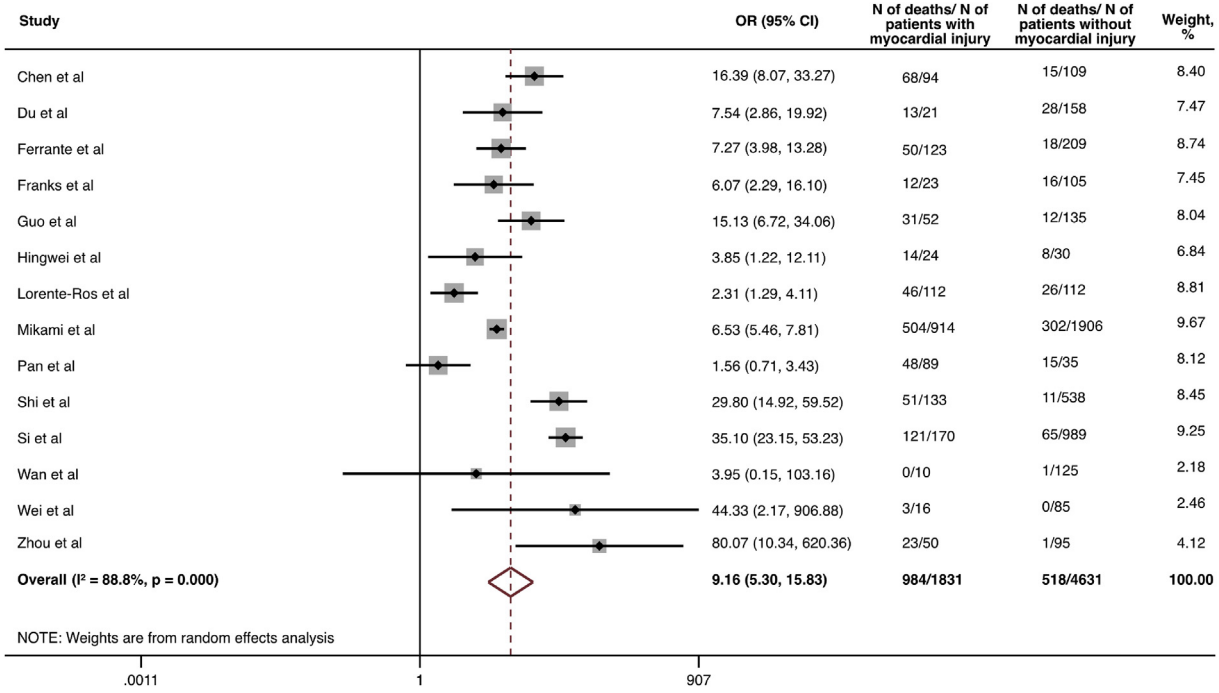

Fig. 1. Risk of all-cause mortality according to the occurrence of myocardial injury. CI: confidence interval, OR: odds ratio, and n/N: number of events/number of patients.

the limited number of patients and the retrospective and observational nature of included studies.

Our findings provide evidence supporting that myocardial injury is associated with an increased risk of mortality in patients with COVID-19. Therefore, in our opinion, troponin determination should be routinely performed in patients with COVID-19 to optimize risk stratification.

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