Correspondence

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

Keywords:
myocardial injury
COVID-19
mortality

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. However, myocardial involvement has been observed in patients with COVID-19 and has been associated with worse clinical outcomes. 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-tnt.” 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 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 I² = 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 I² = 70.9%) that were available in four studies.

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. Shi et al found that cardiac injury was associated with a higher unadjusted risk of in-hospital death (HR 4.26, 95% CI 1.92– 9.49, and p<0.001). 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%). 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).

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. 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. 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...
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.

Acknowledgments

JSS is personally supported by a grant from the Fundación Alfonso Martín Escudero (Madrid, Spain). DV is personally supported by a scholarship from Hellenic Society of Cardiology, Greece.

Table 1

| Study            | No. of patients | Age (years) | Male (%) | Diabetes (%) | Hypertension (%) | Known CAD (%) | Fever (%) | Cough (%) |
|------------------|-----------------|-------------|----------|--------------|------------------|---------------|-----------|-----------|
| Chen et al       | 203             | 62          | 62       | 17           | 34               | 8             | 91        | 68        |
| Du et al         | 179             | 58          | 54       | 18           | 32               | 16            | 99        | 82        |
| Ferrante et al   | 332             | 67          | 71       | 21           | 54               | 15            | —         | —         |
| Franks et al     | 128             | 64          | 57       | —            | —                | —             | —         | —         |
| Guo et al        | 187             | 59          | 49       | 15           | 33               | 11            | —         | —         |
| Hingwe et al     | 54              | 68          | —        | 15           | 24               | 6             | —         | —         |
| Lorente-Ros et al| 224             | 67          | 57       | 25           | 75               | —             | —         | —         |
| Mikami et al     | 2820            | 59          | 54       | 18           | 25               | —             | 20        | —         |
| Pan et al        | 124             | 68          | 69       | 20           | 50               | 15*           | 86        | 69        |
| Shi et al        | 671             | 63          | 48       | 15           | 30               | 9             | —         | —         |
| Si et al         | 1159            | 99          | 82       | 30           | 9                | —             | —         | —         |
| Wan et al        | 135             | 47          | 53       | 9            | 10               | 5             | 89        | 77        |
| Wei et al        | 101             | 49          | 54       | 14           | 21               | 5             | 73        | —         |
| Zhou et al       | 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 or cerebrovascular disease.
† Reported as temperature ≥ 39°C.
‡ Data provided only for patients with elevated troponin.

Table 1

| Study            | OR (95% CI) | N of deaths/ N of patients with myocardial injury | N of deaths/ N of patients without myocardial injury | Weight, % |
|------------------|-------------|-------------------------------------------------|----------------------------------------------------|-----------|
| Chen et al       | 16.39 (8.07, 33.27) | 68/94 | 15/109 | 8.40 |
| Du et al         | 7.54 (2.86, 19.92) | 13/21 | 2/158 | 7.47 |
| Ferrante et al   | 7.27 (3.98, 15.28) | 50/123 | 18/209 | 8.74 |
| Franks et al     | 6.07 (2.29, 16.10) | 12/23 | 16/105 | 7.45 |
| Guo et al        | 15.13 (6.72, 34.06) | 31/52 | 12/135 | 8.04 |
| Hingwe et al     | 3.85 (1.32, 12.11) | 14/24 | 8/30 | 6.84 |
| Lorente-Ros et al| 2.31 (1.29, 4.11) | 4/112 | 29/112 | 8.81 |
| Mikami et al     | 6.53 (5.48, 7.81) | 504/914 | 302/1906 | 9.67 |
| Pan et al        | 1.56 (0.71, 3.43) | 48/89 | 15/55 | 8.12 |
| Shi et al        | 29.80 (14.92, 59.52) | 5/133 | 11/538 | 8.45 |
| Si et al         | 35.10 (23.15, 53.23) | 121/170 | 65/898 | 9.25 |
| Wan et al        | 3.95 (0.15, 103.16) | 0/10 | 1/125 | 2.18 |
| Wei et al        | 44.33 (2.17, 906.88) | 3/16 | 0/85 | 2.46 |
| Zhou et al       | 80.07 (10.34, 620.26) | 23/50 | 1/95 | 4.12 |

Overall (I² = 88.8%, p = 0.000)

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.

References

1. Deftereos SG, Siasos G, Giannopoulos G, et al. The Greek study in the Effects of Colchicine in COVID-19 complications prevention (GRECCO-19 study): rationale and study design. Hellenic J Cardiol. April 2020. https://doi.org/10.1016/j.hjc.2020.03.002.
2. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: Early experience and forecast during an emergency response. JAMA. March 2020. https://doi.org/10.1001/jama.2020.4031.
3. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. March 2020. https://doi.org/10.1001/jamacardio.2020.1017.
4. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients With COVID-19 in Wuhan, China. JAMA Cardiol. March 2020. https://doi.org/10.1001/jamacardio.2020.0950.

Please cite this article as: Sanz-Sánchez J et al., Impact of myocardial injury on mortality in patients with COVID-19: a meta-analysis, Hellenic Journal of Cardiology, https://doi.org/10.1016/j.hjc.2020.07.004
5. Zhou F, Yu T, Du R, et al. Clinical course of and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. March 2020. https://doi.org/10.1016/s0140-6736(20)30566-3.

6. Tousoulis D. Diabetes mellitus: Lessons from the COVID-19 pandemic. Hellenic J Cardiol. May 2020. https://doi.org/10.1016/j.hjc.2020.03.009.

7. Vrachatis DA, Giotaki SG, Giannopoulos G. COVID-19 myocardial injury: We have much more to discover. Int J Cardiol. 2020;314:96. https://doi.org/10.1016/j.ijcard.2020.05.003.

8. Ferrante G, Fazzari F, Cozzi O, et al. Risk factors for myocardial injury and death in patients with COVID-19: insights from a cohort study with chest computed tomography. Cardiovasc Res. July 2020. https://doi.org/10.1093/cvr/cvaa193.

9. Lorente-Ros A, Monteagudo Ruiz JM, Rincón LM, et al. Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. Circ J. June 2020. https://doi.org/10.1253/circj.cj200656.

10. Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. Eur Heart J. 2020;41(22):2070–2079. https://doi.org/10.1093/eurheartj/ehaa408.

11. Si D, Du B, Ni L, et al. Death, discharge and arrhythmias among patients with COVID-19 and cardiac injury. C. Can Med Assoc J. 2020;192(11). https://doi.org/10.1503/cmaj.200879.

12. Vrachatis DA, Giotaki SG, Giannopoulos G. COVID-19 myocardial injury: We have much more to discover. Int J Cardiol. 2020;314:96. https://doi.org/10.1016/j.ijcard.2020.05.003.

13. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. March 2020. https://doi.org/10.1016/s0140-6736(20)30566-3.

14. Du R-H, Liang L-R, Yang C-Q, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J. 2020;55(5). https://doi.org/10.1183/13993003.00524-2020.

15. Franks CE, Scott MG, Farnsworth CW. Elevated cardiac troponin i is associated with poor outcomes in COVID-19 patients at an Academic Medical Center in Midwestern USA. J Appl Lab Med. June 2020. https://doi.org/10.1093/jalm/jaa092.

16. He XW, Lai JS, Cheng J, et al. [Impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients]. Zhonghua Xinxiu- guanbing Za Zhi. 2020;48:E031. https://doi.org/10.3760/cma.j.cn112148-20200228-00137. 0.

17. Mikami T, Miyashita H, Yamada T, et al. Risk factors for mortality in patients with COVID-19 in New York City. J Gen Intern Med. June 2020;1–10. https://doi.org/10.1007/s11606-020-05983-z.

18. Pan F, Yang L, Li Y, et al. Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): a case-control study. Int J Med Sci. 2020;17(9):1281–1292. https://doi.org/10.7150/ijms.66614.

19. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. March 2020. https://doi.org/10.1002/jmv.25783.

20. Wei J-F, Huang F-Y, Xiong T-Y, et al. Acute myocardial injury is common in patients with covid-19 and impairs their prognosis. Heart. April 2020. https://doi.org/10.1136/heartjnl-2020-317067.

Jorge Sanz-Sánchez*
Humanitas Clinical and Research Hospital IRCCS, Rozzano, Milan, Italy
Department of Biomedical Sciences, Universita, Pieve Emanuele, Milan, Italy

Dimitrios A. Vrachatis
Humanitas Clinical and Research Hospital IRCCS, Rozzano, Milan, Italy

* Corresponding author. Giulio G. Stefanini, MD, PhD, MSc, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy. Phone: +39 02 8224 7384. E-mail address: giulio.stefanini@gmail.com (G.G. Stefanini).

5 June 2020
Available online xxx