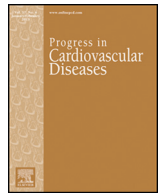




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis[☆]



Keywords:
 Coronavirus
 COVID-19
 Troponin
 Prognosis

To the Editor:

Coronavirus disease 2019 (COVID-19) is an emerging outbreak caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to updated statistics released by the World Health Organization (WHO), COVID-19 has already affected over 110,000 people from over 100 countries worldwide, causing >3800 deaths.¹ In up to 15% of infected patients the clinical course of this pathology may be complicated by the onset of a severe form of interstitial pneumoniae, which may then progress towards acute respiratory distress syndrome (ARDS) and/or multi organ failure (MOF) and death.² People with underlying cardiovascular disease are among the highest risk individuals for severe disease and death. Importantly, among the COVID-19 knowledge gaps are laboratory and diagnostics issues as well as the clinical management of severe and critically ill patients.³ Since major cardiac complications have been reported to develop in a considerable number of patients with pneumonia,⁴ we performed an analysis of the current scientific literature to investigate whether the measurement of cardiac troponin I (cTnI) or cardiac troponin T (cTnT) may help predict clinical severity in patients with COVID-19.

An electronic search was carried out in Medline (PubMed interface), Scopus and Web of Science, using the keywords “laboratory” OR “troponin” AND “coronavirus 2019” OR “2019-nCoV” OR “SARS-CoV-2”, between 2019 and present time (i.e., March 4, 2020), without applying language restrictions. The title, abstract and full text of all documents identified with these search criteria were assessed, and those reporting information on cTnT or cTnI values in COVID-19 patients with or without severe disease (i.e., those needing mechanical ventilation, ICU admission or those who died), were included in a meta-analysis. The reference lists of all documents were also analyzed for identifying additional eligible studies. A meta-analysis was finally carried out, with calculation of standardized mean difference (SMD) and 95% confidence interval (95% CI) of cTnI or cTnT values in COVID-19 patients with or without severe disease. The statistical analysis was performed with MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). Mean and standard deviation of cTnI or cTnT values were extrapolated from sample size, median and interquartile range (IQR), according to Hozo et al.⁵

Overall, 81 documents could be initially identified based on our search criteria, 78 of which ought to be excluded after title, abstract or full text reading, since they were review articles (n = 6), commentaries or other editorial materials (n = 1), they did not deal with COVID-19 disease (n = 65), or did not expressly report the values of cTnI or cTnT in COVID-19 patients with or without severe disease (n = 6). One additional study could be identified from reading the reference list of the three selected documents, so that 4 studies were finally included in our meta-analysis.^{6–9}

All these clinical studies used cTnI (the specific method was not described in the published articles), and all except one⁷ reported the use of high-sensitivity immunoassays. All studies were set in China, included a total number of 341 patients (123 with severe disease; 36%), the sample

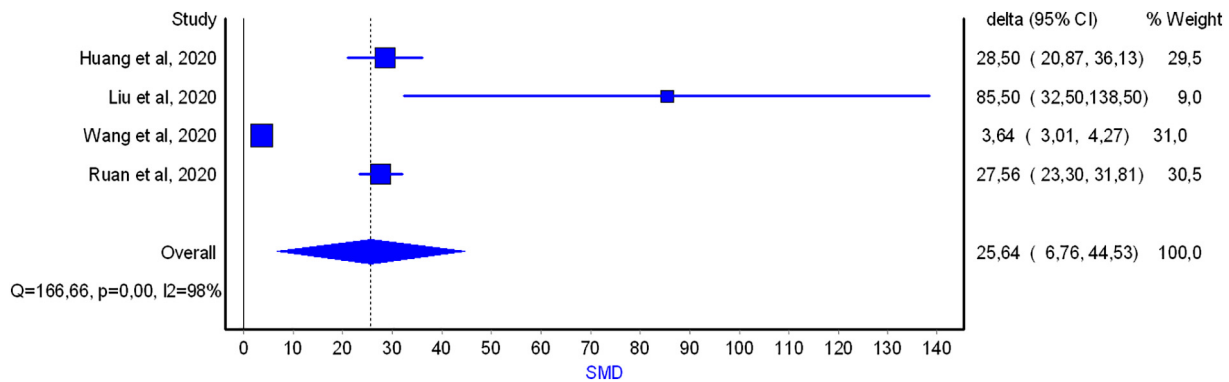


Fig 1. Standardized mean difference (SMD) and 95% confidence interval (95% CI) of cardiac troponin I (cTnI) values in coronavirus disease 2019 (COVID-19) patients with or without severe disease.

[☆] Statement of conflict of interest: See page 391.

size varied between 12 and 150, whilst the clinical outcome was defined as intensive care unit (ICU) admission in 2 studies^{6,8} onset of ARDS in another study,⁷ and death in the remaining investigation.⁹ The SMD of the four studies is summarized in Fig. 1. Although the heterogeneity was considerably high (i.e., I^2 , 98%; $p < 0.001$), the values of cTnI were found to be significantly increased in COVID-19 patients with severe disease than in those without (SMD, 25.6 ng/L; 95% CI, 6.8–44.5 ng/L).

Recent literature data has shown that cTnI concentration is only marginally increased in all patients with SARS-CoV-2 infection, whereby values exceeding the 99th percentile in the upper reference limit (URL) can only be observed in 8–12% of positive cases.¹⁰ Nonetheless, what seems to emerge from our results is that cTnI values are significantly increased in patients with severe SARS-CoV-2 infection compared to those with milder forms of disease. It is hence reasonable to hypothesize that initial measurement of cardiac damage biomarkers immediately after hospitalization for SARS-CoV-2 infection, as well as longitudinal monitoring during hospital stay, may help identifying a subset of patients with possible cardiac injury and thereby predict the progression of COVID-19 towards a worse clinical picture. Urgent studies shall also be planned to define whether or not echocardiographic testing and other adjunctive cardioprotective therapies such as corticosteroids, other anti-inflammatory agents, immunosuppressants, antivirals (antiviral agents and/or interferons) and/or immunomodulatory therapy (immunoglobulins) may be advisable in patients with significant elevation of cardiac injury biomarkers.

Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

References

1. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report – 44. Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/>. Accessed March 5, 2020.
2. Mattiuzzi C, Lippi G. Which lessons shall we learn from the 2019 novel coronavirus outbreak? *Ann Transl Med* 2020;8(3):48 <https://doi.org/10.21037/atm.2020.02.06>.

3. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). Available at: <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf> 16–24 February 2020. Accessed March 5, 2020.
4. Corrales-Medina VF, Suh KN, Rose G, et al. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. *PLoS Med* 2011;8, e1001048 <https://doi.org/10.1371/journal.pmed.1001048>.
5. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13 <https://doi.org/10.1186/1471-2288-5-13>.
6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497–506 [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).
7. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Sci China Life Sci* 2020;63(3):364–374 <https://doi.org/10.1007/s11427-020-1643-8>.
8. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020 <https://doi.org/10.1001/jama.2020.1585>.
9. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020 <https://doi.org/10.1007/s00134-020-05991-x>.
10. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med* 2020 <https://doi.org/10.1515/cclm-2020-0198>.

Giuseppe Lippi

Section of Clinical Biochemistry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy

Carl J. Lavie

John Ochsner Heart and Vascular Institute, Ochsner Clinical School - The University of Queensland School of Medicine, New Orleans, LA, USA

Fabian Sanchis-Gomar

Department of Physiology, Faculty of Medicine, University of Valencia and INCLIVA Biomedical Research Institute, Valencia, Spain *d*

*Address reprint requests to Fabian Sanchis-Gomar, Department of Physiology, Faculty of Medicine, University of Valencia, Av. Blasco Ibañez, 15, 46010 Valencia, Spain.
E-mail address: fabian.sanchis@uv.es