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LETTER TO THE EDITOR

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Myocardial injury characterized by elevated cardiac troponin and in-hospital mortality of COVID-19: An insight from a meta-analysis

To the Editor,

Since December 2019, coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a public health emergency of international concern. As of 22 May 2020, the World Health Organization has declared that approximately 5 000 000 cases of COVID-19 have been confirmed globally with more than 320 000 deaths (https://covid19.who.int/). Patients with COVID-19 show diverse clinical manifestations that range from no symptoms to severe pneumonia and even death. We are now encountering the difficulties in how to identify patients at risk for severe disease early in the course of COVID-19. A number of potential risk factors predicting poor prognosis of COVID-19 have been demonstrated, including older age, the presence of cardiovascular disease, lymphopenia, elevated D-dimer levels, elevated interleukin-6 levels, and high sequential organ failure assessment (SOFA) scores.[1] In recent studies, myocardial injury characterized by elevated high-sensitivity cardiac troponin (hs-cTn) levels has been reported as an independent risk factor for in-hospital mortality in patients with COVID-19.[2,3] Given the lack of a definitive marker for risk stratification of COVID-19, we performed a meta-analysis of currently available studies to clarify the association between myocardial injury assessed by hs-cTn levels and in-hospital mortality in patients with COVID-19.

A systematic search of all existing studies on myocardial injury detected by hs-cTn in patients with COVID-19 was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org). We searched PubMed and Embase through 13 April 2020 using the following search terms: ("coronavirus 2019" OR "2019-nCoV" OR "SARS-CoV-2" OR "COVID-19" OR "COVID" OR "2019 novel coronavirus") AND ("troponin" OR "troponins" OR "TnI" OR "cTnI" OR "TnT" OR "cTnT" OR "CK-MB" OR "creatine kinase MB" OR "cardiac biomarkers" OR "cardiac injury" OR "cardiac damage" OR "myocardial injury" OR "myocardial damage" OR "myocardial infarction" OR "myocarditis" OR "clinical characteristics" OR "clinical features" OR "clinical course" OR "predictors" OR "risk factors" OR "outcomes"). All articles were downloaded for consolidation, elimination of duplicates, and further analyses without language or time restrictions. Studies were selected based on the following criteria: (a) published in peer-reviewed journals; (b) included only patients with laboratory-confirmed COVID-19; (c) reported the in-hospital mortality and myocardial injury defined as elevated hs-cTn levels to avoid arbitrary interference from outcome definitions. In cases where overlap of the study population or enrollment period was found in articles published from the same hospitals, the article with the largest number of patients was only included in the analysis. The pooled odds ratio was calculated using inverse-variance weighted random-effects models. Statistical analyses were performed using Review Manager (RevMan) version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark; https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman) and ProMeta 3.0 (https://idostatistics.com/prometa3/).

Our initial search identified 480 potentially relevant articles from PubMed and 243 articles from Embase. After title, abstract, and full-text evaluation, we identified 21 studies that reported information about hs-cTn levels (Table 1), 15 of which were excluded attributable to the lack of in-hospital mortality by hs-cTn status and suspected large overlapping of patients populations. Finally, six observational studies which included a total of 1231 patients met the search criteria.[1-6] All studies used troponin I as hs-cTn, except for the study by Guo et al,[3] which used troponin T. The percentage of patients with hs-cTn levels varied across the studies (13%-41%). The funnel plot for in-hospital mortality indicated an absence of publication bias (data not shown). Regarding the impact of hs-cTn levels on outcomes in evaluated studies (Figure 1), elevated hs-cTn levels were significantly associated with an increase in in-hospital mortality (pooled odds ratio, 22.7; 95% confidence interval, 13.6-38.1; $P < .001$) with a moderate heterogeneity ($I^2 = 28\%$).

Our meta-analysis results support the previous finding that the levels of hs-cTn might help to identify patients at high risk for adverse clinical events associated with COVID-19. Elevation of hs-cTn is a surrogate of myocardial injury, which appears to be a common complication of COVID-19 with incidence rates ranging from 7% to 44% (Table 1). Although the mechanism of myocardial

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TABLE 1 Characteristics of 21 studies reporting information about hs-cTn levels in patients with COVID-19 by 13 April 2020

Author	Ref no.	PubMed ID	No. of patients	Duration	Mortality by hs-cTn status	Age, y	hs-cTn					
							Type	Cut-off, pg/mL	Time of sampling	Elevated patients	Survivors, pg/mL	Non-survivors, pg/mL
Zhongnan Hospital of Wuhan University (China)												
Cao J	9	32239127	102	3 Jan to 1 Feb 2020	Available	54 (37-67)	I	≥26	On admission	7/55 (13%)	NA	21.5 (9.4-44.1)
Huang Y	Excluded	32114074	34	21 Dec 2019 to 28 Jan 2020	NA	56.2 ± 17.1	I	NA	NA	1/15 (7%)	NA	NA
Wang D	Excluded	32031570	138	1 to 28 Jan 2020	NA	56 (42-68)	I	≥26.2	On admission	10/138 (7%)	NA	NA
Renmin Hospital of Wuhan University (China)												
Shi S	6	32211816	416	20 Jan to 10 Feb 2020	Available	64 (range, 21-95)	I	>40	On admission	82/416 (20%)	NA	NA
Wang L	Excluded	32240670	393	1 Jan to 6 Feb 2020	Available	69 (65-76)	I	>40 (>URL)	NA	70/339 (21%)	7 (6-18)	73 (23-336)
Han H	Excluded	32232979	273	1 Jan to 18 Feb 2020	NA	NA	I	>40	On admission	27/273 (10%)	NA	NA
Tongji Hospital (China)												
Chen T	8	32217556	274	13 Jan to 12 Feb 2020	Available	62.0 (44.0-70.0)	I	>15.6	On admission	83/203 (41%)	3.3 (1.9-7.0)	40.8 (14.7-157.8)
He XW	Excluded	32171190	54	3 to 24 Feb 2020	Available	68 (59.8-74.3)	NA	>34.2	On admission	24/54 (44%)	NA	NA
Chen C	Excluded	32141280	150	Jan to Feb 2020	NA	59 ± 16	I	>26.3	NA	22/150 (15%)	NA	NA
Wang Y	Excluded	32267160	344	25 Jan to 25 Feb 2020	NA	64 (52-72)	I	NA	NA	NA	3.4 (1.4-8.7)	46.7 (11.2-801.3)
Jinyintan Hospital (China)												
Yang X	Excluded	32105632	52	24 Dec 2019 to 26 Jan 2020	Available	59.7 ± 13.3	I	>28	NA	12/52 (23%)	NA	NA
Huang C	Excluded	31986264	41	16 Dec 2019 to 2 Jan 2020	NA	49.0 (41.0-58.0)	I	>28	On admission	5/41 (12%)	NA	NA
Wuhan Pulmonary Hospital (China)												
Du RH	Excluded	32269088	179 (136 definite cases)	25 Dec 2019 to 7 Feb 2020	Available	57.6 ± 13.7	I	≥50	NA	41/179 (23%)	0.0 (0.0-0.0) × 10^3	0.1 (0.0-0.8) × 10^3
Jinyintan Hospital and Tongji Hospital												
Ruan Q	Excluded	32125452	150	NA	NA	NA	NA	NA	NA	NA	3.5 ± 6.2	30.3 ± 151.0
Jinyintan Hospital and Wuhan Pulmonary Hospital												
Zhou F	3	32171076	191	29 Dec 2019 to 31 Jan 2020	Available	56.0 (46.0-67.0)	I	>28	NA	24/145 (17%)	3.0 (1.1-5.5)	22.2 (5.6-83.1)

TABLE 1 (Continued)

Author	Ref no.	PubMed ID	No. of patients	Duration	Mortality by hs-cTn status	Age, y	hs-cTn					
							Type	Cut-off, pg/mL	Time of sampling	Elevated patients	Survivors, pg/mL	Non-survivors, pg/mL
Jinyintan Hospital, Shanghai Public Health Clinical Center (China) and Tongling People's Hospital (China)												
Feng Y	Excluded	32275452	476	1 Jan to 15 Feb 2020	NA	53 (40-64)	NA	NA	NA	86/384 (22%)	NA	NA
Western District of Union Hospital of Tongji Medical College (China)												
Peng YD	Excluded	32120458	112	20 Jan to 15 Feb 2020	NA	62.0 (55.0-67.0)	I	NA	NA	NA	NA	NA
Zhou B	Excluded	32209382	34	5 Feb to 13 Feb 2020	NA	NA	I	≥26.2	NA	9/34 (26%)	NA	NA
Hankou and Caidian Branch of Tongji Hospital (China) and Hankou Branch of Central Hospital of Wuhan (China)												
Deng Y	10	32209890	225	1 Jan to 21 Feb 2020	Available	Range, 22-94	I	>28	NA	66/225 (29%)	NA	NA
Seventh Hospital of Wuhan City (China)												
Guo T	7	32219356	187	23 Jan to 23 Feb 2020	Available	58.5 ± 14.7	T	>URL	NA	52/187 (28%)	NA	NA
Evergreen Hospital (USA)												
Arentz M	Excluded	32191259	21	20 Feb to 5 Mar 2020	NA	70 (range 43-92)	NA	>300	On admission	3/21 (14%)	NA	NA

Note: Values are mean ± standard deviation, median (interquartile range), or n (%).

Abbreviations: COVID-19, coronavirus disease 2019; hs-cTn, high-sensitivity cardiac troponin; NA, not available; URL, 99th percentile upper reference limit.

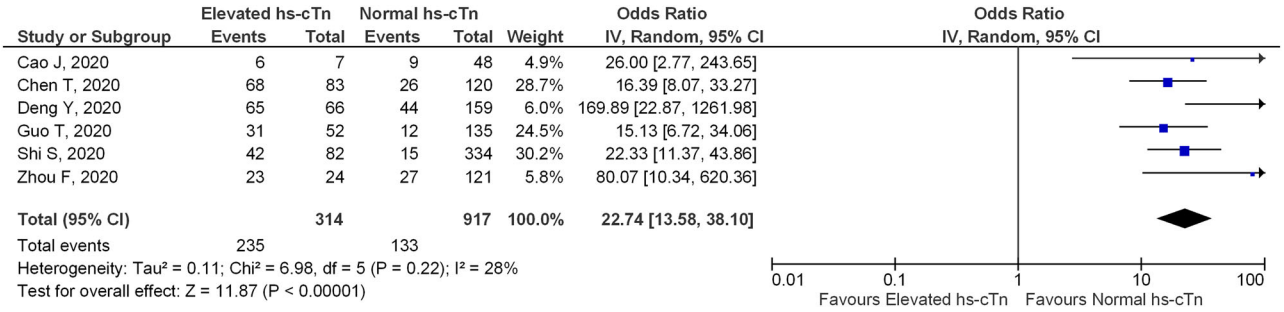

FIGURE 1 Myocardial injury and mortality in patients with confirmed coronavirus disease 2019. Elevated high-sensitivity cardiac troponin (hs-cTn) levels were associated with increased mortality. CI, confidence interval; IV, inverse variance weighted random-effects models

injury associated with COVID-19 is not completely understood, patients with cardiovascular disease are four times likely to have elevated hs-cTn levels than those without.[3] Increased myocardial oxygen demand during acute infection might induce myocardial ischemia due to exacerbations of cardiovascular diseases, including coronary artery disease, atrial fibrillation, and congestive heart failure. In fact, Guo et al[3] has shown a positive correlation between hs-cTn and high-sensitivity C-reactive protein, supporting the theory that patients with cardiovascular disease may be susceptible to myocardial injury associated with severe systemic inflammatory response to COVID-19.[7] Other proposed mechanisms include upregulation of cytokines[1,4] that are toxic to the myocardium and abundance of angiotensin-converting enzyme 2 receptor in the heart, which is the main receptor for SARS-CoV-2 cell entry. Further research studies are needed to assess the continuous relationship between mortality and hs-cTn levels in the early phase of the disease and the role of these mechanisms in patients with and without pre-existing cardiovascular diseases. Larger patient data sets will allow us to adjust hs-cTn levels for other confounding factors and inflammatory biomarkers, which might be helpful to establish hs-cTn as an independent predictor of poor outcome in COVID-19.

So far, five meta-analyses have reported the association between myocardial injury and disease severity or mortality of COVID-19.[8-12] However, those meta-analyses included multiple publications from the same institutions at the overlapped study period, which may result in double counting of patients. We carefully avoided double counting of patients from the same institutions (Table 1). Although the present results are subject to potential bias related to the availability of confounding factors, the lack of the specific purpose and timing of hs-cTn tests, and large differences in the study populations, elevated hs-cTn levels might be used as a reliable marker of disease severity early in the course of COVID-19.

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Tadao Aikawa MD, PhD[1]
Hisato Takagi MD, PhD[2]
Kiyotake Ishikawa MD, PhD[1]
Toshiki Kuno MD, PhD[3]

[1]*Cardiovascular Research Center, Icahn School of Medicine at Mount Sinai, New York, New York*
[2]*Department of Cardiovascular Surgery, Shizuoka Medical Center, Shizuoka, Japan*
[3]*Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, New York*

Correspondence
Toshiki Kuno, MD, PhD, Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, First Ave, 16th St, New York, NY 10003.
Email: toshiki.kuno@mountsinai.org

ORCID

Tadao Aikawa http://orcid.org/0000-0002-1786-0176
Toshiki Kuno http://orcid.org/0000-0002-2487-8366

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