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REVIEW

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Association of cardiac biomarkers and comorbidities with increased mortality, severity, and cardiac injury in COVID-19 patients: A meta-regression and decision tree analysis

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Abstract

Background: Coronavirus disease-2019 (COVID-19) has a deleterious effect on several systems, including the cardiovascular system. We aim to systematically explore the association of COVID-19 severity and mortality rate with the history of cardiovascular diseases and/or other comorbidities and cardiac injury laboratory markers.

Methods: The standardized mean difference (SMD) or odds ratio (OR) and 95% confidence intervals (CIs) were applied to estimate pooled results from the 56 studies. The prognostic performance of cardiac markers for predicting adverse outcomes and to select the best cutoff threshold was estimated by receiver operating characteristic curve analysis. Decision tree analysis by combining cardiac markers with demographic and clinical features was applied to predict mortality and severity in patients with COVID-19.

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; AUC, area under the curve; CI, confidence intervals; CK, creatine kinase; CKD, chronic kidney disease; COVID-19, coronavirus disease-2019; cTnI, cardiac troponin I; ICU, intensive care unit; LDH, lactate dehydrogenase; MERS, Middle East respiratory syndrome; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ROC, receiver operating characteristic; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMD, standardized mean difference.

Results: A meta-analysis of 17 794 patients showed patients with high cardiac troponin I (OR = 5.22, 95% CI = 3.73-7.31, $P < .001$) and aspartate aminotransferase (AST) levels (OR = 3.64, 95% CI = 2.84-4.66, $P < .001$) were more likely to develop adverse outcomes. High troponin I more than 13.75 ng/L combined with either advanced age more than 60 years or elevated AST level more than 27.72 U/L was the best model to predict poor outcomes.

Conclusions: COVID-19 severity and mortality are complicated by myocardial injury. Assessment of cardiac injury biomarkers may improve the identification of those patients at the highest risk and potentially lead to improved therapeutic approaches.

KEYWORDS

cardiac injury, cardiac markers, COVID-19, meta-analysis, outcome, SARS-CoV-2

1 | INTRODUCTION

The first incidence of coronavirus disease-2019 (COVID-19) was in December 2019 in Wuhan city, China which was attributed to viral infection with a newly originating Zoonotic virus. This virus is known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] Indeed, infection with coronavirus was detected before in China in 2002 to 2003 and was also later detected in Saudi Arabia and was given the name of Middle East respiratory syndrome (MERS-CoV).[3,4] Although SARS-CoV-2 infection is considered the most serious infection worldwide, most of the infected individuals suffer from mild or moderate symptoms that begin in the first week after infection. The most common mild symptoms include fever, fatigue, and cough. However, infected patients may suffer from serious complications that vary in their degrees between different individuals such as dyspnea, severe pneumonia, and organ dysfunction.[1] Based on the previous facts, the diagnosis of COVID-19 cannot be based on specific symptom detection and the only specific detection test depends on identification of the viral genome utilizing reverse transcription-polymerase chain reaction (RT-PCR) method.[1]

Although China is the country of origin for COVID-19, it has been spread everywhere all over the world. That is why several prospective and retrospective studies have been directed to characterize COVID-19 and its complications among infected patients. Cardiovascular diseases are classified as one of the main reasons for mortality and morbidity among patients with COVID-19.[5-7] Moreover, the presence of cardiovascular diseases is linked to poor prognosis among infected patients.[8,9] Moreover, it was also detected that SARS-CoV-2 infection is associated with aggravation in inflammation that can trigger cardiac arrhythmia, myocarditis, and inflammation in the vascular system that can induce heart destruction.[8]

Based on the fact that COVID-19 is a recently detected disease, there is no wonder that no sufficient clinical data that characterize the correlation between the severity and complication of COVID-19 and cardiovascular or cerebrovascular diseases. Moreover, data available provide wide variations in results and do not determine the risk factors for COVID-19. Thus, the current meta-analysis aimed to gather a broad range of current studies to characterize the association between the history of cardiovascular diseases and their specific biological markers levels, and the severity of COVID-19 and its rate of mortality.

2 | METHODS

2.1 | Search strategy

This systematic review and meta-analysis were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We selected relevant studies published up to 8 May 2020, by searching Web of Science, PubMed, Scopus, and Science Direct search engines. We applied no language restrictions. Searches initially used the following strings: "Novel coronavirus 2019," "2019 nCoV," "COVID-19," "Wuhan coronavirus," "Wuhan pneumonia," or "SARS-CoV-2." The results of these searches were combined with sets created with "Cardiac biomarkers," "chronic heart disease," "cardiovascular disease," intensive care unit: "ICU," "cardiac injury," and "mortality." Bibliographies of allocated articles were reviewed for possible data sources.

2.2 | Selection criteria

We performed a systematic review of studies that explored pre-existing cardiovascular diseases as risk factors of severe COVID-19, cardiac injury, ICU admission, or mortality. Inclusion criteria for eligibility were as follows: (a) types of studies: a retrospective, prospective, observational, descriptive or case-control studies reporting cardiac biomarkers (including cardiac troponin I (cTnI), creatine kinase (CK), CK-MB, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), myoglobin, or N-terminal-pro hormone B-type

natriuretic peptide (NT-proBNP) in patients with COVID-19; (b) subjects: diagnosed patients with COVID-19; (c) exposure/intervention: enclosing at least one outcome data for severe (defined as acute respiratory distress syndrome, mechanical ventilation, and ICU admission) vs nonsevere, ICU admission vs floor admission, develop cardiac injury (defined as cTnI elevation above 99th percentile) vs not, or survived vs expired cohorts; and (d) outcome indicator: the mean and standard deviation for each laboratory test or event and total sample size for demographics, comorbidities, and complications. The following exclusion criteria were considered: (a) pre-print, case reports, reviews, editorial materials, conference abstracts, and summaries of discussions, (b) insufficient reported data information; or (c) in vitro or in vivo studies.

2.3 | Data abstraction

Two investigators separately conducted literature screening, followed by data abstraction in a predesigned excel sheet by four investigators (RE, AE, MNA, and MEM). Any disagreement was resolved by another investigator (ET). Study characteristics (author name, publication date, journal name, ethnicity, study design, and sample size) and the patients' demographics (age and gender) were collected.

2.4 | Statistical analysis

Data analysis was performed using RevMan version 5.3 and comprehensive meta-analysis software version 3.0.[10] The standardized mean difference (SMD) or odds ratio (OR) and 95% confidence intervals (CIs) were applied to estimate pooled results from studies. Two levels of analysis were conducted; (a) four pairwise comparison for severity, myocardial injury, ICU admission, and mortality, then (b) all studies related to severity, ICU admission, cardiac injury, and mortality were pooled together to compare between patients with poor vs good prognosis. The results of the included studies were performed with random-effect models.[11] Heterogeneity was evaluated using Cochran's Q statistic and quantified by using Higgin's I^2 statistics. If there was statistical heterogeneity among the results, further sensitivity analysis and meta-regression were performed to determine the source of heterogeneity. Receiver operating characteristic (ROC) curve analysis was performed to assess the prognostic performance of cardiac biomarkers and area under the curve (AUC) was calculated. Next, the risk assessment decision tree was employed to identify laboratory and clinical predictor factors for poor prognosis. Accuracy, precision, and recall of model performance were evaluated. R Studio was employed using the following packages: *tidyverse*, *magrittr*, *rpart*, *caret*, and *pROC*. Finally, publication bias was assessed using a funnel plot and quantified using Egger's linear regression test. Asymmetry of the collected studies' distribution by visual inspection or *P*-value < .1 indicated obvious publication bias.[12]

3 | RESULTS

3.1 | Study selection and characteristics

Using the key terms, a total of 4021 articles were retrieved using the search strategy. After screening by the abstract and title of 1541 studies, 160 articles were selected for full-text assessment. Of these, 104 were excluded due to lack of enough data, and 56 were included for qualitative analysis. Pairwise comparison meta-analysis was conducted; 29 articles to compare between the severe and nonsevere presentation of COVID-19 disease, seven records to compare between cohorts who developed cardiac injury and those who are not, six records to compare between patients who were admitted to the ICU and those admitted to the general hospital ward and 16 studies to compare between survivors and expired patients (Figure 1A). The study included a total of 56 studies (52 retrospective and 4 prospective studies) published from 24 January 2020 to 7 May 2020.[1,13-68] These included 17 794 COVID-19 patients from China (13 cities) and overseas (Figure 1B,C). The main characteristics of eligible studies are demonstrated in Table 1.

3.2 | Pooled analysis of demographic characteristics

The demographic characteristics of patients with COVID19 are shown in Table 2. The median age of 17 364 COVID-19 patients across 53 studies ranged from 32 to 74 years in patients with a good prognosis and 47 to 77 years in patients with poor outcomes. Pooled estimates revealed significantly higher age in critical/expired cases (SMD = 1.0, 95% CI = 0.72-1.31, $P < .001$) than the noncritical group. The results from 54 articles with a total sample size of 17 702 patients showed that the proportion of males was significantly higher in critical cases (OR = 1.50, 95% CI = 1.36-1.69, $P < .001$). Evidence of heterogeneity and publication bias were observed for age data ($I^2 = 97.1\%$, $P < .001$, Egger's $P = .041$), but not for gender ($I^2 = 26.5\%$, $P = .041$, Egger's $P = .58$).

3.3 | Pooled analysis of cardiac biomarkers

The laboratory examination of the included studies is demonstrated in Table 2. Meta-analysis showed higher levels of cardiac biomarkers in critical/expired patients; high-sensitivity cTnI (SMD = 0.96, 95% CI = 0.71-1.22, $P < .001$), creatine kinase (SMD = 0.68, 95% CI = 0.47-0.90, $P < .001$), CK-MB (SMD = 0.80, 95% CI = 0.59-1.01, $P < .001$), AST (SMD = 0.71, 95% CI = 0.57-0.84, $P < .001$), LDH (SMD = 1.12, 95% CI = 0.86-1.38, $P < .001$), myoglobin (SMD = 1.16, 95% CI = 0.80-1.51, $P < .001$), and NT-proBNP (SMD = 1.15, 95% CI = 0.83-1.48, $P < .001$). A considerable heterogeneity was observed across studies for all laboratory parameters; cTnI ($I^2 = 91.9\%$, $P < .001$), creatine kinase ($I^2 = 89.3\%$, $P < .001$), CK-MB ($I^2 = 86.6\%$, $P < .001$), AST ($I^2 = 74.7\%$, $P < .001$), LDH ($I^2 = 90.6\%$, $P < .001$), myoglobin ($I^2 = 90.1\%$, $P < .001$), and NT-proBNP ($I^2 = 91.5\%$, $P < .001$). Subgroup

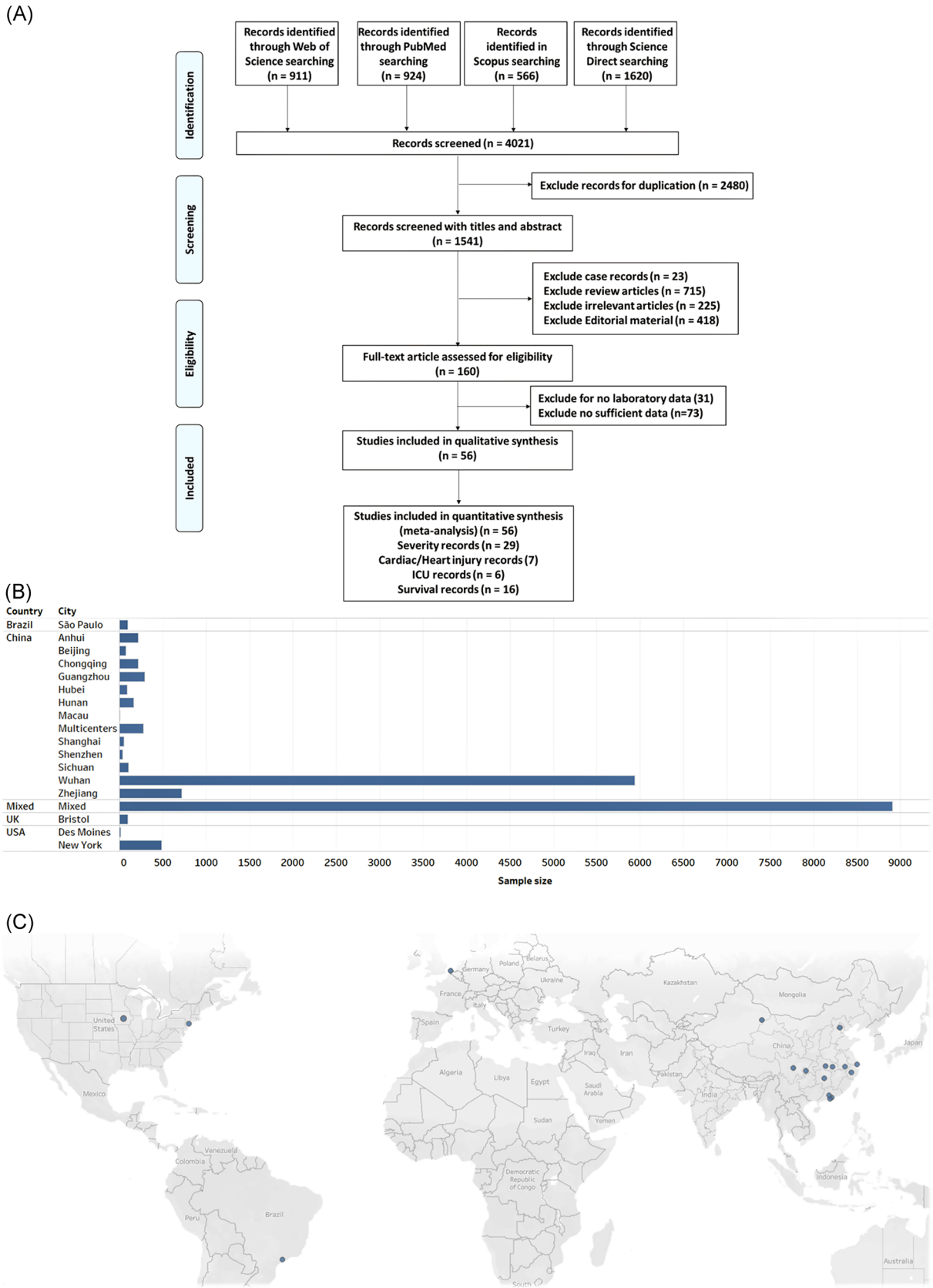


FIGURE 1 Selected studies. A, The workflow of the selection process. PRISMA guidelines were followed. B, The total sample size for each geographic location. Mixed: analysis included data from 169 hospitals located in 11 countries in Asia, Europe, and North America. C, Map of the source of patients with COVID-19 in the eligible studies. COVID-19, coronavirus disease-2019; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

TABLE 1 Characteristics of the included studies

First author (1) Severity	Year	Publication date	Journal name	Continent	Country	Ethnicity	Study design	Sample size		Age		Gender		Reference no.
								Severe	Mild	Severe, M (SD)	Mild, M (SD)	Severe, (M/F)	Mild, (M/F)	
Aggarwal S	2020	29-Apr	Diagnosis (Berl)	Des Moines	USA	American	Retrospective	8	8	58.3 (28.6)	68.2 (40.0)	5/3	7/1	13
Chen C	2020	6-Mar	Zhonghua Xin Xue Guan Bing Za Zhi	Wuhan	China	Asian	Retrospective	24	126	NA	NA	18/6	66/60	14
Chen G	2020	27-Mar	J Clin Invest	Wuhan	China	Asian	Retrospective	11	10	61.2 (7.04)	50.3 (9.8)	10/1	7/3	15
Deng Q	2020	8-Apr	Int J cardiol	Wuhan	China	Asian	Retrospective	67	45	67.3 (14.8)	54 (20.7)	38/29	19/26	16
Fang X	2020	11-Apr	J Infect	Anhui	China	Asian	Retrospective	7	46	54.3 (15.4)	39.9 (15.5)	5/2	22/24	17
Gao L	2020	15-Apr	Respir Res	Wuhan	China	Asian	Retrospective	30	24	67.4 (14.4)	51.6 (13.9)	16/14	8/16	18
He R	2020	12-Apr	J Clin Virol	Wuhan	China	Asian	Retrospective	69	135	62.3 (16.3)	42.3 (16.3)	37/32	42/93	19
Hong Y	2020	8-Apr	Ann Transl Med	Zhejiang	China	Asian	Retrospective	25	50	44.1 (11.3)	47.5 (14.2)	11/14	30/20	20
Lo I	2020	15-Mar	Int J Biol Sci	Macau	China	Asian	Retrospective	4	6	61 (5.0)	37 (19.0)	1/3	2/4	21
Mo P	2020	16-Mar	Clin Infect Dis	Wuhan	China	Asian	Retrospective	85	70	60.7 (14.1)	45.7 (15.6)	55/30	31/39	22
Pereira M	2020	24-Apr	Am J Transplant	New York	USA	American	Retrospective	27	63	65.7 (13.3)	52.3 (18.5)	16/11	37/26	23
Shi Y	2020	18-Mar	Crit Care	Zhejiang	China	Asian	Retrospective	49	438	56 (17.0)	45 (19.0)	36/13	223/215	24
Wan S	2020	21-Mar	J Med Virol	Chongqing	China	Asian	Retrospective	40	95	60.3 (15.6)	42 (11.8)	21/19	52/43	25
Wei Y	2020	17-Apr	J Infect	Anhui	China	Asian	Retrospective	30	137	49 (12.6)	40.8 (15.5)	20/10	75/62	26
Zhang G	2020	9-Apr	J Clin Virol	Wuhan	China	Asian	Retrospective	55	166	62.7 (16.3)	50.4 (20.9)	35/20	73/93	27
Zhang J	2020	19-Feb	Allergy	Wuhan	China	Asian	Retrospective	58	82	58.7 (45.9)	51.8 (38.5)	33/25	38/44	28
Zhao X	2020	29-Apr	BMC Infect Dis	Hubei	China	Asian	Retrospective	30	61	NA	NA	14/16	35/26	29
Zhu Z	2020	22-Apr	Int J Infect Dis	Zhejiang	China	Asian	Retrospective	16	104	57.5 (11.7)	49.9 (15.5)	9/7	73/38	30
Feng Y	2020	10-Apr	Am J Respir Crit Care Med	Wuhan	China	Asian	Retrospective	54	352	57.7 (14.1)	50.3 (19.3)	33/21	190/162	31
Han Y	2020	27-Mar	MedRxiv	Wuhan	China	Asian	Retrospective	24	23	61 (41.5)	62.2 (29.6)	17/7	9/14	32
Ma K	2020	23-Mar	MedRxiv	Chongqing	China	Asian	Retrospective	20	64	60.3 (19.3)	46.8 (11.6)	12/8	36/28	33
Zhao W	2020	30-Mar	MedRxiv	Beijing	China	Asian	Retrospective	20	57	69 (15.0)	45 (17.0)	11/9	23/34	34
Zheng F	2020	24-Mar	Eur Rev Med Pharmacol Sci	Hunan	China	Asian	Retrospective	30	131	56.5 (14.4)	40.7 (14.8)	14/16	66/65	35
Chen X	2020	17-Apr	Clin Infect Dis	Wuhan	China	Asian	Retrospective	10	21	63.9 (15.2)	52.8 (14.2)	9/1	13/8	36
Han H	2020	31-Mar	J Med Virol	Wuhan	China	Asian	Retrospective	60	198	58.9 (14.4)	58.9 (10.8)	21/39	71/127	37
Yang Y	2020	29-Apr	J Allergy Clin Immunol	Shenzhen	China	Asian	Retrospective	25	14	58.3 (26.7)	50.5 (41.5)	14/11	7/7	38

(Continues)

TABLE 1 (Continued)

First author								Sample size		Age		Gender		
(1) Severity	Year	Publication date	Journal name	Continent	Country	Ethnicity	Study design	Severe	Mild	Severe, M (SD)	Mild, M (SD)	Severe, (M/F)	Mild, (M/F)	Reference no.
Li X	2020	12-Apr	J Allergy Clin Immunol	Wuhan	China	Asian	Retrospective	269	279	63.7 (13.3)	55.3 (16.3)	153/116	126/153	39
Zheng C	2020	27-Mar	Int J Infect Dis	Wuhan	China	Asian	Retrospective	21	34	NA	NA	NA	NA	40
Wu J	2020	27-Mar	J Intern Med	Multicenter	China	Asian	Retrospective	83	197	63 (10.2)	37.5 (17.1)	45/38	106/91	41
(2) Cardiac injury								**With**	**Without**	**With, M (SD)**	**Without, M (SD)**	**With, (M/F)**	**Without, (M/F)**	
Guo T	2020	27-Mar	JAMA Cardiol	Wuhan	China	Asian	Retrospective	52	135	71.4 (9.4)	53.5 (13.2)	34/18	57/78	42
Li M	2020	18-Apr	Nutrition, Metabolism & Cardiovascular Diseases	Wuhan	China	Asian	Retrospective	42	41	60 (13.3)	33 (5.2)	18/24	16/25	43
Shi S	2020	25-Mar	JAMA Cardiol	Wuhan	China	Asian	Retrospective	82	334	67.7 (45.2)	57 (51.1)	44/38	161/173	44
Liu Y	2020	16-Mar	MedRxiv	Guangzhou	China	Asian	Retrospective	15	276	64 (12.6)	47 (20.7)	11/4	122/154	45
Wei J	2020	30-Apr	Heart	Sichuan	China	Asian	Prospective	16	85	69.5 (14.4)	45 (16.3)	7/9	47/38	46
He X	2020	30-Apr	Zhonghua Xin Xue Guan Bing Za Zhi	Shanghai	China	Asian	Retrospective	24	30	69.2 (8.5)	66.1 (12.8)	17/7	17/13	47
Peng Y	2020	2-Mar	Zhonghua Xin Xue Guan Bing Za Zhi	Wuhan	China	Asian	Retrospective	16	96	58.2 (6.7)	61.5 (9.2)	9/7	44/52	48
(3) Admission								**ICU**	**Floor**	**ICU, M (SD)**	**Floor, M (SD)**	**ICU, (M/F)**	**Floor, (M/F)**	
Goyal P	2020	18-Apr	N Engl J Med	New York	USA	American	Retrospective	130	263	63.3 (16.2)	61.2 (20.7)	92/38	146/117	49
Chu Y	2020	28-April	J Infect	Zhejiang	China	Asian	Retrospective	7	26	67 (17.7)	64.7 (16.6)	6/1	16/10	50
Du R	2020	7-Apr	Ann Am Thorac Soc	Wuhan	China	Asian	Retrospective	51	58	68.4 (9.7)	72.7 (11.6)	36/15	38/20	51
Huang C	2020	24-Jan	The Lancet	Wuhan	China	Asian	Prospective	13	28	50.3 (14.8)	49.2 (12.2)	11/2	19/9	1
Lei S	2020	4-Apr	EClinicalMedicine	Wuhan	China	Asian	Retrospective	15	19	57.7 (22.2)	44.7 (21.5)	5/10	9/10	52
Wang D	2020	7-Feb	JAMA	Wuhan	China	Asian	Retrospective	36	102	67 (15.6)	50 (20.7)	22/14	53/49	53
(4) Mortality								**Died**	**Alive**	**Died, M (SD)**	**Alive, M (SD)**	**Died, (M/F)**	**Alive, (M/F)**	
Chen T	2020	16-Mar	BMJ	Wuhan	China	Asian	Retrospective	113	161	69 (11.1)	51.3 (21.5)	83/30	88/73	54
Du R	2020	7-May	Eur Respir J	Wuhan	China	Asian	Prospective	21	158	70.2 (7.7)	56 (13.5)	10/11	87/71	55

TABLE 1 (Continued)

(4) Mortality								Died	Alive	Died, M (SD)	Alive, M (SD)	Died, (M/F)	Alive, (M/F)	
Mehra M	2020	1-May	N Engl J Med	Mixed	Mixed	Mixed	Retrospective	515	8395	55.8 (15.1)	48.7 (16.6)	336/179	5003/3392	[56]
Siciliano R	2020	10-Mar	Int J Infect Dis	São Paulo	Brazil	Latin American	Prospective	26	71	NA	NA	19/7	42/29	[57]
Tomlins J	2020	27-Apr	J Infect	Bristol	UK	Caucasian	Retrospective	20	75	78 (9.6)	70.7 (19.3)	12/8	48/27	[58]
Wang L	2020	30-Mar	J Infect	Wuhan	China	Asian	Retrospective	65	274	76.3 (9.6)	68.7 (7.4)	39/26	127/147	[59]
Zhou F	2020	9-Mar	Lancet	Wuhan	China	Asian	Retrospective	54	137	69.3 (9.6)	51.7 (9.6)	38/16	81/56	[60]
Zhou W	2020	21-Feb	Signal Transduction Targeted Therapy	Wuhan	China	Asian	Retrospective	7	8	68 (3.3)	56.3 (10.0)	4/3	6/2	[61]
Deng Y	2020	20-Mar	Chin Med J (Engl)	Wuhan	China	Asian	Retrospective	109	116	68.3 (8.9)	43.3 (17.8)	73/36	51/65	[62]
Fu L	2020	16-Mar	MedRxiv	Wuhan	China	Asian	Retrospective	34	166	NA	NA	16/18	NA	[63]
Li K	2020	27-Mar	MedRxiv	Wuhan	China	Asian	Retrospective	15	87	68 (14.1)	55 (16.3)	48/39	11/4	[64]
Luo X	2020	23-Mar	MedRxiv	Wuhan	China	Asian	Retrospective	100	303	72 (11.1)	49.3 (18.5)	57/43	136/167	[65]
Wang Y	2020	8-Apr	Am J Respir Crit Care Med	Wuhan	China	Asian	Retrospective	133	211	69.7 (11.1)	57.7 (16.3)	74/59	105/106	[66]
Zhang F	2020	24-Mar	MedRxiv	Wuhan	China	Asian	Retrospective	17	31	78.6 (8.3)	66.2 (13.7)	12/5	21/10	[67]
He X	2020	30-Apr	Zhonghua Xin Xue Guan Bing Za Zhi	Shanghai	China	Asian	Retrospective	26	28	69.7 (10.4)	64.8 (11.7)	16/10	18/10	[47]
Wang L	2020	14-Apr	Zhonghua Yan Ke Za Zhi	Wuhan	China	Asian	Retrospective	33	169	74.3 (14.1)	59 (13.3)	23/10	65/104	[68]

analysis by ethnicity and sample size did not resolve heterogeneity. No evidence of publication bias was found for all laboratory tests.

3.4 | Pooled analysis of comorbidities

We then compared the difference of the prevalence of the comorbidities in patients with poor outcomes compared with those with good outcomes. The presence of prior cerebrovascular diseases (OR = 4.49, 95% CI = 2.72-7.40, $P < .001$) or chronic heart diseases (OR = 3.42, 95% CI = 2.65-4.42, $P < .001$) had the highest risk for poor prognosis, followed by chronic obstructive pulmonary disease (COPD) (OR = 0.08, 95% CI = 2.36-4.03, $P < .001$). For all other reported comorbid conditions, their proportion was also statistically higher in critical/expired group; chronic kidney disease (CKD) (OR = 2.75, 95% CI = 1.77-4.28, $P < .001$), hypertension (OR = 2.22, 95% CI = 1.75-2.81, $P < .001$), diabetes mellitus (OR = 1.88, 95% CI = 1.59-2.24, $P < .001$), and malignant neoplasm (OR = 1.97, 95% CI = 1.41-2.76, $P < .001$). Apart of articles for hypertension ($I^2 = 77.8\%$, $P < .001$) and cerebrovascular diseases ($I^2 = 60.8\%$, $P < .001$), homogeneity was observed across studies. Pairwise comparison yielded evidence of publication bias for hypertension (Egger's P-value = .027), chronic heart disease (Egger's P-value = .031), and CKD (Egger's P-value = .046) (Table 2).

3.5 | Pooled analysis of secondary complications

Summarizing analysis revealed a 93% increased risk of poor prognosis in cohorts who experienced chest pain or tightness (OR = 1.93, 95% CI = 1.14-3.28, $P = .014$). In addition, meta-analysis showed that patients with COVID-19 who developed complications were more likely to have adverse outcomes with higher risk of mortality (Table 2). The highest risk was for those with ARDS (OR = 34.8, 95% CI = 13.6-89.2, $P < .001$), shock (OR = 31.4, 95% CI = 6.26-157, $P < .001$), and acute kidney injury (OR = 15.7, 95% CI = 8.24-30.2, $P < .001$), followed by coagulopathy (OR = 5.86, 95% CI = 2.83-12.13, $P < .001$), heart failure (OR = 4.15, 95% CI = 2.41-7.15, $P < .001$), pneumonia (OR = 3.66, 95% CI = 2.04-6.57, $P < .001$), arrhythmia (OR = 3.40, 95% CI = 1.67-6.94, $P < .001$), and liver injury (OR = 2.93, 95% CI = 1.01-8.46, $P = .049$). Obvious heterogeneity was observed across studies. Apart of liver injury articles ($P = .030$), the Egger's test provides no evidence of publication bias.

3.6 | Pooled analysis of COVID-19-related medications

Furthermore, as depicted in Table 2 patients who received antibiotics (OR = 3.36, 95% CI = 1.66-6.77, $P = .001$), glucocorticoids (OR = 3.52, 95% CI = 2.51-4.93, $P < .001$), immunoglobulins (OR = 3.41, 95% CI = 1.90-6.14, $P < .001$), and hydroxychloroquine (OR = 6.67, 95% CI = 2.0-22.2, $P = .002$) had higher risk for poor prognosis. However, noteworthy, there was significant heterogeneity between studies ($I^2 = 67.9\%$-84.6%), and only two studies had reported hydroxychloroquine.

3.7 | Pairwise comparisons for severity, cardiac injury, ICU admission, and mortality

Table S1 summarizes pooled estimates for seven cardiac biomarkers, eight comorbidities, and nine secondary complications in patients with COVID-19 with severe presentation compared with nonsevere cohorts, who developed secondary cardiac injury versus not, ICU admitted patients vs general ward patients and survived vs expired. The Forest plot for the pooled analyses is presented in Figures S1-S11. Funnel plots for assessment of publication bias are depicted in Figure S12. Meta-regression to assess the impact of study characteristics as sample size, the city of the study, and timing of publications as moderators for the study effect size of each pairwise comparison is demonstrated in Table S2.

3.8 | Meta-regression analysis

To assess the impact of study characteristics as sample size, the city of the study, and timing of publications as moderators for the study effect size, meta-regression was performed. Results of studies comparing critical/expired patients with noncritical cases suggested confounding of AST (coefficient = 0.31, 95% CI = 0.03-0.59, $P = .028$) and pneumonia (coefficient = 1.39, 95% CI = 0.04-2.74, $P = .040$) by publication date, and hypertension (coefficient = 0.76, 95% CI = 0.17-1.35, $P = .010$) and chronic heart disease (coefficient = 0.75, 95% CI = 0.28-1.22, $P = .002$) by ethnicity (Table 3).

3.9 | Decision tree classifier model

Receiver operating characteristics (ROC) curves were first employed to analyze the prognostic performance of cardiac markers for predicting adverse outcomes and to select the best cutoff threshold with high sensitivity and specificity. The highest area under the curves (AUC) were for myoglobin (AUC = 0.91 ± 0.07, $P = .002$) and high-sensitive cTnI (AUC = 0.89 ± 0.04, $P < .001$) at the cutoff values of 72 ng/mL and 13.75 ng/L, respectively, followed by NT-proBNP (AUC = 0.86 ± 0.06, $P < .001$) and AST (AUC = 0.84 ± 0.04, $P < .001$). Combining cardiac markers with demographic and clinical features, decision tree analysis was used to predict mortality and severity in patients with COVID-19. Age, cTnI, and AST levels were able to classify patients into high and low-risk patients (Figure 2A,B). High troponin I over 13.75 ng/L combined with either advanced age over 60 years or elevated AST level over 27.72 U/L were the best model to predict poor outcomes (classification accuracy = 81.03%, precision = 74.1%, recall = 86.0%, and diagnostic odds ratio = 20.8). After conversion of SMD to OR, meta-analysis showed that patients with

TABLE 2 Predictors for poor outcomes in patients with COVID-19

Characteristics	Number studies	Sample size			Test of association			Effect size			Heterogeneity		Publication bias
		Total	Poor prognosis	Good prognosis	Statistical method	Effect measure	Analysis model	Estimate	95% CI	*P*-value	I^2	*P*-value	*P* (Egger's test)
Demographic data													
Age	53	17 364	2942	14 422	IV	SMD	Random	1.01	0.72-1.31	**<.001**	**97.11%**	**<.001**	**.041**
Sex (male)	54	17 702	3022	14 680	MH	OR	Random	1.50	1.34-1.69	**<.001**	26.56%	.041	.58
Cardiac biomarkers													
Troponin I	32	4953	1321	3632	IV	SMD	Random	0.96	0.71-1.22	**<.001**	**91.9%**	**<.001**	.46
Creatine kinase	30	4528	1262	3266	IV	SMD	Random	0.68	0.47-0.90	**<.001**	**89.32%**	**<.001**	.55
CK-MB	27	3816	994	2822	IV	SMD	Random	0.80	0.59-1.01	**<.001**	**86.63%**	**<.001**	.12
AST	38	5557	1483	4074	IV	SMD	Random	0.71	0.57-0.84	**<.001**	**74.70%**	**<.001**	.25
LDH	30	3992	1145	2847	IV	SMD	Random	1.12	0.86-1.38	**<.001**	**90.67%**	**<.001**	.57
Myoglobin	10	2232	536	1696	IV	SMD	Random	1.16	0.80-1.51	**<.001**	**90.06%**	**<.001**	.98
NT-proBNP	20	3240	719	2521	IV	SMD	Random	1.15	0.83-1.48	**<.001**	**91.52%**	**<.001**	.80
Presentation													
Chest pain/tightness	18	3325	974	2351	MH	OR	Random	1.93	1.14-3.28	**.014**	**70.23%**	**<.001**	.818
Comorbidities													
Hypertension	50	16 974	2782	14 192	MH	OR	Random	2.22	1.75-2.81	**<.001**	**77.83%**	**<.001**	**.027**
Diabetes	51	17 120	2826	14 294	MH	OR	Random	1.88	1.59-2.24	**<.001**	32.08%	.020	.96
CHD	40	15 864	2508	13 356	MH	OR	Random	3.42	2.65-4.42	**<.001**	49.86%	.011	**.031**
COPD	35	14 658	2148	12 510	MH	OR	Random	3.08	2.36-4.03	**<.001**	10.12%	.30	.42
CVD	21	3791	970	2821	MH	OR	Random	4.49	2.72-7.40	**<.001**	**60.8%**	**<.001**	.85
CKD	26	5212	1450	3762	MH	OR	Random	2.75	1.77-4.28	**<.001**	32.4%	.06	**.046**
Cancer	31	5563	1567	3996	MH	OR	Random	1.97	1.41-2.76	**<.001**	8.35%	.33	.73
Complications													
ARDS	14	2963	877	2086	MH	OR	Random	34.8	13.6-89.2	**<.001**	**87.6%**	**<.001**	.12
Pneumonia	10	1211	348	863	MH	OR	Random	3.66	2.04-6.57	**<.001**	0.0%	.52	.72
AKI	13	2979	844	2135	MH	OR	Random	15.7	8.24-30.2	**<.001**	**57.88%**	**<.001**	.83
Liver injury	11	2050	558	1492	MH	OR	Random	2.93	1.01-8.46	**.049**	**86.55%**	**<.001**	**.030**
Arrhythmia	10	10 421	847	9574	MH	OR	Random	3.40	1.67-6.94	**<.001**	**66.98%**	**<.001**	.35
Heart failure	9	10 391	781	9610	MH	OR	Random	4.15	2.41-7.15	**<.001**	**56.8%**	**.020**	.23
Coagulopathy	4	996	221	775	MH	OR	Random	5.86	2.83-12.13	**<.001**	**50.96%**	**.010**	.71
Shock	12	1915	628	1287	MH	OR	Random	36.9	11.05-123.5	**<.001**	**70.16%**	**<.001**	.73
Sepsis	2	465	167	298	MH	OR	Random	220.0	30.38-1593.71	**<.001**	0.0%	.69	NA

(Continues)

TABLE 2 (Continued)

Characteristics	Number studies	Sample size			Test of association			Effect size			Heterogeneity		Publication bias
		Total	Poor prognosis	Good prognosis	Statistical method	Effect measure	Analysis model	Estimate	95% CI	*P*-value	I^2	*P*-value	*P* (Egger's test)
Treatment													
Antiviral	16	3620	1150	2470	MH	OR	Random	0.985	0.67-1.45	.94	42.84%	.036	.77
Antibiotics	11	2924	920	2004	MH	OR	Random	3.36	1.66-6.77	**.001**	**71.46%**	**<.001**	.73
Glucocorticoids	23	3961	1289	2672	MH	OR	Random	3.52	2.51-4.93	**<.001**	**67.97%**	**<.001**	.83
Immunoglobulin	12	2300	738	1562	MH	OR	Random	3.41	1.90-6.14	**<.001**	**84.66%**	**<.001**	.16
Lopinavir/ritonavir	3	299	122	177	MH	OR	Random	0.620	0.097-3.97	.61	**87.33%**	**<.001**	.72
Oseltamivir	2	494	130	364	MH	OR	Random	0.974	0.61-1.56	.91	5.46%	.30	NA
Interferon	4	842	302	540	MH	OR	Random	0.794	0.285-2.21	.65	**79.84%**	**.002**	.43
Hydroxychloroquine	2	106	35	71	MH	OR	Random	6.67	2.00-22.22	**.002**	0.0%	.35	NA
Azithromycin	2	106	35	71	MH	OR	Random	5.49	1.13-26.66	.03	38.49%	.20	NA

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CHD, chronic heart disease; CI, confidence interval; CKD, chronic kidney disease; CK-MB, creatine kinase myocardial band; COPD, chronic obstructive pulmonary disease; COVID-2019, coronavirus disease-2019; I2, the ratio of true heterogeneity to total observed variation; IV, inverse variance; LDH, lactate dehydrogenase; MH, Mantel-Haenszel; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide; OR, odds ratio; SMD, standardized mean difference. Bold values indicate significance at $P < 0.05$.

high cTnI (OR = 5.22, 95% CI = 3.73-7.31, $P < .001$) and AST levels (OR = 3.64, 95% CI = 2.84-4.66, $P < .001$) were more likely to develop adverse outcomes for COVID-19 disease.

4 | DISCUSSION

Our meta-analysis has several important aspects. We include a robust sample size with broad, global geographic reach. Utilizing a two-arms meta-analysis for 56 articles and 17 794 COVID-19 subjects, our findings reveal the association of COVID-19 mortality with high levels of cardiac biomarkers. We amplify previous smaller meta-analyses and the single site or regional studies. Furthermore, as of 8 May 2020, we enclosed a larger number of studies and patients, and involved more cardiac biomarkers, demographics, and clinical data than prior studies, demonstrating multiple predictors of cardiac injury, poor prognosis, severity, ICU admission, and mortality. In addition, for prognostic risk assessment, we employed decision tree model analysis for both serum biomarkers and the clinical data and performed ROC curves analyses. Although our analysis included 169 hospitals located in 11 countries in Asia and Europe, it is largely retrospective.

Meta-regression analyses indicated the pooled results were independent to study characteristics and decision tree analysis revealed that cTnI, AST, and potentially other serum biomarkers could be predictors of risk. One significant limitation, inherent in the use of meta-analyses to guide further clinical practice is the heterogeneity across studies, including differences in study methods.

COVID-19 pulmonary and cardiac complications are difficult to disaggregate. Before the SARS-CoV-2 pandemic, acute viral infections were associated with acute coronary syndromes.[69] Despite limited elevated cTnI findings in less severe cases, significantly higher cTnI unmasks the subset of patients with poorer outcomes as earlier seen in 341 patients from China.[70]

Similarly, in 112 patients with COVID-19 in China, elevated troponin was linked to severity and mortality despite normal levels of troponin at admission.[16] Another prior systematic literature, from 1 December 2019 to 27 March 2020, in 4189 patients with COVID-19 from 28 studies, higher mean troponin, with a similar trend for CK-MB, myoglobin, and NT-proBNP were associated with higher mortality (summary risk ratio 3.85, 2.13-6.96; $P < .001$).[71]

A recent retrospective single-center cohort study of patients between 28 January 2020 and 16 March 2020, from the Central Hospital of Wuhan, also reported 176 patients (116 survivors, 60 nonsurvivors) with elevated cTnI and increased odds of mortality by the regression models.[72]

Moreover, a larger cohort enrolled 671 patients with severe COVID-19 from 1 January to 23 February 2020. As a predictor of in-hospital mortality, the area under the receiver operating characteristic curve of initial cTnI was 0.92 (95% CI, 0.87-0.96; sensitivity, 0.86; specificity, 0.86; $P < .001$). Overall, multiple abnormal laboratory values on admission were higher in nonsurvivors, including CK-MB, myoglobin, cTnI, and NT-proBNP (all $P < .001$).[73]

TABLE 3 Meta-regression analysis for overall analysis

Parameter	Feature	Categories	Number of studies	Coefficient	Lower bound	Upper bound	*P*-value
(1) Demographic data							
Age	Country of origin	China vs others	48/5	0.74	−0.59	2.08	.28
	Sample size	>50 vs ≤50	42/11	0.57	−0.39	1.54	.25
	Publication date	Jan-Mar vs Apr-May	27/26	0.64	−0.15	1.42	.11
Male gender	Country of origin	China vs others	48/6	0.07	−0.20	0.34	.60
	Sample size	>50 vs ≤50	43/43	0.02	−0.51	0.56	.94
	Publication date	Jan-Mar vs Apr-May	28/26	0.20	−0.01	0.41	.07
(2) Presentation							
Chest pain or tightness	Sample size	>50 vs ≤50	16/2	−0.83	−2.87	1.21	.42
	Publication date	Jan-Mar vs Apr-May	10/8	0.12	−0.92	1.18	.81
(3) Cardiac biomarkers							
Troponin I	Country of origin	China vs others	28/4	0.34	−0.72	1.40	.53
	Sample size	>50 vs ≤50	27/5	0.28	−0.67	1.24	.56
	Publication date	Jan-Mar vs Apr-May	18/14	0.12	−0.57	0.82	.73
Creatine kinase	Country of origin	China vs others	25/5	0.16	−0.52	0.83	.65
	Sample size	>50 vs ≤50	24/6	0.3	−0.35	0.95	.37
	Publication date	Jan-Mar vs Apr-May	18/12	0.36	−0.15	0.87	.17
CK-MB	Country of origin	China vs others	23/4	0.06	−0.62	0.74	.86
	Sample size	>50 vs ≤50	23/4	0.63	−0.1	1.36	.09
	Publication date	Jan-Mar vs Apr-May	13/14	0.48	−0.001	0.96	.05
AST	Country of origin	China vs others	36/2	−0.03	−0.74	0.68	.94
	Sample size	>50 vs ≤50	28/10	0.23	−0.13	0.59	.22
	Publication date	Jan-Mar vs Apr-May	22/16	0.31	0.03	0.59	.028
LDH	Country of origin	China vs others	29/1	−0.1	−1.91	1.71	.91
	Sample size	>50 vs ≤50	22/8	0.27	−0.4	0.93	.43
	Publication date	Jan-Mar vs Apr-May	17/13	0.39	−0.15	0.92	.16
NT-proBNP	Country of origin	China vs others	19/1	0.3	−1.14	1.74	.68
	Sample size	>50 vs ≤50	19/1	0.5	−0.98	1.99	.51
	Publication date	Jan-Mar vs Apr-May	10/10	0.57	−0.07	1.21	.08
(4) Comorbidities							
Hypertension	Country of origin	China vs others	44/6	0.76	0.17	1.35	.010
	Sample size	>50 vs ≤50	41/9	0.43	−0.26	1.12	.22
	Publication date	Jan-Mar vs Apr-May	27/23	0.24	−0.17	0.64	.25
Diabetes	Country of origin	China vs others	45/6	0.3	0.04	0.57	.14
	Sample size	>50 vs ≤50	42/9	0.51	−0.15	1.18	.34
	Publication date	Jan-Mar vs Apr-May	26/25	0.16	−0.1	0.42	.13
CHD	Country of origin	China vs others	37/3	0.75	0.28	1.22	.002
	Sample size	>50 vs ≤50	34/6	0.63	−0.24	1.49	.15
	Publication date	Jan-Mar vs Apr-May	25/15	0.2	−0.2	0.6	.33
COPD	Country of origin	China vs others	30/5	0.61	−0.09	1.32	.09
	Sample size	>50 vs ≤50	31/4	−0.28	−1.96	1.40	.74
	Publication date	Jan-Mar vs Apr-May	15/20	0.19	−0.46	0.83	.57
CVD	Country of origin	China vs others	19/2	1.08	−0.87	3.03	.28
	Sample size	>50 vs ≤50	18/3	0.42	−1.16	2.00	.60
	Publication date	Jan-Mar vs Apr-May	11/10	0.45	−0.48	1.38	.35
CKD	Country of origin	China vs others	23/3	0.62	−0.32	1.56	.20
	Sample size	>50 vs ≤50	22/4	−0.06	−1.47	1.34	.93
	Publication date	Jan-Mar vs Apr-May	13/13	−0.20	−0.62	1.01	.63
Cancer	Country of origin	China vs others	28/3	0.33	−0.88	1.53	.59
	Sample size	>50 vs ≤50	26/5	−0.48	−1.61	0.66	.41
	Publication date	Jan-Mar vs Apr-May	15/16	0.43	−0.25	1.10	.21

(Continues)

TABLE 3 (Continued)

Parameter	Feature	Categories	Number of studies	Coefficient	Lower bound	Upper bound	*P*-value
(5) Complications							
ARDS	Country of origin	China vs others	13/1	−3.82	−11.04	3.41	.30
	Sample size	>50 vs ≤50	12/2	3.95	−1.36	9.26	.15
	Publication date	Jan-Mar vs Apr-May	9/5	0.41	−1.90	2.71	.73
Pneumonia	Country of origin	China vs others	9/1	−3.26	−7.81	1.28	.16
	Sample size	>50 vs ≤50	8/2	0.73	−2.77	4.21	.68
	Publication date	Jan-Mar vs Apr-May	6/4	1.39	0.04	2.74	.040
AKI	Country of origin	China vs others	12/1	−0.71	−4.44	3.02	.71
	Sample size	>50 vs ≤50	12/1	0.23	−1.21	1.67	.75
Liver injury	Country of origin	China vs others	10/1	−0.89	−4.82	3.04	.66
	Sample size	>50 vs ≤50	10/1	−0.68	−2.79	1.44	.53
Arrhythmia	Country of origin	China vs others	7/3	0.82	−1.02	2.66	.38
	Sample size	>50 vs ≤50	8/2	0.83	−1.36	3.01	.46
	Publication date	Jan-Mar vs Apr-May	4/6	0.17	−1.65	2.00	.85
Heart failure	Country of origin	China vs others	6/3	0.76	0.08	1.44	.030
	Publication date	Jan-Mar vs Apr-May	6/3	−0.03	−0.72	0.66	.93
Shock	Sample size	>50 vs ≤50	8/4	1.97	−0.10	4.05	.06
	Publication date	Jan-Mar vs Apr-May	8/4	−1.25	−3.25	0.75	.22
(6) Treatment							
Antiviral	Sample size	>50 vs ≤50	15/4	−0.27	−2.35	1.80	.79
	Publication date	Jan-Mar vs Apr-May	7/12	0.24	−1.25	1.73	.75
Antibiotics	Sample size	>50 vs ≤50	11/4	1.14	−0.99	3.28	.29
	Publication date	Jan-Mar vs Apr-May	10/5	0.59	−0.80	1.99	.40
Glucocorticoids	Sample size	>50 vs ≤50	17/6	0.29	−0.68	1.27	.55
	Publication date	Jan-Mar vs Apr-May	12/11	0.06	−0.63	0.76	.85
Immunoglobulin	Sample size	>50 vs ≤50	10/2	0.25	−1.49	2.01	.77
	Publication date	Jan-Mar vs Apr-May	8/4	0.69	−0.50	1.90	.25

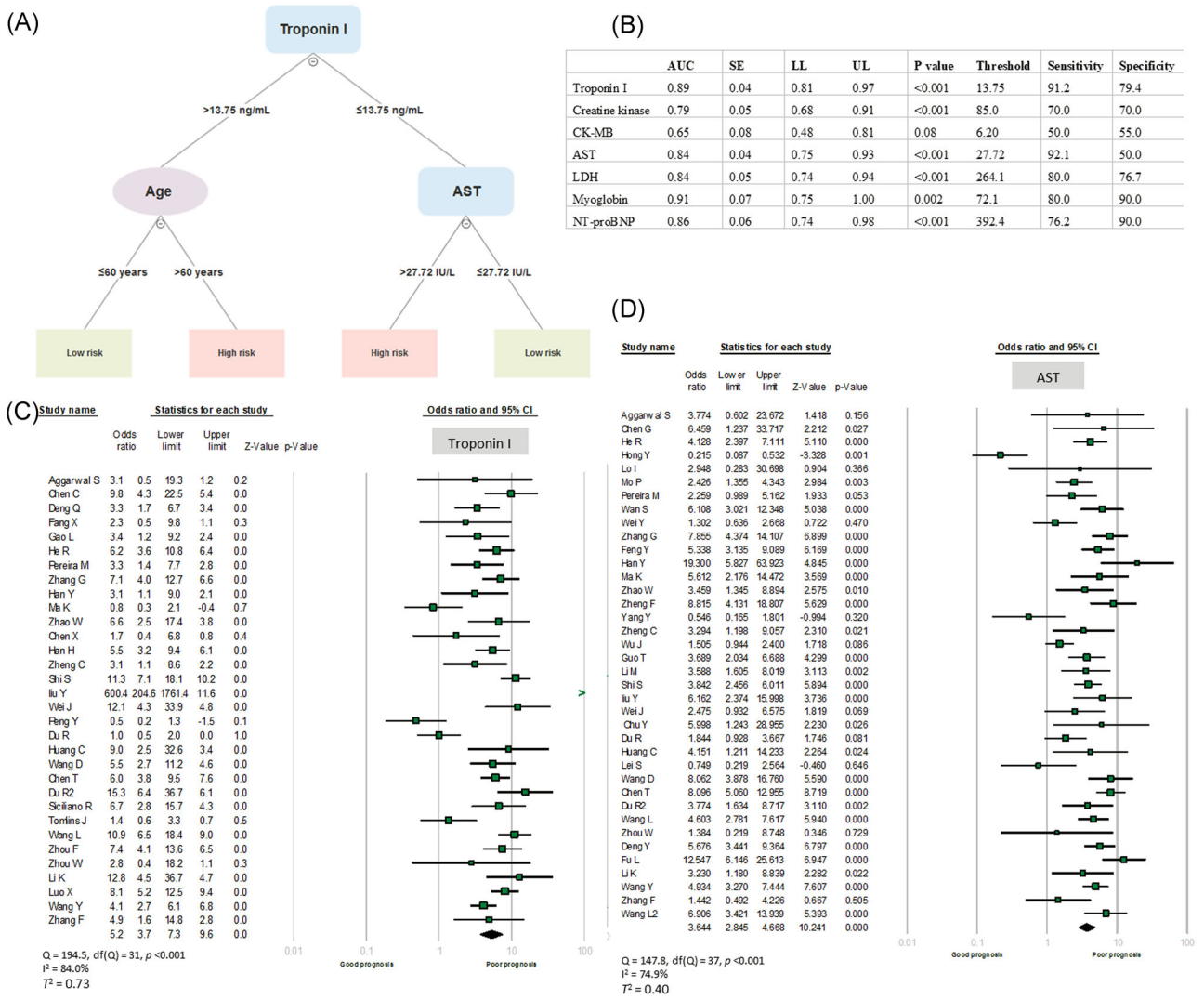
Note: Variables with number of studies ≥10 were included.

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CHD, chronic heart disease; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; LDH, lactate dehydrogenase; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide.

The exact pathway by which elevated biomarkers leads to death with COVID-19 with systemic inflammatory activity may include myocarditis, thrombosis, and additionally unstable coronary atherosclerotic plaque rupture. Hence, beyond the predominant pulmonary complications, severity, and mortality sources include viral myocarditis, cytokine-driven myocardial damage, microangiopathy, and acute coronary syndromes.[74] Therefore, biomarkers may identify a heightened inflammatory response, including endothelial dysfunction and microvascular damage.

There are several limitations to our analysis and review. The actual cause of mortality may be obscured by unmeasured or unknown confounders, underestimated by analysis of multivariable regression. Understanding CVD-associated mortality must integrate biomarker data with cardiac imaging and physiologic and structural abnormalities. In addition, the percentage of patients with sepsis has been underreported in our report and cardiac injury may correlate with the prevalence of shock with severe COVID-19.[75] Another limitation of these data is the lack of a determination of timing and estimated glomerular filtration rate as factors. Although cardiac biomarkers may reflect myocardial injury, inflammation, and remodeling, interpretation of biomarkers in chronic kidney disease (CKD) can be complicated by decreased urinary clearance and/or overall CKD-associated chronic inflammation. The prognostic power of future biomarker analyses for COVID-19 mortality should be trended over time and account for the degree of renal dysfunction.[76] Finally, in consideration of the immense COVID-19 global mortality, over 360 000 deaths,[77] with over 100 000 deaths in the US alone[78] at the time of manuscript submission, despite our relatively large sample size, our data will require ongoing supplementation, to overcome inherent statistical bias and confirming our results.

In conclusion, COVID-19 severity and mortality are compounded by vascular and myocardial injury. Elevated cardiac injury biomarkers may improve the identification of those patients at the highest risk and potentially lead to improved therapeutic approaches.



	AUC	SE	LL	UL	P value	Threshold	Sensitivity	Specificity
Troponin I	0.89	0.04	0.81	0.97	<0.001	13.75	91.2	79.4
Creatine kinase	0.79	0.05	0.68	0.91	<0.001	85.0	70.0	70.0
CK-MB	0.65	0.08	0.48	0.81	0.08	6.20	50.0	55.0
AST	0.84	0.04	0.75	0.93	<0.001	27.72	92.1	50.0
LDH	0.84	0.05	0.74	0.94	<0.001	264.1	80.0	76.7
Myoglobin	0.91	0.07	0.75	1.00	0.002	72.1	80.0	90.0
NT-proBNP	0.86	0.06	0.74	0.98	<0.001	392.4	76.2	90.0

FIGURE 2 A, Decision tree model analysis for clinical and cardiac biomarkers. Based on several inputs (clinical parameters and biomarkers), a model was created by a multilevel split. Each interior node corresponds to one of the input variables, each leaf represents a value of the target variable given the values of the input variables represented by the path from the root to the leaf. B, Receiver operating characteristics for cardiac biomarkers. C, Forest plot of high-sensitivity cardiac troponin I in critical/expired patients compared to noncritical cases. Each horizontal bar represents a study, with lines extending from the symbols representing 95% confidence intervals. The size of the data marker indicates relative weight. Pooled estimates are represented by the black diamond. D, Forest plot for AST in critical/expired patients compared with noncritical cases. AST, aspartate aminotransferase; AUC, area under the curve; CK-MB, creatine kinase myocardial band; LDH, lactate dehydrogenase; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide; LL, lower limit; SE, standard error; UL, upper limit

CONFLICT OF INTERESTS

All the authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

EAT and RME: study design; RME, AE, MNA, ME-M, and ME-M: study identification and data extraction; EAT, RME, and MHH: statistical analysis; EAT, RME, MHH, AE, and MSF: data interpretation; EAT, RME, MHH, AE, MNA, M E-M, M E-M, KCF, and MSF: original draft preparation. All authors revised and approved the final version of the manuscript.

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REFERENCES

1. 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.
2. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. *Travel Med Infect Dis*. 2020;34:101623.
3. Al-Tawfiq JA, Gautret P. Asymptomatic Middle East respiratory syndrome coronavirus (MERS-CoV) infection: extent and implications for infection control: a systematic review. *Travel Med Infect Dis*. 2019;27:27-32.
4. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med*. 2003;348(20):1953-1966.
5. Ahmed I, Azhar A, Eltaweel N, Tan BK. First Covid-19 maternal mortality in the UK associated with thrombotic complications. *Br J Haematol*. 2020;22:19458.
6. Pranata R, Huang I, Lim MA, Wahjoepramono PEJ, July J. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19 - systematic review, meta-analysis, and meta-regression. *J Stroke Cerebrovasc Dis*. 2020:104949.
7. Shi Q, Zhang X, Jiang F, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. *Diabetes Care*. 2020;43(6):dc200598.
8. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020;109(5):531-538.
9. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review [published online ahead of print March 27, 2020]. *JAMA Cardiol*. 2020. https://doi.org/10.1001/jamacardio.2020.1286
10. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Comprehensive meta-analysis (version 2.2.027) [Computer software]. Englewood, NJ: Biostat. *Organ Res Methods*. 2006;11(1):188-191.
11. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007;28(2):105-114.
12. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics*. 2018;74(3):785-794.
13. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): early report from the United States. *Diagnosis (Berl)*. 2020;7(2):91-96.
14. Chen C, Chen C, Yan JT, Zhou N, Zhao JP, Wang DW. [Analysis of myocardial injury in patients with COVID-19 and association between concomitant cardiovascular diseases and severity of COVID-19]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2020;48(0):E008.
15. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130(5):2620-2629.
16. Deng Q, Hu B, Zhang Y, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. *Int J Cardiol*. 2020;311:116-121.
17. Fang X, Mei Q, Yang T, et al. Low-dose corticosteroid therapy does not delay viral clearance in patients with COVID-19. *J Infect*. 2020;81:147-178.
18. Gao L, Jiang D, Wen XS, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. *Respir Res*. 2020;21(1):83.
19. He R, Lu Z, Zhang L, et al. The clinical course and its correlated immune status in COVID-19 pneumonia. *J Clin Virol*. 2020;127:104361.
20. Hong Y, Wu X, Qu J, Gao Y, Chen H, Zhang Z. Clinical characteristics of coronavirus disease 2019 and development of a prediction model for prolonged hospital length of stay. *Ann Transl Med*. 2020;8(7):443.
21. Lo IL, Lio CF, Cheong HH, et al. Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau. *Int J Biol Sci*. 2020;16(10):1698-1707.
22. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China [published online ahead of print March 16, 2020]. *Clin Infect Dis*. 2020. https://doi.org/10.1093/cid/ciaa270
23. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter [published online ahead of print April 24, 2020]. *Am J Transplant*. 2020. https://doi.org/10.1111/ajt.15941
24. Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. *Crit Care*. 2020;24(1):108.
25. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol*. 2020;92:797-806.
26. Wei YY, Wang RR, Zhang DW, et al. Risk factors for severe COVID-19: evidence from 167 hospitalized patients in Anhui, China [published online ahead of print April 17, 2020]. *J Infect*. 2020. https://doi.org/10.1016/j.jinf.2020.04.010
27. Zhang G, Hu C, Luo L, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. *J Clin Virol*. 2020;127:104364.
28. Zhang J, Dong X, Cao Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China [published online ahead of print February 19, 2020]. *Allergy*. 2020. https://doi.org/10.1111/all.14238
29. Zhao XY, Xu XX, Yin HS, et al. Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study. *BMC Infect Dis*. 2020;20(1):311.
30. Zhu Z, Cai T, Fan L, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. *Int J Infect Dis*. 2020;95:332-339.
31. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severity: a multicenter study of clinical features. *Am J Respir Crit Care Med*. 2020;201:1380-1388.
32. Han Y, Zhang H, Mu S, et al. Lactate dehydrogenase, a risk factor of severe COVID-19 patients [published online ahead of print March 27, 2020]. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.24.20040162
33. Li HC, Ma J, Zhang H, et al. COVID-19 myocarditis and severity factors: an adult cohort study. *medRxiv*. 2020;43:396-400.
34. Zhao W, Yu S, Zha X, et al. Clinical characteristics and durations of hospitalized patients with COVID-19 in Beijing: a retrospective cohort study [published online ahead of print March 30, 2020]. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.13.20035436
35. Zheng F, Tang W, Li H, Huang YX, Xie YL, Zhou ZG. Clinical characteristics of 161 cases of corona virus disease 2019 (COVID-19) in Changsha. *Eur Rev Med Pharmacol Sci*. 2020;24(6):3404-3410.
36. Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients [published online ahead of print April 17, 2020]. *Clin Infect Dis*. 2020. https://doi.org/10.1093/cid/ciaa449
37. Han H, Xie L, Liu R, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. *J Med Virol*. 2020;92:819-823.

38. Yang Y, Shen C, Li J, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19 [published online ahead of print April 29, 2020]. *J Allergy Clin Immunol*. 2020. https://doi.org/10.1016/j.jaci.2020.04.027
39. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan [published online ahead of print April 12, 2020]. *J Allergy Clin Immunol*. 2020. https://doi.org/10.1016/j.jaci.2020.04.006
40. Zheng C, Wang J, Guo H, et al. Risk-adapted treatment strategy for COVID-19 patients. *Int J Infect Dis*. 2020;94:74-77.
41. Wu J, Li W, Shi X, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19) [published online ahead of print March 27, 2020]. *J Intern Med*. 2020. https://doi.org/10.1111/joim.13063
42. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19) [published online ahead of print March 27, 2020]. *JAMA Cardiol*. 2020. https://doi.org/10.1001/jamacardio.2020.1017
43. Li M, Dong Y, Wang H, et al. Cardiovascular disease potentially contributes to the progression and poor prognosis of COVID-19 [published online ahead of print April 18, 2020]. *Nutr Metab Cardiovasc Dis*. 2020. https://doi.org/10.1016/j.numecd.2020.04.013
44. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China [published online ahead of print March 25, 2020]. *JAMA Cardiol*. 2020:e200950. https://doi.org/10.1001/jamacardio.2020.0950
45. Liu Y, Li J, liu D, et al. Clinical features and outcomes of 2019 novel coronavirus-infected patients with cardiac injury [published online ahead of print March 16, 2020]. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.11.20030957
46. Wei JF, Huang FY, Xiong TY, et al. Acute myocardial injury is common in patients with covid-19 and impairs their prognosis [published online ahead of print April 30, 2020]. *Heart*. 2020. https://doi.org/10.1136/heartjnl-2020-317007
47. 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 Xin Xue Guan Bing Za Zhi*. 2020;48(0):E011.
48. Peng YD, Meng K, Guan HQ, et al. [Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV]. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2020;48(0):E004.
49. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. *N Engl J Med*. 2020;382:2372-2374.
50. Chu Y, Li T, Fang Q, Wang X. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. *J Infect*. 2020.
51. Du RH, Liu LM, Yin W, et al. Hospitalization and critical care of 109 decedents with COVID-19 pneumonia in Wuhan, China [published online ahead of print April 07, 2020]. *Ann Am Thorac Soc*. 2020. https://doi.org/10.1513/AnnalsATS.202003-225OC
52. Lei S, Jiang F, Su W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. *EClinicalMedicine*. 2020;21:100331.
53. 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;323(11):1061-1069.
54. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.
55. Du RH, Liang LR, Yang CQ, 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):2000524.
56. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19 [published online ahead of print May 01, 2020]. *N Engl J Med*. 2020. https://doi.org/10.1056/NEJMoa2007621
57. Siciliano RF, Gualandro DM, Sommer Bittencourt M, et al. Biomarkers for prediction of mortality in left-sided infective endocarditis. *Int J Infect Dis*. 2020;96:25-30.
58. Tomlins J, Hamilton F, Gunning S, Sheehy C, Moran E, MacGowan A. Clinical features of 95 sequential hospitalised patients with novel coronavirus 2019 disease (COVID-19), the first UK cohort [published online ahead of print April 27, 2020]. *J Infect*. 2020. https://doi.org/10.1016/j.jinf.2020.04.020
59. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect*. 2020;80:639-645.
60. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
61. Zhou W, Liu Y, Tian D, et al. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. *Signal Transduct Target Ther*. 2020;5(1):18.
62. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. *Chin Med J (Engl)*. 2020;133:1261-1267.
63. Bakr AR, Fu GY, Hedeen D. Influence factors of death risk among COVID-19 patients in Wuhan, China: a hospital-based case-cohort study. *medRxiv*. 2020;726:138068. https://doi.org/10.1101/2020.03.13.20035329
64. Li J, Wang X, Huang X, et al. Radiographic findings and other predictors in adults with Covid-19. *medRxiv*. 2020;20:56.
65. Luo X, Xia H, Yang W, et al. Characteristics of patients with COVID-19 during epidemic ongoing outbreak in Wuhan, China [published online ahead of print March 23, 2020]. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.19.20033175
66. Wang Y, Lu X, Li Y, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. *Am J Respir Crit Care Med*. 2020;201:1430-1434.
67. Zhang F, Yang D, Li J, et al. Myocardial injury is associated with in-hospital mortality of confirmed or suspected COVID-19 in Wuhan, China: a single center retrospective cohort study [published online ahead of print March 24, 2020]. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.21.20040121
68. Wang L, He WB, Yu XM, Liu HF, Zhou WJ, Jiang H. [Prognostic value of myocardial injury in patients with COVID-19]. *Zhonghua Yan Ke Za Zhi*. 2020;56(0):E009.
69. Dong M, Liu T, Li G. Association between acute infections and risk of acute coronary syndrome: a meta-analysis. *Int J Cardiol*. 2011;147(3):479-482.
70. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis [published online ahead of print March 10, 2020]. *Prog Cardiovasc Dis*. 2020. https://doi.org/10.1016/j.pcad.2020.03.001
71. Li J-W, Han T-W, Woodward M, et al. The impact of 2019 novel coronavirus on heart injury: a systemic review and meta-analysis [published online ahead of print April 16, 2020]. *Prog Cardiovasc Dis*. 2020. https://doi.org/10.1016/j.pcad.2020.04.008
72. Ni W, Yang X, Liu J, et al. Acute myocardial injury at hospital admission is associated with all-cause mortality in COVID-19 [published online ahead of print May 11, 2020]. *J Am Coll Cardiol*. 2020. https://doi.org/10.1016/j.jacc.2020.05.007
73. 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;41:2070-2079.
74. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with Coronavirus Disease 2019 (COVID-19): possible mechanisms [published online ahead of print April 18, 2020]. *J Card Failure*. 2020. https://doi.org/10.1016/j.cardfail.2020.04.009

75. Savoj J, Becerra B, Kim J, et al. Utility of cardiac biomarkers in the setting of kidney disease. *Nephron*. 2019;141:227-235. https://doi.org/10.1159/000495946
76. Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469. https://doi.org/10.1097/CCM.0000000000004363
77. Leffler CT, Hogan MC. Age-dependence of mortality from novel coronavirus disease (COVID-19) in highly exposed populations: New York transit workers and residents and Diamond Princess passengers [published online ahead of print May 18, 2020]. *medRxiv*. 2020. https://doi.org/10.1101/2020.05.14.20094847
78. New York City Department of H, Mental Hygiene C-RT. Preliminary estimate of excess mortality during the COVID-19 outbreak - New York City, March 11-May 2, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(19):603-605.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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