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.
**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).\(^1\) 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).\(^2,3\) 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.\(^5,7\) 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.\(^9\)

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 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
The standardized 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. 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. Heterogeneity was evaluated using Cochran’s Q statistic and quantified by using Higgin’s I² 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.

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 non-severe 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 2020.113-68 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/expired cases (OR = 1.50, 95% CI = 1.36-1.69, P < .001). Evidence of heterogeneity and publication bias were observed for age data (I² = 97.1%, P < .001, Egger’s P = .041), but not for gender (I² = 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 cTnl (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; cTnl (I² = 91.9%, P < .001), creatine kinase (I² = 89.3%, P < .001), CK-MB (I² = 86.6%, P < .001), AST (I² = 74.7%, P < .001), LDH (I² = 90.6%, P < .001), myoglobin (I² = 90.1%, P < .001), and NT-proBNP (I² = 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.
| First author | Sample size | Age | Gender |
|-------------|-------------|-----|--------|
|             | Severe, M (SD) | Mild, M (SD) | Severe, M (SD) | Mild, M (SD) |
|             | Severe, Mild | Mild, M (SD) | Mild, M (SD) | Reference no. |
| **Aggarwal S** | 8 | 8 | 58.3 (28.6) | 68.2 (40.0) | 5/3 | 13 |
| **Chen C** | 24 | 126 | NA | NA | 18/6 | 66/60 |
| **Chen G** | 11 | 10 | 61.2 (7.04) | 50.3 (9.8) | 10/1 | 7/3 |
| **Deng Q** | 67 | 45 | 67.3 (14.8) | 54 (20.7) | 38/29 | 19/26 |
| **Fang X** | 7 | 46 | 54.3 (15.4) | 39.9 (15.5) | 5/2 | 22/24 |
| **Gao L** | 30 | 24 | 67.4 (14.4) | 51.6 (13.9) | 16/14 | 8/16 |
| **He R** | 69 | 135 | 62.3 (16.3) | 42.3 (16.3) | 37/32 | 42/93 |
| **Hong Y** | 25 | 50 | 44.1 (11.3) | 47.5 (14.2) | 11/14 | 30/20 |
| **Lo I** | 4 | 6 | 61 (5.0) | 37 (19.0) | 1/3 | 2/4 |
| **Mo P** | 85 | 70 | 60.7 (14.1) | 45.7 (15.6) | 55/30 | 31/39 |
| **Pereira M** | 27 | 63 | 65.7 (13.3) | 52.3 (18.5) | 16/11 | 37/26 |
| **Shi Y** | 49 | 438 | 56 (17.0) | 45 (19.0) | 36/13 | 223/215 |
| **Wan S** | 40 | 95 | 60.3 (15.6) | 42 (11.8) | 21/19 | 52/43 |
| **Wei Y** | 30 | 137 | 49 (12.6) | 40.8 (15.5) | 20/10 | 75/62 |
| **Zhang G** | 55 | 166 | 62.7 (16.3) | 50.4 (20.9) | 35/20 | 73/93 |
| **Zhang J** | 58 | 82 | 58.7 (45.9) | 51.8 (38.5) | 33/25 | 38/44 |
| **Zhao X** | 30 | 61 | 57.5 (11.7) | 49.9 (15.5) | 9/7 | 73/38 |
| **Zhu Z** | 54 | 352 | 57.7 (14.1) | 50.3 (19.3) | 33/21 | 190/162 |
| **Han Y** | 24 | 23 | 61 (41.5) | 62.2 (29.6) | 17/7 | 9/14 |
| **Ma K** | 20 | 64 | 60.3 (19.3) | 46.8 (11.6) | 12/8 | 36/28 |
| **Zhao W** | 20 | 57 | 59 (15.0) | 45 (17.0) | 11/9 | 23/34 |
| **Zheng F** | 30 | 131 | 56.5 (14.4) | 40.7 (14.8) | 14/16 | 66/65 |
| **Chen X** | 10 | 21 | 63.9 (15.2) | 52.8 (14.2) | 9/1 | 13/8 |
| **Han H** | 60 | 198 | 58.9 (14.4) | 58.9 (10.8) | 21/39 | 71/127 |
| **Yang Y** | 25 | 14 | 58.3 (26.7) | 50.5 (41.5) | 14/11 | 7/7 |

(Continues)
| First author | Sample size | Age | Gender | Reference no. |
|--------------|-------------|-----|--------|--------------|
| Li X         | 269         | 63.7 (13.3) | 55.3 (16.3) | 39 |
| Zheng C      | 21          | NA   | NA     | 40 |
| Wu J         | 83          | 63 (10.2)  | 37.5 (17.1) | 41 |
|               |             |       |        |              |
|              |             |       |        |              |
| Li X         | 269         | 63.7 (13.3) | 55.3 (16.3) | 39 |
| Zheng C      | 21          | NA   | NA     | 40 |
| Wu J         | 83          | 63 (10.2)  | 37.5 (17.1) | 41 |
|               |             |       |        |              |
|              |             |       |        |              |
| Li M         | 42          | 60 (13.3)  | 33 (5.2)  | 43 |
|              |             |       |        |              |
|              |             |       |        |              |
| Guo T        | 52          | 71.4 (9.4)  | 53.5 (13.2) | 42 |
|              |             |       |        |              |
|              |             |       |        |              |
| Li M         | 42          | 60 (13.3)  | 33 (5.2)  | 43 |
|              |             |       |        |              |
|              |             |       |        |              |
| Shl S        | 82          | 67.7 (45.2) | 57 (51.1)  | 44 |
|              |             |       |        |              |
|              |             |       |        |              |
| Liu Y        | 276         | 64 (12.6)  | 47 (20.7) | 45 |
|              |             |       |        |              |
|              |             |       |        |              |
| Wei J        | 85          | 69.5 (14.4) | 45 (16.3)  | 46 |
|              |             |       |        |              |
|              |             |       |        |              |
| He X         | 24          | 69.2 (8.5)  | 66.1 (12.8) | 47 |
|              |             |       |        |              |
|              |             |       |        |              |
| Peng Y       | 96          | 58.2 (6.7)  | 61.5 (9.2) | 48 |
|              |             |       |        |              |
|              |             |       |        |              |
| Goyal P      | 130         | 63.3 (16.2) | 61.2 (20.7) | 49 |
|              |             |       |        |              |
|              |             |       |        |              |
| Chu Y        | 7           | 67 (17.7)  | 64.7 (16.6) | 50 |
|              |             |       |        |              |
|              |             |       |        |              |
| Du R         | 58          | 68.4 (9.7)  | 72.7 (11.6) | 51 |
|              |             |       |        |              |
|              |             |       |        |              |
| Huang C      | 28          | 50.3 (14.8) | 49.2 (12.2) | 52 |
|              |             |       |        |              |
|              |             |       |        |              |
| Lei S        | 19          | 57.7 (22.2) | 44.7 (21.5) | 53 |
|              |             |       |        |              |
|              |             |       |        |              |
| Wang D       | 36          | 67 (15.6)  | 50 (20.7) | 54 |
|              |             |       |        |              |
|              |             |       |        |              |
| Chen T       | 113         | 69 (11.1)  | 51.3 (21.5) | 55 |
|              |             |       |        |              |
|              |             |       |        |              |
| Du R         | 21          | 70.2 (7.7)  | 56 (13.5) | 56 |
|              |             |       |        |              |
TABLE 1 (Continued)

| (4) Mortality       | Died | Alive | Died, M (SD) | Alive, M (SD) | Died, (M/F) | Alive, (M/F) |
|---------------------|------|-------|--------------|---------------|-------------|--------------|
| Mehra M             | 515  | 8395  | 55.8 (15.1)  | 48.7 (16.6)   | 336/179     | 500/3392     |
| Siciliano R         | 26   | 71    | NA           | NA            | 19/7        | 42/29        |
| Tomlins J           | 20   | 75    | 78 (9.6)     | 70.7 (19.3)   | 12/8        | 48/27        |
| Wang L              | 65   | 274   | 76.3 (9.6)   | 68.7 (7.4)    | 39/26       | 127/147      |
| Zhou F              | 54   | 137   | 69.3 (9.6)   | 51.7 (9.6)    | 38/16       | 81/56        |
| Zhou W              | 7    | 8     | 68 (3.3)     | 56.3 (10.0)   | 4/3         | 6/2          |
| Deng Y              | 109  | 116   | 68.3 (8.9)   | 43.3 (17.8)   | 73/36       | 51/65        |
| Fu L                | 34   | 166   | NA           | NA            | 16/18       | NA           |
| Li K                | 15   | 87    | 68 (14.1)    | 55 (16.3)     | 48/39       | 11/4         |
| Luo X               | 100  | 303   | 72 (11.1)    | 49.3 (18.5)   | 57/43       | 136/167      |
| Wang Y              | 133  | 211   | 69.7 (11.1)  | 57.7 (16.3)   | 74/59       | 105/106      |
| Zhang F             | 17   | 31    | 78.6 (8.3)   | 66.2 (13.7)   | 12/5        | 21/10        |
| He X                | 26   | 28    | 69.7 (10.4)  | 64.8 (11.7)   | 16/10       | 18/10        |
| Wang L              | 33   | 169   | 74.3 (14.1)  | 59 (13.3)     | 23/10       | 65/104       |
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 cTnl (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, cTnl, 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 of 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 | I² | P-value | P (Egger's test) |
| Demographic data         |                   |       |                |               |                |                |                |         |       |         |    |         |              |
| Age                      | 53                | 17364 | 2942           | 14422        | IV             | SMD            | Random         | 1.01     | 0.72-1.31 | <.001   | 97.11 | <.001   | .041            |
| Sex (male)               | 54                | 17702 | 3022           | 14680        | 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   | 97.11 | <.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   | 90.67 | <.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                | 16974 | 2782           | 14192        | MH             | OR              | Random         | 2.22     | 1.75-2.81 | <.001   | 77.83 | <.001   | .027            |
| Diabetes                 | 51                | 17120 | 2826           | 14294        | MH             | OR              | Random         | 1.88     | 1.59-2.24 | <.001   | 320.8% | .020    | .96             |
| CHD                      | 40                | 15864 | 2508           | 13356        | MH             | OR              | Random         | 3.42     | 2.65-4.42 | <.001   | 49.86 | .011    | .031            |
| COPD                     | 35                | 14658 | 2148           | 12510        | 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           | 3969         | MH             | OR              | Random         | 1.97     | 1.41-2.76 | <.001   | 83.5%  | .33     | .73             |
| Complications            |                   |       |                |               |                |                |                |         |         |         |    |         |              |
| ARDS                     | 14                | 2963  | 877            | 2086         | MH             | OR              | Random         | 34.8     | 13.6-92.9 | <.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     | 824-302  | <.001   | 57.8%  | <.001   | .83             |
| Liver injury             | 11                | 2050  | 558            | 1492         | MH             | OR              | Random         | 2.93     | 1.01-8.46 | .049    | 86.55% | <.001   | .030            |
| Arrhythmia               | 10                | 10421 | 847            | 9574         | MH             | OR              | Random         | 3.40     | 1.67-6.94 | <.001   | 66.98% | <.001   | .35             |
| Heart failure            | 9                 | 10391 | 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              |
TABLE 2 (Continued)

| Characteristics | Number of studies | Sample size Total | Poor prognosis | Good prognosis | Test of association Statistical method | Effect measure | Analysis model | Effect size | Heterogeneity | Publication bias |
|-----------------|------------------|------------------|---------------|---------------|--------------------------------------|----------------|----------------|-------------|---------------|----------------|
| Treatment       |                  |                  |               |               | Statistical method | Effect measure | Analysis model | Effect size | Heterogeneity | Publication bias |
| Antiviral       | 16               | 3620             | 1150          | 2470          | MH                      | OR             | Random         | 0.985       | 0.67-1.45     | 94             |
| Antibiotics     | 11               | 2924             | 920           | 2004          | MH                      | OR             | Random         | 3.36        | 1.66-6.77     | .001           |
| Glucocorticoids | 23               | 3961             | 1289          | 2672          | MH                      | OR             | Random         | 3.52        | 2.51-4.93     | <.001           |
| Immunoglobulin  | 12               | 2300             | 738           | 1562          | MH                      | OR             | Random         | 3.41        | 1.90-6.41     | <.001           |
| Lopinavir/ritonavir | 3          | 299              | 122           | 177           | MH                      | OR             | Random         | 0.620       | 0.097-3.97    | <.001           |
| Oseltamivir     | 2                | 494              | 130           | 364           | MH                      | OR             | Random         | 0.974       | 0.61-1.56     | <.001           |
| Interferon      | 4                | 842              | 302           | 540           | MH                      | OR             | Random         | 0.794       | 0.285-2.21    | <.001           |
| Hydroxychloroquine | 2             | 106              | 35            | 71            | MH                      | OR             | Random         | 6.67        | 2.00-22.22    | <.001           |
| Azithromycin    | 2                | 106              | 35            | 71            | MH                      | OR             | Random         | 5.49        | 1.13-26.66    | <.001           |

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.
| 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              | -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)
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 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. The prognostic power of future biomarker analyses for COVID-19 mortality should be trended over time and account for the degree of renal dysfunction. The prognostic power of future biomarker analyses for COVID-19 mortality should be trended over time and account for the degree of renal dysfunction. The prognostic power of future biomarker analyses for COVID-19 mortality should be trended over time and account for the degree of renal dysfunction. 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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. 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. Finally, in consideration of the immense COVID-19 global mortality, over 360 000 deaths, with over 100 000 deaths in the US alone 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.
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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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.
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**SUPPORTING INFORMATION**

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

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