



The Predictive Value of Myoglobin for COVID-19-Related Adverse Outcomes: A Systematic Review and Meta-Analysis

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Objective: Cardiac injury is detected in numerous patients with coronavirus disease 2019 (COVID-19) and has been demonstrated to be closely related to poor outcomes. However, an optimal cardiac biomarker for predicting COVID-19 prognosis has not been identified.

Methods: The PubMed, Web of Science, and Embase databases were searched for published articles between December 1, 2019 and September 8, 2021. Eligible studies that examined the anomalies of different cardiac biomarkers in patients with COVID-19 were included. The prevalence and odds ratios (ORs) were extracted. Summary estimates and the corresponding 95% confidence intervals (95% Cls) were obtained through meta-analyses.

Results: A total of 63 studies, with 64,319 patients with COVID-19, were enrolled in this meta-analysis. The prevalence of elevated cardiac troponin I (cTnI) and myoglobin (Mb) in the general population with COVID-19 was 22.9 (19–27%) and 13.5% (10.6–16.4%), respectively. However, the presence of elevated Mb was more common than elevated cTnI in patients with severe COVID-19 [37.7 (23.3–52.1%) vs.30.7% (24.7–37.1%)]. Moreover, compared with cTnI, the elevation of Mb also demonstrated tendency of higher correlation with case-severity rate (Mb, r = 13.9 vs. cTnI, r = 3.93) and case-fatality rate (Mb, r = 15.42 vs. cTnI, r = 3.04). Notably, elevated Mb level was also associated with higher odds of severe illness [Mb, OR = 13.75 (10.2–18.54) vs. cTnI, OR = 7.06 (3.94–12.65)] and mortality [Mb, OR = 13.49 (9.3–19.58) vs. cTnI, OR = 7.75 (4.4–13.66)] than cTnI.

Conclusions: Patients with COVID-19 and elevated Mb levels are at significantly higher risk of severe disease and mortality. Elevation of Mb may serve as a marker for predicting COVID-19-related adverse outcomes.

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Keywords: COVID-19, myoglobin, cardiac troponin I, predictive value, severe illness, mortality

INTRODUCTION

Coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan City, Hubei province of China in December 2019 (1). The pandemic spread rapidly worldwide from China, resulting in 230 million confirmed cases and more than 4 million deaths by September 22, 2021. Clinical manifestations differ greatly among patients with coronavirus disease 2019 (COVID-19), ranging from asymptomatic infections to severe or critical disease and even death (2). Although SARS-CoV-2 was initially thought to be a respiratory tract virus, it has been widely reported that the adverse prognosis of patients with COVID-19 relates largely to the involvement of multisystem organs such as the heart, liver, kidney, brain, and the nervous system (3–5).

Cardiac injury, manifested as the elevation of cardiac biomarkers, namely, cardiac troponin I (cTnI), lactate dehydrogenase (LDH), creatine kinase (CK), CK isomer-MB (CK-MB), myoglobin (Mb), and B-type natriuretic peptide (BNP) or N-terminal pro-B type natriuretic peptide (NT-proBNP), has been detected in numerous patients with COVID-19, and is closely related to the clinical prognosis (6–9). In particular, elevation of cTnI, which was widely reported in several studies, has been identified as an independent variable associated with in-hospital mortality (10).

Nevertheless, elevation of Mb in patients with COVID-19 has been widely mentioned in several studies (11–15). More importantly, Mb presents a potential predictive value in COVID-19-related adverse outcomes. In a study reported by Qin et al., elevated Mb presented with higher frequency on admission and showed the highest overall performance for predicting the risk of COVID-19 mortality among the various cardiac biomarkers (16). However, to the best of our knowledge, a pooled analysis regarding the advantage of Mb in predicting the prognosis of COVID-19 is lacking. Therefore, we conducted a systematic review and meta-analysis to explore the predictive value of elevated Mb for adverse outcomes of patients with COVID-19.

METHODS

Study Protocol

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines (17, 18). The protocol was preregistered in the International prospective register of systematic reviews (PROSPERO, CRD42020175133). The detailed definitions of laboratory-confirmed COVID-19 cases and severe illness are described in **Supplementary Method S1**.

Search Strategy and Study Selection

Two investigators (DT and JG) independently searched the PubMed, Embase, and Web of Science Core Collection (Clarivate Analytics) databases for relevant articles published between December 2019 and September 8, 2021 using the following keywords: "coronavirus," "nCoV," "HCoV," "SARS-CoV-2," "COVID*," "NCP*," "cardiac injury," "cardiac," "biomarker*," "myocardial," "heart," "troponin," and "myoglobin" alone and in combination. The detailed search strategies are presented in **Supplementary Methods S2**. After removing duplicate studies, three reviewers (CM, DT, and JG) were assigned to independently screen the titles and abstracts, and then examine the full texts. Any disagreement was resolved by the senior authors (YB and XZ). The inclusion criteria were as follows: (1) diagnosis of COVID-19 according to the World Health Organization interim guidance (19), (2) gives the specific number of COVID-19 patients with the elevation of cTnI and/or Mb, (3) studies in English only, and (4) sample size of ≥ 10 individuals. The exclusion criteria were as follows: (1) studies with data that could not be reliably extracted, and (2) editorials, comments, expert opinions, case reports.

Data Extraction and Quality Assessment

Using a predesigned spreadsheet, three authors (DT, CM, and JG) independently extracted the relevant data from the included studies. Corresponding authors were asked via email to clarify or provide additional information. Study quality assessments were performed using the Quality Assessment Forms recommended by the Agency for Healthcare Research and Quality (AHRQ) for cross-sectional studies (**Supplementary Methods S3**). Studies were defined as high quality if a score of \geq 7 was attained. Any conflicts with the assessments were resolved either by consensus or by the adjudicators (XZ and PL).

Statistical Analysis

Effect estimates were presented as pooled prevalence or odds ratio (OR) with 95% confidence interval (CI) and visualized with forest plots. A fixed or random-effects model was used according to heterogeneity across studies (if $I^2 \leq 50\%$, fixed-effects model; if $I^2 > 50\%$, random-effects model) (20). We performed Egger's test and the test performed by Peters et al., and visually inspected the funnel plots to investigate publication bias (21). Sensitivity analyses were performed by systematically removing each study in turn to explore its effect on the outcome. All the analyses were performed using R (version 3.5.3), RStudio (version 1.2.1335), and Comprehensive Meta-Analysis.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, and dissemination plans of our research.

RESULTS

Literature Search and Study Characteristics

A total of 106,925 articles were initially retrieved, of which the full texts of 6,542 articles were reviewed (**Figure 1**). Finally, 63 studies were eligible for our analysis (**Table 1** and **Supplementary Tables S1**, **S2**), and included 64,319 confirmed patients with COVID-19 who presented to a hospital. All these studies were retrospective observational ones. Of the 63 studies, 31 were conducted in China, 18 in the United States, 5 in Italy, 4 in Spain, 2 in Turkey, and 3 in other countries (Libya, Finland,



and Iran) (**Supplementary Table S2**). Among them, 45 studies only mentioned data of cTnI, 3 studies only mentioned Mb, and 15 studies included both Mb and cTnI. Regarding the differences in Mb or cTnI detection methods and criteria among different hospitals, we listed in **Table 1** the average level of Mb or cTnI, cut-off value of abnormal Mb or cTnI, and number of patients with elevated Mb or cTnI in each study. In addition, preexisting cardiovascular conditions, such as the prevalence of coronary artery disease (CAD) and heart failure (HF), and the average level of BNP or NT-proBNP were also summarized (**Table 1**).

Incidence of cTnI/Mb Elevation

Among the 63 included studies, the pooled case-severity rate (CSR), case-fatality rate (CFR), and intensive-care unit (ICU)admission rate were 31.3 (95% CI 23.2–39.4%, $I^2 = 99\%$), 12.5

TABLE 1 | Characteristics of the included studies.

Authors	No.	Cardiovascular condition	Mb	cTnl	Outcome
Arcari L et al.	111	CAD, 12 (11.0); HF, 8 (7.0)	NA	Average level of cTnl, 17 (5–47) pg/mL; cut-off value, 14 pg/ml; elevated patients, 39/103 (37.9%)	Death
Bardaji' A et al.	186	CAD, 20 (10.8); HF, 14 (7.5)	NA	Elevated patients, 41 (22.0%)	Death, admission to ICU
Bhatla A et al.	700	CAD, 76 (11.0); HF, 88 (13.0); BNP, 2,940 (7,962) pg/mL	NA	Cut-off value, 0.01 ng/mL; elevated patients, 82/373 (22.0%)	NA
Cai Q et al.	298	CAD, 25 (8.4); HF, 7 (2.3)	Average level of Mb, 37.1 (29.2–51.5) μg/L; elevated patients, 10/260 (3.8%)	NA	Death, discharge
Calvo-Fernández A et al.	872	CAD, 59 (6.83); HF, 41 (4.73)	NA	Cut-off value, 14.0 ng/L; elevated patients, 225/651 (34.6%)	Death, admission to ICU, mechanical ventilation
Cao J et al.	102	CAD, 5 (4.9); BNP, 12.2 (0–63.1) pg/mL; NT-pro BNP, 417 (132–1,800) pg/mL	NA	Average level of cTnl, 8.0 (3.0–35.7) pg/mL; cut-off value, 0.026 ng/mL; elevated patients, 15/55 (27.3%)	Discharge, death
Cao J et al.	244	NA	Average level of Mb in severe patients, 39.35 (29.21–74.19) μg/L; Cut-off value, 110 μg/L	Cut-off value, 0.04 ng/mL; elevated patients, 27/244 (11.1%)	Severe COVID-19, death, mechanic ventilation
Cao M et al.	198	CAD, 12 (6.0)	Average level of Mb, 5.9 (2.8–15.7) μg/L; cut-off value, 48.8 μg/L; elevated patients, 33/194 (17.0%)	Average level of cTnl, 0.02 (0.01–0.04) ng/ml; cut-off value, 0.04 ng/mL; elevated patients, 22/194 (11.3%)	Severe COVID-19
Chen N et al.	99	CAD, 40 (40.0)	Average level of Mb, 49.5 (32.2–99.8) μg/L; cut-off value, 146.9 μg/L; elevated patients, 15 (15.2%)	NA	Discharge, death
Chorin E et al.	204	CAD, 25 (12.0); HF, 7 (3.0)	NA	Average level of cTnl, 0.02 (0.01–0.04) ng/Ml; cut-off value, 0.05 ng/mL; elevated patients, 84 (41.2%)	Death
Cipriani A et al.	109	CAD, 18 (17.0); HF, 16 (15.0%); BNP, 90 (22–262) pg/ml	NA	Average level of cTnl, 18.0 (7.0–96.0) ng/L; cut-off value, 32 ng/L for males, 16 ng/L for females; elevated patients, 46 (42.2%)	Death, admission to ICU, discharge
Deng Q et al.	112	CAD, 15 (13.4); HF, 6 (5.4); NT-pro BNP, 430.1 (100.6–2859.3) ng/L	NA	Average level of cTnl, 0.01 (0.00–0.14) ng/ml; cut-off value, 0.04 ng/mL; elevated patients, 42 (37.5%)	Severe COVID-19, death
Elhadi M et al.	1,207	CAD, 25 (2.1)	NA	Cut-off value, 26 pg/mL; elevated patients, 90/292 (30.8%)	Death, admission to ICU
Feng Y et al.	476	CAD, 38 (8.0); BNP, 40.85 (21.64–79.37) pg/ml	Average level of Mb, 18.85 (4.8–51.48) μg/L	Elevated patients, 86/384 (22.4%)	Death, discharge, severe COVID-19
Ferguson J et al.	72	NA	NA	Cut-off value, 0.055 ng/mL; elevated patients, 2/45 (4.4%)	Death, mechanical ventilation, admission to ICU
Ferrante G et al.	332	CAD, 49 (14.5); BNP, 72.5 (34.5–198.0) pg/mL	NA	Average level of cTnl, 11.4 (4.7–37.3) mg/L; cut-off value, 0.02 ng/L; elevated patients, 123 (37.0%)	Death, admission to ICU

(Continued)

TABLE 1 | Continued

Authors	No.	Cardiovascular condition	Mb	cTnl	Outcome
Franks C et al.	182	NA	NA	Cut-off value, 0.03 ng/mL; elevated patients, 80/143 (55.9%)	Death
García de Guadiana-Romualdo L et al.	1,280	CAD, 328 (25.6)	NA	Elevated patients, 344 (26.9%)	Death, admission to ICU
Garibaldi BT et al.	832	CAD, 266 (32.0); HF, 127 (15.0); NT-pro BNP 214 (45–960) pg/mL	NA	Elevated patients, 194/682 (28.4%)	Death, severe COVID-19
Guo T et al.	187	CAD, 21 (11.2); NT-pro BNP, 268.4 (75.3–689.1) pg/mL	Average level of Mb, 38.5 (21.0–78.0) μg/L	Elevated patients, 52 (27.8%)	Death
Han H et al.	273	NA	Cut-off value, 110 µg/L; elevated patients, 29/273 (10.6%)	Cut-off value, 0.04 ng/mL; elevated patients, 27/273 (9.9%)	Death, severe COVID-19
Harmouch F et al.	560	Vascular disease, 36 (6.4); HF, 54 (9.6)	NA	Cut-off value, 0.05 ng/mL; elevated patients, 97/482 (20.1%)	Death, mechanical ventilation, admission to ICU
He F et al.	288	CAD, 85 (29.5); BNP, 35 (13–117.5) pg/mL	Elevated patients, 8/276 (2.9%)	Cut-off value, 0.03 ng/mL; elevated patients, 22/190 (11.6%);	Death, admission to ICU
He X et al.	1,031	CAD, 83 (8.1); NT-pro BNP 124 (43–374) pg/mL	NA	Average level of cTnl, 5.3 (2.5–14.0) pg/Ml; elevated patients, 215 (20.9%)	Death
Hu L et al.	323	CAD, 41 (12.7)	NA	Cut-off value, 0.04 pg/mL; elevated patients, 68 (21.1%)	Death, severe COVID-19, mechanical ventilation
Huang C et al.	41	CAD, 6 (15.0)	NA	Average level of cTnl, 3.4 (1.1–9.1) pg/mL; cut-off value, 0.028 ng/mL; elevated patients, 5/41 (12.2%)	Death, severe COVID-19, discharge
Huang J et al.	98	CAD, 6 (6.0); BNP 119 (54–392) pg/mL	NA	Cut-off value, 0.0229 ng/Ml; elevated patients, 7 (7.1%)	Death, discharge, severe COVID-19
Huang R et al.	202	CAD, 5 (2.5)	NA	Elevated patients, 2/103 (1.9%)	Admission to ICU, mechanical ventilation, severe COVID-19
Karbalai Saleh S et al.	386	CAD, 97 (25.1)	NA	Cut-off value, 26 ng/L for males, 11 ng/L for females; elevated patients, 115 (29.8%)	Death, admission to ICU
Lala A et al.	2,736	CAD, 453 (16.6); HF, 276 (10.1)	NA	Cut-off value, 0.03 ng/mL; OR for in-hospital mortality, 1.75 (1.37–2.24); elevated patients, 985 (36.0%)	Death
Li C et al.	2,068	CAD, 182 (8.8); HF, 14 (0.7); NT-pro BNP 108 (36–370) pg/mL	Average level of Mb, 40.7 (28.4–73.8) μg/L; elevated patients, 174/1,554 (11.2%)	Average level of cTnl, 4.2 (1.9–11.0) pg/mL; elevated patients, 181 (8.8%)	Death, severe COVID-19
Li X et al.	548	CAD, 34 (6.2)	NA	Cut-off value, 15.6 pg/mL; elevated patients, 119 (21.7%)	Discharge, death, severe COVID-19
Maeda T et al.	181	CAD, 36 (19.9); HF, 24/180 (13.3)	NA	Elevated patients, 54 (29.8%)	Death
Majure D et al.	6,247	CAD, 833 (13.0); HF, 529 (9.0)	NA	Cut-off value, 0.045 ng/mL; elevated patients, 1,821 (29.1%)	Death, admission to ICU, mechanical ventilation

(Continued)

TABLE 1 | Continued

Authors	No.	Cardiovascular condition	Mb	cTnl	Outcome
Manocha KK et al.	446	CAD, 94 (21.1); HF, 38 (8.5); BNP 84 (25–300) pg/mL	NA	Average level of cTnl, 0.05 (0–0.34) ng/Ml; cut-off value, 0.34 ng/mL; elevated patients, 112 (25.1%)	Death, admission to ICU
Merugu GP et al.	217	NA	NA	Elevated patients, 34/201 (16.9%)	Death
Mikami T et al.	6,493	NA	NA	Average level of cTnl, 0.03 (0.02–0.10) ng/dl; cut-off value, 0.03 ng/dL; elevated patients, 1,312/2,526 (51.9%)	Death
Özyilmaz S et al.	105	CAD, 14 (21.1)	NA	Average level of cTnl, 2.6 (0–1774.5) pg/mL ^a ; cut-off value, 7.8 ng/mL; elevated patients, 21 (20.0%)	Death
Palaiodimos L et al.	200	CAD, 33 (16.5); HF, 34 (17.0)	NA	Cut-off value, 0.01 ng/mL; elevated patients, 56 (28.0%)	Mortality, intubation, O ₂ requirement, ARDS, ICU, AKI, RRT, length of stay
Peiró ÓM et al.	196	CAD, 19 (9.7); HF, 14 (7.1)	NA	Average level of cTnl, 14 (4–37) ng/L; cut-off value, 21 ng/L; elevated patients, 77 (39.3%)	Death, admission to ICU, mechanical ventilation
Price-Haywood E et al.	3,481	CAD, 139 (4.0); HF, 128 (3.7)	NA	Cut-off value, 0.06 ng/mL; elevated patients, 270/1,084 (24.9%)	Death, admission to ICU
Qin J et al.	3,219	CAD, 206 (6.4)	Elevated patients, 228/1,895 (12.0%); HR for in-hospital mortality, 6.84 (4.95–9.45) AUC for mortality, 0.83 (0.80–0.86)	Elevated patients, 95/1,462 (6.5%); HR for in-hospital mortality, 9.59 (6.36–14.47); AUC for in-hospital mortality, 0.78 (0.73–0.84)	Death
Richardson S et al.	5,700	CAD, 595 (11.1); HF, 371 (6.9); BNP, 385.5 (160–1996.8), <i>n</i> = 1,818	NA	Elevated patients, 801/3,533 (22.7%)	Admission to ICU, mechanical ventilation, kidney replacement therapy, Death
Schiavone M et al.	674	HF, 111 (16.5)	NA	Average level of cTnl, 18 (8–40) ng/L; elevated patients, 130 (19.3%)	Death, admission to ICU, mechanical ventilation
Shah P et al.	309	CAD, 28 (9.1); HF, 65 (21.0)	NA	Elevated patients, 116 (37.5%)	Death, admission to ICU, mechanical ventilation
Shen Y et al.	325	NA	Cut-off value, 48.8 µg/L; elevated patients, 28/325 (8.6%)	Cut-off value, 0.04 ng/mL; elevated patients, 80/325 (24.6%)	Death, discharge
Singh N et al.	276	Vascular disease, 49 (17.8); HF, 56 (20.3)	NA	Cut-off value, 0.017 ng/mL; elevated patients, 132/276 (47.8%) OR for in-hospital mortality, 4.43 (1.61–12.19)	Death
Stefanini G et al.	397	Prior MI, 33/395 (8.4); HF, 18/395 (4.6); BNP, 67 (30–191) pg/mL	NA	Average level of cTnl, max 10.8 (4.3–39.5) ng/L, baseline 7.8 (4.5–25.6) ng/L; elevated patients, 130 (32.7%)	Death, admission to ICU, discharge
Suleyman G et al.	463	CAD, 59 (12.7); HF, 49 (10.6)	NA	Elevated patients, 107 (23.1%)	Death, admission to ICU

(Continued)

TABLE 1 | Continued

Authors	No.	Cardiovascular condition	Mb	cTnl	Outcome
Tanboga IH et al.	14,855	CAD, 2,341 (15.3); HF, 776 (5.1)	NA	Average level of cTnl, 0.08 (0.00–0.28) ng/mL; elevated patients, 1,027 (6.9%)	Death, admission to ICU, mechanical ventilation
Tomasoni D et al.	692	CAD, 148 (21.4); HF, 90 (13.0); NT-pro BNP 303 (96–1,201) pg/mL	NA	Elevated patients, 272/605 (45.0%)	Death
Wang D et al.	138	CAD, 20 (14.5)	NA	Average level of cTnl, 6.4 (2.8–18.5) pg/mL; cut-off value, 0.0262 ng/mL; Elevated patients, 10 (7.2%)	Admission to ICU
Wang Z et al.	293	CAD, 21 (7.2)	Average level of Mb, 57.6 (30.8–116.4) μg/L; cut-off value, 110 μg/L; elevated patients, 58/213 (27.2%)	Average level of cTnl, 0.007 (0.006–0.046) ng/mL; cut-off value, 0.0796 ng/mL; elevated patients, 36/216 (16.7%)	Death
Wei J et al.	101	CAD, 5 (5.0); NT-pro BNP, 71.2 (31.6–237.5) pg/mL	NA	Average level of cTnl, 6.8 (4.3–10.1) pg/mL; cut-off value, 0.014 ng/mL; elevated patients, 16 (15.8%)	Death, severe case, admission to ICU, mechanical ventilation
Wu Y et al.	125	CAD, 11 (8.8); BNP, 65.0 (23.0–178.0) pg/mL	Average level of Mb, 35.0 (27.7–75.65) μg/L; cut-off value, 154.9 μg/L; elevated patients, 14 (11.2%)	Average level of cTnl, 3.9 (1.9–10.3) pg/ml; cut-off value, 0.0342 ng/mL; elevated patients, 10 (8.0%)	Long-term hospitalization
Xu P et al.	703	CAD, 35 (5.0)	Elevated patients, 33/181 (18.2%)	NA	Death, admission to ICU, mechanical ventilation
Zeng J et al.	416	CAD, 13 (3.1); HF, 5/57 (8.8)	Cut-off value, 100 μg/L; elevated patients, 30/174 (17.2%)	Cut-off value, 0.026 ng/mL; elevated patients, 29/345 (8.4%)	Death, discharge
Zhang G et al.	221	CAD, 22 (10.0)	NA	Average level of cTnl, 7.6 (3.6–21.5) pg/mL; cut-off value, 0.0262 ng/mL; elevated patients, 17 (7.7%)	Discharge, death, severe COVID-19
Zhang Q et al.	41	CAD, 1 (2.4)	Average level of Mb, 26.0 (19.7–118.6) μg/L; elevated patients, 11 (26.8%)	Average level of cTnl; 1.5 (0.8–5.0) ng/mL; elevated patients, 41 (100%)	Severe COVID-19
Zhang Y et al.	166	CAD, 30 (18.1); NT-proBNP, 179.0 (67.0–457.0) pg/mL	Average level of Mb, 54.8 (33.8–127.2) μg/L; cut-off value, 106 μg/L; elevated patients, 28/166 (16.9%)	Average level of cTnl, 5.0 (2.2–10.7) pg/mL; cut-off value, 0.0156 ng/mL; elevated patients, 17 /166 (10.2%)	Discharge, death
Zhao M et al.	1,000	CAD, 60 (6.0)	Average level of Mb, 44.54 (28.5–85.05) μg/L; cut-off value, 110 μg/L; elevated patients, 132/754 (17.5%)	Average level of cTnl, 0.006 (0.006–0.018) ng/mL; cut-off value, 0.0796 ng/mL; elevated patients, 66/758 (8.7%)	Death, discharge
Zhao X et al.	91	HF, 14 (15.4)	NA	Cut-off value, 0.01 ng/mL; elevated patients, 3/88 (3.4%)	Death, discharge
Zhou F et al.	191	CAD, 15 (8.0); HF, 44 (23.0)	NA	Average level of cTnl, 4.1 (2.0–14.1) ng/mL; cut-off value, 28 ng/mL; elevated patients, 24/145 (16.6%)	Death, admission to ICU

No., confirmed number of patients with coronavirus disease 2019(COVID-19); Mb, myoglobin; cTnl, cardiac troponin I; CAD, coronary artery disease; HF, heart failure; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B type natriuretic peptide; ICU, intensive-care unit; NA, data not available. ^aMedian (range).

(95% CI 10.7–14.6%, $I^2 = 98\%$), and 20.1% (95% CI 15.3– 24.9%, $I^2 = 99\%$) (**Supplementary Figure S1**). The prevalence of elevated cTnI and Mb in the general population with COVID-19 was 22.9 (95% CI 19–27%, $I^2 = 99\%$) and 13.5% (95% CI 10.6–16.4%, $I^2 = 92\%$), respectively (**Figure 2**). Furthermore, the meta-analysis showed that elevated cTnI occurred in 30.7% (24.7–37.1%, $I^2 = 86\%$) of the patients in the severe disease group, while the estimated rate of elevated Mb was 37.7% (23.3– 52.1%, $I^2 = 90\%$) in patients with severe COVID-19. For the non-survivor group, the elevation rate of Mb and cTnI was 53.4 (95% CI 46.9–59.9%, $I^2 = 0\%$) and 55.5% (95% CI 47.1–64%, $I^2 = 94\%$), respectively (**Figure 3**).

Meta-regression demonstrated that both CSR and CFR were positively associated with the proportion of patients with elevated cTnI or Mb. Regarding logit CSR, the prevalence of elevated Mb showed tendency of higher regression coefficient compared with cTnI (Mb: r = 13.9, [95% CI 3.51–24.29, p < 0.01] vs. cTnI: r = 3.93, [95% CI 0–8.52, p < 0.05]). A similar trend was observed in logit CFR (Mb: r = 15.42, [95% CI 11.2–19.65, p < 0.0001] vs. cTnI: r = 3.04, [95% CI 1.84–4.25, p < 0.0001]) (Figure 4).

Risk of Elevated cTnl/Mb for Adverse Outcomes

The ORs of elevation of Mb/cTnI for the development of severe illness and death were further estimated. In the overall analysis, patients COVID-19 and elevated cTnI were at higher risk of severe illness (OR = 7.06, 95% CI 3.94–12.65, n = 15, $I^2 = 88\%$). Nevertheless, elevated Mb showed tendency of better predictive value for severe illness (OR = 13.75, 95% CI 10.2–18.54, n = 6, $I^2 = 39\%$) compared with cTnI. Regarding in-hospital mortality, elevated cTnI (OR = 7.75, 95% CI 4.4–13.66, n = 13, $I^2 = 95\%$) and Mb (OR = 13.49, 95% CI 9.3–19.58, n = 3, $I^2 = 0\%$) were associated with COVID-19-related deaths (**Figure 5**).

Sensitivity Analysis and Publication Bias

Sequential removal of each trial from the analysis revealed no meaningful differences (**Supplementary Figure S2**). We observed no evidence of publication bias by inspecting the funnel plot or with Egger's test, Begger's test or the test used by Peters et al. (p > 0.05; **Supplementary Figure S3**).

DISCUSSION

This systematic review and meta-analysis of 63 high-quality retrospective studies systematically investigated the predictive value of Mb for COVID-19-related severe disease or death compared with cTnI. The main findings of the study are as follows: (1) more patients with COVID-19-related severe disease showed elevated Mb compared with elevated cTnI; (2) elevated Mb presented obvious superiority over cTnI for predicting severe illness, showing 3-fold higher meta-regression coefficient and 2fold higher OR; (3) furthermore, Mb elevation was more strongly associated with high risk of COVID-19-related death compared with cTnI.

Severe acute respiratory syndrome coronavirus 2 has been reported to be more contagious than previously discovered

human coronaviruses (22), with the progression of the COVID-19 pandemic worldwide, there has been increasing concern regarding the "destructive power" of SARS-CoV-2 for multiple system organ damage, such as in the heart, liver, kidney, brain, and the nervous system (5, 23). Among them, myocardial injury is an important manifestation (6). Madjid et al. reported that up to 15% of hospitalized patients with COVID-19 exhibit myocardial injury, with some developing significant cardiac complications, such as biventricular heart failure, arrhythmias, and cardiogenic shock (9, 24). Liu et al. demonstrated that the mortality rate of patients with COVID-19 and cardiovascular disease was as high as 10.5%, which was 11.67 times higher than that of patients with COVID-19 with no preexisting conditions (25). Consistently, our analysis showed that the pooled incidence rate of cardiac injury was 22.9% in the general population, while the rate increased to 55.5% in the non-survivor group, indicating that cardiac injury was common in patients with COVID-19, especially those with poor prognosis.

Abnormal levels of cardiac biomarkers, including cTnI, CK-MB, Mb, and NT-proBNP, have been identified as indicators for COVID-19-related poor prognosis, such as severe illness (26), ICU admission and in-hospital mortality (27, 28). However, there is no consensus on the optimal biomarker for predicting COVID-19-related outcomes. cTnI elevation has been widely studied for its high prevalence in patients with COVID-19. However, in a study by Qin et al., elevated Mb presented with obviously higher frequency on admission compared with cTnI (12 vs. 6.5%) (16). Similarly, our subgroup analysis revealed that elevated Mb was more common in patients with severe COVID-19 than cTnI. Several recent studies have highlighted elevated cTnI as an important risk factor for adverse outcomes, such severe illness (29, 30), ICU admission (31, 32), and death (10, 26, 33). However, our meta-regression analysis suggested that the elevation rate of Mb presented 3-fold stronger association with CSR and 5fold stronger association with CFR than cTnI. Notably, elevated Mb level showed higher risk of severe illness and mortality compared with cTnI. The results suggested that Mb may serve as a better biomarker for the severity of COVID-19. Accordingly, the dynamic monitoring of Mb might facilitate timely initiation of intensive care, thereby reducing the risk of other adverse events, such as COVID-19-related death.

Myoglobin is an iron and oxygen-binding protein that plays an important role in the storage of oxygen in skeletal and cardiac muscles (34). Previously, it was generally believed that Mb, while sensitive, was not specific for cardiac injury per se. Therefore, the prognostic value of Mb as a marker of myocardial injury in patients with COVID-19 has not been taken seriously (35). However, our meta-analysis suggested that Mb has a potential advantage over cTnI in predicting COVID-19-related adverse outcomes, such as the occurrence of severe illness and death. The mechanistic link between Mb and COVID-19 prognosis is unclear, but it may be the distribution of Mb in skeletal muscle besides myocardium, making it more sensitive to the dynamics of systemic states (36). de Andrade-Junior et al. reported that patients with severe COVID-19 are prone to develop muscle wasting and impaired muscle function (37). Moreover, Mb can be rapidly released into the blood in response

Study	Events	Total		Proportion	95%-CI	Weight (fixed)	Weight (random)
Cai O et al.	10	260		0.038	[0.019:0.070]	9.9%	7.7%
Cao M et al.	33	194		0.170	[0.120; 0.231]	1.9%	6.4%
Chen N et al.	15	99		0.152	[0.087; 0.238]	1.1%	5.5%
Han H et al.	29	273		0.106	[0.072; 0.149]	4.1%	7.2%
He F et al.	8	276		0.029	[0.013; 0.056]	13.8%	7.8%
Li C et al.	174	1554		0.112	[0.097; 0.129]	22.0%	8.0%
Qin J et al.	228	1895		0.120	[0.106; 0.136]	25.5%	8.0%
Sheh Y et al.	28	213		- 0.080	[0.058; 0.122]	3.8% 1.5%	6 194
Wu Y et al	14	125	<u> </u>	0.112	[0.063: 0.181]	1.5%	6.3%
Xu P et al.	33	181		0.182	[0.129: 0.246]	1.7%	6.3%
Zeng J et al.	30	174	· · · ·	0.172	[0.119; 0.237]	1.7%	6.3%
Zhang Q et al.	11	41		0.268	[0.142; 0.429]	0.3%	3.0%
Zhang Y et al.	28	166		0.169	[0.115; 0.234]	1.7%	6.2%
Zhao M et al.	132	754	-	0.175	[0.149; 0.204]	7.4%	7.6%
Fixed effect model		6530	\$	0.106	[0.098; 0.113]	100.0%	
Random effects model	0.01			0.135	[0.106; 0.164]		100.0%
Heterogeneity: 7 = 92%, 1 = 0.0028, 7	5 < 0.01		0.1 0.2 0.3	3 0.4			
В						144.1.1.4	
Study	Events	Total		Proportion	95%-CI	(fixed)	(random)
Arcari L et al.	39	103	:	0.379	[0.285; 0.480]	0.2%	1.6%
Bardaji' A et al.	41	186	÷+	0.220	[0.163; 0.287]	0.4%	1.7%
Bhatla A et al.	82	373		0.220	[0.179; 0.265]	0.7%	1.7%
Calvo-Fernández A et al.	225	651	-	0.346	[0.309; 0.384]	1.3%	1.7%
Cao J et al.	15	55	÷+	0.273	[0.161; 0.410]	0.1%	1.5%
Cao J et al.	27	244		0.111	[0.074; 0.157]	0.5%	1.7%
Cao M et al.	22	194	+:	0.113	[0.072; 0.167]	0.4%	1.7%
Chorin E et al.	84	204	; ~	0.412	[0.344; 0.483]	0.4%	1.7%
Cipriani A et al.	46	109		0.422	[0.328; 0.520]	0.2%	1.6%
Deng Q et al.	42	112		0.375	[0.285; 0.471]	0.2%	1.6%
Elhadi M et al.	90	292	· · ·	0.308	[0.256; 0.365]	0.6%	1.7%
Feng Y et al.	86	384		0.224	[0.183; 0.269]	0.8%	1.7%
Ferguson J et al.	122	45 .		0.044	[0.005; 0.151]	0.1%	1.5%
Franks C et al	80	143		0.559	[0.318, 0.423] [0.474: 0.642]	0.770	1.6%
García de Guadiana–Romualdo L et al.	344	1280	+	0.269	[0.245: 0.294]	2.5%	1.7%
Garibaldi BT et al.	194	682	-	0.284	[0.251: 0.320]	1.4%	1.7%
Guo T et al.	52	187		0.278	[0.215: 0.348]	0.4%	1.7%
Han H et al.	27	273	+	0.099	[0.066; 0.141]	0.5%	1.7%
Harmouch F et al.	97	482	+	0.201	[0.166; 0.240]	1.0%	1.7%
He F et al.	22	190		0.116	[0.074; 0.170]	0.4%	1.7%
He X et al.	215	1031	44-	0.209	[0.184; 0.235]	2.1%	1.7%
Hu L et al.	68	323	++-	0.211	[0.167; 0.259]	0.6%	1.7%
Huang C et al.	5	41		0.122	[0.041; 0.262]	0.1%	1.5%
Huang J et al.	7	98		0.071	[0.029; 0.142]	0.2%	1.6%
Huang R et al.	2	103 -		0.019	[0.002; 0.068]	0.2%	1.6%
Karoalai Salen S et al.	115	386	;	0.298	[0.253; 0.346]	0.8%	1.7%
Laia A et al. Li C et al	985	2/30		0.360	[0.342; 0.378]	5.4% 1 10/	1.7%
Li V et al.	101	2008	- :	0.088	[0.070; 0.101]	4.1%	1.7%
Maeda T et al.	54	181		0.217	[0.233.0.371]	0.4%	1.7%
Majure DT et al.	1821	6247		0.291	[0.280: 0.303]	12.4%	1.7%
Manocha KK et al.	112	446	; .	0.251	[0.212; 0.294]	0.9%	1.7%
Merugu GP et al.	34	201	-+-	0.169	[0.120; 0.228]	0.4%	1.7%
Mikami T et al.	1312	2526	+	0.519	[0.500; 0.539]	5.0%	1.7%
Özyilmaz S et al.	21	105		0.200	[0.128; 0.289]	0.2%	1.6%
Palaiodimos L et al.	56	200	;	0.280	[0.219; 0.348]	0.4%	1.7%
Peiró OM et al.	77	196	·	0.393	[0.324; 0.465]	0.4%	1.7%
Price-Haywood EG et al.	270	1084	. 1*	0.249	[0.224; 0.276]	2.2%	1.7%
Qiii J et al. Richardson S at al	95	1462		0.065	[0.055; 0.079]	2.9%	1.7%
Schiavone M et al	130	5555	1	0.227	[0.213; 0.241]	1.0%	1.7%
Shah P et al	130	309		0.193	[0.321.0.432]	0.6%	1./70
Shen Y et al.	80	325		0.375	[0.200. 0.297]	0.6%	1.7%
Singh N et al.	132	276	÷	0.478	[0.418: 0 5391	0.5%	1 7%
Stefanini GG et al.	130	397	÷	0.327	[0.281: 0.376]	0.8%	1.7%
Suleyman G et al.	107	463	<u>-</u>	0.231	[0.193; 0.272]	0.9%	1.7%
Tanboga IH et al.	1027	14855	•	0.069	[0.065; 0.073]	29.5%	1.7%
Tomasoni D et al.	272	605	÷ +	0.450	[0.409; 0.490]	1.2%	1.7%
Wang D et al.	10	138	+- i i	0.072	[0.035; 0.129]	0.3%	1.6%
Wang Z et al.	36	216		0.167	[0.120; 0.223]	0.4%	1.7%
Wei J et al.	16	101		0.158	[0.093; 0.244]	0.2%	1.6%
Wu Y et al.	10	125	+ ; i	0.080	[0.039; 0.142]	0.2%	1.6%
Zeng J et al.	29	345	+ ;	0.084	[0.057; 0.118]	0.7%	1.7%
Zhang G et al.	17	221	+ :	0.077	[0.045; 0.120]	0.4%	1.7%
Zhang Q et al.	41	41		- 1.000	[0.914; 1.000]	0.1%	1.5%
Zhang Y et al.	17	166		0.102	[0.061; 0.159]	0.3%	1.7%
Zhao M et al.	66	758	+ :	0.087	[0.068; 0.109]	1.5%	1.7%
	3	88		0.034	[0.007; 0.096]	0.2%	1.6%
Zhao X et al.		1.4.5		0.166	10 109:0 2361	0.3%	1.6%
Zhao X et al. Zhou F et al.	24	145		0.100	[otros, otheo]		
Zhao X et al. Zhou F et al. Fixed effect model	24	50284		0.188	[0.184; 0.191]	100.0%	
Zhao X et al. Zhou F et al. Fixed effect model Random effects model	24	145 50284		0.188	[0.184; 0.191] [0.190; 0.270]	100.0%	 100.0%

FIGURE 2 | Forest plot for the pooled prevalence of elevated (A) Mb and (B) cTnl in general population. Mb, myoglobin; cTnl, cardiac troponin I. Proportions are presented with fixed-effects when $l^2 \leq 50\%$ and random-effects otherwise.

Study	Events	Total			Proportion	95%-CI	Weight (fixed)	Weight (random)
	0	50			0.455	10 070 0 0741	47.00/	10.00/
Cai Q et al.	9	38			0.155	[0.073; 0.274]	17.8%	18.8%
Han H et al.	18	75			0.240	[0.149; 0.353]	16.6%	18.7%
He F et al.	6	28			0.214	[0.083; 0.410]	6.7%	16.6%
Li C et al.	122	311			0.392	[0.338; 0.449]	52.5%	19.8%
Xu P et al.	17	24		-	- 0.708	[0.489; 0.874]	4.7%	15.4%
Zhang Q et al.	6	8			0.750	[0.349; 0.968]	1.7%	10.8%
Fixed effect model Random effects model		504			0.334 0.377	[0.295; 0.373] [0.233; 0.521]	100.0% 	 100.0%
Heterogeneity: $I^2 = 90\%, \ \ell = 0.0265, p$	< 0.01		0.2 0.4	0.6 0.8				
В							Weight	Weight
Study	Events	Total			Proportion	95%-CI	(fixed)	(random)
Cao J et al.	26	153			0.170	[0.114; 0.239]	7.4%	8.1%
Deng Q et al.	39	67			0.582	[0.455; 0.702]	3.3%	7.0%
Feng Y et al.	27	88			0.307	[0.213; 0.414]	4.3%	7.5%
Garibaldi BT et al.	44	149	<u> </u>		0.295	[0.223: 0.375]	7.2%	8.1%
Han H et al.	17	75			0 227	[0.138: 0.338]	3.6%	7 2%
He F et al	9	18	1		0.500	[0 260: 0 740]	0.0%	1 30/
He V at al	100	501			0.000	[0.225. 0.424]	2/ 20/	0.00/
	109	301			0.377	[0.335; 0.421]	24.2%	0.0%
Hu L et al.	47	144			0.326	[0.251; 0.409]	1.0%	8.1%
Huang J et al.	6	22			0.273	[0.107; 0.502]	1.1%	4.8%
Huang R et al.	0	14	}		0.000	[0.000; 0.232]	0.7%	3.8%
Li C et al.	144	476	++-		0.303	[0.262; 0.346]	22.9%	8.8%
Li X et al.	94	269			0.349	[0.293: 0.410]	13.0%	8.5%
Zhang G et al	16	55			0.291	[0 176: 0 429]	2 7%	6.7%
Zhang O et al.	8	8			1 000	[0.631.1.000]	0.1%	2 7%
	0	0			1.000		0.470	2.1 /0
Zhao X et al.	2	30			0.067	[0.008; 0.221]	1.5%	5.5%
Fixed effect model		2069	\$		0.316	[0.295; 0.337]	100.0%	
Heterogeneity: $I^2 = 86\%$, $f^2 = 0.0121$, p	< 0.01					[0.247, 0.071]		100.070
^			0 0.2 0.4	0.6 0.8	1			
	-					05% 01	Weight	Weight
Study	Events	lotal			Proportion	95%-CI	(fixed)	(random)
Li C et al.	57	104			0.548	[0.447; 0.646]	46.0%	46.0%
Li C et al. Wang Z et al.	57 50	104 101			0.548 0.495	[0.447; 0.646] [0.394; 0.596]	46.0% 44.3%	46.0% 44.3%
Li C et al. Wang Z et al. Xu P et al.	57 50 13	104 101 20			0.548 0.495 0.650	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846]	46.0% 44.3% 9.6%	46.0% 44.3% 9.6%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model	57 50 13	104 101 20 225			0.548 0.495 0.650 0.534	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599]	46.0% 44.3% 9.6% 100.0%	46.0% 44.3% 9.6%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, $t^2 = 0$, $p = 0.39$	57 50 13	104 101 20 225			0.548 0.495 0.650 0.534 0.534	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599]	46.0% 44.3% 9.6% 100.0%	46.0% 44.3% 9.6% 100.0%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: I^2 = 0%, f^2 = 0, p = 0.39	57 50 13	104 101 20 225	0.4 0.5 0.	.6 0.7	0.548 0.495 0.650 0.534 0.534 0.8	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599]	46.0% 44.3% 9.6% 100.0%	46.0% 44.3% 9.6% 100.0%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0$, $p = 0.39$ D	57 50 13	104 101 20 225	0.4 0.5 0.	 	0.548 0.495 0.650 0.534 0.534 0.8	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599]	46.0% 44.3% 9.6% 100.0% 	46.0% 44.3% 9.6% 100.0% Weight
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0$, $p = 0.39$ D Study	57 50 13 Events	104 101 20 225 Total	0.4 0.5 0.		0.548 0.495 0.650 0.534 0.534 0.8	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599]	46.0% 44.3% 9.6% 100.0% Weight (fixed)	46.0% 44.3% 9.6% 100.0% Weight (random)
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0$, $p = 0.39$ D Study Cao J et al.	57 50 13 Events 12	104 101 20 225 Total	0.4 0.5 0.		0.548 0.495 0.650 0.534 0.534 0.8 Proportion - 0.800	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-CI [0.519; 0.957]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0, p = 0.39$ D Study Cao J et al. Cipriani A et al.	57 50 13 Events 12 18	104 101 20 225 Total 15 20	0.4 0.5 0.	 6 0.7	0.548 0.495 0.650 0.534 0.534 0.8 Proportion - 0.800 0.900	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-Cl [0.519; 0.957] [0.683; 0.988]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0$, $p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al.	57 50 13 Events 12 18 62	104 101 20 225 Total 15 20 121	0.4 0.5 0.		0.548 0.495 0.650 0.534 0.8 Proportion 0.800 0.900 0.512	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-CI [0.519; 0.957] [0.683; 0.988] [0.420: 0.604]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0$, $p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romueldo L et al.	57 50 13 Events 12 18 62 109	104 101 20 225 Total 15 20 121 187	0.4 0.5 0.		0.548 0.495 0.650 0.534 0.534 0.8 Proportion - 0.800 0.512 0.583	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-CI [0.519; 0.957] [0.683; 0.988] [0.420; 0.604] [0.509 0.654]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0, p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romualdo L et al. García de TZ et al.	57 50 13 Events 12 18 62 109 7	104 101 20 225 Total 15 20 121 187	0.4 0.5 0.	 6 0.7	0.548 0.495 0.650 0.534 0.534 0.8 Proportion - 0.800 0.512 0.583 0.524	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-Cl [0.519; 0.957] [0.683; 0.988] [0.420; 0.664] [0.509; 0.654] [0.509; 0.654]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\hat{\tau} = 0$, $p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romualdo L et al. García de Factal.	57 50 13 Events 12 18 62 109 78	104 101 20 225 Total 15 20 121 187 114	0.4 0.5 0.	 6 0.7	0.548 0.495 0.650 0.534 0.8 Proportion 0.800 0.900 0.512 0.583 0.684	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-CI [0.519; 0.957] [0.683; 0.988] [0.420; 0.604] [0.509; 0.654] [0.591; 0.768]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 4.7%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3% 8.1%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0, p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romualdo L et al. Garibaldi BT et al. Harmouch F et al.	57 50 13 Events 12 18 62 109 78 35	104 101 20 225 Total 15 20 121 187 114 68			0.548 0.650 0.534 0.534 0.8 Proportion 0.900 0.512 0.583 0.684 0.515	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-CI [0.519; 0.957] [0.683; 0.988] [0.420; 0.664] [0.591; 0.768] [0.390; 0.654]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 4.7% 2.4%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3% 8.1% 7.5%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0, p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. Garibaldi BT et al. Harmouch F et al. Li C et al.	57 50 13 Events 12 18 62 109 78 35 83	104 101 20 225 Total 15 20 121 187 114 68 183		6 0.7	0.548 0.650 0.534 0.534 0.8 Proportion − 0.800 0.512 0.583 0.684 0.515 0.454	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-Cl [0.519; 0.957] [0.683; 0.988] [0.420; 0.604] [0.599; 0.654] [0.590; 0.638] [0.380; 0.529]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 4.7% 6.6%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.1% 8.1% 7.5% 8.3%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\hat{\tau} = 0$, $p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romualdo L et al. García de Guadiana–Romualdo L et al. Harmouch F et al. Harmouch F et al. Harmouch F et al. Merugu GP et al.	57 500 13 Events 12 18 62 109 78 35 83 37	104 101 20 225 Total 15 20 121 187 114 68 183 23		 6 0.7	0.548 0.495 0.650 0.534 0.534 0.8 Proportion 0.900 0.512 0.583 0.684 0.515 0.454 0.545	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-CI [0.519; 0.957] [0.683; 0.988] [0.420; 0.604] [0.509; 0.654] [0.591; 0.768] [0.390; 0.6329] [0.380; 0.529]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 4.7% 2.4% 6.6% 1.0%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3% 8.1% 7.5% 8.3% 8.3% 6.2%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0, p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romualdo L et al. Garibaldi BT et al. Harmouch F et al. Harmouch F et al. Merugu GP et al. Mikami T et al.	57 50 13 Events 12 18 62 109 78 35 83 7 504	104 101 20 225 Total 15 20 121 187 114 68 183 23 718			0.548 0.650 0.534 0.534 0.8 Proportion 0.800 0.900 0.512 0.583 0.684 0.515 0.454 0.304 0.702	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] [0.469; 0.599] [0.469; 0.599] [0.519; 0.957] [0.683; 0.988] [0.420; 0.664] [0.591; 0.768] [0.390; 0.654] [0.390; 0.654] [0.390; 0.6529] [0.132; 0.529] [0.627; 0.7351]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 4.7% 2.4% 6.6% 1.0% 30.5%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3% 8.1% 7.5% 8.3% 8.3% 8.3% 8.2% 8.7%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0, p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. Garibaldi BT et al. Harmouch F et al. Li C et al. Merugu GP et al. Mikami T et al. Pan F et al.	57 50 13 Events 12 18 62 109 78 35 83 7 504 48	104 101 20 225 Total 15 20 121 187 114 68 183 23 718 89			0.548 0.650 0.534 0.534 0.8 Proportion 0.900 0.512 0.583 0.684 0.515 0.454 0.304 0.702 0.539	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-Cl [0.519; 0.957] [0.683; 0.988] [0.420; 0.604] [0.599; 0.6543] [0.390; 0.638] [0.380; 0.529] [0.132; 0.529] [0.430; 0.6461]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 4.7% 6.6% 1.0% 30.5% 3.2%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3% 8.1% 7.5% 8.3% 6.2% 8.3% 6.2% 8.7% 7.8%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\hat{\tau} = 0$, $p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romualdo L et al. Garialdi BT et al. Harmouch F et al. Li C et al. Merugu GP et al. Mikami T et al. Pan F et al. Tanbaga IH et al.	57 500 13 Events 12 18 62 109 78 355 83 7 504 48 280	104 101 20 225 Total 15 20 121 187 114 68 183 23 718 828			0.548 0.495 0.650 0.534 0.8 Proportion 0.800 0.512 0.583 0.684 0.515 0.454 0.515 0.454 0.515 0.454 0.512	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-Cl [0.519; 0.957] [0.683; 0.988] [0.420; 0.604] [0.599; 0.654] [0.390; 0.638] [0.380; 0.529] [0.132; 0.529] [0.667; 0.735] [0.430; 0.646] [0.407; 0.472]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 4.7% 2.4% 6.6% 1.0% 30.5% 31.2%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3% 8.3% 8.3% 8.3% 8.3% 8.3% 8.3% 8.3
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0, p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romualdo L et al. Garibaldi BT et al. Harmouch F et al. Harmouch F et al. Mirami T et al. Pan F et al. Tanboga IH et al.	57 50 13 Events 12 109 78 35 83 7 504 48 388 20	104 101 20 225 Total 15 20 121 187 114 68 183 3718 89 8822 202			0.548 0.650 0.534 0.534 0.8 Proportion 0.900 0.900 0.900 0.512 0.583 0.684 0.515 0.454 0.454 0.304 0.304 0.304 0.304 0.304	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] [0.469; 0.599] [0.469; 0.599] [0.469; 0.957] [0.683; 0.988] [0.420; 0.604] [0.509; 0.654] [0.390; 0.638] [0.390; 0.629] [0.132; 0.529] [0.667; 0.735] [0.430; 0.646] [0.407; 0.435]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 4.7% 2.4% 6.6% 1.0% 30.5% 3.2%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3% 8.1% 7.5% 8.3% 6.2% 8.7% 7.8% 8.7%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0$, $p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. Garibaldi BT et al. Harmouch F et al. Harmouch F et al. Li C et al. Mikami T et al. Pan F et al. Tanboga IH et al. Wang Z et al. Tanboga IH et al.	57 50 13 Events 12 18 62 109 78 35 83 7 504 48 388 36	104 101 20 225 Total 15 20 121 187 114 68 183 23 718 89 882 103			0.548 0.650 0.534 0.534 0.8 Proportion − 0.800 0.900 0.512 0.583 0.684 0.515 0.454 0.515 0.454 0.304 0.300 0.300 0.300	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-Cl [0.519; 0.957] [0.683; 0.988] [0.420; 0.604] [0.591; 0.768] [0.390; 0.654] [0.390; 0.654] [0.380; 0.529] [0.667; 0.735] [0.430; 0.646] [0.407; 0.473] [0.258; 0.450]	46.0% 44.3% 9.6% 100.0% 100.0% 0.8% 2.0% 4.3% 6.8% 4.7% 2.4% 6.6% 1.0% 30.5% 31.8% 4.0%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3% 8.1% 7.5% 8.3% 6.2% 8.3% 6.2% 8.3% 8.7% 8.7% 8.7%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romualdo L et al. Garibaldi BT et al. Harmouch F et al. Harmouch F et al. Micami T et al. Pan F et al. Tanboga IH et al. Wang Z et al. Zhou F et al.	57 50 13 Events 12 18 62 109 78 35 83 7 504 48 388 36 23	104 101 20 225 Total 15 20 121 187 114 68 183 23 718 89 882 103 50			0.548 0.495 0.650 0.534 0.8 Proportion − 0.800 0.900 0.512 0.583 0.684 0.515 0.454 0.304 0.304 0.702 0.539 0.440 0.350 0.460	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] 95%-CI [0.519; 0.957] [0.683; 0.988] [0.420; 0.664] [0.591; 0.768] [0.390; 0.654] [0.390; 0.654] [0.390; 0.6529] [0.667; 0.735] [0.430; 0.646] [0.407; 0.473] [0.258; 0.450] [0.318; 0.607]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 1.0% 30.5% 3.2% 31.8% 4.0% 1.8%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 8.3% 8.1% 7.5% 8.3% 8.3% 8.7% 8.7% 8.7% 8.7% 8.0% 7.2%
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Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0, p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romualdo L et al. Garibaldi BT et al. Harmouch F et al. Harmouch F et al. Mirauji T et al. Pan F et al. Tanboga IH et al. Wang Z et al. Zhou F et al. Fixed effect model Random effects model Heterozeneity: $I^2 = 0.0210$ =	57 50 13 Events 12 109 78 35 83 7 504 48 388 36 23	104 101 20 225 Total 15 20 121 187 114 68 183 23 718 89 882 103 50 2573			0.548 0.650 0.534 0.534 0.534 0.8 Proportion 0.900 0.512 0.583 0.684 0.515 0.454 0.354 0.304 0.512 0.583 0.684 0.354 0.304 0.702 0.539 0.440 0.350 0.460	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] [0.469; 0.599] [0.469; 0.599] [0.59%-CI [0.59; 0.988] [0.420; 0.604] [0.591; 0.768] [0.390; 0.634] [0.390; 0.634] [0.390; 0.629] [0.132; 0.529] [0.667; 0.735] [0.430; 0.646] [0.407; 0.473] [0.258; 0.450] [0.318; 0.607] [0.539; 0.576] [0.471; 0.640]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 4.7% 2.4% 6.6% 3.2% 31.8% 4.0% 1.8% 1.8%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 7.3% 8.0% 7.5% 8.3% 6.2% 8.7% 8.7% 8.7% 8.7% 8.7% 8.0% 7.2%
Li C et al. Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, $l^2 = 0$, $p = 0.39$ D Study Cao J et al. Cipriani A et al. Elhadi M et al. García de Guadiana–Romualdo L et al. García de Guadiana–Romualdo L et al. Garibaldi BT et al. Harmouch F et al. Harmouch F et al. Mikami T et al. Pan F et al. Tanboga IH et al. Wang Z et al. Zhou F et al. Fixed effect model Random effects model Heterogeneity: $l^2 = 94\%$, $l^2 = 0.0212$, p	57 50 13 Events 12 109 78 35 83 7 504 48 388 36 23 < 0.01	104 101 20 225 Total 15 20 121 187 114 68 183 23 718 89 882 103 50 2573			0.548 0.495 0.650 0.534 0.8 Proportion 0.900 0.512 0.583 0.684 0.515 0.454 0.304 0.702 0.539 0.440 0.350 0.460 0.355	[0.447; 0.646] [0.394; 0.596] [0.408; 0.846] [0.469; 0.599] [0.469; 0.599] [0.469; 0.599] [0.469; 0.599] [0.469; 0.957] [0.683; 0.988] [0.420; 0.604] [0.509; 0.654] [0.390; 0.638] [0.390; 0.638] [0.390; 0.529] [0.132; 0.529] [0.667; 0.735] [0.430; 0.646] [0.407; 0.473] [0.258; 0.450] [0.318; 0.607] [0.539; 0.576] [0.471; 0.640]	46.0% 44.3% 9.6% 100.0% Weight (fixed) 0.8% 2.0% 4.3% 6.8% 4.7% 2.4% 6.6% 3.2% 31.8% 4.0% 1.8% 100.0%	46.0% 44.3% 9.6% 100.0% Weight (random) 5.9% 7.3% 8.0% 7.5% 8.3% 8.1% 7.5% 8.3% 8.7% 8.7% 8.7% 8.7% 8.7% 8.7% 8.0% 7.2%

FIGURE 3 | Forest plot for the pooled prevalence of elevated Mb and cTnl in the severe disease and non-survivor groups. (A) Prevalence of elevated Mb in the severe disease group. (B) Prevalence of elevated cTnl in the severe disease group. (C) Prevalence of elevated Mb in the non-survivor group. (D) Prevalence of elevated cTnl in the non-survivor group. Mb, myoglobin; cTnl, cardiac troponin I. Proportions are presented with fixed-effects when $l^2 \leq 50\%$ and random-effects otherwise.



FIGURE 4 | Meta-regression of logit CSR or CFR on the rate of elevation of Mb or cTnl. (A) Regression of logit CSR on rate of elevation of Mb; R = 13.9, 95% Cl 3.51–24.29, p < 0.01. (B) Regression of logit CSR on rate of elevation of cTnl; r = 3.93, 95% Cl 0–8.52, p < 0.05. (C) Regression of logit CFR on rate of elevation of Mb; r = 15.42, 95% Cl 11.2–19.65, p < 0.0001. (D) Regression of logit CFR on rate of elevation of cTnl; r = 3.04, 95% Cl 1.84–4.25, p < 0.0001. CSR, case-severity rate; CFR, case-fatality rate; Mb, myoglobin; cTnl, cardiac troponin I. Each circle represents one study; size of the circle is proportional to the population size of each study.

to inflammatory stimuli (38). Wang et al. reported that oxidized Mb can act as a useful marker of myocardial inflammation (39). Furthermore, emerging evidence suggests that inflammatory responses, such as lymphopenia and cytokine storm, are closely associated with severe COVID-19 and high mortality (40, 41). Therefore, besides myocardial injury, the link between elevated Mb and COVID-19 prognosis may also be explained by inflammation and muscle injury. In addition to SARS-CoV-2 infection, increased Mb may also be caused by other preexisting comorbidities, such as chronic obstructive pulmonary disease (COPD), liver diseases, kidney diseases, and cardiovascular diseases, which have also been identified as risk factors for COVID-19 severity and mortality (42-45). Taken together, elevated Mb may be involved in damage directly caused by SARS-COV-2 infection and subsequent multiple organ failure, which partly explains the predictive value of Mb for adverse prognosis of COVID-19.

In the past year, the development and application of vaccines against SARS-CoV-2 brought hope to people worldwide. Notably, for the prevention of adverse outcomes of COVID-19, Chung et al. reported that two doses of mRNA COVID-19 vaccines were highly effective against symptomatic infection and severe consequences (46). Cornberg et al. demonstrated that priority vaccination for COVID-19 in patients with chronic liver diseases may be an important measure to intervene in the course of severe COVID-19 (47). However, the exact efficacy of COVID-19 vaccines against various comorbidities associated with myoglobin elevation is unknown and remains to be elucidated.

This meta-analysis had several potential limitations. First, all the studies included in this meta-analysis were retrospective, and there were relatively few studies involving both Mb and cTnI. Hence, the superiority of Mb over cTnI in predicting value should be interpreted as an observational conclusion.

A	Se	evere	_ Non-s	severe				Weight	Weigh
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	(fixed)	(random
Cai O et al.	9	58	1	202		36.92	[4.57: 298.32]	1.9%	5.7%
Han H et al.	18	75	11	198		5.37	[2.40: 12.03]	23.3%	22.7%
He F et al	6	28	2	258		34 91	[6 65: 183 32]	1.6%	8 4%
LiCetal	122	311	52	1238	· · · ·	14 72	[10.28: 21.08]	64 4%	39.19
Xu P et al	17	24	16	157		21.40	[7,71:59,40]	6.3%	17.29
Zhang Q et al.	6	8	5	33		16.80	[2.61; 108.12]	2.5%	6.9%
Fixed effect model		504		2086	•	13.75	[10.20: 18.54]	100.0%	
Random effects model Heterogeneity: $l^2 = 39\%$, $l^2 = 0.1539$, $p = 1$	1 15					14.29	[8.40; 24.28]		100.0%
r = 0.1333, p = 0.13333, p = 0.133333, p = 0.133333, p = 0.1333333, p = 0.1333333, p = 0.1333333, p = 0.13333333, p = 0.133333, p = 0.133333, p = 0.133333, p = 0.13333333, p = 0.133333333, p = 0.1333333333333333333333333333333333333	5.15			0.	01 0.1 1 10 100				
В	Se	evere	Non-s	severe				Weight	Weigh
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	(fixed)	(random
Cao J et al.	26	153	1	91		18.43	[2.46; 138.27]	0.9%	4.6%
Deng Q et al.	39	67	3	45	- (* * -	19.50	[5.49; 69.29]	1.4%	6.9%
Feng Y et al.	27	88	59	296		1.78	[1.04; 3.04]	17.0%	9.4%
Garibaldi BT et al.	44	149	66	507	→ }	2.80	[1.81; 4.33]	19.2%	9.79
Han H et al.	17	75	10	198		5.51	[2.39; 12.70]	3.9%	8.5%
He F et al.	9	18	13	171	- <u>-</u>	12.15	[4.11; 35.91]	1.1%	7.69
He X et al.	189	501	26	530	ļ.,	11.74	[7.61: 18.12]	14.3%	9.79
Hu L et al.	47	144	21	100		1.82	[1.01: 3.30]	15.2%	9.30
Juang J et al.	6	22	1	76		28.13	[3,16: 249,98]	0.3%	4.29
Juang R et al	0	14	2	89		1.21	[0.06:26.44]	0.6%	2.69
i C et al	144	476	37	1592		18.23	[12 46: 26 66]	10.8%	9.80
i X et al	0/	260	25	270		5.46	[12.40, 20.00]	14 5%	0.60
Thong G at al	16	55	25	166	ī	67.60	[9.57, 0.05]	0.30/	1.50
Thang O et al.	10	0	22	22		07.09	[0.71, 525.95]	0.0%	4.5
Chang Q et al.	0	20	33	55		4.07	10 25. 46 941	0.0%	2.70
Lhao X et al.	2	30	1	28		4.07	[0.35; 46.84]	0.6%	3.1%
Fixed effect model		2069		4231	\$	6.67 7.06	[5.64; 7.89]	100.0%	100.0%
Heterogeneity: $I^{-} = 88\%, \tau = 0.8634, p < 0$	0.01			(0.01 0.1 1 10 100				
C	Non-sur	vivor	Su	ırvivor				Weight	Weigh
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI	(fixed)	(random
Li C et al.	57	104	117	1445		13.77	[8.96; 21.16]	57.3%	69.0%
				110			55 60 00 151	20.90/	19.19
Wang Z et al.	50	101	8	113		12.87	[5.68; 29.15]	30.070	
Wang Z et al. Xu P et al.	50 13	101 20	8 19	113		12.87 13.78	[5.68; 29.15] [4.89; 38.84]	11.9%	11.9%
Wang Z et al. Xu P et al. ∓ixed effect model	50 13	101 20 225	8 19	113 160 1718		12.87 13.78 13.49	[5.68; 29.15] [4.89; 38.84] [9.30; 19.58]	11.9%	11.9%
Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\hat{\tau} = 0$, $p = 0.99$	50 13	101 20 225	8 19	113 160 1718		12.87 13.78 13.49 13.59	[5.68; 29.15] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43]	11.9%	11.9% 100.0%
Wang Z et al. Xu P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$, $f^2 = 0$, $p = 0.99$	50 13	101 20 225	8 19	113 160 1718	0.1 0.5 1 2 10	12.87 13.78 13.49 13.59	[5.68; 29.15] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43]	100.0%	11.9% 100.0%
Vang Z et al. Ku P et al. Fixed effect model Random effects model leterogeneity: $I^2 = 0\%$, $f^2 = 0$, $p = 0.99$	50 13 Non-sur	101 20 225 vivor	8 19 Su	113 160 1718	0.1 0.5 1 2 10	12.87 13.78 13.49 13.59	[5.68; 29.13] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43]	100.0%	11.99 - 100.09 Weigh
Vang Z et al. (u P et al. Tixed effect model tandom effects model leterogeneity: $I^2 = 0\%$, $f^2 = 0$, $p = 0.99$) tudy	50 13 Non-sur Events	101 20 225 vivor Total	8 19 Su Events	113 160 1718 Irvivor Total	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59	[5.68; 29.13] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-Cl	100.0%	11.9 - 100.09 Weigh (random
Vang Z et al. Ku P et al. Fixed effect model tandom effects model leterogeneity: $l^2 = 0\%$, $l^2 = 0$, $p = 0.99$ Constant Cao J et al.	50 13 Non-sur Events 12	101 20 225 vivor Total	8 19 Su Events 15	113 160 1718 urvivor Total	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 OR 10.67	[5.68; 29.13] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-CI [2.64; 43.14]	11.9% 100.0% Weight (fixed) 0.5%	11.9 - 100.0 Weigł (randon 6.1
Vang Z et al. (u P et al. ixed effect model tandom effects model leterogeneity: $I^2 = 0\%$, $f^2 = 0$, $p = 0.99$ b tudy (ao J et al. (ipriani A et al.	50 13 Non-sur Events 12 18	101 20 225 vivor Total	8 19 Su Events 15 28	113 160 1718 Irvivor Total	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 OR 10.67 19.61	[5.68; 29.15] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-Cl [2.64; 43.14] [4.25; 90.35]	100.0% 100.0% Weight (fixed) 0.5% 0.4%	11.9 - 100.0 Weigł (randon 6.1 5.7
Vang Z et al. (u P et al. ixed effect model tandom effects model leterogeneity: $I^2 = 0\%$, $P^2 = 0, p = 0.99$ b tudy Vao J et al. Lipriani A et al. Libadi M et al.	50 13 Non-sur Events 12 18 62	101 20 225 vivor Total	8 19 Su Events 15 28 28 28	113 160 1718 Irvivor Total 55 89 171	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 OR 10.67 19.61 5.37	[5.68; 29.13] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-Cl [2.64; 43.14] [4.25; 90.35] [3.13; 9.21]	Weight (fixed) 0.5% 0.4% 4.2%	11.9" - 100.0" Weigh (random 6.1" 5.7" 9.0"
Vang Z et al. Ku P et al. Fixed effect model Random effects model Reterogeneity : $I^2 = 0\%$, $f^2 = 0$, $p = 0.99$ Study Cao J et al. Cipriani A et al. Cipriani A et al. Circia de Guadiana–Romualdo L et al.	50 13 Non-sur Events 12 18 62 109	101 20 225 vivor Total 15 20 121 187	8 19 Su Events 15 28 28 28 235	113 160 1718 1718 1718 1718 55 89 171 1093	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 0R 10.67 19.61 5.37 5.10	[5.68; 29.13] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-Cl [2.64; 43.14] [4.25; 90.35] [3.13; 9.21] [3.69; 7.06]	Weight (fixed) 0.5% 0.4% 0.4% 10.7%	11.9" - 100.0" Weigh (randon 6.1" 5.7" 9.0" 9.4"
Vang Z et al. Ku P et al. Fixed effect model tandom effects model leterogeneity: $l^2 = 0\%$, $l^2 = 0$, $p = 0.99$ Constant Study Cao J et al. Dipriani A et al. Libadi M et al. Jarcia de Guadiana–Romualdo L et al. Jaribaldi BT et al.	50 13 Non-sur Events 12 18 62 109 78	101 20 225 vivor Total 15 20 121 187 114	8 19 Su Events 15 28 23 28 235 116	113 160 1718 1718 1718 55 89 171 1093 568	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 0R 10.67 19.61 5.37 5.10 8.44	[5.68; 29.15] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-Cl [2.64; 43.14] [4.25; 90.35] [3.13; 92] [3.69; 7.06] [5.41; 13.17]	Weight (fixed) 0.5% 0.4% 4.2% 10.7%	11.9" - 100.0" Weigł (randon 6.1" 5.7" 9.0" 9.4" 9.2"
Vang Z et al. Ku P et al. Fixed effect model kandom effects model leterogeneity: $l^2 = 0\%$, $t^2 = 0$, $p = 0.99$ Study Cao J et al. Cipriani A et al. Cipriani A et al. Cipriani A et al. Ciaria de Guadiana—Romualdo L et al. Ciaria del Guadiana—Romualdo L et al. Ciaria del Guadiana—Romualdo L et al. Ciaria de Guadiana—Romualdo L et al.	50 13 Non-sur Events 12 18 62 109 78 35	101 20 225 vivor Total 15 20 121 187 114 68	8 19 Su Events 15 28 28 235 116 662	113 160 1718 1718 1718 55 89 171 1093 568 411	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 0R 10.67 19.61 5.37 5.10 8.44 5.97	[5.68; 29.15] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-Cl [2.64; 43.14] [4.25; 90.35] [3.13; 9.21] [3.69; 7.06] [5.41; 13.17] [3.46; 10.32]	Weight (fixed) 0.5% 0.4% 4.2% 10.7% 4.6% 3.2%	11.9" 100.0 " Weigh (random 6.1" 5.7" 9.0" 9.4" 9.2" 8.9"
Vang Z et al. Ku P et al. Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%, \ \hat{\tau} = 0, p = 0.99$ Study Cao J et al. Dipriani A et al. Dipriani A et al. Diracia de Guadiana–Romualdo L et al. Jaribaldi BT et al. Harmouch F et al. Li C et al.	50 13 Non-sur Events 12 18 62 109 78 35 83	101 20 225 vivor Total 15 20 121 187 114 68 8	8 19 Su Events 15 28 235 116 62 98	113 160 1718 Irvivor Total 55 89 171 1093 568 411 1885	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 0R 10.67 19.61 5.37 5.10 8.44 5.97	[5.68; 29.13] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-Cl [2.64; 43.14] [4.25; 90.35] [3.13; 9.21] [3.69; 7.06] [5.41; 13.17] [3.46; 10.32] [10.61: 21 50]	Weight (fixed) 0.5% 0.4% 4.2% 10.7% 4.6% 3.2%	11.9"
Vang Z et al. Ku P et al. Fixed effect model Random effects model leterogeneity: $l^2 = 0\%$, $t^2 = 0$, $p = 0.99$ Study Cao J et al. Cipriani A et al. Cipriani A et al. Cipriani A et al. Circia de Guadiana–Romualdo L et al. Garcia de Guadiana–Romualdo L et al.	50 13 Non-sur Events 12 18 62 109 78 35 83 7	101 20 225 vivor Total 15 20 121 187 114 683 23	8 19 Su Events 28 235 5116 62 98 27	113 160 1718 Irvivor Total 55 89 171 1093 568 411 1885 78	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 0R 10.67 19.61 5.10 8.44 5.97 15.13 2.45	[5.68; 29.13] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-Cl [2.64; 43.14] [4.25; 90.35] [3.13; 9.21] [3.69; 7.06] [5.41; 13.17] [3.46; 10.32] [10.61; 21.59] [0.92; 6.51]	Weight (fixed) 0.5% 0.4% 4.2% 3.2% 3.6%	11.9" 100.0 " Weigl (randon 6.1" 5.7" 9.0" 9.4" 9.2" 8.9" 9.4" 7.6"
Vang Z et al. (u P et al. ixed effect model tandom effects model leterogeneity: $I^2 = 0\%$, $\hat{\tau} = 0$, $p = 0.99$ b itudy Cao J et al. Dipriani A et al. Lhadi M et al. Liarcia de Guadiana–Romualdo L et al. Lairibaldi BT et al. Larmouch F et al. Larmouch F et al. C et al. (i C et al. Herugu GP et al.	50 13 Non-sur Events 12 18 62 109 78 35 83 7 7	101 20 225 vivor Total 15 20 121 187 114 68 183 23 218	8 19 Su Events 15 28 235 116 62 98 27 802	113 160 1718 1718 1718 171 1093 568 411 1885 178 1885 1898	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 0R 10.67 19.61 5.37 5.10 8.44 5.97 15.13 2.45 2.91	[5.68; 29.15] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-Cl [2.64; 43.14] [4.25; 90.35] [3.13; 9.21] [3.69; 7.06] [5.41; 13.17] [3.46; 10.32] [10.61; 21.59] [0.92; 651] [2.40; 3.51]	Weight (fixed) 0.5% 0.4% 4.2% 10.7% 4.6% 3.2% 3.6% 1.6%	11.9" 100.0 " Weigl (randon 6.1" 5.7" 9.0" 9.4 9.2' 8.9 9.4 7.6 9.4 9.2' 8.9 9.4 7.6 9.4
Vang Z et al. Ku P et al. Fixed effect model tandom effects model leterogeneity: $l^2 = 0\%$, $l^2 = 0, p = 0.99$ Study Cao J et al. Carola de al. Chadi M et al. Chadi M et al. Chadi M et al. Chadi BT et al. Carola de Guadiana—Romualdo L et a	50 13 Non-sur Events 12 18 62 109 78 62 109 78 35 83 7 504 49	101 20 225 vivor Total 15 20 121 187 114 68 183 23 718	8 19 Su Events 15 28 28 235 116 62 98 27 808	113 160 1718 Irvivor Total 55 89 171 1093 568 411 1885 178 1808 25	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 0R 10.67 19.61 5.37 5.10 8.44 5.97 15.13 2.45 2.91	[5.68; 29.15] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] 95%-Cl [2.64; 43.14] [4.25; 90.35] [3.13; 9.21] [3.69; 7.06] [5.41; 13.17] [3.46; 10.32] [10.61; 21.59] [0.92; 6.51] [2.42; 3.51] [0.42; 3.42]	Weight (fixed) 0.5% 0.4% 4.2% 10.7% 4.6% 3.2% 10.7% 51.4% 3.7%	11.9
Vang Z et al. (u P et al. ixed effect model tandom effects model leterogeneity: $I^2 = 0\%$, $\hat{\tau} = 0, p = 0.99$ itudy Vao J et al. (ipriani A et al. lihadi M et al. Jarcia de Guadiana–Romualdo L et al. iaribaldi BT et al. larmouch F et al. t C et al. Merugu GP et al. Aikami T et al. an F et al.	50 13 Non-sur Events 12 18 62 109 78 35 83 7 504 48 282	101 20 225 vivor Total 15 20 121 187 114 68 183 23 718 89 9	8 19 Su Events 15 28 235 116 62 98 27 808 15 5 620	113 160 1718 Irvivor Total 55 89 171 1093 568 411 1888 178 1808 352	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 0 R 10.67 19.61 5.37 5.10 8.44 5.97 15.13 2.45 2.91 1.56	[5.68; 29.13] [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] [9.51; 19.43] [2.64; 43.14] [4.25; 90.35] [3.13; 9.21] [3.69; 7.06] [5.41; 13.17] [3.46; 10.32] [10.61; 21.59] [0.92; 6.51] [2.42; 3.51] [0.71; 3.43]	Weight (fixed) 0.5% 0.4% 4.2% 10.7% 4.6% 3.2% 3.2% 51.4% 51.4%	11.9 100.0 Weigl (random 6.1 5.7 9.0 9.4 9.2 8.9 9.4 7.6 9.6 8.2 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7
Vang Z et al. (u P et al. ixed effect model tandom effects model leterogeneity: $l^2 = 0\%$, $l^2 = 0$, $p = 0.99$ b itudy Cao J et al. Cipriani A et al. Lihadi M et al. Liarcia de Guadiana–Romualdo L et al. Liaribaldi BT et al. Larmouch F et al. Larmouch F et al. Areugu GP et al. Mikami T et al. an F et al. an F et al.	50 13 Non-sur Events 12 18 62 109 78 35 83 37 504 48 388	101 20 225 vivor Total 15 20 121 187 114 68 8183 23 718 89 882 23	8 19 Su Events 235 116 62 98 27 808 815 639	113 160 1718 1718 1718 1718 1718 1718 1709 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 17191719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 1719 171	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 0R 10.67 19.61 5.10 8.44 5.97 15.13 2.45 2.91 1.56 16.46	(5.68; 29.15) [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] (9.51; 19.43] [2.64; 43.14] [4.25; 90.35] [3.13; 92.1] [3.69; 7.06] [5.41; 13.17] [3.46; 10.32] [10.61; 21.59] [0.92; 6.51] [2.42; 3.51] [0.71; 3.43] [14.10; 19.22]	Weight 100.0% Weight (fixed) 0.5% 0.4% 4.2% 3.6% 1.6% 51.4% 3.7% 15.9%	11.9 Weigl (random 6.1 5.7 9.0 9.4 9.2 8.9 9.4 7.6 8.2 9.7 2.7 2.7 2.7 2.7 2.7 2.7 2.7 2
Vang Z et al. Ku P et al. Fixed effect model tandom effects model leterogeneity: $l^2 = 0\%$, $\hat{r} = 0$, $p = 0.99$ Study Cao J et al. Privani A et al. Dipriani A et al. Dipriani A et al. Diaribaldi BT et al. Iarmouch F et al. Iarmouch F et al. Aerugu GP et al. Mair et al. an F et al. T et al	50 13 Non-sur Events 12 18 62 109 78 35 83 7 504 48 388 36 62 22	101 20 225 vivor Total 15 20 121 187 114 68 183 23 718 89 882 103 50	8 19 Su Events 15 28 235 116 62 98 27 808 815 639 0	113 160 1718 1718 1718 1718 1718 1718 1718 1718 1 093 568 411 1885 1703 568 411 1885 1808 35 14033 177 95	0.1 0.5 1 2 10 Odds Ratio	12.87 13.78 13.49 13.59 13.59 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	(5.68; 29.15) [4.89; 38.84] [9.30; 19.58] [9.51; 19.43] (9.51; 19.43] [2.64; 43.14] [4.25; 90.35] [3.13; 92] [3.69; 7.06] [5.41; 13.17] [3.46; 10.32] [10.61; 21.59] [0.92; 6.51] [2.42; 3.51] [0.71; 3.43] [14.10; 19.22] [11.62; 3171.85] [10.34; 620.24]	30.8% 11.9% 100.0% Weight (fixed) 0.5% 0.4% 4.6% 3.2% 3.6% 1.6% 51.4% 3.7% 15.9% 0.1%	11.9" Weigl (randon 6.1" 5.7" 9.0" 9.4 9.2' 8.9 9.4.4 7.6 9.6 8.2' 9.7' 2.9' 4.2'' 9.7' 2.9''
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FIGURE 5 | Forest plot for the association of coronavirus disease 2019 (COVID-19)-related adverse outcomes with abnormal level of Mb or cTnl. (A) Severe illness and elevation of Mb. (B) Severe illness and elevation of cTnl. (C) In-hospital mortality and elevation of Mb. (D) In-hospital mortality and elevation of cTnl. Mb, myoglobin; cTnl, cardiac troponin I. Odds ratios (ORs) are presented with fixed-effects when $l^2 \leq 50\%$ and random-effects otherwise.

Further high-quality comparative studies are needed to confirm the difference between Mb and cTnI in predicting prognosis of COVID-19. Second, because of the nature of meta-regression and high heterogeneity across the analyses, we were unable to obtain a definite causal relationship between elevated Mb and poor prognosis of COVID-19. The potential sources of heterogeneity include different cutoffs of elevated cTnI or Mb, mean ages (48, 49), and sex ratios (50) in different studies. Therefore, considering the confounding factors, our results need to be further confirmed by rigorous prospective studies and randomized controlled trials. Third, because of the limited number of included studies, this meta-analysis did not analyze the predictive value of CK-MB, NT-proBNP, LDH, and other cardiac markers except Mb and cTnI. Fourth, studies enrolled in this meta-analysis had a relatively short follow-up period. Therefore, the predictive value of Mb for long-term prognosis of COVID-19 needs to be further explored.

In summary, this meta-analysis showed that patients with COVID-19 and elevated Mb levels are at higher risk of severe disease and mortality. Hence, elevated Mb could be used as a predictor of adverse outcomes in COVID-19. However, high-quality studies are required to confirm these findings and establish the link between elevated Mb and prognosis of patients with COVID-19.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

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AUTHOR CONTRIBUTIONS

PL, XZ, and YB were the judicators and contributed to the conception of the study. CM, DT, JG, YB, ZG, and HW designed the protocol. CM, DT, and JG searched the databases and finished data extraction, quality assessment, and statistical analysis. CM and DT wrote the first draft of the manuscript. All authors reviewed the manuscript, provided critical revision, and have approved the final version for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm. 2021.757799/full#supplementary-material

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