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Keywords: creatine kinase-MB, COVID-19 severity, mortality

Abstract

Objectives: We conducted a systematic review and meta-analysis with meta-regression of creatine kinase-MB (CK-MB), a biomarker of myocardial injury, in COVID-19 patients.

Methods: We searched PubMed, Web of Science, and Scopus, for studies published between January 2020 and January 2021 that reported CK-MB, COVID-19 severity, and mortality (PROSPERO registration number: CRD42021239657).

Results: Fifty-five studies in 11,791 COVID-19 patients were included in the meta-analysis. The pooled results showed that CK-MB concentrations were significantly higher in patients with high disease severity or non-survivor status than patients with low severity or survivor status (standardized mean difference, SMD, 0.81, 95% CI 0.61 to 1.01, p < 0.001). The rate of patients with CK-MB values above the normal range was also significantly higher in the former than the latter (60/350 vs 98/1,780; RR = 2.84, 95%CI 1.89 to 4.27, p < 0.001; I² = 19.9, p = 0.254). Extreme between-study heterogeneity was observed (I² = 93.4%, p < 0.001). Sensitivity analysis, performed by sequentially removing each study and re-assessing the pooled estimates, showed that the magnitude and direction of the effect size was not modified (effect size range, 0.77 to 0.84). Begg’s (p = 0.50) and Egger’s (p = 0.86) t-tests did not show publication bias. In meta-regression analysis, the SMD was significantly and positively associated with the white blood count, aspartate aminotransferase, myoglobin, troponin, brain natriuretic peptide, lactate dehydrogenase, and D-dimer.

Conclusions: Higher CK-MB concentrations were significantly associated with severe disease and mortality in COVID-19 patients. This biomarker of myocardial injury might be useful for risk stratification in this group.

1. Introduction

Several clinical and demographic factors have been shown to be significantly associated with measures of coronavirus disease 2019 (COVID-19) severity, based on clinical and imaging findings and/or the need for aggressive single- and multi-organ support, and mortality [1,2]. The evidence of excessive inflammatory activity in severe COVID-19, captured during the early phases of the pandemic, prompted the investigation of the clinical role of specific biomarkers of inflammatory and immunomodulating pathways, particularly C-reactive protein (CRP), white blood cell count (WBC), neutrophils, lymphocytes, platelets, procalcitonin, ferritin, and serum amyloid A [3–6]. Additional research has shown that patients with COVID-19 can also experience structural and functional abnormalities of specific organs and systems, e.g., cardiovascular, hematological, gastrointestinal, and neurological, in addition to the well-known respiratory compromise, characterized by the development of interstitial pneumonia and acute respiratory distress syndrome (ARDS) [7–9]. In particular, COVID-19 patients might present with subclinical or overt evidence of myocardial necrosis, which might manifest as acute coronary syndrome, myocarditis, arrhythmias, or heart failure [10]. While the exact mechanisms involved in the pathogenesis of cardiac complications in COVID-19 remain to be established, the presence of myocardial necrosis has been shown to be independently associated with more severe disease, transfer to the intensive care unit (ICU) and mortality [11–13]. Biomarkers of myocardial damage, particularly creatine kinase-MB (CK-MB) and troponin, have been increasingly
investigated in COVID-19 patients in terms of their predictive capacity and potential to assist with clinical decisions [14]. A number of systematic reviews and meta-analyses on troponin and COVID-19 have been published [15–18]. Similarly, meta-analyses have sought to critically appraise the available evidence regarding the clinical role of CK-MB [19–22], with the largest meta-analysis identifying a total of 25 studies in 5,626 COVID-19 patients [21]. While CK-MB is less used in the diagnosis and the monitoring of myocardial necrosis in contemporary clinical practice since the advent of high-sensitivity troponin, additional retrospective and prospective studies have since been published on the associations between serum CK-MB concentrations, COVID-19 severity, and adverse outcomes. Furthermore, the assessment of CK-MB in COVID-19 patients might provide specific clinical information, independent of myocardial necrosis and cardiac complications, for early risk stratification in this group. We sought to address these issues by conducting an updated systematic review and meta-analysis of studies reporting serum CK-MB concentrations in COVID-19 patients with different disease severity, based on clinical guidelines or need for hospitalization, mechanical ventilation, or transfer to the ICU, and survival status during follow up. Additionally, a meta-regression analysis was performed to investigate possible associations between the effect size of the differences in CK-MB concentrations and a number of plausible clinical, demographic and biochemical factors.

2. Materials and methods

2.1. Search strategy, eligibility criteria, and study selection

We conducted a systematic literature search using the terms “CK-MB” or “creatine kinase MB” and “coronavirus disease 19” or “COVID-19”, in the electronic databases PubMed, Web of Science and Scopus, for peer-reviewed studies published from January 2020 to January 2021 that reported serum CK-MB concentrations in COVID-19 patients (PROSPERO registration number: CRD42021239657). The reference lists of the retrieved articles were also searched to identify additional studies. Eligibility criteria included: (a) studies reporting continuous data on CK-MB concentrations in COVID-19 patients, (b) articles investigating COVID-19 patients with different degrees of disease severity and/or survival status, (c) adult patients, (d) English language, (e) ≥10 COVID-19 patients, and (f) full-text available. Two investigators independently screened the abstracts. If relevant, the full articles were independently reviewed. The Newcastle-Ottawa scale was used to assess the quality of each study [23]. A score ≥6 indicated good quality when converting the scale to the Agency for Healthcare Research and Quality standards [24].

2.2. Statistical analysis

Standardized mean differences (SMD) and 95% confidence intervals (CIs) were calculated to build forest plots of continuous data and to evaluate differences in CK-MB concentrations between COVID-19 patients with low vs. high disease severity or survivor vs. non-survivor status. A p-value <0.05 was considered statistically significant. If studies reported CK-MB concentrations as median and interquartile range (IQR) or median and range, the corresponding means and standard deviations were estimated as previously described [25,26]. The Q-statistic was used to assess the heterogeneity of SMD values across studies with a significance level set at p<0.10. Inconsistency across studies was evaluated through the I² statistic, with I² values <25% indicating no heterogeneity, between 25 and 50% moderate heterogeneity, between 50 and 75% large heterogeneity, and >75% extreme heterogeneity [27,28]. A random-effect model was used to calculate the pooled SMD and corresponding 95% CIs in the presence of significant heterogeneity. In sensitivity analyses, the influence of each study on the overall effect size was assessed using the leave-one-out method [29]. The presence of publication bias was assessed using the Begg’s adjusted rank correlation test and the Egger’s regression asymmetry test at the p<0.05 level of significance [30,31], and further evaluated using the Duval and Tweedie “trim and fill” procedure. The latter, a funnel-plot-based method of testing and adjusting for publication bias, is a nonparametric (rank-based) data augmentation technique that increases the observed data, so that the funnel plot is more symmetric, and recalculates the pooled SMD based on the complete data [32]. To explore possible contributors to the between-study variance, we investigated the effects of several biologically and/or clinically plausible factors on the SMD by univariate meta-regression analysis. These factors included age, gender, clinical endpoint, month of recruitment commencement, diabetes, hypertension and cardiovascular disease, biomarkers of inflammation (CRP, WBC), liver damage (aspartate aminotransferase - AST, alanine aminotransferase - ALT, albumin), cardiac damage (myoglobin, troponin, brain natriuretic peptide - BNP), renal damage (serum creatinine), tissue damage and sepsis (lactate dehydrogenase - LDH, procalcitonin), and pro-thrombotic tendency (D-dimer). Statistical analyses were performed using Stata 14 (STATA Corp., College Station, TX, USA). The study was fully compliant with the PRISMA statement regarding the reporting of systematic reviews and meta-analyses [33].

3. Results

3.1. Literature search and study selection

Fig. 1 describes the flow chart of the screening process. We initially identified 661 studies. A total of 600 studies were excluded after the first screening because they were either duplicates or irrelevant. After a full-text revision of the remaining 61 articles, 6 were further excluded because they did not meet the inclusion criteria. Thus, 55 studies in 11,791 COVID-19 patients, 9,596 (48% males, mean age 54 years) with low severity or survivor status and 2,195 (62% males, mean age 66 years) with high severity or non-survivor status during follow up, were included in the meta-analysis (Table 1) [14,34–87].

Two studies were conducted in Turkey [34,58], 1 in the USA [57], 1 in Korea [52], and the remaining 51 in China [14,35–51,53–56,59–87]. Three studies were prospective [42,53,68], 47 retrospective [34–41,43–48,50–52,54–65,67,69–85,87], whereas the remaining 5 did not report information regarding the study design [14,49,66,71,86]. Clinical endpoints included disease severity based on current clinical guidelines in 21 studies [38,43,45,48–52,54,56,60,63,64,66,72,74,79,80,82,84,85], admission to ICU in 4 [41,58,78,86], clinical progress in 2 [65,71], presence of ARDS in 1 [70], need for mechanical ventilation in 1 [37], and combined clinical outcomes in 2 [42,53], and survival status in 24 [14,34–36,39,40,44,46,47,55,57,59,61,62,67–69,73,75–77,81,83,87]. Only 1 study reported the highest CK-MB serum concentrations during hospitalization [61], whereas the remaining 54 reported a single CK-MB concentration within the first 24–48 h from admission.

3.2. Meta-analysis

The overall SMD in CK-MB concentrations between COVID-19 patients with low vs. high disease severity or survivor vs. non-survivor...
| First Author, Study Country [reference] | Study design | Endpoint | NOS (stars) | Mild disease or survivor | Severe disease or non-survivor |
|----------------------------------------|--------------|----------|-------------|--------------------------|-----------------------------|
|                                       |              |          |             | n | Age (Years) | Gender | CK-MB (U/L) (Mean ±SD) | n | Age (Years) | Gender | CK-MB (U/L) (Mean ±SD) |
| Aladag N et al., Turkey [34]           | R            | Survival status | 7 | 35 | 68 | 22/13 | 29 ± 23 | 15 | 68 | 6/9 | 33 ± 25 |
| Cao L et al., China [63]               | R            | Survival status | 7 | 78 | 68 | 33/45 | 0.8 ± 0.4* | 22 | 81 | 12/10 | 4.9 ± 5.4* |
| Chen FF et al., China [36]             | R            | Survival status | 7 | 577 | 63 | 297/280 | 1.1 ± 0.6* | 104 | 73 | 65/39 | 3.7 ± 3.1* |
| Chen J et al., China [37]              | R            | Mechanical ventilation | 7 | 68 | 67 | 38/30 | 36 ± 77 | 30 | 68 | 18/12 | 10 ± 13 |
| Deng M et al., China [38]              | R            | Disease severity | 7 | 53 | 35 | 24/29 | 10 ± 5 | 12 | 33 | 12/0 | 10 ± 13 |
| Deng P et al., China [39]              | R            | Survival status | 7 | 212 | 63 | 97/115 | 1.1 ± 0.6* | 52 | 75 | 33/19 | 2.0 ± 0.5* |
| Dong X et al., China [60]              | R            | Survival status | 7 | 65 | 54 | 30/35 | 24 ± 15 | 54 | 70 | 38/16 | 39 ± 29 |
| Du RH et al., China [41]               | R            | ICU admission | 5 | 58 | 68 | 38/20 | 3.7 ± 4.1* | 51 | 79 | 36/15 | 5.4 ± 6.7* |
| Feng X et al., China [62]              | P            | Composite endpoint| 7 | 94 | 63 | 58/36 | 18 ± 6 | 20 | 69 | 13/7 | 21 ± 14 |
| Feng Y et al., China [43]              | R            | Disease severity | 5 | 352 | 51 | 190/162 | 13 ± 4 | 124 | 60 | 81/43 | 16 ± 7 |
| Gao S et al., China [44]               | R            | Survival status | 5 | 175 | 70 | 79/96 | 9 ± 4 | 35 | 74 | 22/13 | 13 ± 8 |
| Gong J et al., China [65]              | R            | Disease severity | 5 | 161 | 45 | 72/89 | 12 ± 5 | 28 | 64 | 16/12 | 16 ± 17 |
| Guo H et al., China [46]               | R            | Survival status | 7 | 28 | 59 | NR | 6 ± 21* | 46 | 72 | NR | 11 ± 49* |
| Guo J et al., China [47]               | R            | Survival status | 6 | 43 | 60 | 22/21 | 11 ± 4 | 31 | 68 | 21/10 | 18 ± 7 |
| Han H et al., China [48]               | R            | Disease severity | 5 | 198 | 60 | 71/127 | 1.0 ± 0.6* | 75 | 59 | 26/49 | 1.3 ± 1.1* |
| He B et al., China [49]                | NR           | Disease severity | 5 | 32 | 42 | 15/17 | 0.6 ± 0.2* | 21 | 57 | 13/8 | 1.6 ± 1.2* |
| Hu J et al., China [50]                | R            | Disease severity | 7 | 130 | 63 | 58/72 | 13 ± 17 | 52 | 64 | 42/10 | 42 ± 93 |
| Hu X et al., China [51]                | R            | Disease severity | 7 | 175 | 41 | 80/95 | 9.2 ± 4.5 | 38 | 53 | 22/16 | 8.9 ± 4.4 |
| Jang JG et al., Korea [52]             | R            | Disease severity | 7 | 87 | 68 | 34/53 | 1.9 ± 1.8* | 23 | 54 | 14/9 | 5.3 ± 4.1* |
| Ji L et al., China [53]                | P            | Composite endpoint| 7 | 243 | 52 | 121/122 | 0.4 ± 0.2 | 37 | 71 | 20/17 | 14 ± 20 |
| Li N et al., China [54]                | R            | Disease severity | 7 | 103 | 61 | 48/55 | 0.8 ± 0.7* | 35 | 67 | 23/12 | 2.7 ± 2.9* |
| Li Y et al., China [55]                | R            | Survival status | 7 | 64 | 54 | 30/34 | 11.7 ± 3.7 | 37 | 72 | 23/14 | 22.3 ± 16.3 |
| Liu SL et al., China [56]              | R            | Disease severity | 5 | 194 | 43 | 91/103 | 9.3 ± 3.4 | 31 | 64 | 17/14 | 13.7 ± 7.4 |
| McKae MP et al., USA [57]              | R            | Survival status | 5 | 117 | 63 | 52/65 | 5.5 ± 7.5* | 43 | 73 | 30/13 | 8.6 ± 11.8* |
| Mertoglu C et al., Turkey [58]         | R            | ICU admission | 7 | 532 | 48 | 306/226 | 16.4 ± 5.5 | 23 | 59 | 13/10 | 49 ± 52 |
| Qin W et al., China [59]               | R            | Survival status | 7 | 239 | 63 | 113/126 | 0.9 ± 0.4* | 23 | 69 | 10/13 | 2.0 ± 1.3* |
| Tao Z et al., China [60]               | R            | Disease severity | 7 | 202 | 54 | 72/130 | 4.1 ± 5.5* | 20 | 65 | 8/12 | 2.5 ± 2.2* |
| Tao H et al., China [61]               | R            | Survival status | 5 | 96 | 51 | 38/58 | 0.8 ± 0.6* | 52 | 69 | 29/23 | 2.8 ± 2.3* |
| Wang B et al., China [62]              | R            | Survival status | 7 | 54 | 62 | 40/14 | 24 ± 23 | 50 | 72 | 40/10 | 29 ± 22 |
| Wang C et al., China [63]              | R            | Disease severity | 6 | 35 | 38 | 17/18 | 16 ± 13 | 10 | 43 | 6/4 | 20 ± 7 |
| Wang D et al., China [64]              | R            | Disease severity | 5 | 72 | 44 | 29/43 | 13 ± 5 | 71 | 65 | 44/27 | 14 ± 8 |
| Wang F et al., China [65]              | R            | Disease progression | 7 | 253 | 41 | 109/144 | 0.6 ± 0.6* | 70 | 60 | 45/25 | 0.7 ± 0.7* |
| Wang G et al., China [66]              | NR           | Disease severity | 7 | 193 | 42 | 95/98 | 60 ± 55 | 16 | 54 | 10/6 | 8.4 ± 4.6 |
| Wang JH et al., China [67]             | R            | Survival status | 7 | 1074 | 61 | 502/572 | 0.8 ± 0.4* | 61 | 74 | 43/18 | 2.5 ± 2.7* |
| Wang K et al., China [68]              | P            | Survival status | 7 | 277 | 46 | 129/148 | 14 ± 4 | 19 | 66 | 11/8 | 21 ± 8 |

(continued on next page)
Table 1 (continued)

| First Author, Country [reference] | Study design | Endpoint (stars) | NOS (stars) | Mild disease or survivor | Severe disease or non-survivor |
|-----------------------------------|--------------|------------------|-------------|-------------------------|-------------------------------|
| Wang Z et al., China [69]         | R            | Survival status  | 7           | Age (Years) | Gender | CK-MB U/L | Age (Years) | Gender | CK-MB U/L |
| Wu C et al., China [70]           | R            | Presence of ARDS | 6           | 117        | 48/64 | 15.3 ± 5.2 | 84          | 59/60 | 16.8 ± 5.6 |
| Xie J et al., China [71]          | NR           | Disease progression | 6         | 75        | 51/45 | 19.3 ± 5.9 | 29          | 66/18 | 22.7 ± 7.4 |
| Xie Y et al., China [72]          | R            | Disease severity | 5           | 38        | 61/14 | 0.6 ± 0.4 | 24          | 72/13 | 0.8 ± 0.5 |
| Xu B et al., China [73]           | R            | Survival status  | 5           | 117       | 56/59 | 14 ± 6 | 28          | 73/17 | 21 ± 10 |
| Yang A et al., China [74]         | R            | Disease severity | 5           | 99        | 49/49 | 11 ± 10 | 15          | 60/7  | 12.1 ± 7.2 |
| Yang C et al., China [75]         | R            | Survival status  | 7           | 145       | 57/77 | 13 ± 6 | 58          | 67/38 | 19 ± 7  |
| Yang J et al., China [14]         | R            | Survival status  | 5           | 332       | 55/170 | 1.2 ± 1.0 | 25          | 75/15 | 7 ± 6.7  |
| Yao Q et al., China [76]          | R            | Survival status  | 6           | 96        | 51/36 | 16 ± 5 | 12          | 65/7  | 23 ± 10 |
| Yu Z et al., China [77]           | R            | Survival status  | 7           | 123       | 80/46 | 7.3 ± 3.7 | 18          | 84/11 | 8.8 ± 6.1 |
| Zeng Z et al., China [78]         | R            | ICU admission    | 7           | 406       | 43/206 | 10.6 ± 5.5 | 55          | 60/33 | 12 ± 6.4 |
| Zhang C et al., China [79]        | R            | Disease severity | 5           | 56        | 44/24 | 0.5 ± 0.7 | 24          | 65/9  | 1.1 ± 1.2 |
| Zhang G et al., China [80]        | R            | Disease severity | 5           | 166       | 51/73 | 12.3 ± 3.7 | 55          | 62/35 | 22.3 ± 15.6 |
| Zhang JI et al., China [81]       | R            | Survival status  | 7           | 240       | 53/119 | 1.2 ± 1.0 | 49          | 69/25 | 2.3 ± 1.9 |
| Zhang Q et al., China [82]        | R            | Disease severity | 7           | 47        | 61/18 | 9.3 ± 3.0 | 27          | 72/18 | 16.3 ± 8.9 |
| Zhang XB et al., China [83]       | R            | Survival status  | 7           | 410       | 53/219 | 7.1 ± 7.6 | 22          | 66/11 | 19.4 ± 19.6 |
| Zhao Y et al., China [84]         | R            | Disease severity | 7           | 336       | 43/145 | 0.8 ± 0.4 | 81          | 56/53 | 1.1 ± 0.4 |
| Zhou C et al., China [85]         | R            | Disease severity | 7           | 95        | 35/38 | 6.9 ± 3.7 | 28          | 40/17 | 8.0 ± 2.0 |
| Zhou J et al., China [86]         | NR           | ICU admission    | 5           | 156       | 40/75 | 11.1 ± 6.2 | 45          | 57/27 | 9.3 ± 4.7 |
| Zou Y et al., China [87]          | R            | Survival status  | 5           | 73        | 73/39 | 1.8 ± 1.3 | 29          | 62/19 | 7.2 ± 8.7 |

Abbreviations: ICU, intensive care unit; NOS, Newcastle-Ottawa quality assessment scale for case–control studies; NR, Not Reported; P, prospective; R, retrospective; ARDS, acute respiratory distress syndrome.

- ng/mL or μg/L.
- Survival status on discharge, disease severity, and mechanical ventilation.
- Survival status on discharge, presence of ARDS.

status during follow up is shown in Fig. 2. In 5 studies, patients with high severity or non-survivor status had lower CK-MB concentrations when compared to those with low severity or survivor status (mean difference range, -0.07 to -0.97) [37,51,60,66,86], although only 1 study reported a statistically significant difference [66]. In 1 study, no difference was observed (mean difference 0.00) [38], whereas in the remaining 49 studies the CK-MB concentrations were lower in patients with low severity or survivor status (mean difference range, 0.11 to 2.91), with a non-significant difference in 17 [34,38,41,42,46,57,62–65,70–72,74,77,78,85]. The pooled results confirmed that the CK-MB concentrations were statistically significantly higher in patients with high disease severity or non-survivor status during follow up (SMD 0.81, 95% CI 0.61 to 1.01, p < 0.001; Fig. 2). An extreme heterogeneity between studies was observed (I² = 93.4%, p < 0.001). A sub-group of 11 studies reported the proportion of patients with CK-MB concentrations above the normal range in COVID-19 patients with high severity or non-survivor status vs. those with low severity or survivor status during follow-up [38,41,44,48,51,52,58,76,77,81,86]. The rate of participants with CK-MB values above the normal range was statistically significantly higher in the former than the latter (60/350 vs 98/1,780; RR = 2.84, 95%CI 1.89 to 4.27, p < 0.001; I² = 19.9, p = 0.254) (Fig. 3).

Sensitivity analysis, performed by sequentially removing each study and re-assessing the pooled estimates, showed that the magnitude and the direction of the effect size were not influenced (effect size range, between 0.77 and 0.84) (Fig. 4). CK-MB concentrations remained statistically significantly higher (SMD 0.72, 95% CI 0.54 to 0.90, p < 0.001; I² = 90.2%, p < 0.001) in patients with high severity or non-survivor status after excluding 5 relatively large studies that accounted for nearly 28% of the overall sample size [36,58,67,78,83].

No publication bias was observed with the Begg’s (p = 0.50) and Egger’s (p = 0.86) t-tests. Accordingly, the trim-and-fill analysis showed that no study was missing or should be added (Fig. 5).

3.3. Meta-regression analysis

In univariate meta-regression analysis, the SMD was statistically significantly and positively associated with the WBC (t = 3.51, p = 0.001), AST (t = 2.81, p = 0.007), myoglobin (t = 2.91, p = 0.01),
troponin (t = 3.83, p = 0.001), BNP (t = 2.67, p = 0.02), LDH (t = 2.40, p = 0.02), and D-dimer (t = 2.47, p = 0.02) (Table 2). By contrast, no statistically significant associations were observed between the SMD and age (t = 0.43, p = 0.67), gender (t = 0.54, p = 0.59), month of recruitment commencement (t = 1.44, p = 0.15; Fig. 6), CRP (t = 1.17, p = 0.25), ALT (t = -0.73, p = 0.47), creatinine (t = 1.17, p = 0.25), procollagen (t = 1.75, p = 0.10), albumin (t = -1.53, p = 0.13), diabetes (t = -0.56, p = 0.58), hypertension (t = -0.80, p = 0.43) and cardiovascular disease (t = -0.59, p = 0.56) (Table 2).

In sub-group analysis, the pooled SMD in studies assessing disease severity (SMD 0.52, 95% CI 0.32 to 0.72, p = 0.001; I² = 84.6, p<0.001) was statistically significantly lower than that observed in studies assessing survival status (SMD 1.18, 95% CI 0.89 to 1.46, p<0.001; I² = 92.0, p<0.001; t = 3.38, p = 0.002) (Fig. 7). However, the between-study variance remained extreme regardless of the type of endpoint studied.

We further sought to identify additional, more homogeneous, study sub-groups according to endpoint reported, study design (retrospective or prospective), country, and assay type (measurement of CK-MB on the basis of activity or mass). In particular, a sub-group of 13 retrospective studies conducted in China [40,44,47,55,62,69,73,75–77,81,83,87]...
assessed survival and measured CK-MB using an assay based on activity evaluation. Funnel plot analysis showed that 3 of these studies were located outside of the plot (Fig. 8A) [62,77,83]. After removing these studies, the effect size of the remaining 10 studies confirmed that the CK-MB concentrations were statistically significantly higher in patients with high disease severity or non-survivor status during follow up (SMD 0.97, 95% CI 0.84 to 1.09, p < 0.001) (Fig. 8B). However, a substantially lower heterogeneity between studies was observed (I² = 0.0%, p = 0.72).

4. Discussion

In this updated systematic review and meta-analysis, the serum concentrations of CK-MB, measured within 24–48 h from admission in virtually all studies, were statistically significantly higher in patients with COVID-19 who had a more severe clinical picture, based on available guidelines, disease progress, need for mechanical ventilation, or transfer to ICU, or did not survive, during follow up. The magnitude of the observed SMD value suggests the presence of a clinically relevant between-group difference in CK-MB concentrations [88]. Whilst the study heterogeneity was extreme, the sequential omission of individual
studies did not exert tangible effects on the SMD value. Furthermore, there was no evidence of publication bias according to the Begg’s and Egger’s t-tests and the trim and fill analysis. Previous systematic reviews and meta-analyses have reported associations between serum CK-MB concentrations and COVID-19 severity and mortality [19–22]. Our meta-analysis has captured more than double the number of studies, 55 vs. 25, and participants, 11,791 vs. 5,626, than the largest previously published meta-analysis [21]. Furthermore, we investigated possible associations between the observed SMD and a number of biologically and clinically plausible factors. Using meta-regression analysis, there were statistically significant and positive associations between the SMD and the WBC and the concentrations of AST, myoglobin, troponin, BNP, LDH, and D-dimer.

CK-MB, one of the three CK isoenzymes, is present in high concentrations in the myocardium although it can also be detected in the brain and the skeletal muscle [89]. The release of CK-MB in the circulation, and its consequent increase in serum concentrations, has been used for many years to diagnose myocardial necrosis and its clinical manifestations, e.g., myocardial infarction, until more sensitive and specific biomarkers, i.e., high-sensitivity troponin, were introduced in clinical practice [89,90]. The results of our meta-analysis might primarily reflect the presence of significant myocardial damage in COVID-19 patients with more compromised clinical presentations and high-risk of mortality. However, the associations observed in meta-regression indicate that the clinical information provided by CK-MB might complement, rather than duplicate, that of other cardiac biomarkers. While, not surprisingly, the CK-MB SMD was statistically significantly associated with troponin, myoglobin, and BNP, the additional associations observed suggest that the elevations of CK-MB in high-risk COVID-19 patients can also reflect a state of excess

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**Table 1.**

| Study Name | SMD (95% CI) | % Weight |
|------------|-------------|----------|
| Overall    | 0.67 (0.47, 0.87) | 100.00   |
| Subtotal   | 0.67 (0.47, 0.87) |          |
| Severe vs Nonsevere | 0.00 (0.03, 0.03) | 2.01     |
| Deng M et al. | 0.61 (0.40, 0.81) | 2.45     |
| Cao L et al. | 0.50 (0.10, 0.91) | 2.25     |
| Han H et al. | 0.39 (0.12, 0.66) | 2.37     |
| He B et al. | 1.03 (0.70, 1.39) | 2.30     |
| Lu Y et al. | 1.01 (0.58, 1.44) | 2.23     |
| Yang C et al. | 0.95 (0.63, 1.27) | 2.33     |
| Yang J et al. | 2.91 (2.45, 3.37) | 2.30     |
| Yao G et al. | 1.22 (0.60, 1.84) | 2.02     |
| Xu Z et al. | 0.07 (-0.13, 0.87) | 2.16     |
| Zhu Y et al. | 1.43 (0.96, 1.87) | 2.22     |
| Subtotal   | 1.14 (0.68, 1.60) | 2.20     |
| Survivor vs NonSurvivor | 0.16 (-0.45, 0.76) | 2.04     |
| Anadaj N et al. | 1.62 (1.10, 2.15) | 2.13     |
| Cao L et al. | 1.96 (1.72, 2.19) | 2.39     |
| Deng P et al. | 1.55 (1.22, 1.88) | 2.32     |
| Dong Y et al. | 0.67 (0.30, 1.04) | 2.28     |
| Gao S et al. | 0.82 (0.45, 1.19) | 2.28     |
| Guo H et al. | 0.12 (-0.25, 0.59) | 2.19     |
| Guo J et al. | 1.28 (0.78, 1.79) | 2.15     |
| Li Y et al. | 1.03 (0.00, 2.03) | 2.30     |
| Qin W et al. | 2.04 (1.58, 2.51) | 2.19     |
| Sun H et al. | 1.55 (1.01, 1.78) | 2.28     |
| Wang B et al. | 0.22 (-0.16, 0.61) | 2.27     |
| Wang JH et al. | 2.32 (2.04, 2.59) | 2.36     |
| Wang K et al. | 1.61 (1.12, 2.09) | 2.17     |
| Wang Z et al. | 1.07 (1.39, 1.79) | 2.30     |
| Xu et al. | 1.01 (0.58, 1.44) | 2.23     |
| Yang C et al. | 0.95 (0.63, 1.27) | 2.33     |
| Yang J et al. | 2.91 (2.45, 3.37) | 2.30     |
| Yao G et al. | 1.22 (0.60, 1.84) | 2.02     |
| Xu et al. | 0.07 (-0.13, 0.87) | 2.16     |
| Zhu Y et al. | 1.43 (0.96, 1.87) | 2.22     |
| Subtotal   | 1.14 (0.68, 1.60) | 2.20     |

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Fig. 6. Bubble plot reporting univariate meta-regression analysis between the month of recruitment commencement and SMD. Each study is represented by a circle (bubble) with the size area proportional to the study precision (the inverse of its within-study variance).

Fig. 7. Forest plot of studies examining CK-MB concentrations in patients with COVID-19 according to disease severity or survival status. The diamond represents the point estimate and confidence intervals after combining and averaging all individual studies. The vertical line through the vertical points of the diamond represents the point estimate of the averaged studies.
inflammation (WBC), single- and multi-organ damage (AST and LDH), and pro-thrombotic tendency (D-dimer). Notably, these biomarkers have, in turn, shown significant associations with COVID-19 severity and adverse outcomes [16,91].

4.1. Limitations of the study

The extreme heterogeneity observed between the studies, together with the exclusion of articles written in non-English language, e.g., Chinese, is a limitation of our meta-analysis. However, the trend and magnitude of the reported differences in CK-MB were maintained, in presence of a significantly reduced heterogeneity, in a sub-group of 10 studies that were homogeneous for endpoint, study design, country, and assay used. In addition, it is important to emphasize that there was no evidence of publication bias and that the overall effect size was not affected in sensitivity analyses. A number of unreported factors might have contributed to the heterogeneity, particularly the coexistence of rhabdomyolysis, reported in COVID-19 patients and a common cause of increased serum CK-MB concentrations [92–94], and the fact that virtually all selected studies reported a single measurement of CK-MB rather than serial assessments.

5. Conclusions

In conclusion, our updated systematic review and meta-analysis with meta-regression has shown that higher serum CK-MB concentrations are
significantly associated with worse clinical status and reduced survival in patients with COVID-19. Further research is warranted to establish the clinical utility of this biomarker, in conjunction with other patient characteristics, for early risk stratification and acute management in this group.

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The Author contribution
Study design: Angelo Zinellu.
Data collection: Angelo Zinellu.
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Manuscript preparation: Angelo Zinellu, Salvatore Sotgia, Alessandro Fois, Arduino Manogoni.
Literature search: Angelo Zinellu, Arduino Manogoni, Alessandro Fois.
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Declaration of competing interest
The authors declare no conflict of interests.

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A. Zinellu et al. Advances in Medical Sciences 66 (2021) 304–314

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