



Letter to the Editor

Elevated Creatine Kinase-MB Is an Independent Risk Factor for Mortality of COVID-19: Based on Adjusted Data



Quanman Hu, MBBS¹; Cheng Cheng, MM¹; Yang Li, BS¹; Guangcai Duan, MD, PhD^{1*}; Shuaiyin Chen, MD, PhD^{1*}

¹College of Public Health, Zhengzhou University, Zhengzhou, Henan, People's Republic of China

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Dear Editor,

We recently read an article titled “Cardiac Complications in COVID-19: A Systematic Review and Meta-analysis” published by Sahranavard et al¹ in the *Archives of Iranian Medicine*. The authors found that the combined incidence of myocardial injury in COVID-19 patients is 17.85% and the pooled level of unadjusted troponin-I was significantly higher in expired cases compared with the surviving. However, the author did not compare the level of creatine kinase-MB (CK-MB) between the survival group and the death group, and only calculated its incidence in COVID-19 patients. CK-MB was considered to be an important marker for the diagnosis of myocardial injury as same as troponin.² As Guo et al³ and Zhang et al⁴ reached different conclusions about the role of CK-MB in predicting the mortality of COVID-19, we conducted a meta-analysis based on adjusted data to settle the dispute and complement the research by Sahranavard et al.

We carried out an electronic search in PubMed, Web of Science and EMBASE until March 9, 2021. The keywords used for the search were (“Coronavirus Disease 2019” or “severe acute respiratory syndrome coronavirus 2” or “Corona Virus Disease 2019” or “2019 novel coronavirus” or COVID-19 or SARS-CoV-2 or 2019-nCoV) and (“Creatine Kinase-MB” or CK-MB). The titles and abstracts of the obtained articles were screened, and appropriate papers were downloaded. The inclusion and exclusion criteria were shown in [Figure S1](#) (see [Supplementary file 1](#)). The inclusion criteria were as follows: (1) The research must be observational without any intervention. (2) The object of the study was patients with COVID-19, and the outcome was death. (3) The sample size included in the study was not less than 50. (4) Research must be adjusted for confounding factors. The exclusion criteria were as follows: (1) Reviews, errata, comments and articles reporting other indicators or effects. (2) Incomplete data. (3) The connection between CK, CK-MB and the severity of COVID-19 was not reported. (4) Articles using univariate analysis. (5) Inconspicuous outcome effect. Effect estimates were presented as relative risk (RR) or hazard risk (HR) or odds ratio (OR) with 95% confidence interval (CI). The combined effect with 95% CI was estimated by fixed-effects model ($I^2 < 50\%$

in heterogeneity test) or random-effects model ($I^2 > 50\%$ in heterogeneity test). All analyses were performed using Stata 12.0 (Stata Corp, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

We identified 1313 studies using predefined search terms, and based on the strict inclusion and exclusion criteria, a total of 10 studies were included in this meta-analysis. All articles were assessed for quality according to the Newcastle Ottawa Scale (NOS).⁵ The results reported that the quality of all included articles was greater than 3 points and the specific characteristics are shown in [Table S1](#). The results of this meta-analysis revealed a significant link between elevated CK-MB and the mortality of COVID-19 on the basis of adjusted effect estimates (pooled effect = 2.24, 95% CI: 1.43–3.50; $I^2 = 90.7\%$, $P < 0.001$; random-effects model; [Figure 1a](#)). In order to explore the source of heterogeneity, we observed a result in the subgroup analyses by Male% (Male% ≥ 50 : pooled effect = 4.34, 95% CI: 2.34–8.05; $I^2 = 54.2\%$, $P = 0.088$; Male% < 50 : pooled effect = 1.10, 95% CI: 0.91–1.33, $I^2 = 56.5\%$, $P = 0.043$, [Figure 1c](#)). Sensitivity analysis indicated that our results were reliable and robust ([Figure 1b](#)). Publication bias was not found in Begg's test ($P = 0.283$, [Figure 1d](#)).

In the study by Sahranavard et al, the articles on troponin were based on crude effect estimates; among them, there would be some confounding factors that affected the troponin level in patients with COVID-19, such as gender, age, etc. However, the articles included in this study were all based on adjusted effect estimates, so our conclusions were more convincing.

In summary, this meta-analysis reported that elevated CK-MB was an important index in helping identify clinical outcomes of COVID-19 patients, and this could be used as a supplement to the study by Sahranavard et al. Nevertheless, this meta-analysis had a high degree of heterogeneity, although it was found through subgroup analysis that the sex ratio may be the source of heterogeneity. More articles were needed to improve this research.

Authors' Contribution

All authors report that they have no potential conflict of interest.

*Corresponding Authors: Shuaiyin Chen, PhD; Department of Epidemiology, College of Public Health, Zhengzhou University, No. 100 Kexue Avenue, Zhengzhou, Henan Province 450001, China, Email: sychen@zzu.edu.cn; Guangcai Duan, College of Public Health, Zhengzhou university, Zhengzhou, Henan, People's Republic of China. Email: gcduan@zzu.edu.cn

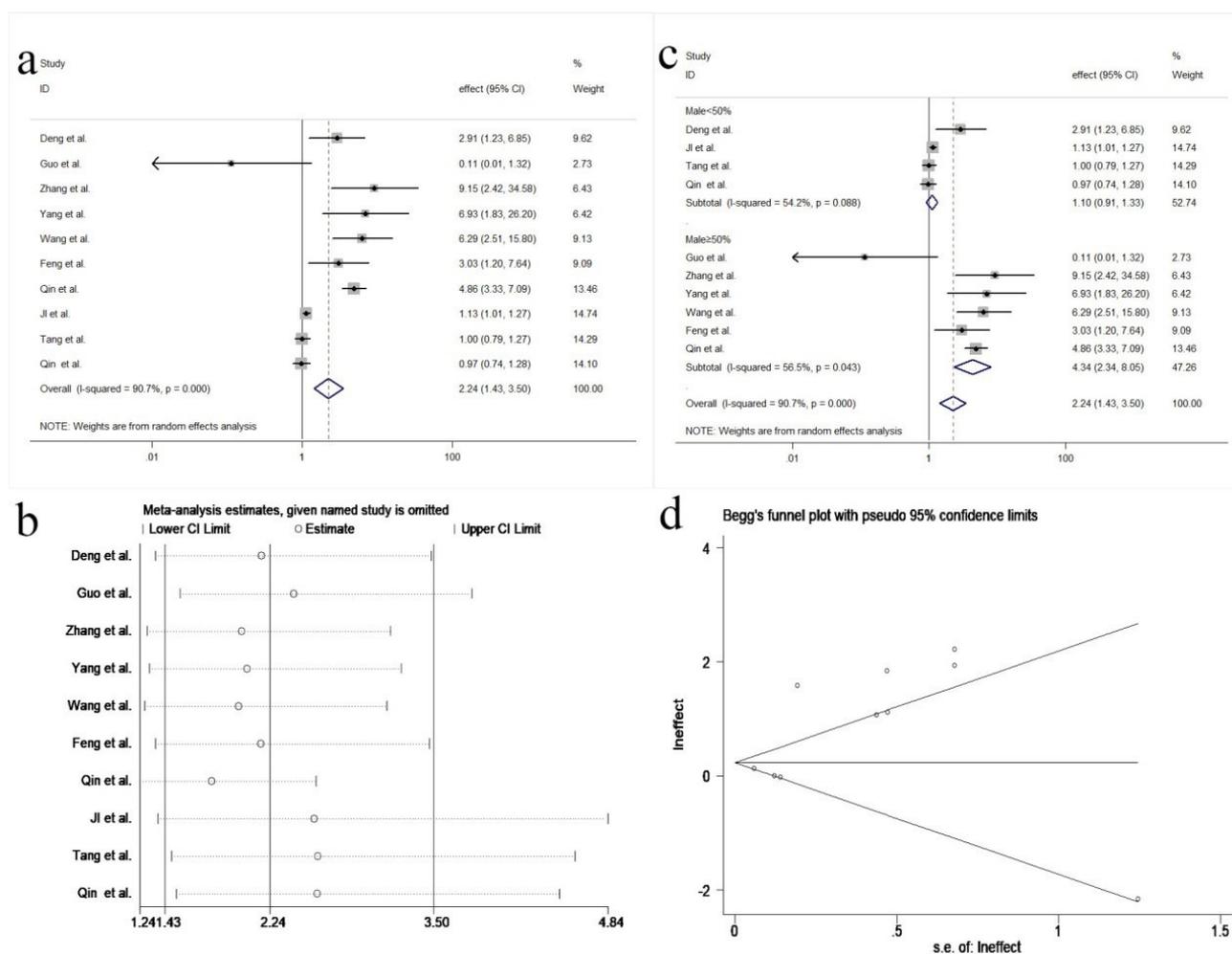


Figure 1. (a) Forest plot; (b) Sensitivity analysis; (c) Subgroup analysis on male%; (d) Begg's test.

Authors' Contribution

SC conceptualized the study. QH and CC performed literature search and extracted the data. YL and QH analyzed the data. QH wrote and GD reviewed the manuscript. All the authors approved the final version of this manuscript.

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Supplementary Materials

Supplementary file 1 contains Table S1 and Figure S1.

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