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## Meta-Analysis of Relation of Creatine kinase-MB to Risk of Mortality in Coronavirus Disease 2019 Patients



A published paper by Dr. Li and colleagues<sup>1</sup> revealed that the elevated levels

of creatine kinase-MB (CK-MB) were associated with the severity of coronavirus disease 2019 (COVID-19) patients. Recently, several emerging papers have focused on the association of the CK-MB levels with the risk of mortality in COVID-19 infected patients. However, the conclusions drawn from different studies are inconsistent.<sup>2-4</sup> In order to obtain a definitive conclusion on the association between the levels of CK-MB and the risk of mortality in COVID-19 patients, a quantitative meta-analysis was conducted on the basis of published data.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was strictly enforced throughout the design and implementation of this meta-analysis.<sup>5</sup> Chinese National Knowledge Infrastructure, Web of Science and PubMed databases were extensively searched by 2 of the authors (Li Shi and Ying Wang) prior to May 5, 2020 with the following keywords: "characteristics," "clinical," "laboratory," "SARS-CoV-2," "2019-nCoV," "COVID-19," "coronavirus 2019," "outcome," "death," and "mortality." The mean and standard deviation could be estimated by sample size, median and interquartile range according to Wan et al's paper.<sup>6</sup> The screening criterion was that studies provided mean (standard deviation) or median (interquartile range) for levels of CK-MB in both non-survival and survival COVID-19 infected patients. The pooled standardized mean difference and 95% confidence interval were used to assess the effect sizes, since the units of CK-MB are different among the eligible studies.<sup>7</sup> We chose different models based on the incongruity index ( $I^2$ ;  $I^2 < 50\%$  for the fixed-effects model;  $I^2 \geq 50\%$  for the random-effects model).<sup>8</sup> In addition, sensitivity analysis was performed by sequentially omitting single study to test the stability of our final results.<sup>9</sup> The potential presence of publication bias was examined by Begg's regression test and Egger's linear regression test.<sup>10,11</sup> All statistical analyses were

conducted by using the Stata 11.2 software package (StataCorp, College Station, Texas).  $p < 0.05$  was regarded as statistical significance.

Five studies performed in China were finally included in this meta-analysis through detailed screening of 1,630 studies. A total of 1,170 COVID-19 infected patients including 280 non-survivors and 890 survivors were from the First People's Hospital of Jiangxia District,<sup>3</sup> Renmin Hospital,<sup>12</sup> Tongji hospital,<sup>13</sup> Jinyintan Hospital,<sup>4</sup> Zhongnan Hospital and Xishui Hospital.<sup>2</sup> More details of the included studies are demonstrated in Table 1.

Due to the high heterogeneity ( $I^2 = 86\%$ ,  $p < 0.001$ ), we chose a random-effects model to conduct this synthetic analysis. The overall results showed that the elevated levels of CK-MB were significantly associated with an increased risk of the mortality in COVID-19 infected patients (standardized mean difference 0.99; 95% confidence interval 0.57 to 1.42;  $p < 0.001$ ; Figure 1). As indicated in Figure 1, no single study was found to have obvious effects on the overall results, which suggests the stability of our results. As for the publication bias, both Begg's test ( $p = 0.806$ ) and Egger's test ( $p = 0.642$ ; Figure 1) exhibited that there was no publication bias in our present meta-analysis.

Patients with severe pneumonia have varying degrees of myocardial injury due to hypoxemia and toxicity of the pathogen.<sup>14-16</sup> So do patients with COVID-19.<sup>1,17,18</sup> CK-MB mainly exists in the outer plasma layer of myocardial cells, and is the most specific enzyme in the myocardial enzyme spectrum for clinical diagnosis of myocardial injury.<sup>19,20</sup> A previous meta-analysis by Li et al observed that the elevated CK-MB levels were associated with the severity of COVID-19 patients.<sup>1</sup> Our present meta-analysis suggests that the elevated levels of CK-MB were significantly associated with an increased risk of the mortality in COVID-19 infected patients.

Table 1  
Characteristics of the included studies

Author	Location	Case	Nonsurvival patients				Survival patients			
			n	Age (years)	Male	creatinine kinase-MB	n	Age (years)	Male	Creatinine kinase-MB
Wang D et al. <sup>2</sup>	China	107	19	73.0 (64.0-81.0)	16 (84%)	18 (13-44) U/L	88	44.5 (35.0-58.8)	41 (47%)	13 (9-16) U/L
Wang K et al. <sup>3</sup>	China	296	19	65.6±12.6	11 (58%)	17.5 (16.7-28.1) U/L	277	46.0±14.4	129 (47%)	13.5 (11.4-17.1) U/L
Wang L et al. <sup>12</sup>	China	339	65	76 (70-83)	39 (60%)	2.95 (1.30-4.30) ng/mL	274	68 (64-74)	127 (46%)	1.15 (0.81-1.91) ng/mL
Wang Y et al. <sup>13</sup>	China	344	133	70 (62-77)	74 (56%)	2.5 (1.2-6.1) ng/mL	211	57 (47-69)	105 (50%)	0.4 (0.3-1.2) ng/mL
Wu C et al. <sup>4</sup>	China	84	44	68.5 (59.3-75.0)	29 (66%)	17.00 (13.00-20.00) U/L	40	50.0 (40.3-56.8)	31 (78%)	16.00 (13.00-20.75) U/L

All values are n (%), median (IQR), or mean ± SD.

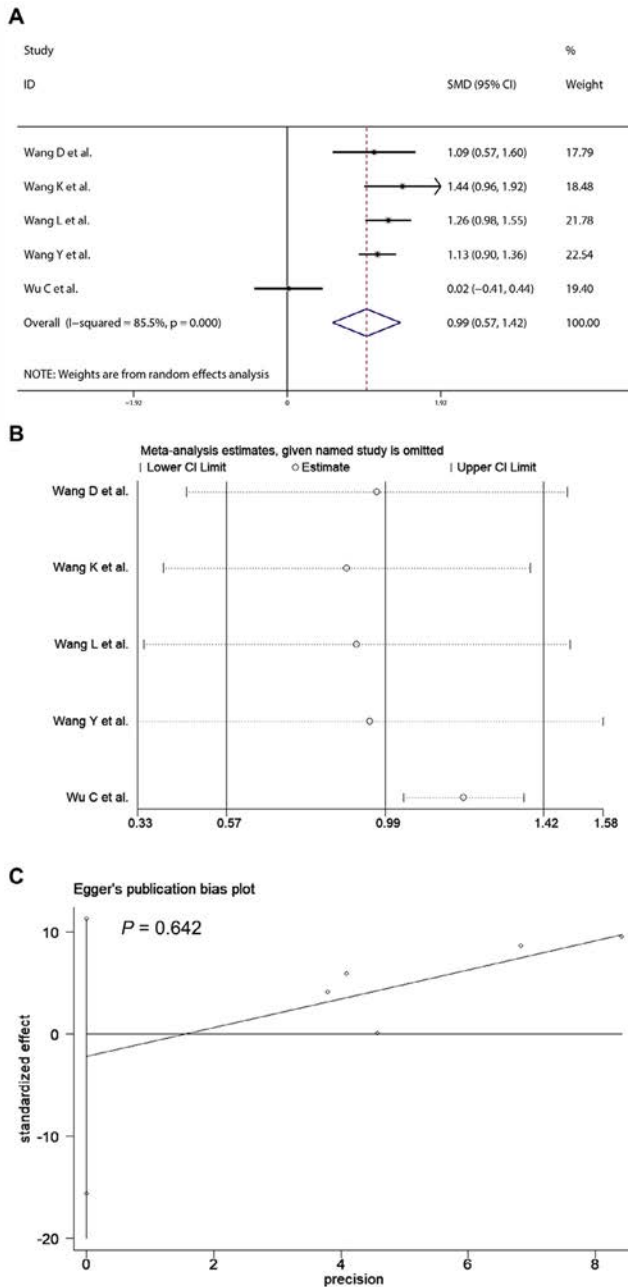


Figure 1. Forest plot (A), sensitivity analysis (B) and Egger's test (C) of creatine kinase-MB levels in non-survival COVID-19 patients vs. survival COVID-19 patients.

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12 May 2020

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## Tendonopathy Due to Simvastatin and Ezetimibe, Amyloidosis or Both?



We reported in 2007 in *AJG* a patient with rupture of his left biceps tendon when lifting a box out of his car 4 months after starting the combination of simvastatin (20 mg) and ezetimibe (10 mg).<sup>1</sup> The tendon was surgically repaired. He was restarted on the combination of simvastatin (10 mg) and ezetimibe (10 mg) 2 months after the repair and promptly developed right biceps tendinitis. We attributed his tendonopathy to the combination of statin and ezetimibe and raised the possibility that statins caused tendonopathy by reducing matrix metalloproteinase activity.<sup>1</sup> Matrix metalloproteinases are required to cleave and clear damaged collagen as part of tendon repair.<sup>1</sup>

This patient was seen recently for evaluation of “hypertrophic cardiomyopathy” diagnosed by echocardiography. His echocardiogram showed normal left ventricular (LV) systolic function and global longitudinal strain, biatrial enlargement, and diastolic LV septal and posterior wall thicknesses of 1.8 and 1.4 cm, respectively. He was asymptomatic and had no history of hypertension or familial hypertrophic cardiomyopathy. His ECG did not show LV hypertrophy. Because transthyretin amyloidosis (ATTR) can cause biceps tendon rupture years before symptomatic cardiomyopathy,<sup>2</sup> we obtained a technetium-99m pyrophosphate cardiac amyloidosis scan which showed diffuse uptake, consistent with ATTR cardiac amyloidosis. Subsequent serum and urine testing showed no evidence of a monoclonal gammopathy, excluding AL amyloidosis, and genetic testing was negative for hereditary ATTR amyloid. The patient has been started on Tafamidis 61 mg daily.

We update this case to attribute less responsibility for the patient’s tendonopathy to the statin/ezetimibe treatment. This case illustrates the importance of considering amyloidosis in even asymptomatic patients with increased cardiac wall thickness especially if they have a history of tendonopathy. This case also raises the question of whether statins increase tendonopathies in patients with tendon amyloidosis.

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26 May 2020

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<https://doi.org/10.1016/j.amjcard.2020.06.005>

## Statins in primary prevention of cardiovascular disease – should we start while young and healthy?



Recently published meta-analysis by Kostis et al. indicates a definite, statistically significant and clinically relevant benefit of statin treatment for primary prevention of atherosclerotic cardiovascular disease (CVD) in elderly persons (>75 years of age).<sup>1</sup> However, it also prompts a question about the optimal time for initialization of such a treatment in primary CVD prevention. Atherogenesis often begins in childhood, with the rate of plaque progression and occurrence of CVD events depending on the present CVD risk factors, primarily plasma level and duration of exposure to LDL-C.<sup>2,3</sup> Higher LDL-C value at younger age is predictive for atherosclerotic disease later in life, independently of subsequent LDL-C values.<sup>2</sup> In almost 70% of the general population, with decades of exposure to borderline or slightly elevated LDL-C levels, the risk of atherosclerotic disease is 3–4 times higher than in people

who have had decades of low LDL-C levels.<sup>2</sup> Finally, even when the increased levels of LDL-C were significantly reduced at later age with the use of statins, the risk of atherosclerotic disease remained significant.<sup>2</sup> At the same time, early intervention to significantly lower LDL-C levels may substantially reverse, or even eradicate, earlier stages of atherosclerosis.<sup>3</sup> Moreover, numerous evidence suggest that the atherosclerotic process would not occur if LDL-C levels were <50 mg/dl.<sup>3</sup>

In recently published study, early subclinical atherosclerosis was detected in 61.8% of apparently healthy middle-aged (40–54 years old) men and women and its progression was observed in ~40% of participants over a 3-year follow-up, even in those with low CVD risk; during the same period 31.2% of previously disease-free individuals developed atherosclerotic changes. Dyslipidemia was confirmed as the strongest modifiable independent predictor of onset and short-term atherosclerosis progression.<sup>4</sup> In light of these data, it can be expected that without lipid lowering therapy, majority of people will develop manifest CVD or will have clinically silent advanced calcified atherosclerotic lesions by the time they reach age >75 years. On the other hand, even the intensive statin therapy has significantly weaker effect on more advanced atherosclerotic lesions and, also, the statin-associated CVD risk reduction is achieved after in average 5 years of therapy.<sup>2,5</sup> Evidence suggest that despite a successful reduction in CVD events accomplished in patients with atherosclerotic diseases treated with intensive statin therapy, their incidence in this patient population is still significantly higher than that seen in individuals with long-standing low LDL-C levels.<sup>2</sup> Therefore, although elderly people with additional risk factors and no known CVD may benefit from statin treatment, the onset of statin administration in senior age did not provide maximal preventive effect and their application was nevertheless overdue. It is clear that initiation of statin therapy as primary CVD prevention should start much earlier, in men at the latest between 30 and 40 years of age, in women in the perimenopause or early menopause, because long-term exposure even to LDL-C values for which current guidelines do not