An updated meta-analysis of AST and ALT levels and the mortality of COVID-19 patients

To the Editor,

With great interest, we read the recent paper titled "Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data" by Martins-Filho et al. published in the European Journal of Internal Medicine [1]. This study is extremely interesting. The authors observed that several biomedical markers such as albumin, blood urea nitrogen, creatinine, creatinine kinase, hypersensitive cardiac troponin I (hs-cTnI) and lactate dehydrogenase (LDH) were positively associated with the risk of mortality in coronavirus disease 2019 (COVID-19) patients based on four published studies. But the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were not observed to be associated with the risk of mortality in COVID-19 patients. Recently, some emerging papers are reporting the association of AST and ALT with the risk of mortality in COVID-19 patients, so an updated meta-analysis was performed on the basis of the last data. We hope that our results will provide comprehensive evidence for the association between AST and ALT levels and the risk of mortality in COVID-19 patients.

An electronic search was conducted in PubMed, Web of Science and China National Knowledge Infrastructure (CNKI) until April 30, 2020, using the keywords: (("coronavirus" or "COVID-19" or "SARS-CoV-2" or "2019-nCoV") and ("laboratory" or "clinical") and ("mortality" or "outcome")). Articles reporting AST and ALT levels for both non-survival and survival COVID-19 patients were included. Articles with potential overlapping reports were excluded (by checking the hospital where the patients came from, the author's organization and other information). The mean and standard deviation were estimated using the sample size, median and interquartile range (IQR) [2]. The pooled effects were presented as standardized mean difference (SMD) and 95% confidence interval (CI). Heterogeneity was checked using the I^2 statistic. We used Stata 11.2 (StataCorp, College Station, TX) to perform the analysis, and $P < 0.05$ was considered significant.

We found a total of 966 records, and 741 remained after the removal of duplicates. 42 remained after reading the title and abstract. After reading the full texts, we excluded 35 studies that did not report AST or ALT levels for both non-survival and survival COVID-19 patients, or reported patients may overlap with other articles. Finally, seven eligible studies were enrolled in this meta-analysis [3-9]. Data were collected from patients admitted to Jinyintan Hospital, Hankou and Caidian branch of Tongji Hospital, Hankou branch of Central Hospital of Wuhan, Tongji Hospital, Renmin Hospital, Zhongnan Hospital, and Xishui Peoples Hospital. The basic characteristics of the included studies are shown in Table 1.

All the studies we included were from China, with a total of 1370 COVID-19 patients. We observed there was a significant association between the elevated AST levels and an increased risk of mortality in COVID-19 patients (SMD = 0.75, 95% CI: 0.33–1.17, $P < 0.001$; $I^2 =$ 89.9%, $P = 0.000$) using a random-effects model (Fig. 1A). The ALT values showed similar result (SMD = 0.35, 95% CI: 0.13–0.57, $P =$ 0.002; $I^2 = 70.4\%$, $P = 0.002$) (Fig. 1B). The results of the leave-one-out sensitivity analysis indicated any single study had no obvious effects on the combined SMD, suggesting our results were robust (Fig. 1C and D). Begg's test (All $P > 0.05$) and Egger's test (All $P > 0.05$) suggest no significant publication bias.

Table 1
Characteristics of the included studies.

Author	Location	Cases	Non-survival patients					Survival patients				
			n	Age (IQR)	Male	ALT (U/L)	AST (U/L)	n	Age (IQR)	Male	ALT (U/L)	AST (U/L)
Zhou Fei et al. (PMID: 32171076)	China	191	54	69 (63–76)	38 (70%)	40 (24–51)	NR	137	52 (45–58)	81 (59%)	27 (15–40)	NR
Ruan Qiurong et al. (PMID: 32253449)	China	150	68	67 (15–81)	49 (72%)	170.8 ± 991.6	288.9 ± 1875.5	82	50 (44–81)	53 (65%)	48.68 ± 83.1	40.7 ± 57.8
Deng Yan et al. (PMID: 32209890)	China	225	109	69 (62–74)	73 (67%)	22 (15–34)	34 (27–47)	116	40 (33–57)	51 (44%)	18.7 (13–30.38)	22 (17.65–31.75)
Wu Chaomin et al. (PMID: 32167524)	China	84	44	68.5 (59.3–75)	29 (66%)	39 (20.5–52.5)	37 (30–52)	40	50 (40.3–56.8)	31 (78%)	35 (23.25–55.25)	38.5 (32.25–57.25)
Chen Tao et al. (PMID: 32217556)	China	274	113	68 (62–77)	83 (73%)	28 (18–47)	45 (31–67)	161	51 (37–66)	88 (55%)	20 (14.8–32)	25 (20—33)
Wang Lang et al. (PMID: 32240670)	China	339	65	76 (70–83)	39 (60%)	24 (19–49)	43 (30–68)	274	68 (64–74)	127 (46%)	28 (17–43)	29 (22–43)
Wang Dawei et al. (PMID: 32354360)	China	107	19	73 (64–81)	16 (84%)	47 (22–66)	67 (38–90)	88	44.5 (35–58.8)	41 (47%)	22 (15–34)	29 (23–41)

All values are n (%), median (IQR), or mean ± SD; ALT, alanine transaminase; AST, aspartate transaminase; NR, not reported.
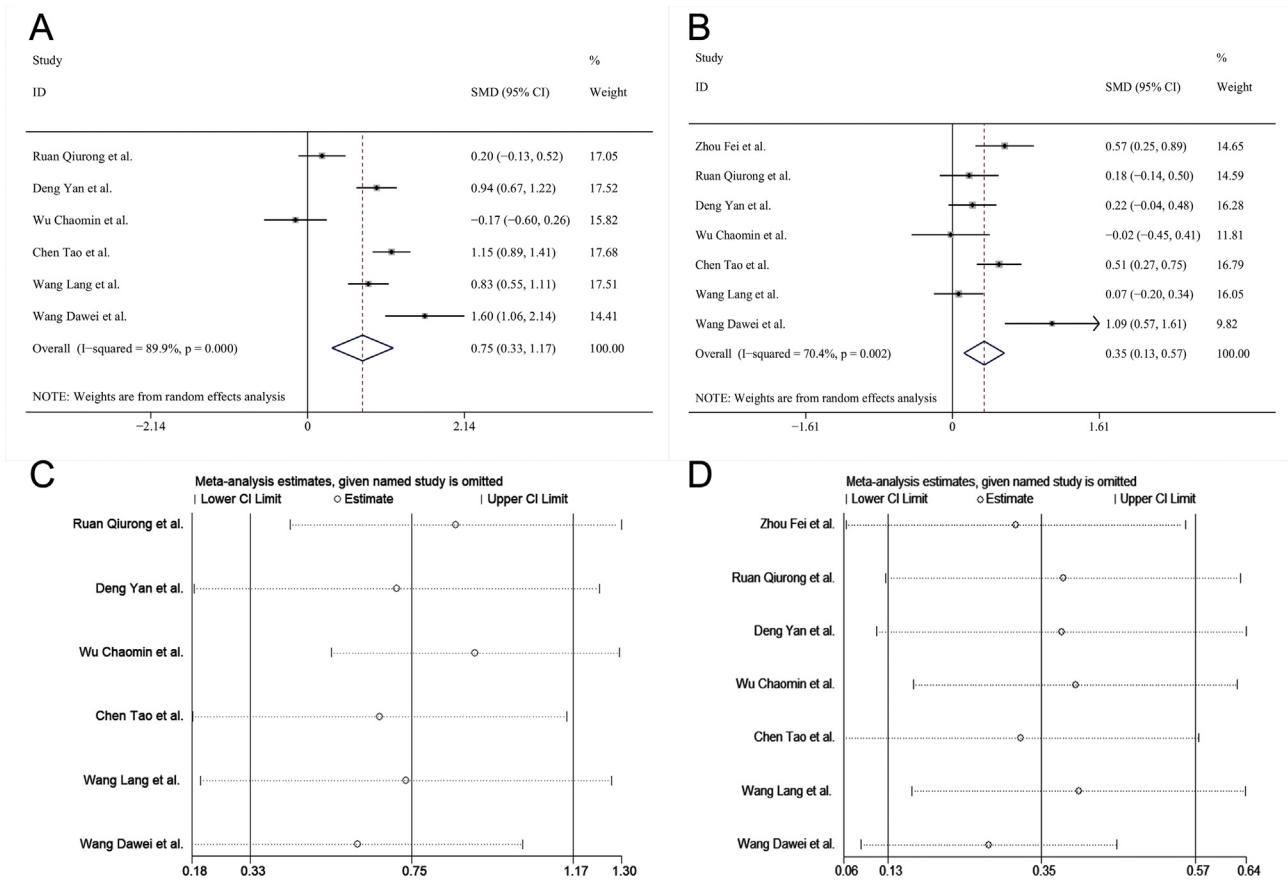
Fig. 1. Standardized mean difference and 95% confidence interval (CI) of aspartate aminotransferase (AST) (A) and alanine aminotransferase (ALT) (B), and sensitivity analysis for AST (C) and ALT (D) between non-survival and survival coronavirus disease 2019 patients by random-effects model.

In summary, AST and ALT should be considered as predictors of clinical outcomes such as mortality in COVID-19 patients based on the last data. To reach a definitive conclusion, more studies with large sample size are needed to validate the association between the levels of AST and ALT and the risk of mortality in COVID-19 patients in the future.

Declaration of competing interest

None.

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Ying Wang
Li Shi
Department of Epidemiology, School of Public Health, Zhengzhou University, Zhengzhou 450001, China

Yadong Wang
Department of Toxicology, Henan Center for Disease Control and Prevention, Zhengzhou 450016, China

Haiyan Yang
Department of Epidemiology, School of Public Health, Zhengzhou University, Zhengzhou 450001, China
Corresponding author at: Department of Epidemiology, School of Public Health, Zhengzhou University, No. 100 of Science Avenue, Zhengzhou 450001, China.
E-mail address: yhy@zzu.edu.cn

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