

LETTER TO THE EDITOR

Albumin and total bilirubin for severity and mortality in coronavirus disease 2019 patients

To the Editor,

The novel coronavirus disease 2019 (COVID-19) has given rise to a worldwide pandemic. As of May 15, 2020, according to the latest data report from the World Health Organization, there have been 4 338 658 confirmed cases worldwide, resulting in 297 119 deaths.¹ Previous papers have reported the abnormalities of albumin values and total bilirubin values among COVID-19 patients.² We aimed to investigate the differences in albumin values and total bilirubin values in the progression of COVID-19 patients and to provide evidence for clinical treatment.

The databases of PubMed, Web of Science, and medRxiv were searched for related studies up to May 16, 2020. Search terms included the keywords: ([“coronavirus” or “COVID-19” or “SARS-CoV-2” or “2019 nCoV”] and “laboratory”). There is no language restriction. Articles were screened by title, abstract, and full texts for the data. All articles that reported information on the albumin values or total bilirubin values in COVID-19 patients with or without the severe disease (ie, ICU admission or acute respiratory distress syndrome) or between non-survivors and survivors were included. The I^2 test was applied to assess the statistical heterogeneity among studies. The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated to estimate the pooled effects of albumin values. The standardized mean difference (SMD) and 95% CI were calculated to estimate the pooled effects of total bilirubin values owing to different detection methods and data representation unit among studies.³ The sample size, median, and interquartile range (IQR) were used to estimate the mean and standard deviation.⁴ Egger's and Begg's tests were used to assess the publication bias. All statistical analyses were conducted using *Stata* 11 (*StataCorp*) software package, and $P < .05$ was considered significant.

Initially, a total of 2165 studies were identified in the search. By reading titles and abstracts, 2077 studies were excluded. By reading the full texts, 64 studies were excluded owing to that they did

not report albumin values or total bilirubin values. At last, 24 studies were enrolled in our meta-analysis.⁵⁻²⁸ The main characteristics of the included studies are shown in Table 1.

A total of 2948 COVID-19 patients, totaling in 24 studies, reported albumin values or total bilirubin values, of these, 1713 patients in 17 studies were divided into severe and non-severe groups, and 1319 patients in 8 studies were divided into non-survival and survival groups. The pooled WMD indicated that the albumin values were significantly lower in COVID-19 patients with the severe disease than in those without by using a random-effects model (WMD = -4.39 g/L, 95% CI: -5.64 , -3.15 ; $P < .001$; $I^2 = 70.2\%$, $P = .001$) (Figure 1A). The result of SMD showed that total bilirubin values were considerably higher in COVID-19 patients with the severe disease than in those without by using a fixed-effects model (SMD = 0.51 , 95% CI: 0.36 , 0.66 ; $P < .001$; $I^2 = 10.9\%$, $P = .343$) (Figure 1B). The changes of albumin levels and total bilirubin levels in non-survival patients versus survival patients were similar to that in severe patients versus non-severe patients by using a random-effects model (Albumin WMD = -4.06 g/L, 95% CI: -4.98 , -3.14 ; $P < .001$; $I^2 = 49.2\%$, $P = .096$. Total bilirubin SMD = 0.71 , 95% CI: 0.50 , 0.91 ; $P < .001$; $I^2 = 38.6\%$, $P = .149$) (Figure 1C,D). No publication bias was found by Egger's test (all $P > .05$) and Begg's test (all $P > .05$).

Our results demonstrated that there were significant differences in albumin values and total bilirubin values in COVID-19 patients with varying degrees of disease severity, suggesting that alterations in these two biomarkers' values can predict changes in the patients' condition. Besides, studies have shown that patients with COVID-19 have elevated alanine aminotransferase and aspartate aminotransferase values,²⁹ suggesting that patients with COVID-19 may have liver damage. Our results also supported this notion that COVID-19 infection could cause liver damage in other aspects to a certain extent. However, the majority of patients in the included studies came from China, and the sample size was limited. Further analyses including more studies are needed to verify our findings.

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TABLE 1 Characteristics of the included studies

Author	Location	Age	Male	Severe/non-survival			Non-severe/survival		
				n	Albumin (g/L)	Total bilirubin	n	Albumin (g/L)	Total bilirubin
Peng Yudong et al ⁵	China	62 (median)	53 (47.3)	16	NR	13.05 (mmol/L) (9.4-16.65)	96	NR	11.4 (mmol/L) (8.7-14.8)
Mo Pingzheng et al ⁶	China	54 (median)	86 (55.5)	85	36 (32-40)	NR	70	39 (36-42)	NR
Huang Chaolin et al ⁷	China	49 (median)	30 (73.2)	13	27.9 (26.3-30.9)	14 (mmol/L) (11.9-32.9)	28	34.7 (30.2-36.5)	10.8 (mmol/L) (9.4-12.3)
Qian Guoqing et al ⁸	China	50 (median)	37 (40.7)	9	38.55 (36.33-39.25)	NR	82	40.2 (38-42.4)	NR
Wu Chaomin et al ⁹	China	51 (median)	128 (63.7)	84	30.4 (27.15-33.35)	12.9 (mg/dL) (9.5-17.05)	117	33.7 (30.95-36.3)	10.5 (mg/dL) (8.6-13.65)
Liu Yanli et al ¹²	China	55 (median)	59 (54.1)	53	NR	10.5 (mmol/L) (6.2-14.8)	56	NR	8.3 (mmol/L) (6.8-11.7)
Li Jie et al ¹¹	China	45.1 (mean)	9 (52.9)	12	NR	19.3 (mmol/L) ± 14.8	5	NR	12.2 (mmol/L) ± 4.8
Liu Jing et al ¹³	China	48.7 (mean)	15 (37.5)	13	NR	13.2 (μmol/L) ± 5.5	27	NR	8.8 (μmol/L) ± 4.1
Liu Jingyuan et al ¹⁰	China	40 (median)	31 (50.8)	17	43 (37-45.5)	NR	44	44 (41-47)	NR
Huang Huang et al ¹⁴	China	44.87 (mean)	63 (50.4)	32	33.49 ± 4.79	NR	93	39.83 ± 4.49	NR
Liu Min et al ¹⁵	China	35 (mean)	10 (33.3)	4	35 ± 1.1	NR	26	42 ± 3.4	NR
Liu Wei et al ¹⁶	China	38 (median)	39 (50.0)	11	36.62 ± 6.6	NR	67	41.27 ± 4.55	NR
Ling Yun et al ¹⁷	China	49.9 (mean)	154 (52.7)	21	35.8 ± 4.6	NR	271	40.9 ± 3.8	NR
Wang Dawei et al ²⁸	China	56 (median)	75 (54.3)	36	NR	11.5 (mmol/L) (9.6-18.6)	102	NR	9.3 (mmol/L) (8.2-12.8)
Wang Feng et al ¹⁸	China	68.6 (mean)	21 (75.0)	14	NR	15.8 (μmol/L) ± 6.8	14	NR	9.1 (μmol/L) ± 3.6
Zheng F. et al ¹⁹	China	45 (median)	80 (49.7)	30	NR	12.7 (μmol/L) (9.2-16.9)	131	NR	10.7 (μmol/L) (8.18-15.3)
Lei Shaoqing et al ²⁰	China	55 (median)	14 (41.2)	15	NR	13.0 (μmol/L) (9.1-19.2)	19	NR	8.1 (μmol/L) (6.5-12.9)
Yang Xiaobo et al ²¹	China	59.7 (mean)	35 (67.0)	32	NR	19.5 (μmol/L) ± 11.6	20	NR	13.1 (μmol/L) ± 4.3
Zhou Fei et al ²²	China	56 (median)	119 (62.0)	54	29.1 (26.5-31.3)	NR	137	33.6 (30.6-36.4)	NR
Ruan Qiurong et al ²³	China	NR	102 (68.0)	68	28.8 ± 3.8	18.1 (μmol/L) ± 10.7	82	32.7 ± 3.8	12.8 (μmol/L) ± 6.8
Wang Yang et al ²⁴	China	64 (median)	179 (52.0)	133	31 (28-34)	12.9 (mmol/L) (9.8-19.2)	211	36 (33-39)	8.5 (mmol/L) (6.3-11.3)
Wu Chaomin et al ⁹	China	58.5 (median)	60 (71.4)	44	29.1 (26.2-31.55)	14.5 (mg/dL) (10.35-19.8)	40	31.35 (27.7-34.2)	11.65 (mg/dL) (9.33-15.15)
Tomlins Jennifer et al ²⁵	US	75 (median)	60 (63.0)	20	30 (24-32)	NR	75	32 (27-36)	NR
Wang Dawei et al ²⁶	China	51 (median)	57 (53.3)	19	NR	11.3 (mmol/L) (9.4-20.7)	88	NR	9.5 (mmol/L) (8.4-12.9)
Wang Kun et al ²⁷	China	NR	140 (47.3)	19	NR	10.2 (μmol/L) (5.9-17)	277	NR	8.2 (μmol/L) (5.5-11.8)

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

Abbreviation: NR, not reported.

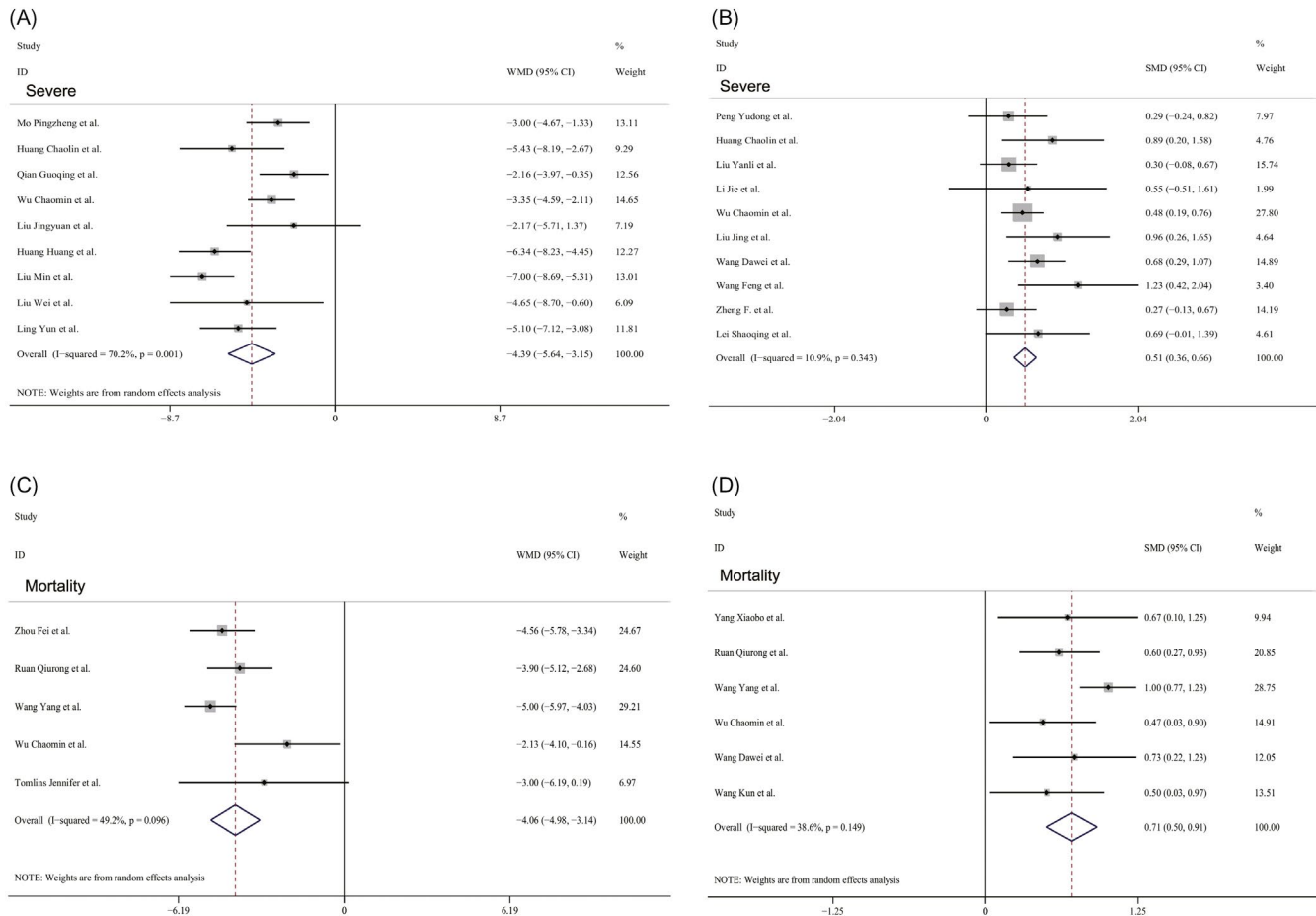


FIGURE 1 Forest plots of albumin values (A) and total bilirubin values (B) in severity patients with COVID-19, and forest plots of albumin values (C) and total bilirubin values (D) in mortality patients with COVID-19

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