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Review Article

Liver injury is associated with severe coronavirus disease 2019 (COVID-19) infection: A systematic review and meta-analysis of retrospective studies

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The coronavirus disease 2019 (COVID-19) outbreak is a major threat to human beings. Lung injury has been reported as the major outcome of COVID-19 infection. However, liver damage has also been considered to occur in severe cases. The current meta-analysis of retrospective studies was carried out to summarize available findings on the association between liver injury and severity of COVID-19 infection. Online databases including PubMed, Scopus, Web of Science, and Cochrane Library were searched to detect relevant publications up to 1 April 2020, using relevant keywords. To pool data, a fixed- or random-effects model was used depending on the heterogeneity between studies. Furthermore, publication bias test and sensitivity analysis were also applied. In total, 20 retrospective studies with 3428 COVID-19 infected patients (severe cases, n =1455; mild cases, n =1973), were included in this meta-analysis. Higher serum levels of aspartate aminotransferase (weighted mean difference, 8.84 U/L; 95% confidence interval [CI] 5.97 to 11.71; P <0.001), alanine aminotransferase (weighted mean difference, 7.35 U/L; 95% CI, 4.77 to 9.93; P <0.001), total bilirubin (weighted mean difference, 2.30 mmol/L; 95% CI, 1.24 to 3.36; P <0.001), and lower serum levels of albumin (weighted mean difference, −4.24 g/L; 95% CI, −6.20 to −2.28; P <0.001) were associated with a significant increase in the severity of COVID-19 infection. The incidence of liver injury, as assessed by serum analysis (aspartate aminotransferase, alanine aminotransferase, total bilirubin, and albumin levels), seems to be higher in patients with severe COVID-19 infection.

Key words: COVID-19, liver, meta-analysis, novel coronavirus, SARS-CoV-2

INTRODUCTION

IN DECEMBER 2019, a cluster of severe acute respiratory syndrome (SARS), now known as coronavirus disease 2019 (COVID-19), occurred in Wuhan, the capital of Hubei Province, China.[1–3] The disease has rapidly spread from China to other countries. As of 4 April 2020, a total of 1 051 635 COVID-19 confirmed cases and 56 985 deaths in 206 countries and territories have been reported.[4] Full-genome sequencing indicated that COVID-19 is a distinct clade from the beta-coronaviruses associated with human SARS and Middle East respiratory syndrome (MERS).[5]

Severe acute respiratory syndrome, MERS, and COVID-19 can cause intestinal, respiratory, neuronal, and hepatic diseases, and could lead to respiratory distress syndrome, organ failure, and even death in severe cases.[5–7] Several studies have reported the clinical characteristics and laboratory findings associated with different degrees of liver injury in patients with COVID-19 infection.[8–27] We are not aware of any meta-analysis that summarized available findings in this regard. Thus, in this systematic review and meta-analysis, the laboratory findings and mechanism of liver injury caused by COVID-19 infection were summarized.

METHODS

Study protocol

A SYSTEMATIC SEARCH of published works and a quantitative meta-analysis were planned, carried out,

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and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[28]

Search strategy

We undertook a search of published works using the online databases of PubMed, Scopus, Web of Science, and Cochrane Library for relevant publications up to 1 April 2020. The following medical subject headings (MeSH) and non-MeSH keywords were used in our search strategy: ("COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "novel coronavirus" OR "2019-nCoV") AND ("alanine transaminase" OR "alanine aminotransferase" OR "SGPT" OR "aspartate aminotransferase" OR "SGOT" OR "bilirubin" OR "serum albumin" OR "liver"). The search was undertaken by two reviewers (MP and SY). We also searched the reference lists of the articles to identify missed studies. No restriction was applied on time of publication or language. To facilitate the screening process of studies from online databases, all search results were downloaded into an EndNote library (version X8; Thomson Reuters, Philadelphia, PA, USA). The search strategy is presented in detail in Table S1.

Eligibility criteria

Studies were included if they met the following inclusion criteria: (i) observational studies with retrospective design; (ii) all articles assessing the association between serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, bilirubin, and severe outcome from COVID-19 infection as the major outcomes of interest and reported mean (standard deviation [SD]) or median (interquartile range [IQR]) for serum levels of AST, ALT, albumin, and bilirubin in both severe and non-severe COVID-19 infected patients. Expert opinion articles, review articles, books, and theses were excluded.

Data extraction and assessment for study quality

Two reviewers (MP and AS) extracted the following data from the studies: author's name, publication year, study design, sample size, age and gender of patients, serum levels of AST, ALT, albumin, and bilirubin, and outcome assessment methods.

The Newcastle–Ottawa Scale (NOS) was used for assessing the quality of the included studies.[29] Based on the NOS, a maximum of nine points can be awarded to each article. In this review, studies with a NOS score of ≥5 were considered as high quality publications.

Statistical analysis

Mean (SD) or median (IQR) for serum levels of AST, ALT, albumin, and bilirubin were used to estimate the effect size. The fixed or random-effect model was used based on the heterogeneity test. Heterogeneity between studies was evaluated using the Cochrane Q test.[30] Publication bias was evaluated by the visual inspection of funnel plot and Egger's regression tests.[31] The sensitivity analysis was done to assess the effect of each study on the pooled effect size. All statistical analyses were undertaken using the Stata 14 software package (Stata, College Station, TX, USA).

RESULTS

Search results

OVERALL, 212 ARTICLES were identified in our initial literature search. Of these, 35 duplicates, 29 non-English, 3 non-human, 18 reviews, and 95 papers that did not fulfill our inclusion criteria were excluded, leaving 32 articles for further evaluation. Out of the remaining 32 articles, 12 were excluded because they did not report mean (SD) or median (IQR). Finally, we included 20 articles in this systematic review and meta-analysis (Fig. 1).

Study characteristics

All studies were carried out in China and used a retrospective design.[8–27] The sample size of studies ranged from 21 to 651 patients (mean age, 53.3 years). All studies used real-time reverse transcription–polymerase chain reaction (RT-PCR) to identify COVID-19 infection. The Newcastle–Ottawa Scale scores ranged between 4 to 9. The characteristics of the included articles are presented in Table 1.

Serum levels of AST, ALT, total bilirubin, and albumin and severity of COVID-19 infection

In the overall pooled estimate of 20 studies with 3428 COVID-19 infected patients (severe cases, n =1455; mild cases, n =1973), it was shown that higher serum levels of AST (weighted mean difference, 8.84 U/L; 95% confidence interval [CI], 5.97 to 11.71; P <0.001; I^2 =73.4%; $P_{heterogeneity}$ <0.001; number of studies, 17) (Fig. 2), ALT (weighted mean difference, 7.35 U/L; 95% CI, 4.77 to 9.93; P <0.001; I^2 =57.2%; $P_{heterogeneity}$ =0.001; number of studies, 18) (Fig. 3), and total bilirubin (weighted mean difference, 2.30 mmol/L; 95% CI, 1.24 to 3.36; P <0.001; I^2 =68.8%; $P_{heterogeneity}$ <0.001; number of studies, 11) (Fig. 4) were associated with a significant increase in the severity of COVID-19 infections. In addition, combined results from the random-effects model showed that lower serum levels of albumin (weighted

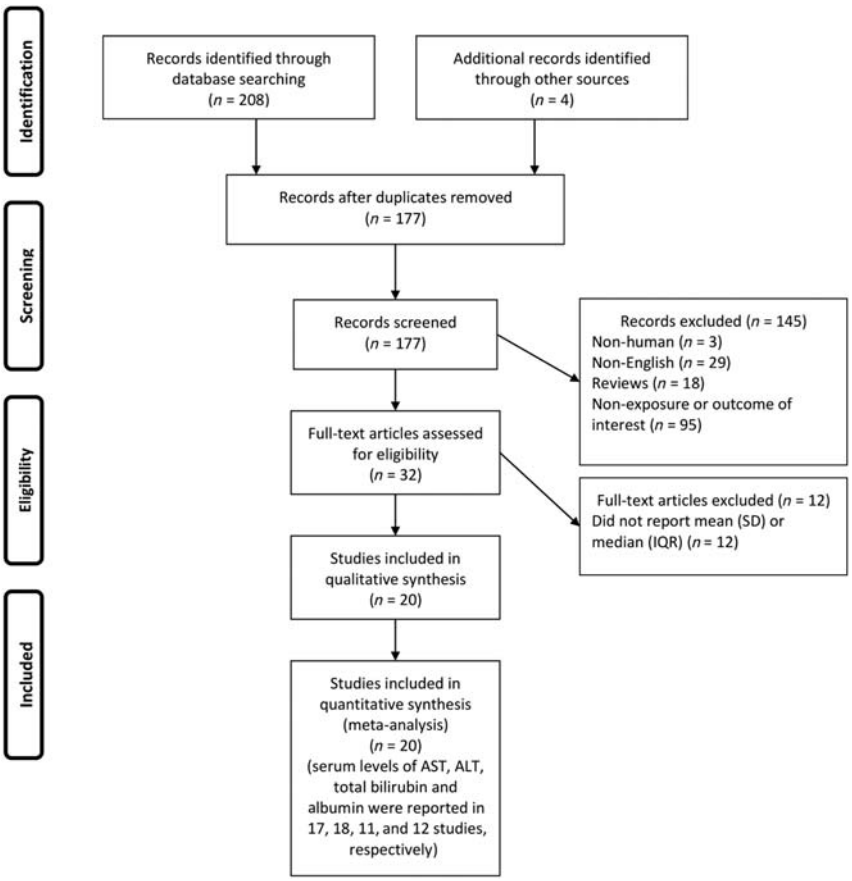

Figure 1 Flowchart of selection of studies reporting liver injury and severe COVID-19 infection. ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range.

mean difference, −4.24 g/L; 95% CI, −6.20 to −2.28; P <0.001; I^2 =95.7%; $P_{heterogeneity}$ <0.001; number of studies, 12) (Fig. 5), significantly increased severity of the disease.

Publication bias and sensitivity analysis

Based on the results of Egger's test (AST, P =0.465; ALT, P = 0.171; total bilirubin, P =0.663; and albumin, P =0.802) and visual inspection of funnel plots, we found no evidence of publication bias (Figs S1–S4). Furthermore, findings from sensitivity analyses showed that overall estimates did not depend on a single study (Figs S5–S8).

DISCUSSION

FINDINGS FROM THIS meta-analysis supported the hypothesis that liver injury is associated with severe outcomes in patients with COVID-19 infection. To our knowledge, this study is the first systematic review and meta-analysis to assess the association between serum levels of AST, ALT, total bilirubin, and albumin with severity of COVID-19 infection.

Our results are in agreement with previous narrative review.[32] Previously, liver damage has been reported as an important risk factor for severe outcome and death in SARS and MERS.[33–36]

Mild cases of COVID-19 showed symptoms of dry cough, fever, fatigue, myalgia, and diarrhea. In severe cases, viral pneumonia, dyspnea, and hypoxemia occurred 1 week after the onset of the disease, which could progress to acute respiratory distress syndrome, metabolic acidosis, septic shock, and even death.[12] Previous studies have shown that the incidence of liver injury in severe COVID-19 patients ranged from 58% to 78%,[37,38] mainly indicated by elevated AST, ALT, and total bilirubin levels accompanied by slightly decreased albumin levels.[12,21,24,39] Currently, studies on the mechanisms of COVID-19-related liver dysfunction are limited.

Table 1 Characteristics of reports included in the meta-analysis of studies of coronavirus disease 2019 (COVID-19) infection

Primary author (year)	Design of study	Country	Mean age (years)	Sample size (severe cases/mild cases)	Sex (male/female)	Pre-existing chronic liver disease, *n* (%)	COVID-19 detection	Disease severity criteria	Serum levels in severe cases (mean±SD)	Serum levels in mild cases (mean±SD)	Time interval between laboratory tests and disease severity
Chen G et al. (2020)	Retrospective	China	56.50	21 (11/10)	(17/4)	Not reported	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China	ALT, 42.00±12.96 AST, 47.00±34.44 Bilirubin, 8.80±1.92 Albumin, 29.60±3.25	ALT, 16.00±6.29 AST, 24.00±3.70 Bilirubin, 7.80±2.29 Albumin, 37.20±2.22	Laboratory tests and disease severity were assessed at the same time on admission
Chen T et al. (2020)	Retrospective	China	59.50	274 (113/161)	(171/103)	Not reported	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China	ALT, 28.00±21.48 AST, 45.00±26.66 Bilirubin, 12.60±4.40 Albumin, 30.10±3.77	ALT, 20.00±12.74 AST, 25.00±9.85 Bilirubin, 8.40±4.00 Albumin, 36.30±4.29	Laboratory tests and disease severity were assessed at the same time on admission
Deng Y et al. (2020)	Retrospective	China	54.50	225 (109/116)	(124/101)	Not reported	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China	ALT, 22.00±14.07 AST, 34.00±14.81	ALT, 18.70±13.20 AST, 22.00±10.44	Laboratory tests and disease severity were assessed at the same time on admission
Gao Y et al. (2020)	Retrospective	China	44.08	43 (15/28)	(26/17)	Not reported	Real-time RT-PCR	Patients were diagnosed according to the WHO interim guidance for COVID-19	ALT, 27.00±14.81 AST, 27.80±11.42	ALT, 24.50±16.29 AST, 33.21±18.24	Mild patients used data from their first laboratory test on admission; severe patients had their most recent laboratory test before their clinical diagnosis
Huang C et al. (2020)	Retrospective	China	49.00	41 (13/28)	(30/11)	Severe cases: 0 Mild cases: 1 (3.57%)	Real-time RT-PCR	Diagnosis of pneumonia was based on clinical characteristics, chest imaging, and the ruling out of common bacterial	ALT, 49.00±63.70 AST, 44.00±29.62	ALT, 27.00±15.18 AST, 34.00±12.22	Laboratory tests and disease severity were assessed at the same time on admission

(*Continues*)

Table 1. *(Continued)*

Primary author (year)	Design of study	Country	Mean age (years)	Sample size (severe cases/mild cases)	Sex (male/female)	Pre-existing chronic liver disease, *n* (%)	COVID-19 detection	Disease severity criteria	Serum levels in severe cases (mean±SD)	Serum levels in mild cases (mean±SD)	Time interval between laboratory tests and disease severity
								and viral pathogens that cause pneumonia	Bilirubin, 14.00±15.55	Bilirubin, 10.80±2.14	
Jin X et al. (2020)	Retrospective	China	45.61	651 (74/577)	(331/320)	Severe cases: 8 (10.81%) Mild cases: 17 (2.95%)	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China	ALT, 25.00±16.82 AST, 29.35±13.14 Bilirubin, 10.00±4.92 Albumin, 40.13±4.92	ALT, 21.50±13.18 AST, 24.40±9.62 Bilirubin, 9.60±4.51 Albumin, 41.50±3.80	Laboratory tests and disease severity were assessed at the same time on admission
Liu W et al. (2020)	Retrospective	China	51.50	78 (11/67)	(39/39)	Not reported	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (4th edition, in Chinese) by the National Health Commission of China	ALT, 17.40±22.22 AST, 21.60±24.88 Albumin, 36.62±6.60	ALT, 18.50±11.25 AST, 20.00±12.59 Albumin, 41.27±4.55	Laboratory tests and disease severity were assessed at the same time on admission
Mo P et al. (2020)	Retrospective	China	53.50	155 (85/70)	(86/69)	Severe cases: 5 (5.88%) Mild cases: 2 (2.85%)	Real-time RT-PCR	Diagnosis of pneumonia was based on clinical characteristics and chest imaging	ALT, 28.00±18.51 AST, 37.00±29.62 Albumin, 36.00±5.92	ALT, 20.00±13.33 AST, 32.00±11.11 Albumin, 39.00±4.44	Laboratory tests and disease severity were assessed at the same time on admission
Pan L et al. (2020)	Retrospective	China	52.91	204 (103/101)	(107/97)	Severe cases: 2 (1.94%) Mild cases: not reported	Real-time RT-PCR	Patients were diagnosed according to the WHO interim guidance for COVID-19	ALT, 42.24±43.83 AST, 35.12±26.58 Bilirubin, 13.83±12.03 Albumin, 36.16±6.49	ALT, 29.53±23.58 AST, 27.48±23.98 Bilirubin, 13.46±8.11 Albumin, 35.84±5.63	Laboratory tests and disease severity were assessed at the same time on admission
Qian GQ et al. (2020)	Retrospective	China	57.50	91 (9/82)	(37/54)	Not reported	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (4th and 5th editions, in Chinese) by	ALT, 19.90±8.88 AST, 27.00±2.40	ALT, 18.00±11.85 AST, 21.00±8.88	Laboratory tests and disease severity were assessed at the same time on admission

(*Continues*)

Table 1. *(Continued)*

Primary author (year)	Design of study	Country	Mean age (years)	Sample size (severe cases/mild cases)	Sex (male/female)	Pre-existing chronic liver disease, *n* (%)	COVID-19 detection	Disease severity criteria	Serum levels in severe cases (mean±SD)	Serum levels in mild cases (mean±SD)	Time interval between laboratory tests and disease severity
								the National Health Commission of China	Albumin, 38.55±2.16	Albumin, 40.20±3.25	
Qu R et al. (2020)	Retrospective	China	54.72	30 (3/27)	(16/14)	Patients with liver disease were excluded.	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China	ALT, 36.00±19.52 AST, 45.33±12.9	ALT, 33.59±24.54 AST, 43.56±21.03	Laboratory tests and disease severity were assessed at the same time on admission
Ruan Q et al. (2020)	Retrospective	China	58.50	150 (68/82)	(102/48)	Severe cases: 1 (1.47%) Mild cases: 3 (3.65%)	Real-time RT-PCR	Diagnosis of pneumonia was based on clinical characteristics and chest imaging	Bilirubin, 18.10±10.70 Albumin, 28.80±3.80	Bilirubin, 12.80±6.80 Albumin, 32.70±3.80	Not reported
Wan S et al. (2020)	Retrospective	China	50.00	135 (40/95)	(72/63)	Severe cases: 1 (2.50%) Mild cases: 1 (1.05%)	Real-time RT-PCR	Patients were diagnosed according to the WHO interim guidance for COVID-19	ALT, 26.60±13.92 AST, 33.60±13.70 Bilirubin, 9.80±5.77 Albumin, 36.00±4.07	ALT, 21.70±16.37 AST, 22.40±10.07 Bilirubin, 8.60±6.22 Albumin, 49.90±4.59	Laboratory tests and disease severity were assessed at the same time on admission
Wang D et al. (2020)	Retrospective	China	58.50	138 (36/102)	(75/63)	Severe cases: 0 Mild cases: 4 (3.92%)	Real-time RT-PCR	Patients were diagnosed according to the WHO interim guidance for COVID-19	ALT, 35.00±28.14 AST, 52.00±29.62 Bilirubin, 11.50±6.66	ALT, 23.00±15.55 AST, 29.00±12.59 Bilirubin, 9.30±3.40	Laboratory tests were done on admission. The median time from admission to developing severe outcome was 1 day (IQR, 0–3 days)
Wang Z et al. (2020)	Retrospective	China	53.75	69 (14/55)	(32/37)	Severe cases: 0 Mild cases: 1 (1.82%)	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (3rd edition, in Chinese) by the National Health Commission of China	ALT, 31.50±21.48 AST, 40.50±28.1	ALT, 24.00±17.77 AST, 26.00±13.33	Laboratory tests were done on admission. The median time from admission to developing severe outcome was 1 day (IQR, 0–2 days).

(*Continues*)

Table 1. *(Continued)*

Primary author (year)	Design of study	Country	Mean age (years)	Sample size (severe cases/mild cases)	Sex (male/female)	Pre-existing chronic liver disease, *n* (%)	COVID-19 detection	Disease severity criteria	Serum levels in severe cases (mean±SD)	Serum levels in mild cases (mean±SD)	Time interval between laboratory tests and disease severity
Wu C et al. (2020)	Retrospective	China	53.25	201 (84/117)	(128/73)	All patients: 7 (3.48%)	Real-time RT-PCR	Patients were diagnosed according to the WHO interim guidance for COVID-19	ALT, 35.00±22.96 AST, 38.00±16.66 Bilirubin, 12.90±5.59 Albumin, 30.40±4.59	ALT, 27.00±17.40 AST, 30.00±10.74 Bilirubin, 10.50±3.74 Albumin, 33.70±3.96	Laboratory tests were done on admission. The median time from admission to developing severe outcome was 2 days (IQR, 1–4 days)
Yang X et al. (2020)	Retrospective	China	58.25	52 (32/20)	(35/17)	Severe cases: 9 (28.12%) Mild cases: 6 (30.00%)	Real-time RT-PCR	Patients were diagnosed according to the WHO interim guidance for COVID-19	Bilirubin, 19.50±11.60	Bilirubin, 13.10±4.30	Laboratory tests and disease severity were assessed at the same time on admission
Zhang X et al. (2020)	Retrospective	China	40.77	645 (573/72)	(328/317)	Severe cases: 23 (4.01%) Mild cases: 2 (2.77%)	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (5th edition, in Chinese) by the National Health Commission of China and the WHO interim guidance for COVID-19	ALT, 29.37±25.71 AST, 30.08±20.37 Bilirubin, 11.26±8.04 Albumin, 41.02±4.47	ALT, 25.53±19.96 AST, 25.67±15.52 Bilirubin, 9.11±4.86 Albumin, 42.53±4.70	Laboratory tests were done on admission. The time from onset to COVID-19 infection confirmation was 5.0 (2.5–7.0) days among patients with severe outcome
Zhou B et al. (2020)	Retrospective	China	65	34 (8/26)	(17/17)	Not reported	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (4th edition, in Chinese) by the National Health Commission of China	ALT, 49.00±34.07 AST, 44.00±16.29	ALT, 34.00±29.62 AST, 32.00±14.81	Laboratory tests and disease severity were assessed at the same time on admission
Zhou F et al. (2020)	Retrospective	China	60.50	191 (54/137)	(119/72)	Not reported	Real-time RT-PCR	Guidelines for diagnosis and management of COVID-19 (6th edition, in Chinese) by the National Health Commission of China and the WHO interim guidance for COVID-19	ALT, 40.00±20.00 Albumin, 29.10±3.55	ALT, 27.00±18.51 Albumin, 33.60±4.29	Laboratory tests and disease severity were assessed at the same time on admission

ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; M, male; RT-PCR, reverse transcription–polymerase chain reaction.

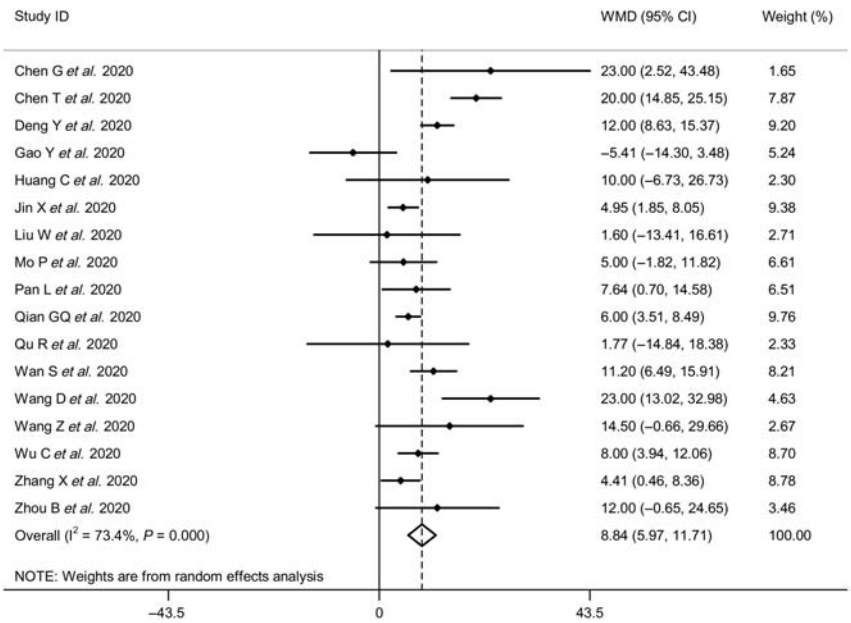

Figure 2 Forest plot for the association between serum levels of aspartate aminotransferase and severity of COVID-19 infection using random-effects model. CI, confidence interval; WMD, weighted mean difference.

COVID-19 uses the angiotensin converting enzyme 2 (ACE2) as the binding site to enter the host cell in lungs, kidneys, and heart.[40] A previous study showed that both liver and bile duct cells express ACE2.[41] In addition, the ACE2 expression of bile duct cells is much greater than that of liver cells. Bile duct epithelial cells are known to play important roles in initiation and regulation of immune responses and liver regeneration.[42] However, it is unclear

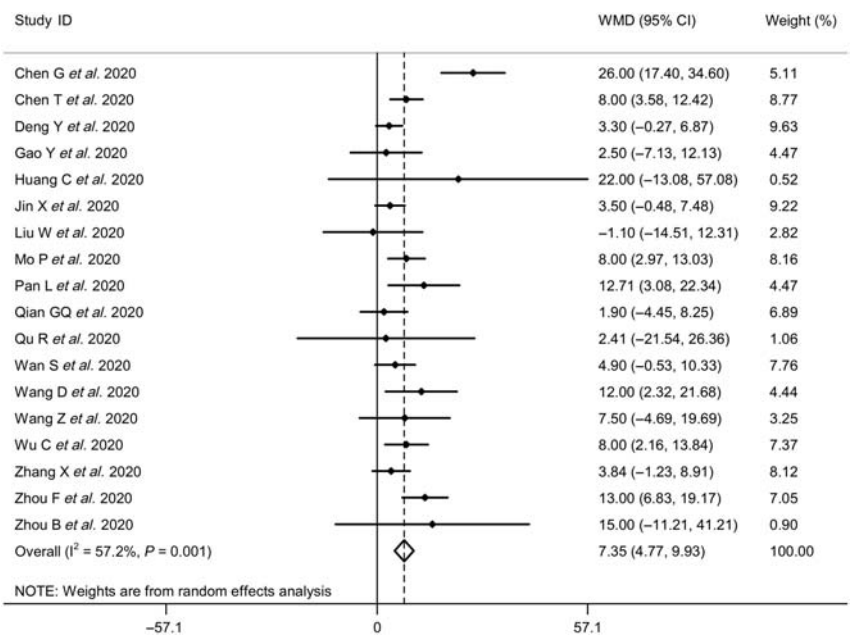

Figure 3 Forest plot for the association between serum levels of ALT and severity of COVID-19 infection using random-effects model. CI, confidence interval; WMD, weighted mean difference.

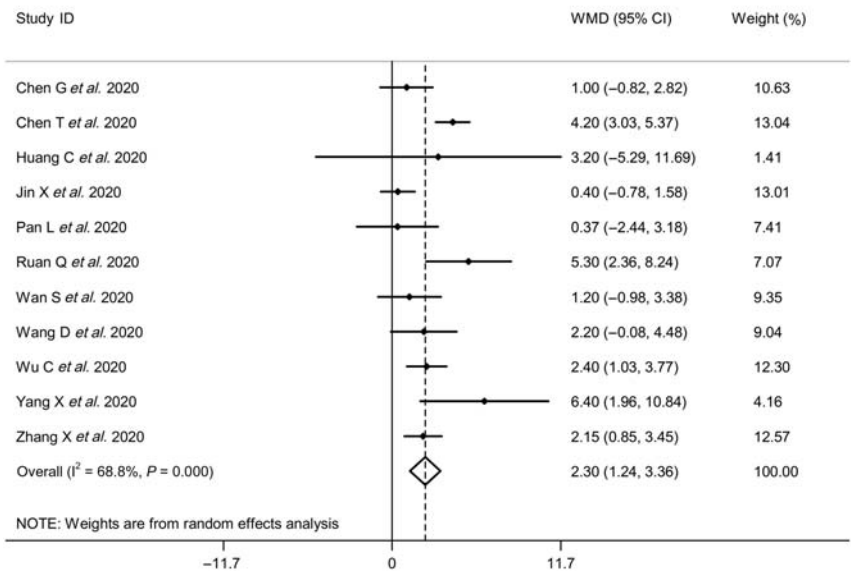

Figure 4 Forest plot for the association between serum levels of total bilirubin and severity of COVID-19 infection using random-effects model. CI, confidence interval; WMD, weighted mean difference.

whether liver injury is due to direct liver and bile duct involvement by the virus or due to multiorgan failure in patients with COVID-19 infection.

Serum concentrations of pro-inflammatory cytokines, including interleukin-1β, interleukin-6, and tumor necrosis factor-α increased in the majority of severe cases, suggesting cytokine storm syndrome might be associated with disease severity.[43] Similarly, SARS and MERS were also characterized by exuberant inflammatory responses and end-organ damage.[44,45] Cytokine storm syndrome

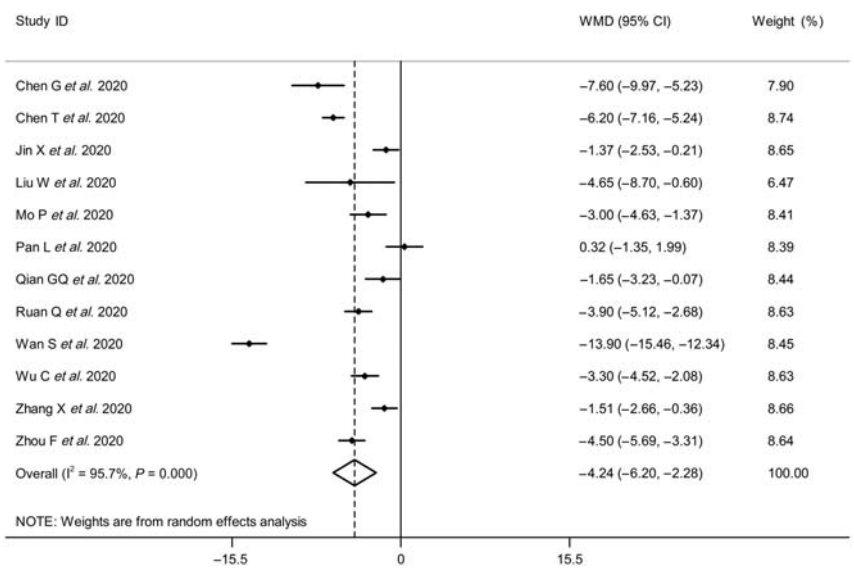

Figure 5 Forest plot for the association between serum levels of albumin and severity of COVID-19 infection using random-effects model. CI, confidence interval; WMD, weighted mean difference.

was observed in severe COVID-19 cases,[43] yet whether it results in liver injury in patients remains to be investigated.

Mild lobular and portal activity along with moderate microvascular steatosis were observed in liver biopsy specimens, which might be caused by either COVID-19 infection or drug-induced liver injury.[46] Similar to the situation in SARS and MERS, steroids, antivirals, and antibiotics are widely used for the treatment of COVID-19 patients.[47–49] Although these drugs are potential causes of liver dysfunction, there is little evidence that currently available drug combinations impair liver function in patients with COVID-19 infection.[24] Actually, a recent study showed that the liver dysfunction might be caused by lopinavir/ritonavir, which is used as an antiviral for the treatment of COVID-19 patients.[50]

The present study has some limitations. First, interpretation of our meta-analysis findings might be limited by the small sample size. Second, there is a lack of reports that liver failure occurs in COVID-19 patients with chronic liver diseases and our meta-analysis did not include data such as chronic hepatitis B or C infection.

CONCLUSION

IN THIS META-ANALYSIS of 3428 patients with confirmed COVID-19 in China, liver dysfunction as assessed by serum analysis (AST, ALT, total bilirubin, and albumin levels) was associated with severe outcome from COVID-19 infection. From a clinical perspective, attention should be paid to monitor the occurrence of liver dysfunction in patients with COVID-19 infection.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found online in the Supporting Information section at the end of the article.

Table S1 Systematic literature review search terms and strategy.

Figure S1 Funnel plot for the association between serum levels of aspartate aminotransferase (AST) and severity of COVID-19 infection. Based on visual inspection of funnel plots, we found no evidence of publication bias.

Figure S2 Funnel plot for the association between serum levels of alanine aminotransferase (ALT) and severity of COVID-19 infection. Based on visual inspection of funnel plots, we found no evidence of publication bias.

Figure S3 Funnel plot for the association between serum levels of total bilirubin and severity of COVID-19 infection. Based on visual inspection of funnel plots, we found no evidence of publication bias.

Figure S4 Funnel plot for the association between serum levels of albumin and severity of COVID-19 infection. Based on visual inspection of funnel plots, we found no evidence of publication bias.

Figure S5 Sensitivity analysis graph for the association between serum levels of aspartate aminotransferase (AST) and severity of COVID-19 infection. The results of the sensitivity analysis showed that no study had an obvious influence on the outcomes of this meta-analysis.

Figure S6 Sensitivity analysis graph for the association between serum levels of alanine aminotransferase (ALT) and severity of COVID-19 infection. The results of the sensitivity analysis showed that no study had an obvious influence on the outcomes of this meta-analysis.

Figure S7 Sensitivity analysis graph for the association between serum levels of total bilirubin and severity of COVID-19 infection. The results of the sensitivity analysis showed that no study had an obvious influence on the outcomes of this meta-analysis.

Figure S8 Sensitivity analysis graph for the association between serum levels of albumin and severity of COVID-19 infection. The results of the sensitivity analysis showed that no study had an obvious influence on the outcomes of this meta-analysis.