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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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Running title: Liver injury and severity of COVID-19 infection

Abstract

Aim: 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. Current meta-analysis of retrospective studies was done to summarize available findings on the association between liver injury and severity of COVID-19 infection.

Methods: 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 done.

Results: In total, 20 retrospective studies with 3,428 COVID-19 infected patients (severe cases = 1,455 and mild cases = 1,973), were included in this meta-analysis. Higher serum levels of Aspartate aminotransferase (weighted mean difference = 8.84 U/L, 95% 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.

Conclusions: The incidence of liver injury, as assessed by serum analysis (AST, ALT, total Bilirubin and Albumin levels), seems to be higher in patients with severe COVID-19 infection.

Keywords: 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 city, the capital of Hubei Province, China¹⁻³. The disease has rapidly spread from China to other countries. As of April 4, 2020, a total of 1,051,635 COVID-19 confirmed cases and 56,985 deaths in 206 countries and territories have been reported⁴. 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.

SARS, MERS and COVID-19 can cause intestinal, respiratory, neuronal and hepatic diseases, and may lead to respiratory distress syndrome, organ failure, and even death in severe cases⁵⁻⁷. Several studies have reported the clinical characteristics and laboratory findings associated with different degrees of liver injury in patients with COVID-19 infection⁸⁻²⁷. We are aware of no 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.

Materials and methods

Study protocol

A systematic literature search and a quantitative meta-analysis were planned, conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines ²⁸.

Search strategy

We conducted a literature search 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 Aminotransferases” OR “SGOT” OR “Bilirubin” OR “Serum Albumin” OR “Liver”). The literature search was performed 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 and 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, USA). The search strategy is presented in detail in Supplementary Table 1.

Eligibility Criteria

Studies were included if they met the following inclusion criteria: (1) observational studies with retrospective design; (2) 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 (SD) or median (IQR) for serum levels of AST, ALT, Albumin, 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 was used for assessing the quality of the included studies²⁹. Based on the NOS, a maximum of nine points can be awarded to each article. In this review, studies with the Newcastle–Ottawa Scale 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 heterogeneity test. The heterogeneity between studies was evaluated using the Cochrane Q test³⁰. The publication bias was evaluated by the visual inspection of funnel plot and Egger's regression tests³¹. The sensitivity analysis was done to assess the effect of each study on the pooled effect size. All statistical analyses were performed using the Stata 14 software package (Stata Corp, 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 remaining 32 articles, 12 were excluded because of the following reason: did not report mean (SD) or median (IQR). Finally, we included 20 articles in this systematic review and meta-analysis (Figure 1).

Study characteristics

All studies were conducted in China and used retrospective design⁸⁻²⁷. The sample size of studies ranged from 21 to 651 patients (mean age, 53.3 years). All studies used real-time reverse transcriptase–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, Albumin and severity of COVID-19 infection

In the overall pooled estimate of 20 studies with 3,428 COVID-19 infected patients (severe cases = 1,455 and mild cases = 1,973), it was shown that higher serum levels of AST (weighted mean difference = 8.84 U/L, 95% CI = 5.97 to 11.71, $P < 0.001$, $I^2 = 73.4\%$, $P_{\text{heterogeneity}} < 0.001$, number of studies: 17) (Figure 2), ALT (weighted mean difference = 7.35 U/L, 95% CI = 4.77 to 9.93, $P < 0.001$, $I^2 = 57.2\%$, $P_{\text{heterogeneity}} = 0.001$, number of studies: 18) (Figure 3) and total Bilirubin (weighted mean difference = 2.30 mmol/L, 95% CI = 1.24 to 3.36, $P < 0.001$, $I^2 = 68.8\%$, $P_{\text{heterogeneity}} < 0.001$, number of studies: 11) (Figure 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 mean difference = -4.24 g/L, 95% CI = -6.20 to -2.28, $P < 0.001$, $I^2 = 95.7\%$, $P_{\text{heterogeneity}} < 0.001$, number of studies: 12) (Figure 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 (Supplementary Figures 1-4). Furthermore, findings from sensitivity analysis showed that overall estimates did not depend on a single study (Supplementary Figures 5-8).

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 review³². Previously, liver damage has been reported as an important risk factor for severe outcome and death in SARS and MERS³³⁻³⁶.

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 may progress to acute respiratory distress syndrome, metabolic acidosis, septic shock and even death¹². 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. COVID-19 uses the angiotensin converting enzyme 2 (ACE2) as the binding site to enter the host cell in lungs, kidneys and heart ⁴⁰. 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 whether liver injury is due to direct liver and bile duct involvement by the virus or due to multi-organ failure in patients with COVID-19 infection.

Serum concentrations of pro-inflammatory cytokines, including IL-1 β , IL-6 and TNF- 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}. Besides, the cytokine storm syndrome 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/litonavir, which is used as antivirals 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.

Conclusion

In this meta-analysis of 3,428 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.

Declarations of interest: none

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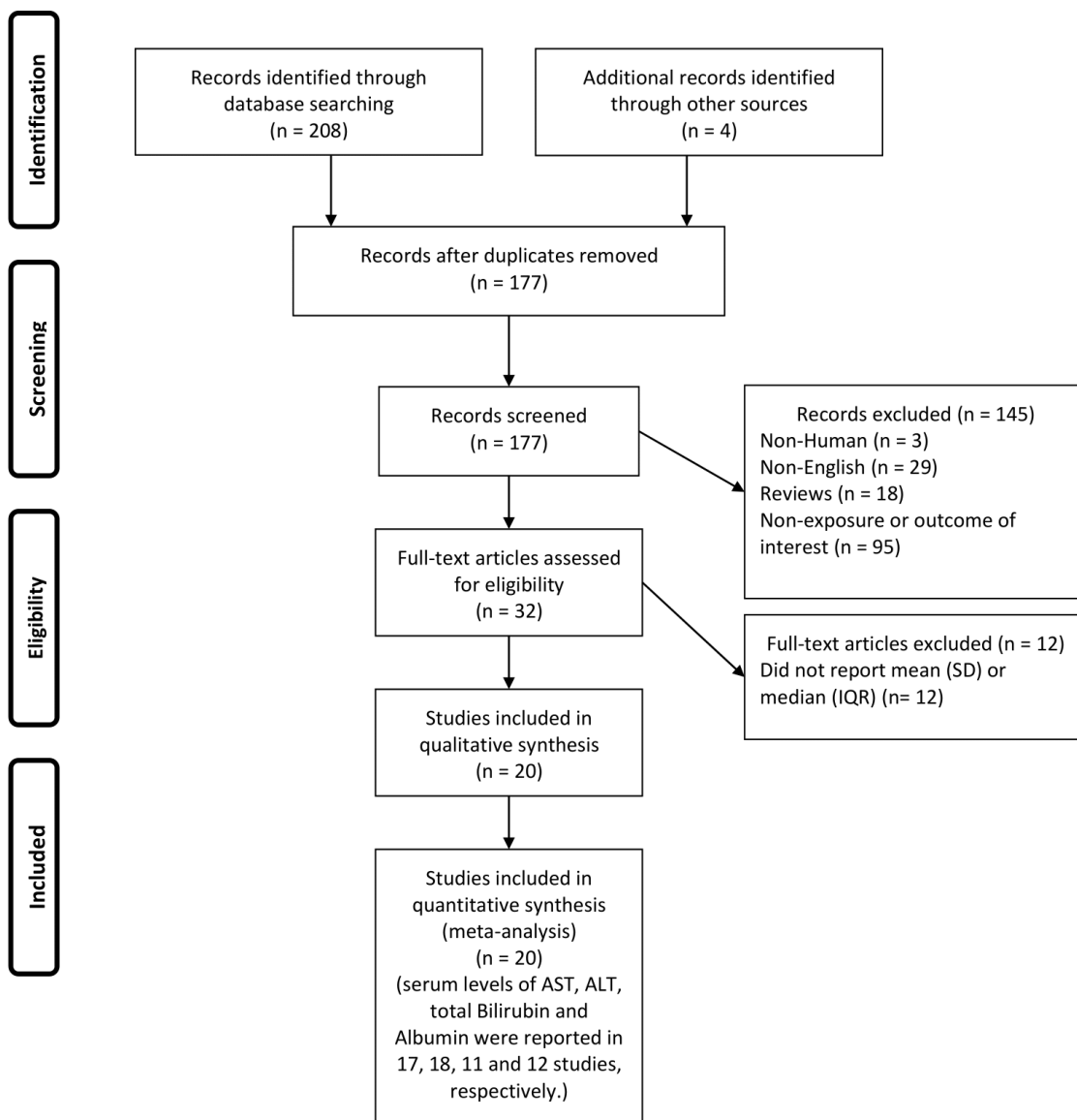


Figure 1. Flow chart of study selection.

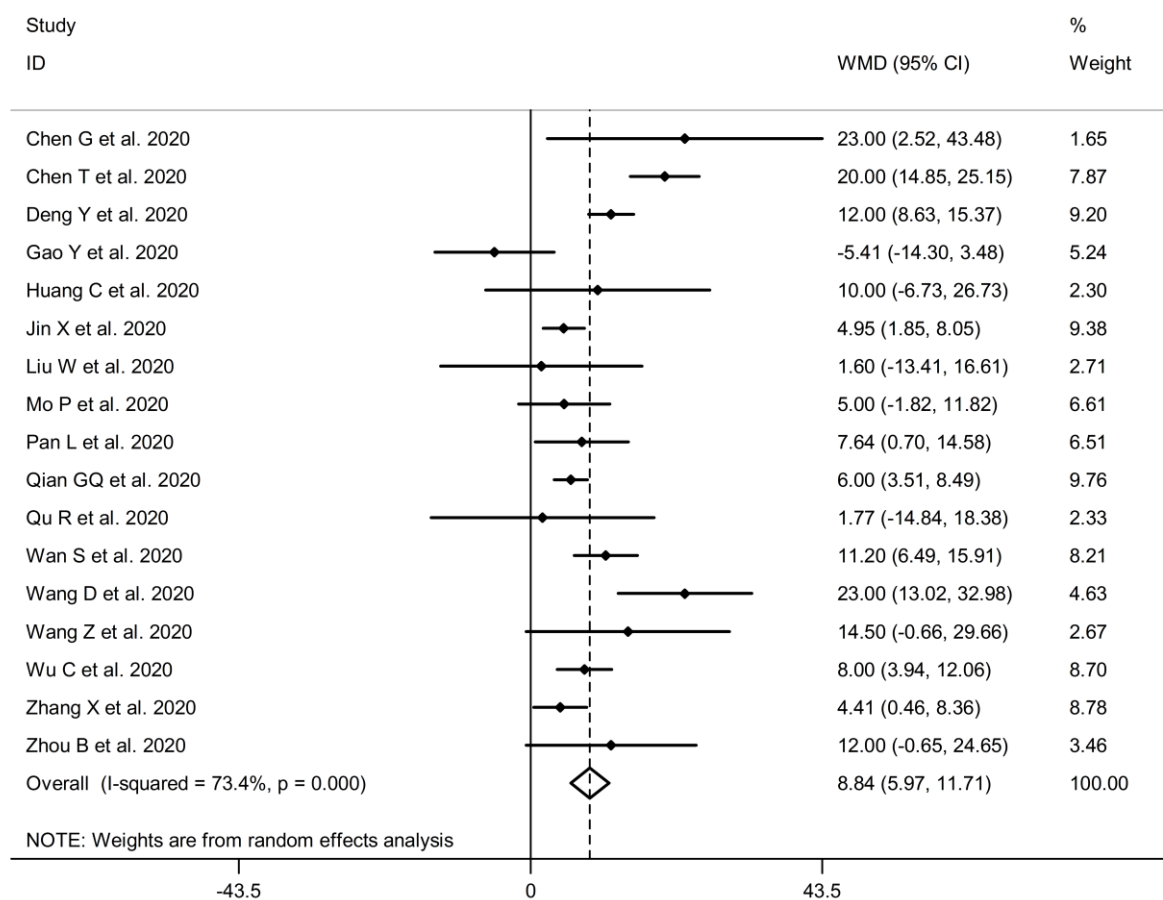


Figure 2. Forest plot for the association between serum levels of AST and severity of COVID-19 infection using random-effects model.

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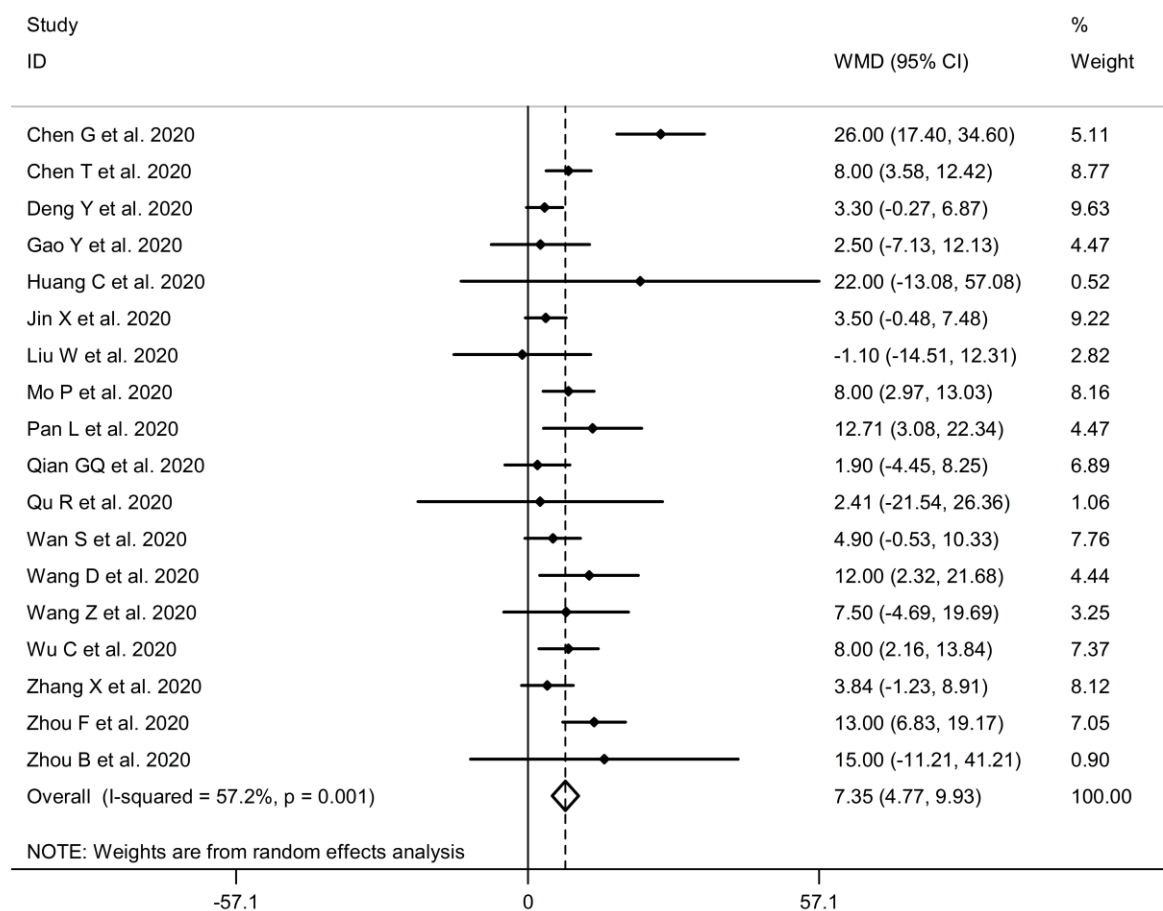


Figure 3. Forest plot for the association between serum levels of ALT and severity of COVID-19 infection using random-effects model.

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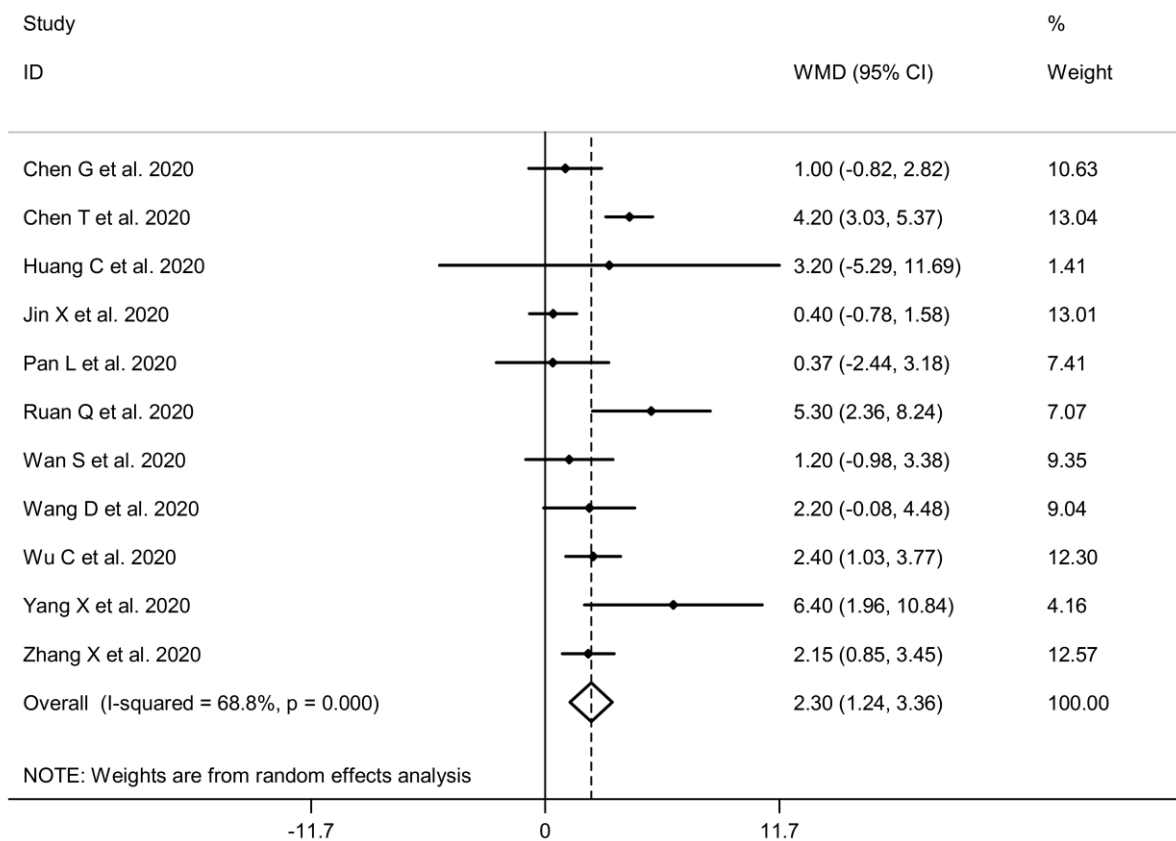


Figure 4. Forest plot for the association between serum levels of total Bilirubin and severity of COVID-19 infection using random-effects model.

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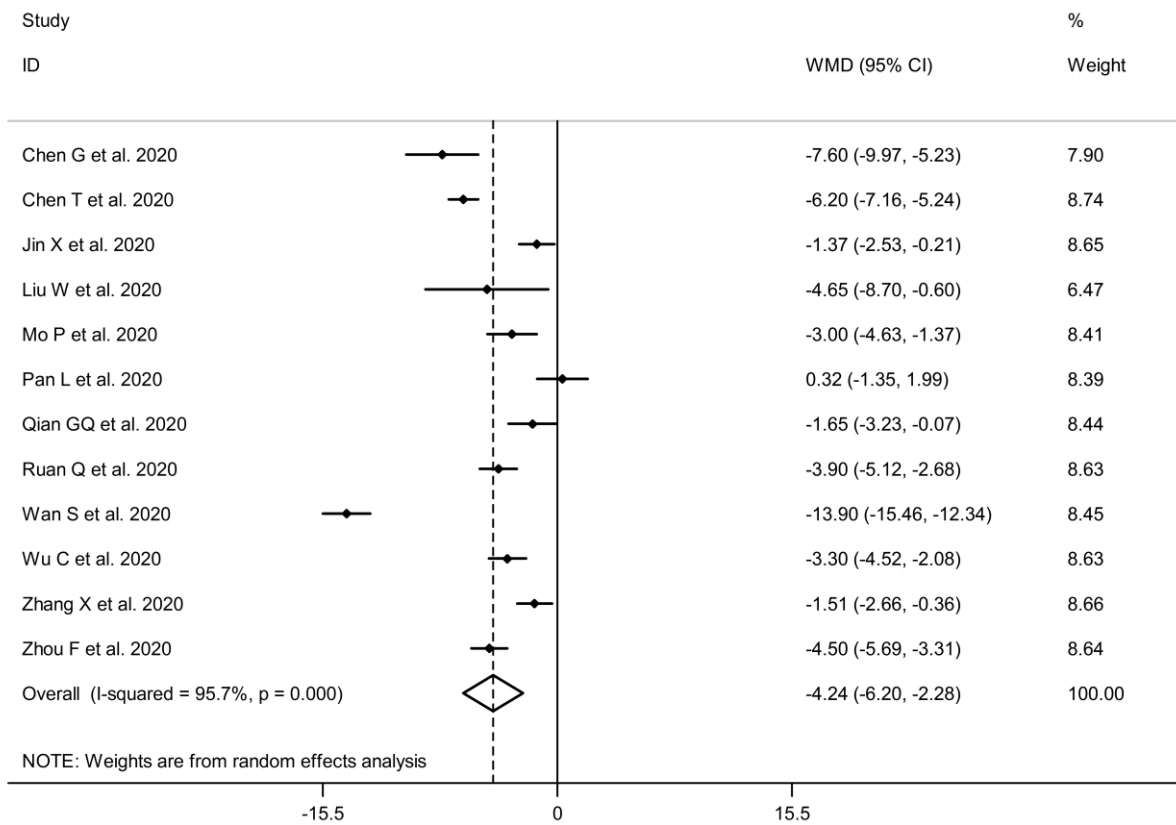


Figure 5. Forest plot for the association between serum levels of Albumin and severity of COVID-19 infection using random-effects model.

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Table 1. Characteristics of studies included in the meta-analysis.

Authors (year)	Design of study	Country	Mean age (y)	Sample size	Sex	Pre-existing chronic liver disease No. (%)	COVID-19 ^a detection	Disease severity criteria	Serum levels in severe cases (mean±SD)	Serum levels in mild cases (mean±SD)	The time interval between laboratory tests and disease severity
Chen G et al. (2020)	Retrospective	China	56.50	21 Severe cases: 11 Mild cases: 10	F/M	Not reported	real-time RT-PCR	The guidelines for diagnosis and management of COVID-19 (6 th 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 Severe cases: 113 Mild cases: 161	F/M	Not reported	real-time RT-PCR	The guidelines for diagnosis and management of COVID-19 (6 th 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 Severe cases: 109 Mild cases: 116	F/M	Not reported	real-time RT-PCR	The guidelines for diagnosis and management of COVID-19 (6 th 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 Severe cases: 15 Mild cases: 28	F/M	Not reported	real-time RT-PCR	The Patients were diagnosed according to the World Health Organization 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, while severe patients had their most recent laboratory test before their

Huang C et al. (2020)	Retrospective	China	49.00	41 Severe cases: 13 Mild cases: 28	F/M	Severe cases: 0 Mild cases: 1 (3.57%)	real-time RT-PCR	The diagnosis of pneumonia was based on clinical characteristics, chest imaging, and the ruling out of common bacterial and viral pathogens that cause pneumonia.	ALT: 49.00±63.70 AST: 44.00±29.62 Bilirubin: 14.00±15.55	ALT: 27.00±15.18 AST: 34.00±12.22 Bilirubin: 10.80±2.14	clinical diagnosis laboratory tests and disease severity were assessed at the same time on admission
Jin X et al. (2020)	Retrospective	China	45.61	651 Severe cases: 74 Mild cases: 577	F/M	Severe cases: 8 (10.81%) Mild cases: 17 (2.95%)	real-time RT-PCR	The guidelines for diagnosis and management of COVID-19 (6 th 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 Severe cases: 11 Mild cases: 67	F/M	Not reported	real-time RT-PCR	The guidelines for diagnosis and management of COVID-19 (4 th 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 Severe cases: 85 Mild cases: 70	F/M	Severe cases: 5 (5.88%) Mild cases: 2 (2.85%)	real-time RT-PCR	The 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 Severe cases: 103 Mild cases: 101	F/M	Severe cases: 2 (1.94%) Mild cases: not reported	real-time RT-PCR	The Patients were diagnosed according to the World Health Organization 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	Retrospective	China	57.50	91 Severe	F/M	Not reported	real-time	The guidelines for	ALT: 19.90±8.88	ALT: 18.00±11.85	laboratory tests and disease

al. (2020)				cases: 9 Mild cases: 82			RT-PCR	diagnosis and management of COVID-19 (4 th and 5 th edition, in Chinese) by the National Health Commission of China	AST: 27.00±2.40 Albumin: 38.55±2.16	AST: 21.00±8.88 Albumin: 40.20±3.25	severity were assessed at the same time on admission
Qu R et al. (2020)	Retrospective	China	54.72	30 Severe cases: 3 Mild cases: 27	F/M	Patients with liver disease were excluded.	real-time RT-PCR	The guidelines for diagnosis and management of COVID-19 (6 th edition, in Chinese) by the National Health Commission of China	ALT: 36.00±19.52 AST: 45.33±12.90	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 Severe cases: 68 Mild cases: 82	F/M	Severe cases: 1 (1.47%) Mild cases: 3 (3.65%)	real-time RT-PCR	The 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 Severe cases: 40 Mild cases: 95	F/M	Severe cases: 1 (2.50%) Mild cases: 1 (1.05%)	real-time RT-PCR	The Patients were diagnosed according to the World Health Organization 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 Severe cases: 36 Mild cases: 102	F/M	Severe cases: 0 Mild cases: 4 (3.92%)	real-time RT-PCR	The Patients were diagnosed according to the World Health Organization 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 Severe cases: 14 Mild cases: 55	F/M	Severe cases: 0 Mild cases: 1 (1.82%)	real-time RT-PCR	The guidelines for diagnosis and management of COVID-19	ALT: 31.50±21.48 AST: 40.50±28.14	ALT: 24.00±17.77 AST: 26.00±13.33	laboratory tests were done on admission. The median time

								(3 rd edition, in Chinese) by the National Health Commission of China			from admission to developing severe outcome was 1 day (IQR, 0-2 days).
Wu C et al. (2020)	Retrospective	China	53.25	201 Severe cases: 84 Mild cases: 117	F/M	All patients: 7 (3.48%)	real-time RT-PCR	The Patients were diagnosed according to the World Health Organization 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 Severe cases: 32 Mild cases: 20	F/M	Severe cases: 9 (28.12%) Mild cases: 6 (30.00%)	real-time RT-PCR	The Patients were diagnosed according to the World Health Organization 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 Severe cases: 573 Mild cases: 72	F/M	Severe cases: 23 (4.01%) Mild cases: 2 (2.77%)	real-time RT-PCR	The guidelines for diagnosis and management of COVID-19 (5 th edition, in Chinese) by the National Health Commission of China and the World Health Organization 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 Severe cases: 8 Mild cases: 26	F/M	Not reported	real-time RT-PCR	The guidelines for diagnosis and management of COVID-19 (4 th edition, in Chinese) by the National Health	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 Severe cases: 54 Mild cases: 137	F/M	Not reported	real-time RT-PCR	Commission of China The guidelines for diagnosis and management of COVID-19 (6 th edition, in Chinese) by the National Health Commission of China and the World Health Organization 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
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Abbreviation: ^aCOVID-19: Coronavirus diseases 2019