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COVID-19 and Liver Injury: A Systematic Review and Meta-Analysis

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Abstract

Background and Aims

The prevalence and extent of liver damage in coronavirus disease 2019 (COVID-19) patients remain poorly understood, primarily due to small-sized epidemiological studies with varying definitions of "liver injury". We conducted a meta-analysis to derive generalizable, well-powered estimates of liver injury prevalence in COVID-19 patients. We also aimed to assess whether liver injury prevalence is significantly greater than the baseline prevalence of chronic liver disease (CLD). Our secondary aim was to study whether the degree of liver injury was associated with the severity of COVID-19.

Materials and Methods

Electronic databases (PubMed and Scopus) were systematically searched in June 2020 for studies reporting the prevalence of baseline CLD and current liver injury in hospitalized COVID-19 patients. Liver injury was defined as an elevation in transaminases >3 times above the upper limit of normal. For the secondary analysis, all studies reporting mean liver enzyme levels in severe versus non-severe COVID-19 patients were included. A random-effects model was used for meta-analysis. Proportions were subjected to arcsine transformation and pooled to derive pooled proportions and corresponding 95% confidence intervals (CIs). Subgroup differences were tested for using the chi-square test and associated p-value. Means and their standard errors were pooled to derive weighted mean differences (WMDs) and corresponding 95% CIs.

Results

Electronic search yielded a total of 521 articles. After removal of duplicates and reviewing the full-texts of potential studies, a total of 27 studies met the inclusion criteria. Among a cohort of 8,817 patients, the prevalence of current liver injury was 15.7% (9.5%-23.0%), and this was significantly higher than the proportion of patients with a history of CLD (4.9% [2.2%-8.6%]; p < 0.001). A total of 2,900 patients in our population had severe COVID-19, and 7,184 patients had non-severe COVID-19. Serum ALT (WMD: 7.19 [4.90, 9.48]; p < 0.001; I² = 69%), AST (WMD: 9.02 [6.89, 11.15]; p < 0.001; I² = 73%) and bilirubin levels (WMD: 1.78 [0.86, 2.70]; p < 0.001; I² = 82%) were significantly higher in patients with severe COVID-19 when compared to patients with non-severe disease. Albumin levels were significantly lower in patients with severe COVID-19.
COVID-19 (WMD: -4.16 [-5.97, -2.35]; p < 0.001; I² = 95%).

Conclusions

Patients with COVID-19 have a higher than expected prevalence of liver injury, and the extent of the injury is associated with the severity of the disease. Further studies are required to assess whether hepatic damage is caused by the virus, medications, or both.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), the virus responsible for coronavirus disease 2019 (COVID-19), mainly affects the respiratory system causing symptoms of fever, fatigue, cough, dyspnea, loss of appetite, muscle and joint pains [1]. However, the incidence of vomiting, nausea, and diarrhea have also been reported, suggesting the involvement of gastrointestinal and hepatobiliary systems [1,2]. SARS-Cov-2 enters cells through the angiotensin-converting enzyme-2 (ACE2) protein. Apart from type II alveolar epithelial cells of the lung, ACE2 protein is also expressed in the bile ducts cells [3]. This suggests that SARS-Cov-2 could potentially infect bile duct cells and cause abnormal liver function tests. According to one recent study, liver biopsy specimens of COVID-19 patients demonstrated moderate microvascular steatosis and mild lobular and portal activity, suggesting liver injury [4].

Although, in theory, liver injury in COVID-19 patients is possible, the actual prevalence and extent of liver damage in these patients remain poorly understood. This is primarily because most published COVID-19 studies are small-sized, often lack adjustment for baseline chronic liver disease (CLD), and have inconsistent definitions of "liver injury". In this meta-analysis, we aim to provide well-powered and generalizable estimates of the prevalence of liver injury in COVID-19 patients while making sure to keep the definition of "liver injury" consistent. We also seek to assess whether the prevalence of liver injury in COVID-19 patients is significantly different from the prevalence of baseline CLD in these patients. A secondary aim of this study is to assess for any significant differences in serum biomarkers of liver injury (alanine transaminase [ALT], aspartate transaminase [AST], total bilirubin, and albumin) in patients with severe versus non-severe COVID-19.

Materials And Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines [5].

Literature search

PubMed and Scopus were searched from the inception of databases till June 18, 2020, using the following search string: ("novel coronavirus" OR "2019-nCoV" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2" OR "coronavirus disease 2019" OR "COVID-19") AND ("Aspartate Aminotransferases" OR "SGOT" OR "Alanine Transaminase" OR "SGPT" OR "Albumin" OR "Bilirubin" OR "Liver") AND ("hepatic injury" OR "liver damage" OR "liver abnormality"). Google Scholar was also searched for grey literature. No language and time restrictions were set. The search strategy for both databases is shown in Table 1.
TABLE 1: Search strategy for electronic databases

| Electronic database | Search strategy |
|---------------------|-----------------|
| PubMed              | ((((("novel coronavirus"[All Fields] OR "2019-nCoV"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "SARS-CoV-2"[All Fields]) OR "coronavirus disease 2019"[All Fields]) OR "COVID-19"[All Fields]) AND (((("Aspartate Aminotransferases"[All Fields] OR "SGOT"[All Fields]) OR "Alanine Transaminase"[All Fields]) OR "Alanine aminotransferase"[All Fields]) OR "SGPT"[All Fields]) OR "Albumin"[All Fields]) OR "Bilirubin"[All Fields]) OR "Liver"[All Fields]) AND ((("hepatic injury"[All Fields] OR "liver injury"[All Fields]) OR "liver damage"[All Fields]) OR "liver abnormality"[All Fields])) AND (("aspartate transaminase" OR "SGOT" OR "SGPT") AND TITLE-ABS-KEY ("ALT" OR "alanine transaminase" OR "SGPT") AND TITLE-ABS-KEY ("AST" OR "Aspartate transaminase" OR "SGOT") AND TITLE-ABS-KEY ("bilirubin" OR "total bilirubin") AND TITLE-ABS-KEY ("albumin" OR "serum albumin") AND TITLE-ABS-KEY ("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease")) |
| Scopus              | ( TITLE-ABS-KEY ("liver injury" OR "liver failure" OR "hepatic damage" OR "liver function abnormality" OR "hepatic abnormality") AND TITLE-ABS-KEY ("ALT" OR "alanine transaminase" OR "SGPT") AND TITLE-ABS-KEY ("AST" OR "Aspartate transaminase" OR "SGOT") AND TITLE-ABS-KEY ("bilirubin" OR "total bilirubin") AND TITLE-ABS-KEY ("albumin" OR "serum albumin") AND TITLE-ABS-KEY ("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease")) |

Study selection

All the articles were exported to EndNote Reference Library version X4 (Clarivate Analytics, Philadelphia, PA) for screening and removal of duplicates. Studies were narrowed down based on titles and abstracts, and final inclusion was performed after reviewing the full texts of articles. Studies were selected independently by two reviewers, and a third reviewer resolved any conflict regarding inclusion.

Inclusion criteria and definitions

We included all studies among COVID-19 patients that defined liver injury as an elevation in transaminases >3 times above the upper limit of normal (ULN). To study whether the extent of liver injury was associated with severity of COVID-19, all studies that reported serum ALT, AST, total bilirubin, or albumin levels in severe versus non-severe COVID-19 patients were included. Most of the studies assessed COVID-19 severity according to either the World Health Organization interim guidance for COVID-19 or the guidelines for the diagnosis and management of COVID-19 by the National Health Commission of China, thus ensuring minimum heterogeneity in severity criteria. Case reports and studies that did not report the definition of liver injury were excluded.

Data extraction

Data extraction was performed independently by two reviewers, and, in case of any conflict, the opinion of a third reviewer was sought. Characteristics of included studies, patients’ baseline information, liver injury biomarkers, and criteria for liver injury were extracted from the studies on a predesigned form.

Statistical analysis

Open MetaAnalyst and Review Manager Version 5.4 were used for all statistical analyses. Proportions from studies were subjected to arcsine transformation and pooled using a random-effects model to derive the pooled proportions and corresponding 95% confidence intervals (CIs). The chi-square test was used to assess for any significant differences between baseline
CLD prevalence and prevalence of liver injury. Continuous variables were also pooled using a random-effects model to derive the weighted mean difference (WMD) and 95% CIs. The Higgins I² statistic was used to evaluate heterogeneity and a value of 25%-50% was considered mild, 50%-75% as moderate, and >75% as severe heterogeneity. Publication bias was assessed through visual inspection of the funnel plot. A p-value of less than 0.05 was considered significant in all cases.

**Results**

The initial search yielded 513 potential articles, and eight records were identified through references of relevant studies. After exclusions, 27 studies were used in our quantitative analysis [1,2,4,6-29]. The PRISMA flowchart (Figure 1) summarizes the results of our literature search. The baseline characteristics and outcomes of included studies are given in Table 2. Visual inspection of the funnel plot (based on serum ALT outcome) showed no publication bias (Figure 2).
| Author name | Location | Study design | Total | Males (%) | Age (years) | Baseline CLD (%) | Outcomes |
|-------------|----------|--------------|-------|-----------|-------------|-----------------|----------|
| Bloom et al. [2] | USA | Prospective | 60 | 39 (65.0) | 57 | 4 (7.0) | Liver injury |
| Cai et al. [6] | China | Retrospective | 298 | 145 (48.7) | 47.5 | 28 (9.4) | Liver injury; biomarkers: ALT, AST, and T. bilirubin |
| Cai et al. [7] | China | Cross-sectional | 417 | 298 (71.5) | 47.32 | 21 (5.04) | Liver injury; biomarkers: ALT, AST, and T. bilirubin |
| Chen et al. [8] | China | Retrospective | 21 | 17 (81.0) | 56.5 | NR | Biomarkers: ALT, AST, T. bilirubin, and albumin |
| Chen et al. [4] | China | Retrospective | 274 | 171 (62.0) | 59.5 | NR | Biomarkers: ALT, AST, T. bilirubin, and albumin |
| Deng et al. [9] | China | Retrospective | 225 | 124 (55.1) | 54.5 | NR | Biomarkers: ALT and AST |
| Fu et al. [10] | China | Retrospective | 355 | 190 (53.5) | >60=115 | 9 (2.5) | Biomarkers: ALT, AST, T. bilirubin, and albumin |
| Gao et al. [11] | China | Retrospective | 43 | 26 (60.5) | 44.08 | NR | Biomarkers: ALT and AST |
| Huang C et al. [1] | China | Retrospective | 41 | 30 (73.0) | 49 | 1 (3.6) | Biomarkers: ALT and AST |
| Jin et al. [12] | China | Retrospective | 651 | 331 (50.8) | 45.61 | 25 (3.8) | Biomarkers: ALT, AST, T. bilirubin, and albumin |
| Lei et al. [13] | China | Retrospective | 5,771 | 2,724 (47.2) | 56 | 81 (1.4) | Liver injury |
| Liu et al. [14] | China | Retrospective | 78 | 39 (50.0) | 51.5 | NR | Biomarkers: ALT, AST, and albumin |
| Mo et al. [15] | China | Retrospective | 155 | 86 (55.5) | 53.5 | 7 (4.5) | Biomarkers: ALT, AST, and albumin |
| Pan et al. [16] | China | Retrospective | 204 | 107 (52.5) | 52.9 | 2 (0.01) | Biomarkers: ALT, AST, T. bilirubin, and albumin |
| Phipps et al. [17] | USA | Retrospective | 2,273 | 1,297 (57.1) | 65 | 114 (5.0) | Liver injury |
| Qian et al. [18] | China | Retrospective | 91 | 37 (40.7) | 57.5 | NR | Biomarkers: ALT, AST, and albumin |
| Qu et al. [19] | China | Retrospective | 30 | 16 (53.3) | 54.7 | Excluded (0) | Biomarkers: ALT and AST |
| Study                | Country | Study Design | n    | Age Median (Range) | Sex | Disease | Biomarkers                  |
|---------------------|---------|--------------|------|--------------------|-----|---------|----------------------------|
| Ruan et al. [20]    | China   | Retrospective | 150  | 102 (68)           | 58.5 | 4 (2.7) | T. bilirubin and albumin   |
| Wan et al. [21]     | China   | Retrospective | 135  | 72 (53.3)          | 50  | 2 (1.5) | ALT, AST, T. bilirubin, and albumin |
| Wang et al. [22]    | China   | Retrospective | 138  | 75 (54.3)          | 58.5 | 4 (2.9) | ALT, AST, and T. bilirubin |
| Wang et al. [23]    | China   | Retrospective | 69   | 32 (46)            | 53.7 | 1 (1.4) | ALT and AST                |
| Wu et al. [24]      | China   | Retrospective | 201  | 128 (63.7)         | 53.25 | 7 (3.5) | ALT, AST, T. bilirubin, and albumin |
| Xie et al. [25]     | China   | Retrospective | 79   | 44 (55.7)          | 60  | Excluded (0) | ALT, AST, and T. bilirubin |
| Yang et al. [26]    | China   | Retrospective | 52   | 35 (67.0)          | 58.25 | 16 (30.8) | T. bilirubin               |
| Zhang et al. [27]   | China   | Retrospective | 645  | 328 (50.9)         | 40.77 | 25 (3.9) | ALT, AST, T. bilirubin, and albumin |
| Zhou et al. [28]    | China   | Retrospective | 34   | 17 (50.0)          | 65  | NR      | ALT and AST                |
| Zhou et al. [29]    | China   | Retrospective | 191  | 119 (62.0)         | 60.5 | NR      | ALT and albumin            |

**TABLE 2: Baseline characteristics and demographics of the included studies**

CLD, chronic liver disease; ALT, alanine transaminase; AST, aspartate transaminase; T. bilirubin, total bilirubin; NR, not reported
Liver injury

Liver injury was defined as an elevation in transaminases >3 times above the ULN. Five studies, including 8,817 COVID-19 positive patients, met the pre-defined inclusion criteria for liver injury \([2,6,7,13,17]\). The pooled proportion of patients with a history of CLD was 4.9% (2.2%-8.6%). The prevalence of liver injury was 15.7% (9.5%-23.0%), as shown in Figure 3, and this was significantly higher than the baseline CLD prevalence (p < 0.001).
Levels of liver biomarkers were reported by 25 studies comprising 10,084 patients (2,900 severe COVID-19 and 7,184 non-severe COVID-19 patients) [1,4-6,16,18-29]. Our analysis shows that serum ALT (WMD: 7.19 [4.90, 9.48]; p < 0.001; I² = 69%), AST (WMD: 9.02 [6.89, 11.15]; p < 0.001; I² = 73%), and total bilirubin levels (WMD: 1.78 [0.86, 2.70]; p < 0.001; I² = 82%) were significantly higher in patients with severe COVID-19 when compared to patients with non-severe disease. Albumin levels were significantly lower in patients with severe COVID-19 (WMD: -4.16 [-5.97, -2.35]; p < 0.001; I² = 95%). The individual forest plots for ALT, AST, total bilirubin, and albumin are shown in Figures 4-7, respectively.
FIGURE 4: Forest plot showing the association between serum ALT levels and severity of disease in COVID-19 patients

SD, standard deviation; IV, inverse variance; CI, confidence interval; ALT, alanine transaminase; COVID-19, coronavirus disease 2019

FIGURE 5: Forest plot showing the association between serum AST levels and severity of disease in COVID-19 patients

SD, standard deviation; IV, inverse variance; CI, confidence interval; AST, aspartate transaminase; COVID-19, coronavirus disease 2019
The serum levels of all biomarkers for severe and non-severe COVID-19 patients in each study are given in Table 3. The criterion used to diagnose COVID-19 in each study is given in the Appendices section.
| Authors          | N  | M  | Param1 | Param2 | Param3 | Param4 | Param5 | Param6 | Param7 | Param8 | Param9 | Param10 | Param11 | Param12 | Param13 | Param14 | Param15 | Param16 | Param17 | Param18 | Param19 | Param20 | Param21 | Param22 | Param23 | Wu et al. |
|------------------|----|----|--------|--------|--------|--------|--------|--------|--------|--------|--------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Cai et al. [6]   | 58 | 240| 26.85±16.32 | 20±12.11 | 36±15.9 | 26±10.83 | 11.25±7.76 | 10.9±1.18 | -      | -      | -      | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       |
| Cai et al. [7]   | 85 | 233| 67±42.0 | 41±33.47 | 58±41.08 | 34±14.41 | 22±7.88 | 19±10.38 | -      | -      | -      | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       |
| Chen et al. [8]  | 11 | 10 | 42±12.96 | 16±6.29 | 47±34.44 | 24±3.70  | 8.80±1.92 | 7.80±1.29 | 29.60±3.25 | 37.20±2.22 |
| Chen et al. [4]  | 113| 161| 28.00±21.48 | 20.00±12.74 | 45.00±26.66 | 25.00±9.85 | 12.60±4.4 | 8.40±1.18 | 30.10±3.77 | 36.30±4.29 |
| Deng et al. [9]  | 109| 116| 22.00±14.07 | 18.70±13.2 | 34.00±14.81 | 22.00±10.44 | -      | -      | -      | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       |
| Fu et al. [10]   | 88 | 211| 23.0±20.39 | 22.0±15.99 | 29.0±24.5 | 26.0±11.94 | 10.9±6.47 | 7.80±2.29 | 37.3±5.0 | 40.5±5.75 |
| Gao et al. [11]  | 15 | 28 | 27.00±14.81 | 24.50±16.29 | 27.80±11.42 | 33.21±3.77 | -      | -      | -      | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       |
| Huang et al. [1] | 13 | 28 | 49.00±63.7 | 27.00±15.18 | 44.00±29.62 | 34.00±12.22 | 14.00±15.55 | 10.80±2.14 | -      | -      | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       |
| Jin et al. [12]  | 74 | 577| 25.00±16.82 | 21.50±13.18 | 29.35±13.14 | 24.40±2.69 | 10.00±4.92 | 9.60±2.29 | 40.13±4.92 | 41.50±3.8 |
| Lei et al. [13]  | 1186| 4585| 26.0±22.47 | 23.0±18.31 | 31.0±20.01 | 22.0±11.05 | 10.8±5.62 | 10.3±4.84 | -      | -      | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       |
| Liu et al. [14]  | 11 | 67 | 17.40±22.22 | 18.50±11.25 | 21.60±24.88 | 20.00±12.59 | -      | -      | 36.62±6.6 | 41.27±4.55 |
| Mo et al. [15]   | 85 | 70 | 28.00±18.51 | 20.00±13.33 | 37.00±29.62 | 32.00±11.11 | -      | -      | 36.00±5.92 | 39.00±4.44 |
| Pan et al. [16]  | 103| 101| 42.24±43.83 | 29.53±23.58 | 35.12±26.58 | 27.48±23.98 | 13.83±12.03 | 13.46±8.11 | 36.16±6.49 | 35.84±5.63 |
| Qian et al. [18] | 9  | 82 | 19.90±8.88 | 18.00±11.85 | 27.00±2.4 | 21.00±8.88 | -      | -      | 38.55±2.16 | 40.20±3.25 |
| Qu et al. [19]   | 3  | 27 | 36.00±19.52 | 33.59±24.54 | 45.33±12.9 | 43.56±21.03 | -      | -      | -      | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       |
| Ruan et al. [20] | 68 | 82 | -      | -      | -      | -      | -      | -      | 18.10±10.7 | 12.80±6.8 | 28.80±3.8 | 32.70±3.8 |
| Wan et al. [21]  | 40 | 95 | 26.60±13.92 | 21.70±16.37 | 33.60±13.70 | 22.40±10.07 | 9.80±5.77 | 8.60±2.22 | 36.00±4.0 | 49.90±4.59 |
| Wang et al. [22] | 36 | 102| 35.00±28.14 | 23.00±15.55 | 52.00±29.62 | 29.00±12.59 | 11.50±6.66 | 9.30±3.40 | -      | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       |
| Wang et al. [23] | 14 | 55 | 31.50±21.48 | 24.00±17.77 | 40.50±28.14 | 26.00±13.33 | -      | -      | -      | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       | -       |

**Note:** The table provides a summary of parameters across different studies. Each row represents a study, with columns indicating various parameters and values.
TABLE 3: Serum levels of ALT, AST, total bilirubin, and albumin among severe and non-severe COVID-19 patients in the included studies
COVID-19, coronavirus disease 2019; ALT, alanine transaminase; AST, aspartate transaminase

| Study          | N  | Age (mean±SD) | ALT (mean±SD) | AST (mean±SD) | Total Bilirubin (mean±SD) | Albumin (mean±SD) |
|----------------|----|---------------|---------------|---------------|--------------------------|-------------------|
| Xie et al. [24] | 84 | 35.00±22.96   | 27.00±17.40   | 38.00±16.66   | 30.00±10.74              | 10.50±3.74        |
|                |    |               |               |               |                          |                   |
| Yang et al. [25]| 28 | 36.5±41.31    | 30.0±17.6     | 35±22.95      | 28±20.34                 | 12.7±5.6          |
|                |    |               |               |               |                          |                   |
| Zhang et al. [26] | 32 | -             | -             | -             | 19.5±11.6                | 13.1±4.3          |
|                |    |               |               |               |                          |                   |
| Zhou et al. [27]| 573| 29.37±25.1    | 25.53±19.96   | 30.08±20.37   | 25.57±15.52              | 9.11±4.86         |
|                |    |               |               |               |                          |                   |
| Zhou et al. [28]| 8  | 49.00±34.07   | 34.00±29.62   | 44.00±16.29   | 32.00±14.81              | -                 |
|                |    |               |               |               |                          |                   |
| Zhou et al. [29]| 54 | 40.00±20.0    | 27.00±18.51   | -             | -                        | 29.10±3.55        |
|                |    |               |               |               |                          |                   |

Discussion

Our meta-analysis has three salient findings. Firstly, almost 16% of the COVID-19 positive patients had a substantial elevation in enzymes (>3 times the ULN). Secondly, the prevalence of current liver injury in hospitalized COVID-19 patients was significantly higher than the prevalence of patients with known pre-COVID CLD. Thirdly, the extent of liver damage was associated with the severity of COVID-19.

Although our study demonstrates a clear association between COVID-19 and liver injury, mechanisms for liver injury remain unclear. Direct injury by SARS-CoV-2 has been proposed as a likely mechanism [3]. The expression of ACE2 protein (entry receptor for SARS-CoV-2) on bile duct cells supports the possibility of virus-mediated liver damage [3]. However, there is a lower frequency of receptors found in liver cells than bile duct cells, and trends show an elevation in aminotransferases rather than alkaline phosphate and gamma-glutamyl transferase [3,6,7,17]. Thus, alternate mechanisms must be considered as well.

Apart from direct viral-mediated injury, drug-induced liver injury must also be given consideration. Acetaminophen, a drug commonly used by COVID-19 patients, is known to cause hepatic injury at doses >7.5 to 10 g in adults [30]. In addition, the simultaneous use of multiple antiviral therapies and antibiotics in these patients can be hepatotoxic [17,21-23]. Aggressive treatment in patients with more severe disease may explain the association of liver injury with disease severity seen in our study.

Systemic effects of COVID-19 could be another possible explanation for the liver injury. It is proven that SARS-CoV-2 infects the lung causing hypoxia and, in severe cases, acute respiratory distress syndrome, sepsis, and multi-organ failure [1,4,9,17]. It can be imagined that sepsis in COVID-19 leads to hypoxic injury and ischemia of the liver, causing elevated liver biochemistries, which further explains why serum ALT, AST, and total bilirubin levels are higher in severe/ICU COVID-19 patients than non-severe patients, as demonstrated in our
To the best of our knowledge, this is the first meta-analysis to report the prevalence of liver injury in COVID-19 patients while keeping the definition of liver injury standard and accounting for baseline CLD history. Thus, these results should be generalizable across cohorts of hospitalized COVID-19 patients. Our results should stimulate further research interest in the area in order to uncover mechanisms contributing to liver injury.

**Limitations**

This study has certain important limitations. Firstly, the quality of data-collection methods and data reported in individual studies cannot be ascertained. Secondly, patients can sometimes be unaware of underlying CLD (e.g., in non-alcoholic fatty liver disease), and these patients may be misclassified as having no CLD. This could have led to an underestimation of baseline CLD prevalence. Third, as shown, estimates from our study had significantly high heterogeneity. This is likely due to the inclusion of primarily small studies with varied prevalence. Lastly, all included studies were of observational nature, and there is a need for randomized trials on this aspect of COVID-19. Although meta-analysis can increase the power and provide better estimates, the results are intended to offer early insight and should not be considered a replacement for large-scale observational studies that are being awaited.

**Conclusions**

This systematic review and meta-analysis shows that COVID-19 is associated with an increased incidence of liver injury. Furthermore, the extent of derangement in serum liver function markers is associated with the severity of COVID-19. Future studies should adopt a pre-defined criterion for reporting liver injury and exclude those patients from the analyses that had any form of baseline derangement in liver enzymes and biomarkers at hospital admission. A standard protocol should be formed for COVID-19 patients to identify them as 'with liver injury' or 'without liver injury', as this will lead to uniform reporting and low bias in studies.

**Appendices**

| Author name | Diagnostic criteria |
|-------------|---------------------|
| Cai et al. [6] | WHO interim guidance for COVID-19 |
| Cai et al. [7] | Handbook of Prevention and Treatment of the Pneumonia Caused by the 2019-nCoV by National Health Commission of China |
| Chen et al. [8] | 6th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
| Chen et al. [4] | 6th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
| Deng et al. [9] | 6th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
| Fu et al. [10] | Diagnosed on basis of typical clinical manifestations accompanied with characteristic chest radiology changes |
| Author(s) | Reference | Diagnosis of pneumonia or guidelines for COVID-19 |
|-----------|-----------|--------------------------------------------------|
| Gao et al. [11] | WHO interim guidance for COVID-19 |
| Huang et al. [1] | Diagnosis of pneumonia was based on clinical characteristics, chest imaging, and excluding common pathogens that cause pneumonia |
| Jin et al. [12] | 6th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
| Lei et al. [13] | WHO interim guidance for COVID-19 |
| Liu et al. [14] | 4th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
| Mo et al. [15] | Diagnosis of pneumonia was based on clinical characteristics and chest imaging |
| Pan et al. [16] | WHO interim guidance for COVID-19 |
| Qian et al. [18] | 4th and 5th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
| Qu et al. [19] | 6th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
| Ruan et al. [20] | Pneumonia was diagnosed on clinical characteristics and chest imaging |
| Wan et al. [21] | WHO interim guidance for COVID-19 |
| Wang et al. [22] | WHO interim guidance for COVID-19 |
| Wang et al. [23] | 6th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
| Wu et al. [24] | WHO interim guidance for COVID-19 |
| Xie et al. [25] | WHO interim guidance with laboratory-identified COVID-19 |
| Yang et al. [26] | WHO interim guidance for COVID-19 |
| Zhang et al. [27] | WHO interim guidance for COVID-19 and 6th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
| Zhou et al. [28] | 4th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
| Zhou et al. [29] | WHO interim guidance for COVID-19 and 6th edition guidelines for diagnosis and management of COVID-19 by the National Health Commission of China |
TABLE 4: Diagnostic criteria used for the assessment of severity of COVID-19 among patients in the included studies

WHO, World Health Organization; COVID-19, coronavirus disease 2019; 2019-nCoV, 2019 novel coronavirus

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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