

# Risk of hepatic failure in COVID-19 patients: A systematic review and meta-analysis

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## SUMMARY

Liver injury has been reported to occur during the disease in severe cases. Therefore, this meta-analysis study aims to investigate the incidence of liver injury among published literature from 2019-Jan-01 to 2020-April-03 to provide an outline for further studies on the liver injury of COVID-19.

Four databases including Pubmed, Embase, Web of Science, and the Scopus were searched for studies published from 2019-Jan-01 to 2020-April-03. Data analysis and drawing of charts were performed using the Comprehensive Meta-Analysis Software Version 2.2 (Biostat, USA).

The search yielded 450 publications, of which 64 potentially eligible studies were identified for full-text review and 21 studies fulfilling the inclusion criteria remained. A total of 4191 COVID-19 patients were included in our meta-analysis. The pooled prevalence of

liver injury was 19.5% (95% CI: 14.3-26.1). According to our results, there was significant heterogeneity among the 19 studies ( $X^2=738.5$ ;  $p<0.001$ ;  $I_2=94.34\%$ ). Among 288 death cases, the pooled prevalence of liver injury was 22.8% (95% CI: 11.7-39.8).

In summary, the COVID-19 disease itself can result in severe and even fatal respiratory diseases and even may lead to ARDS and multiple organ failure. The results of this systematic review highlight the importance of liver injury that may assist clinicians anywhere in the globe in controlling COVID-19-related infection and complications. Moreover, the prevalence of liver injury can be higher in severe cases than in mild cases.

*Keywords:* SARS-CoV-2, COVID-19, Liver injury, Meta-analysis.

## INTRODUCTION

Since December 2019, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) emerged in Wuhan city of central China [1]. These viruses can cause respiratory, intestinal, hepatic, and neuronal diseases and may lead to acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), and even death in severe cases [2, 3]. Mild cases of COVID-19 presented symptoms like fever dry cough, fatigue, vomit,

and diarrhea [4]. In severe cases, respiratory distress and/or hypoxemia occurred one week after the onset of the disease and then deteriorated into ARDS, septic shock, metabolic acidosis, and even death [5]. Recent studies have reported the presence and expression of angiotensin-converting enzyme 2 (ACE2) as a functional receptor for SARS-CoV-2 in pulmonary epithelial cells. Also, it has been observed probably in cardiomyocytes and renal tubular epithelial cells [6-8]. To date, a comprehensive analysis of clinical manifestations of COVID-19 revealed that SARS-CoV-2 infection not only caused severe acute respiratory syndrome but also multiple organ injuries, including lymphocyte reduction, myocardial dysfunction, and even acute renal failure. In many clinical sur-

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veys, liver dysfunction has also been observed, indicating a possibility that in patients with COVID-19 may cause hepatic injury [9].

Recent investigations on complications of COVID-19 have revealed that the occurrence of liver injury ranged from 14.8% to 53%. Also, it is accompanied mainly by abnormal ALT/AST levels followed by slightly elevated bilirubin levels [10]. The proportion of liver injury in death cases and severe COVID-19 patients was significantly higher than that in mild patients [11, 12]. Currently, studies on the proportion of liver injury caused by SARS-CoV-2 are limited.

Thus far, several studies have investigated the characteristics of liver injury caused by SARS-CoV-2 infection; however, a larger number of systematic reviews are needed to understand the proportion of liver injury in COVID-19 patients. Therefore, this meta-analysis study aims to investigate the incidence of liver injury among published literature from 2019-Jan-01 to 2020-April-03 to provide an outline for further studies on the liver injury of COVID-19.

## ■ METHODS

### *Search strategies*

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines by searching databases including Pubmed, Embase, Web of Science, and the Scopus from 2019-Jan-01 to 2020-April-03 to find relevant studies.

The search strategy was based on the following keywords: COVID-19, severe acute respiratory syndrome coronavirus 2, novel coronavirus, SARS-CoV-2, nCoV disease, SARS2, COVID19, Wuhan coronavirus, Wuhan seafood market pneumonia virus, 2019-nCoV, coronavirus disease-19, coronavirus disease 2019, 2019 novel coronavirus, Wuhan pneumonia, "Liver injury" OR "Liver abnormality" OR "Liver damage" OR "hepatic damage" OR "liver function abnormality" OR "hepatocellular injury". These keywords were used in the titles, abstracts, and keywords fields. The reference list for each selected paper and relevant review articles were checked to identify missing studies.

### *Selection criteria and quality assessment*

Two reviewers checked the search results in the databases with relevant keywords independent-

ly and analyzed the titles, abstracts, and full texts to apply eligibility for inclusion according to inclusion criteria, and discrepancies were resolved through discussion. No restriction based on the publication language was set, but at least the abstract must be available in English.

Included studies met the following inclusion criteria: patients were confirmed and diagnosed according to the criteria recommended by WHO (i.e., epidemiological history, clinical symptoms, and laboratory or radiological findings), and the data for complication findings and liver abnormalities were included. All of the studies that reported any kind of hepatic failure were included. Duplicate publications, unpublished papers, case reports, reviews, animal studies, and letters were excluded. Studies with lacking information about patients' characteristics and complications were also excluded.

Only available data from published articles were collected. If all laboratory findings related to liver function were reported but the rate of Liver injury of any population studies was not reported, it was regarded as "not available" and excluded from the meta-analysis. The procedure of the literature search is shown in Fig. 1.

### *Quality assessment and data extraction*

Reporting of Observational Studies in Epidemiology (STROBE) statement was used for assessing the quality of studies independently by two researchers, and any disagreements were resolved by consensus [13]. Criteria related to title and abstract, introduction, methods, results, discussion, and other information were assessed and a score was assigned to each item. Then, the following data were extracted from eligible studies by two researchers including first authors, location of study, year of publication, detection methods of SARS-CoV-2, age of patients, the sample size of confirmed COVID-19, and the incidence of liver injury. Inconsistencies between the researchers were discussed to reach consensus.

### *Statistical analysis*

The meta-analysis was performed using the random-effects model to estimate the pooled prevalence and corresponding 95% confidence interval (CI). Heterogeneity between studies was assessed using the Cochran's Q statistic and I-square (I<sup>2</sup>) test. Publication bias was assessed graphically

using a funnel plot and mathematically using the Begg’s rank correlation and Egger’s weighted regression test. Through these analyses,  $P < 0.05$  was considered indicative of statistically significant publication bias. Analysis of data and construction of graphs was performed by Comprehensive Meta-Analysis Software Version 2.2 (Biostat, USA).

## RESULTS

The search yielded 450 publications, of which 64 were identified as potentially eligible for full-text review. Finally, 21 studies fulfilled the inclusion criteria (Figure 1, Table 1) [3, 5, 9, 12, 14-29]. Also, except for one study performed in the USA, all studies were conducted in China. The sample size of the studies ranged from 21 to 788 patients. The real-time reverse transcriptase-polymerase chain reaction (RT-PCR) was applied to detect SARS-CoV-2 infection. A total of 4191 COVID-19 patients were included in our meta-analysis. Moreover, 288 death cases were included.

Nineteen studies have considered liver injury among patients suffering from COVID-19. The pooled prevalence of liver injury was 19.5% (95% CI: 14.3-26.1) (Figure 2). According to our results, there was significant heterogeneity among these 19 studies ( $X^2 = 738.5$ ;  $p < 0.001$ ;  $I^2 = 94.34\%$ ).

Also, Begg’s and Egger’s tests were performed to evaluate the publication bias. Based on the results of Begg’s ( $z = 0.31$ ,  $p = 0.75$ ) and Egger’s tests ( $t = 0.24$ ,  $p = 0.4$ ), there was no significant publication bias (Figure 3).

Among the 288 death cases, the pooled prevalence of liver injury was 22.8% (95% CI: 11.7-39.8) (Figure 4). Based on our results, there was significant heterogeneity among the four studies ( $X^2 = 296.2$ ;  $p < 0.01$ ;  $I^2 = 85.93\%$ ). Moreover, Begg’s and Egger’s tests were performed to evaluate the publication bias. Based on the results of Begg’s ( $z = 0.31$ ,  $p = 0.75$ ) and Egger’s tests ( $t = 1.05$ ,  $p = 0.4$ ), there was no significant publication bias. The funnel plot for publication bias did not show any evidence of asymmetry (Figures 3 and 5).

**Figure 1** - Flow chart of the study selection for inclusion in the systematic review.

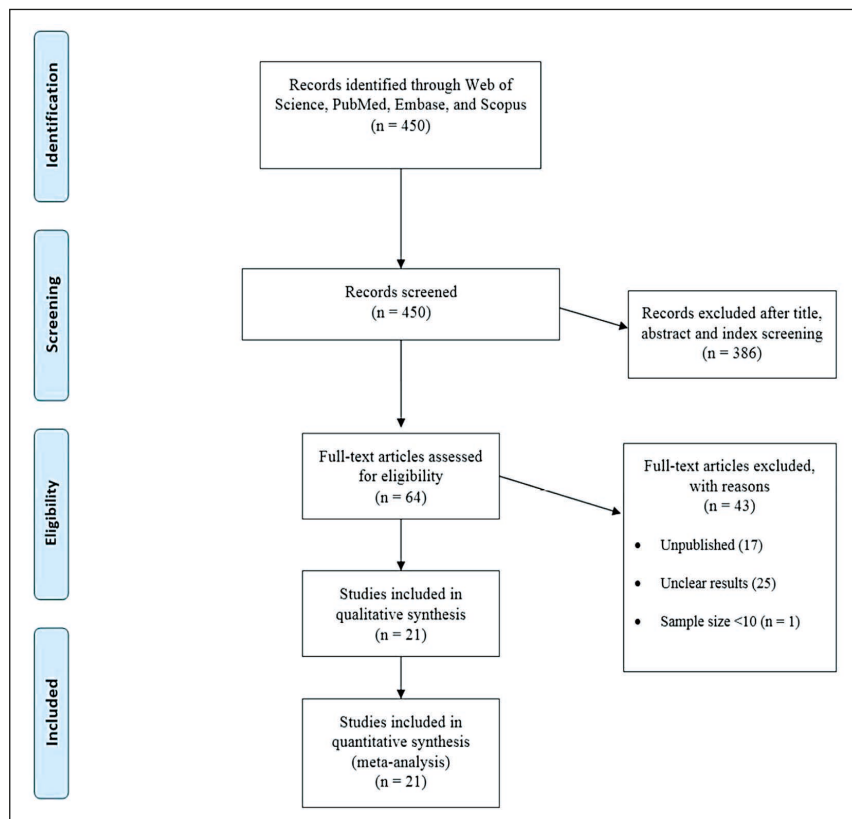


Table 1 - The characteristics of studies included in the meta-analysis a) active patients, b) dead patients.

a)

Number	Author	Location	Year	Age (Median)	SARS-CoV-2 Detection method	Case of COVID 19 No.	Case with liver damage or injury after admission No.	Ref
1.	Fu et al.	China	2020	-	RT-PCR	355	101	[20]
2.	Zhenyu et al.	China	2020	50.5	RT-PCR	148	41	[9]
3.	Ya et al.	China	2020	44 in older group 1.3 in younger group	RT-PCR	32	10	[21]
4.	Na et al.	China	2020	53.8	RT-PCR	40	22	[27]
5.	Chen et al. (A)	China	2020	56.3	RT-PCR	21	1	[16]
6.	Qingxian et al.	China	2020	47	RT-PCR	298	44	[15]
7.	Wu et al.	China	2020	46.1	RT-PCR	80	3	[25]
8.	Chen et al. (B)	China	2020	55.5	RT-PCR	99	43	[17]
9.	Jin et al.	China	2020	45.1	RT-PCR	651	64	[22]
10.	Chen et al. (C)	China	2020	62	RT-PCR	387	23	[18]
11.	Zhang et al. (A)	China	2020	46.6	RT-PCR	645	81	[29]
12.	Arentz et al.	USA	2020	70	RT-PCR	21	3	[14]
13.	Tang et al.	China	2020	67	RT-PCR	73	33	[3]
14.	Wang et al.	China	2020	69	RT-PCR	404	118	[5]
15.	Yang et al.	China	2020	59.7	RT-PCR	52	15	[12]
16.	Xie et al.	China	2020	60	RT-PCR	79	29	[26]
17.	Lian et al.	China	2020	68.2 in older group 41.1 in younger group	RT-PCR	788	82	[23]
18.	Liu et al.	China	2020	68 in older group 47 in younger group	RT-PCR	56	10	[24]
19.	Zhang et al. (B)	China	2020	57	RT-PCR	140	8	[28]

b)

Number	Author	Location	Year	Age (Median)	COVID-19a detection	Death case of COVID 19 No	Case with liver damage or injury after admission No	Ref
1.	Li et al.	China	2020	73	RT-PCR	25	5	[35]
2.	Chen et al.	China	2020	68	RT-PCR	113	10	[18]
3.	Wang et al.	China	2020	76	RT-PCR	65	22	[5]
4.	Du et al.	China	2020	65.8	RT-PCR	85	30	[19]

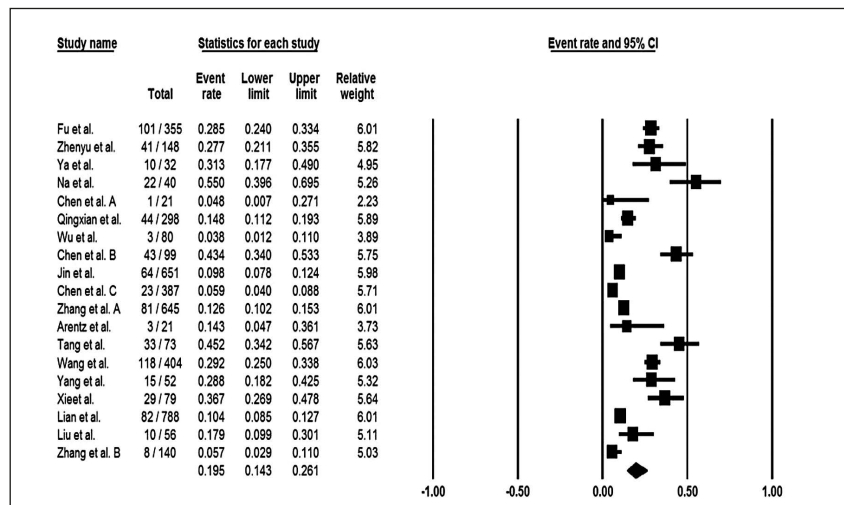
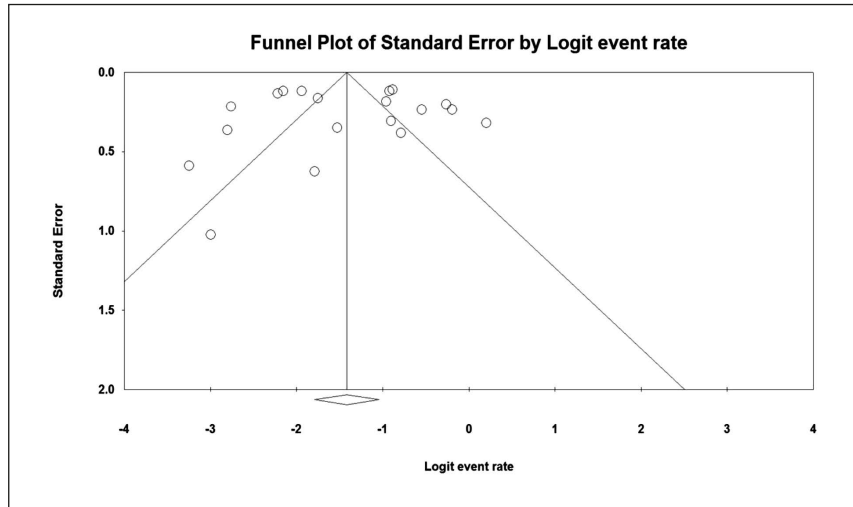
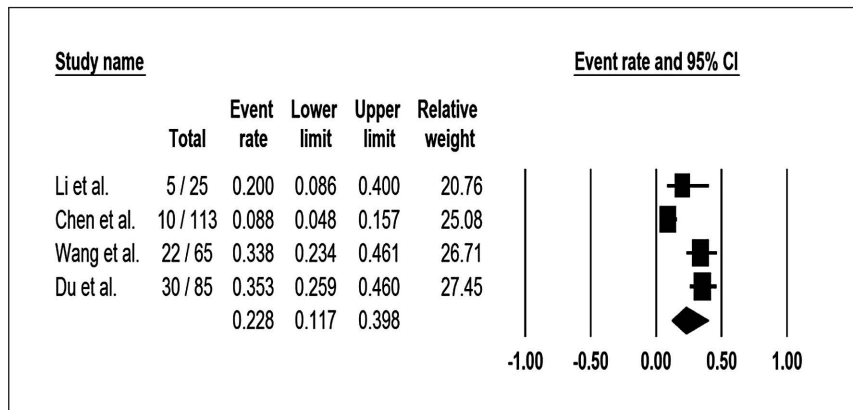


Figure 2 - Forest plots of the overall prevalence of liver injury among active COVID-19 patients.

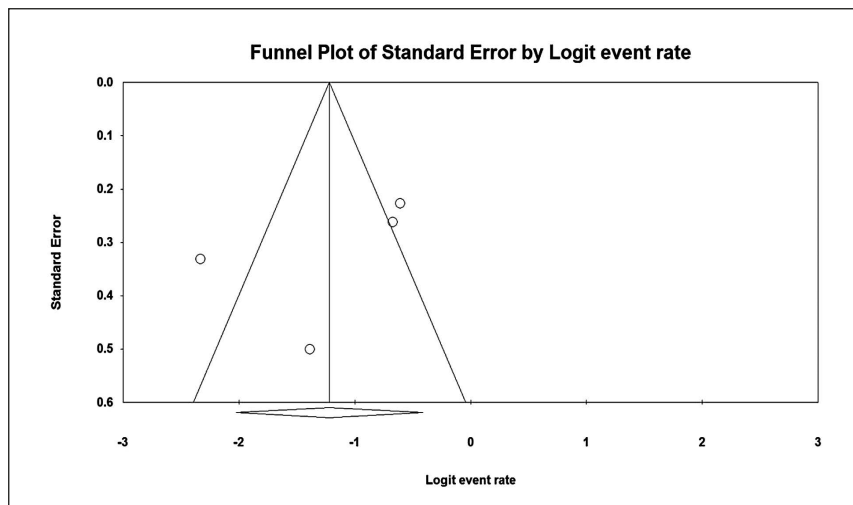
**Figure 3** - Funnel plot of publication bias for the included studies (Active patients).



**Figure 4** - Forest plots of the overall prevalence of liver injury among dead COVID-19 patients.



**Figure 5** - Funnel plot of publication bias for the included studies (dead patients).



## ■ DISCUSSION

In this study, we assessed the liver injury and epidemiologic features of COVID-19 to gain a better insight into this complication caused by SARS-CoV-2. According to our analysis, the pooled prevalence of liver injury in these patients was 19.5%. The previous meta-analysis revealed that acute hepatitis was the most common complication in 13.3% of cases, followed by cardiac injury [30]. These results are lower than the rate reported in our study. The main reason for the discrepancy of liver injury may be due to a small sample size of the previous meta-analysis and the data was reported only in 3 studies, while 19 studies were analyzed in our study [30]. The range of liver injury among the included studies was between 3% and 55% [21, 25]. Liver damage has been considered as an important risk factor for severe outcomes and death in some viral infections including MERS and SARS [10]. Previous studies have shown that liver injury mainly is investigated using elevated the level AST, ALT, and Total Bilirubin followed by slightly decreased Albumin levels [31]. Findings from this meta-analysis and other studies supported the hypothesis that liver injury is the most frequently damaged outside of the respiratory system [10, 30].

SARS-CoV-2 uses ACE2 as an entry receptor to enter into a host cell in the lungs, kidneys, and heart. Previous studies showed that endothelial cells of the liver cells and bile duct cells abundantly express ACE2 [32]. Therefore, it has been shown that the liver is a potential target for SARS-CoV. Moreover, the previous finding suggested that the liver damage might be due to the damage to bile duct cells, but not liver cells by the virus infection in COVID-19 patients [10].

Another important finding is a significant heterogeneity in the pooled analysis. This heterogeneity may be due to different sample sizes, various populations studied, and different assessment criteria for liver injury; therefore, the results should be interpreted with caution.

The mechanisms of liver injury during SARS-CoV-2 infection remain mainly unclear. Several factors may contribute to liver injuries such as viral infection in liver cells or other causes including antibiotics, antivirals, and steroids, psychological stress, systemic inflammation induced by cytokine storm, and pneumonia-associated hypoxia

induced by liver injury [33]. However, there is insufficient evidence for SARS-CoV-2 infected hepatocytes or virus-related liver injury in COVID-19 at present. In this regard, Fan et al. suggested that some drugs such as lopinavir/ritonavir should be prescribed with caution. In this regard, their results revealed that a significant proportion of hospitalized patients with impaired liver function had received lopinavir/ritonavir after admission [9].

The current study showed that the pooled prevalence of liver injury (22.8%) in death cases is slightly higher than the active cases. This finding showed that severe or death cases of COVID-19 have a higher percentage of liver injury compared to mild cases of COVID-19; this result is consistent with the findings in previous reports [26, 34]. According to a systematic review for sex distribution of COVID-19-related liver dysfunction by Feng et al., the proportion of infected men with liver injury was higher than that reported in infected women. Moreover, the age distribution of COVID-19-related liver dysfunction indicated that none of the children had abnormal serum liver enzymes and probably older age is associated with a higher likelihood of liver damage/dysfunction [1].

As one restriction of this study, interpretation of our meta-analysis findings might be limited by the small sample size.

In summary, the COVID-19 disease itself can result in severe and even fatal respiratory diseases and lead to ARDS and multiple organ failure. In this study, we reported the rate of liver injury caused by SARS-CoV-2 infection. The results of this systematic review highlight the importance of liver injury that may assist clinicians anywhere in the globe in controlling the COVID-19-related infection and complications. Moreover, the prevalence of liver injury can be higher in severe cases than in mild cases.

### Competing interests

The authors declare that they have no competing interests.

### Funding

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