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COVID-19 is associated with a high prevalence of liver damage: A systematic review and meta-analysis

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Abstract

Introduction: The Coronavirus Disease 2019 (COVID-19) outbreak is a serious threat to humans, and the impact of COVID-19 on the liver remains unexplored. At present, no meta-analysis has summarized available findings of COVID-19 patients with liver injury in depth. Thus, we aimed to scrutinize the association of the liver in COVID-19 patients and approximate the prognosis of COVID-19 patients with liver injury thoroughly.

Method: We searched different databases for qualified studies between December 2019 to May 2021. Finally, meta-analysis was carried out using fixed-effect or random-effect models based on the heterogeneity.

Result: Our Meta-analysis includes 32 studies with a total of 6,933 COVID-19 patients. The pooled prevalence of chronic liver disease (CLD) was 3.5%. Overall, the rates of severity and mortality in COVID-19 patients with underlying CLD were 4.6% and 19.2%, respectively. Additionally, the incidence of acute on chronic failure (ACLF) among COVID-19 patients with CLD was 25.1%. The prevalence of an increase in serum ALT, AST, TBil, and LDH levels was 39.5%, 28.6%, 26.5%, and 55.5%, respectively. Similarly, PT was prolonged in 8.3% of cases, and albumin was decreased in 66.8% of cases. The pooled prevalence of liver injury among COVID-19 patients was 28.2%. Strikingly, the patients with liver injury had significantly more severe disease (42.3%) and a higher incidence of mortality (18.5%) than the patients without liver injury.

Conclusion: In conclusion, more than one in five of the COVID-19 patients is at risk of developing a liver injury. Further, patients with liver injury have significantly more severe disease and a higher incidence of mortality than patients without liver injury. Thus, careful monitoring of liver function is advisable while treating COVID-19 patients.

Keywords: Coronavirus, COVID-19, Liver Injury, Liver Disease, SARS-CoV-2, Liver Function Test

Introduction

Coronavirus Disease 2019 (COVID-19) is common is a contemporary pandemic caused by severe acute respiratory syndrome 2 (SARS-CoV-2) virus.¹ Although, COVID-19 shows mild flu-like symptoms in the majority of the affected patients, in severe cases the disease may typically cause extensive damage to lungs and other vital organs leading to an acute respiratory distress syndrome (ARDS), multiple organ failures, and even death.^{2,3} Despite, the cause of apparent death in most of the patients is invariably respiratory failure, it has been evident that disease prognosis has largely been influenced by multiorgan involvement; hence, it is urgent to elucidate further clinical characteristics to improve sufficiently our understanding of the true magnitude of COVID-19, to improve diagnostic and treatment capabilities and reduce its overall impact on the disease progression.

The functional receptor for SARS-CoV-2 is typically angiotensin-converting enzyme 2 (ACE2) and is adequately expressed in different organ tissues like lungs, heart, kidney, intestine, and more recently in the liver.⁴⁻⁶ Indeed, a recent study found SARS-CoV-2 viral RNA in the liver tissue of COVID-19 patients.⁷ Furthermore, several published studies on COVID-19 have suggested there is a liver injury in COVID-19 patients and an abnormal liver function was positively associated with the disease severity and mortality.⁸ However, the results of recent studies have been inconsistent, with a vast disparity in reporting of liver injury.⁹⁻¹¹

At present, no meta-analysis has sufficiently summarized available findings of COVID-19 patients with liver injury in considerable depth. Therefore, we sincerely believe our meta-analysis is the first to carefully scrutinize the possible association of the liver in COVID-19 patients and approximate the possible prognosis of COVID-19 patients with liver injury thoroughly.

Method

Search strategy, Qualified studies for this systematic review and meta-analyses were carefully searched in-between December 2019 to 15 May 2021 in PubMed/MEDLINE, Embase, Cochrane Library databases, WHO database of COVID-19 publications, and COVID-19 resource center of various journals like Gastroenterology, American Journal of Gastroenterology, The Lancet, JAMA, BMJ, GUT, Hepatology, and New England Journal of Medicine by two authors (DKY and AS) independently with prior settled convention. The search was carried out with the proper use of the following Medical Subject Headings (MeSH) and non-MeSH terms: Coronavirus, novel Coronavirus, Coronavirus Disease 2019, COVID-19, severe acute respiratory syndrome coronavirus 2, and SARS-CoV-2. Additionally, the relevant bibliography lists of an article were looked to identify other published studies. Precisely, our extensive search was generally limited to, articles mainly published in English only. We didn't include any studies from the preprint databases such as medRxiv and bioRxiv since those are not peer-reviewed and the results presented in those papers might be misleading before any peer-review. We implemented the PRISMA guidelines¹² to carefully carry out this meta-analysis.

Study selection, To perform this meta-analysis, both retrospective and prospective studies were considered eligible in regards to the outcomes. Subsequently, properly considering the outcome aim and to safeguard the quality of this meta-analysis, we only considered full published original studies, and others like abstract, case reports, duplicate articles, and review articles were excluded. Moreover, we also designed pre-defined eligibility criteria for the preferential selection of studies with at least one outcome of interest. To overcome any problem with duplicate studies, we managed all our search results in EndNote (version X7.0).

Inclusion criteria, The inclusion criteria remain as follows: 1. The study with the confirmed cases of COVID-19. 2. The

published study with sufficient data to conduct a meta-analysis, like demographics, clinical features, liver function test panel, the prevalence of abnormal liver function, underlying liver disease, liver injury, and gastrointestinal findings in COVID-19 patients. 3. Adult participants (> 18 years of age).

Exclusion criteria, The exclusion criteria remain as follows: 1. Study without human population. 2. Study with pediatric patients and pregnant women. 3. A study without comparison arms. 4. Study with duplicate data from the same institution. 5. The articles, such as review, editorials, case reports, case series less than 10 subjects, conference, meta-analysis, and letters.

Data extraction, All data were meticulously extracted according to the pre-defined study selection criteria. The actual data were collected in a standardized data form in Microsoft Excel 2007 (Microsoft Corp). The extracted data routinely included the first author, study characteristics (year of publication, country, institution, and study design), population characteristics (age of the patients, sample size of comparison groups), patients comorbidities with liver disease, liver function related indexes, inflammation-related indexes, complications, and outcomes. Moreover, in the event of insufficient data, investigators were approached to collect more relevant results. Conflicts in data extraction were resolved by discussion or consensus with the 3rd reviewer.

Definitions, In most of the studies, the diagnosis of COVID-19 and classification was usually done according to World Health Organization (WHO) guidance and the recommendations based on the diagnostic criteria by the National Centers for Disease Control and Prevention of China (CDC China).^{13,14}

The severity of COVID-19 was defined often according to the studies, which was primarily based on the chest radiography, clinical examination, and presenting symptoms at the time of diagnosis, like following patients were

classified under severe cases: specific need of hospital admission,¹⁵ abnormal imaging findings,¹ need of admission in the intensive-care unit (ICU),⁹ progressions of disease,¹⁶ patients with pulse oxygen saturation (SpO₂) ≤90%,¹⁷ and patient with ARDS.² A clinical outcome of the disease was defined as the survivor or non-survivor and died or discharged.

There were no proper consensus definitions on liver injury between studies. Most of the studies frequently defined liver injury when there was an increase in values of liver function-related indexes like alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), gamma-glutamyltransferase (GGT), and alkaline phosphatase (ALP) above the baseline value.

Quality assessment, We thoroughly evaluated the quality of included studies with the Newcastle-Ottawa scale (NOS).¹⁸ The scale consists of three assessment factors: 1) assessment of a selection of the study groups; 2) comparability of the two groups; and 3) outcome assessment. The NOS ranges from 0 to 9. Studies with scores ≥ 7 were generally treated as a high quality, scores between 4 to 6 were treated as moderate quality, and scores ≤ 4 were treated as a low quality (Supplementary Table 1). Publication bias was accordingly examined using funnel plots (Supplementary Figure 10).

Statistical analysis, All data collected from the included studies were double-checked. To accurately estimate the mean and standard deviation (SD) from the given median and range value, we employed the preferred method devised by Hozo et. al.,¹⁹ and to customarily combine means and SD of the two given arms, we popularly used formula provided by Altman et. al.²⁰ A pooled meta-analysis was carried out with an OpenMeta Analyst and other all meta-analysis were carried out with RevMan Version 5.3 (Review Manager, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Outcomes are presented as pooled odds

ratios (ORs) and standardized mean difference (SMD) with 95% confidence intervals (CIs). Fixed-effect or random-effect models were used to estimate summary, according to the evaluation of heterogeneity. The Z-test was used to evaluate overall effects, and heterogeneity was assessed by using Cochran's χ^2 test. The I^2 statistic was used to evaluate heterogeneity, which was considered as low, moderate, or high with I^2 estimates $>25\%$, $>50\%$, and $>75\%$, respectively. Two-sided $P < 0.05$ was considered statistically significant.

Result

Study search and included studies, The database scan recognized 3,676 references for assessment, 171 full-text articles were assessed for eligibility. Further, 159 articles were excluded for not meeting the inclusion criteria or with insufficient data. The remaining 32 retrospective studies with a total of 6,933 patients were eligible according to the inclusion criteria, Figure 1. The necessary characteristics of the included studies in our meta-analysis are presented in Supplementary Table 2a, 2b.^{1-3,8-11,14-17,21-41} Out of 32 included studies, 18 studies^{1,2,8,9,11,14-17,21-28,30} compared the mild and severe groups of patients, nine studies^{3,31-38} compared survivor and non-survivor groups of patients, two studies^{40,41} compared survivor and non-survivor patients with chronic liver disease (CLD), and two compared patients with the liver injury and without liver injury.^{10,29} In addition, two studies^{14,26} of the mild and severe group also compared the patients stratified according to the liver injury.

Although we identified 32 studies for inclusion in the analysis, some of the studies were from the same institution or authors, Supplementary Table 3. These studies were only identified to calculate the outcome of interest and were not used together for any pooled meta-analysis. In the case of studies from the same institution or authors, for pooled meta-analysis or subgroup analysis, we only selected the studies with the higher

number of patients samples or those having sufficient data for carrying out a meta-analysis. All studies included in our meta-analysis were generally from China, except one from the USA,¹⁵ and one from the UK.⁴⁰

Meta-analysis

COVID-19 with underlying chronic liver CLD, From the total included studies, 12 studies^{1,2,8,10,14,15,17,21,25,28,33-35} reported data on the underlying CLD at the time of diagnosis, the pooled estimate of the prevalence of CLD was 3.5% (95% CI: 2.3–4.8; $I^2=80\%$; Figure 2). The most commonly reported CLD was liver cirrhosis and hepatitis B. When we compared CLD between the mild and severe group of COVID-19 patients there was not any significant difference between the groups (OR: 0.53; 95% CI: 0.21 to 0.1.33; $I^2= 59\%$; $P= 0.17$; Supplementary Figure 1a).^{1,8,14,15,17,21,25,28} In the same way, there was no any substantial variance between the survivor and non-survivor group for COVID-19 patients with underlying CLD (OR: 0.76; 95% CI: 0.13 to 4.39; $I^2= 92\%$; $P= 0.76$; Supplementary Figure 1b).^{32-36,40,41} However, from the trend of a forest plot, COVID-19 patients with underlying CLD seem to have more severe disease and considerable risk of mortality. Overall, the rates of severity and mortality in COVID-19 patients with underlying CLD were 4.6% (84/1838) and 19.2% (69/359), respectively. Additionally, the incidence of acute on chronic failure (ACLF) among COVID-19 patients with CLD was 25.1% (64/177) Figure 3.^{40,41}

Liver function related indexes in COVID-19,

The pooled mean ALT, AST, GGT, TBil, albumin, prothrombin time (PT), lactate dehydrogenase (LDH), and ALP were 28.53 U/L, 30.53 U/L, 35.27 U/L, 11.16 $\mu\text{mol/L}$, 35.52 g/L, 11.27s, 252.99 U/L, and 63.21 U/L, respectively. (Supplementary Table 4a; Supplementary Figure 2)

We analyzed the liver function-related indexes in between the mild and severe groups. A meta-analysis using a random-effect model exhibit that compared to the patients in the mild group, patients in the severe group had a tangible increased level of serum ALT,

AST, GGT, TBil, and LDH. However, the level of serum albumin was significantly decreased in the severe group compared to that of the mild group (SMD: 3.12; 95% CI: 1.92 to 4.32; $I^2= 98\%$; $P < 0.00001$). Yet, there were no considerable differences in PT and ALP between both groups, Supplementary Table 4b; Supplementary Figure 3.

Likewise, we also analyzed the liver function-related indexes between the survivor and non-survivor groups. A meta-analysis using a random-effect model revealed that compared to patients in the survivor group, patients in the non-survivor group had increased levels of serum ALT, AST, and LDH. Additionally, the PT was notably prolonged (SMD: -2.32; 95% CI: -3.95 to -0.69; $I^2= 99\%$; $P= 0.005$) and the level of serum albumin was significantly decreased (SMD: 2.47; 95% CI: 0.07 to 4.88; $I^2= 99\%$; $P = 0.04$) in the non-survivor group compared to that of the survivor group. There were no significant differences in serum GGT and TBil levels between both groups. Further, there were no data to carry out a meta-analysis of serum ALP level, Supplementary Table 4c; Supplementary Figure 4.

Prevalence of abnormal liver function related indexes in COVID-19, The pooled prevalence of increased in serum ALT, AST, TBil, and LDH level were 39.5%, 28.6%, 26.5%, and 55.5%, respectively. Correspondingly, PT was prolonged in 8.3%, and albumin was decreased in 66.8% of the cases. Not enough data were found to calculate the pooled prevalence of increase in serum GGT. However, only one study¹⁴ reported a total prevalence of increase in serum ALP level i.e. 9.7%, Supplementary Table 4d; Supplementary Figure 5.

We analyzed the prevalence of abnormal liver function related indexes in between the mild and severe groups, our meta-analysis found that compared to the patients in the mild group a significant proportion of the patients in the severe group had increased prevalence of serum ALT, AST, TBil, and LDH level compared to the mild group of COVID-19 patients. There were not enough data to

compare the prevalence of abnormal levels of GGT, ALP, PT, and albumin among the patients between these two groups, Supplementary Table 4e; Supplementary Figure 6.

Likewise, when we analyzed the prevalence of abnormal liver function-related indexes in between the survivor and non-survivor groups. We found that a significant number of the patients in the non-survivor groups had an increased prevalence of serum ALT and LDH levels compared to the survivor group. However, there were not enough data to compare the prevalence of abnormal levels of AST, TBil, GGT, ALP, PT, and albumin among the patients between both groups, Supplementary Table 4f; Supplementary Figure 7.

Prevalence of the liver injury in COVID-19, The pooled prevalence of liver injury, from 9 studies^{1,10,14,26,29-31,33,35,39,40} was 28.2% (95% CI: 20–36.4; $I^2=97\%$; Figure 4). We further stratified studies according to the liver injury, i.e. with and without liver injury. Additionally, when we compared age between these two groups, using a random-effect model we found that the patients in the liver injury group were proportionally older than the patients in without liver injury group (SMD: 0.64; 95% CI: 0.12 to 1.16; $I^2= 90\%$; $P= 0.02$; Supplementary Figure 8.^{10,14,26,29,39}

Associated complications and prognosis of COVID-19 patients with liver injury, The stratified studies according to the liver injury were further analyzed for associated complications and prognosis of COVID-19 patients. When we sought an association between the liver injury and gastrointestinal symptoms (i.e. diarrhea and nausea) in COVID-19 patients, we didn't find any significant difference between the patients with liver injury and without liver injury for gastrointestinal symptoms^{10,26,29,39} (OR: 0.69; 95% CI: 0.37 to 1.32; $I^2= 0\%$; $P= 0.27$; Supplementary Figure 9). We were equally interested in analyzing other complications associated with COVID-19 i.e. ARDS, acute kidney injury (AKI), and sepsis between the

patients with liver injury and without liver injury. However, there were not enough data to conduct the meta-analysis for these complications between the liver injury and without liver injury groups.

Using a random-effect model we found that patients with liver injury had significantly more severe disease^{1,10,14,30,39} (OR: 2.64; 95% CI: 1.55 to 4.48; I²= 52%; P= 0.0003) and a higher prevalence of mortality^{10,31,33,35,39} (OR:

1.74; 95% CI: 1.10 to 2.74; I²= 25%; P= 0.02) than patients without liver injury. However, length of hospital stay^{10,26,29,39} (SMD: 0.02; 95% CI: -1.53 to 1.56; I²= 98%; P= 0.98) was not varied between both the groups. In overall, the rate of severity and mortality in COVID-19 patients with liver injury were 42.3% (160/307) and 18.5% (45/243), respectively, Figure 5.

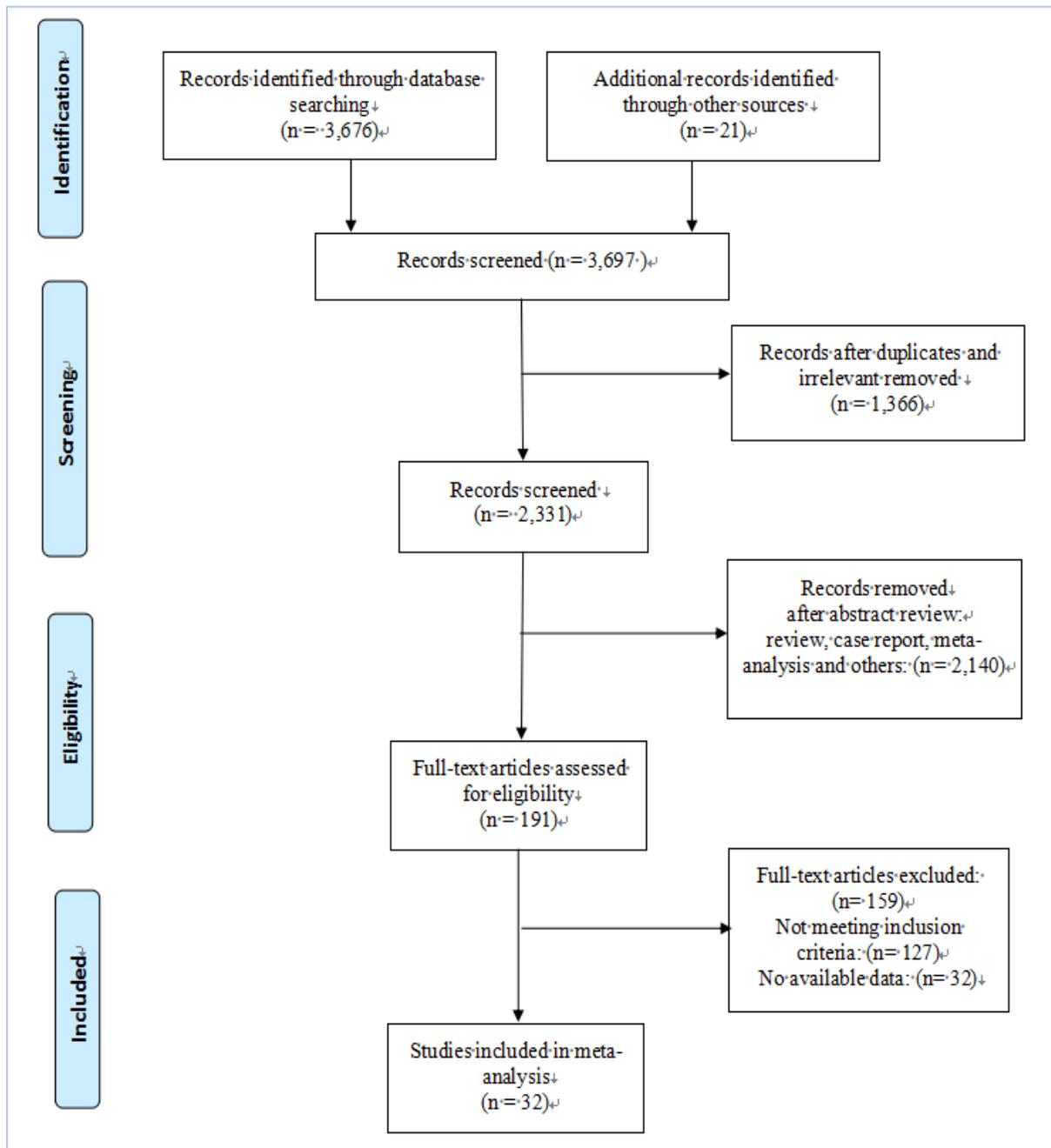


Figure 1. Flow diagram for literature search.

Drugs used in the treatment of COVID-19, We further analyzed drugs used in the treatment of COVID-19 patients stratified according to the liver injury i.e. with and without liver injury, three studies^{10,14,39} reported data on the drugs used in COVID-19 patients eg. Lopinavir/ritonavir, oseltamivir, antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs). We observed no significant differences between both the groups for the use of Lopinavir/ritonavir, Oseltamivir, antibiotics, and NSAIDs, Supplementary Table 4g.

Inflammation related Indexes in COVID-19, We analysed the inflammation related indexes in between the liver injury and without liver injury groups, liver injury group had significantly higher C-reactive protein (CRP)^{10,26,29,39} (SMD: 1.42; 95% CI: 0.33 to 2.50; I²= 96%; P= 0.01), erythrocyte sedimentation

rate (ESR)^{10,26,39} (SMD: 1.45; 95% CI 0.72 to 2.18; I²= 89%; P<0.0001), D-dimer^{26,39} (SMD: 1.08; 95% CI 0.80 to 1.36; I²= 0%; P< 0.00001) and absolute neutrophils count^{26,29,39} (SMD: 3.97; 95% CI: 1.50 to 6.43; I²= 98%; P= 0.002) level compared to without liver injury group. Likewise, absolute lymphocyte count^{10,26,29,39} (SMD: -0.88; 95% CI: -1.16 to -0.60; I²= 47%; P< 0.00001) was markedly decreased in liver injury group compared to without liver injury group. However, there was no obvious difference for procalcitonin level^{10,39} (SMD: 1.99; 95% CI: -1.93 to 5.91; I²= 99%; P= 0.32) between the both groups. Further, there were no enough data to perform a meta-analysis for other inflammation related markers like ferritin and interleukin 6 (IL-6) between both the groups, Supplementary Figure 10)

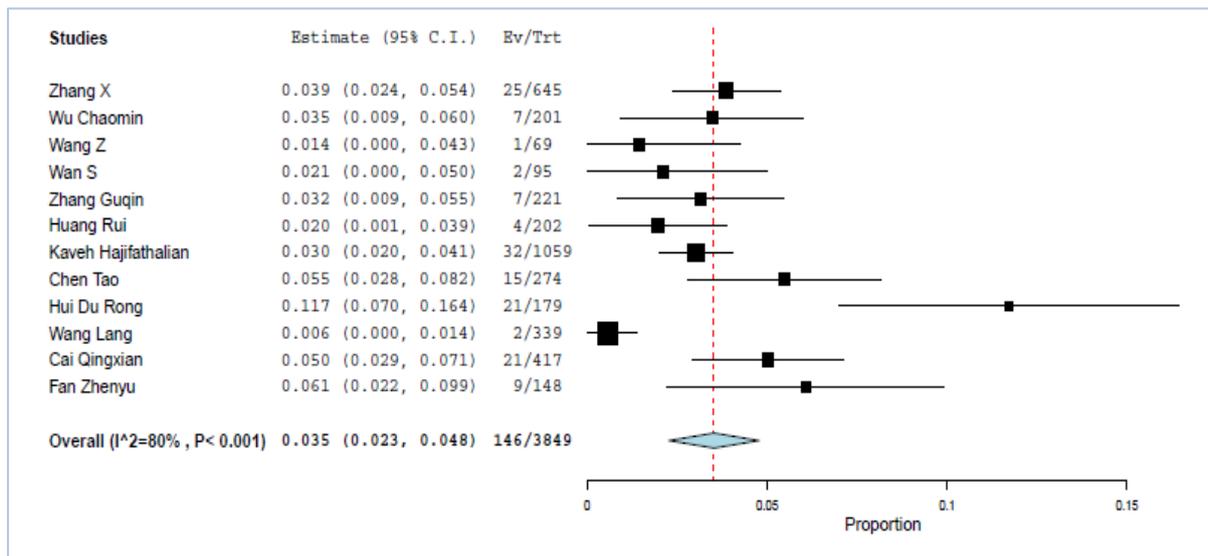


Figure 2. Forest plot for pooled estimate of the prevalence of chronic liver disease in COVID-19 patients.

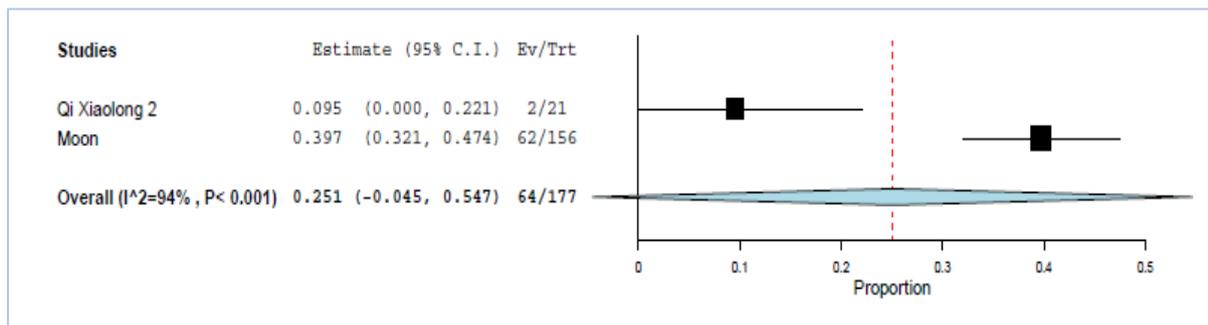


Figure 3. Forest plot for pooled estimate of the prevalence of ACLF in COVID-19 patients with chronic liver disease.

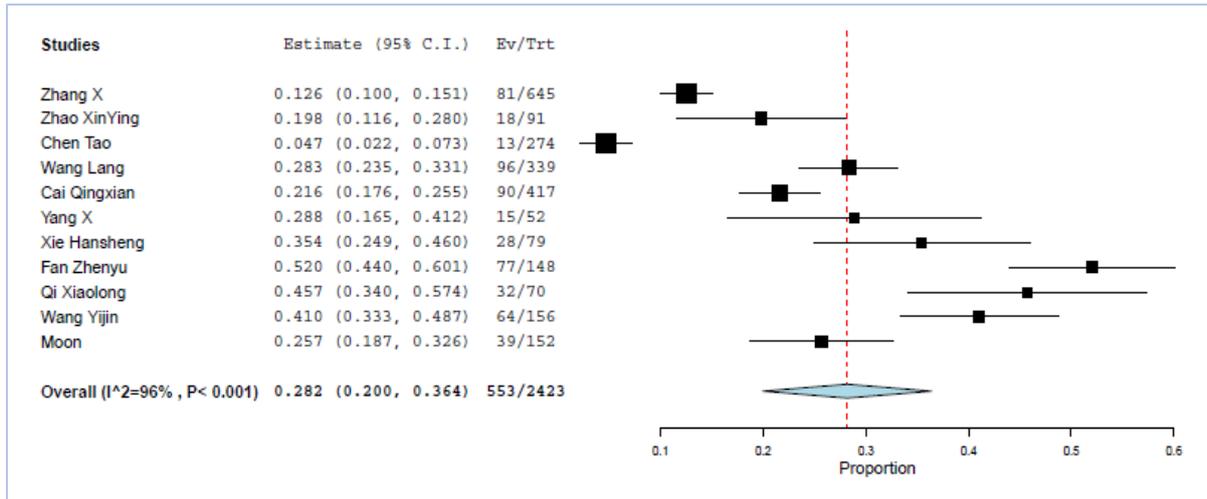


Figure 4. Forest plot for the pooled prevalence of liver injury in COVID-19 patients.

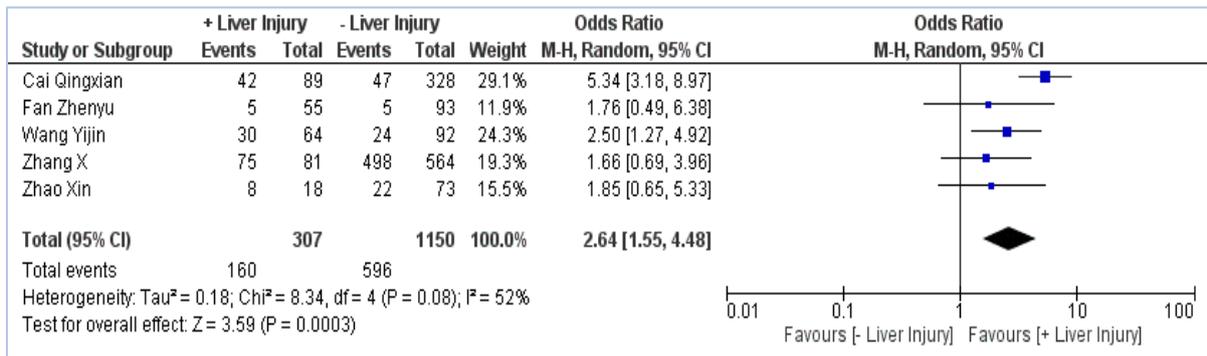


Figure 5a. Forest plot for prognosis of COVID-19 patients with liver injury, severity

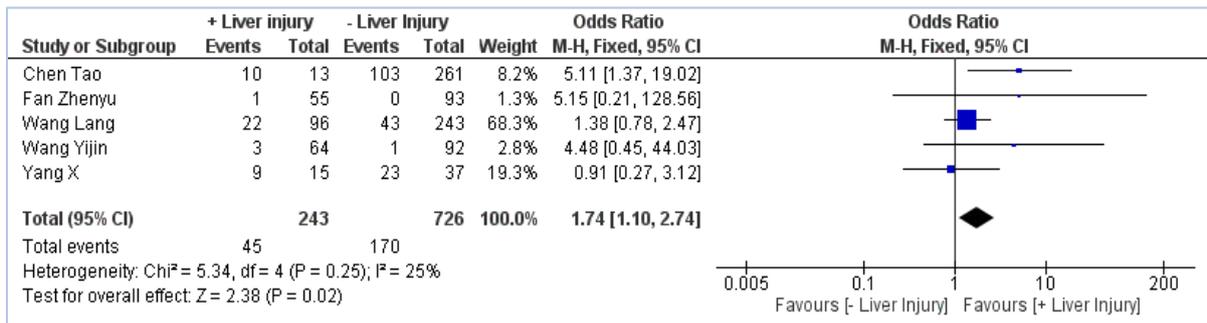


Figure 5b. Forest plot for prognosis of COVID-19 patients with liver injury, mortality

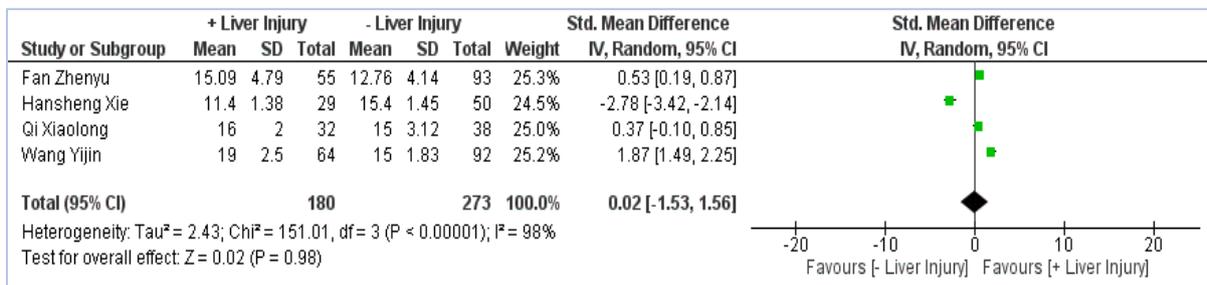


Figure 5c. Forest plot for prognosis of COVID-19 patients with liver injury, length of hospital stay

Discussion

Even though, many COVID-19 patients have abnormal liver function tests at the time of diagnosis¹⁰ the vast number of the published studies on COVID-19 only reported the disease severity and mortality based on respiratory complications. Thus, these studies might have overlooked the fact of the deleterious effect of COVID-19 on the liver. Besides, patients with underlying liver comorbidities might be at significant risk of severe disease and even death.

To date, only scarce meta-analyses have been carried out to contemplate the impact of COVID-19 on various vital organs. However, an earlier meta-analysis that was reported was not specific to the liver injury, and most of them haven't attempted to analyze the prevalence of the liver injury and its outcome in COVID-19 patients. Apart from this most of the previous meta-analyses used repeated studies from the same institutions which might have influenced the results of the meta-analysis. Our meta-analysis aimed to scrutinize the association of the liver in COVID-19 patients and approximate the prognosis of COVID-19 patients with liver injury. We assume it is the first meta-analysis to rigorously examine the impact of COVID-19 on the liver.

Liver injury in COVID-19 patients should be observed as harm to the liver developed during disease progression or treatment independent of prior liver comorbidities. Studies have demonstrated a wide range of abnormal liver function tests and prevalence of liver injury in COVID-19 patients.⁴² Fan et al.,¹⁰ found that 37.2% of the COVID-19 patients had an abnormal liver function at the time of admission. Comparably, Cai et al. also reported 76.3% of abnormal liver function tests in the patients admitted to their hospital.¹⁴ Roughly, there is primarily increased AST and ALT level, and bilirubin level in 14% to 64.15% of COVID-19 patients.^{9,10,14} Additionally, 48.74% of the hospitalized COVID-19 patients are reported to have raised in serum GGT level.¹⁴ Whereas,

albumin was decreased to 26.3-30.9 g/l in severe cases.⁴² Our findings showed the pooled prevalence of an increase in serum ALT, AST, TBil, and LDH levels were 39.5%, 28.6%, 26.5%, and 55.5%, respectively. Uniformly, PT was prolonged in 8.3%, and albumin was decreased in 66.8% of the cases.

Emerging data from the studies found the incidence of liver injury in COVID-19 was 21.5% to 45.71%.^{14,29} Pooled results from our meta-analysis suggest the incidence of liver injury was 28.2% among all COVID-19 patients. That means more than one out of the five COVID-19 patients are at risk of developing a liver injury. Of note, elderly COVID-19 patients were at a higher risk of liver injury. Consequently, careful monitoring of the liver function is advisable while managing COVID-19 patients.

An atypical liver function test might be as a result of a direct effect of SARS-CoV-2 replication in hepatic cells^{5,7} or others like cellular immune deficiency and cytokine storm,⁴ ARDS induced hypoxic hepatitis,^{6,42} drugs induced liver injury (DILI),^{6,14} sepsis (liver injury due to dysbiosis of gut microbiome),^{6,45-47} and AKI induced liver injury (Kidney-Liver Axis).⁶

Studies have shown SARS-CoV-2 aggravate infection to the host cells by fastening the spike protein of the virus to ACE2.^{4,5,7} Apart from ACE2 expression in other tissues like lungs, heart, esophagus, ileum, colon, kidney, testes, and bladder^{48,49} high expressions of ACE2 has also been observed in the liver and biliary epithelial cells.^{10,50} Hereby, the liver may be a potential target for SARS-CoV-2 infection and this justifies frequently reported abnormal liver functions tests in many studies as an extrapulmonary clinical presentation in COVID-19 patients. The liver biopsy of COVID-19 patients found moderate microvesicular steatosis and mild lobular and portal activity, attributing that the injury could have been as a result of direct SARS-CoV-2 infection or due to DILI.⁷ Strikingly, reverse transcription-polymerase chain reaction (RT-PCR) of the liver biopsy demonstrated direct evidence of

the viral sequence in the liver.⁵ Notwithstanding, it is still debatable whether, if SARS-CoV-2 triggers infection directly to the liver cells or cholangiocytes, and if these cells can discharge infective particles of the viruses. Further studies are needed in this regard.

Similarly, a large portion of the COVID patients presents with a marked decrease in CD4 and CD8 counts,⁹ and high amounts of interleukin 6, interleukin 1 beta, interferon-gamma, interferon gamma-induced protein 10, granulocyte colony-stimulating factor, macrophage inflammatory protein-1 alpha, tumor necrosis factor- α and monocyte chemotactic protein 1.⁴³ These suggest the severity of the disease is associated to cytokine storm and might pose severe damage to the liver and other vital organs.^{9,43} Additionally, raised inflammatory markers like D-dimer, ferritin, neutrophil counts, and CRP are more pronounced in severe cases of COVID-19.⁹ Alike, results from our meta-analysis also revealed a convincing increase in CRP, ESR, D-dimer, and absolute neutrophils count in the liver injury group. Additionally, a significant decrease in absolute lymphocyte count was also noticed in the liver injury group.

In addition, as explained earlier DILI might be a cause of liver injury in COVID-19 patients. It's not uncommon for COVID-19 patients to use NSAIDs for fever, which can cause liver injury. Moreover, most of the drugs (antiviral and antibiotics) currently used in the treatment of COVID-19 patients might induce hepatotoxicity.^{9,14} Cai and colleagues found that Lopinavir/Ritonavir was associated with liver injury.¹⁴ In contrast, Fan and colleagues didn't find any significant difference in the prevalence of the liver injury when they analyzed the liver function between those on medication and those without medication, stratified according to pre-hospital medication.¹⁰ According to our subgroup analysis, we found no difference in the incidence of drug use between liver injury and without liver injury groups. However, the trend of a forest plot showed that patients

using Lopinavir/Ritonavir were more likely to have a liver injury.

Over half of the patients with COVID-19 are found to have gastrointestinal symptoms like diarrhea, vomiting, or abdominal pain.⁶ In addition, it has also been suggested that the presence of gastrointestinal symptoms correlates with the severity of the disease.⁵¹ However, from our study there was not any significant difference for gastrointestinal symptoms between the mild and severe COVID-19 patients (results not shown). Further, there was also no difference between patients with liver injury and without liver injury for gastrointestinal symptoms. It is hypothesized that the presence of gastrointestinal symptoms in COVID-19 patients may either be as a result of direct infection of gut cells by SARS-CoV-2 virus⁴ or as a result of the gut-lung axis, where both lung and gut are connected through mucosal system.⁴⁶ Involvement of gut either directly by a viral infection or due to stress associated with a high level of cytokines and inflammatory mediators may further lead to dysbiosis of the gut microbiome.⁴⁵ It has been found that dysbiosis of the gut microbiome increases intestinal permeability of gut microorganisms and pathogen-associated molecular patterns (PAMPs) which can directly influx into the portal circulation and activate a pro-inflammatory cascade that might cause abnormality in the liver function.⁴⁷

Furthermore, COVID-19 patients with underlying CLD might be at risk of developing ACLF as a "second hit" in response to an immune-mediated systemic inflammatory response induced by SARS-CoV-2 infection. Moon et. al.,⁴⁰ found that COVID-19 patients with underlying CLD and cirrhosis are associated with a high incidence of mortality. The study further revealed that hepatic decompensation occurred in 36.9% of cases, and deaths occurred in 12.2% of CLD without cirrhosis, and 63.0% Child-Turcotte-Pugh (CTP)-C cirrhosis. According to results from our meta-analysis, the prevalence of CLD was 3.5% among patients with COVID-19. We

found no significant difference in the prevalence of CLD between the mild and severe group or survivor and a non-survivor group of COVID-19 patients. Yet, from the trend of a forest plot, our results also suggested that COVID-19 patients with underlying CLD seem to have more severe disease and a high risk of mortality. The insignificant result in our study might be due to a low reporting of CLD events in the included study for this meta-analysis. Overall, the rates of severity and mortality in COVID-19 patients with CLD were 4.5% and 19.2%, respectively. Whereas, the incidence of ACLF in these patients was 25.1%.

Besides, our study also found that disease severity and mortality were remarkably increased in COVID-19 patients with liver injury. However, no obvious difference was found in the length of hospital stay between the patients with liver injury and without liver injury. Overall, the rates of severity and mortality in COVID-19 patients with liver injury were 42.3% (160/307) and 18.5% (45/243), respectively. Here again, the insignificant result for the length of hospital stay in our study might be due to the least number of patients included in our meta-analysis.

Limitations, despite the relatively high quality of the studies included in our meta-analysis, there are some shortcomings. Firstly, there is a potential publication bias, only English language studies were included in this meta-analysis, so the quality of outcomes might have been compromised to some extent. Secondly, we couldn't identify more comparative two-arm studies comparing the patients with liver injury and without liver injury. Additionally, the data presented in the studies comparing the patients with liver injury and without liver injury were not sufficient to compare other factors like associating complications (ARDS, AKI, and sepsis, etc.) and inflammatory markers (ferritin and IL-6) between the liver injury and without liver injury group; this would have been of great importance to compare these factors stratified according to the liver injury.

Lastly, the criteria for the classification of COVID-19 based on the severity and the definition used for the liver injury was not the same between the studies, this might have contributed to the high heterogeneity in our meta-analysis. Nonetheless, this meta-analysis is still of great significance for comparing different factors and outcomes between the COVID-19 patients based on the severity, liver injury, and outcome (mortality), and may prove beneficial for the clinicians in understanding the impact caused by COVID-19 on the liver, so that management of the COVID-19 patients can be done effectively; hence, reducing the morbidity and mortality.

Conclusion

In conclusion, COVID-19 patients are at risk of developing a liver injury. Of note, COVID-19 patients with liver injury have more severe disease and a higher incidence of mortality. Thus, careful monitoring of liver function is advisable while treating COVID-19 patients.

Conflict of Interest

None

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Author Contribution

Study Design: DKY, BXL, LT; Preparation of the manuscript: DKY, AS, AS, RKY; All authors reviewed and approved the final draft.

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Supplement

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