



Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis

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Abstract

Background Liver function derangements have been reported in coronavirus disease (COVID-19), but reported rates are variable.

Methods We searched PubMed and Embase with terms COVID and SARS-COV-2 from December 1, 2019 till April 5, 2020. We estimated overall prevalence, stratified prevalence based on severity, estimated risk ratio (RR), and estimated standardized mean difference (SMD) of liver function parameters in severe as compared to non-severe COVID. Random effect method utilizing inverse variance approach was used for pooling the data.

Results In all, 128 studies were included. The most frequent abnormalities were hypoalbuminemia [61.27% (48.24–72.87)], elevations of gamma-glutamyl transferase (GGT) [27.94% (18.22–40.27)], alanine aminotransferase (ALT) [23.28% (19.92–27.01)], and aspartate aminotransferase (AST) [23.41% (18.84–28.70)]. Furthermore, the relative risk of these abnormalities was higher in the patients with severe COVID-19 when compared to non-severe disease [Hypoalbuminemia—2.65 (1.38–5.07); GGT—2.31 (1.6–3.33); ALT—1.76 (1.44–2.15); AST—2.30 (1.82–2.90)]. The SMD of hypoalbuminemia, GGT, ALT, and AST elevation in severe as compared to non-severe were –1.05 (–1.27 to –0.83), 0.76 (0.40–1.12), 0.42 (0.27–0.56), and 0.69 (0.52–0.86), respectively. The pooled prevalence and RR of chronic liver disease as a comorbidity was 2.64% (1.73–4) and 1.69 (1.05–2.73) respectively.

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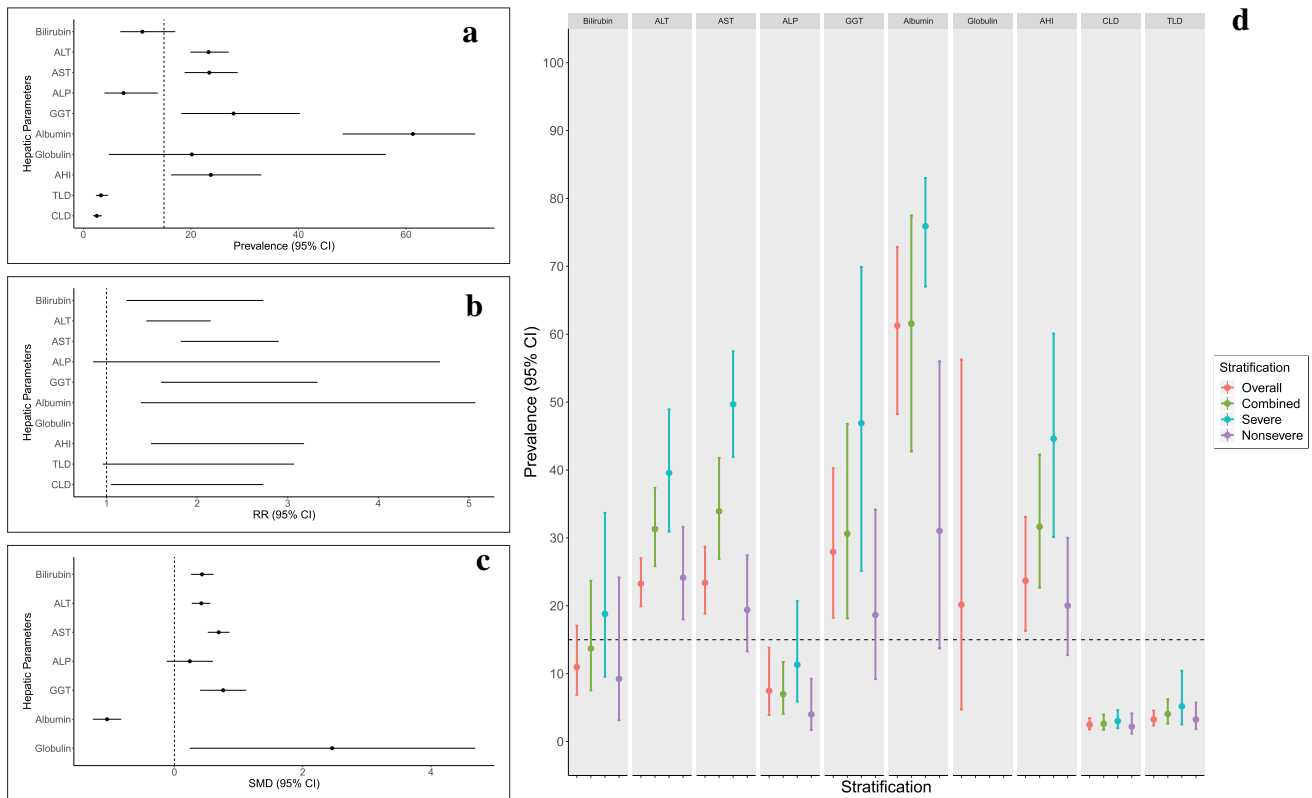
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Conclusion The most frequent abnormality in liver functions was hypoalbuminemia followed by derangements in gamma-glutamyl transferase and aminotransferases, and these abnormalities were more frequent in severe disease. The systematic review was, however, limited by heterogeneity in definitions of severity and liver function derangements.

Graphic abstract

Graphical depiction of the summary of meta-analytic findings a) pooled prevalence of abnormalities b) Risk ratio of abnormality in severe versus non-severe COVID-19 c) standardized mean difference (SMD) between severe and non-severe group and d) pooled prevalence for parameters based on severity stratification for bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, globulin and acute hepatic injury (AHI). Also estimates for overall/total liver disease (TLD) and chronic liver disease (CLD) amongst COVID-19 patients are depicted in a, b, d. For d) In addition to severity stratification, Overall (all studies for a particular estimate) and combined (only those studies which reported severity) estimates are provided.



Keywords SARS-CoV-2 · COVID-19 · Cirrhosis · Histology · Transplantation

Introduction

Coronavirus disease (COVID-19) was first brought to light with the appearance of cases of viral pneumonia in December 2019 in Wuhan city of the Chinese Hubei province [1]. Since then, the disease has spread globally and is recognized as a global pandemic by the World Health Organization (WHO). The disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been responsible for large numbers of hospital admissions and mortality, resulting in a severe stress on health care

resources. With time, the understanding of the disease has also improved and it has become apparent that it involves not just the pulmonary system but also the gastrointestinal system, heart, and the liver [2].

The hepatic involvement has been well recognized in the two recent pathogenic coronaviruses, i.e., SARS-COV and Middle East Respiratory Syndrome Coronavirus (MERS-COV). These two viruses had striking genetic similarity (especially SARS-COV) with the novel coronavirus, i.e., SARS-CoV-2 and, therefore, hepatic involvement in this is not entirely unexpected [3]. Indeed, multiple reports have suggested that elevation of liver transaminases does occur

with the infection of SARS-CoV-2. The purported mechanisms include the possibility of direct effect of the virus on hepatocytes or biliary epithelium, liver injury related to accentuated immune response (cytokine storm) and immune mediated damage, drug toxicity (because of drugs like acetaminophen, antivirals and hydroxychloroquine), and ischemic hepatitis which could occur in patients having multiorgan dysfunction including hemodynamic instability [4]. The biliary epithelium expresses the angiotensin-converting enzyme (ACE-2) receptor which is the known binding site of SARS-CoV-2, while the expression in hepatocytes is possibly much lower. However, the receptor expression has been shown to be upregulated in animals' models of liver injury [4].

The literature regarding hepatic involvement in COVID-19 is heterogenous with variability in the definitions of liver dysfunction and differences in the clinical presentation and disease severity of patients included in the published reports [5, 6]. Therefore, we planned to systematically study the occurrence of liver injury in COVID-19 and also determine the frequency of liver involvement in COVID-19. We also planned to identify any differences in frequency of liver dysfunction with varying disease severity, and identify differences in frequency of liver dysfunction in COVID-19 vis-a-vis non-COVID disease and also the frequency of underlying liver as a comorbidity in COVID-19 disease.

Materials and methods

We conducted this systematic review and meta-analysis as per the guidance provided by the PRISMA statement [7].

Search and study selection

We searched PubMed and Embase on 5th April 2019 for publications using the keywords ‘COVID’, ‘Novel coronavirus’ or ‘SARS-CoV-2’ for all publications after 1st December 2019. No other restrictions for language or ethnicity or type of papers were used. The detailed search strategy is shown in Supplementary Table 1. The results obtained from the two databases were then combined and duplicates removed. Two reviewers (PKM, SM) separately did a title and abstract screening to select any studies reporting on data about underlying hepatic comorbidities or liver dysfunction. The studies selected for full-text screening were seen by two authors (SM and VS) for data extraction. Three other authors checked the data for accuracy and completeness (DKJ, JS, and AC). The bibliography of selected papers and relevant reviews were also sought to identify any additional eligible papers and an additional search was done using the original search terms AND ‘Liver’ (both databases) to identify any additional papers as on 23rd April 2020. The detailed flow

of the study selection is shown using the PRISMA flowchart (Fig. 1).

Selection of studies

Two investigators (VS and SM) separately determined if the studies were eligible for inclusion in the meta-analysis and the disagreements were discussed with the third author (PKM) for final decision.

We included studies (1) reporting on frequency of various liver function abnormalities including serum bilirubin, alanine aminotransferases (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or gamma-glutamyl transferase (GGT) in human patients infected with SARS-CoV-2, (2) reporting their median/mean levels for severe and non-severe disease or (3) reporting the frequency of underlying liver disease as a comorbidity in patients with COVID-19.

These studies were included irrespective of age, gender, ethnicity of the reported population, the study designs (cohort, case series, randomized trials), and the language of publication. We excluded the studies (1) if number of patients were < 5, (2) if studies did not have confirmed cases of COVID-19, (3) if none of the relevant liver functions or data on liver disease as a comorbidity were reported, and (4) study designs like comments, editorials, reviews and systematic reviews which did not provide primary data. These studies were, however, looked at to identify additional papers from bibliography.

Study groups and analysis plan

We planned to find the pooled prevalence of liver function abnormalities in cases of COVID-19 and compare the frequencies of liver derangements between severe and non-severe COVID-19. We also planned to compare the frequencies of liver derangements between COVID cases and non-COVID cases if such data were available. We also planned to determine the pooled prevalence of underlying liver disease in patients with COVID-19 and compare if this frequency was different between severe and non-severe disease and between COVID and non-COVID disease. Additionally, we planned to compare the standard mean difference between severe and non-severe COVID and COVID and non-COVID cases.

Data extraction

We extracted data as per: authors, location of study, type of study, type of included patients, number of included patients, frequency of various hepatic derangements (elevation of serum bilirubin, ALT, AST, GGT, ALP, serum albumin) in patients with COVID-19 and separately for

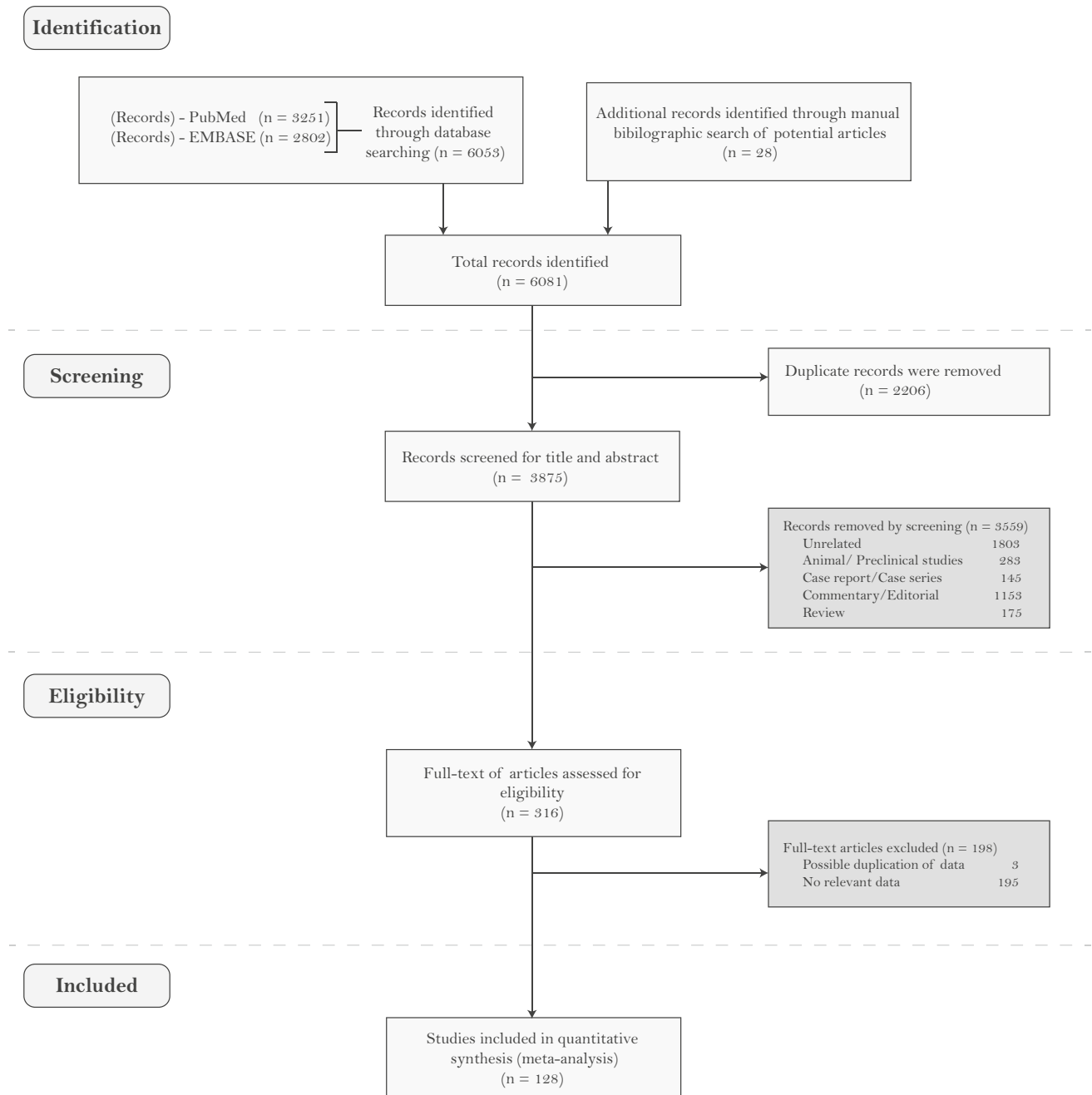


Fig. 1 PRISMA chart showing the flow of study inclusion for the meta-analysis

those with severe and non-severe disease, mean/median values with standard deviation/interquartile range/range of these parameters from studies which compared severe and non-severe disease and also COVID and non-COVID cases. The details regarding the definition of disease severity in each study and details of definition of acute hepatic injury (or hepatic dysfunction) were also extracted.

Statistical analysis

The statistical analysis was performed using R statistical software (version 3.6.1) [8]. In addition to the base package, meta, readxl, and ggplot2 packages were used [9–11]. The number of events were summarized as events per 100 observations. The inverse variance method with logit

transformation along with Clopper Pearson confidence interval for individual studies was used for the meta-analytic pooled prevalence in the overall and subgroup population. For difference in prevalence between subgroups, the inverse variance method was used for summarizing. A continuity correction of 0.5 was applied for studies with zero cell frequency. For continuous variable standardized mean differences (SMD) were computed between the evaluated subgroups and inverse variance method was used for summarizing. Hedges's *g* correction was used for bias correction of standardized mean differences. For studies reporting mean and standard deviation, we directly took the reported values for analysis. For studies reporting median and interquartile range or median and range, the mean and standard deviation were computed from the reported values based on Luo 2018 and Wan 2014 methodology [12, 13]. For studies reporting only mean along with *p* value, the *t* statistics were computed, which was then used for calculation of standard deviation. For studies reporting individual data, we computed mean and SD from the data. Heterogeneity of prevalence, RR, and SMD were tested with *p* value of heterogeneity ($p < 0.10$) and I^2 was computed. I^2 value was taken for reporting for heterogeneity as, in addition to quantifying heterogeneity, it also assesses the impact of heterogeneity on the meta-analysis. Random effects models were used for summarizing results irrespective of heterogeneity. For prevalence, 95% CI of pooled prevalence was reported. For studies comparing prevalence and SMD between two groups, *p* value of < 0.05 was considered statistically significant and 95% confidence intervals (CIs) were reported. The forest plots were constructed for visualization of results.

Results

Search results and included studies

The search yielded a total of 6053 citations and additional 28 papers were identified from other sources like bibliography search. After removal of 2206 duplicates, 3875 papers were screened for title and abstract. After removal of 3559 papers for various reasons (Fig. 1), a total of 316 papers were eligible for full-text screening. Eventually a total of 128 papers were included in at least one of the different analyses which were conducted as part of the meta-analysis (Supplementary Table 2).

Overall frequency of various abnormalities in liver function in COVID-19

The pooled prevalence of hyperbilirubinemia reported in various studies was 10.98% (95% CI 6.87–17.08; I^2 94%) (Fig. 2a). The pooled prevalence of alanine aminotransferase

(ALT) and aspartate aminotransferase (AST) elevation reported in various studies was 23.28% (19.92–27.01; 90%) and 23.41% (18.84–28.70; 95%), respectively (Figs. 3a and 4a). The pooled prevalence of ALP and GGT elevation among overall reported studies was 7.48% (3.91–13.83; 75%) and 27.94% (18.22–40.27; 93%), respectively (Supplementary Fig. 1 and Fig. 5A). The pooled prevalence of hypoalbuminemia among overall reported studies was 61.27% (48.24–72.87; 91%) (Fig. 6a). The overall pooled frequency of increased globulin levels reported was 20.17% (4.73–56.25; 95%) (Supplementary Fig. 2). The pooled frequency of acute hepatic injury as reported in various studies is shown in Supplementary Fig. 3. The pooled prevalence of hepatitis B, fatty liver, total liver disease, and chronic liver disease as a comorbidity are shown in Supplementary Figs. 4–7. The pooled prevalence of chronic liver disease as a comorbidity in various studies was 2.49% (1.79–3.46, 84%) (Supplementary Fig. 7). The pooled frequency of hepatitis B, non-alcoholic fatty liver disease, and total frequency of any liver disease are shown in Supplementary Figs. 4, 5 and 6.

Comparison between severe and non-severe COVID-19

The pooled prevalence of bilirubin abnormality among the studies which reported the finding on the basis of underlying severity of COVID-19 was 13.71% (95% CI 7.53–23.69; I^2 95%). The pooled frequency of hyperbilirubinemia in severe COVID disease was 18.80% (9.55–33.67; 91%), while in non-severe disease, it was 9.24% (3.15–24.17; 97%) (Fig. 2b). The risk ratio (RR) of deranged bilirubin concentration in severe as compared to non-severe subgroups was 1.82 (95% CI 1.22–2.73; I^2 66%) (Fig. 2c). The SMD for bilirubin concentration between the severe and non-severe group was 0.43 (95% CI 0.26–0.61; I^2 66%) (Fig. 2d).

The pooled prevalence of ALT and AST abnormality among the studies reporting severity was 31.31% (25.82–37.37; 87%) (Fig. 3b) and 33.95% (26.90–41.79; 91%) (Fig. 4b). The pooled frequency of ALT elevation was 39.58% (30.92–48.94; 80%) for severe and 24.15% (17.98–31.63; 90%) for non-severe disease (Fig. 3c). The pooled frequency of AST elevation was 49.68% (41.90–57.49; 73%) and 19.40% (13.27–27.45; 91%), respectively, for severe and non-severe disease (Fig. 4c). The RR of SGPT and SGOT abnormality in the severe as compared to non-severe subgroups were 1.76 (1.44–2.15; 65%) and 2.30 (1.82–2.90, 67%), respectively (Figs. 3d and 4d). The SMD for SGPT and SGOT concentration between the severe and non-severe groups were 0.42 (0.27–0.56; 70%) and 0.69 (0.52–0.86; 76%), respectively (Figs. 3e and 4e).

The pooled prevalence of ALP and GGT abnormality among the studies reporting severity was 6.99%

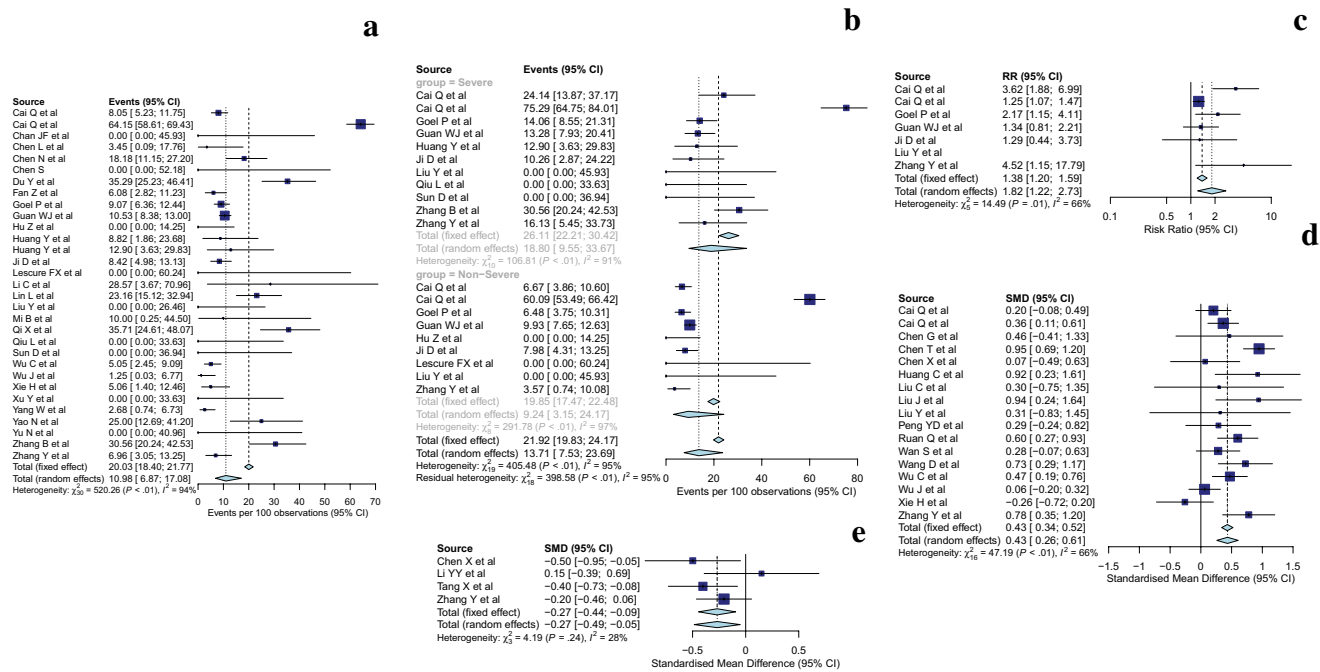


Fig. 2 Forest plots of bilirubin. Random effects summary were reported in the manuscript. The heterogeneity was measured across studies by I^2 and p value of heterogeneity. **a** Pooled prevalence of hyperbilirubinemia reported in various studies. **b** Pooled prevalence of hyperbilirubinemia among the studies which reported the findings on the basis of underlying severity of COVID-19. **c** Risk ratio (RR) of hyperbilirubinemia in severe as compared to non-severe subgroups.

For RR, the middle vertical line at 1 stands for line of no-difference. **d** SMD for bilirubin concentration between the severe and non-severe groups. For SMD, the middle vertical line at 0 stands for line of no difference. **e** SMD of bilirubin concentration between COVID and non-COVID subgroups. SMD standardized mean difference, RR risk ratio, CI confidence interval

(4.08–11.72; 59%) (Supplementary Fig. 1b) and 30.62% (18.13–46.79; 94%) (Fig. 5b) with subdivision for ALP being 11.33% (5.89–20.69; 42%) for severe and 4% (1.68–9.26; 64%) for non-severe and for GGT being 46.90% (25.13–69.92; 89%) and 18.66% (9.20–34.18; 93%). The RR of ALP and GGT abnormality in severe as compared to non-severe subgroups were 1.99 (0.85–4.68; 22%) (Supplementary Fig. 1c) and 2.31 (1.6–3.33; 55%) (Fig. 5c), respectively. The SMD for ALP and GGT concentration between the severe and non-severe groups were 0.24 (–0.12 to 0.60; 83%) (Supplementary Fig. 1d) and 0.76 (0.40–1.12; 82%) (Fig. 5d), respectively.

The pooled prevalence of albumin abnormality among the studies reporting severity was 61.57% (42.73–77.48; 90%) with subdivision of 75.91% (67.02–83.02; 35%) for severe and 31.04% (13.72–56.02; 84%) for non-severe (Fig. 6b). The RR of albumin abnormality in severe as compared to non-severe subgroup was 2.65 (1.38–5.07; 79%) (Fig. 6c). The SMD for albumin concentration between the severe and non-severe groups was –1.05 (–1.27 to –0.83; 77%) (Fig. 6d). The SMD for globulin concentration between severe and non-severe groups was 2.46 (0.24–4.69, 99%) (Supplementary Fig. 2b).

The pooled prevalence of chronic liver disease (CLD) among studies reporting severity was 2.64% (1.73–4; 72%) with 3.03 (1.97–4.64; 21%) among severe and 2.20% (1.16–4.15; 83%) among non-severe (Supplementary Fig. 7b). The RR of CLD in severe as compared to non-severe subgroup was 1.69 (1.05–2.73; 0%) (Supplementary Fig. 7c).

Presence of acute hepatic injury (supplementary Fig. 3)

The pooled prevalence of acute hepatic injury among overall reported studies was 23.70% (95% CI 16.31–33.11; I^2 97%) (Supplementary Fig. 3a). Among the studies reporting severity, the total frequency of acute hepatic injury was 31.66% (22.66–42.27; 91%), whereas in severe disease, it was 44.63% (30.13–60.11; 88%), and in non-severe disease, it was 20.02% (12.74–30.02; 88%) (Supplementary Fig. 3b). The RR of acute hepatic injury in severe as compared to non-severe was 2.18 (1.49–3.18, 67%) (Supplementary Fig. 3c).

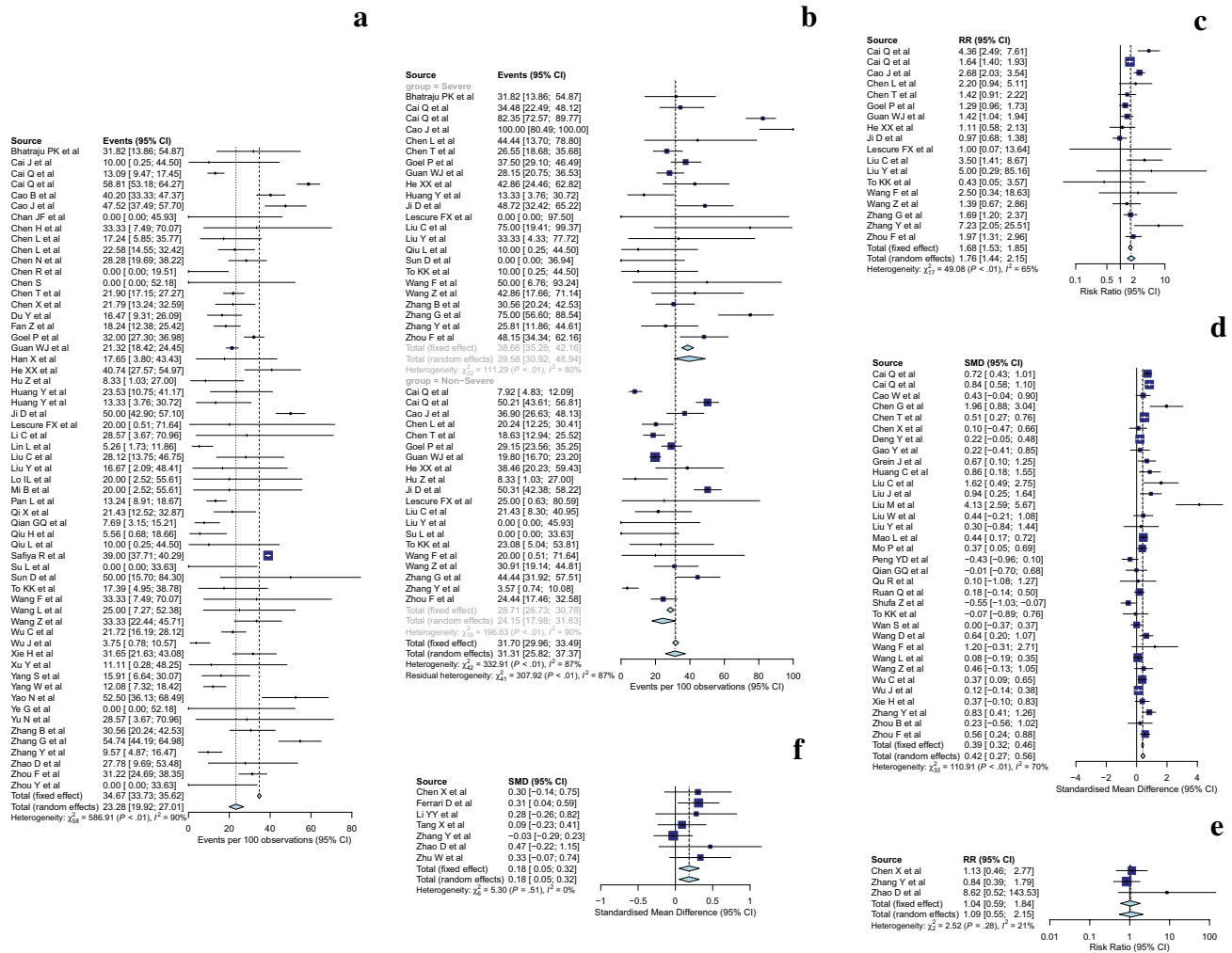


Fig. 3 Forest plots of alanine aminotransferase (ALT). Random effects summary were reported in the manuscript. The heterogeneity was measured across studies by I^2 and p values of heterogeneity. **a** Pooled prevalence of ALT elevation reported in various studies. **b** Pooled prevalence of ALT elevation among the studies which reported the finding on the basis of underlying severity of COVID-19. **c** Risk ratio (RR) of ALT elevation in severe as compared to non-

severe subgroups. For RR, the middle vertical line at 1 stands for line of no-difference. **d** SMD for ALT elevation between the severe and non-severe groups. For SMD, the middle vertical line at 0 stands for line of no difference. **e** RR of ALT elevation in the COVID as compared to non-COVID subgroups. **f** SMD of ALT elevation between COVID and non-COVID subgroup. SMD standardized mean difference, RR risk ratio, CI confidence interval

Comparison between COVID and non-COVID disease

The RR of ALT and AST abnormality in the COVID as compared to non-COVID subgroups were 1.09 (95% CI 0.55–2.15; I^2 21%) and 1.02 (0.45–2.30; 48%), both statistically non-significant (Figs. 2e and 3e). The SMD for SGPT and SGOT concentration between the COVID and non-COVID group were 0.18 (0.05–0.32; 0%) and 0.02 (–0.47 to 0.52; 91%) (Figs. 2f and 3f). The SMD of bilirubin, GGT, and albumin concentration between COVID and non-COVID subgroups were –0.27 (–0.49 to –0.05, 28%), 0.12 (–0.24 to 0.48; 58%) and 0.82 (0.30–1.33; 82%), respectively (Figs. 2e, 5e, 6e).

Hepatic histological findings in COVID-19

Only limited cases have reported findings on liver histology using either post-mortem histology or liver biopsy in patients with COVID-19 and are tabulated in Supplementary Table 3. The findings reported are non-specific and include sinusoidal dilation, mild activity in portal area, and lobules and occasional necrosis. It is unclear if these are a manifestation of virus mediated liver injury or due to other factors like drugs or immune injury.

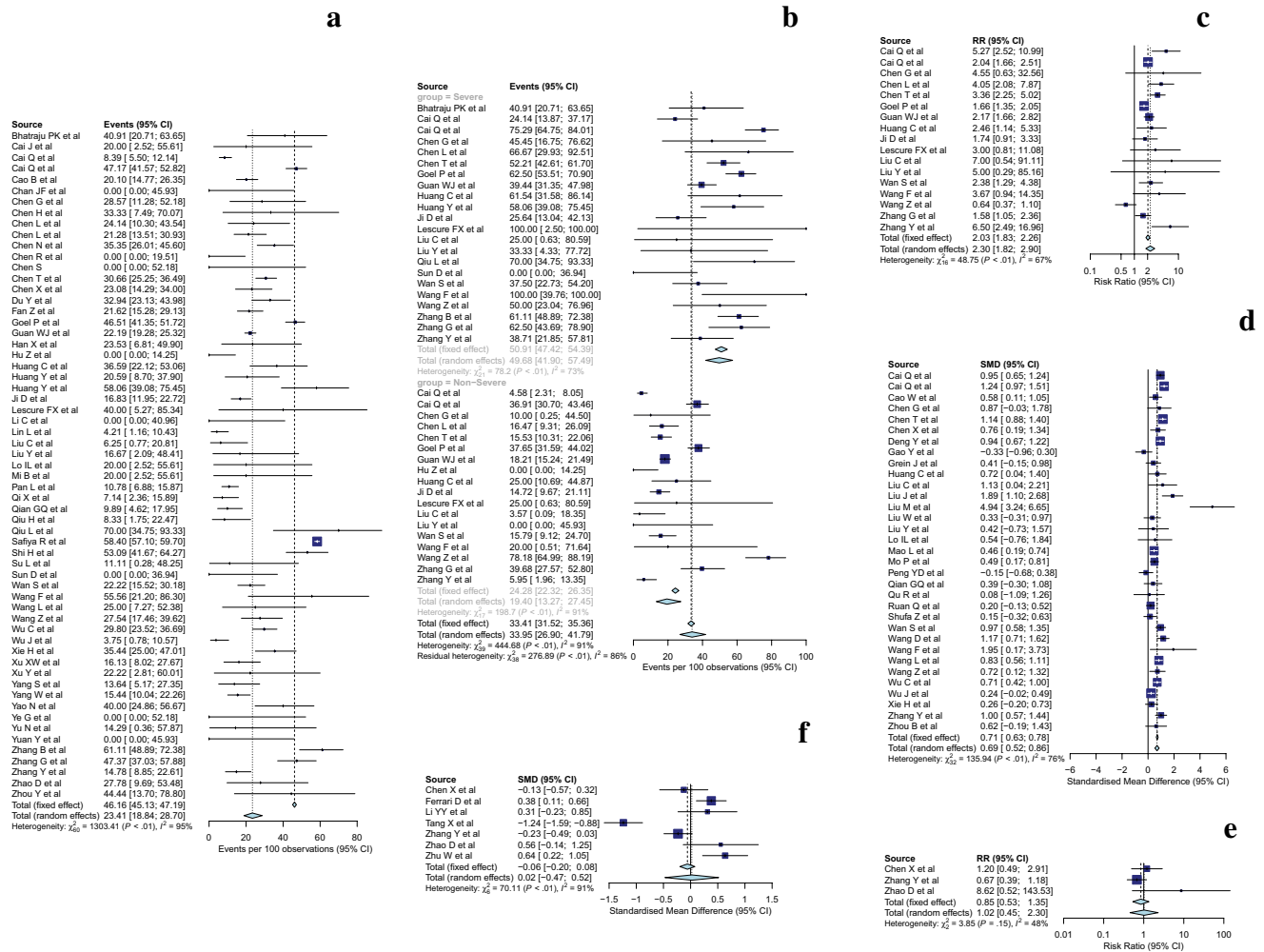


Fig. 4 Forest plots of aspartate aminotransferase (AST). Random effects summary were reported in the manuscript. The heterogeneity was measured across studies by I^2 and p values of heterogeneity. **a** Pooled prevalence of AST elevation reported in various studies. **b** Pooled prevalence of AST elevation among the studies which reported the finding on the basis of underlying severity of COVID-19. **c** Risk ratio (RR) of AST elevation in severe as compared to non-

severe subgroups. For RR, the middle vertical line at 1 stands for line of no-difference. **d** SMD for AST elevation between the severe and non-severe groups. For SMD, the middle vertical line at 0 stands for line of no difference. **e** RR of AST elevation in the COVID as compared to non-COVID subgroups. **f** SMD of AST elevation between COVID and non-COVID subgroups. SMD standardized mean difference, RR risk ratio, CI confidence interval

COVID-19 in liver transplant recipients

Some case reports and studies have reported the outcomes of COVID-19 in patients with liver transplant and are shown in Supplementary Table 4.

Discussion

In this systematic review, we found that the derangements of liver functions were frequently noted in patients with COVID-19. The most frequent abnormality noted was hypoalbuminemia followed by elevations of gamma-glutamyl transferase, aminotransferases, bilirubin, and alkaline

phosphatase. Furthermore, when comparison of severe with non-severe COVID-19 cases was done, liver function abnormalities like hypoalbuminemia, GGT, and aminotransferase and bilirubin elevations were more frequent in those with severe disease. However, serum alkaline phosphatase elevations were not significantly higher in the severe group of patients. The pooled frequency of elevation of ALT and AST was similar in the overall COVID cases, but, interestingly, the prevalence of AST elevations was more than ALT in the severe COVID disease.

The most frequent abnormality noted in our meta-analysis was hypoalbuminemia. This is possibly related to the fact that albumin is a negative acute phase reactant rather than a manifestation of a hepatic synthetic dysfunction. Our

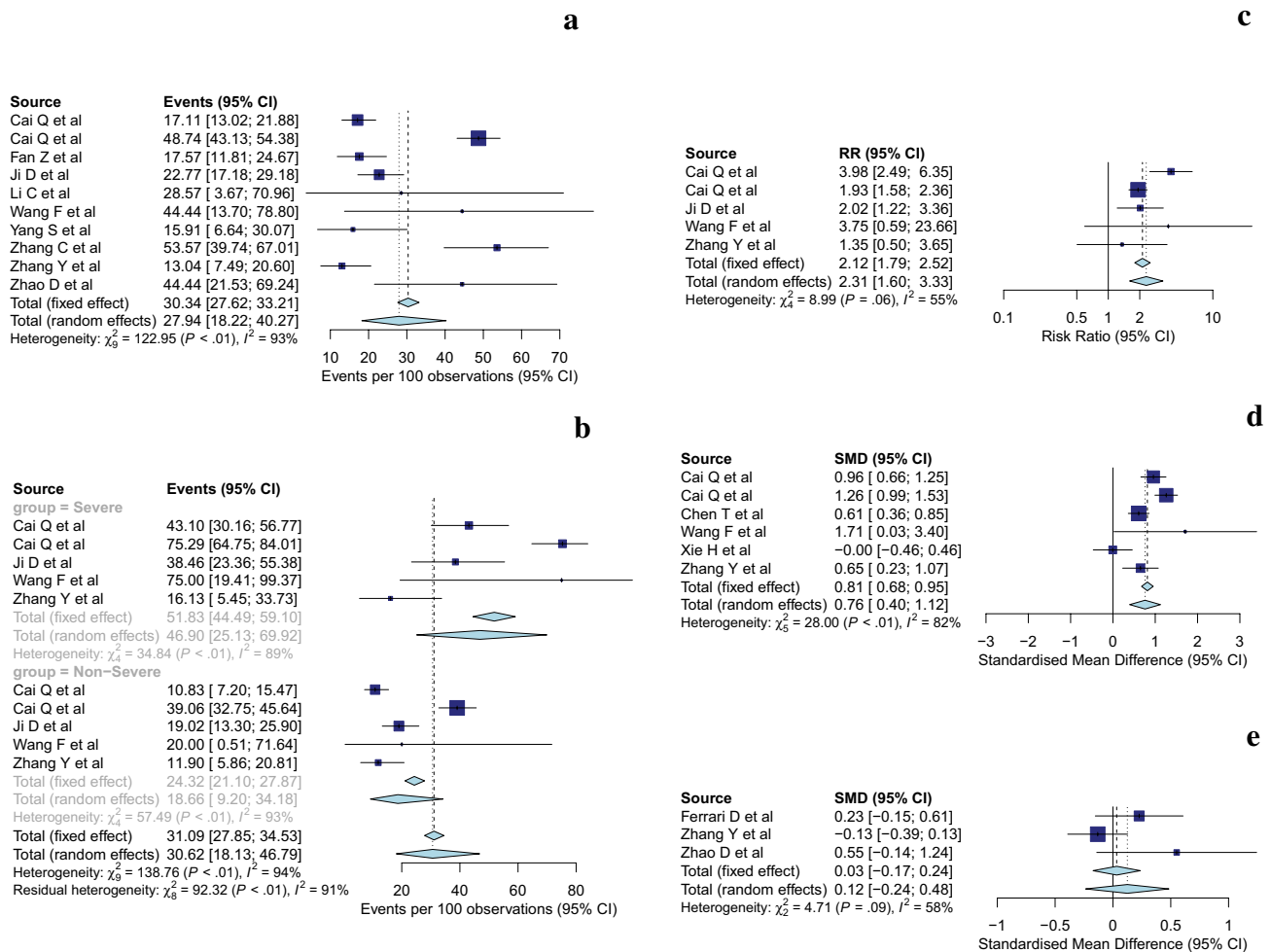


Fig. 5 Forest plots of gamma-glutamyl transferase (GGT). Random effects summary were reported in the manuscript. The heterogeneity was measured across studies by I^2 and p values of heterogeneity. **a** Pooled prevalence of GGT elevation reported in various studies. **b** Pooled prevalence of GGT elevation among the studies which reported the finding on the basis of underlying severity of COVID-19. **c** Risk ratio (RR) of GGT elevation in severe as compared to non-

severe subgroups. For RR, the middle vertical line at 1 stands for line of no-difference. **d** SMD for GGT elevation between the severe and non-severe groups. For SMD, the middle vertical line at 0 stands for line of no difference. **e** SMD of GGT elevation between COVID and non-COVID subgroup. SMD standardized mean difference, RR risk ratio, CI confidence interval

meta-analysis confirms that the liver enzyme elevations in COVID-19, even in the severe COVID category, are mild-to-moderate in most of the cases. Although there are a few reports of aminotransferase elevation to a high degree (> 10 times of upper limit), this is an uncommon phenomenon [14, 15]. Furthermore, liver failure is exceedingly rare with only a single case report available in a patient who had severe COVID associated with use of multiple drugs and progression of liver function derangement after admission [14]. As of now, it is not possible to conclusively ascribe these elevations to be related to direct viral injury. Most of the studies included in our analysis reported use of multiple drugs like antibiotics, antivirals (lopinavir/ritonavir combination, arbidol, oseltamivir, favipiravir, remdesvir, hydroxychloroquine), and steroids. Many of these drugs

could have contributed to occurrence of liver dysfunction after hospitalization. Furthermore, ischemia and immune mediated injury due to cytokine storm could be responsible for liver dysfunction in patients with severe COVID disease.

SARS-CoV-2 uses the ACE-2 receptor for gaining entry into the cells including the type 2 alveolar epithelial cells in the lungs. Chai et al. analyzed the expression of ACE-2 receptors in liver tissue and found that their expression on cholangiocytes (59.7%) was much stronger than on hepatocytes (2.6%) [16]. It has also been observed that ACE-2 expression increases in hepatocytes, in cases of liver injury [4, 17]. At least, one report suggests that viral RNA could be detected in liver tissue raising the possibility of viral mediated liver injury [18]. On the other hand, Chu et al. demonstrated a significant replication of SARS-CoV-2 on

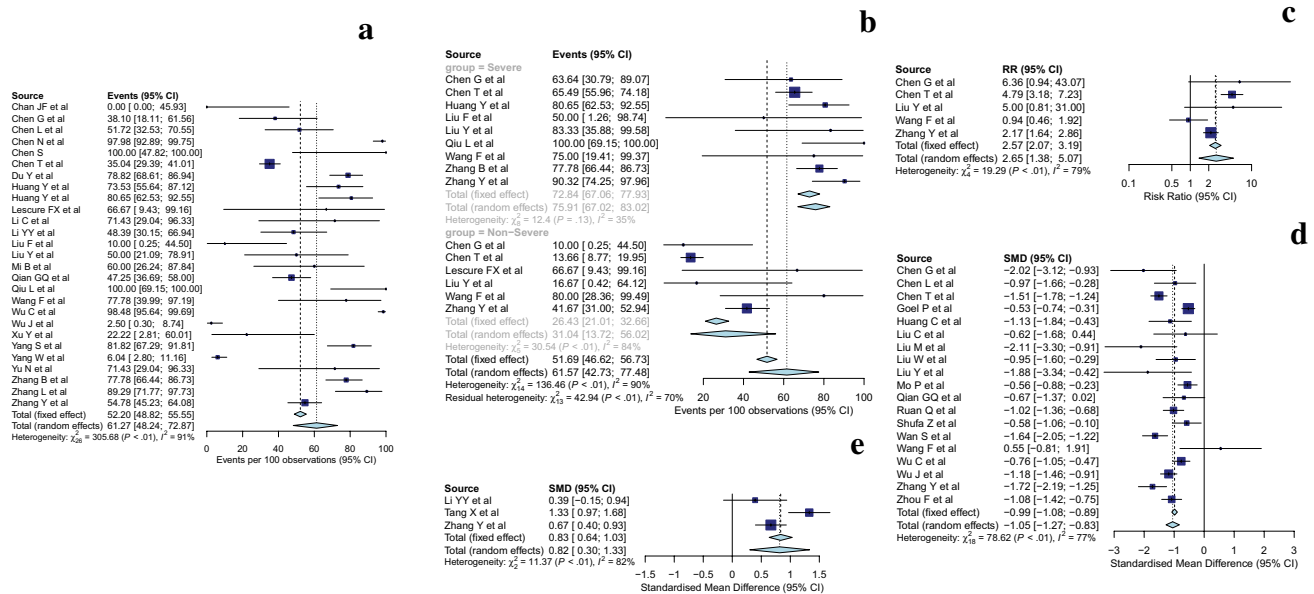


Fig. 6 Forest plots of albumin. Random effects summary were reported in the manuscript. The heterogeneity was measured across studies by I^2 and p values of heterogeneity. **a** Pooled prevalence of hypoalbuminemia reported in various studies. **b** Pooled prevalence of hypoalbuminemia among the studies which reported the finding on the basis of underlying severity of COVID-19. **c** Risk ratio (RR) of hypoalbuminemia in severe as compared to non-severe subgroups.

Huh7 (hepatic) cell lines. They also noted that cytopathic effects were seen in a minority of cases, cautioning against an over reliance on the same [19]. Yet, the limited histological reports available fail to demonstrate clear cytopathic changes of SARS-Cov-2 (See Supplementary Table 3). Furthermore, the comparison of liver function showed that most abnormalities were equally frequent in non-COVID disease suggesting the lack of any specificity for the diagnosis of COVID.

Another interesting finding was that the elevations in GGT were similar in frequency to elevations in aminotransferases and were higher than the elevations in alkaline phosphatase. Furthermore, the frequency of patients with elevation of GGT was higher in severe COVID disease when compared to non-severe disease, but this was not noted with alkaline phosphatase. The exact reason for this is unclear, but GGT is recognized as a surrogate marker for increased oxidative stress and chronic inflammation [20]. It is uncertain if these elevations are related to acute inflammatory stress or are a marker of biliary injury and this finding needs further evaluation.

We also looked at the prevalence of underlying liver disease as a comorbidity in the patients with COVID-19 and compared the frequency of liver disease as a comorbidity in severe and non-severe COVID cases. We found that the underlying liver disease was found in a significant number of

For RR, the middle vertical line at 1 stands for line of no-difference. **d** SMD for hypoalbuminemia between the severe and non-severe groups. For SMD, the middle vertical line at 0 stands for line of no difference. **e** SMD of hypoalbuminemia between COVID and non-COVID subgroups. *SMD* standardized mean difference, *RR* risk ratio, *CI* confidence interval

patients with COVID-19. However, the frequency of underlying liver disease was statistically not different between severe and non-severe diseases. Unfortunately, our meta-analysis cannot directly provide evidence regarding the effect of underlying liver disease on outcomes of disease or whether it predisposes to severe COVID illness. Furthermore, the group ‘total liver disease’ is also a heterogeneous group comprising chronic hepatitis B, non-alcoholic fatty liver disease, and chronic liver disease. Therefore, we also did additional analysis of the frequency of chronic liver disease and underlying hepatitis B separately, and the findings regarding frequency of underlying liver disease in severe and non-severe COVID did not seem to change except that the relative risk of underlying chronic liver disease was more in those with severe COVID disease. The effect of COVID on patients with previous transplant has been reported infrequently and data are still unclear if these patients are at an increased risk of severe disease. (Supplementary Table 4).

There are some limitations to the current systematic review and meta-analysis. The most important concern is the variability in the definitions of liver dysfunction or acute liver injury (Supplementary Table 5), differences in the normal values of liver enzymes in various studies, and heterogeneity in definition of severe and non-severe COVID groups, while most studies defined severe disease as per WHO criteria, many others have defined severe

disease as ICU admissions, non-survivors, etc. (Supplementary Table 6). This adds significant heterogeneity, because a study only on ICU patients (which compares survivors and non-survivors) is likely to have almost all cases qualifying to the WHO definition of severity [1]. Similarly, although we compared the liver dysfunction in COVID and non-COVID disease, the analysis was limited by the small number of participating studies and heterogeneity in definition of non-COVID cases in various reports. Furthermore, although some studies indicate that the elevation of liver enzymes is a delayed phenomenon and may occur in the second week of illness, we are not able to clarify if this is because of worsening inflammation as part of disease course, or other factors like multiple drugs used in these patients [21]. Also, most of the included studies are from China, the country of initial impact of COVID-19, and, therefore, may not be representative of differences among various populations. Furthermore, the impact of COVID-19 on outcomes in patients with underlying liver disease is less clear. Some case reports have suggested that SARS-CoV2 could be the cause of acute deterioration in patients with underlying chronic liver disease, resulting in Acute-on-Chronic Liver Failure (ACLF) [22, 23]. However, there are multiple strengths of the meta-analysis, as we have compared multiple parameters of liver function, and for most of these, a fair number of studies were available. Also, the study clarifies the frequency of liver function abnormalities in severe and non-severe diseases. Furthermore, the pooled prevalence of underlying liver disease as a comorbidity has also been clarified.

To conclude, liver function abnormalities, especially hypoalbuminemia, GGT, and aminotransferase elevations, are frequent in patients with COVID-19 disease and the patients with severe disease are more likely to have these liver function derangements.

Author contributions PKM: conception, data extraction and validation, analysis, manuscript review, and approval. SM: data extraction, initial draft, manuscript review, and approval. DKJ, JS, and AC: data extraction and validation, manuscript review, and approval. RM, HSM, and UD: important intellectual content, manuscript review, and approval. VS: conception, data extraction, validation, initial draft, important intellectual content, manuscript review, and approval.

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Compliance with ethical standards

Conflict of interest M. Praveen Kumar, Shubhra Mishra, Daya Krishna Jha, Jayendra Shukla, Arup Choudhury, Ritin Mohindra, Harshal S. Mandavdhare, Usha Dutta, and Vishal Sharma declare that they have no conflict of interest.

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