

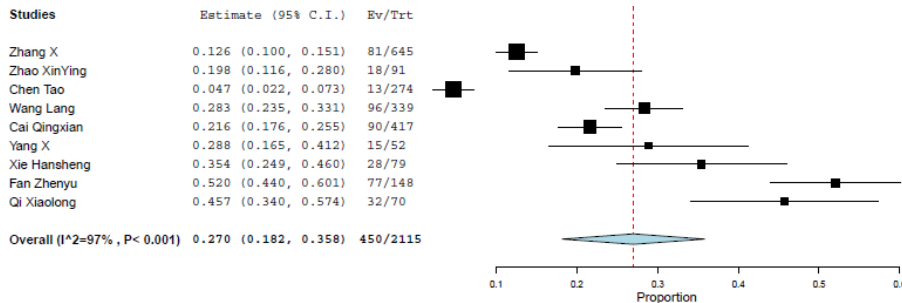
## Involvement of liver in COVID-19: systematic review and meta-analysis

We have read with interest the recent study by Qi *et al.*<sup>1</sup> Currently, the impact of COVID-19 on the liver remains unexplored. Although majority of patients with COVID-19 have abnormal liver

function, most studies on COVID-19 only attribute the severity of disease on the ground of respiratory complications. Thus, we aimed to perform a meta-analysis to estimate the prognosis of patients with COVID-19 stratified according to liver injury. Our meta-analysis includes nine studies<sup>2-10</sup> with a total of 2115 patients (online supplementary file).

Abnormal liver function in patients with COVID-19 is possibly multifactorial; that is, drug-induced liver injury (DILI), severe acute respiratory syndrome coronavirus 2 replications in the liver<sup>10</sup> and interorgan cross-talk in acute inflammation.<sup>9</sup> Published studies on COVID-19 have shown that 37.2%–76.3% of patients have abnormal liver function.<sup>2-9</sup> Similarly, the prevalence of liver injury is reported in about 21.5%–45.71% of patients.<sup>2-10</sup> Generally, 7.14%–64.15% of patients with COVID-19 had increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT) and bilirubin levels, whereas albumin was decreased to 27.9–33.0 g/L in non-survivor patients.<sup>6</sup> Besides, patients with COVID-19 with chronic liver disease (CLD) might develop decompensated liver as a systemic inflammatory response induced by COVID-19.<sup>1</sup> We found that the prevalence of CLD was 4% (95% CI 1.5 to 6.4,  $I^2=89\%$ ) among patients with COVID-19, with cirrhosis and hepatitis B being the most common. Likewise, the incidence of liver injury was 27% (95% CI 18.2 to 35.8,  $I^2=97\%$ ; [figure 1](#)).<sup>2-10</sup> Of note, older patients with COVID-19 had a higher risk of liver injury (standardised mean difference (SMD): 0.81, 95% CI 0.32 to 1.29,  $I^2=85\%$ ,  $p=0.001$ ).

Again, most patients with COVID-19 had a noticeable reduction in CD4 and CD8 counts.<sup>9</sup> In contrast, severe patients with COVID-19 had increased



**Figure 1** Forest plot for the pooled prevalence of liver injury in patients with COVID-19.<sup>2-10</sup> Ev/Trt, events/treated.

inflammatory markers like interleukin-6, erythrocyte sedimentation rate (ESR), D-dimer, ferritin, neutrophil counts and C reactive protein (CRP), suggesting a 'cytokine storm'. Concurrently, our meta-analysis showed a significantly lower absolute lymphocyte count (SMD: -0.81, 95% CI -1.22 to -0.41, I<sup>2</sup>=62%, p<0.0001) and higher ESR (SMD: 1.65, 95% CI 0.61 to 2.70, I<sup>2</sup>=90%, p=0.002) in the liver injury group compared with the non-liver injury group. However, no remarkable difference in CRP and absolute neutrophil count was observed between the two groups.

As evidence, DILI should not be overlooked in patients with COVID-19. Cai and colleagues found that the use of lopinavir/ritonavir was significantly associated with liver injury.<sup>2</sup> Contrarily, Fan *et al* did not find any difference in the prevalence of liver injury among patients with and without medication.<sup>9</sup> Our analysis found that the liver injury group had considerably more use of lopinavir/ritonavir than the group without liver injury (OR: 4.15, 95% CI 2.36 to 7.29, I<sup>2</sup>=0%, p<0.00001). Meanwhile, insignificant difference was observed in the usage of other drugs.

Furthermore, we also examined the prognosis of patients with COVID-19 with liver injury, and we found that

patients with liver injury had obviously more severe disease (OR: 2.57, 95% CI 1.25 to 5.26, I<sup>2</sup>=62%, p=0.01) and a higher prevalence of mortality (OR: 1.66, 95% CI: 1.04 to 2.64, I<sup>2</sup>=35%, p=0.03) (figure 2).<sup>6-9</sup> However, length of hospital stay was not significantly different among the groups (SMD: -0.61, 95% CI -2.37 to 1.15, I<sup>2</sup>=98%, p=0.50). The overall rate of severity and mortality in patients with COVID-19 with liver injury was 53.5% (130/243) and 23.5% (42/179),<sup>6-9</sup> respectively.

To conclude, patients with COVID-19 have a high prevalence of liver injury, and patients with COVID-19 with liver injury are at an increased risk of severity and mortality. Thus, special attention should be given to any liver dysfunction while treating patients with COVID-19.

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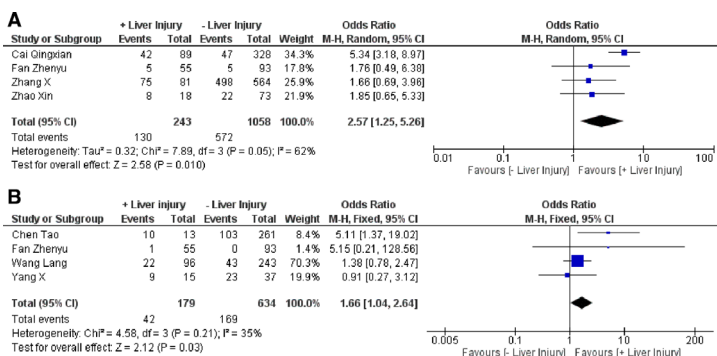
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**Figure 2** Forest plot for the prognosis of patients with COVID-19 with liver injury. (A) Severity.<sup>2,4,5,9</sup> (B) Mortality.<sup>6-9</sup>

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