Risk factors in patients with COVID-19 developing severe liver injury during hospitalisation

We read with interest the work by Weber *et al*[1] reporting that severe liver failure was observed in a patient during SARS-CoV-2 infection. They suggested that close monitoring of liver function is necessary, and further investigation is required to elucidate the risk factors for liver failure in patients with COVID-19. Previous studies have indicated that liver injury could affect the prognosis of patients with COVID-19, and mortality rate was significantly increased in patients with severe liver injury.[2 3] However, the risk factors in patients with COVID-19 developing severe liver injury during hospitalisation have not been thoroughly investigated. Thus, in this study, patients with COVID-19 were recruited to identify the risk factors in patients with COVID-19 with severe liver injury.

A total of 192 patients diagnosed with COVID-19 were consecutively hospitalised at Chongqing Public Health Medical Center from January to March 2020, and 12 patients with existing liver disease had been excluded in this study. Liver injury was detected in 75 (39.06%) enrolled patients at admission and 133 (69.27%) during hospitalisation, respectively. Interestingly, liver injury was observed in 25 out of 29 (86.21%) patients with severe COVID-19. In consistence with our findings, Qi *et al*[4] revealed that 45.71% of the patients had liver injury at admission; furthermore, Fan *et al*[5] reported that 48.4% of the patients with normal liver function developed liver injury during hospitalisation, suggesting that a high percentage of patients with COVID-19 have liver injury.

Therefore, identification of the risk factors contributing to severe liver injury during hospitalisation is essential for the treatment of COVID-19. The results indicated that the number of T lymphocyte subsets ($CD3^+$, $CD4^+$ and $CD8^+$ T cells) were significantly reduced in patients with severe liver injury, while the proportion of ritonavir, the number of neutrophils and monocytes, and the production of IL-6 and IL-10 were remarkably increased (online supplementary table 1). Univariate analysis indicated that ritonavir, $CD3^+$, $CD4^+$ and $CD8^+$ T cells, IL-6 and IL-10 were potential risk factors in patients with COVID-19 with severe liver injury during hospitalisation ($p<0.05$, table 1); multivariate analysis revealed that ritonavir (OR 5.63, 95% CI 2.86 to 18.63, $p<0.001$), IL-6 (OR 2.21, 95% CI 1.09 to 4.67, $p=0.006$), IL-10 (OR 1.78, 95% CI 1.08 to 3.12, $p=0.014$) and $CD4^+$ T cells (OR 3.24, 95% CI 1.05 to 6.38, $p<0.001$) were independent risk factors in patients with COVID-19 with severe liver damage (table 1), suggesting that the progression of liver injury was associated with medication, T lymphocyte subsets and inflammatory cytokines.

SARS-CoV-2–mediated liver injury might be a key factor in liver damage.[6] SARS-CoV-2 may directly target ACE2-positive cholangiocytes and hepatocytes, further leading to liver cell damage and bile duct cell dysfunction, consequently aggravating liver damage. Dysregulated immune response was observed in patients with COVID-19.[7] Furthermore, previous studies have indicated that the SARS-CoV-2 infection may primarily affect T lymphocytes, particularly $CD4^+$ and $CD8^+$ cells, which are involved in pro-inflammatory responses.[7 8] At present, no specific treatment is available for patients with COVID-19. The commonly used antiviral drugs lopinavir/ritonavir are mainly metabolised in the liver but exhibit side effects such as liver dysfunction. In addition, overdose of ribavirin induces hemolysis and exacerbates tissue hypoxia, leading to the elevation of serum liver enzymes.[9 10] A recent study revealed higher proportion in patients with liver dysfunction following the treatment with lopinavir/ritonavir during hospitalisation.[5]

In conclusion, potential risk factors in patients with COVID-19 developing severe liver injury were ritonavir, elevated IL-6 and IL-10, and reduced $CD4^+$ T cells. In addition, the underlying mechanisms of liver injury in patients with COVID-19 involve immune response, cytokine production, drug-induced liver injury and potential SARS-CoV-2–mediated liver damage (figure 1). Therefore, during the treatment of COVID-19, liver function, inflammatory cytokines and T lymphocyte subsets should be closely monitored, and drug-induced liver damage could be considered in clinical practice.

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Table 1 Identification of putative risk factors in patients with COVID-19 developing severe liver injury during hospitalisation

Variable	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Ritonavir	5.24 (0.69 to 16.39)	<0.001	5.63 (2.86 to 18.63)	<0.001
IL-6, pg/mL	2.13 (1.08 to 3.21)	<0.001	2.21 (1.09 to 4.67)	0.006
IL-10, pg/mL	1.82 (1.03 to 2.85)	0.004	1.78 (1.08 to 3.12)	0.014
$CD4^+$ T cell, per µL	2.90 (1.85 to 5.96)	<0.001	3.24 (1.05 to 6.38)	<0.001
$CD8^+$ T cell, per µL	1.88 (1.03 to 3.15)	0.005		
$CD4^+$ T/$CD8^+$ T cell	1.08 (0.99 to 1.35)	0.163		
$CD3^+$ T cell, per µL	0.43 (0.19 to 0.88)	0.034		
Neutrophil count, $\times10^9$/L	1.11 (1.02 to 1.25)	0.077		
Monocyte count, $\times10^9$/L	3.41 (1.05 to 17.99)	0.106		

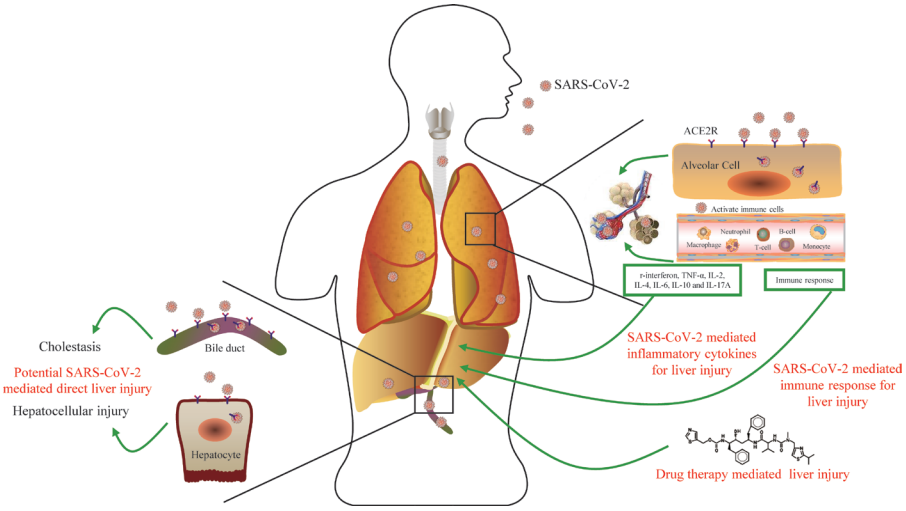

Figure 1 Host immune responses and potential liver injury during the viral infection of SARS-CoV-2.

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Contributors ZM, AZ, GY and SL initiated and designed the study. KZ, JL, LL, KY, LQ and CL collected the data. KZ, SL and YB analysed the data. KZ, SL and JL wrote the letter. SL drafted the figure. ZM, AZ and GY reviewed and edited the letter. All authors read and approved the final version for publication.

Funding This work was supported by the Chongqing Special Research Project for Prevention and Control of COVID-19 (grant no. cstc2020jscx-fyzx0103).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Chongqing Public Health Medical Center (2020-025-KY).

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2020-321913).

KZ and SL are joint first authors.

To cite Zhan K, Liao S, Li J, *et al*. *Gut* 2021;**70**:628–629.

Received 21 May 2020
Revised 12 June 2020
Accepted 13 June 2020
Published Online First 22 June 2020

Gut 2021;**70**:628–629. doi:10.1136/gutjnl-2020-321913

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