Serum albumin: a potential biomarker for liver involvement in SARS-CoV-2 infection

*Neha Gupta and Bishuang Cai**

Division of Liver Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, 10029, USA

eBioMedicine
2025;112: 105565
Published Online 25 January 2025
https://doi.org/10.1016/j.ebiom.2025.105565

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in the rapid infection of millions of people worldwide. The initial symptoms of COVID-19 were confined to the respiratory system, but soon the effects on other organs became apparent. The onset of severe complications—such as neurological disorders, rapid gastrointestinal disease, cardiopulmonary edema, liver damage, and kidney damage—emphasizes the profound and complex nature of the disease.[1] The widespread multi-organ damage seen in patients with COVID-19 can be partly explained by the extensive distribution of SARS-CoV-2 receptors throughout different tissues and organs. Angiotensin-converting enzyme 2 (ACE2) is the main receptor for SARS-CoV-2, enabling the virus to enter host cells. ACE2 is highly expressed not only in the respiratory tract but also in the cardiovascular system, gastrointestinal tract, kidneys, liver, and central nervous system.[2,3]

The liver is vulnerable to COVID-19 through direct infection of hepatocytes and cholangiocytes via ACE2 receptors, causing cellular damage. Additionally, the virus triggers the systemic inflammatory response, with elevated pro-inflammatory cytokines (*e.g.,* IL-6, TNF-α), which can worsen liver injury through immune-mediated mechanisms and microvascular thrombosis.[4] Hypoxic injury from severe respiratory distress further affects liver function. Initial COVID-19 data suggest that both healthy individuals and those with pre-existing liver conditions infected with SARS-CoV-2 show abnormal liver function tests (LFTs), indicating that the virus may directly contribute to liver damage. In general, the mechanism by which SARS-CoV-2 infects hepatocytes is still unclear, and interestingly, the degree of liver damage is related to the severity of COVID-19 infection.

In a recent issue of *eBioMedicine*, Chen and colleagues presented clinical evidence of liver infection with SARS-CoV-2 and proposed assessing fluctuations in serum albumin concentration as a potential method for evaluating the risk of death in patients with COVID-19.[5] Specifically, they detected viral S and N proteins in the livers of diseased and severely infected patients with COVID-19 but not in moderately infected patients. They combined immunohistochemistry staining with spatial transcriptomics and identified hepatocytes and erythroid cells in hepatic sinusoids as the major cells affected by SARS-CoV-2 (Fig. 1). Surprisingly, ACE2 was not detected in hepatocytes, indicating the involvement of other receptors, such as ASGR1, for the entry of the virus. However, substantial evidence is required to support this mode of entry. Furthermore, T-cell enrichment was observed in surviving severe patients. Interestingly, more $CD3^+$ cells were observed adjacent to viral-positive cells in surviving severe patients, but not in deceased patients, indicating the role of T cells in intrahepatic virus clearance. Moreover, increased apoptosis, an overall decrease in transcription, and a decrease in albumin concentration were observed in the livers of diseased patients. A retrospective study of albumin levels in deceased patients confirmed its decline, while in hospitalized patients, albumin recovery was linked to clinical improvement. Conversely, a decrease or low serum albumin concentrations were associated with a higher risk of death.

These findings suggest that downregulated serum albumin expression could serve as a potential indicator of liver involvement in SARS-CoV-2 infection. Although the recent study by Chen and colleagues has shed much-needed light on the clinical evidence for liver infection of SARS-CoV-2, the mechanism of liver infection remains unanswered. While the study suggests that serum albumin levels can be used to assess mortality risk, it does not provide clear guidelines or thresholds for clinical practice. A key factor in the severity of COVID-19 is the dysregulated immune response, which triggers a cytokine storm. While cytokines are meant to defend the host against infection, their overproduction and uncontrolled release could worsen the condition. Additionally, pre-existing liver conditions and co-infections with other viruses could exacerbate liver injury, leading to a worse prognosis.[6] Therefore, future research is required to ascertain the mechanism of virus infection and T-cell activation for better clinical management of long-term hepatic consequences of COVID-19.

DOI of original article: https://doi.org/10.1016/j.ebiom.2024.105517
*Corresponding author.
E-mail address: bishuang.cai@mssm.edu (B. Cai).

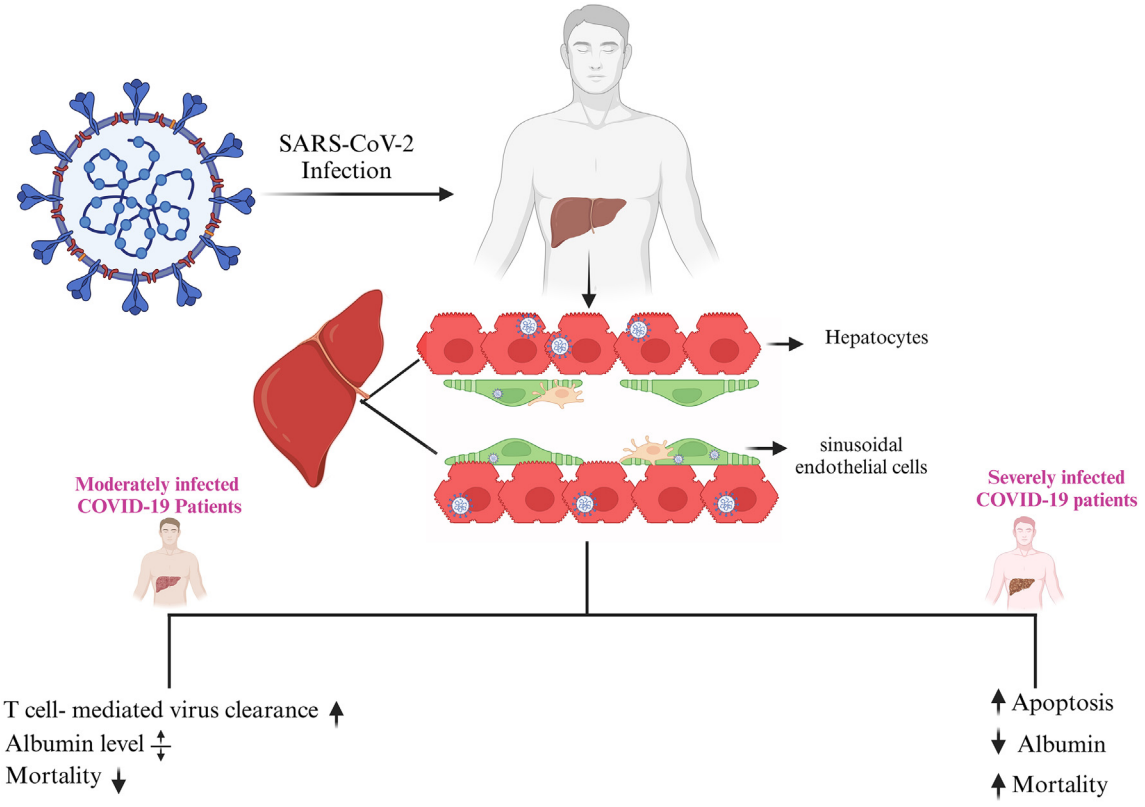

Fig. 1: **SARS-CoV-2 infection impairs liver function**.

Contributors
Literature search, writing, and editing: N.G., and B.C. Both authors read and approved the final manuscript.

Declaration of interests
The authors declare no conflict of interest.

Acknowledgements
This work was supported by NIH grants R01DK134610 and R35GM147269 (to B.C.). The graphic scheme was made by BioRender.

References

1 Guarienti FA, Goncalves JIB, Goncalves JB, Antonio Costa Xavier F, Marinowic D, Machado DC. COVID-19: a multi-organ perspective. *Front Cell Infect Microbiol*. 2024;14:1425547. https://doi.org/10.3389/fcimb.2024.1425547.
2 Hikmet F, Mear L, Edvinsson A, Micke P, Uhlen M, Lindskog C. The protein expression profile of ACE2 in human tissues. *Mol Syst Biol*. 2020;16:e9610. https://doi.org/10.15252/msb.20209610.
3 Chen R, Wang K, Yu J, et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. *Front Neurol*. 2020;11:573095. https://doi.org/10.3389/fneur.2020.573095.
4 Sanyaolu A, Marinkovic A, Abbasi AF, et al. Effect of SARS-CoV-2 infection on the liver. *World J Virol*. 2023;12:109–121. https://doi.org/10.5501/wjv.v12.i2.109.
5 Chen S, Zhang Y, Ashuo A. Combination of spatial transcriptomics analysis and retrospective study reveals liver infection of SARS-COV-2 is associated with clinical outcomes of COVID-19. *eBioMedicine*. 2024;111:105517. https://doi.org/10.1016/j.ebiom.2024.105517.
6 Verduyn M, Allou N, Gazaille V, et al. Co-infection of dengue and COVID-19: a case report. *PLoS Neglected Trop Dis*. 2020;14:e0008476. https://doi.org/10.1371/journal.pntd.0008476.