



SARS-CoV-2 infection in people with pre-existing liver disease: Further research is warranted

Henu Kumar Verma, LVKS Bhaskar

ORCID number: Henu Kumar Verma
[0000-0003-1130-8783](https://orcid.org/0000-0003-1130-8783); LVKS Bhaskar
[0000-0003-2977-6454](https://orcid.org/0000-0003-2977-6454).

Author contributions: Verma HK
and Bhaskar LVKS wrote and
revised the letter.

Conflict-of-interest statement: The
authors declare no conflict of
interest for this article.

Country/Territory of origin: Italy

Specialty type: Gastroenterology
and hepatology

Provenance and peer review:
Invited article; Externally peer
reviewed.

**Peer-review report's scientific
quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an
open-access article that was
selected by an in-house editor and
fully peer-reviewed by external
reviewers. It is distributed in
accordance with the Creative
Commons Attribution
NonCommercial (CC BY-NC 4.0)
license, which permits others to
distribute, remix, adapt, build
upon this work non-commercially,

Henu Kumar Verma, Department of Immunopathology, Institute of lungs Biology and Disease,
Comprehensive Pneumology Center, Neuherberg 85764, Munich, Germany

LVKS Bhaskar, Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur 495001, Chhattisgarh, India

Corresponding author: Henu Kumar Verma, PhD, Research Scientist, Department of
Immunopathology, Institute of lungs Biology and Disease, Comprehensive Pneumology Center,
Helmholtz Zentrum, Neuherberg 85764, Munich, Germany. henu.verma@yahoo.com

Abstract

Patients with severe liver disease who have been infected with severe acute respiratory syndrome coronavirus-2 (coronavirus disease 2019) frequently develop acute respiratory distress syndrome and multiple organ failure, with a high mortality rate, as a result of the hyper-proinflammatory state known as the cytokine storm. Clinicians must recognize cytokine storms earlier to avoid intensive care admission and multi-organ damage, a critical life-threatening condition with prognostic and therapeutic implications

Key Words: Cytokine storm; Liver disease; Angiotensin-converting enzyme 2; Therapeutics; Inflammatory markers

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Understanding the hepatic consequences of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and its molecular mechanism has greatly evolved. Evidence suggests that coronavirus disease 2019 fatalities are primarily due to cytokine storm and abnormal immune function. Throughout the infection, interleukin-6, nuclear factor kappa B, and tumor necrosis factor-alpha are inflammatory cytokines released by SARS-CoV-2-infected macrophages and monocytes that cause acute liver injury. Anti-viral treatment with anti-inflammatory receptors, such as monoclonal antibodies, can be used to reduce the morbidity and mortality associated with SARS-CoV-2 infection.

Citation: Verma HK, Bhaskar L. SARS-CoV-2 infection in people with pre-existing liver disease: Further research is warranted. *World J Gastroenterol* 2021; 27(45): 7855-7858

and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Received: May 4, 2021

Peer-review started: May 4, 2021

First decision: June 12, 2021

Revised: June 13, 2021

Accepted: September 8, 2021

Article in press: September 8, 2021

Published online: December 7, 2021

P-Reviewer: Kashyap MK, Pham TTT

S-Editor: Fan JR

L-Editor: Wang TQ

P-Editor: Wang LYT



URL: <https://www.wjgnet.com/1007-9327/full/v27/i45/7855.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v27.i45.7855>

TO THE EDITOR

Recently we have seen a paper entitled “Impact of cytokine storm and systemic inflammation on liver impairment patients infected by SARS-CoV-2: Prospective therapeutic challenges” contributed by Ali *et al*[1] in your well-regarded journal “*World J Gastroenterology*”[1]. Regarding this paper, we would like to draw your attention to several valuable and interesting aspects. The current scenario is that the second wave of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [coronavirus disease 2019 (COVID-19)] pandemic is much more aggressive, with many more cases reported in various countries. As of April 2021, nearly 2.5 million deaths worldwide have been attributed to COVID-19. Based on the geographical distribution of the COVID-19 pandemic, it was found that in areas with a higher frequency, such as China, the rate of SARS-CoV-2 infected patients with liver impairment is also higher [2]. Most hospitalized COVID-19 patients have elevated liver biomarkers, primarily aminotransferase and bilirubin, which cause multi-organ failure[3,4]. This review paper by Ali *et al*[1] shows great public health interest. In their article, the authors elegantly described the impact of SARS-CoV-2 on hepatic impairment conditions. Besides, they focused on several current studies that indicated the role of the hyperinflammatory state that is known as “cytokine storm” concerning the angiotensin-converting enzyme 2 (ACE2) receptor as the main factor for the high rate of SARS-CoV-2 spreading and mortality and its putative therapies[5].

The SARS-CoV-2 directly enters the host cell through surface receptors and binds to ACE2[6]. ACE2 expression has been reported in different normal human organs, including the liver, where its expression is significantly low compared to the duodenum, kidney, and small intestine[7]. Accumulating evidence indicated the hepatic sharing of ACE2 after virus entry into the host cell. The underlying mechanisms of liver injury in COVID-19 patients are currently indistinguishable. However, human liver single-cell RNA-seq data indicated the co-expression of ACE2 and transmembrane serine protease 2 in liver progenitor cells, suggesting that the liver is the target of coronavirus disease[8].

Further, there is a 59.7% increase in ACE2 expression in cholangiocytes compared to 2.6% in hepatocytes, indicating that SARS-CoV-2 may directly bind to the ACE2 receptor, and the liver may be a good host for SARS-CoV-2[9,10]. Histological analysis of liver biopsies of COVID-19 patients revealed moderate microvascular steatosis, mild lobular, portal activity, and T cell overexpression, showing that the liver injury could have been caused by either SARS-CoV-2 infection or treatment[3,11]. A hospital-based study in China revealed elevated levels of proinflammatory cytokines, chemokines, and growth factors in COVID-19 patients compared to healthy adults[12,13]. Further, the patients with severe COVID-19 show hepatic dysfunction or liver disorders, including chronic liver disease, hepatitis viruses (types B, C, D, and E), hepatotropic virus infection, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis with elevated platelet, neutrophil, and lymphocyte counts, resulting in the worst outcomes from acute respiratory distress syndrome[14,15].

There is no consensus among researchers regarding liver damage in COVID-19 patients; some studies proposed the immediate cytopathic effect of the virus on hepatocytes or the biliary epithelium *via* ACE receptors[16,17]. Others postulated inflammatory and immune-mediated liver failure in patients with multiple organ damage[18]. However, hepatic inflammation involving cytokine activation was well-documented. A case study of COVID-19 patients demonstrated that the C-reactive protein (CRP) of 20 mg/L and a lymphocyte count of 1.1 10⁹/L were independent risk factors for liver injury[19]. Kupffer cell activation is indeed a common finding in the liver of SARS-CoV-2 infected patients. Further, the altered macrophage polarization in SARS-CoV-2-infected patients with NAFLD suggests that SARS-CoV-2 has mechanisms to divert macrophage polarization in their preferred direction and increase the synthesis of inflammatory cytokines[18].

Regardless of the precise definition, the combinations of clinical manifestation and inflammatory markers (such as elevated plasma levels of CRP, lactate dehydrogenase, interleukin (IL)-6, IL-1, tumour necrosis factor-alpha (TNF)-α, and ferritin) could be used to define the “cytokine storm syndrome” in COVID-19 patients[20-22]. Besides this, treatment with anti-IL-6 receptor monoclonal antibodies (sarilumab and

tocilizumab), anti-IL-6 monoclonal antibodies (siltuximab), IL-1 inhibitors (Anakinra, Rilonacept, and Canakinumab), and TNF- α inhibitors (adalimumab, etanercept, and infliximab) showed promising results against SARS-CoV-2-induced cytokine storm[23-25]. In addition, corticosteroids that are known to alter the nuclear factor kappa B pathway central to the cytokine storm were used to manage the severe SARS and Middle East respiratory syndrome patients[26]. As a cytokine storm is a critical life-threatening condition and has prognostic and therapeutic implications, the clinicians must recognize cytokine storms earlier to avoid intensive care admission and multi-organ damage.

REFERENCES

- 1 Ali FEM, Mohammedsaleh ZM, Ali MM, Ghoghar OM. Impact of cytokine storm and systemic inflammation on liver impairment patients infected by SARS-CoV-2: Prospective therapeutic challenges. *World J Gastroenterol* 2021; **27**: 1531-1552 [PMID: 33958841 DOI: 10.3748/wjg.v27.i15.1531]
- 2 Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, Poucke SV, Liu WY, Zheng MH. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. *J Clin Transl Hepatol* 2020; **8**: 18-24 [PMID: 32274342 DOI: 10.14218/JCTH.2020.00018]
- 3 Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. *Liver Int* 2020; **40**: 1278-1281 [PMID: 32251539 DOI: 10.1111/liv.14470]
- 4 Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. *Lancet Gastroenterol Hepatol* 2020; **5**: 428-430 [PMID: 32145190 DOI: 10.1016/S2468-1253(20)30057-1]
- 5 Yongzhi X. COVID-19-associated cytokine storm syndrome and diagnostic principles: an old and new Issue. *Emerg Microbes Infect* 2021; **10**: 266-276 [PMID: 33522893 DOI: 10.1080/22221751.2021.1884503]
- 6 Krishnamurthy S, Lockey RF, Kolliputi N. Soluble ACE2 as a potential therapy for COVID-19. *Am J Physiol Cell Physiol* 2021; **320**: C279-C281 [PMID: 33502950 DOI: 10.1152/ajpcell.00478.2020]
- 7 Kumar P, Sah AK, Tripathi G, Kashyap A, Tripathi A, Rao R, Mishra PC, Mallick K, Husain A, Kashyap MK. Role of ACE2 receptor and the landscape of treatment options from convalescent plasma therapy to the drug repurposing in COVID-19. *Mol Cell Biochem* 2021; **476**: 553-574 [PMID: 33029696 DOI: 10.1007/s11010-020-03924-2]
- 8 Seow JJW, Pai R, Mishra A, Shepherdson E, Lim TKH, Goh BKP, Chan JKY, Chow PKH, Ginhoux F, DasGupta R, Sharma A. Single-Cell RNA-seq Reveals Angiotensin-Converting Enzyme 2 and Transmembrane Serine Protease 2 Expression in TROP2⁺ Liver Progenitor Cells: Implications in Coronavirus Disease 2019-Associated Liver Dysfunction. *Front Med (Lausanne)* 2021; **8**: 603374 [PMID: 33968947 DOI: 10.3389/fmed.2021.603374]
- 9 Lindskog C. The potential clinical impact of the tissue-based map of the human proteome. *Expert Rev Proteomics* 2015; **12**: 213-215 [PMID: 25925092 DOI: 10.1586/14789450.2015.1040771]
- 10 Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, Zhou J, Shi G, Fang N, Fan J, Cai J, Lan F. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV infection. 2020 Preprint. Available from: bioRxiv:2020.2002.2003.931766 [DOI: 10.1101/2020.02.03.931766]
- 11 Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020; **73**: 451-453 [PMID: 32278005 DOI: 10.1016/j.jhep.2020.03.044]
- 12 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]
- 13 Li J, Gong X, Wang Z, Chen R, Li T, Zeng D, Li M. Clinical features of familial clustering in patients infected with 2019 novel coronavirus in Wuhan, China. *Virus Res* 2020; **286**: 198043 [PMID: 32502551 DOI: 10.1016/j.virusres.2020.198043]
- 14 Tian D, Ye Q. Hepatic complications of COVID-19 and its treatment. *J Med Virol* 2020; **92**: 1818-1824 [PMID: 32437004 DOI: 10.1002/jmv.26036]
- 15 Kudravalli P, Saleem SA, Ibeche B, John S. Case series and review of liver dysfunction in COVID-19 patients. *Eur J Gastroenterol Hepatol* 2020; **32**: 1244-1250 [PMID: 32568805 DOI: 10.1097/MEG.0000000000001806]
- 16 Roedl K, Jarczack D, Drolz A, Wichmann D, Boenisch O, de Heer G, Burdelski C, Frings D, Senses B, Nierhaus A, Lütgehetmann M, Kluge S, Fuhrmann V. Severe liver dysfunction complicating course of COVID-19 in the critically ill: multifactorial cause or direct viral effect? *Ann Intensive Care* 2021; **11**: 44 [PMID: 33721137 DOI: 10.1186/s13613-021-00835-3]
- 17 Huang C, Li Q, Xu W, Chen L. Molecular and cellular mechanisms of liver dysfunction in COVID-19. *Discov Med* 2020; **30**: 107-112 [PMID: 33382966]
- 18 Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]

- 19 **Li L**, Li S, Xu M, Yu P, Zheng S, Duan Z, Liu J, Chen Y, Li J. Risk factors related to hepatic injury in patients with corona virus disease 2019. 2020 Preprint. Available from: medRxiv:2020.2002.2028.20028514 [DOI: [10.1101/2020.02.28.20028514](https://doi.org/10.1101/2020.02.28.20028514)]
- 20 **Chen G**, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; **130**: 2620-2629 [PMID: [32217835](https://pubmed.ncbi.nlm.nih.gov/32217835/) DOI: [10.1172/JCI137244](https://doi.org/10.1172/JCI137244)]
- 21 **Qin C**, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 2020; **71**: 762-768 [PMID: [32161940](https://pubmed.ncbi.nlm.nih.gov/32161940/) DOI: [10.1093/cid/ciaa248](https://doi.org/10.1093/cid/ciaa248)]
- 22 **Verma HK**. Radiological and clinical spectrum of COVID-19: A major concern for public health. *World J Radiol* 2021; **13**: 53-63 [PMID: [33815683](https://pubmed.ncbi.nlm.nih.gov/33815683/) DOI: [10.4329/wjrv.v13.i3.53](https://doi.org/10.4329/wjrv.v13.i3.53)]
- 23 **Atal S**, Fatima Z. IL-6 Inhibitors in the Treatment of Serious COVID-19: A Promising Therapy? *Pharmaceut Med* 2020; **34**: 223-231 [PMID: [32535732](https://pubmed.ncbi.nlm.nih.gov/32535732/) DOI: [10.1007/s40290-020-00342-z](https://doi.org/10.1007/s40290-020-00342-z)]
- 24 **Sarzi-Puttini P**, Giorgi V, Sirotti S, Marotto D, Ardizzone S, Rizzardini G, Antinori S, Galli M. COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin Exp Rheumatol* 2020; **38**: 337-342 [PMID: [32202240](https://pubmed.ncbi.nlm.nih.gov/32202240/)]
- 25 **Rizk JG**, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmacologic Immunomodulatory Therapy in COVID-19. *Drugs* 2020; **80**: 1267-1292 [PMID: [32696108](https://pubmed.ncbi.nlm.nih.gov/32696108/) DOI: [10.1007/s40265-020-01367-z](https://doi.org/10.1007/s40265-020-01367-z)]
- 26 **Tang Y**, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Front Immunol* 2020; **11**: 1708 [PMID: [32754163](https://pubmed.ncbi.nlm.nih.gov/32754163/) DOI: [10.3389/fimmu.2020.01708](https://doi.org/10.3389/fimmu.2020.01708)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

