ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2021 December 7; 27(45): 7739-7865

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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Weekly Volume 27 Number 45 December 7, 2021

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE

December 7, 2021

INSTRUCTIONS TO AUTHORS

https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/GerInfo/287

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https://www.wjgnet.com/bpg/gerinfo/242

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World J Gastroenterol 2021 December 7; 27(45): 7855-7858

DOI: 10.3748/wjg.v27.i45.7855

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

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

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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

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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

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

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.

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