Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision

Specific Comments to Authors: This article reviews coronavirus disease 2019 (COVID-19) treatment-related drug-induced liver injury (DILI) and its possible genetic factors. The recent outbreak of COVID-19 caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has resulted in a world-wide pandemic. Infection with this virus not only causes respiratory symptoms but may also involve the patient's liver to varying degrees during the course of the disease. The reasons for the occurrence of liver damage in COVID-19 patients are multifactorial. In addition to cytopathic injury induced directly by the virus via ACE 2, DILI adverse events have a significant impact. This manuscript includes a fairly comprehensive list of the hepatotoxic effects of various types of COVID-19 therapeutic agents, as well as summaries and explorations into etiology and genetics.

I am not aware from this manuscript whether there are currently uniform and clear specific criteria for determining or assessing DILI associated with COVID-19 treatment. If so, please describe; if not, what is the potential evidence that warns of the presence of DILI?

Author's response: Suggested modifications have been incorporated in the manuscript as:

There is a deficit of uniformity and standardization as to DILI, owing to lack of reliable and exclusive evidence pointing towards the drugs used in the treatment of COVID-19 disease, as the sole culprits. Moreover, there is considerable overlap and commonality in the presenting symptoms of hepatic damage due to COVID-19 infection per se and due to drugs given for its treatment. Increased vigilance on the part of the clinicians is warranted, so that cases of severe liver damage suspected to be caused by the drugs can be reported and entered into the National/International Database. The R-value, defined as serum alanine aminotransferase (ALT)/upper limit of normal (ULN) divided by serum alkaline phosphatase (Alk P)/ULN can be considered as a diagnostic approach for the pattern of liver injury; i.e., R>5 to be considered as hepatocellular DILI, R<2 as cholestatic DILI, and 2<R<5 as mixed DILI.

The authors mentioned the nature and characteristics of liver injury triggered by some drugs. Is DILI caused by different types of drugs of the same type? Is there any difference in the degree of risk? Perhaps a further systematic summary and comparison of the similarities or differences and severity of different drug-induced liver injuries could be made.

Author's response: Suggested modifications have been incorporated in the manuscript as:

Author's response: Table 2 depicts the commonly employed therapeutic drugs for COVID-19, with its hepatic side effects and 'Likelihood Score' by the LiverTox Database (44).

Table: Hepatoxicity and likelihood score of therapeutic agents of COVID-19

Drug	Hepatotoxicity	Likelihood Score
Remdesivir	A duration of 7-14 days of administration caused elevation of serum aminotransferases up to <5 times of ULN. Elevations of >5 times ULN were reported in 9% of patients but returned to normal after discontinuation. Prolonged and more severe effects were seen in critically ill patients with multi-organ involvement, pre-existing co-morbidities and who had received combination therapy with other hepatotoxic agents like amiodarone.	D
Lopinavir/Ritonavir	A greater degree of rise in serum aminotransferase levels (>5 times UNL) is mostly seen in association with immunodeficiency states. The pattern varies from hepatocellular to cholestatic or mixed type. Discontinuation leads to the normalization of enzyme levels. However severe cases of acute liver failure or end stage liver disease are also reported with re-exposure of the drug.	D
Tocilizumab	Reported to cause mild elevation of aminotransferases commonly, that is usually transient and asymptomatic but rare instances of liver injury manifesting as jaundice and reactivation of hepatitis-B is seen. ALT elevation (1-3 times UNL) was seen in 10%-50% of patients which returned to baseline within 8 weeks after stopping treatment. No effect on bilirubin or ALP levels were seen.	C
Hydroxychloroquine	Clinically apparent liver injury is rare. In clinical trials for COVID-19 prevention and treatment, there were no reports of hepatotoxicity and serum enzyme elevation was also low	C
Corticosteroids	Long term use and high doses can result in hepatomegaly and steatosis. Can also trigger or exacerbate pre-existing or co-existing	A

	conditions like NASH, viral hepatitis or autoimmune hepatitis. Serum aminotransferase levels can rise up to 10-40 times ULN	
Enoxaparin	4%-13% of patients showed mild elevation in serum aminotransferase levels. Rapid onset of liver injury symptoms after starting the drug (within 3-5 days) but rapid recovery (1-4 weeks) after discontinuation of therapy is seen.	E
Favipiravir	Pre-treatment with other hepato-toxic drugs like Lopinavir/Ritonavir and IF-β 1B lead to increase in liver transaminase and bilirubin levels by manifold suggesting cholestatic injury. Isolated use is not known to cause any severe liver injury	D

A: Well know hepatotoxicity; B: Highly likely hepatotoxicity; C: Probably hepatotoxicity; D: Possible hepatotoxicity; E: Unlikely hepatotoxicity

There are a number of minor language flaws. Please double-check the grammar throughout, especially the incorrect use of plural and singular forms (e.g., "devastating effect" and "variant of interests").

Author's response: Language has been modified to meet the requirements.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: Dear author, The considerations pointed out are to adapt the manuscript to the rules of WJG.

1. Please note that the manuscript must be prepared using 12 pt Book Antiqua font and 1.5 line spacing.

Author's response: Suggested modifications have been incorporated in the manuscript.

2. Information on authorship, institution, ORCID number, contributions of authors, corresponding author were not provided.

Author's response: All were provided in the manuscript submission system. Now we are adding in the manuscript also as suggested.

3. Abstract (no less than 200 words), keywords and core tip were not presented.

Author's response: Already it was provided, can be seen in your manuscript submission system. Don't know how reviewer missed it.

4. In the INTRODUCTION (page 1) is the term "S20 site" correct?

Author's response: Yes, it is correct

5. In the INTRODUCTION (page 1) the term "golgi" should be written in capital letter.

Author's response: Suggested modifications have been incorporated in the manuscript.

6. In the INTRODUCTION (page 1) there is no hyphen in "In-fact".

Author's response: Suggested modifications have been incorporated in the manuscript.

7. In the RESULTS (page 5): "showed a >5 UNL". What's UNL mean?

Author's response: Upper normal limit, correction have been incorporated in the revised manuscript.

8. Please standardize the citation of references in the text. Sometimes the surname and the initial of the first name are mentioned, other times only the author's surname is provided – "Delgado A et al"; "Carothers et al". 9.

Author's response: Suggested modifications have been incorporated in the manuscript.

In the RESULTS (page 7) – "Sporadic cases of mild increases in serum bilirubin and alkaline phosphatase is reported." Please check this sentence. Best regards

Author's response: Suggested modifications have been incorporated in the manuscript.

Reviewer #3:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: This is a review on COVID19 mechanisms related to liver injury. Although this focuses on the mechanisms of a single organ only, the concepts expressed throughout might be of relevance for a broader audience.

Author's response: We sincerely appreciate the given feedback.

Company editor-in-chief:

I recommend the manuscript to be published in the World Journal of Virology. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Author's response: In the initial manuscript itself suggested points were incorporated i.e., RCA search.