

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 79923

Title: COVID-19 associated liver injury (COVALI): a general review with special consideration of pregnancy and obstetric outcomes

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00742373

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2022-09-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-26 02:17

Reviewer performed review: 2022-09-29 07:41

Review time: 3 Days and 5 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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SPECIFIC COMMENTS TO AUTHORS

The review manuscript titled “Covid associated liver injury(COVALI): a general review with special consideration of pregnancy and obstetric outcomes” summarized the clinical features of COVALI and the pathophysiology in literatures on COVALI during pregnancy and general population. The authors synthesized data try to help set the approaches for COVALI in obstetrics. The manuscript concluded that the COVALI is typically a hepatocellular or mixed pattern liver injury with AST predominant transaminitis, or total bilirubin and alkaline phosphatase elevation, which is usually related to the severity of the disease. The review summarized that these changes are likely due to a combination of systemic inflammation in pathophysiology, which include the underline liver disease, pharmacologic agents, ACE-2 expression, hypoxemia, immune dysregulation, endotheliopathy, thrombosis, and cytokines. For obstetric clinical study, the manuscript reviewed literature on Covid-19 during pregnancy shown higher prevalence of COVALI in pregnant patients compared to non-pregnant patients and more severely elevated liver enzymes in pregnant patients with COVALI compared to non-pregnant patients with COVALI. It may indicate that COVID-19 confers an increased risk of liver injury specific to pregnancy. The authors collected typical patients of Covid-19 during pregnancy and discussed the worse obstetric outcomes of hospitalization, severity of the disease, maternal mortality, and acute liver injury. They also concluded a worse post-partum outcomes of COCALI as an independent factor. It is not widely in literature to explore COVIDLI during pregnancy. At present, there is no unique diagnostic criteria for COVID-19 associated liver injury (COVALI) during pregnancy. COCALI during pregnancy is of serious clinical significance because liver

injury can strongly influence decisions regarding delivery. This review gave a clear figure of liver injury from Covid-19 during pregnancy. It will help researchers and clinicians to understand the specific pathophysiology mechanism of COVALI during pregnancy and pay more attention on the diagnosis and management to improve the obstetric outcomes. It is a very good topic which has great significance for reproductive health. Comments: • The abstract is lack of the major point of the review conclusion. The readers may feel not know the key conclusion after reading the abstract. • “Covid associated liver injury (COVALI)” was used in the title and most places of the manuscript, but in some places and in figure 1, the author used COVID-19-induced liver injury. It could be better to use one, or please explain the difference. • Line 117, improve grammar(period?).

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Peer-review model: Single blind

Reviewer's code: 05374991

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor, Master's Student, Research Assistant

Reviewer's Country/Territory: Germany

Author's Country/Territory: United States

Manuscript submission date: 2022-09-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-26 08:39

Reviewer performed review: 2022-10-03 21:45

Review time: 7 Days and 13 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

General Impression: The authors conducted a review to summarize the main clinical characteristics and pathoetiology of Covid-19-associated liver injury. The manuscript is thorough, informative, and novel. It gives a detailed explanation of the disease and potential causes. The manuscript is well-structured and the figure and tables are clear. Some parts of the manuscripts are longer than needed and could be summarized. I humbly believe that this manuscript is worth publishing subject to minor revisions.

Comments: 1) In the abstract (line 32), please specify whether the Covid-19-associated liver injury is the occurrence of a newly diagnosed hepatic biochemical injury during a Covid-19 infection or it is the exaggeration of an old hepatic injury after contracting Covid-19. The definition in its current form is a little bit confusing and should be better stated. 2) In the whole text, please correct the name of the Covid-19 virus from "SARS-2-CoV" to "SARS-CoV-2". The first abbreviation is incorrect. 3) The introduction is well-written but deviated to some extent from the main focus of this paper. It contains a lot of general information about Covid-19, which is slightly irrelevant to the aim of this manuscript. I suggest summarizing the general information about Covid-19 in a few lines and focusing the introduction on the Covid-19-associated liver injury. 4) In the introduction section (lines 79 and 80), I slightly disagree with this statement. Promoting open access publishing and research equity is done by publishing in open access journals (as you are doing by submitting to WJG). Focusing on papers published in open access journals only is a weakness in this review because it may lead to missing important papers published in journals with subscriptions. 5) In the clinical consideration paragraph (line 101), please clarify whether the liver enzymes peak "at least five times



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higher" or "less than five times higher" than the upper limit in patients with Covid-19-associated liver injury. The current sentence is unclear. 6) In the paragraph Clinical Cases (lines 318-345), I believe it is not necessary to give a summary of each case. I suggest focusing on the main findings and writing a briefer paragraph. The manuscript is interesting and informative, but also long paragraphs are not really desired. 7) The conclusions typically are a 6 to 7-line paragraph that gives recommendations for future research perspectives or clinical suggestions for improving the practice. A conclusion of 1-page length is not acceptable. Please summarize it.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05480683

Position: Peer Reviewer

Academic degree: PhD

Professional title: Academic Fellow, Academic Research, Adjunct Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: United States

Manuscript submission date: 2022-09-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-30 15:38

Reviewer performed review: 2022-10-05 19:22

Review time: 5 Days and 3 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

-Journal - World Journal of Gastroenterology - Manuscript ID 79923 -Type: REVIEW

-Title: Covid associated liver injury (COVALI): a general review with special consideration of pregnancy and obstetric outcomes This is a well written review manuscript covering different aspects of COVID-19 associated liver injury (COVALI), which is a clinical syndrome encompassing all patients with COVID-19 infection and biochemical liver injury such as transaminitis. The systematic review is overall well written and of high quality and has the merit to summarize the relatively reduced literature in this topic, helping readers to find all the relevant information. Reported scientific facts are correctly cited, referenced, and acknowledged. Major comments • There is a vast literature on the co-infective potential of SARS-COV-2 with hepatitis B infection (DOI: 10.3851/IMP3382) I suggest including notions on this topic. Is there any link between COVALI and hepatitis B? • Lines 250-257 A large variety of additional cytokines have been reported to be released during SARS-COV-2 infection. The authors can check PMID: 32961074 Here some, minor, observations Line 30 COVID-19 sohuld be mentioned as Coronavirus disease 2019 (COVID-19) when mentioned for the first time Line 35 better pregnant females Line 44 SARS-2-CoV should be replaced with SARS-CoV-2, while its complete name is severe acute respiratory syndrome coronavirus 2 Line 48 coronaviridae should be in italic style. Lines 54, 60 as well as many others: unnecessary spaces between sentences should be removed Lines 65, 66 given the topic of the work, reproductive system as a possible infective target of SARS-COV-2 infection should be mentioned DOI: 10.1186/s43043-020-00046-z Line 99 it can be replaced with COVALI Line 123 as well as other acronyms should be carefully checked and



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mentioned with their complete name the first itme being mentioned Line 201 I whould mitigate this point, this is not completely true DOI: 10.1038/s41575-021-00426-4 Lin 244 In vivo should be in italic style. Please revise the entire manuscript for additional style errors Lines 233 and 250 please uniform the style. In line 250 is should be IL-6 Lines 376-377 please revise the typo after the word “thus” Lines 400-407 as stated, a physiological systemic inflammation occur during advanced pregnancy. At the same time, during pregnancy, the circulating levels of alpha1-antitrypsin, which is a plasma protease inhibitor released by the liver, has been reported to increase (DOI: 10.3389/fcell.2020.550543). An impairment of this phenomenon in the liver might make pregnant females more prone to SARS-CoV-2 infection, as reported (doi: 10.4254/wjh.v13.i10.1367). In this context, a connection between SARS-CoV-2, COVALI and an alpha1-antitrypsin release impairment cannot be excluded. Authors should at least briefly include these notions and aforementioned supporting references