

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 79930

Title: Clinical Implications of COVID-19 in Patients with Metabolic-Associated Fatty Liver Disease

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06302021

Position: Peer Reviewer

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: United Kingdom

Manuscript submission date: 2022-09-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-13 07:02

Reviewer performed review: 2022-09-19 07:45

Review time: 6 Days

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 Grade E: Do not publish
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 type="checkbox"/> Minor revision <input checked="" 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 manuscript: "Clinical implication of COVID-19 in patients with metabolic-associated fatty liver disease" describing the implications of COVID 19 in patients with MAFLD is very interesting and easy to understand, and it could be very useful in clinical therapy. However, in my opinion, it should be changed, in particular in the second part concerning the "Clinical intervention and management". First, for each drug or therapeutic of possible use, it would be preferable to describe its effectiveness, side effects and contraindications patients with significant underlying liver disorders. Moreover, you need to detail the time of use (at what stage of infection by SARS Cov2 and in what clinical condition of liver disease) In addition: Pag. 11: The list of the compound used to treat COVID-12 infection is not exhaustive (it is better to use a table with specific columns with comments and references). In addition, this table could also include any hepatotoxic or cytotoxic effects of the drugs. Cloroquine: you should specify mechanism of action of inhibiting the SARS-CoV-2 entry into host cells (via the angiotensin-converting enzyme 2 (ACE2)). In addition, it is useful to also clarify that chloroquine has been reported to cause damage to the CV system (with referenes). Antiviral agents: you should explain their action mechanisms. Pag. 12: Vaccines: You should explain if the vaccines currently used in these patients are equally immunogenic, compared to healthy people, and if they can induce further adverse effects in MAFLD people (red flags?). I also suggest to better explain the paragraph: COVID19 and liver biochemistry... (pag. 4) Moreover, there are little shape and formatting errors (e.g. pag 9: Patients with COVID-19: liver biopsy : lowercase character; liver biopsy: liver: lowercase character, etc.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05040445

Position: Editorial Board

Academic degree: MD

Professional title: Associate Professor, Chief Physician, Professor

Reviewer's Country/Territory: China

Author's Country/Territory: United Kingdom

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Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2022-10-28 02:03

Reviewer performed review: 2022-10-28 03:36

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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
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 type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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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

This review is well written and generally meet the journal requirements. I just don't agree with the authors idea because the real state of the COVID-19 is hard to evaluate in some contries and that data from those contry is not the real state of people.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05628603

Position: Peer Reviewer

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: United Kingdom

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Review time: 3 Days and 8 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
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: ☒ Anonymous ☐ Onymous

Conflicts-of-Interest: ☐ Yes ☒ No

SPECIFIC COMMENTS TO AUTHORS

In this study, the authors addressed the severity of COVID-19 in patients with prior MAFLD and its potential implications and therapeutic administration in the clinical setting. The selected topic is close to the clinical reality, has a certain timeliness and practicality, and can be used to guide the clinical. However, I still have the following concerns about this study, specifically as follows: 1. Figure 1: The interplay between COVID-19 and metabolic-associated fatty liver disease (MAFLD). It is not possible to directly show its relevance through this picture. It is recommended to refine and enrich the contents of the picture. 2. From the perspective of the writing structure of this question, the author aims to review the pathogenesis, diagnosis and intervention strategies. However, as far as the mechanism part is concerned, it is redundant and recommended to simplify, while the treatment part should be updated and refined, and the summary should be more comprehensive. 3. Through reading the full text, although the author has carried out a detailed literature search on the relationship between MAFLD and COVID-19, the summary and inspiration of the review still need to be further refined. Especially in the core tip part, at least I can't fully understand the central idea that the author wants to clarify and the inspiration that the article gives to readers from this passage. In my opinion, at the end of each subtitle of the article, there should be a summary and inspiration of the author's personal views. 4. Some grammar and technical terms involved in the article need to be carefully considered.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03476715

Position: Editorial Board

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Professional title: Professor

Reviewer's Country/Territory: China

Author's Country/Territory: United Kingdom

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" 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 type="checkbox"/> Yes <input checked="" type="checkbox"/> No

**Peer-reviewer
statements**

Peer-Review: ☒ Anonymous ☐ Onymous

Conflicts-of-Interest: ☐ Yes ☒ No

SPECIFIC COMMENTS TO AUTHORS

This review focuses on the impact of MAFLD disease status on the development and prognosis of COVID-19, vice-versa. Besides, some aspects about diagnosis and treatments. Searching in PUBMED with the key words COVID-19 and MAFLD, we found two articles similar to this one, such as: 1. Chen H, Chen Q. COVID-19 Pandemic: Insights into Interactions between SARS-CoV-2 Infection and MAFLD. *Int J Biol Sci.* 2022 Jul 11;18(12):4756-4767. doi: 10.7150/ijbs.72461. PMID: 35874945; PMCID: PMC9305262. 2. Campos-Murguía A, Román-Calleja BM, González-Regueiro JA, Hurtado-Díaz-de-León I, Solís-Ortega AA, Flores-García NC, García-Juárez I, Ruiz-Margáin A, Macías-Rodríguez RU. Clinical perspectives, assessment, and mechanisms of metabolic-associated fatty liver disease in patients with COVID-19. *World J Gastroenterol.* 2021 Sep 7;27(33):5502-5519. doi: 10.3748/wjg.v27.i33.5502. PMID: 34588748; PMCID: PMC8433612. Thus, the clinical significance of this study is limited. There are some suggestions below: (1) In Altered Liver Response section, lipid metabolism is affected by COVID-19. How about liver detoxification and protein synthesis? (2) It may be true that FIB-4 index negatively associated with COVID-19 prognosis. However, this did not reflect the impact of COVID-19 on the progression of MAFLD. (3) It is obscure in section of increased hepatic decompensation rates in cirrhotic patients, which conveyed the message that the cirrhotic patients with COVID-19 infection had higher probability developing hepatic decompensation than those without COVID-19. (4) Inflammatory cytokines is associated with severity of COVID-19. Are those cytokines MAFLD-related. (5) A significant proportion of patients with MAFLD present only with metabolic disorders without obesity. Only discussing

obesity and COVID-19 seems to be off topic. As same as pre-existing MAFLD on COVID-19 disease severity.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05208113

Position: Editorial Board

Academic degree: PhD

Professional title: Assistant Professor, Lecturer

Reviewer's Country/Territory: China

Author's Country/Territory: United Kingdom

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Reviewer chosen by: Dong-Mei Wang

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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
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input checked="" 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 type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

This work was aimed to investigate the implications of COVID-19 on liver injury and disease severity and vice-versa, as well as address the severity of COVID-19 in patients with prior MAFLD and its potential implications and therapeutic administration in the clinical setting. It is interesting for readers of this journal. However, the content seemed tremendous but also unfocused. It's better to refine the content by shrinking some inessential chapters. Besides, the following issues should be addressed. 1. "In contrast to hepatocytes, which comprise only 3% of the liver cells; most cells are cholangiocytes (60%) and endothelial cells, which express ACE2 receptors." Really? 2. Page 6: Two sections described that COVID-19 causes symptoms to appear in the upper respiratory tract, lung and gastrointestinal tract. What's the relationship between these sections and MAFLD? It is very common that section content was disconnected with section title, and it was hard to find the logic and correlation between chapters, as well as between sections. 3. Page 20: Detection of ACE2 polymorphism. What's the authors want to talk for putting this chapter here? 4. Chapter - Clinical Interventions and Management: is there a necessity for this chapter? Too much general content focus on interventions of COVID-19, while too little content focus on COVID-19 + MAFLD patients. I did not see the specific intervention for COVID-19 + MAFLD patients, in such huge content but with limited significance. 5. Too many long and obscure sentences throughout text.

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Peer-review model: Single blind

Reviewer's code: 06302021

Position: Peer Reviewer

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: United Kingdom

Manuscript submission date: 2022-09-12

Reviewer chosen by: Ze-Mao Gong

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Reviewer performed review: 2022-11-28 08:16

Review time: 2 Days and 13 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
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
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

-The analysis of the correlation between MALF and the course of COVID is very useful in evaluating more in-depth manner the risk factors and the therapies to be administered to this category of subjects. - Among the future directions it it will be good to analyse, also through meta-analytic studies, which are the best therapeutic approaches for this category of subjects.