

PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 78885

Title: Liver Injury in COVID-19: Holds Ferritinophagy-mediated Ferroptosis Accountable

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04870360

Position: Editorial Board

Academic degree: MSc, PhD

Professional title: Assistant Professor, Lecturer, Research Scientist

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

Manuscript submission date: 2022-07-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-07-21 07:21

Reviewer performed review: 2022-08-03 09:19

Review time: 13 Days and 1 Hour

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 Grade E: Do not publish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

SPECIFIC COMMENTS TO AUTHORS

In the manuscript entitled “Liver Injury in COVID-19: Hold Ferritinophagy-mediated Ferroptosis Accountable”, the authors investigated the relationship between the severity of hepatic injury induced by SARS-Cov infection and ferritinophagy-mediated ferroptosis mechanism. The authors assumed that the ferritinophagy-mediated ferroptosis could be associated with SARS-CoV-2 infection and may be a potential target for future therapeutic challenges. Indeed, the study is merit and interesting. However, several issues may be raised to improve the manuscript. 1- This article may consider a minireview article. 2- A table of summarizing should be added 3- Previously published article “10.3748/wjg.v27.i15.1531” may be useful for this study specifically in the part of “Systemic Inflammation-related Liver Dysfunction in COVID-19” 4- More recent studies should be added to comprehensively the review idea.

Comments to reviewers

1- This article may consider a minireview article.

✓ Thank you for your comments. The submitted manuscript type is a minireview.

2- A table of summarizing should be added

✓ Thank you for your advice. Although plenty of researchers have reported liver injuries in COVID-19, as a matter of fact, no direct evidences about ferritinophagy-mediated ferroptosis in the pathological process are found. As described in our manuscript, a few investigators noticed iron overload and ferroptosis in liver injury caused by COVID-19. In this review, we hypothesize that ferritinophagy intermediates liver injury caused by COVID-19. For the past 4 years, ferritinophagy has been involved in physiology and pathology process of liver, including hepatic insulin resistance, hepatocyte senescence, ferroptosis process in hepatic stellate cells, hepatocellular carcinoma and liver fibrosis.



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Therefore, we added a supplementary table listing the implication of ferritinophagy in physiology and pathology process of liver in the revised manuscript.

- 3- Previously published article “10.3748/wjg.v27.i15.1531” may be useful for this study specifically in the part of “Systemic Inflammation-related Liver Dysfunction in COVID-19”

✓ Thank you very much for providing with the information, which is very useful. We reviewed it in the revised manuscript.

- 4- More recent studies should be added to comprehensively the review idea.

✓ Considering your suggestion, more recent studies have been added in the revised manuscript.

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Title: Liver Injury in COVID-19: Holds Ferritinophagy-mediated Ferroptosis Accountable

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05334153

Position: Peer Reviewer

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

Manuscript submission date: 2022-07-20

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2022-10-15 14:14

Reviewer performed review: 2022-10-28 14:40

Review time: 13 Days

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
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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

Jia F in this manuscript report on "Liver Injury in COVID-19: Hold Ferritinophagy-mediated Ferroptosis Accountable". The manuscript is very well written and of clinical and academic interest. However, the author needs to address few minor points as follows: - While dealing with a very hot and extremely rapidly evolving topic like COVID-19, you need to use very very recent references. None of your references involve the year 2022. In several paragraphs you mentioned (recently,.....) then you referred to a reference in 2018 and 2019. So, please update your references. - Are there any studies tried to use iron chelators as a cytoprotective agent to reduce the inflammatory response in COVID-19 patients? (like the case in acetaminophen toxicity mentioned in reference number 57?) - Please revise the manuscript for few editing mistakes. Thanks

Comments to reviewers

1. -While dealing with a very hot and extremely rapidly evolving topic like COVID-19, you need to use very very recent references. None of your references involve the year 2022. In several paragraphs you mentioned (recently,.....) then you referred to a reference in 2018 and 2019. So, please update your references.

✓ Thank you for your suggestion, and we have added the recently published references, especially in 2022.

2. - Are there any studies tried to use iron chelators as a cytoprotective agent to reduce the inflammatory response in COVID-19 patients? (like the case in acetaminophen toxicity mentioned in reference number 57?)

✓ Yes, iron depletion or chelation has been considered as a potential antiviral therapy to

protect against extreme inflammatory responses and tissue damage by sequestering iron and preventing oxygen radical formation and lipid peroxidation in patients with COVID-19^[1]. It is mentioned that deferasirox administered orally, as well as intravenous deferoxamine made iron chelation therapy effective for COVID-19 victims^[2]. A case-control study showed that iron chelators which reduced iron intake could be considered a therapeutic goal of COVID-19^[3]. In addition, receptor binding of SARS-CoV-2 for entry into host cells can be prevented by lactoferrin, an iron chelator^[4,5].

Refs:

1. **Perricone C**, Bartoloni E, Bursi R, Cafaro G, Guidelli G M, Shoenfeld Y, and Gerli R. COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. *Immunol Res* 2020; 68(4): 213-224 [PMID: 32681497 DOI: 10.1007/s12026-020-09145-5].
2. **Poonkuzhi Naseef P**, Elayadeth-Meethal M, Mohammed Salim K T, Anjana A, Muhas C, Abdul Vajid K, and Saheer Kuruniyan M. Therapeutic potential of induced iron depletion using iron chelators in Covid-19. *Saudi J Biol Sci* 2022; 29(4): 1947-1956 [PMID: 34924800 DOI: 10.1016/j.sjbs.2021.11.061].
3. **Bastin A**, Shiri H, Zanganeh S, Fooladi S, Momeni Moghaddam M A, Mehrabani M, and Nematollahi M H. Iron Chelator or Iron Supplement Consumption in COVID-19? The Role of Iron with Severity Infection. *Biol Trace Elem Res* 2022; 200(11): 4571-4581 [PMID: 34825316 DOI: 10.1007/s12011-021-03048-8].
4. **Rainey N E**, Moustapha A, Saric A, Nicolas G, Sureau F, and Petit P X. Iron chelation by curcumin suppresses both curcumin-induced autophagy and cell death together with iron overload neoplastic transformation. *Cell Death Discov* 2019; 5: 150 [PMID: 31839992 DOI: 10.1038/s41420-019-0234-y].
5. **Chang R**, Ng T B, and Sun W Z. Lactoferrin as potential preventative and adjunct treatment for COVID-19. *Int J Antimicrob Agents* 2020; 56(3): 106118 [PMID: 32738305 DOI: 10.1016/j.ijantimicag.2020.106118].

3. - Please revise the manuscript for few editing mistakes. Thanks

✓ Thank you for your kindness. We carefully corrected the whole manuscript. Hopefully the revised manuscript could be satisfactory.

We greatly appreciate both your help and that of the reviewers' concerning improvement to this paper. I hope that the revised manuscript is now suitable for publication.