RESPONSE TO THE REVIEWER COMMENTS

Reviewer # 1

Comment

Thank you so much for submitting this article But unfortunately this manuscript is not well organized at all and does not follow a clear flow. The necessary standards for writing mini review articles have not been met. The scattering of unnecessary content is too much. Most of the content presented in this draft is on the two titles of (Pathogenesis of Pre-eclampsia and HELLP syndrome) and (Pathogenesis of COVID-19), so it is not necessary to present this volume of content and it can be summarized in the introduction section. But instead, the content presented on the two titles of (Evidence on COVID-19 and HELLP syndrome) and (Pathophysiology linkage between COVID-19 and HELLP syndrome) has been presented very, very briefly, As the main discussion of this manuscript is considered. Also, there is no information about the relationship between COVID-19 , HELLP syndrome and pregnancy, which is the main topic of this mini-review. Due to the presentation of such materials in this manuscript, novelty was not observed.

Response: We thank the reviewer for the peer review and comments. This article is written as an opinion mini-review (solicited by the journal's editor-in-chief). We have revised the manuscript considerably with additional information on the pathophysiology linkage between COVID-19 and HELLP syndrome using p53 MPAK pathway. We have also discussed the published studies in greater detail, including a new figure (Figure 3) exploring the pathogenesis linkage between COVID-19 and HELLP syndrome. We believe that the revised manuscript will be very helpful to readers to evaluate the current evidence on the topic and areas of future studies.

Reviewer # 3

Comment: The review entitled "COVID-19 AND HEMOLYSIS, ELEVATED LIVER ENZYMES AND THROMBOCYTOPENIA (HELLP) SYNDROME - ASSOCIATION OR CAUSATION?" by Nasa et. al is a well written informative review of the risk of HELPP syndrome in the context of SARS CoV-2 infection. There are some minor suggestions, which if incorporated would help in better understanding of the review. The text does not refer to the figures provided at the end. There needs to be link

between the figures and the text. An additional figure that summarizes the proposed mechanism by which COVID patients could be developing HELPP would help in better appreciation of the mechanisms.

Response: We thank the reviewer for the kind peer review and suggestions. We have revised the manuscript considerably with the citation of all figures in the text and included a new figure (Figure 3) exploring the pathogenesis linkage between COVID-19 and HELLP syndrome.

Reviewer #4

Comment: The presented manuscript entitled " COVID-19 AND HEMOLYSIS, ELEVATED LIVER ENZYMES AND THROMBOCYTOPENIA (HELLP) SYNDROME - ASSOCIATION OR CAUSATION?" (Manuscript NO: 79269) aims to establish a relationship between SARS-CoV-2 infection and HELLP syndrome by reviewing and summarizing some studies. The manuscript can be accepted for publication in “World Journal of Gastroenterology”, after revision. The authors should revise the manuscript according to the following comments: 1. First of all, there are several grammatical errors and misspellings throughout the manuscript. Authors are obliged to take action to address these shortcomings. For example, in the abstract, the " unfavourable" is used incorrectly instead of the word unfavorable. Other examples: foetal tissue, high titre, analysed (analyzed), hospitalized (hospitalised), …

Response: We appreciate the reviewer for the peer-review and comprehensive comments. The manuscript is reviewed with the identification and correction of grammatical errors. A language expert has also reviewed the manuscript, and a language check certificate is provided with the revised manuscript.

Comment 2. The “Abstract” and “Conclusion” sections are very brief. The most important findings of this review need to be presented in Abstract section.

Response: We thank the reviewer for the comment. The manuscript is reviewed with the identification and correction of grammatical errors. A language expert has also

reviewed the manuscript, and a language check certificate is provided with the revised manuscript.

Comment 3. The manuscript seems too small to be published as a mini-review. Therefore, it is suggested that the authors logically try to increase the number of references used. If this is not possible and the number of suitable studies is small, it is recommended to change the type of article to commentary or perspective in consultation with the editor.

Response: We thank the reviewer for the observation made. The manuscript has been revised to include the role of p53 MAPK pathways in the pathogenesis of COVID-19 and HELLP syndrome. All published studies on the topic are included in the revised manuscript, and the total number of references now stands at 50. We believe the revised manuscript will satisfy the journal's mini-review criteria and provide readers with a comprehensive overview of the topic.

Comment 4. In the introduction section, after the sentences: (.....These include age above 75 years, male sex, preexisting cardiovascular disease, chronic lung, kidney or liver disease, sickle cell disease, diabetes, active cancer, severe obesity, and pregnancy .....), it is necessary to refer to the appropriate reference.

Response: We thank the reviewer for the observation. The reference has been added for the statement in the revised manuscript

Comment 5. The statement that "Risk factors for developing severe COVID-19 in pregnant women include obesity, smoking history, and diabetes mellitus [1,2]. .....) is incomplete. Other important risk factors, including pulmonary comorbidities, hypertensive disorders, etc. which are not mentioned here. Therefore, it is necessary for the authors to provide more complete and accurate information here and to refer to valid reports.

Response: We thank the reviewer for this comment. We have included all risk factors in the revised manuscript.

Comment 6. ……..(Pregnancy, per se, does not increase the susceptibility to SARS-CoV-2 infection. However, being pregnant increases the risk of severe disease with SARS-CoV-2 infection and is associated with adverse pregnancy and perinatal outcomes [3]…….). omment: There are contradictions in the sentences and they are not well expressed.

Response: We are thankful to the reviewer for this comment. The statement has been redrafted to "Pregnancy, per se, does not increase the susceptibility to SARS-CoV-2 infection. However, pregnant women are at increased risk of development of severe illness with SARS-CoV-2 infection compared to non-pregnant and are associated with adverse pregnancy and perinatal outcomes"

On the other hand, reference 3 does not seem appropriate here.

We have corrected the reference.

Comment: 7. …… (Renin-angiotensin-aldosterone system (RAAS) plays a vital role in placenta homeostasis,…… ATII causes vascular constriction, endothelial injury, and vascular smooth cell proliferation, contributing to pre-eclampsia [12])……...

Comment: In this part of the article, the relationship between the Renin-angiotensin-aldosterone system (RAAS) and pre-eclampsia is discussed. Some recent studies have investigated the relationship between the severe complications of the COVID-19 disease and the abnormal activation of the p38 MAPK signaling pathway, which is affected by the disruption of the RAAS pathway (DOIs: 10.1021/acsptsci.2c00045, 10.1016/j.yjmcc.2020.05.007, 10.1002/ddr.21961, 10.1080/15384101.2021.1982509, and 10.1080/15384101.2022.2100575). On the other hand, there are some studies that have established a logical connection between the abnormal activation of p38 MAPK and pre-eclampsia as well as HELLP syndrome (DOIs: 10.1093/molehr/gal071, 10.3109/14767058.2016.1144744, 10.1002/jcb.28778, and 10.1007/s12192-009-0125-x). In this part of the article, I strongly suggest that the possible relationships between the p38 MAPK pathway and the mentioned cases (RAAS pathway, p38 MAPK, pre-

eclampsia, and also HELLP syndrome) should be considered and described in a separate section. This suggested section can look at the etiology of the disorders mentioned in the title and introduction of the article from a new angle, which can potentially be interesting and useful for readers.

Response: We thank the reviewer for this suggestion. The manuscript has been revised to include the role of p53 MAPK pathways in the pathogenesis of COVID-19 and HELLP syndrome. All published studies on the topic are included in the revised manuscript. The sections on pathophysiology of "Pre-eclampsia and HELLP syndrome", "pathogenesis of COVID-19", "Pathophysiology linkage between COVID-19 and HELLP syndrome" have been revised.

Comment 8. The contents of the studies mentioned above can also be used to describe the next sections of the manuscript, such as "Pathogenesis of COVID-19" and "Evidence on COVID-19 and HELLP syndrome", and "Conclusion".

Response: We thank the reviewer for this suggestion. The manuscript's abstract and conclusion has been revised with inclusion of summary of studies on p53 MAPK in COVID-19 and HELLP syndrome.