OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://brieflands.com/briefland/knowledgebase/category/tree.html#opr.html

Hepatitis Monthly
Article DOI: https://doi.org/10.5812/hepatmon-129836
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Peer Review Report for "The Efficacy of Antiviral Treatment for Chronic Hepatitis B Patients with Normal ALT Levels: A Systematic Review and Meta-analysis"

Author(s): Zhe Qian, Meixin Hu, Houji Wu, Hongjie Chen, Guichan Liao, Zixin Kang, Xiaoli Lin, Jie Peng

Review Timeline:

Submit Date:	19 Jul 2022
Revised Date:	3 Oct 2022
Accepted Date:	6 Oct 2022

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | Revision (0)

28 Jul 2022

This manuscript is a well-written systematic review and meta-analysis on the efficacy of different antiviral treatments for chronic hepatitis B in patients with normal and elevated ALT levels. Authors have included 14 relevant studies and observed that the efficacy of two recommended first-line treatments for HBV infection (Tenofovir and Lamivudine) is similar between patients with normal and elevated ALT.

Here are some comments:

• Abstract methods description should be explained in greater detail. Also, the abstract conclusion can be expanded on.

• Introduction: line 53-55: “Family history of HCC or cirrhosis and extrahepatic manifestations are emphasized when serum ALT levels do not fit the indications” this

sentence seems vague and can be rewritten.

• Introduction: line 58-59: “When non-invasive tests show evidence of significant fibrosis, patients >35 years or with a family history of HCC or cirrhosis should receive a liver biopsy” please add the reference

• Introduction: line 67: please define ULN when using it for the first time in the manuscript.

• Methods: line 100-103: Please add the reference guideline and level for ALT ULN.

• Methods: line 118: Please spell out HAI

• Results: I think the results can be described in greater detail to address all significant findings of this study.

• Discussion: I would recommend revising this section, especially the first few paragraphs, to improve the coherency of the discussion. Some irrelevant studies and sentences are seen in a row in some paragraphs without an appropriate comparison of the studies or raising any arguments that come to a conclusion.

• Limitations: Authors may try to revise this part to address all the possible limitations.

• Figure 1: The flow chart contains many grammatical errors and should be revised.

REFEREE: Reviewer | **Revision** (0) 3 Aug 2022

First of all I should congratulate you for this article with interesting topic. It would be interesting to determine the efficacy of antiviral treatment for chronic hepatitis B patients with normal ALT levels.
However, the manuscript needs to be revised in Introduction, methodological details, results, and language.

Abstract:
1- In Keywords please check it again because some of words are not in Mesh

Introduction:
1- There is not very clear explaining about the main problem in your Introduction!! (Your Research problem and Question)What question led you to do this? Please more explain about your Research question in Introduction? What we didn’t know!!?
2- It would be better if you wrote in more detail about the last research

Method:
1- All Study selection was carried out exactly according to the PRISMA guideline?
2-how you assessed the quality of included papers?
(What was your critical appraisal form?)
Based on this system and considering the mentioned factors, you should include papers

were categorized as low, moderate, and high quality ones and should be used in the sensitivity analysis based on this assessment.
3- What method did you use in your analysis? Your confidence interval (CI)? What software did you use for your data analysis?
5- What was your exclusion criteria?

Result:

1- In Figure 1(Flow chart) you should calculate it again. The numbers is not correct.
2-please separate the different part of results. The word “Result “must be written in the first part of the results.
Discussion:
Should be thoroughly revised, needs language revision

Reference:
The references are outdated; please use more current references for the article, especially for the discussion section.

REFEREE: Reviewer | **Revision** (0) 5 Aug 2022

Authors should reformat the manuscript based on the Hepatitis Monthly style. I have some comments on the methodology of this project
1- Authors have selected the PubMed database for searching and retrieving articles. What is the reason for not searching other databases like Scopus and Cochrane?
2- What were the approaches of the authors for searching grey literature?
3- The search date should be updated.
4- Does this project have a Prospero Code?
5- The author should provide some necessary information regarding their approaches for performing meta-analyses in the methods section such as the name of the used software and related statistical tests. (Reformatting the article and providing these data into the methods section and not in the results section)
6- It is highly recommended that authors mention their approach for the quality assessment of included studies in the methods section. Furthermore, the results of this assessment which is a very important step in performing a systematic review should be provided in the results section.
7- The type and number of extracted data from included studies should be provided in the methods section.
8- In addition to the clinical trials, case-control projects, and retrospective cohort studies, I think that prospective cohort studies can be suitable for inclusion in this project and should be added to the eligibility criteria.
9- In the eligibility criteria section, we need to have some information about including or excluding patients with or without HCV or HIV co-infection.
10- What was the background reason for selecting such a cut-off for the ALT level for dividing and categorizing patients?
11- I think that authors should check the possibility of publication bias in their project.

Best Regards
Reviewer

REFEREE: Associate Editor | **Revision** (0) 6 Aug 2022

Dear Editor in Chief
Thanks for assigning me as associate editor to handle the manuscript NO.129836 entitled "The efficacy of antiviral treatment for chronic hepatitis B patients with normal ALT levels: A systematic review and meta-analysis".
I appreciate the authors' work to collect these data from the literature. Although the subject is important, there are some major concerns regarding the methodology and scientific writing of the manuscript, that should be addressed by the authors before further considerations. See the attached peer-review comments for more information.

Regards
AE

Seyed Moayed Alavian: EIC | **Revision** (0) 7 Aug 2022

Dear Authors,

Please follow the peer-review comments and submit a revision.

Regards,
EIC

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Hepatitis Monthly
Manuscript ID：129836
Title ： The efficacy of antiviral treatment for chronic hepatitis B patients with normal ALT levels: A systematic review and meta-analysis
Dear Associate Editor and Editor in Chief,

Thank you and the reviewers for the comments on our manuscript 129836 entitled "**The efficacy of antiviral treatment for chronic hepatitis B patients with normal ALT levels: A systematic review and meta-analysis**", which was submitted to ***Hepatitis Monthly***.

Based on the reviewer's comments, we have added more details in the revised manuscript. Parts of the manuscript has been re-written and the part of *Method* and *Result* have been re-structed. Assessment of quality of included studies and publication bias were added in. We have searched the PubMed database again to find the published researches from clinical trials from 2020.11 to 2022.8 and two studies were added in for meta-analysis. Every question of the reviewers was answered point by point.

We wanted to add one more author in our author list for his great help in our revision work. All the changes modified were highlighted in the manuscript.

We have revised the manuscript to address each concern of the reviewers and the associated editor. In summary, we thank the reviewers and editor for their thorough reviews. We hoped that these changes have improved our manuscript, so that it fulfills the publication requirements of your esteemed journal.

Thanking you in anticipation.
Yours sincerely,
Dr. Zhe Qian

Responses to the comments of Reviewers

Reviewer#1:

Comments to the Author :
Authors should reformat the manuscript based on the Hepatitis Monthly style. I have some comments on the methodology of this project
1. Authors have selected the PubMed database for searching and retrieving articles. What is the reason for not searching other databases like Scopus and Cochrane?
Response: We thank the reviewer for this comment. PubMed is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics. Some of the researches recorded in can be available for full texts. Many of these researches are highly duplicated in all three databases which you mentioned above. For accessibility of the full text of the researches, we choose to search the database of PubMed and Web of Science. We have designed a comprehensive search strategy for this purpose and finally obtained 1000 more included researches after the primary search. Nevertheless, we thank a lot for your most precious suggestion on diversity of data acquisition sources. We will try other databases the next time we produce a similar literature review and we believe it will obviously improve the quality of our review.

2. What were the approaches of the authors for searching grey literature?
Response: We thank the reviewer for this comment. The "Luxembourg definition", discussed and approved at the Third International Conference on Grey Literature in 1997, defined grey literature as "that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers". In our review, all the researches included in our review were published clinical trials by professional academic press. According to this definition, there were not any “grey literature” included in our review. However, grey literature plays an increasingly important role in the production of a review. Your professional suggestion provided a very helpful insight for us for our further research.

3. The search date should be updated.
Response: We thanks the reviewer for this comment. We have searched the PubMed and Web of Science database again to find the published researches of clinical trial from 2020.11 to 2022.8. There were 103 researches included for censoring and 2 met the inclusion criteria for further meta-analysis. Moreover, some newly published researches having advances have been added to the discussion section of the manuscript. The search date has been updated accordingly.

4. Does this project have a Prospero Code?
Response: We thank the reviewer for this comment. This project did not have a

Prospero Code.

5. The author should provide some necessary information regarding their approaches for performing meta-analyses in the methods section such as the name of the used software and related statistical tests. (Reformatting the article and providing these data into the methods section and not in the results section)

Response: We thank the reviewer for this comment. We have re-edited the article according to your suggestion and highlighted the edition part.

6. It is highly recommended that authors mention their approach for the quality assessment of included studies in the methods section. Furthermore, the results of this assessment which is a very important step in performing a systematic review should be provided in the results section.

Response: We thank the reviewer for this comment. We have added a part of quality assessment of included studies in the *Method* and the result of assessment was prepared for submission as *Supplementary Material Figure 1*.

7. The type and number of extracted data from included studies should be provided in the methods section.

Response: We thank the reviewer for this comment. We have added this section as you suggested.

8. In addition to the clinical trials, case-control projects, and retrospective cohort studies, I think that prospective cohort studies can be suitable for inclusion in this project and should be added to the eligibility criteria.

Response: We thank the reviewer for this comment. We have added more details in the part of *Eligibility Criteria* as you suggested.

9. In the eligibility criteria section, we need to have some information about including or excluding patients with or without HCV or HIV co-infection.

Response: We thank the reviewer for this comment. Researches included this category of patients co-infected with HIV or other hepatitis viruses were excluded in our previous inclusion criteria. We have added more details in the part of *Eligibility Criteria*.

10. What was the background reason for selecting such a cut-off for the ALT level for dividing and categorizing patients?

Response: We were very pleasant to answer the question. The aim of this systematic review and meta-analysis was to assess and compare the antiviral efficacy of NAs among the two groups of CHB patients with elevated and normal ALT levels. Thus, we need to divide CHB patients into experimental group as with elevated ALT levels and control group as with normal ALT levels. We choose 40IU/L as a cut-off value as upper limit of normal of ALT levels based on several CHB guidelines adopted in China clinically. [The guidelines of prevention and

treatment for chronic hepatitis B (2019 version)]. Zhonghua Gan Zang Bing Za Zhi, 2019. 27(12): p. 938-961. 1. Sarin, S.K., et al., Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int, 2016. 10(1): p. 1-98.

11. I think that authors should check the possibility of publication bias in their project.

Response: We thank the reviewer for this comment. We have added assessment of publication bias in the part of *Method* and the part of *Result*.

Best Regards

Reviewer

Response: We thank the reviewer for the very valuable and helpful reviews which have obviously improved the quality of our manuscript.

Reviewer #2:

This manuscript is a well-written systematic review and meta-analysis on the efficacy of different antiviral treatments for chronic hepatitis B in patients with normal and elevated ALT levels. Authors have included 14 relevant studies and observed that the efficacy of two recommended first-line treatments for HBV infection (Tenofovir and Lamivudine) is similar between patients with normal and elevated ALT.

Response: We thank the reviewer for the summary of this manuscript.

Here are some comments:

1. Abstract methods description should be explained in greater detail. Also, the abstract conclusion can be expanded on.

Response: We thank the reviewer for this comment. We have added some details in the *Abstract* and the conclusion was also expanded.

2. Introduction: line 53-55: "Family history of HCC or cirrhosis and extrahepatic manifestations are emphasized when serum ALT levels do not fit the indications" this sentence seems vague and can be rewritten.

Response: We thank the reviewer for this comment. We have re-written and highlighted the revised sentence.

3. Introduction: line 58-59: "When non-invasive tests show evidence of significant fibrosis, patients >35 years or with a family history of HCC or cirrhosis should receive a liver biopsy" please add the reference

Response: We thank the reviewer for this comment. We have added the relative reference in the manuscript.

4. Introduction: line 67: please define ULN when using it for the first time in the manuscript.

Response: We thank the reviewer for this comment. We have used the full name of ULN that is "upper limit of normal" in the manuscript for the first time.

5. Methods: line 100-103: Please add the reference guideline and level for ALT ULN.

Response: We thank the reviewer for this comment. We have added the relative reference in the manuscript.

6. Methods: line 118: Please spell out HAI

Response: We thank the reviewer for this comment. We have modified the section you mentioned.

7. Results: I think the results can be described in greater detail to address all significant findings of this study.

Response: We thank the reviewer for this comment. We have re-edited and re-structed the part of *Result* with more details. The newly added and modified parts

were highlighted.

8. Discussion: I would recommend revising this section, especially the first few paragraphs, to improve the coherency of the discussion. Some irrelevant studies and sentences are seen in a row in some paragraphs without an appropriate comparison of the studies or raising any arguments that come to a conclusion.

Response: We thank the reviewer for this comment. The part of *Discussion* has been re-edited throughout with updated references. More details were also added in as you suggested. All the edited part was highlighted.

9. Limitations: Authors may try to revise this part to address all the possible limitations.

Response: We thank the reviewer for this review. The *limitation* has been revised with more information.

10. Figure 1: The flow chart contains many grammatical errors and should be revised.

Response: We thank the reviewer for this review. The Figure 1 Flow chart has been revised and the grammatical errors have been corrected.

Reviewer #3:

First of all, I should congratulate you for this article with interesting topic. It would be interesting to determine the efficacy of antiviral treatment for chronic hepatitis B patients with normal ALT levels.

Response: We thank the reviewer for this comment. We thank your appreciation for this manuscript and we are very pleased to answer your questions. Every point you mentioned in the manuscript has been revised.

However, the manuscript needs to be revised in Introduction, methodological details, results, and language.

Abstract:

1. In Keywords please check it again because some of words are not in Mesh

Response: We thank the reviewer for this comment. We have re-checked and corrected the *Keywords*.

Introduction:

2. There is not very clear explaining about the main problem in your Introduction!! (Your Research problem and Question) What question led you to do this? Please more explain about your Research question in Introduction? What we didn't know!!?

Response: We thank the reviewer for this comment. The part of *Introduction* has been re-edited. The points you mentioned were revised with emphasis. All the modified section were visible highlighted.

3. It would be better if you wrote in more detail about the last research

Response: We thank the reviewer for this comment. The point you mentioned has been revised highlighted.

Method:

4. All Study selection was carried out exactly according to the PRISMA guideline?

Response: We thank the reviewer for this comment. It is a claim that all the procedure of this meta-analysis was carried out under the PRISMA guideline. Relative presentation was added.

5. How you assessed the quality of included papers?

(What was your critical appraisal form?)

Based on this system and considering the mentioned factors, you should include papers were categorized as low, moderate, and high-quality ones and should be used in the sensitivity analysis based on this assessment.

Response: We thank the reviewer for this comment. There was an assessment of quality of included studies in the revised version. The quality of the RCTs, CCTs, and cohort studies were assessed according to the Cochrane Collaboration Risk of Bias Tool (ROB), Methodological Index for Non-randomized Studies (MINORS), and Newcastle–Ottawa Scale (NOS), respectively. The part of *Quality assessment*

was added in the *Method*.

6. What method did you use in your analysis? Your confidence interval (CI)? What software did you use for your data analysis?

Response: We thank the reviewer for this comment. The meta-analysis was performed with Stata 17 and Review Manager. The Mantel-Haenszel formula was used to generate a pooled effect estimate with ORs and 95% CIs. The relative part has been already added in the manuscript.

7. What was your exclusion criteria?

Response: We thank the reviewer for this comment. There were no specific exclusion criteria in our study selection process. Proper studies assessed as high quality met the inclusion criteria would be included in our review for further analysis. Others were excluded.

Result:

8. In Figure 1(Flow chart) you should calculate it again. The numbers is not correct.

Response: We thank the reviewer for this comment. The Flow chart was remade with the number was re-calculated. The Flow chart was updated.

9. Please separate the different part of results. The word "Result "must be written in the first part of the results.

Response: We thank the reviewer for this comment. The part of *Result* has already been revised with a new format to make it expressed clearly and exactly.

Discussion:

10. Should be thoroughly revised, needs language revision.

Response: We thank the reviewer for this comment. The part of *Discussion* has been revised. And the language has been polished by professional academic language workers.

Reference:

11. The references are outdated; please use more current references for the article, especially for the discussion section.

Response: We thank the reviewer for this comment. We have searched the PubMed database again to find the published researches of clinical trial from 2020.11 to 2022.8. There were 103 researches included for censoring and 2 met the inclusion criteria for further meta-analysis. Moreover, newly published researches have been added in the *Discussion* section. And the references have also been updated.

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Seyed Moayed Alavian: EIC | **Revision** (1) 21 Sep 2022

Dear Authors,

I am delighted to inform that your manuscript is accepted for publication in Hepatitis Monthly.

Regards,
EIC

REFEREE: Associate Editor | **Revision** (1) 5 Oct 2022

Dear Editor in Chief,
Thanks for assigning me as associate editor to handle the revised version of the manuscript NO.129836 entitled "The efficacy of antiviral treatment for chronic hepatitis B patients with normal ALT levels: A systematic review and meta-analysis".
I appreciate the authors' work to revise their manuscript, they have addressed all of the peer-review comments by this revision. I think this version of the manuscript is suitable to be published in Hepatitis Monthly journal.

Regards,
AE