OPEN PEER REVIEW

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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

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Peer Review Report for "Serum Fibroblast Growth Factor 19 as a Biomarker in Hepatitis B Virus-Related Liver Disease"

Author(s): Xin Miao, Guicheng Wu, Xuan An, Xiqing Guo, Chuyan Peng

Review Timeline:

Submit Date: 9 Aug 2022
Revised Date: 4 Oct 2022
Accepted Date: 21 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.

Seyed Moayed Alavian: EIC | Revision (0) — 6 Aug 2022

Dear Authors,

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

Regards,
EIC

REFEREE: Reviewer | Revision (0) — 9 Sep 2022

The paper introduces a novel biomarker, FGF19, whose expression level increases sequentially in the progression of different HBV-related liver diseases and correlates with indexes related to cholestasis, hepatocyte damage, liver fibrosis, and synthetic liver function. It is considered that serum FGF19 levels can be used as a new biomarker to predict the progression of these diseases.

Some general comments and typo corrections are listed below:

1.In Conclusion of the Abstract section, ‘FGF19’ misspelled as ‘KBL’.
2. When citing an article in the main body, list the first author and add "et al." instead of listing all authors.
3.In introduction section, you mention “Due to the lack of heparin binding domain, FGF19 has a weak affinity for heparin sulfate (HS), which is easily diffused from the secreted site into the blood and acts as a hormone to regulate bile acid homeostasis, metabolism of carbohydrates, protein synthesis, lipid metabolism and so on.” Dose ‘which’ refer to FGF19 or heparin sulfate (HS)? If it represents FGF19, it is recommended to rewrite this sentence. If it is heparin sulfate (HS), this sentence does not seem to be related to the theme of this paper, and it is recommended to delete it.
In the last sentence of introduction section, you mention “explore the clinical significance of serum FGF19 as a new biomarker for HBV-related diseases.” The paper discusses HBV-related liver diseases only and does not mention other HBV-related diseases like systemic vasculitides, glomerulonephritis, and cutaneous manifestations. Consider replacing it with appropriate words
4. Please correct unit notation into IU/mL, pg/mL, etc.
5. Interpretation of Figure 1 in Results 3.4 can be placed in the legend.
6. The article proposes that FGF19 is associated with HBV-related liver diseases progression, which is associated with the duration of HBV infection. Does FGF19 increase with the duration of HBV infection?
7. It is mentioned in the article that FGF19 is related to age. And the age of the hepatitis group is significantly lower than that of the liver cirrhosis and liver cancer group. How to exclude age as a confounding factor?
8. Consider using a grammar check software like Grammarly to rectify grammatical errors.

REFEREE: Reviewer | **Revision** (0) 15 Sep 2022

Dear AE,
This article is reviewed carefully. There are some comments that need to be noted and corrected in the manuscript:

• The abstract should have been started with a background of the study and then the purpose should be mentioned. Overall, the balance between different parts of the abstract is not well respected.
• Grammatical errors need to be amended.
• Please explain more about the novelty of your work. There is a similar article with lower limitations and higher sample size than yours. You can find that through https://doi.org/10.1186/s12885-019-6322-9 .
• In the first paragraph of discussion, please summarize the most important results of the study. Also, this paragraph is written with no references mentioned.
• In discussion, the main results should be better discussed in each section. Alternatively, if any, the authors have to express the comparison with other studies in favor of the similarities and differences. In fact, the main results should be discussed with possible reasons.

REFEREE: Associate Editor | **Revision** (0) 16 Sep 2022

The manuscript "Evaluation of serum fibroblast growth factor 19 as a biomarker in hepatitis B virus-related liver disease" was reviewed. In this study, the authors compared FGF19 in spectrum HBV-related diseases and showed that it can be an indicator of disease progression. The topic is important but this manuscript needs to improve. According to our review, the paper is acceptable for publication with minor revisions. Please find all the comments:

My comment:
Some sentences in Introduction and Discussion need to be addressed. For example
“FGF19 plays an important role in the occurrence, development, and prognosis of liver cancer.”
It is better to be deleted “(including 18 and 75 years)” or “1. Under the age of 18 or over 75” or “(serial number: 21300111)”
Was nonparametric test used to compare the difference between groups when the data satisfied normality and nonhomogeneity of variance?
The authors must make the Result shorter due to repetition between text and tables. For example “In addition, ALT exists in the cytoplasm of liver cells, and AST exists in the mitochondria of liver cells, both of which are mostly used to monitor the extent of hepatocellular damage.” needs to be discussed in discussion as it did.
Which one is measured N-terminal propeptide of type III procollagen or type III procollagen?

Rewrite this sentence better “In addition, no significant differences of serum FGF19 levels were observed between genders, glucose (GLU), HBV-DNA levels.”
The data was not shown in the manuscript. “We found a significant positive correlation between Child-Pugh classification and serum FGF19 levels in patients with cirrhosis caused by HBV infection.”
It is better to address the burden of HBV-related disease instead of this sentence.
“According to studies on the burden of liver diseases worldwide, it is estimated that approximately 1 million people deaths per year due to complications of cirrhosis, and 1 million dies of viral hepatitis and HCC.”
Did almost all data in Table1 have nonnoramality distribution and analyze by Kruskal–Wallis? Please note it.
Table 2: The correlation was calculated for all patients or one group? Please write the number of participants. Which test is used for each parameter? Spearman rank, Pearson’s correlation, or Point Biserial correlation method.
Why was not serum FGF19 levels between groups shown in Table 1?
What is the result of Child-Pugh classification? Define the number of patients in each class.
MELD-Na sore or Score?

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.

List of Responses

Dear Editors and Reviewers:

Thank you for your letter and for the comments concerning our manuscript entitled “Evaluation of serum fibroblast growth factor 19 as a biomarker in hepatitis B virus-related liver disease” (ID: 130652). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in yellow in the paper. The main corrections in the paper and the responds to the reviewer's and comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

1. Response to comment: In Conclusion of the Abstract section, ‘FGF19’ misspelled as ‘KLB’

Response: We are sorry for the misspelling, it should be “FGF19”, which has been corrected in the updated version.

2. Response to comment: When citing an article in the main body, list the first author and add "et al." instead of listing all authors

Response: We thank the reviewer for raising this question. But this citation style required by the journal.

3. Response to comment: In introduction section, you mention “Due to the lack of heparin binding domain, FGF19 has a weak affinity for heparin sulfate (HS), which is easily diffused from the secreted site into the blood and acts as a hormone to regulate bile acid homeostasis, metabolism of carbohydrates, protein synthesis, lipid metabolism and so on.” Dose ‘which’ refer to FGF19 or heparin sulfate (HS)? If it represents FGF19, it is recommended to rewrite this sentence. If it is heparin sulfate (HS), this sentence does not seem to be related to the theme of this paper, and it is recommended to delete it.

In the last sentence of introduction section, you mention “explore the clinical significance of serum FGF19 as a new biomarker for HBV-related diseases.” The paper discusses HBV-related liver diseases only and does not mention other HBV-related diseases like systemic vasculitides, glomerulonephritis, and cutaneous manifestations. Consider replacing it with appropriate words.

Response: We thank the reviewer for spotting this unclear formulation. Firstly, the “which” in this sentence refer to “FGF19”. According to the reviewer’s recommendation, we modify the presentation of this sentence to “Due to the lack of a heparin-binding domain, FGF19 has a weak affinity for heparin sulfate (HS) and is effortless to spread from the secretory site to the blood as a hormone to regulate bile acid homeostasis, metabolism of carbohydrates, protein synthesis, lipid metabolism, etc.” Secondly, it is really true as reviewer suggested that we need to replace the “HBV-related disease” in the last sentence of introduction section with “HBV-related liver disease”, and we corrected in the revised manuscript. We have made sure there are no ambiguous statements in the text.

4. Response to comment: Please correct unit notation into IU/mL, pg/mL, etc.

Response: Thank you for noticing this error; the units are now correct.

5. Response to comment: Interpretation of Figure 1 in Results 3.4 can be placed in the legend.

Response: As reviewer suggested, we have replaced the position of result 3.4 in the legend.

6. Response to comment: The article proposes that FGF19 is associated with HBV-related liver diseases progression, which is associated with the duration of HBV infection. Does FGF19 increase with the duration of HBV infection?

Response: Thank you for asking this important question. Because HBV infection is an insidious process, the duration of HBV infection cannot be accurately obtained, so the relationship between serum FGF19 and the duration of HBV infection cannot be

analyzed.

7. Response to comment: It is mentioned in the article that FGF19 is related to age. And the age of the hepatitis group is significantly lower than that of the liver cirrhosis and liver cancer group. How to exclude age as a confounding factor?

Response: Thank you very much for pointing out our problem with not excluding age as a confounding factor. In order to exclude the influence of age on the results, we used ordered logistic regression to analysis these data, and the results showed that age was not an independent risk factor for FGF19 elevation in patients with HBV-related liver disease (regression coefficient=0.022, P=0.116).

8. Response to comment: Consider using a grammar check software like Grammarly to rectify grammatical errors.

Response: The manuscript has been checked thoroughly again and some grammar errors were corrected.

Reviewer #2:

1. Response to comment: The abstract should have been started with a background of the study and then the purpose should be mentioned. Overall, the balance between different parts of the abstract is not well respected.

Response: We thank the reviewer for such a valuable comment and this section accordingly in the revised manuscript have been revised.

2. Response to comment: Grammatical errors need to be amended.

Response: We are very sorry for our incorrect writing and we have corrected the grammatical mistake in our revised manuscript.

3. Response to comment: Please explain more about the novelty of your work. There is a similar article with lower limitations and higher sample size than yours. You can find that through *https://doi.org/10.1186/s12885-019-6322-9https://doi.org/10.1186/s12885-*

019-6322-9.

Response: Thank you for asking this important question. As for the concern of the reviewer about innovation and comparison, we have further summarized the characteristic of this article, and we hope that this will help the reviewer and readers to better understand our work. Firstly, the focus of this paper (*https://doi.org/10.1186/s12885-019-6322-9*) is to compare and analyze the diagnostic efficacy of FGF19 with conventional tumor markers alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) for HCC. However, we pay more attention to the relationship between FGF19 and general clinical biochemical indicators and the clinical significance of FGF19 in the process of disease progression, not limited to the diagnosis of HCC, which is extremely important for the disease. Although our sample size is relatively small, the results of this study also show that FGF19 plays an important role in the progression of HBV-related liver disease. Secondly, an interesting finding was made in our experiment. Unlike previous studies which reported that serum FGF19 was negatively correlated with the degree of fibrosis in alcoholic hepatitis and non-alcoholic fatty liver disease, we found that serum FGF19 was significantly positively correlated with fibrosis indicators in HBV-related liver disease. This suggests that there may be differences in dynamic changes of serum FGF19 levels in liver diseases caused by different etiologies. Therefore, it may be more convincing to analyze the levels of serum FGF19 in liver diseases caused by different etiologies separately.

4. Response to comment: In the first paragraph of discussion, please summarize the most important results of the study. Also, this paragraph is written with no references mentioned.

Response: Thank you to the reviewer for making this point. We have changed this part in the revised manuscript.

5. Response to comment: In discussion, the main results should be better discussed in each section. Alternatively, if any, the authors have to express the comparison with other studies in favor of the similarities and differences. In fact, the main results should be

discussed with possible reasons.

Response: Thanks to the reviewer for pointing this out and this part has now been changed in the revised manuscript.

Finally, the editor's questions have also been corrected in the revised manuscript.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in yellow in revised paper. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions.

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Revision (1)

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

REFEREE: EIC | **Revision (1)** 4 Oct 2022

Based on the reviewer and AE decision, this article is now suitable for publication. Please also send us reviewer comments in your final PDF file.

REFEREE: Associate Editor | **Revision (1)** 20 Oct 2022

The manuscript "Evaluation of serum fibroblast growth factor 19 as a biomarker in hepatitis B virus-related liver disease" was reviewed again. Most of the concerns were addressed however a few concerns were not considered accordingly. Please find my comments:

1. Authors should follow the comments carefully and respond to the comments one by one including editor's comments in the “Reply to Reviewers” file not “the editor's questions have also been corrected in the revised manuscript.”

2. 33 patients in the HBV-cirrhosis group and 27 patients in the HBV-HCC group are 60 not 61. “61 HBV-infected patients had cirrhosis (33 patients in the HBV-cirrhosis group and 27 patients in the HBV-HCC group)”

3. The patients admitted from June 2019 to November 2021 were recruited for the study group but the Ethics Committee of Chongqing University Three Gorges Hospital (dated: 28/01/2022) approved the study. Did the all tests perform in time close or during 2-3 years? I didn’t see anything about other tests procedure except for FGF-19.

4. Background or Objective in the abstract?

5. In abstract “Past research has found” refers to one research or more?

6. When citing an article in the main body, list the first author and add "et al." instead of listing all authors.

7. “.And” is a conjunction word and doesn’t need for point and capital A. and “. Such as in the study by”

8. Two times reference 28 was used in one sentence. “In addition, de Guevara, Dagher, Arruda, Nakajima and Kudo (28) found that the Child-Pugh classification could be used to evaluate the safety of sorafenib for HCC patients (28)”

9. Some sentences need to be revised. “ALT accumulated in the cytoplasm of liver cells is released into circulation in cases of liver damage”, “This is consistent with the significant positive correlation between serum FGF19 and MELD score observed in PBC-AIH OS in the past (8). Because the MELD-Na score studied in this paper is a modified version of MELD. Or “This study found significant differences between serum FGF19 levels and serum markers of cholestasis, including TBIL, DBIL, GGT, ALP, and TBA. “Notably, it was a significant positive correlation between TBIL and FGF19, DBIL and FGF19, GGT and

FGF19, ALP and FGF19, TBA and FGF19 in the serum of patients with HBV-related liver disease in this study."

10. overexpression of FGF19 in mice or FGF-15 in mice?

11. It must be added in section 3.4. The diagnostic threshold of serum FGF19 for HBV-related HCC was 165.3pg/ml with a sensitivity of 81.25% and specificity of 58.57%.

12. Did almost all data in Table1 have nonnoramality distribution and analyze by Kruskal–Wallis? Please note it.

13. Was nonparametric test used to compare the difference between groups when the data satisfied normality and nonhomogeneity of variance?

14. CHB is the abbreviated form for the first time in 2.1 Patients

15. I didn't find this sentence in Ref 16. "Child-Pugh classification is a common index for quantitative evaluation of liver functional reserve in patients with cirrhosis (16)"

16. Could the authors show that the chi-square test used for which variables?

17. Delete these from "The levels of serum FGF19 correlated with these serum indexes of liver dysfunction, liver fibrosis, etc."

18. "Notably, ordered logistic regression analyses showed that age was not an independent risk factor for FGF19 elevation in patients with HBV-related liver disease (data not shown)"is in contrast to "FGF19 levels between the healthy control group and the CHB group were found in this study, which may be caused by insufficient sample size and age differences."