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: 10.5812/hepatmon-128106
Published in: Hepatitis Monthly: 22(1); e128106

Peer Review Report for "Elevated Pancreatic Enzymes Associated with Acute Liver Injury Were Mediated by Tumor Necrosis Factor-Alpha Signaling"

Author(s): Takeshi Goya, Miho Kurokawa, Tomonobu Hioki, Tomomi Aoyagi, Motoi Takahashi, Koji Imoto, Shigeki Tashiro, Hideo Suzuki, Masatake Tanaka, Masaki Kato, Motoyuki Kohjima, Yoshihiro Ogawa

Review Timeline:

Submit Date:	12 Jun 2022
Revised Date:	9 Aug 2022
Accepted Date:	10 Aug 2022

Revision (0)

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

Raika Jamali: Reviewer | **Revision** (0) 16 Jun 2022

Dear Associate Editor,
Thank you for sending me the article entitled “Elevated pancreatic enzymes associated with acute liver injury were mediated by tumor necrosis factor alpha signaling” for review. This cross sectional study evaluated the association between pancreatic enzymes with acute liver failure severity. The result showed the relationship between pancreatic enzymes and ALF severity. It concluded that findings provide novel insights into the pathogenesis of ALF. There are some comments as the followings:
1-According to the result section in abstract: “The elevation of pancreatic enzymes was associated with ALF severity. High level of serum tumor necrosis factor alpha (TNFα) was associated with the elevation of pancreatic enzymes.” Please define the mean values and the significance level for the reported variables.
2-The conclusion is the repetition of the result. Defining these associations might show the

role of pancreatic enzyme level in the pathogenesis of ALF.
3-In the aim section of the study it is explained that “This study aimed to reveal the mechanism of Elevation of pancreatic enzymes associated with acute liver injury”. In fact this is not the situation. The aim of study is comparing the level of pancreatic enzyme in cohort of subjects with acute liver failure (not liver injury).
4-The rationale for performing the study is not enough in the introduction section. I am not satisfied for the necessity for performing the project.
5-Please define the reference for the acute liver failure criteria established by the Intractable Hepato-Biliary Diseases Study Group in Japan.
6-Please define if the etiologies for ALF were checked in the research (including viral, toxic, and medication induced). One important issue in this evaluation is clarifying the biliary obstruction. Were the patients with extra-hepatic cholestatsis excluded from the project? Biliary obstruction could cause both pancreatitis and cholangitis.
7-Please define the main findings of the study in the first paragraph of discussion section. The respect authors used the term “acute liver injury” and “acute liver failure” several times in the manuscript. These terms are not equivalent and have separate meaning. Please define which term is considered (acute liver failure or acute liver injury).
8-Please use update references in discussion.

REFEREE: Reviewer | **Revision** (0) 26 Jun 2022

First of all I should congratulate you for this article with interesting topic. It would be interesting to determine the pathogenesis of ALF.
However, the manuscript needs to be revised in terms of introduction, methodological details, results, and language.

Abstract:
1-Words count of abstract is 200, you should write more
2-please check it again the Keywords in Mesh
Introduction:
1-You mentioned in the introduction that” At present, the mechanism behind the development of pancreatic disorder in patients with ALI remains unclear” but your article is not about the mechanism and related process. We can understand explain the relationship between Excessive increase pancreas enzymes and patients prognosis. You should delete the word “mechanism”
2- It has been repeating many times “mechanism” in your text, but you didn’t explain about mechanism!!

Method:
1-How did you divide the patients into 2 groups (elevation group and non-elevation)? Explain it in Method and also criteria’s
2- Did you have missing data? Were there patients who quit or leaving the research?
3-you should more explain labor measurement in your Method (which method, device)?
4- Explain about exclusion criteria and inclusion criteria?

Result:

1- Is the etiologies of liver injury (hepatitis A virus 13%, hepatitis B virus 23%, autoimmune hepatitis 13 %….), accompanied with pancreatic enzymes, with severity or prognosis?
2- Please explain each part of the result in the different sections (the two different groups)

Discussion:
Should be thoroughly revised, needs language revision
1-youre mentioned that" Moreover, in our analysis, we did not find differences in etiologies, and patients with nonviral liver injury presented elevated pancreatic enzymes similar to those with viral hepatitis" but it was not mentioned in result that you compare pancreatic level enzyme with etiology!!!!.

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

REFEREE: Associate Editor | **Revision** (0) 17 Jul 2022

Dear EIC,

The manuscript was reviewed by 2 experts in the field. In addition to comments by the reviewers, I have more comments:

1. Authors should include the study type/design in the beginning of Methods section of Abstract.

2. Why did authors select 1.5X of normal enzyme liver for stratification of the study population?

3. Authors can add more numerical data to results section of abstract to support their statements such as those in Lines 16-18.

4. There is inconsistency in presentation of strength of the main piece of evidence obtained in this study. Mainly, you can find it in Title presented as definite modulation of pancreatic enzymes by TNF-alpha and a tentative statement in the conclusion of manuscript presented as "which may be mediated by TNFα signaling".

5. There is ambiguity with presentation of ALI and ALF in the manuscript. They are used many times together and for the presentation of a single group of study participants. Authors should clarify and remove the ambiguity.

6. The Figure 1 can be removed and its data can be moved to Table 1.

7. I prefer to add numerical data in pie graphs of Figure 2. The analytical data of the comparisons can be added to figure caption.

8. In Table 3, the units for WBC and Plt looks confusing. I guess authors should correct

them.

Regards

Seyed Moayed Alavian: EIC | **Revision** (0) 17 Jul 2022

Dear Authors,

Thank you for your submission. 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.

Dear Editors and Reviewers

Thank you for reviewing our manuscript and offering valuable advice.
We have addressed your comments with point-by-point responses and revised the manuscript accordingly.

Responses to the Comments by the reviewer 1:

Abstract-1: Words count of abstract is 200, you should write more

Reply:

Thank you very much for your kind review. We added text and words count become 254.

Abstract-2: please check it again the Keywords in Mesh

Reply:

I check the keywords in Mesh. “Acute liver failure” has MeSH Unique ID: D017114. “Pancreatic enzyme” is not Mesh term. I changed to “amylases” (MeSH Unique ID: D000681) and “lipase” (MeSH Unique ID: D008049). “Tumor necrosis factor-alpha” has MeSH Unique ID: D014409. (lines 24)

Introduction-1: You mentioned in the introduction that” At present, the mechanism behind the development of pancreatic disorder in patients with ALI remains unclear” but your article is not about the mechanism and related process. We can understand explain the relationship between Excessive increase pancreas enzymes and patients prognosis. You should delete the word “mechanism”

In accordance with your comment, we delete the word “mechanism” and revised the text. (lines 38-39)

Introduction-2: It has been repeating many times "mechanism" in your text, but you didn't explain about mechanism!!

Acording to your suggestion, we delete the word "mechanism" and revised the text. (lines 7, 9, 38, 43, 127-128, 146)

Method-1 :How did you divide the patients into 2 groups (elevation group and non-elevation)? Explain it in Method and also criteria's

To divide the patients into two group, we use the elevation of serum amylase or lipase above 1.5 times the upper limit of normal as a cut-off value. We added the criteria in Method section. (lines 73-75)

Method-2: Did you have missing data? Were there patients who quit or leaving the research?

There were no patients who quit or leave this research. We did not have missing data.

Method-3: you should more explain labor measurement in your Method (which method, device)?

According to your suggestion, we added the explanation in method sections (lines 49-56).

Method-4: Explain about exclusion criteria and inclusion criteria?

Thank you for your suggestion. We excluded patients with malignant tumors and liver cirrhosis. We added the explanation in method section. (lines, 55-56)

Result-1: Is the etiologies of liver injury (hepatitis A virus 13%, hepatitis B virus 23%, autoimmune hepatitis 13 %….), accompanied with pancreatic enzymes, with severity or prognosis?

As you mentioned, it is possible that etiologies were correlated with severity and prognosis and affect the elevation of pancreatic enzymes. To exclude this possibility, we performed the comparison between elevation group and no elevation group in subgroups divided depend on severity or prognosis. There were no significant differences. We added these result in result sections. (Lines, 115-124)

Result-2: Please explain each part of the result in the different sections (the two different groups)

According to your suggestion, we added the result sections about the correlation between etiologies and elevation of pancreatic enzymes in subgroups divided based on severity or prognosis. (Lines, 115-124)

Discussion:Should be thoroughly revised, needs language revision

Discussion 1:youre mentioned that" Moreover, in our analysis, we did not find differences in etiologies, and patients with nonviral liver injury presented elevated pancreatic enzymes similar to those with viral hepatitis" but it was not mentioned in result that you compare pancreatic level enzyme with etiology!!!!.

We tested the association between the elevation of pancreatic enzymes and etiologies of liver injury by $\chi 2$ test. We mentioned this on result sections (lines 109-111).

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

According to your suggestion, we added the reference. (Lines191-192)

Reviewer 2:

Dear Associate Editor,

1- According to the result section in abstract: "The elevation of pancreatic enzymes was associated with ALF severity. High level of serum tumor necrosis factor alpha (TNFα) was associated with the elevation of pancreatic enzymes." Please define the mean values and the significance level for the reported variables.

Thank you very much for your kind review. The serum TNFα concentrations in healthy volunteers were reported to be less than 1.0 pg/ml. We added in result section (128-129).

2- The conclusion is the repetition of the result. Defining these associations might show the role of pancreatic enzyme level in the pathogenesis of ALF.

In accordance with your comment, We added the text in the conclusion section on abstract. (lines, 23-24)

3- In the aim section of the study it is explained that "This study aimed to reveal the mechanism of Elevation of pancreatic enzymes associated with acute liver injury". In fact this is not the situation. The aim of study is comparing the level of pancreatic enzyme in cohort of subjects with acute liver failure (not liver injury).

In accordance with your comment, We revised manuscript. However, the patients enrolled in this study consisted the patients with ALI. (lines 43-44)

4- The rationale for performing the study is not enough in the introduction section. I am not satisfied for the necessity for performing the project.

Thank you for your suggestion. We revised manuscript. (Lines 34-38)

5- Please define the reference for the acute liver failure criteria established by the Intractable Hepato-Biliary Diseases Study Group in Japan.

In accordance with your comment, We added the reference. (line 57)

6- *Please define if the etiologies for ALF were checked in the research (including viral, toxic, and medication induced). One important issue in this evaluation is clarifying the biliary obstruction. Were the patients with extra-hepatic cholestatsis excluded from the project? Biliary obstruction could cause both pancreatitis and cholangitis.*

We checked the etiologies for ALI. Moreover, we excluded extra-hepatic cholestatsis by CT imaging. We added the text in Method section. (lines, 49-55)

7- *Please define the main findings of the study in the first paragraph of discussion section. The respect authors used the term "acute liver injury" and "acute liver failure" several times in the manuscript. These terms are not equivalent and have separate meaning. Please define which term is considered (acute liver failure or acute liver injury).*

Thank you for your suggestion. We added the main findings in the first paragraph of discussion sections. (lines, 135-137).

We use the term "acute liver injury" as entire acute liver injury, and ALI contained the mild liver injury which did not satisfy the criteria of acute liver failure. We used the terms ALI and ALF separately in this manuscript. Furthermore, we also use ALI as subgroup which did not satisfy the criteria of acute liver failure. Although this is ambiguous, "ALI" had above two meaning and we thought this usage of term were unavoidable.

8-Please use update references in discussion.

In accordance with your comment, we added the reference. (Lines190-191)

Associate Editor 1:

1. Authors should include the study type/design in the beginning of Methods section of Abstract.

Thank you very much for your kind review. We added the texts in abstract. (line 10)

2. Why did authors select 1.5X of normal enzyme liver for stratification of the study population?

We select the 1.5 times ULN according to Common Terminology Criteria for Adverse Events (CTCAE) grade1.

3. Authors can add more numerical data to results section of abstract to support their statements such as those in Lines 16-18.

Thank you for your suggestion. We added numerical data in results section of abstract. (Lines 17, 19-20).

4. There is inconsistency in presentation of strength of the main piece of evidence obtained in this study. Mainly, you can find it in Title presented as definite modulation of pancreatic enzymes by TNF-alpha and a tentative statement in the conclusion of manuscript presented as "which may be mediated by TNFα signaling".

Thank you for your suggestion. We revised the manuscript. (Line 177).

5. There is ambiguity with presentation of ALI and ALF in the manuscript. They are used many times together and for the presentation of a single group of study participants. Authors should clarify and remove the ambiguity.

We use the term “acute liver injury” as entire acute liver injury, and ALI contained the mild liver injury which did not satisfy the criteria of acute liver failure. We used the terms ALI and ALF separately in this manuscript. Furthermore, we also used ALI as subgroup which did not satisfy the criteria of acute liver failure. As you mentioned, this

is ambiguous, however “ALI” had above two meaning and we thought this usage of term were unavoidable.

6. The Figure 1 can be removed and its data can be moved to Table 1.

According your suggestion, we removed Figure1 and moved to Table.1.

7. I prefer to add numerical data in pie graphs of Figure 2. The analytical data of the comparisons can be added to figure caption.

Thank you for your suggestion, we added numerical data in pie graphs and p values in figure caption.

8. In Table 3, the units for WBC and Plt looks confusing. I guess authors should correct them.

Thank you for your suggestion, we changed the units ”/ml” to “/mm^3”.

Again, thank you for giving us the opportunity to strengthen our manuscript with your valuable comments and queries. We have worked hard to incorporate your feedback and hope that these revisions persuade you to accept our submission.

Yours sincerely,

Motoyuki Kohjima, M.D, Ph.D.
Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences
Kyushu University3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582 Japan
Tel: +81-92-642-5282 Fax: +81-92-642-5287

E-mail: kohjima@med.kyushu-u.ac.jp

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.

REFEREE: Reviewer | **Revision** (1) 5 Aug 2022

Thank you for your response
I would like to tell you a few other small objections
1-In Abstract you mention that "we evaluated patients.....the association between ALI and other organ failure" whats meaning of other Organ failure? your study based of your title is pancreatic enzymes associated with ALI!! which organ do you mean?
but based your Introduction you mention that"we focused on the elevation of pancreatic enzymes in ALI patients" not other organ failure

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

Dear EIC,

One of the reviewers has asked for an additional correction. The manuscript can be accepted after addressing this minor comment.

Regards,
AE

Seyed Moayed Alavian: EIC | **Revision** (1) 5 Aug 2022

Dear Authors,

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

Regards,
EIC

OPEN PEER REVIEW

Revision (2)

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.

Dear Editors and Reviewers

Thank you for reviewing our manuscript and offering valuable advice.
We have addressed your comments with point-by-point responses and revised the manuscript accordingly.

Responses to the Comments by the reviewer 1:

Thank you for your response
I would like to tell you a few other small objections
1-In Abstract you mention that "we evaluated patients.....the association between ALI and other organ failure" whats meaning of other Organ failure? your study based of your title is pancreatic enzymes associated with ALI!! which organ do you mean?
but based your Introduction you mention that"we focused on the elevation of pancreatic enzymes in ALI patients" not other organ failure

Reply:

Thank you very much for your kind review. We are sorry for such confusing description. The meaning of “other Organ failure” in the manuscript is pancreatic disorder. We revised text. (Line 9)

Again, thank you for giving us the opportunity to strengthen our manuscript with your valuable comments and queries. We have worked hard to incorporate your feedback and hope that these revisions persuade you to accept our submission.

Yours sincerely,

Motoyuki Kohjima, M.D, Ph.D.
Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences
Kyushu University3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582 Japan
Tel: +81-92-642-5282 Fax: +81-92-642-5287
E-mail: kohjima@med.kyushu-u.ac.jp

OPEN PEER REVIEW

Revision (2)

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

Heidar Sharafi: Associate Editor | **Revision** (2) 10 Aug 2022

Dear EIC,

I have no more comments.

Thanks

Seyed Moayed Alavian: EIC | **Revision** (2) 10 Aug 2022

Dear Authors,

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

Regards,
EIC