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Peer Review Report for "Post-Intervention Plasma IL-10 Level Predicts Early Tumor Response in Hepatocellular Carcinoma Treated with Transarterial Chemoembolization"

Author(s): Mengxuan Shan, Jing Fan, Xinmiao Xiong, Na Liu, Lili Wang, Wei Ye

Review Timeline:

Submit Date:	17 Jun 2022
Revised Date:	7 Sep 2022
Accepted Date:	22 Sep 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) 19 Jul 2022

The present study investigated the role of IL-10 in predicting the outcomes after TACE. The results showed that post-intervention plasma IL-10 levels could predict the short-term prognosis of HCC patients receiving TACE treatment. The results are interesting and meaningful. Some minor points are listed as below.

1. Was the plasma level of IL-10 correlated with the parameters related to liver functions such as bilirubin and coagulation?

2. Why did the authors select 7 days after TACE treatment as the time point? Would the results be different if the time point was selected shorter or longer than 7 days?

REFEREE: Reviewer | **Revision** (0) 29 Jul 2022

First of all I should congratulate you for this article with interesting topic. It would be interesting to determine early tumor response in hepatocellular carcinoma treated with transarterial chemoembolization.

However, the manuscript needs to be revised in terms of methodological details, results,

and language.

Method:
1-You have not reported the use of drugs and drug history
Please tell us about medication history of participants and Etiology of HCC.
2-how you recognize the HCC in Patients, what was your diagnosis Method?
(You mentioned that the “Diagnose of unresectable HCC is based on the guidelines of European Association" but how did you diagnose HCC in Patients?)
3-Were there any limitations in your study (patient admission or...)
4-how you can find your Sample size? Based on which formula did you calculate this sample size? Was performed randomly?
5- What was your exclusion criteria?

Result:
1-Please explain each part of the result in the different sections
2-is the etiology of HCC related with plasma IL-10 level? Is there any correlation between cytokines and early tumor response with etiology of disease?
3- Factors such as medications and patient history, such as chronic disease, considered in your analysis?
Discussion:
Should be thoroughly revised, needs language revision
1-please more detail about mechanism of IL-10 in Tumor response in other studies.
2-based of “It is reported that serum IL-10 is associated with liver injury caused by cirrhosis and can also been an independent prognostic factor for unresectable HCC .In your result it’s important to know that the patients have cirrhosis or not.” Serum IL-10 is independent factor for HCC", that mean without any therapy you can measure it and determine the prognosis!!! but you're study is not about prognosis, you mentioned at the ends of discussion that due to sample size you couldn't say the prognosis!!! But based on your title you should not say either. I didn’t understand this part of your discussion which you discuss about Prognosis…

3- In Meta-analysis which you mentioned in your discussion "IL-10 is associated with tumor prognosis”. You measure the IL-10 to determine the Tumor response after therapy. What you mean about IL-10 as a prognosis detector!!

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

Heidar Sharafi: Associate Editor | **Revision** (0) 15 Aug 2022

Dear EIC,

I have additional comments:

1. "Informed Consent: Our study is in vitro.". In vitro studies regularly are experimental

studies performed in the laboratory setting and out of the context of a living organism. Definitely, their study cannot considered as an in vitro study since it is not an experimental study.

2. Authors should include study design and type in the beginning of the methods sections of abstract and main manuscript body.

3. In abstract and main manuscript body, 95%CI for AUC included as "1.05-27.01". Each upper limit and lower limit of 95%CI for AUC cannot be more than 1.

4. "Diagnosis of unresectable HCC is based on the guidelines of European Association for the Study of the Liver" authors should cite to the guideline.

5. "-80 °C refrigerator" or freezer?

6. In manuscript body, "RECIST criteria" should be written in full term as well as abbreviation and the criteria should be cited.

7. The manuscript should be edited for English syntax and academic presentation by a commercial service or a colleague who is proficient in English writing. Also, there are many typos through the manuscript.

8. "The level of IL-10 has no significant correlation with maximum tumor size, tumor metastasis ($p > 0.05$) (Figure 2)." Tumor size or tumor metastasis? In Figure 2, only tumor size is included.

9. In Table 1, ALT and AST are presented by range, however it looks like IQR since they are looking like normal levels.

10. What was the non-parametric test used for comparisons in Table 2? Authors should add it in Table caption.

11. I am not sure if using HR is right for showing the correlates of early tumor response after TACE.

12. In Table 3, among 9 cytokines evaluated in study, only 5 included in univariate analysis. What is the authors justification?

13. In Figure 2A and 2B, what are the lines and bars presenting? It should be mentioned in the figure caption.

Regards

Seyed Moayed Alavian: EIC | **Revision** (**0**) 15 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.

> Reviewers' Comments:

Reviewer 1:

The present study investigated the role of IL-10 in predicting the outcomes after TACE. The results showed that post-intervention plasma IL-10 levels could predict the short-term prognosis of HCC patients receiving TACE treatment. The results are interesting and meaningful. Some minor points are listed as below.

1. Was the plasma level of IL-10 correlated with the parameters related to liver functions such as bilirubin and coagulation?

Answer： Coagulation was represented by INR in our study. The plasma level of IL-10 had no significant correlation with both bilirubin and INR.

2. Why did the authors select 7 days after TACE treatment as the time point? Would the results be different if the time point was selected shorter or longer than 7 days?

Answer: Considering the actual clinical situation and literature report, we chosen to collect plasma 7 days after TACE[1]. We did not know if the point was selected shorter or longer than 7 days would change the results. We will study the cytokines in plasma at different time points after TACE in the future. Thank you for your advice.

Reviewer 2:

First of all I should congratulate you for this article with interesting topic. It would be interesting to determine early tumor response in hepatocellular carcinoma treated with transarterial chemoembolization.

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

Method:

1-You have not reported the use of drugs and drug history

Please tell us about medication history of participants and Etiology of HCC.

Answer: All patients received routine and symptomatic treatments, without the

use of targeted drugs or immune drugs. The etiology of HCC cause is mentioned in the table1 (HBV or HCV).

2-how you recognize the HCC in Patients, what was your diagnosis Method?
(You mentioned that the “Diagnose of unresectable HCC is based on the guidelines of European Association" but how did you diagnose HCC in Patients?)

Answer: We diagnosed HCC patients according to the guideline and determined those who were not appropriate for surgery. We enrolled patients who couldn’t receive surgery according to the guideline or who refused surgery. Our diagnostic criteria of HCC patients were as follows:

1) **Past Medical History;**
2) **According to the symptoms: discomfort in the liver area, possibly right upper abdominal pain;**
3) **Blood examination: hepatocellular carcinoma related tumor indicators, AFP, AFP-L3, DCP were increased;**
4) **Imaging: B ultrasound, CT, MRI, DSA.**

3-Were there any limitations in your study (patient admission or...)

Answer: We are aware that this study has limitations. First of all, this study was a single center and the sample size was small. Second, we only measured cytokine levels once after TACE treatment. We didn’t follow the dynamic changes of each cytokine and its influence on treatment response. Finally, due to the limited follow-up time, we didn’t evaluate the overall survival.

We added this part in the end of the discussion. Thank you for your advice.

4-how you can find your Sample size? Based on which formula did you calculate this sample size? Was performed randomly?

Answer: We refer to some articles, they also do not calculate the sample number according to the formula[2; 3]. We collected samples from patients who met the inclusion criteria in a period of time. However, due to the rarity of samples, we

randomly selected some samples and used the other samples for other studies.

5- What was your exclusion criteria?

Answer: The exclusion criteria were as follows: i) with TACE contraindications; ii) have ever taken immunological drugs; iii) with serious underlying diseases; iv) poor compliance; v) clinical data were incomplete.

Result:

1- Please explain each part of the result in the different sections

Answer: We explain each part of the result in the discussion part. The specific experimental results are presented in our results section. Thank you for your advice.

2- is the etiology of HCC related with plasma IL-10 level? Is there any correlation between cytokines and early tumor response with etiology of disease?

Answer: Of the 30 HCC patients enrolled, 28 had HBV infection and 2 had HCV infection. In this study, we focused on the changes of cytokines in HCC patients before and after TACE. Considering the number of enrolled cases, we didn't know for sure the correlation between cytokines and early tumor response with etiology of disease. We think this is a good topic to pursue and we will look into it in the future. Thank you for your advice.

3- Factors such as medications and patient history, such as chronic disease, considered in your analysis?

Answer: When patients met the inclusion criteria, we enrolled them in the study. Based on the exclusion criteria, we excluded patients who had taken immunological drugs. We don't think much about patient history, such as chronic disease. Our main objective was to observe the relationship between cytokines pre- and post-TACE and postoperative outcome. We think that`s a good topic. We'll look into that in the future. Thank you for your advice.

Discussion:

Should be thoroughly revised, needs language revision

1- please more detail about mechanism of IL-10 in Tumor response in other studies.

Answer: Thank you for your advice. In order to discuss the function of IL-10 in more depth, we added the content about the immunosuppression and immune activation of IL-10.

2-based of “It is reported that serum IL-10 is associated with liver injury caused by cirrhosis and can also been an independent prognostic factor for unresectable HCC. In your result it’s important to know that the patients have cirrhosis or not.” Serum IL-10 is independent factor for HCC", that mean without any therapy you can measure it and determine the prognosis!!!

but you're study is not about prognosis, you mentioned at the ends of discussion that due to sample size you couldn't say the prognosis!!! But based on your title you should not say either. I didn’t understand this part of your discussion which you discuss about Prognosis…

Answer: According to the literatures, IL-10 is associated not only with cirrhosis but also with tumor load[4; 5]. We didn't make that clear in this section. And we made it clear and added literatures in the article. Our study indeed is not about prognosis. In order not to cause ambiguity, we removed the content about prognosis.

3- In Meta-analysis which you mentioned in your discussion "IL-10 is associated with tumor prognosis”. You measure the IL-10 to determine the Tumor response after therapy. What you mean about IL-10 as a prognosis detector!!

Answer: Our study confirmed that serum level of IL-10 at 7 days after TACE can predict tumor response at 4-6 weeks after TACE.

Reference:

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

Answer: we added some new reference in the article.

> Associate Editor's Comments:

Associate Editor 1:

Dear EIC,

I have additional comments:

1. "Informed Consent: Our study is in vitro.". In vitro studies regularly are experimental studies performed in the laboratory setting and out of the context of a living organism. Definitely, their study cannot considered as an in vitro study since it is not an experimental study.

Answer: Thank you for your advice. We provide the informed consent by Chinese version.

2. Authors should include study design and type in the beginning of the methods sections of abstract and main manuscript body.

Answer: We added the manuscript type in the main manuscript body and added more detail about study design in the methods sections of abstract.

3. In abstract and main manuscript body, 95%CI for AUC included as "1.05-27.01". Each upper limit and lower limit of 95%CI for AUC cannot be more than 1.

Answer: I have corrected it in the manuscript. It`s 0.598-0.939.

4. "Diagnosis of unresectable HCC is based on the guidelines of European Association for the Study of the Liver" authors should cite to the guideline.

Answer: We added the reference in this part.

5. "-80 ℃ refrigerator" or freezer?

Answer: Plasma was stored in -80 ℃ refrigerator.

6. In manuscript body, "RECIST criteria" should be written in full term as well as abbreviation and the criteria should be cited.

Answer: We written the full term and abbreviation of "RECIST criteria" in the manuscript body. And the reference was cited.

7. The manuscript should be edited for English syntax and academic presentation by a commercial service or a colleague who is proficient in English writing. Also, there are many typos through the manuscript.

Answer: We invited colleagues who are proficient in English to polish the language. At the same time, we corrected many typos.

8. "The level of IL-10 has no significant correlation with maximum tumor size, tumor metastasis ($p > 0.05$) (Figure 2)." Tumor size or tumor metastasis? In Figure 2, only tumor size is included.

Answer: This is our mistake. We modified it like this: "The level of IL-10 has no significant correlation with maximum tumor size ($p > 0.05$) (Figure 2)."

9. In Table 1, ALT and AST are presented by range, however it looks like IQR since they are looking like normal levels.

Answer: It meant IQR which was annotated by the note. I have revised it according to your suggestion. Thank you.

10. What was the non-parametric test used for comparisons in Table 2? Authors should add it in Table caption.

Answer: Wilcoxon matched-pairs were used in Table 2. We added that in Table

caption

11. I am not sure if using HR is right for showing the correlates of early tumor response after TACE.

Answer: It really shouldn't be HR. It should be OR. I have corrected it now.

12. In Table 3, among 9 cytokines evaluated in study, only 5 included in univariate analysis. What is the authors justification?

Answer: All the other results were negative, so I picked a few cytokines that I thought were meaningful. I have completed the content now.

13. In Figure 2A and 2B, what are the lines and bars presenting? It should be mentioned in the figure caption.

Answer: the lines and bars are presenting mean and standard deviation (SD), respectively. We added it in the figure caption.

References

[1] Guo W C, He X F, Li Y H, et al. The effect of sequential transcatheter arterial chemoembolization (TACE) and portal venous embolizations (PVE) vs. TACE or PVE alone on rabbit VX2 liver carcinoma and on liver regeneration[J]. Eur Rev Med Pharmacol Sci, 2016, 20(15): 3186-93.

[2] Kamfar S, Alavian S M, Houshmand M, et al. Liver Mitochondrial DNA Copy Number and Deletion Levels May Contribute to Nonalcoholic Fatty Liver Disease Susceptibility[J]. Hepat Mon, 2016, 16(12): e40774.

[3] O E A, Buchter M, H A B, et al. Performance and Utility of Transient Elastography and Non-Invasive Markers of Liver Fiibrosis in Patients with Autoimmune Hepatitis: A Single Centre Experience[J]. Hepat Mon, 2016, 16(11): e40737.

[4] Zhang X, Lu M, Xu Y, et al. IL-10 promoter hypomethylation is associated with increased IL-10 expression and poor survival in hepatocellular carcinoma[J]. Transl Cancer Res, 2019, 8(4): 1466-1475.

[5] Mirlekar B. Tumor promoting roles of IL-10, TGF-beta, IL-4, and IL-35: Its implications in cancer immunotherapy[J]. SAGE Open Med, 2022, 10:

20503121211069012.

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) 29 Aug 2022

Dear Authors,

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

Thanks
EIC

Heidar Sharafi: Associate Editor | **Revision** (1) 22 Sep 2022

Dear EIC,

Authors has addressed all the comments/concerns. I have no more comments.

Regards,