OPEN PEER REVIEW

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Peer Review Report for "Relationship Between Cardiovascular Disease Risk Factors and Quality of Life in Patients with Metabolic-Associated Fatty Liver Disease"

Author(s): Raika Jamali, Soroush Veisi, Arsia Jamali, Mehdi Yaseri

Review Timeline:

Submit Date: 27 Mar 2022
Revised Date: 19 May 2022
Accepted Date: 20 May 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) 17 Apr 2022

Hello

Abstract
- “In this study, we aim to check the association between QoL and the cardiovascular Framingham risk score (FRS) in an NAFLD population.”
cardiovascular disease risk factors may be better.

-“All domains of QoL were associated with older age, hypertension, smoking, diabetes mellitus (DM), higher systolic blood pressure, and lower highdensity lipoprotein (HDL) in univariate regression analysis.” This sentence needs to be more P-value.

-“showed that age, smoking, DM, hypertension, and FRS were correlated with the overall QoL score.” This sentence needs to be more P-value.

Introduction

- The manuscript needs both grammar and syntax editing.

Methods

-Please mention the inclusion criteria (such as age range, gender limitation, …) and exclusion criteria.

- Subtitles are recommended, Such as 2.1``` 2.2 ``` 2.3```

Results

- Subtitles are recommended, Such as3.1```3.2```3.3```

- the return rate of the questionnaire?

Discussion

-This section needs language and syntax editing.

- Please use more recent studies to expand the discussion.

Table

Specify the unit of the variable.

References

- The manuscript needs more recent studies to cite.

General

- The manuscript needs both grammar and syntax editing.

Thanks

REFEREE: Reviewer | **Revision** (0) 17 Apr 2022

Dear AE

This is an interesting study investigating the association of cardiovascular risk factors and quality of life in patients with NAFLD. The idea and findings can be considered novel, particularly for Iran. However, the manuscript needs substantial revisions in terms of methodological details, presentation of results, and English language writing. The introduction does not consist of solid paragraphs describing the gap in knowledge and convincing the reader for necessity of the present study in this setting. The methods section should be revised thoroughly to be explained in much greater details. In general, all sections are too summarized and lack adequate details which limits the reproducibility and reliability of the study.

Introduction:

The introduction is too summarized. I suggest expanding on the background and gap in knowledge in the introduction section, and describe the results of some similar research studies.

Methods:

Methods should be described in much greater details.

The first paragraph is too long and can be divided into 2-3 paragraphs with subheadings.

How was the recruitment process? How did you choose the participants?

Where was the study site? Please provide detailed information about the site both in abstract and methods section.

What are the inclusion and exclusion criteria?

How you assessed the prior medical conditions? Were they self-report data, or confirmed by any lab tests or documents?

Anthropometric and other measurements should be described in greater details.

Units for measurements should be added.

Pars Azmoon kits were used for which laboratory assessments?

NAFLD diagnosis criteria should be defined accurately and in details.

Results:

Results should be presented in greater details and significant numbers should be mentioned in the text.

Please remove the unnecessary decimals (e.g., line 1 and 3)

The first half of paragraph 3 belongs to the methods section not results.

Please revise for clarity: “These findings suggest that multicollinearity does not seem to be a problem in the analysis”

Discussion:

The first paragraph can be rewritten; this paragraph should contain 3-4 sentences describing the most significant findings of the study.

Please briefly describe the study population in those papers that you are comparing their

results to the present study (e.g., Trevisol et al, Uchmanowicz et al., etc.)

Discussion should be revised thoroughly, especially paragraphs 3,4,5 and 6. Authors should try to be more focused in the discussion, and explain the translation of their results to provide solid arguments instead of just comparing the statistics results of the present work with other studies.

These are some updated studies on quality of life that I found and may be helpful in discussion or introduction:

1. Huang R et al. Health-related quality of life in Chinese population with non-alcoholic fatty liver disease: a national multicenter survey. Health Qual Life Outcomes. 2021

2. Huber Y et al. Health-related Quality of Life in Nonalcoholic Fatty Liver Disease Associates With Hepatic Inflammation. Clin Gastroenterol Hepatol. 2019

3. Grønkjær LL, Lauridsen MM. Quality of life and unmet needs in patients with chronic liver disease: A mixed-method systematic review. JHEP Rep. 2021

4. Funuyet-Salas J, Pérez-San-Gregorio MÁ, Martín-Rodríguez A, Romero-Gómez M. Quality of Life and Coping in Nonalcoholic Fatty Liver Disease: Influence of Diabetes and Obesity. Int J Environ Res Public Health. 2021

5. McSweeney L et al. Health-related quality of life and patient-reported outcome measures in NASH-related cirrhosis. JHEP Rep. 2020

6. Mehmet Sayiner et al. Assessment of health utilities and quality of life in patients with non-alcoholic fatty liver disease. BMJ Open Gastro. 2016

Conclusion:

Conclusion is full of abbreviations and is a repetition of results. Authors may revise this section.

Tables:

Abbreviations and vague categories (like obesity I, II, III) should be defined in the footnotes.

In table 2 and 3, “P” should be defined in the footnotes or be substituted by “p-value”

REFEREE: Reviewer | **Revision** (0) 21 Apr 2022

Dear AE,

First of all I should congratulate you for this article with interesting topic. It would be interesting to determine the quality of life of patients with fatty liver disease, especially among Iranians.
However, the manuscript needs to be revised in terms of introduction, methodological details, results, and language.
Introduction:
1-You must mention in the introduction why you think this research is very important between Iranians at this time (Is number of fatty liver disease high?). What made you think of doing this research among Iranians?
2- It would be better if you wrote in more detail about the last research

Method:
1-you should mention the inclusion criteria and exclusion criteria
2- Did you have missing data? Were there patients who quit, leaving their research in the process?
3-you should more explain about Anthropometric indices. What do you mean exactly and how it did exactly measured?
4- You explain the NAFLD criteria, but you should explain more in detail. For example, you should mention the degree of fatty liver, was it measured or not?
Result:

1-about the grade of fatty liver dieses, you did not adjust with CVA and quality of live. Please mention in result
2- Please explain each part of the result in the different sections

Discussion:
Should be thoroughly revised, needs language revision
1-please more detail about the importance of conducting this study among Iranians, Reasons and comparison with similar studies.
2-Are there any studies that have been conducted in a particular country or Nations? Comparing with your data, are there any differences or similar? Because your patients are Iranian and you should better compare your data with those of other nations
Reference:
The references are outdated; please use more current references for the article, especially for the discussion section.

REFEREE: Associate Editor | **Revision** (0) 21 Apr 2022

Dear Editor in Chief
Thanks for assigning me as academic editor to handle the manuscript NO.124229 entitled "Relationship between cardiovascular disease risk factors and quality of life in patients with non-alcoholic fatty liver disease".
I appreciate the authors' work to collect these data and to write its manuscript. Although the title is interesting, there are some major concerns that should be addressed by the authors. See the detailed peer-review comments attached.

Regards
AE

Seyed Moayed Alavian: EIC | **Revision** (0) 21 Apr 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 Editor in Chief

Thank you for giving me the opportunity to improve my manuscript based on respect reviewers' comments. I accepted all the comments and revised the paper accordingly.

Reviewer 1:
This is an interesting study investigating the association of cardiovascular risk factors and quality of life in patients with NAFLD. The idea and findings can be considered novel, particularly for Iran. However, the manuscript needs substantial revisions in terms of methodological details, presentation of results, and English language writing. The introduction does not consist of solid paragraphs describing the gap in knowledge and convincing the reader for necessity of the present study in this setting. The methods section should be revised thoroughly to be explained in much greater details. In general, all sections are too summarized and lack adequate details which limits the reproducibility and reliability of the study.

Introduction:

The introduction is too summarized. I suggest expanding on the background and gap in knowledge in the introduction section, and describe the results of some similar research studies.

Reply: I revised the introduction section completely. I tried to describe the gap of knowledge regarding the Importance of defining the CVD risk factors that are related to Qol in MAFLD patients. I also referred to the introduced references in the introduction.

Methods:

Methods should be described in much greater details.
The first paragraph is too long and can be divided into 2-3 paragraphs with subheadings.
How was the recruitment process? How did you choose the participants?
Where was the study site? Please provide detailed information about the site both in abstract and methods section.
What are the inclusion and exclusion criteria?
How you assessed the prior medical conditions? Were they self-report data, or confirmed by any lab tests or documents?
Anthropometric and other measurements should be described in greater details.
Units for measurements should be added.
Pars Azmoon kits were used for which laboratory assessments?
NAFLD diagnosis criteria should be defined accurately and in details.

Reply: I rewrote the method section according to the respect reviewer's suggestions.

Results:

Results should be presented in greater details and significant numbers should be mentioned in the text.

Please remove the unnecessary decimals (e.g., line 1 and 3)

The first half of paragraph 3 belongs to the methods section not results.

Please revise for clarity: "These findings suggest that multicollinearity does not seem to be a problem in the analysis"

Reply: I described the results in greater details and mentioned significant numbers in the text. I removed the unnecessary decimals. The first half of paragraph 3 removed from result section to the method part. "These findings suggest that multicollinearity does not seem to be a problem in the analysis" was added by the study consultant biostatistician.

Discussion:

The first paragraph can be rewritten; this paragraph should contain 3-4 sentences describing the most significant findings of the study.

Please briefly describe the study population in those papers that you are comparing their results to the present study (e.g., Trevisol et al, Uchmanowicz et al., etc.)

Discussion should be revised thoroughly, especially paragraphs 3,4,5 and 6. Authors should try to be more focused in the discussion, and explain the translation of their results to provide solid arguments instead of just comparing the statistics results of the present work with other studies.

These are some updated studies on quality of life that I found and may be helpful in discussion or introduction:

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2. Huber Y et al. Health-related Quality of Life in Nonalcoholic Fatty Liver Disease Associates With Hepatic Inflammation. Clin Gastroenterol Hepatol. 2019

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5. McSweeney L et al. Health-related quality of life and patient-reported outcome measures in NASH-related cirrhosis. JHEP Rep. 2020

6. Mehmet Sayiner et al. Assessment of health utilities and quality of life in patients with non-alcoholic fatty liver disease. BMJ Open Gastro. 2016

Reply: I revised the discussion according to respect reviewer's suggestions.

Conclusion:

Conclusion is full of abbreviations and is a repetition of results. Authors may revise this section.

Reply: I revised the conclusion according to respect reviewer's suggestions.

Tables:

Abbreviations and vague categories (like obesity I, II, III) should be defined in the footnotes.

In table 2 and 3, "P" should be defined in the footnotes or be substituted by "p-value"

Reply: I revised the tables according to respect reviewer's suggestions.

Reviewer 2:
Abstract
- "In this study, we aim to check the association between QoL and the cardiovascular Framingham risk score (FRS) in an NAFLD population." cardiovascular disease risk factors may be better.

-"All domains of QoL were associated with older age, hypertension, smoking, diabetes mellitus (DM), higher systolic blood pressure, and lower highdensity lipoprotein (HDL) in univariate regression analysis." This sentence needs to be more P-value.

-"showed that age, smoking, DM, hypertension, and FRS were correlated with the overall QoL score." This sentence needs to be more P-value.

Introduction
- The manuscript needs both grammar and syntax editing.

Methods
-Please mention the inclusion criteria (such as age range, gender limitation, …) and exclusion criteria.

- Subtitles are recommended, Such as 2.1``` 2.2 ``` 2.3```

Results

- Subtitles are recommended, Such as3.1```3.2```3.3```

- the return rate of the questionnaire?

Discussion
-This section needs language and syntax editing.

- Please use more recent studies to expand the discussion.

Table
Specify the unit of the variable.

References
- The manuscript needs more recent studies to cite.

General
- The manuscript needs both grammar and syntax editing.

Reply: I revised the manuscript according to respect reviewer's suggestions.

Reviewer 3:
First of all I should congratulate you for this article with interesting topic. It would be interesting to determine the quality of life of patients with fatty liver disease, especially among Iranians.
However, the manuscript needs to be revised in terms of introduction, methodological details, results, and language.
Introduction:
1-You must mention in the introduction why you think this research is very important between Iranians at this time (Is number of fatty liver disease high?). What made you think of doing this research among Iranians?
2- It would be better if you wrote in more detail about the last research

Method:
1-you should mention the inclusion criteria and exclusion criteria
2- Did you have missing data? Were there patients who quit, leaving their research in the process?
3-you should more explain about Anthropometric indices. What do you mean exactly and how it did exactly measured?
4- You explain the NAFLD criteria, but you should explain more in detail. For example, you should mention the degree of fatty liver, was it measured or not?
Result:

1-about the grade of fatty liver dieses, you did not adjust with CVA and quality of live. Please mention in result
2- Please explain each part of the result in the different sections

Discussion:

Should be thoroughly revised, needs language revision

1-please more detail about the importance of conducting this study among Iranians, Reasons and comparison with similar studies.

2-Are there any studies that have been conducted in a particular country or Nations? Comparing with your data, are there any differences or similar? Because your patients are Iranian and you should better compare your data with those of other nations

Reference:

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

Reply: I revised the manuscript according to respect reviewer's suggestions.

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 May 2022

Dear AE,

The manuscript has been much improved by this round of revision, especially in terms of methods description. However, since a point-by-point answer to reviewer's comments is not provided, it is very hard to find the implemented changes related to each comment throughout the text. Although some parts have been highlighted, I was unable to find answers to all of my previous comments. I suggest revising the introduction and discussion once again carefully according to the comments that were provided before by both reviewers, and submitting a point-by-point answer document together with the revised manuscript. And no rush!
Here are some additional comments:

Introduction: This section needs to be revised thoroughly for fluency. You are jumping from the world to Iran, then China, etc. Try to divide the introduction into 3-4 solid paragraphs; each paragraph should contain a logical beginning, flow, and ending (background knowledge, gap in knowledge, description of similar studies, and which questions the present study tries to address)

Methods: This section has been improved vastly by revision.

Results: Clinical and sociodemographic characteristics: for demographics, there is no need to mention all percentages, only the most prevalent groups are sufficient. For example, in this sentence: "In terms of marital status, 29 (14.5%) individuals were single, 142 (71%) 150 were married, 23 (11.5%) were divorced, and 6 (3%) were widowed." You can only mention that the majority (71%, n=150) were married.

Table 1: Units like cmHg and mg/dl can be written in symbols and be described in the footnotes.

Discussion: Should be revised according to the previous comments.

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

Dear Editor in Chief

Thanks for assigning me as associate editor to handle the revised version of manuscript NO.124229 entitled "Relationship between cardiovascular disease risk factors and quality of life in patients with metabolic associated fatty liver disease".
I appreciate the authors' work to revise their manuscript. Although this version of manuscript is significantly improved, some minor issues need to be addressed by the authors before being published. See the pee-review comments for further details.
Regards
AE

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

Dear Authors,

Please follow the peer-review comments and submit the 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 Associate Editor,

Thank you for sending me the respect reviewer's comments. I accepted all the suggestions and revised the paper accordingly. Please find my reply to reviewers point by point as the followings. I hope these explanations persuade the respect reviewers to accept the paper for publication. Our recent literature review showed the paucity of literature in this field and we still believe this is a novel idea.

Introduction: This section needs to be revised thoroughly for fluency. You are jumping from the world to Iran, then China, etc. Try to divide the introduction into 3-4 solid paragraphs; each paragraph should contain a logical beginning, flow, and ending (background knowledge, gap in knowledge, description of similar studies, and which questions the present study tries to address)

Reply: Thank you for the comment. I separate the introduction into the following paragraphs:

In the first paragraph I described the importance of MAFLD due to the increasing burden of disease in Iran and worldwide. I defined why assessment of factors related to QoL is important in MAFLD.

In the second paragraph, I provided data regarding the overall impact of MAFLD on QoL.

In the third paragraph, I argued about the association of MAFLD and cardiovascular disease, and its influence on QoL. Considering the paucity of literature, we notified that it would be a reasonable approach to define the CVD risk factors that impact on QoL in a cohort of Iranian MAFLD.

Methods: This section has been improved vastly by revision.

Results: Clinical and sociodemographic characteristics: for demographics, there is no need to mention all percentages, only the most prevalent groups are sufficient. For example, in this sentence: "In terms of marital status, 29 (14.5%) individuals were single, 142 (71%) 150 were married, 23 (11.5%) were divorced, and 6 (3%) were widowed." You can only

mention that the majority (71%, n=150) were married.

Reply: Thank you for the comment. We revised this section as the followings:

The majority of subjects (71%, n=142) were married. In terms of the education status, near half of the individuals had master degree (49%, n=98). The low income individuals (11.5%, n=23), and low-middle income (47.5%, n=95), had the highest frequency in the studies population. The BMI was normal in 5 (5.5%), overweight in 58 (29%), and obese in 131 (94.5%) of the participants.

Table 1: Units like cmHg and mg/dl can be written in symbols and be described in the footnotes.

Reply: Thank you for the comment. We used the cm/Hg and mg/dl in the table 1. I described the units in the table one foot note.

Discussion: Should be revised according to the previous comments.

Reviewer 1:

The first paragraph can be rewritten; this paragraph should contain 3-4 sentences describing the most significant findings of the study.

Reply: Thank you for the comment. In the first paragraph we described the most important findings in the project as the followings:

"CVD risk factors were quite prevalent among the study population. FRS was inversely associated with QoL. Univariate regression analysis revealed statistically significant correlations between 6 out of 8 factors present in the FRS equation and the QoL scores. When controlling for confounding factors that affects QoL, the hierarchical multiple linear regression model output proved that four of these factors have significant impacts on QoL. It's noteworthy that HTN was the best predictor of QoL in all domains as well as the overall score. DM and smoking were the second and third best predictors of QoL in this experiment"

Please briefly describe the study population in those papers that you are comparing their results to the present study (e.g., Trevisol et al, Uchmanowicz et al., etc.)

Reply: Thank you for the comment. We added the details of studies as the followings:

"systematic review by Trevisol *et al*. showed that QoL score in both the physical or mental health domain was inversely related to HTN (26). This meta analysis compared the QoL between hypertensive and normotensive individuals by extracting the data of 20 qualified studies. It showed lower scores in physical and mental domains based on FS36 questionnaire in hypertensive group. Uchmanowicz *et al.* found that lower QoL results in reduced adherence to therapeutic recommendations (27). Their study in 186 elderly hypertensive patients showed that QoL scores were dramatically decreased in patients with low compliance regarding "appointment keeping" and "medication taking"."…

"The result of a trial on 207 hypertensive individuals, revealed that controlling HTN not only reduced CVD risk but also improved QoL (28). Similar to our observation, Oza *et al*. found that SBP was negatively associated with QoL (29). This study included 269 hypertensive patients and QoL was assessed by WHOQOL-BREF and MINICHAL scale. On the other hand, Katsi *et al*. described that stage and awareness of hypertension did not affect physical and mental health (30). This survey used SF-36 for the evaluation of QoL and included 189 hypertensive patients. We believe the controversial results between the mentioned researches could be due to the differences of study population regarding socioeconomic factors and the type of questionnaire used for QoL evaluation.…..

Goldenberg *et al*. reported that smokers develop an impaired QoL over their lifetime. This meta analysis evaluated 54 studies. It stated that the magnitude of this negative association is related to the number of cigarettes smoked per day (32). This finding is consistent with our results that showed smoking had negative effect on QoL.

To the best of our knowledge, there is no data regarding relationship between dyslipidemia and QoL in MAFLD population at the current literature. However, controversy exists around the association of QoL and dyslipidemia in the non-MAFLD cohorts (33, 34).The survey by Zhang et al. on 756 post-myocardial infarction patients showed that lipid control could improve QoL.

They used EQ-5D score for assessment of QoL. On the contrary, Souto et al. demonstrated that Familial hypercholesterolemia (FH) was not associated with QoL. This project included subjects with high risk for FH undergoing genetic screening. QoL was measured by SF-12 questionnaire before awareness of molecular test result. The mean QoL scores were not different between affected and non-affected cases with FH. Neither the presence of mutation, nor the pharmacological treatments were related to the QoL; however, previous CVD was negatively related to QoL."

Discussion should be revised thoroughly, especially paragraphs 3,4,5 and 6. Authors should try to be more focused in the discussion, and explain the translation of their results to provide solid arguments instead of just comparing the statistics results of the present work with other studies.

Reply: Thank you for the comment. We thoroughly rewrote the paragraph 3,4,5,and 6 in the discussion section as mentioned above.

Reviewer 2:

-This section needs language and syntax editing.

Reply: Thank you for the comment. We edited the discussion.

- Please use more recent studies to expand the discussion.

Reply: Thank you for the comment. We included recent studies in the discussion (references28, 33 and 34)

28. Arija V, Villalobos F, Pedret R, Vinuesa A, Jovani D, Pascual G, Basora J. Physical activity, cardiovascular health, quality of life and blood pressure control in hypertensive subjects: randomized clinical trial. Health Qual Life Outcomes. 2018 Sep 14;16(1):184.

33. Zhang M, Chen P, Zhang Y, Su X, Chen J, Xu B, Tao J, Wang Z, Li H, Ma A. Predictors of Quality of Life in Patients With Myocardial Infarction Combined With Dyslipidemia. Front Public Health. 2021 Oct 6;9:713480.

34. Souto AC, Miname MH, Fukushima J, Jannes CE, Krieger JE, Hagger M, Pereira AC, Santos RD. Health related quality of life in individuals at high risk for familial hypercholesterolemia undergoing genetic cascade screening in Brazil. Atherosclerosis. 2018 Oct;277:464-469.

Reviewer 3:

1-please more detail about the importance of conducting this study among Iranians, Reasons and comparison with similar studies.
Reply: This is a novel idea. We performed the study in Iran, since we had access to the Iranian patients.

2-Are there any studies that have been conducted in a particular country or Nations? Comparing with your data, are there any differences or similar? Because your patients are Iranian and you should better compare your data with those of other nations

Reply: Thank you for the comment. To the best of knowledge this is a novel study regarding the evaluation of QoL and CVD in a cohort of MAFLD patients. At the recent review literature we did not find any similar research in this field. This is our major concern to publish this novel idea as soon as possible.

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.

REFEREE: Associate Editor | **Revision** (2) 20 May 2022

Dear Editor in Chief
Thanks for assigning me as associate editor to handle the second revision of the manuscript NO.124229 entitled "Relationship between cardiovascular disease risk factors and quality of life in patients with metabolic associated fatty liver disease".
I appreciate the authors' work to revise their manuscript. This version of the manuscript is acceptable to be published in Hepatitis Monthly.
Regards
AE

Seyed Moayed Alavian: EIC | **Revision** (2) 20 May 2022

Dear Authors,

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

EIC