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.

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Advantages of "Open Peer Review" process

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- 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://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

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Peer Review Report for "Association Between Serum Ferritin Level and Gene Mutations in Patients with Thalassemia Major and Intermediate"

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Review Timeline:

Submit Date: 13 Oct 2020
Revised Date: 9 Nov 2020
Accepted Date: 10 Nov 2020

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 Oct 2020

Dear AE,
The present manuscript has some organizational and content problems that require attention before it can be ready for publication. So I would like to recommend major and minor revisions to improve your manuscript properly.

Title

↴ Since your study is descriptive-cross-sectional and not a correlation study, it is recommended to replace the word "correlation" with the word “Association”.

Abstract

Introduction

↴ Please put a period after the word “worldwide”.

Method

↴ Please mention the type of study, the method of selecting participants, and the data collection method.

↴ What do you mean by “P.C transfusion”? For the first time, every term needs to be written in full, you can then use the acronym form throughout the text.

↴ Please clarify what is meant by “the age of the first P.C transfusion”?

Conclusion

↴ What do you mean by “higher sample size”? I think you mean “larger sample size”.

Please check it throughout the manuscript.

⇒ Please clarify what is meant by “it can be considered that some of the studied cases are insignificant due to the role of these cases”? The role of what cases?

Introduction

⇒ You are expected to provide readers with the definition of Beta-thalassemia following the below- mentioned sentence. This is only one example that this section needs clearer step by step organization so the reader is not confused. “Beta-thalassemia is one of the most important health problems worldwide”.

⇒ In the following sentence, you have stated that “The results of studies show…” but you have provided only one reference. “The results of studies show that this disease is more prevalent in the north and south of Iran”.

⇒ As the title of your manuscript indicates, one of the aims of this study was to investigate the association between serum ferritin levels and gene mutations in patients with Intermediate and Major Thalassemia, but you have not provided your readers with any information about the importance of investigating this association. Using the results of various studies, you are expected to show that there is a relationship between serum ferritin levels in patients with beta-thalassemia major and genetic factors. Again these are only some examples that indicate that this part of your manuscript is not very well organized. So please consider re-organization this section of your manuscript in a clearer step by step way. It would be important to clarify what is known, what is not known, and what your study contributes to filling that gap.

Method

⇒ It is suggested that the type of the study be written as “descriptive-cross-sectional”.

⇒ I think you mean “by the ethics committee of Ahvaz Jundishapur University of Medical Sciences” in this phrase “in the ethics committee of Ahvaz Jundishapur University of Medical Sciences”.

⇒ How was your sampling method? Have you reviewed all patients’ records?

⇒ Did you have any inclusion or exclusion criteria?

⇒ How did you collect and classify the data? Did you use a specific checklist?

⇒ Please mention the significant level in this section of your manuscript. For example “The significance level was set at 0.05”.

Results

⇒ I suggest replacing “samples” with “patients” in this phrase “Of the 132 samples studied”.

⇒ Please mention the number of patients in addition to providing a percentage. For example “(56.8%, n=?) Were male”.

⇒ Please specify in the following sentence which statistical test have you applied? “Also, there was no statistically significant difference between mutated genes and patients' blood ferritin levels (P = 0.2)”.

⇒ I don’t understand the reason for providing the following information in this part of your manuscript. “Since our patients were randomly selected and there was no intervention in the conditions of drug use and compliance of patients, and in general the conditions were the same”. It also seems to contain errors of language, so it needs to be re-written for clarity.

⇒ The following sentence needs to be re-written for clarity. I mean once again, language errors appeared and it seems they are not limited to these examples and the manuscript needs to reviewed and revised by a native English speaker with academic writing skills. “This means that a higher percentage of patients with hemoglobin levels 6 to 7, received

blood that there was a higher percentage with IVSII-I mutation gene".

⇒ I think the following information should not be provided in this section of the manuscript. Instead, it should be discussed in the discussion section. "However, due to the fact that many mutations are occasional, this case cannot be used as an indicator of the severity of the disease and there is a need to conduct studies with a higher sample size".

⇒ You are expected to organize your research findings in the form of tables, but I have not seen anywhere in your manuscript that you refer readers to a table.

Discussion

⇒ Please provide references for the following sentence. "Comparisons between different provinces of the country show that the distribution of mutations varies considerably in type and frequency".

⇒ "The relationship between different gene mutations and ferritin levels, as well as the first hemoglobin before P.C transfusion and the age of the first time to receive P.C.". Once again! Language errors. I think you mean "the relationship between different gene mutations and ferritin levels, as well as the first hemoglobin before P.C transfusion and the age of the first time to receive P.C transfusion was investigated".

⇒ In general, the discussion seems not to be very in-depth and critical. You are merely presenting the results of various studies without comparing your findings with these studies and interpreting the results. In fact, the discussion could focus more on the interpretation of the results; provide more explanation of the why and how of the results and on possible methodological and other important factors that could account for the findings of the present study and of the inconsistency in findings across studies.

⇒ It is also necessary to identify the strengths and limitations of the study in this section.

References

⇒ In which part of your manuscript did you use reference number two? I couldn't find it anywhere in the main body of the text. Please specify it.

⇒ As you know, the references used in every study should be related to the last 5 years if possible. Therefore, it is recommended to add more up-to-date references to your study if possible.

General comments

The present manuscript has several organizational, structural, and content problems that require attention before it can be ready for publication.

Thanks.

REFEREE: Reviewer | **Revision** (0) 18 Oct 2020

Dear AE,

In this article, the authors studied 132 patients recorded documents to assess the correlation between Serum Ferritin Level and Gene Mutations in Patients with Intermediate and Major Thalassemia.

The main idea is interesting, although there are some minor flaws that need to be corrected:

- The authors used the abbreviation (P.C) in the abstract without mentioning the main word, which is not right.
- Check out the keywords and make sure they are based on MeSH.
- Through the main text, the authors did not mention the main word for their abbreviations (for example P.C once again!). Please correct this.

- Instead of P.C transfusion, use “blood transfusion”.
- Thalassemia is not a disease. Thalassemia is a blood disorder. Please change disease to disorder.
- I downloaded the PDF from my dashboard and surprisingly I found no tables and figures attached at all! Authors could have added more details about their patients in a table. Please add a table to demonstrate patients’ epidemiologic details (age, sex, mutation status, a form of thalassemia and etc.)
- It is very important to remember that a high level of serum ferritin is a very common finding in most thalassemia major patients, which is caused by repetitive blood transfusion. Therefore, there is an indirect relationship between serum ferritin level and gene mutations in patients with Thalassemia. This should be discussed in better and more details in discussion.
- The English language needs an edit.
- In the end, I recommend these articles to authors:
- Iron Overload in Beta Thalassaemia Major and Intermedia Patients (PMID: 24790662)
- Cardiomyopathy in Thalassemia: Quick Review from Cellular Aspects to Diagnosis and Current Treatments (DOI: 10.1093/labmed/lmz052)
- Elevated Prevalence of Abnormal Glucose Metabolism and Other Endocrine Disorders in Patients with β-Thalassemia Major: A Meta-Analysis (DOI: 10.1155/2019/6573497)
- Molecular basis of β thalassemia and potential therapeutic targets (DOI: 10.1016/j.bcmd.2017.06.001).

Thanks.

REFEREE: Associate Editor | **Revision** (0) 27 Oct 2020

Dear EIC,
Thanks for submitting this manuscript to JJCDC. Based on our reviewers' comments the article needs some revisions in all parts. I recommend the authors revise the manuscript and get it back as soon as possible.
With regards.

REFEREE: EIC | **Revision** (0) 27 Oct 2020

Dear Author,
Thank you for submitting your manuscript to JJCDC. This study is interesting in the chronic illness field. Based on our reviewers' comments your article needs some revisions in all parts. I recommend you revise the manuscript and get it back as soon as possible.
With regards.

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.

Reviewer1

The first thing that the reviewer 1 wanted me to correct was about the word "P.C" which I changed it to "blood transfusion" because the word "P.C" is not based on MeSH. (Line number: 28) (1

The second thing that the reviewer 1 wanted me to correct was about the word "disease" which I changed it to disorder because thalassemia is not a disease in fact it is a blood disorder. (Line number: 50) (2

The third thing that the reviewer 1 wanted me to use was about tables which I added them in my submission file. (Page number: 3 and 4) (3

The fourth thing that the reviewer 1 wanted me to correct was about this fact that there is an indirect relationship between serum ferritin level and gene mutations in patients with thalassemia which it is caused by repetitive blood transfusion and I mentioned it in the discussion. (Line number: 165-168) (4

Reviewer2

1) The first thing that the reviewer 2 wanted me to correct was about the title which I replaced the word "correlation" with the word "association" because my study was a descriptive cross-sectional not a correlation study. (Line number: 1)

2) The second thing that the reviewer 2 wanted me to correct was about the first sentence of the abstract in the background section and he asked me to put a period after the word "worldwide" and I have done it. (Line number: 15)

3) The third thing that the reviewer 2 wanted me to correct was about the type of study and the method of selecting participants and data collection method which the type of study was descriptive cross- sectional study and we did not use a method for selecting participant due to we reviewed all patients' records and for data collection we used a checklist consisting of demographics questions like type of thalassemia, kind of gene mutation, serum ferritin level, age, sex, ethnicity, Hemoglobin level before the first blood transfusion and age of the patients in month before the first blood transfusion. (Line number: 82 and 85-88)

4) The fourth thing that the reviewer 2 wanted me to correct was about the word "P.C" which i changed it to blood transfusion because the word "P.C" is not based on MeSH. (Line number: 28)

5) The fifth thing that the reviewer 2 wanted me to clarify was about this sentence "the age of the first blood transfusion". We wanted to know if the patient received blood transfusion in younger age would have related to some types of gene mutations or not. (Line number: 163-165)

6) The sixth thing that the reviewer 2 wanted me to correct was about the word higher in the sentence "higher sample size" which I replaced the word larger instead of the word higher. (Line number: 42)

7) The seventh thing that the reviewer 2 wanted me to clarify was about this sentence "it can be considered that some of the studied cases are insignificant due to the role these cases", I meant because the influence of the other accompanying genes and polymorphism can play an

important role in the clinical manifestations of genetic diseases, therefore the reason of some negative results in our study can be because of them. (Line number: 42-45s)

8) The eighth thing that the reviewer 2 wanted me to correct was about the definition of beta thalassemia which I have done it in the introduction. (Line number: 50-53)

9) The ninth thing that the reviewer 2 wanted me to correct was about providing a reference for the sentence "the results of studies show that this disease is more prevalent in the north and south of Iran", which I have done it and put the references one and two for it in the parentheses. (Line number: 54-55)

10) The tenth thing that the reviewer 2 wanted me to correct was about providing the importance of investigating the association between serum ferritin level and gene mutations in patients with intermediate and major thalassemia which I explained it in the background section and i mentioned it that in some studies the association between serum ferritin and gene mutations in some diseases like hereditary hemochromatosis were investigated but there is no study had done to study this association in patient with thalassemia. To this end by knowing this association it can be helpful to diagnose patients more quickly and take action when genetic test is not possible. (Line number: 65-71)

The eleventh thing that the reviewer 2 wanted me to correct was about the type of study and (11
I described it as descriptive cross-sectional study. (Line number: 82)

The twelfth thing that the reviewer 2 wanted me to correct was about this sentence "in the (12
ethics committee of Ahvaz Jundishapur University of Medical Science" and I replaced the word "by" instead of the word "in". (Line number: 83)

The thirteenth thing that the reviewer 2 wanted me to correct was about sampling method (13
which we reviewed all patients' record. (Line number: 85-86)

The fourteenth thing that the reviewer 2 wanted me to correct was about inclusion criteria in (14
which our inclusion criteria were: 1) all the patients were older than 1 years old. 2) all the patients were transfusion dependent. 3) all the patients underwent at least 10 blood transfusions. 4) all the patients were received the first blood transfusion younger than two years old. (Line number: 89-91)

The fifteenth thing that the reviewer 2 wanted me to correct was about checklist in which (15
we used a checklist consisting of demographics questions like type of thalassemia, kind of gene mutation, serum ferritin level, age, sex, ethnicity, hemoglobin level before the first blood transfusion and age of the patients in month before the first blood transfusion. (Line number: 86-88)

The sixteenth thing that the reviewer 2 wanted me to correct was about significant level (16
which I mentioned it was set at 0.05. (Line number: 89-90)

The seventeenth thing that the reviewer 2 wanted me to correct was about this phrase "Of (17
the 132 samples studied" which I replaced the word patients instead of the word samples. (Line number: 96-97)

The eighteenth thing that the reviewer 2 wanted me to correct was about mentioning the number of patients in addition to providing a percentage of them, which I have done it. (Line number: 101) (18

The nineteenth thing that the reviewer 2 wanted me to correct was about this sentence "there was no statistically significant difference between mutated genes and patients' blood ferritin level" and the reviewer asked me to mention the statistically test that I have used and it was Chi-squired test. (Line number: 117-118) (19

The twentieth thing that the reviewer 2 wanted me to correct was about this sentence "Since our patients were randomly selected and there was no intervention in the conditions of drug use and compliance of patients, and in general the conditions were the same". The .reviewer asked me to delete it from the result section, which I have deleted it (20

The twenty-first thing that the reviewer 2 wanted me to correct was about some language errors in the result section, which I have corrected them. (Line number: 122-124) (21

The twenty-second thing that the reviewer 2 wanted me to correct was about transferring this sentence " However, due to the fact that many mutations are occasional, this case cannot be used as an indicator of the severity of the disease and there is a need to conduct studies with a larger sample size" to discussion section, which I have transferred it. (Line number: 223-226) (22

The twenty-third thing that the reviewer 2 wanted me to correct was about using tables which I added them in my submission file. (Page number: 3 and 4) (23

The twenty-fourth thing that the reviewer 2 wanted me to correct was about providing reference for this sentence "Comparisons between different provinces of the country show that the distribution of mutations varies considerably in type and frequency", which I have done it. (Line number: 159) (24

The twenty-fifth thing that the reviewer 2 wanted me to correct was about this sentence " The relationship between different gene mutations and ferritin levels, as well as the first hemoglobin before blood transfusion and the age of the first time to receive blood transfusion " and the reviewer mentioned that it had language error, which I added "was investigated in the end of it. (Line number: 162-163) (25

The twenty-sixth thing that the reviewer 2 wanted me to correct was about discussion section in which I should compare our findings with other studies. (Line number: 176-177and 209-211) (26

The twenty-seventh thing that the reviewer 2 wanted me to correct was about mentioning the strengths and limitations of the study which I mentioned it in the article that because many mutations in our study were random and we had just one or two patients with these mutations, We need to conduct studies with larger sample size until we can use serum ferritin and hemoglobin as an indicator for disease severity. (Line number: 223-226) (27

The twenty-eighth thing that the reviewer 2 wanted me to correct was about mentioning the reference number two which I mentioned it in the revised file. (Line number: 159) (28

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) 10 Nov 2020

Dear AE,
The manuscript is revised and good enough for publishing.
Thanks.

REFEREE: Associate Editor | **Revision** (1) 10 Nov 2020

Dear EIC,
Based on our reviewers' comments, your manuscript is acceptable.
With the best

REFEREE: EIC | **Revision** (1) 10 Nov 2020

Dear Author,
Your manuscript is acceptable in the current format.
Thank you very much