Journal of Comprehensive Pediatrics
Volume 14 · Issue 4 · e133639

OPEN PEER REVIEW

COVID-19 Serological Status in Beta-thalassemia Patients in Iran: A Retrospective Descriptive Study

Shahla Ansari Damavandi, Shirin Sayyahfar, Neda Ashayeri, Maryam Shamspour, Masoumeh Jafari, Sarvenaz Salahi

SUBMITTED	REVISED	ACCEPTED	DOI
8 Feb 2023	30 May 2023	17 Jun 2023	10.5812/compreped-133639

About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

Contents

1 **Original submission** Referee 1, Referee 2, Houman Hashemian, Associate Editor, Editor-in-Chief 2
2 **Revision 1** Referee 1, Referee 2, Associate Editor, Editor-in-Chief 4
Authors' reply to reviewers 5
Reviewer and editor comments 8
3 **Revision 2** Referee 2, Associate Editor, Editor-in-Chief 10
Authors' reply to reviewers 11
Reviewer and editor comments 14

1 Original submission

5 comments · 9 Feb 2023 – 17 Feb 2023

Referee 1 Reviewer

REJECT 9 Feb 2023

Thank you for your study, but it has many problems.
The method is wrong. You need to study a control group of healthy pediatric patients for comparison.
You wrote two titles, "COVID-19 infection in Beta-thalassemia population; Is the severity of Covid-19 infection different in thalassemia patients? A study from Iran" and "COVID-19 Serology in Patients with Beta-thalassemia", for your study.
You studied patients across a wide age range, not a pediatric population.
The severity of clinical manifestations differs depending on age, so you should study patients within a narrow age range and compare them with the control group.
You have to explain how the severity of COVID-19 infection is defined.

Referee 2 Reviewer

MAJOR REVISION 11 Feb 2023

Dear author
Thank you for your submission.
There are some notes.
It is a good article, but the characteristics of the cases are not clear. The objective is not well clarified, and the variables in the methods part of the abstract and in Method do not match. The rationale for choosing the variables, for example, blood group, is not clear. English editing is mandatory. The results part is not well designed.
Abstract:
1-The aim of this study, based on the title, is to estimate the severity of COVID-19 in children with thalassemia.
2- Please change all instances of covid or other spellings to COVID-19 in the article.
3-Method: What is the meaning of pain in your variables?
4- Please check the keywords against MeSH.
Introduction:
1-Please describe the severity and symptoms of COVID-19 in children with thalassemia in the first part.
2- As stated in your study, the author is not going to characterize SARS-CoV-2 disease features in pediatric patients with BT and determine the risk factors for COVID-19 complications in this specific population. Please change this part at the end of the introduction. Comparison of the results with the general population requires a group of normal children. If you don't have a control group, the comparison cannot be the aim of your study.
Method:
1- What are the exact characteristics of the cases in this article? Were they all seropositive for COVID-19, and where do the PCR-positive cases fit in?
2- The variables in the abstract and the methods part don't match, for example, pain. Please check this.
3- How did you choose your cases? Were all of them PCR-positive, or what were the inclusion and exclusion criteria for cases?
4- What was the importance of blood group in the cases?
5- Did you have any information about the number of blood transfusions in your cases?
Results:
1- As mentioned in the Method part, all cases were serologically positive for COVID-19. What, then, is the

interpretation of the sentence “In the positive IgG/ positive IgM group, the mean age was 27.80(SD, 9.12) years while it was 22.62 (SD, 8.50) (p=0.017) in the negative IgG /negative IgM group”?
Discussion:
1- If all cases in this study are seropositive, then what is the interpretation of this sentence: “In this study, 57.1% of all participants were serologically positive for COVID-19 while 20% of positive cases did have the history of clinical manifestations compatible with Covid 19 infection.”?
2- As we know, IgG-positive cases may have acquired the disease previously, so our IgG-positive cases may not have symptoms.
3- If the mean age of the study cases was 24.84 ± 9.08, it seems that the majority of cases are not children. What are the median and quartiles of age in your study?
4- What are the advantages of your study?
5- Please give the results of other studies on other variables such as thalassemia type, blood group, history of splenectomy, and other symptoms such as cough, pain, and anosmia.
Best Regards

Houman Hashemian Reviewer

MAJOR REVISION 15 Feb 2023

Thanking the respected authors for their valuable research, I would like to draw their attention to the following:
1- Determining the history of vaccination against COVID-19 in these patients is important because it affects the severity of the disease and antibody levels.
2- Considering that the severity and complications of COVID-19 have changed over time due to the increase in the level of community immunity, it is important to compare these patients with a community-level control group with similar intervening and contextual variables during the same period for more accurate conclusions. If it is not possible to create a control group, at least community-level statistical information from the specified period should be used.
3- Considering that the study of the clinical symptoms and severity of the disease was based on the recollections of the patients or their parents and caregivers, and that the reported illness cannot confidently be considered confirmed COVID-19, it is necessary to mention these conditions in the limitations of the study.
4- The manuscript text needs to be edited.

Associate Editor

MAJOR REVISION 17 Feb 2023

Dear EIC,
In this study, the author aimed to characterize SARS-CoV-2 disease features and serology in pediatric BT patients.
It is a useful study but needs some revision as requested by the reviewers. Also, the study design should be mentioned in the first sentence of the Method section of the abstract.

Editor-in-Chief

MAJOR REVISION 17 Feb 2023

Dear Author,
Thank you for submitting the article. It needs some revision. Please revise it based on the reviewers' and AE's comments.

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Answers to Reviewers' Comments:

Dear Reviewer1

Thank you for reviewing this manuscript. Here is answers to your useful comments.
English edition is mandatory: English edition has been done.

Abstract:
1-The aim of this study is to estimate the severity of Covid19 in thalassemia children based on Title: The title has changed according to the comments.
2- Plz change all covid or other writhing to COVID-19 in the article: Has been changed.
3-Method: what is the meaning of pain in your variables?It was wrong and omitted
4- Plz check the keywords with Mesh: has been corrected according to Mesh
Introduction:
1-Please describe about the severity and symptoms of COVID19 in children with thalassemia in the first part: It has described.
2- As it is said in your study the author is not going to characterize SARS-CoV-2 disease features in BT pediatrics and determine the risk factors of COVID-19 complications in this specific populations. Please change this part at the end of introduction part. Comparison of the results with general population needs a group of normal children, if you don't have a control group the comparison cannot be the aim of your study.: It has been changed.
Method:
1- It is not clear what the exact characteristic of cases in this article is? Were they all seropositive for COVID19 and what is the place of positive PCR cases? No, they were not all seropositive. They were all thalassemia patients that had been checked for COVID serology. So, some of them were seropositive and some of them were seronegative.
2- Variables in the abstract and method part don't match together, for example pain. plz check it: It has been corrected
3- How did you choose your cases, were all of them PCR positive or what was the Inclusion and exclusion criteria for cases: No, In that time we had limitation to do PCR for all patients. So They were all thalassemia patients that had been checked for COVID serology. Then, some of them were seropositive and some of them were seronegative. And finally we assessed the serological status and clinical presentation in all thalassemia patients.
4- What was the importance of blood group in cases: According to some recent studies, blood group can have effects on COVID and its severity. These references has been added in new edition of the manuscript
5- Did you have any information about the number of blood transfusions in your cases? Generally, Number of transfusion in our center is between 2-4 times a month in our center. But this number was not in our variables.
Results:
1- As it was mentioned in the Method part all cases were serologically positive for covid19 then what is the interpretation of "In the positive IgG/ positive IgM group, the mean age was 27.80 (SD, 9.12) years while it was 22.62 (SD, 8.50) (p=0.017) in the negative IgG /negative IgM

group" sentence: No, they were not all seropositive. They were all thalassemia patients that had been checked for COVID serology. So, some of them were seropositive and some of them were seronegative.

Discussion:
1- If all cases of this study are seropositive then what is the interpretation of this sentence "In this study, 57.1% of all participants were serologically positive for COVID-19 while 20% of positive cases did have the history of clinical manifestations compatible with Covid 19 infection."? No, they were not all seropositive. They were all thalassemia patients that had been checked for COVID serology. So, some of them were seropositive and some of them were seronegative.

2- As we know IgG positive cases may acquire the disease previously so our IgG positive cases may not have symptoms. Yes. It's completely correct. We only describe the clinical presentation in that time.
3- If the mean age of study cases was 24.84 ± 9.08, it seems the majority of cases are not child, what is the median and quartile of age in your study. Yes, although our hospital is a center for pediatric patients, due to the condition of thalassemia patients, most of our patients are not children in that department. Therefore, according to your completely correct comments, we removed the word "child" from the article.

*4- What are the advantages of your study .*Because in the time of our study, PCR tests in Iran were limited, only some patients were able to do this test and in that situation serology tests were very useful to distinguish positive cases. Also COVID vaccination was not started in Iran in that time. Consequently, we had not any positive serology cases because of vaccination. So, we only decided to describe serological status and clinical presentation in thalassemia patients in that period of time.
5- Please give the results of other studies on other variables such as thalassemia type, blood group, history of splenectomy and other symptoms such as cough, pain and anosmia.: It has been added in the article

The answers to dear Reviewer 2:

Thank you for reviewing this manuscript. Here is answers to your useful comments.

1- Determining the history of vaccination against covid-19 in these patients is important because it affects the severity of the disease and antibody levels.: COVID vaccination was not started in Iran in that time. Consequently, we had not any positive serology cases because of vaccination
2- Considering that the severity and complications of the covid disease have changed over time due to the increase in the level of community immunity, it is important to compare with the control group at the community level with similar intervening and contextual variables at the same period of time for more accurate conclusions. If it is not possible to create a control group, at least the statistical information of the community level should be used in the mentioned time period.: According to your great comment, some information about community in that time has been added to article.
3- Considering that the study about the clinical symptoms and severity of the disease was based

on the memory of the patients or their Parents and caregivers, and in addition, it is not possible to confidently consider the said disease to be a proven covid, so it is necessary to mention these conditions in the limitations of the study.: It has been added.
4- The manuscript text needs to be edited.: It has been edited.

The answers to dear Reviewer 3:

Thank you for reviewing this manuscript. Here is answers to your useful comments.

.
The method is wrong. you need to study the control group of normal pediatrics to compare.: We had not control group. All participants in this study were thalassemia patients and this study was only a descriptive survey. According to your useful comments the title has been changed to a descriptive study. Also some information about community in that time has been added to article.

You wrote two titles"COVID-19 infection in Beta-thalassemia population; Is the severity of Covid-19 infection different in thalassemia patients? A study from Iran" and "COVID-19 Serology in Patients with Beta-thalassemia" for your study. :The title has been corrected.
You studied a wide range of patients' ages, not pediatrics.: Yes, although our hospital is a center for pediatric patients, due to the condition of thalassemia patients, most of our patients are not children in that department. Therefore, according to your completely correct comments, we removed the word "child" from the article.

The severity of clinical manifestation is different base on the age then you should study a narrow range of patients' age and compare it with the control group. We had not control group. All participants in this study were thalassemia patients and this study was only a descriptive survey. According to your useful comments the title has been changed to a descriptive study.
You have to explain a definition for the severity of COVID-19 infection.: The clinical manifestation has been described.

2 Revision 1

4 comments · 3 May 2023 – 5 May 2023

Referee 1 Reviewer

REJECT 3 May 2023

"However, in another study the association between blood group and risk of COVID-19 infection. In that study, blood group A was at a higher risk of infection, whereas blood group O was protective against the infection"
What is the meaning of this sentence? How did you find that individuals with blood group A were at a higher risk of infection, whereas blood group O was protective?
This is just a retrospective descriptive study. It does not give any results regarding the severity of the disease.
Method and discussion are very weak.
You discussed a series of studies on patients of different ages and said that their patients were different from your patients in terms of age, but you compared disease severity in your patients with that in those studies in the discussion part.
First, it is necessary to mention some indices of disease severity and compare them with those in the control group, so your study is only descriptive.

Referee 2 Reviewer

MAJOR REVISION 5 May 2023

Dear author
Thank you for your submission.
Title:
1- The author didn't check the clinical findings of patients with Beta thalassemia, so please correct the title accordingly.
Abstract:
1- Please decrease the number of words to 250.
Method:
Please define your cases by giving inclusion and exclusion criteria. Was a positive PCR result mandatory for inclusion in the study?
Method:
1- This study was performed in a children's hospital, but the age range of your cases extends beyond 20 years. Please explain the reason.
2- The author recorded the clinical findings of patients in this part, but the findings are not reported in the results section. What is the reason?
Results:
1- The findings in the results section are not arranged correctly. Please give the p-value for a finding after its statistical result, for example, in age groups.
2- The author gives the mean age and other variables in different serologic conditions. It is recommended to show these findings in a table and add the p-value in the last column.
3- In this sentence, " However, in another study the association between blood group and risk of COVID-19 infection. In that study, blood group A was at a higher risk of infection, whereas blood group O was protective against the infection", you gave the result of another study without a reference and in the results section. Please give your interpretation of the results in the discussion section with a reference.
Discussion:
1- Please add the results of splenectomy in different groups of thalassemia reported by other authors and discuss them.

2- Please give the advantages of your study.
Best regards

Associate Editor

MAJOR REVISION 5 May 2023

Dear EIC,
The great effort in improving the manuscript is highly appreciated. However, there is room for further improvement, which the authors should consider.
All reviewers' comments should be answered one by one, and concerns should be resolved until the reviewers are satisfied.

Editor-in-Chief

MAJOR REVISION 5 May 2023

Dear Author,
Some errors still exist. Please revise the manuscript based on the reviewers' and AE's comments.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Answers to Reviewers' Comments:

Dear Reviewers

Thank you for reviewing this manuscript. Here is answers to your useful comments.

Reviewer 1

1. *"However, in another study the association between blood group and risk of COVID-19 infection. In that study, blood group A was at a higher risk of infection, whereas blood group O was protective against the infection"What is the meaning of this sentence? How did you find that blood group A was at a higher risk of infection, whereas blood group O was protective?*
   this is just a retrospective descriptive study. It does not give any results regarding the severity of the disease.
   Because our study is a descriptive study, as you said, we did not state anything about the effect of blood group on the severity of the disease in our study. This paragraph is ***about another study*** *and mentioned "another study" and has a separate reference number.*

2. *You discussed a series of studies on patients of different ages and said that their patients were different from our patients in terms of age, but you compared the severity of your illness with them in the discussion part.*
   We did not have any articles with the same age of patients, so we discussed about these articles and also mentioned that the age is not exactly the same.
   First, it is necessary to mention some indices for the severity of the disease and compare it with the control group, so your study is only descriptive
   Yes, you are exactly true. This study is a descriptive study, but because it was about the early months of COVID-19 we don't have enough information about that virus and we couldn't do PCR for all the thalassemia patients so it seems it had its advantage as a descriptive study.

   Reviewer 2:
   Dear editor-in-chief, I would like to inform you that the issues I mentioned in the previous review have been corrected by the

respected authors in the new version or the necessary answers have been given. Thank you

Reviewer 3:

Title:
1- The author didn't check the clinical findings of patients with Beta thalassemia then pls correct the title accordingly
Thank you for your comment. We omit the clinical part from the title
Abstract:
1- Please decrease the number of words to 250. We decreased the number of words to 250

*2. Please give a definition for your cases, by giving inclusion and exclusion criteria. Was positive PCR mandatory for inclusion in the study? We described in the method, "*All the major and intermedia β-thalassemia patients who were dependent on blood transfusion and had a consent (filled by the patients or their guardians) were enrolled in this study."
PCR was not mandatory for enrolling in the study
Method:
1- This study was performed in children hospital but the age range of your cases is higher than 20 years. Please explain the reason
Although our hospital is a center for pediatric patients, due to the condition of thalassemia patients that their treatment started from childhood and continues lifelong, they continue their treatment here even after childhood and consequently, most of our patients are not children in this department.

2- The author recorded the clinical findings of patients in this part but the findings are not reported in the result part. What is the reason?
The clinical finding highlighted in the result part of the new edition.

Results:
1- The findings in result part are not arranged correctly. Please give the P value of one findings after its statistical finding for example in age groups.
We corrected this part.
2- The author gives the mean age and other variables in different serologic conditions. It is recommended to show these findings in table and add p value in the last column
3- In this sentence" However, in another study the association between blood group and risk of COVID-19 infection. In that study, blood group A was at a higher risk of infection, whereas blood group O was protective against the infection" you gave the result of another

study without reference and in the result part. Please give your interpretation of results in the discussion part with reference

This part omitted from the result part

Discussion:

1- Please add the results of splenectomy in different groups of thalassemia from other authors and discuss on it.

There are not any same publication that mentioned exactly this relationship but we added two studies that assess the effect of splenectomy on the severity and mortality of the patients

2- Please give the advantages of your study

Because in the time of our study, PCR tests in Iran were limited, only some patients were able to do this test and in that situation serology tests were very useful to distinguish positive cases. Also COVID vaccination was not started in Iran in that time. Consequently, we had not any positive serology cases because of vaccination. So, we only decided to describe serological status and clinical presentation in thalassemia patients in that period of time.

Althogh t*his study is a descriptive study, but because it was about the early months of COVID-19 we don't have enough information about that virus and we couldn't do PCR*

for all the thalassemia patients so it seems it had its advantage as a descriptive study.

3 Revision 2

3 comments · 16 Jun 2023 – 17 Jun 2023

Referee 2 Reviewer

MINOR REVISION 16 Jun 2023

Dear Author:
Thank you for your revision.
There are still some notes:
1- “Antibody assessment against” has no meaning; it is better to say “anti COVID-19 antibody measurement.”
2- Many sentences need English editing. For example, “ We put blood group as a variable because some studies showed the association of this variable with risk of COVID-19 infection and consequent complications.” can be revised to “ Since blood group showed association with risk of COVID-19 infection and consequent complications we checked this variable in our study.”
3- Please specify the exclusion and inclusion criteria and sample size calculation.
4- In the discussion section, please specify the country in each referenced article and give an explanation for each difference or similarity.
5- Table 1 should include complete information on the patients' characteristics, including which patients were studied, where, and when.
6- Please give the advantages of your study in the discussion section.
BEST REGARDS

Associate Editor

MAJOR REVISION 17 Jun 2023

Dear EIC,
The authors have not convinced the reviewer with their response.

Editor-in-Chief

ACCEPT 17 Jun 2023

Dear Author,
The manuscript still needs revision. This is the last time that you can revise it.