Archives of Pediatric Infectious Diseases
Volume 11 · Issue 3 · e132819

OPEN PEER REVIEW

Clinical Characteristics, Laboratory Features, and Outcomes of 151 Pediatric Patients with COVID-19 and MIS-C: A Single-center Study in the Northwest of Iran

Mahmoud Samadi, Mahboobeh Azadi, Amir Saeed, Akbar Molaei, Shahram Abdoli Oskouie, shamsi ghaffari, Ahmad Jamei Khosroshahi, Sara Kaveh

SUBMITTED	REVISED	ACCEPTED	DOI
13 Nov 2022	13 Apr 2023	21 Apr 2023	10.5812/pedinfect-132819

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, Associate Editor 2
2 **Revision 1** Associate Editor 4
Authors' reply to reviewers 5
Reviewer and editor comments 12
3 **Revision 2** Associate Editor 13
Authors' reply to reviewers 14
Reviewer and editor comments 17
4 **Revision 3** Associate Editor 18
Authors' reply to reviewers 19
Reviewer and editor comments 21
5 **Revision 4** Associate Editor 22
Authors' reply to reviewers 23
Reviewer and editor comments 25

1 Original submission

2 comments · 30 Dec 2022 – 15 Mar 2023

Referee 1 Reviewer

MINOR REVISION 30 Dec 2022

Dear author
Thank you for your submission.
1- COVID and MIS-C are different entities, but comparing their outcomes in children is important. Since there is extensive discussion of cardiovascular involvement in the results and discussion, it is better to change the title accordingly.

ABSTRACT:
1-The abstract is 290 words. Please shorten it to 250 words.
2-Please provide brief statistical results in the abstract.
3- Please change the keywords to MeSH terms.
INTRODUCTION:
1-Please change all instances of covid to COVID-19.
METHOD:
1-If possible, please provide the name of your hospital and its characteristics, for example, the number of beds and available medical services.
2- In line 73, you mentioned the division of cases into COVID and MIS-C, but these cases had been separated previously and were not divided by the author.

RESULTS:
1- The results do not describe the differences and changes that occurred in the two follow-up courses.
DISCUSSION:
1- The discussion is mainly focused on the cardiovascular assessment of patients; different parts of the analysis were not discussed. Please check the results one by one and explain the results and their similarities and differences in the discussion.
2- ASA use and its relation to mortality were not assessed in your study, so there is no reason to explain this in the discussion.
3- Please describe the advantages of the study.
CONCLUSION:
1- Please provide your recommendations for changes needed in the management and follow-up of patients with COVID and MIS-C, with special attention to cardiovascular involvement.
Best regards

Associate Editor

MAJOR REVISION 15 Mar 2023

Dear authors
Your manuscript [ID Number 132819] has passed through the review stage and is ready for revision.

Editorial comments
To ensure the Editor and Reviewers can recommend that your revised manuscript is accepted, please pay careful attention to each of the comments posted underneath this email. This way we can avoid future rounds of clarifications and revisions, moving swiftly to a decision.

1. Please provide a point-by-point response to the Editor's and reviewers' comments.
2. Please highlight all the amendments in your manuscript in yellow.
3. Use line numbering and page numbers in the next submission.
4. Improve the English language of the manuscript. There are some grammatical and spacing errors that need to be corrected throughout the manuscript.

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.

Answer letter

Article code: 132819

Article title: Clinical Characteristics, Laboratory Features, and Outcomes of 151 Pediatric Patients with COVID-19 and MIS-C: A Single Center Study in the Northwest of Iran

Dear honorable editor:

According to your valuable suggestions, major revision was made to the article which is highlighted, and the answers are presented in the table as follows:

The honorable editor comments	The answer
Totally COVID and MIS-C are different entities, but comparison for their outcomes in children is important. Since there are many explanations about cardiovascular involvement in results and discussion, it is better to change the title accordingly	Since this article includes other organ manifestations, we used this title
The abstract is 290 words pls change to 250 words	Change was made
Pls give the brief statistical results in abstract	Change was made
Pls change the key words to Mesh	Changes were made
Pls arrange all covid words to COVID-19	Changes were made in whole document.
If it is possible pls give the name of your hospital and its	The name of the hospital is:” Tabriz children’s hospital “

characteristics for example bed numbers and available Medical Services	It has 307 bed and it has all internal and also pediatric general surgery wards.
In line 73 you mentioned about division of cases to COVID and MIS-C but these cases were separated previously and they were not divided by author	We only used this sentence to emphasize more on the grouping according to the offered definition.
The results is not talking about the differences and changes occurred in the two follow up courses	It was mentioned that in the third month F/U no abnormality in the respiratory , gastrointestinal and neurologic system was detected and for most of the patient with cardiac involvement, ventricular and valvar function reached to the normal range.
Discussion part is mainly focused on cardiovascular assessment of patient, different parts of analysis was not discussed please check the results one by one and explain the results and their similarities and differences in discussion part	Change was made
ASA use and its relation to mortality was not assessed in your study, so there is no reason to explain it in discussion part.	Data about the effect of ASA was added to result
Pls give the advantages of study	It is among the first studies which describes the follow up. Moreover, study includes comparison of

	features of PICU and non-PICU admitted patients and presents the risk factors for PICU admission as well as cardiac involvement as one of the most serious organ involvement following this disease.
Pls give your recommendation in changes needed in manage and follow up of patients with COVID and MIS-C with special attention to cardiovascular involvement.	Follow up should be done for every pediatric patient even in those no abnormality is found in the initial evaluation. Evaluation of cardiac conduction system should also be done in each session.
This research is not so novel	It is among the first studies which describes the follow up. Moreover, study includes comparison of features of PICU and non-PICU admitted patients and presents the risk factors for PICU admission as well as cardiac involvement as one of the most serious organ involvement following this disease.
32% of 73 people had a pcr positive test, it is not logical because MIS_C is a postinfection procces.	Having PCR+ or IgG-COVID can be seen in these patients and none of them can ruled out it
Aspirin with an anti-inflammatory dose is not recommended in thrombocytopenia	It was not prescribed for the thrombocytopenic patients.
Thrombocytopenia is not specified	Please explain more about it.
It is not known how many people	It was added to the result: All the

had thrombocytopenia and how many people took high-dose aspirin and what was the result	patients who received ASA survived while only 92.34% of those for whom ASA was not prescribed were discharged from the hospital (p-value 0.043)
Was The dose of IVIG and prednisone the same in all of them(COVID &MIS_C)?	Neither IVIG nor prednisolone were prescribed for COVID-19 patients.
It is suggested that the content in the results be more concise, because it is repeated in the discussion content and it is a bit boring.	Change was made to the discussion.
It is suggested to refer to the recent articles in this field, for example, the article with DOI: https://doi.org/10.5812/pedinfect-120863 *Reviewer 3:*	Change was made to the discussion.
In line 17-18, you said "Among those who survived, in the third month follow-up (F/U), no abnormality in the neurologic, respiratory, and gastrointestinal system was detected", please explain how did you get this result? In statistical analysis and results section, you didn't report the result of time analysis.	In each follow up patients underwent complete physical examination and if needed complementary Paraclinical evaluation and finally the sum of that would define the patients' status; improved or worsen. Each patient would undergo evaluation by the subspecialist.
Please more explain about two groups under study, Covid-19 patients and MIS-c patients, you	Criteria used for selection of MIS-C patients is included in the method.

should point out that MIS-c happen after getting Covid-19	
In line 62-63, you claimed that "this is the first pediatric COVID study in Iran that consists of the comparison between PICU and non-PICU admitted patients", but you didn't report any results and tables that compare these two groups. Please explain about it.	New table was added.
In line 58, stated that, you follow the patients, so your study is cohort retrospective study, please correct it.	Changes was made.
In statistical analysis part, based on line 183 that you report the results of logistic regression, you should also add logistic regression model to statistical tests used.	Changes was made.
In line 91, you reported that "The mean± SD of the age of the participants was 5.34 ± 4.11 years", and in line 9, you stated that your study on the patients under 18 years, please report minimum and maximum age of your cases and correct the age entry criteria.	We used 18 years old as definition for child age. However, the maximum age of the participants was 15 y/o.
In line 118, Please determine two groups clearly, because in your	Changes was made (line 119).

study, you have two types of grouping.	
In line 130, what patients with what conditions choose for cardiac enzyme analysis? Please explain about it	Those who had tachycardia that was disproportionate with degree of fever underwent cardiac enzyme evaluation because they were suspicious to have myocarditis and it is not surprising that in the early stage of myocarditis the patient may have normal echo finding.
In line 156, please correct spelling mistake. "Covid-19".	Change was made.
Refer to line 183, please explain about predictor variables that you entered in logistic regression model, and also illustrate about what method you used in regression models?	First the relation between different variables (age, sex, diagnosis, outcome, clinical presentation, Paraclinical and laboratory findings, etc.) and ICU stay were assessed and then each variable for which the p-value was less than 0.2 was entered to the logistic regression using stepwise forward method.
In table 3, you reported cardiac involvement related to all of patients, don't you think it is better present for each group under study?	Since it was one of the factors that increases the risk of ICU admission we decided not to separate these two groups.
Please in tables specified the statistically significant variables, and also determine the statistical tests that you used under the tables.	Changes were made.

Yours sincerely

2 Revision 1

1 comment · 27 Mar 2023

Associate Editor

MINOR REVISION 27 Mar 2023

Dear authors
Thank you for the revision.
The manuscript's overall presentation has improved after amendments and is now more readable; however, the manuscript still needs minor corrections:
1. Serostatus of anti-SARS-CoV-2 antibody (IgM/IgG) and nasopharyngeal PCR results should be provided for Tables 1 and 4 (both for MISC/COVID-19 and for PICU/non-PICU patients).
2. Regarding the reviewer's comment in the previous round of peer review, "Aspirin with an anti-inflammatory dose is not recommended in patients with thrombocytopenia", you did not explain this point in the edited version. Add more details in this regard in the "Method" section.
3. Regarding your response to the reviewer's comment, the statement "Neither IVIG nor prednisolone was prescribed for COVID-19 patients." differs from the data presented in Table 1.
4. Regarding the reviewer's comment in the previous round, "what patients with
what conditions choose for cardiac enzyme analysis?", add your response to the "Method" section.
5. Add the following statement in the "Method" section: "The comparison of study variables (including age, sex, diagnosis, outcome, clinical presentation, and lab findings) were assessed between PICU and non-PICU patients by univariate analysis and those with p-value <0.2 were entered to the logistic regression using the stepwise forward method to predict PICU admission"
6. I do not find that you tested "cardiac involvement" in the tested model.
7. A full table of the logistic regression model, in addition to p-values and results for odds ratios with 95%CI, should be provided.
8. Table 4 headings (PICU and non-PICU) seem to be mentioned inaccurately. Recheck the data presented with the headings.

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.

In the name of God

Answer letter

Article code: 132819

Article title: Clinical Characteristics, Laboratory Features, and Outcomes of 151 Pediatric Patients with COVID-19 and MIS-C: A Single Center Study in the Northwest of Iran

Dear honorable editor:

According to your valuable suggestions, minor revision was made to the article which is highlighted, and the answers are presented in the table as follows:

The honorable editor comments	The answer
Serostatus of anti-SARS-CoV-2 antibody (IgM/IgG) and nasopharyngeal PCR results should be provided for Tables 1 and 4 (both for MISC/COVID-19 and for PICU/non-PICU patients)	Data was added to the tables.
Based on the reviewer's comment in the previous round of peer review, "Aspirin with an anti-inflammatory dose is not recommended in patients with thrombocytopenia", but you did not explain this point in the edited version. Add more details in this regard in the "Method" section.	Change was made.
Regarding your response to the reviewer's comment: "Neither	In the COVID-19 patients, IVIg was prescribed for those

IVIG nor prednisolone was prescribed for COVID-19 patients.", this statement differs from the data presented in Table 1	with resistant shock status. For those with severe respiratory involvement following COVID-19 infection “ Dexamethasone” was used while prednisolone was used only in MISC group.
Regarding the reviewer's comment in the previous round: "what patients with what conditions choose for cardiac enzyme analysis?". Add your response to the "Method" section.	Change was made.
Add the following statement in the "Method" section: "The comparison of study variables (including age, sex, diagnosis, outcome, clinical presentation, and lab findings) were assessed between PICU and non-PICU patients by univariate analysis and those with p-value <0.2 were entered to the logistic regression using the stepwise forward method to predict PICU admission"	Change was made.
I do not find that you test "cardiac involvement" in the tested model.	Different systems involvement status were also entered to the model and among them it was

	statistically significant only for cardiac involvement.
Full table of the logistic regression model in addition to p-values and results of odds ratio with 95%CI should be provided	Table was added.(Table 4)
Table 4 headings (PICU and non-PICU) seem to be mentioned inaccurately. Recheck data presented with the headings.	Change was made.

Yours sincerely,

Mahboobeh Azadi.

3 Revision 2

1 comment · 1 Apr 2023

Associate Editor

MINOR REVISION 1 Apr 2023

Dear authors
Thank you for the revision.
Please correct the following shortcomings:
1. The titles of tables 1 to 5 (except 4) are non-informative. The title should specify the total number of cases analyzed and the groups investigated.
2. Regarding Table 4: The purpose of presenting a table that characterizes the full model is to include all variables examined to predict hospitalization in the PICU, including all univariate analyses regardless of P-values (heading 1) and results of the multivariable analysis, which includes variables with a P-value <0.2 (heading 2). Similar tables could be found anywhere. Heading 2 must include both P-values and 95% CIs.

4

Revision 3

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.

In the name of God

Answer letter

Article code: 132819

Article title: Clinical Characteristics, Laboratory Features, and Outcomes of 151 Pediatric Patients with COVID-19 and MIS-C: A Single Center Study in the Northwest of Iran

Dear honorable editor:

According to your valuable suggestions, minor revision was made to the article which is highlighted, and the answers are presented in the table as follows:

The honorable editor comments	The answer
The titles of tables 1 to 5 (except 4) are non-informative. The title should specify the total number of cases analyzed and the groups investigated.	Change was made.
Regarding Table 4: The purpose of presenting a table that characterizes the full model is to include all variables examined to predict hospitalization in the PICU including all univariate analyses regardless of P-values (heading 1) and results of the multivariable analysis which includes variables with P-value <0.2	Table 4 was added. All study variables (including demographic data, diagnosis, outcome, clinical and Paraclinical findings) were assessed between PICU and non-PICU admitted patients and a summary of that (not all of them) is presented in the table because if we wanted to include all variables here it

(heading 2). Similar tables could be found anywhere. Heading 2 must include both P-values and 95%CIs.	would elongate the table and make it boring for the readers.

Yours sincerely,

Mahboobeh Azadi.

4 Revision 3

1 comment · 11 Apr 2023

Associate Editor

MINOR REVISION 11 Apr 2023

Dear authors
Thanks for the revision.
Please address the following shortcomings:
1. Line 473: replace "Associated factors of cardiac involvement" with clearer wording.
2. Line 478: The Table 4 title should be corrected as follows: "Predictors of PICU admission in the pediatric patients with MISC and COVID-19. The results of the binary logistic regression analysis."

3. Line 483: Table 5 is a duplicate. Omit the first one.
4. Table 5 should be substituted with Table 4. The related text should be reordered in the results section accordingly.
5. "Diagnose", "Outcome", "Inotrope agent", "Duretic", and "Antibiotic" all have $p<0.2$. Why did you not include them in the full model? Add your response as a table footnote (in the table that describes logistic regression analysis).
6. "Neurologic" and "Mucocutaneous" both have $p>0.2$. Why did you include them in the full model? Add your response as a table footnote (in the table that describes logistic regression analysis).

5

Revision 4

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.

In the name of God

Answer letter

Article code: 132819

Article title: Clinical Characteristics, Laboratory Features, and Outcomes of 151 Pediatric Patients with COVID-19 and MIS-C: A Single Center Study in the Northwest of Iran

Dear honorable editor:

According to your valuable suggestions, minor revision was made to the article which is highlighted, and the answers are presented in the table as follows:

The honorable editor comments	The answer
Line 473: replace "Associated factors of cardiac involvement" with more clear words.	Change was made.
Line 478: Table 4 title should be correct as follow: "Predictors of PICU admission in the pediatric patients with MISC and COVID-19. The results of the binary logistic regression analysis."	Change was made.
Line 483: Table 5 is a duplicate. Omit the first one.	Table was omitted.
Table 5 should be substituted with Table 4. The related text should be reordered in the result	Change was made.

section accordingly.	
"Diagnose", "Outcome", "Inotrope agent", "Diuretic", and "Antibiotic" all have p<0.2. Why did not include them in the full model? Add your response as a table footnote (in the table that describes logistic regression analysis)	Change was made
"Neurologic" and "Mucocutaneous" both have p>0.2, why did you include them in the full model? Add your response as a table footnote (in the table that describes logistic regression analysis) "Neurologic" and "Mucocutaneous" both have p>0.2, why did you include them in the full model? Add your response as a table footnote (in the table that describes logistic regression analysis)	Change was made.

Yours sincerely,

Mahboobeh Azadi.

5 Revision 4

1 comment · 17 Apr 2023

Associate Editor

ACCEPT 17 Apr 2023

I read the revised manuscript.
I have no further comments to add. I thank the authors for their very detailed replies to my comments.