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OPEN PEER REVIEW

Clinical and Paraclinical Findings of Primary Pulmonary Hypertension in Children

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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.

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1 Original submission

2 comments · 9 Jul 2021 – 31 Jul 2021

Associate Editor

MAJOR REVISION 9 Jul 2021

Manuscript ID: 114419

Dear EIC

-The article is a retrospective study of the clinical signs and paraclinical findings of a small number of patients with pulmonary artery hypertension, which is a well-known topic and not new.
-In the study, the severity of pulmonary hypertension and tricuspid regurgitation was not related to clinical symptoms, which seems to be due to the small sample size. (The sample size should be increased.)
-It is necessary to provide information about catheterization and echo data in the text of the article and compare their results.
-The tables provide information about treatment with different drugs, but in the article, there is nothing about medical treatment. The protocol for different drug treatments and how to select them should be mentioned in the text of the article.
-Results of medical treatment are listed in the Table of Clinical findings; they must be listed in a separate table.
-The right column of Table 3 is not visible.
-In the discussion section, explanations of the pathophysiology and symptoms of the disease should be summarized. They should present the results of the recent study and their application and compare them with those of previous studies in this section.
-Conclusions differ between the abstract and the final part of the article and are not related to the title of the article; this must be corrected.
-The article needs to be edited for English writing.

Sincerely

Editor-in-Chief

MAJOR REVISION 31 Jul 2021

Dear Authors,
Thank you for submitting your valuable manuscript.
I would like to inform you that, according to the journal's expert reviewers' comments, your article needs major revision before publication. Please consider all the comments point by point during the revision process.

Warm Regards
Alireza A. Ghavidel MD
EIC

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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.

Reviewer 1:

1_This article has been studied in Iran,then the results are quite valuable.

Q2_Regarding the electrocardiograph finding,it seems that due to less data in the files,it was expected these findings would be more examined in this article.

A2: ECG findings were added to the manuscript in new table 3.

Q3-There is no finding on cardiac biomarkers in IPAH patients, that could be valuable.

A3: This statement is quite right, and it will be mentioned as study limitations.

Reviewer 2:
Q1-This is a descriptive – retrospective study on small population of children with PAH.

A1: Primary pulmonary hypertension is very rare in contrast to secondary pulmonary hypertension. Some patients go undiagnosed and some die before diagnosis. The sample size is large considering rarity of the disease and similar articles confirm this statement.

Q2-The authors state the purpose of the study as follow; "This study aimed to evaluate the clinical and paraclinical findings of idiopathic pulmonary arterial hypertension in children (iPAH)" and , But in conclusion of the abstract stated that: "The results of the present study can determine the role of non-invasive methods in comparison to invasive methods in the diagnosis of pediatric PAH."

A2: This statement is totally true, we corrected the glaring mistake.

Q3:In this study , the comparison between the diagnostic methods was not performed. only some clinical picture and descriptive information of PH were presented. These clinical signs are well known in PH.

A3: We have recently reported the comparison between the diagnostic methods in iPAH precisely in another manuscript which is under publication, also there is limited data about Iranian population with iPAH, due to rarity of the disease.

Q4-In the result section : “In general, 56.3% and 43.8% of the patients expired and survived, respectively.” This sentence need to be corrected.

A4: It was corrected

Q5- in discussion section: “Based on the electrocardiogram (ECG) findings of the study carried out by Kovacs et al., prominent pulmonary conus was reported as 43% in PAH children”. This sentence is repeated in the previous segment.!!!!

A5: We corrected it, and highlighted with yellow color.

Q6- conclusion of the article: This section should summarize the findings of the study and not a general discussion of the disease.

A6: Done

Q7-Long description of the pathophysiology of the preterm infant with PH was presented in discussion section.

A7: we omitted additional description

Associate Editor's Comments:

Associate Editor 1:
Manuscript ID: 114419

Q1-The article is a retrospective study of the clinical signs and paraclinical findings of a small number of patients with pulmonary artery hypertension which is a well-known topic and not new.

A1: Considering that there has been few studies conducted on pediatric PAH in Iran and the rarity of this disease the present study has been carried out in a referral tertiary pediatric cardiac center over 10 years.

Q2-In the study, there was no relationship between the severity of pulmonary hypertension and tricuspid regurgitation with clinical symptoms, which seems to be due to the small sample size, (The sample size should be increased)

A2: Primary pulmonary hypertension is very rare in contrast to secondary pulmonary hypertension. Some patients go undiagnosed and some die before diagnosis. The sample size is large considering rarity of the disease and similar articles confirm this statement.

Q3-It is necessary to provide information about catheterization and echo data in the text of the article and compare their results.

A3: We have recently and with great precision reported "The Predictability of Echocardiography in Children with Primary Pulmonary Hypertension and Its Comparison with Cardiac Catheterization Parameters" in another manuscript which is under publication.

Q4-The tables provide information about treatment with different drugs, but in the article, there is nothing about medical treatment. The protocol of different drug treatments and how to select them, should be mentioned in the text of the article.

A4: Treatment protocols are not the subject of this study so the table was replaced with another table which demonstrates ECG findings

Q5-Results of medical treatment are listed in the Table of Clinical findings, they must be listed in a separate table.

A5: The section of drugs in the table is removed, and the table was replaced totally with a table which shows ECG findings

Q6-The right column of Table 3 is not visible.

A6: Done

Q7-In the discussion section, explanations of the pathophysiology and symptoms of the disease should be summarized. They should present the results of the recent study and their application and compare it with the previous studies in this section.

A7; Done

Q8-Conclusions are different in the abstract and the final part of the article and not related to the title of the article, it must be corrected.

A8: Done

Q9-The article needs to be edited for English writing.

English editing is done.

Sincerely

2 Revision 1

4 comments · 18 Sep 2021 – 4 Mar 2022

Referee 1 Reviewer

MINOR REVISION 18 Sep 2021

1. Although the title of the article is Clinical and Paraclinical Symptoms of Pulmonary Hypertension, the introduction does not mention the signs and symptoms of the disease and their prevalence. It is better to mention the types of pulmonary hypertension symptoms in children and their prevalence in each age group, as well as the prevalence of paraclinical findings.
2. Lines 67,68: change to "All the medical records of patients were reviewed, and those with other causes of PH, including pulmonary and hematologic problems, were excluded."
3. Line 73: In general, 20 patients were selected using the census method.
4. In the results section, echocardiographic and angiographic findings are not mentioned.
5. Table 3: only 8 patients had an ECG!?
6. In line 116: In electrocardiography, the heart rate was " 124.12 ± 21.72".
7. The text mentioned in line 146 of the article is not related to the title and text of reference No. 22.
8. Reference number 8 is not correct according to the Vancouver style.

Referee 2 Reviewer

MINOR REVISION 7 Oct 2021

Considering the rarity of the disease, the raw data are valuable for further investigations, but some findings could not be statistically analyzed.
The manuscript can be published after minor revisions:

Abstract/Result
line 14: The results of the present study showed a higher frequency of iPAH among the females (70%) than the males and also in the term neonates in comparison to the preterm newborns.

These are the demographic findings of a small study population and cannot be presented as a frequency report. It is sufficient to mention the number of cases (male vs. female, preterm vs. term).

Results
Line 116: In Electrocardiography heart rate was 21.72±124.12 ….
The heart rate value should be mentioned as 124.12±21.72.

Discussion
Line 125: In summary, the results of the present study showed that the incidence of PAH was higher among the females.

As mentioned above, this is a demographic finding in a small study population and cannot be presented as a frequency report.

Line 158: In addition, the present study showed that the prominent pulmonary conus, RAE, and RVH were the most common CXR findings

The sentence should be corrected as a raw report; for example:
The most common CXR findings in our study population were prominent pulmonary conus, RAE, and RVH.

Associate Editor

MINOR REVISION 14 Oct 2021

Manuscript ID: 114419
Dear EIC
Some of the issues that were recommended to be corrected in the initial review have been resolved, but the following issues still need to be corrected:

1-In the abstract section (line 21), does “PRPG” mean the peak pressure gradient of the pulmonary regurgitation jet? If so, the phrase “peak systolic PG” in the text and Table 2 should be changed to Peak diastolic PG.

2-The abstract section (line 24) states: “The results confirmed a significant relationship between MPAP and consanguinity”, while the relevant table (3) does not mention consanguinity, which needs to be added.

3-Patient data collection covers a 17-year period; therefore, it is better to present the death rate as 5-year and 10-year survival rates.

4-The abstract (line 27) states “37.5% of deaths were in younger children”; the meaning of younger children should be explained.

5-The clinical signs mentioned in the conclusion are different from those in the abstract section; they must be the same and should be corrected.

6-The study design section (line 77) states: “computed tomography angiography was applied to produce the images of blood vessels and tissues”, but the results are not presented in the article and need to be added.

7-The results section (line 114) states: “a significant difference was observed between palpitation and children with PAH at different age groups (P=0.01)”, while the relevant table (1) does not mention the relationship between clinical symptoms and different age groups, which needs correction.

8-The results section (line 121) states: "Table 3 presents the relationship between the survival rate and clinical findings", while Table 3 is related to ECG findings, and there is no table with this title in the article. This table should be added.

9-The finding “Lack of association between clinical symptoms and severity of PH and higher prevalence of PH in term neonates” obtained in this study is contrary to all previous studies, and it is better to point out the confounding factors that caused these results in this study.

10-The information on paraclinical findings, including CXR, echo, and cath (similar to the clinical information and ECG), should be provided in separate tables.

Sincerely

Editor-in-Chief

MINOR REVISION 4 Mar 2022

Dear Authors
First of all, I would like to apologize for the prolonged review process. Your potentially accepted manuscript needs minor revision before publication.

Regards
EIC

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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.

EIC Decision:

Dear Authors
First of all, I would like to apologize for the prolonged review process. Your potentially accepted manuscript needs minor revision before publication.

> Reviewers' Comments:

Reviewer 1:
1. Although the title of the article is Clinical and Paraclinical Symptoms of Pulmonary Hypertension, the introduction does not mention the signs and symptoms of the disease and their prevalence. It is better to mention the type of pulmonary hypertension symptoms in children and their prevalence in each age group, as well as the prevalence of paraclinical findings.
The prevalence was written in the 4th line of the introduction and in the next line, the most common pulmonary hypertension symptoms were added.

2. Line 67,68 change to "All the medical records of patients were reviewed, and those with other causes of PH, including pulmonary and hematologic problems, were excluded."
Done. We've changed it as you requested.

3. Line 73: In general, 20 patients were selected using the census method.
Done. We've changed it as you requested.

4. In the results section, echocardiographic and angiographic findings are not mentioned.
Electrocardiographic findings were available in table 3. Echocardiographic and angiographic were categorized and summarized in the concept of the text in the result section. I've highlighted to make them more obvious.

5. Table 3: only 8 patients had ECG!?
Unfortunately Yes! The study was retrospective and the other ECGs weren't available. All accessible data including ECGs were mentioned.

6. In line 116: In Electrocardiography heart rate was" 124.12 ± 21.72".
Yes. You're completely right. The numbers had been reversed. I made it correct.

7. The text mentioned in line 146 of the article is not related to the title and text of reference No. 22.
Thanks for your comment. I corrected the reference.

8. reference number 8 is not correct according to Vancouver
Done

Reviewer 2:
Considering the rarity of the disease, the raw data is valuable for further investigations, but some findings could not be statistically analyzed.
The manuscript can be published after minor revisions:

Abstract/Result
line 14: The results of the present study showed a higher frequency of iPAH among the females (70%) than the males and also in the term neonates in comparison to the preterm newborns.

These are the demographic findings of a small study population and could not be mentioned as a frequency report. That is enough to mention the number of the cases (male vs female, preterm vs term)

Thanks. You're right. I omitted the word "frequency".

Results
Line 116: In Electrocardiography heart rate was 21.72±124.12 ….
The number of heart rate should be mentioned as 124.12±21.72

Yes. We corrected it. Unfortunately, it had been reversed in Microsoft word technically.

Discussion
Line 125: In summary, the results of the present study showed that the incidence of PAH was higher among the females.

As mentioned above this is a demographic finding in a small study population and could not be mentioned as a frequency report.

The word was changed as you stated above as well as in this line.

Line 158: In addition, the present study showed that the prominent pulmonary conus, RAE, and RVH were the most common CXR findings

The sentence should be corrected as a raw report; for example:
The most common CXR findings in our study population were prominent pulmonary conus, RAE, and RVH.

OK. We made it different as you said.

> Associate Editor's Comments:

Associate Editor 1:
Manuscript ID: 114419

Dear EIC
Some of the issues that were recommended to be corrected in the initial review have been resolved, but the following issues still need to be corrected:

1-In the abstract section (line 21), does "PRPG" mean peak pressure gradient of pulmonary regurgitation jet? If so, the phrase "peak systolic PG" in the text and Table 2 should be changed to Peak diastolic PG.
Peak systolic Pressure Gradient. We Changed the badly written abbreviation

2-In the abstract section(line24) mentioned: "The results confirmed a significant relationship between MPAP and consanguinity", while the relevant table (3) does not mention the consanguinity, which needs to be added.

Table 3 is about "Electrocardiographic findings in patients" and it's not related to the subject of consanguinity. In table 1, consanguinity in the section on the parental relationship was available. More information on the availability of the raw primary data wasn't easily accessible to add due to the prolonged delay of the journal response if I am not mistaken more than a year! Thank you for your comment.

3-Patient data collection is related to a 17-year period, therefore, it is better to present the death rate as 5-year and 10-year survival rates.
Non-survived patients (50%) were higher in the age group of 0-5 years. In addition, two-quarters of the non-survived patients were within the age ranges of 6-11 and 12-18 years (each, 25%). This sentence is available in the last lines of the result which mentioned what you want.

4-In the abstract(line27) mentioned "37.5% of deaths were in younger children", the meaning of younger children should be explained.
0-5 years! As we mentioned in the last comment.

5-The clinical signs mentioned in the conclusion are different from the abstract section, they must be the same and should be corrected.

It was corrected in the last revision, we highlighted it in the text.

6-In the study design section (line 77) mentioned: "computed tomography angiography was applied to produce the images of blood vessels and tissues" but the results are not presented in the article, which needs to be added.

Yes, due to the lack of limitation for more tables, we've just added the concept of the text. You can see it in highlighted form in the last revision file of the manuscript.

7-In the results section (line 114) mentioned: "a significant difference was observed between palpitation and children with PAH at different age groups (P=0.01)", while the relevant table(1) does not mention the relationship between clinical symptoms and different age groups, which needs correction.

In table 1, we just wanted to mention the descriptive information, as the title has shown ''Demographic data and clinical symptom of

children hospitalized at cardiac ward". Also, the relationships you meant were stated in the text-result section.

8-In the results section(line 121) mentioned: "Table 3 presents the relationship between the survival rate and clinical findings", while Table 3 is related to ECG findings and there is no table with this title in the article that should be added.
Yes. You are right. Due to the limitation of the tables' number, we omitted the old table 3 during the submission and of course, the numbers of tables have changed to the new order, but we forget to omit this sentence. So, I deleted the mentioned sentence. Thanks for your attention and also the comment.

9- "Lack of association between clinical symptoms and severity of PH and higher prevalence of PH in term neonates" which is obtained from this study, is contrary to all previous studies and it is better to point out the confounding factors that caused these results in this study.

Yes, and that's the reason making us write this manuscript, the different outcomes. The difference makes it bold to publish; however, the sample size is considered. Unfortunately, due to prolonged delays and after many revisions, it's not easy for us to gather the primary issues; however, as much as it makes it understandable we mentioned before in the text.

10-The Information of paraclinical findings including CXR, echo, and cath (similar to the clinical information and ECG) should be provided in separate tables.

Lack of permission for more tables. Also, as much as it is needed and was available, we guess we mentioned it in the text and the present tables. And in the last revision, we added more data that was accessible. Thanks for your recommendation

Sincerely

> EIC Decision:

Dear Authors
First of all, I would like to apologize for the prolonged review process. Your potentially accepted manuscript needs minor revision before publication.

3 Revision 2

1 comment · 20 Apr 2023

Editor-in-Chief

ACCEPT 20 Apr 2023

Dear authors
Thank you for the revision of the manuscript, and I apologize for the delay in the review process.
I would like to inform you that the manuscript was accepted by the reviewers and will be published in upcoming issues.

Regards
EIC