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OPEN PEER REVIEW

Comprehensive Investigation of Demographic, Clinical, and Paraclinical Findings in Hospitalized Children with COVID-19

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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

1 comment · 30 Mar 2024

Associate Editor

MAJOR REVISION 30 Mar 2024

reviewer 1
Dear Editor
I read the manuscript with interest. The authors are advised to consider the following comments.
1- The abstract does not provide a new and useful message.
2- The descriptive findings in the abstract section did not cover the sex and age distribution.
3- The finding has been reported without frequency or objective findings.
4- The conclusion has been drawn based on statistical significance without considering the clinical importance of the results.
5- The authors have reported an equation to estimate sample size. However, they did not report any details, including the objective of the sample size estimation.
6- The methods, including the statistical analyses, are not specific.
7- The authors need to revise the tables for greater clarity.
8- The adopted approach to analyze and compare the mild and severe groups is inappropriate for drawing interesting conclusions. It would be better if the authors used a multivariable logistic or ordinal regression.
Decision:
Major revision

Reviewer 2
Dear Author
Thank you for your article.
Overall, since this is a comparative study and severe cases are defined as having more severe clinical findings, it is obvious that the severe group has more hypoxia, organ involvement, and radiologic findings, as reported in the results sections of the abstract and article. The logic of this interpretation is not clear, and this is an important problem.
English editing is mandatory.
Abstract:
Please decrease the total word count to 250.
Introduction:
1- Please rearrange the information on COVID19 cases in Iran and other countries and give the main objective of the study at the end.
Method:
1- What is the meaning of relevant physician?
2- Please give a reference for your inclusion criteria.
3- The sample size cannot be derived directly from another author's study. Please give your own statistical process for determining the number of cases and explain why there is such a large difference in size between the severe and mild groups.
4- Please check all variables against your results; this means that all variable measurements mentioned in the methods section may be presented in the results section.
Result:
1- What is normal disturbance?
2- Tables: Please do not give too much information in the tables, and omit unnecessary columns, for example, the total and statistics columns. Where is the title of table 4?

3- Please give the more important findings in the text of the results section.
Disscusion:
1- Given the many findings in the results section, the discussion section is very short and does not provide a good literature review or interpretation of the findings. It is recommended that this section be revised completely.
Conclusion:
1- Please do not give the results in this section. The conclusion can include the main, important finding of the study and its recommendation for future studies.
Best regards
Decision:
Major revision

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.

Reviewer 1:
Dear Editor
I read with interest the manuscripts. Authors are advised to consider the following comments.
1- The abstract does not provide a new and useful message.

We appreciate your comment. we revised it.

2- The descriptive findings in the abstract section did not cover the sex and age distribution.

We appreciate your comment. we revised it.

3- The finding has been reported without frequency and objective findings.

We appreciate your comment. we revised it.

4- The conclusion has been made based on statistical significance without the clinical importance of the results.

We appreciate your comment. we revised it.

5- The authors have reported an equation to estimate sample size. However. they did not report any detail, including the sample size estimation objective.

We appreciate your comment. we revised it.

6- The methods including the statistical analyses are not specific.

We appreciate your comment. we revised it.

7- The authors need to revise the tables for more clarification.

We appreciate your comment. we revised it.

Reviewer 2:
Dear Author
Thank you for your article .
Totaly since this study is a comparative study and definition of sever cases are having more sever clinical findings , so it is obvious that the sever group have more hypoxia and organ

involvement and radiologic findings as reported in result part of abstract and article. This is not obvious what is the logic of this interpretation and it is an important problem.
English edition is Mandatory
Abstract:
Pls decrease the total word number to 250

We appreciate your comment. we revised it.

Introduction:
1- pls rearrange the information on COVID19 cases in IRAN and other countris and give your main objective of study at the end.

We appreciate your comment. we revised it.

Method:
1- What is the meaning of relevant physician

We appreciate your comment. we revised it.

2- Please give reference for your inclusion criteria

4- Pls check all variables with your results findings, it means all variable measues mentioned in method part may be present in the result part
Result:
1- What is normal disturbance?

Sodium and potassium had normal distribution.

2- Tables : Pls dont give a lot of information in tables and omit unnecessary columns for example the total and statistics column . Where is the titile of table 4?

We appreciate your comment. we revised it.

3- Pls give the more important findings in the text part of result
Disscusion:
1- Based on a lot of findings in result part the discussion part is very short and dosent perform a good literature review and interpretation of findings. it is recommended to revise this part completely

We appreciate your comment. we revised it.

Conclusion:
1- Pls dont give the result findings in this part. Conclusion can include the important and main findig of study and its recommendation for future studies

We appreciate your comment. we revised it.

Best regards

2 Revision 1

2 comments · 4 May 2024 – 12 May 2024

Referee 1 Reviewer

MINOR REVISION 4 May 2024

Dear Editor
The revised version of the manuscript has been amended substantially. The authors need to consider the following comments.
1- All decimal values in the tables should be written using a decimal point (dot), as in 2.5, not 2/5.
2- In the column header of Table 2, please use % to avoid inserting the percentage symbol in all of the cells.
Reviewer,

Associate Editor

MAJOR REVISION 12 May 2024

Reviewer1

Dear author
Thank you for the revision.
There are still some notes.
1- Abstract: The sleep disorders mentioned in the conclusion section are not reported in the result section. Please give some information about this variable in the result section.
2-Method: A-Pediatric Infectionist is not a correct name. Do you mean a pediatric infectious diseases subspecialist? B- Please clarify the definition of the group with severe COVID19. What do you mean by the respiratory distress group? Please give a reference for your definition. What are the criteria for patients with severe and mild disease?
3-Result: A-Please check the variables in the method and result sections. B- In the first part of the result section, please note that the variables in table 1 are demographic variables. C- Why is the mean number of lymphocytes higher in the severe group?
4- Discussion: Please discuss the differences between your results and those of other studies.
5- Conclusion: Please check sleep disturbances.
Best Regards

Reviewer2
Dear author
The revised version of the manuscript has been amended substantially. Authors need to consider the following comments.
1- All decimal numbers in the tables should be written using a decimal point (dot), as in 2.5, not 2/5.
2- In the column's header of Table 2, please use % to avoid inserting the percentage in all of the cells.

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.

Dear editor in chief,

We appreciate your reviewers' great comments. We revised our manuscript based on your valuable comments.

Reviewer 1:
Dear author
Thank you for revision
there are still some notes
1- Abstract : sleep disorders that are mentioned in the conclusion part has no report in the result part . Pls give some information about this variable in the result part.

We appreciate your comments. We revised our manuscript based on your valuable comment.

Severe cases exhibited a higher frequency of sleepiness (40%) and shortness of breath (41.3%).

2-Method: A-Pediatric Infectionist is not a correct name, Do you mean pediatric infectious diseases sub specialist?

We appreciate your comments. We revised our manuscript based on your valuable comment.

pediatric infectious diseases sub specialist

B- Pls clearly clarify what is the definition of sever group with COVID19. what do you mean by respiratory distress group ? Pls give reference for your definition . It means what is the criteria of a patient with sever and mild disease. ?

We appreciate your comments. We revised our manuscript and added the reference based on your valuable comment.

The severe disease was indicated by the presence of a respiratory distress exhibiting tachypnea, respiratory retractions, and nasal flaring, or hypoxia (SPO2 less than 90%), or the intensive care unit admission, or respiratory failure or multiplicity, or septic shock, or involvement of more than 50% of the lungs in CT scans will be classified as severe. Those not meeting these criteria were placed in the non-severe or mild group(14).

3-Result:

A-Pls check for variables in the method and result part .

We appreciate your comments. We revised our manuscript based on your valuable comment.

B- in the first part of result pls note that variables in table 1 are demographic variables

We appreciate your comments. We revised our manuscript based on your valuable comment.

Table 1 shows the demographic characteristics of patients.

A total of 16 individuals (6.1%) in the mild disease group compared to 10 individuals (15.2%) in the severe group reported a percentage less than 5% of weight, which was statistically significant (P-value = 0.047). (Table 1)

Table 1: Determining and comparing demographic variables in two severe and mild groups of children with COVID-19 disease

demographic variables		Mild covid 19 cases	Severe covid 19 cases	P-value
age		55.78±46.19	64.84±65.82	0.270 *
Weight percentile	normal	212(80.3%)	47(71.2%)	0.047**
	<5	16(6.1%)	10(15.2%)	
	>95	36(13.6%)	9(13.6%)	
gender	Female	125(42.2%)	31(41.3%)	0.888**
	Male	(57.8%)171	(58.7%)44	
location	Rural	111(38.3%)	34(50%)	0.076**
	Urban	179(61.7%)	34(50%)	
comorbidity	no	257(85.7%)	58(77.3%)	0.078**
	yes	43(14.3%)	17(22.7%)	

*t-test

** chi-square test

C- Why the mean number of lymphocytes is higher in sever group ?

As you may know, we have just mentioned the quantitative results of lymphocytes. Therefore, the significant difference was only based on the number and not the percentage of lymphocytosis or lymphopenia.

4- Discussion: Pls discuss the differences of your results with other studies.

We tried to mention previous investigations in the discussion section after your previous great comment.

Our study presents demographic, clinical, and paraclinical aspects of hospitalized children with confirmed COVID-19 in Iran. The results of the present study showed that among the demographic findings, children with a weight percentile below 5% were more likely in the severe group and among the symptoms related to COVID-19, sleepiness and shortness of breath significantly were more common in the severe group than mild group. Also, among the clinical signs related to COVID-19, respiratory rate and heart rate were significantly higher in severe cases than in mild cases, and blood oxygen percentage was significantly lower in severe cases. In our study, lung involvement in X-rays was significantly more in severe cases. White blood cells, neutrophils, lymphocytes, glucose, BUN, creatinine, ALT, and AST were significantly higher in severe cases than in mild cases, and alkaline phosphatase was lower in severe cases than in mild cases.

Results revealed that patients with severe COVID-19 tend to be older, although statistically is not significant. In the study of Fahimzad et al., children with a younger age were more likely to suffer from severe COVID-19, $p = 0.02$ (15). The larger sample size in our study may enhance the effectiveness of the results, thereby increasing their reliability. Furthermore, the severity of the disease tends to be more pronounced in infants, while it escalates with age, particularly in adults. Although the precise pathogenic mechanisms of COVID-19 remain incompletely understood, it's evident that the disease inflicts organ damage due to the spike protein's strong affinity for the human angiotensin-converting enzyme 2 (ACE2) cell receptor, which is prominently expressed in organs like the lungs, heart, liver, kidneys, and brain. Generally, clinical severity and mortality rates of the disease are lower in children compared to adults, potentially attributed to the reduced presence of ACE2-expressing AT2 cells and lower ACE2 protein levels in children relative to adults (16, 17).

The frequency of male gender was higher in severe cases, urging increased attention to affected boys, although more studies in this field are necessary. Studies by Hayden et al. and Wang et al. have indicated increased mortality and morbidity associated with older age, male gender, cardiovascular diseases, diabetes, and smoking (18, 19). Williamson et al. found that older age and male gender are primary risk factors for severe outcomes in COVID-19. Many pre-existing conditions such as cardiovascular diseases, hypertension, diabetes, respiratory diseases, and cancer are associated with a higher risk of mortality (20).

The number of mild cases was higher in urban residents in the study. This result can be because people living in the city have access to health facilities and ease of reaching the hospital compared to people living in the village.

As previously mentioned, the S protein of the virus binds to the ACE2 receptor, facilitating entry into host cells alongside the transmembrane protease TMPRSS2. In individuals whose immune response is sufficiently robust, infection spread within the lower respiratory tract can be swiftly contained, resulting in either asymptomatic or mild illness. However, inadequate initial immune response allows unchecked viral replication, potentially leading to severe acute respiratory distress syndrome or systemic disease characterized by hyperinflammation, multiorgan failure, and prolonged recovery, often necessitating hospitalization and posing life-threatening risks. Thus, a thorough comprehension of COVID-19's pathogenesis is crucial for devising effective clinical management strategies. Addressing specific pathogenic mechanisms at various disease stages is imperative for mitigating severity and lowering morbidity and mortality rates associated with SARS-CoV-2 infection (21).

Regarding the importance of this novel virus, we tried to assess the symptoms of severe cases to have a concise prediction and rapid management. In our study, more severe cases reported fever, aligning with other studies. Notably, severe cases exhibited higher rates of respiratory symptoms such as shortness of breath. The study emphasized the correlation between sleepiness intensity and COVID-19 severity. In Fahimzad et al.'s study, shortness of breath was significantly higher in severe cases than in mild cases, which is consistent with our study (15). So, in cases of shortness of breath, the patient needs more special care. In the study of Wang et al., fatigue and lethargy were reported more in severe cases than in mild cases ($p<0.0001$) (19). This is consistent with our study in terms of reducing the level of consciousness. So, if the patient is sleepy, it is better to be under more care.

Vital signs and laboratory parameters differed significantly between severe and mild cases. Severe cases demonstrated lower oxygen levels, higher heart and respiratory rates, and abnormal chest X-rays, consistent with other

research. In the study of Babamahmoudi et al., high breathing rate, high heart rate, and lower blood oxygen percentage during hospitalization are related to increased mortality (7). Therefore, it is very important to determine the vital signs of the patient upon entering the hospital and it can predict the severity of the disease (22). In the study of Sediqi et al., patchier opacities were seen in the graph of severe cases of the disease than in mild cases(23).

COVID-19 has the potential to trigger severe acute respiratory distress syndrome (ARDS), potentially escalating to multiorgan failure. This progression is thought to be driven by the dysregulation of inflammation and the onset of cytokine storms. Given the pivotal role of inflammatory processes in severe cases, indicators like fever, leukocytosis, and C-reactive protein levels are acknowledged as predictors of severe illness. Additionally, a range of other biomarkers have been pinpointed as valuable prognostic tools for patients battling COVID-19 infection (24).

The results of this study showed that the frequency of white blood cells, neutrophils, lymphocytes, glucose, BUN, creatinine, ALT, and AST in the two investigated groups had statistically significant differences, so all these parameters in the severe group were more than the mild group. Wang's study also revealed significant differences in inflammatory factors, including white blood cell count, neutrophil percentage, lymphocyte percentage, and glucose, among mild and severe groups (19). Babamahmoudi's study found an association between increased creatinine, AST, ALT, CRP, decreased lymphocyte count, increased WBC count, and higher mortality rates (22).

5- Conclusion: Pls check sleep disturbances.

We appreciate your comments. We revised our manuscript based on your valuable comment.

Conclusion

Our results noted important points regarding demographic, clinical, and paraclinical findings in hospitalized children with COVID-19 which can shed light on this novel phenomenon. As sleepiness and shortness of breath significantly were more common in the severe group than mild group, the study recommended close monitoring of patients with these problems to prevent disease progression to a severe state. Regarding the emerging nature of COVID-19 and the importance of performing comprehensive investigations, further prospective studies are recommended to focus on larger samples from multiple centers to validate these findings.

Best Regards
Reviewer 2:
Dear Editor
The revised version of the manuscript has been amended substantially. Authors need to consider the following comments.
1- All of the decimal places/ digits should be written using point (dot) symbole as 2.5, not 2/5 in the tables.

We appreciate your comments. We revised our manuscript based on your valuable comment.

clinical symptoms		Severity of covid 19		P-value
		(%)Mild	(%)severe	
fever	no	42(19.4)	5(16.1)	0.553
	mild	140(64.8)	23(74.2)	
	severe	34(15.7)	3(9.7)	
shivering	no	(91.3)274	(96.0)72	0.176
	yes	(8.7)26	(4.0)3	
Body pain	no	(93.0)279	(96.0)72	0.342
	yes	(7.0)21	(4.0)3	
Sore throat	no	(92.3)277	(97.3)73	0.121
	yes	(7.7)23	(2.7)2	
Nasal discharge	no	(80.0)240	(85.3)64	0.292
	yes	(20.0)60	(14.7)11	
anosmia	no	(99.3)298	(100.0)75	0.999
	yes	(0.7)2	(0.5)2	

Dry cough	no	(69.7)209	48(64.0)	0.345
	yes	(30.3)91	(36.0)27	
Productive cough	no	(92.3)277	(93.3)70	0.768
	yes	(7.7)23	(6.7)5	
dizziness	no	(98.7)296	(98.7)74	0.999
	yes	(1.3)4	(1.3)1	
Sleepiness	No	(72.7)218	(60.0)45	0.032
	Yes	(27.3)82	(40.0)30	
Chest pain	No	(98.0)294	(98.7)74	0.703
	Yes	(2.0)6	(1.3)1	
Shortness of breath	No	(89.3)268	(58.7)44	0.001>
	Yes	(10.7)32	(41.3)31	
abdominal pain	No	(89.7)269	(94.7)71	0.183
	Yes	(10.3)31	(5.3)4	
Vomiting	No	(62.7)188	(69.3)52	0.282
	Yes	(37.3)112	(30.7)23	
diarrhea	No	(79.3)238	(84.0)63	0.364
	Yes	(20.7)62	(16.0)12	
Respiratory rate(per minute)		25(22-30)	35(25-46.5)	0.000
Pulse rate(per minute)		110(100-120)	120(100-140)	0.011
(%)O2 saturation		98(97-99)	92(88-98)	0.000
Systolic blood pressure(mm Hg)		95(90-100)	95(90-110)	0.095

Diastolic blood pressure(mmHg)	60(60-70)	60(60-68.75)	0.71

2- In the column's header of Table 2, please use % to avoid inserting the percentage in all of the cells.

We appreciate your comments. We revised our manuscript based on your valuable comment.

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Systolic blood pressure(mm Hg)	95(90-100)	95(90-110)	0.095
Diastolic blood pressure(mmHg)	60(60-70)	60(60-68.75)	0.71

3 Revision 2

1 comment · 29 Aug 2024

Associate Editor

ACCEPT 29 Aug 2024

Hi,
The authors have addressed the comments raised by the respected reviewers, so the article is approved.