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OPEN PEER REVIEW

# Investigation of the Clinical Laboratory Indexes in COVID-19 Patients with Ocular Symptoms in Iran: A Single-Center Experience

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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.

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

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## 1 Original submission

3 comments · 30 Jul 2021 – 18 Aug 2021

### Referee 1 Reviewer

MAJOR REVISION 30 Jul 2021

Dear author:
Thank you for submitting the article “Association of clinical laboratory indexes and ocular symptoms in COVID-19 patients”.
There are some notes:
Totally: English language editing is mandatory, and the findings should be arranged in a comprehensive and understandable manner.
Abstract: Please include the main laboratory parameters in the Material and Method part. Please check the keywords against MESH.
Introduction: In the sentence “These clinical symptoms are prevalent in SARS-CoV-2-infected patients and may create a complication in the treatment of ocular diseases”, how do the clinical symptoms create a complication in the treatment of ocular diseases?
Material and Method: Please omit the subtitles in this part. What is the age range of the cases? Please give the exact scientific definition of each ocular symptom, for example, epiphoria, itching, and photophobia. Please mention the ethical issues at the end of the Material and Method part. What is “The persent of oxygen saturation (SPO2)”? What was the setting of your laboratory, and how did you confirm the accuracy of the laboratory results? Why was the Mann Whitney test used for statistical analysis? Please consult with your statistics advisor.
Result: The results should be rewritten entirely. First, the number of cases and epidemiologic findings should be presented, and then the statistical findings should be reported in a comprehensive manner. Please arrange the results in a table.
Discussion: This section should be entirely rewritten. The author is recommended to review the literature about ocular findings of COVID-19.
Best regards

### Referee 2 Reviewer

MAJOR REVISION 31 Jul 2021

Thanks for your manuscript. There are some comments:
Abstract
-Needs some English revision. “Indices” is correct, not “indexes.” Association is better than correlation.
Introduction
-English revision is mandatory.
-In the introduction, you should include some other studies and explain the necessity of your investigation.
Material and Methods
-The time of your study should be mentioned.
-Replace correlation with association.
-Your sample size calculation should be mentioned.
Results
-Your results should be brief and comprehensive. The results section is too long.
-What are the frequency and percentage of ocular signs and symptoms?
-Your tables are too long. Please delete them and write your results briefly.
-You mentioned in the materials and methods part that the Mann-Whitney U test was used as a non-

parametric test. So, mean ± SD is meaningless, and you should report the median (IQR). In your tables, you reported mean ± SD.
Discussion
-In the first part of the discussion, you have to write your main results briefly and then compare them with other studies.
-Ocular involvement in TB is not relevant to your study. Please delete it.
-Some studies, such as that by Fang et al., are not related to your study. Please delete them. Overall, you have to compare your study with other relevant studies.
-Your discussion is weak. You should compare your results with those of others and name the probable causes of the differences.
-The limitations of your study should be mentioned.
-The conclusion has to be written in a maximum of 6 sentences.
Footnotes
-Funding support is not stated. Your grant number should be mentioned.
-Authors' contributions should be written.

## Associate Editor

MAJOR REVISION 18 Aug 2021

Your manuscript has now passed through the review stage and is ready for revision.

Editorial comments
To ensure the Editor and Reviewers will be able to recommend that your revised manuscript is accepted, please pay careful attention to each of the comments that have been pasted 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 comments.
2. Please highlight all the amendments in your manuscript.
3. Use continuous line numbering and page numbers in the next submission.
4. Your response in the cover letter should refer to page and line numbers.

Other shortcomings
First of all, how did you distinguish COVID-related ocular signs and symptoms from those associated with other differential diagnoses, such as concurrent drug adverse events or other systemic diseases?
Second, providing the time interval between the first COVID-19 symptoms and the onset of ocular manifestations is of utmost importance. Add more information in this regard (mean-time).
Change the title: "Investigation of the clinical laboratory indexes in COVID-19 patients with ocular symptoms, a single-center experience, Iran"
Depict the frequency of ocular signs and symptoms using a graph.
Compare the incidence of ocular signs and symptoms with the severity of COVID-19 phenotypes.

Thanks

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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.

***9.2.2021***
***To Dear Editor-in-chief***

Hi,
Following the review of our manuscript, we received your valuable comments. We performed our bests to satisfy you and dear reviewers. Please find our responses as below:

**To Dear Reviewer 1:**

At first, thank you for your valuable time expending for advice our manuscript. Please find our responses for your comments. We tried our bests for response.

1- Needs some English revision. Indices is correct not indexes. Association is better than correlation. Introduction.

**Answer:** Thank you for your comment. The English errors (e.g., grammatical and orthographical) were corrected in all sections of manuscript. Please find the changes in all sections of manuscript in yellow highlights.

3- In introduction you should bring some other studies and explain about the necessity of your investigation.

**Answer:** Thank you for your comment. Two other study were cited and described in introduction to explain the necessity of our investigation. Please find the changes in line49 to 51, page 3 in yellow highlights.

4- The time of your study should be mentioned.

**Answer:** Thank you for your comment. It was added in material and methods section. Please find the changes in line 59, page 3 in yellow highlights.

5- Replace association instead of correlation.

**Answer:** Thank you for your comment. It replaced. Please find the changes all sections of manuscript in yellow highlights.

6- Your sample size calculation should be mentioned.

**Answer:** Thank you for your comment. It was added in material and methods section. Please find the changes in line 63, page 4 in yellow highlights.

7- Your results should be brief and comprehensive. It is too long.

**Answer:** Thank you for your comment. The result section was re-writhed and some sections were merged. Now, it is comparative. Please find the changes in line 86, page 4 to line115, page5 in yellow highlights.

8- What is the frequency and percent of ocular signs and symptoms?

**Answer:** Thank you for your comment. It was added in first paragraph of result section. Please find the changes in line 87, page 4 to line93, page 5 in yellow highlights.

9- Your tables are too long. Please delete them and write your results briefly.

**Answer:** Thank you for your comment. All tables were merged in an informative table. Please find the changes in attached table.

10- You mentioned in materials and methods part that Mann-Whitney U test used as a non-parametric test. So, mean ± SD is meaningless and you should report median (IQR). In your Tables you reported mean ± SD.

**Answer:** Thank you for your comment. As a biostatistics adviser, it is not necessary to report Median (IQR) for the Mann–Whitney test. So, the reporting of Mean ± SD is not wrong. Also, please find the phrase mentioned below and its references to certify our response:

“A measure of the central tendencies of the two groups (means or medians; since the Mann–Whitney is an ordinal test, medians are usually recommended)

https://stats.stackexchange.com/questions/87403/how-do-you-report-a-mann-whitney-test

https://en.wikipedia.org/wiki/Mann%E2%80%93Whitney_U_test

11- At first part of discussion you have to write your main results briefly and then compare them with other studies.

**Answer:** Thank you for your comment. In this manuscript, we had a huge number of results. So, we added a brief report of our results in first paragraph of discussion in three lines. Complete descriptive results are separated in each paragraph of discussion. Please find the changes in line 120 to 123, page 6 in yellow highlights.

12- Ocular involvement in TB is not relevant to your study. Please delete it.

**Answer:** Thank you for your comment. It was deleted.

13- Some studies such as Fang et al. is not related to your study. Please delete it. In overall, you have to compare your study with relevant other studies. Your discussion is weak. You should compare your results with others and name the probable causes of their differences.

**Answer:** Thank you for your comment. The study of Fang et al. was deleted. Also, it should be noted that the correlation of ocular manifestations and clinical laboratory indexes are a novel approach in COVID-19. So, there is not many studies to comparing. All accessible publications are mentioned in manuscript.

15-Limitations of your study should be mentioned.

**Answer:** Thank you for your comment. It was added in material and methods section. Please find the changes in line 179 to 184, page 8 in yellow highlights.

16-Conclusion have to be written in maximum 6 sentences.

**Answer:** Thank you for your comment. It was added in last section. Please find the changes in line 186 to 190, page 8 in yellow highlights.

17-Funding support is not written. Your grant number should be mentioned.

**Answer:** There is no funding support or grant regarding this manuscript. Please find the changes in line 197 and 198, page 8 in yellow highlights.

18-Authors’ contributions should be written.

**Answer:** Thank you for your comment. It was added in last section. Please find the changes in line 200 to 201, page 8 in yellow highlights.

**To Dear Reviewer 2:**

At first, thank you for your valuable time expending for advice our manuscript. Please find our responses for your comments. We tried our bests for response.

19- The English edition is mandatory and finding should be arranged in a comprehensive and understandable manner.

**Answer:** Thank you for your comment. The English errors (e.g., grammatical and orthographical) were corrected in all sections of manuscript. Please find the changes all sections of manuscript in yellow highlights.

20- Plz bring main laboratory parameters in Material and Method Part.plz check the key words with MESH.
**Answer:** Thank you for your comment. Some important clinical laboratory indexes were added in abstract. Also, the keywords were double-checked and replaced with MeSH words. Please find the changes in line 17,18 and 33, page 2 in yellow highlights.

21- in the “These clinical symptoms are prevalent in SARS-CoV-2-infected patients and may create a complication in the treatment of ocular diseases” how the clinical symptoms create a complication in treatment of ocular disease.
**Answer:** Thank you for your comment. We correct it in revised version. Please find them in introduction. Please find the changes in line 49, page 3 in yellow highlights.

22- Plz omit the subtitles in this part. What is the age range of cases? Please give the exact scientific definition of each variable in ocular symptoms for example epiphoria, itching and photophobia.

**Answer:** Thank you for your comment. The age range of participants were added. Also, we believe that epiphoria, itching, photophobia, and other ocular manifestations are really routine words, in both medical terminology and even in colloquial English language.

23- Plz mention the ethics issues at the end of material and method part., what is “The persent of oxygen saturation (SPO2)”?

**Answer:** Thank you for your comment. All ethics, including inclusion and exclusion criteria, were added in material and method sections. Please find the changes in all sections of manuscript in yellow highlights.

24- what was the setting of your laboratory and how did you confirm the accuracy of laboratory results.?

**Answer:** Thank you for your comment. All clinical laboratory tests were performed in Ayatollah Rouhani Hosptial, department of Clinical laboratory and Pathology. So, the accuracy of laboratory results is

confirmed by technician experts, not just for patients but for this experiment. All accuracy conformations are based on QC and QA sets (Westgard rules).

25- Why Mann Whitney test used for statistical analysis, please consult with your statistics advisor.

**Answer:** Thank you for your comment. As a biostatistics advisement, the Mann-Whitney U test is suitable for this analysis, which is a popular nonparametric test to compare outcomes between two independent groups. So, there is no conflict for the application of this test in our experiment.

26- the result should be rewritten totally.

**Answer:** Thank you for your comment. The result section was re-writhed and some sections were merged. Now, it is comparative. Please find this section in yellow highlights. Please find the changes in line 86, page 4 to line115, page 5 in yellow highlights.

27- First the number of cases and epidemiologic findings should be written and then the statistical findings should be reported in a comprehensive manner. Plz arrange the results in a table.

**Answer:** Thank you for your comment. The epidemiologic findings were added in first section of results. The result section was re-writhed and some sections were merged. Now, it is comparative. also, all tables were merged in an informative table. Please find the changes in line 87, page 4 to line 92, page 4 in yellow highlights.

28-Should be totally rewritten. The author is recommended to review the literature about ocular findings of covid19.

**Answer:** Thank you for your comment**.** We added a brief report of our results in first paragraph of discussion in three lines. Complete descriptive results are separated in each paragraph of discussion. It should be noted that the correlation of ocular manifestations and clinical laboratory indexes are a novel approach in COVID-19. So, there is not many studies to comparing. All accessible publications are mentioned in manuscript. Please find the changes in line 120 to 123, page 6 in yellow highlights.

**To Dear Associated Editor:**

At first, thank you for your valuable time expending for advice our manuscript. Please find our responses for your comments. We tried our bests for response.

29- First of all, how did you exclude COVID-related ocular signs and symptoms from other differential diagnoses such as concurrent drug adverse events or other systemic diseases?

**Answer:** Thank you for your comment. The mentioned criteria were added in material and methods section as Inclusion and exclusion criteria. Please find the changes in line 65 to 69, page 4 in yellow highlights.

30- Second, providing time-interval between first COVID-19 symptoms and onset of ocular manifestations is an utmost important issue, add more information in this regard (mean-time).

**Answer:** Thank you for your comment. The time-interval was first day of hospitalization. Please find the changes in line 61 and 62, page 3 in yellow highlights.

31- Change title: "Investigation of the clinical laboratory indexes in COVID-19 patients with ocular symptoms, a single-center experience, Iran"

**Answer:** Thank you for your comment. It changed. Please find the changes in title page in yellow highlights.

32- Depict the frequency of ocular signs and symptoms using a graph.

**Answer:** Thank you for your comment. We added the frequencies at first paragraph of results section. Please find the changes in line 87, page 4 to line 93, page 5 in yellow highlights.

33- Compare the incidence of ocular signs and symptoms with the severity of COVID-19 phenotypes.

**Answer:** Thank you for your comment. Unfortunately, in time-interval the severity of COVID-19 phenotypes was missed, and we did not access to them at this moment.

## 2 Revision 1

3 comments · 1 Oct 2021 – 10 Nov 2021

### Referee 1 Reviewer

MINOR REVISION 1 Oct 2021

Dear author:
Thank you for your revision.
There are some notes.
Abstract: Please don't use etc. in the abstract. All the parameters you studied can be shown, or you can move them to the Material and method part. ESR does not have a serum level. It is not a measured parameter in blood.
Introduction:
In line 52, "In many cases, the paraclinical indexes indicate clinical symptoms (11, 12)" is not clear. Please explain further.
Material and Mehods: How was the diagnosis of COVID 19 confirmed (was it based on clinical symptoms or PCR)? How did you estimate P in the sample size formula?
Discussion:
Please check all the variables one by one and compare them with the literature. Please give the reasons for the increased parameters and ocular manifestations. An increase in procalcitonin and its relation to photophobia are not necessarily accompanied by a poor prognosis. Ocular redness can be seen in Kawasaki Disease Like Cases with Multiple Inflammatory Syndrome. Please check the literature. What were the results of reference No. 25?
Best Regards

### Referee 2 Reviewer

MINOR REVISION 6 Oct 2021

Thanks for your revision.
- Methods: The sample size calculation should be reported according to a reference, and the formula shouldn't be written. Please consult with your statistician. P, d, and α should be reported based on another study, with its reference.
- Your table is boring and should be deleted. Only the main results should be reported briefly.
- English revision is mandatory.

### Associate Editor

MINOR REVISION 10 Nov 2021

Dear authors
The manuscript's overall presentation improved after amendments; however, some correction is warranted.

What is the mean time to ocular manifestations after the first COVID-19 signs and symptoms in the studied cases?
Replace this part: "Also, various laboratory indexes, i.e., SpO2, RBC, Fe, TIBC, ESR, CRP, CPK, etc., were measured using standard laboratory methods. SPSS ver.25 was used for statistical analysis." with this: "Routine laboratory investigation was done according to the standard management in patients with COVID-19 infection".
Many words start with a capital letter within the text. Correct all (Epiphora, Procalcitonin, ...).

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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.

The authors did not provide a point-by-point response to the reviewers' comments in this round.

## 3 Revision 2

1 comment · 13 Dec 2021

### Associate Editor

MINOR REVISION 13 Dec 2021

Dear authors,
The manuscript's overall presentation improved after amendments. Please spell out all abbreviations in the abstract section.
Thanks

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.

**Revision letter**

**12.23.2021**

**Comment**: The manuscript's overall presentation improved after amendments, please spell out all abbreviations in the abstract section.
**Answer**: All abbreviations were spell out. Please find the highlights in revised manuscript.

## 4 Revision 3

0 comments

*No public comments in this round.*