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OPEN PEER REVIEW

Adrenal Insufficiency in Patients 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 · 28 May 2023

Associate Editor

MAJOR REVISION 28 May 2023

In this manuscript, the authors considered "Investigation of serum cortisol level and response to cosintropin test in covid 19 patients". This study addressed a challenging issue; however, the manuscript should be improved to make it more robust and suitable for publication. I invite the authors to revise the manuscript according to the following comments.

Title: The title should be rephrased: "Investigation of serum cortisol level and response to cosintropin test. . .." The correct term is cosyntropin test. What is meant by covid19 patients?

Abstract:
The objectives should be rewritten more concisely.
Introduction:
In this part, the scientific relationship between COVID-19, serum cortisol level, and ACTH response has not been investigated; it should be improved with a more valuable literature review.

Methods: In this part, only cortisol measurement and the ACTH test have been discussed. The characteristics of the patients, the timing of the test during hospitalization, and whether it was performed before or after glucocorticoid treatment were not described.
"Phase 2 of the disease based on SPO2 (88 %≤ SPO2≤93%)" is not sufficient to define this.
Results: In the first paragraph, this sentence should be rewritten: " Variable frequency of the sex of the patients is displayed. . .. . .. "
The amount of cortisol should be expressed quantitatively and given in the table.

It is not appropriate to confirm the diagnosis of adrenal insufficiency in a hospitalized patient by using the phrase "suspected of adrenal insufficiency." Has the researcher tested the patients again after discharge?
Line 245: What is the meaning of ($p > 0.005$)?
P-values should be rewritten in the correct format.
Table3: What is meant by general population? Did the researcher have a control group? (This is not mentioned.)
The tables should be rewritten.

Discussion: In this part, the results have been repeated.
The first lines, 264,265, should be omitted.
The authors should compare the results of their study with other studies and explain the reasons for the differences if they do not match.
This manuscript needs thorough English editing.

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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.

[Your Name]

[Your Affiliation]

Date: 23-06-2023

Dear Associate Editors,

Thank you for reviewing my paper titled "Investigation of serum cortisol level and Response to cosyntropin test in SARS-CoV-2". I appreciate your thoughtful comments, valuable suggestions, and constructive feedback. Your input has been instrumental in improving the quality of my work, and I am grateful for the opportunity to address your concerns.

Associate Editor 1:

Title: should be rephrased "Investigation of serum cortisol level and response to cosintropin test….." cosyntropin test is correct, What is the meaning of covid19 patients?

Thank you very much for your helpful comment. The title of the article has been modified based on your advice.

Abstract: Objectives should be rewritten in shorter than current.

The objectives have been revised more concisely, considering your valuable input.

Introduction: In this part, the scientific relationship between covid-19 and serum cortisol level , ACTH response has not been investigated; it should be improved with more valuable literature review.

We sincerely appreciate your valuable comment. In response to your input, we have incorporated the relevant literature on the association between COVID-19 infection and serum cortisol levels and the ACTH response by conducting an extensive review of texts. Furthermore, the introduction section underwent a significant revision, with the major changes indicated using corresponding colour markings.

Methods: In this part ,only cortisol measurement and ACTH test has been discussed , The characteristics of the patients and the time of the test in the hospital and whether it

was before or after glucocorticoid treatment were not written. "Phase 2 of the disease based on SPO2 (88 %≤ SPO2≤93%)" is not enough for definition of this.

The method section has already included information about the time of the test in the hospital and the state of not receiving corticosteroids. In addition, we have provided a more comprehensive explanation of the patient selection procedure, including a discussion of the rationale behind specific selection criteria. These specific items are highlighted in yellow for easy reference.

Results: In the first paragraph, this sentence should be rewrite" Variable frequency of the sex of the patients is displayed…….. "
The amount of cortisol should be expressed quantitatively and given in the table .

At the beginning of the second paragraph, the sentence has been rewritten and highlighted in blue, and the amount of cortisol expressed quantitatively in Table 1

It is not appropriate to confirm the diagnosis of adrenal insufficiency in a hospitalized patient by using the word suspected of adrenal insufficiency. Has the researcher tested the patients again after discharge?

After conducting baseline cortisol examinations, it was found that 31.7% of the patients were identified as suspected cases. Subsequently, these suspicious patients underwent cosyntropin testing, leading to a definitive diagnosis of adrenal insufficiency in 29.2%.

Importantly, based on Williams' reference, the diagnostic steps employed in our study have been visually presented as a flowchart in Figure 1. This flowchart outlines the sequential diagnosis process and can serve as a helpful visual reference.

These items are highlighted in light green.

Line 245:What is meaning of (p > 0.005)?

Pvalues should rewrite in correct forms.

We appreciate your attention to detail. The mentioned issue has been rectified in the second paragraph of the results section, and it is now highlighted in red to draw attention to the correction.

Table3 : What is meaning of general population? Has the researcher had control group?(not mentioned)
The tables should rewrite.

The manuscript has been revised regarding Williams. As a result, we classified the studied patients as critical, which led to eliminating all the tables that we initially considered normal populations. It is important to note that studies have shown higher baseline cortisol levels in patients with Covid-19 compared to the general population. Therefore, the patients were investigated according to the flowchart shown in Figure 1.

Discussion: In this part the results have been repeated.
The first lines 264,265 should omitted.

Thank you. This was considered.

The authors should compare the results of their study with other studies and explain the reasons for the differences if they do not match.

The results obtained from our study have been incorporated into the discussion section, along with several relevant articles. In cases where the results deviated from expectations, we thoroughly discussed the possible reasons behind these disparities.

This manuscript needs to well English editing.

We sincerely appreciate your constructive comment. The text of the article has been carefully edited to enhance its English language quality.

Associate Editor 2:

We sincerely appreciate your valuable comments, as they have played a significant role in enhancing the quality of the statistical results presented in our article. Your input has been instrumental in improving the overall strength of our research.

1. Please revise "equated patients with the general population and critical patients".

The manuscript has been revised regarding Williams. As a result, we classified the studied patients as critical. This led to eliminating all the tables that we initially considered a normal population. It is important to note that studies have shown higher baseline cortisol levels in patients with Covid-19 compared to the general population. Therefore, the patients were investigated according to the flowchart shown in Figure 1.

2. Please revise "higher than normal in patients who were considered equivalent to the general population".

As previously mentioned in your initial inquiry, patients from the normal population were excluded from the study.

3. Transfer the following in the results section "Our results also showed that there is a direct and significant relationship between baseline cortisol and 60-minute cortisol. Serum cortisol levels were not significantly lower than normal levels if considered equivalent to cortical patients".

This was done in the results section. The relevant text and its table are highlighted in dark yellow.

4. Report exact P-values in the abstract.

This item was added in the abstract and highlighted in red.

5. The sample size estimation is not acceptable.

The following text was added in the method section:

Due to the lack of similar studies at the time of the approval of this research and only a few case reports in the investigations conducted according to the following formula, we considered the initial sample size of 97 patients. But in the continuation of the work, due to the initial lack of cosyntropin ampoule and the significant drop of patients due to the recent receipt of corticosteroids, finally 60 patients were included in the study.

$$n = \frac{z^2_{1-\alpha/2} \times p(1-p)}{d^2}$$

(α=0.05, d=0.1 , p=0.5)

6. To compare Cortisol levels at baseline and the 60th minute repeated measurement was used? But the paired T-test is appropriate.

To compare the mean serum cortisol levels, a Wilcoxon test was conducted. Since no repeated measurements were available, the comparison was limited to the baseline cortisol level and the cortisol level measured after 1 hour, shown in Table 2.

7. Kruskal-Wallis tests were used to compare between two groups if the results were not normal? But Man-Whitney is appropriate.

You are right. We actually used the Mann-Whitney U test in the study. The Kruskal-Wallis test is commonly used to compare three or more independent groups when the data do not meet assumptions of normality. However, if we compare only two groups, the Mann-Whitney U test (also known as the Wilcoxon rank sum test) is more appropriate. The Mann-Whitney U test compares two independent groups when the data are not normally distributed. Therefore, the Mann-Whitney U test is more suited than the Kruskal-Wallis test.

8. To compare the average response to Cosyntropin tests in COVID-19 patients to normal amounts, paired sample T-tests were used!?

In the data analysis section, there was an error in which "t-test" was mistakenly written as " Wilcoxon signed-rank test." However, considering the limitation on the number of tables in the results section, this particular item has been removed from the revised version of the article.
Due to the abnormality of the base Cortisol serum level variable, Wilcoxon signed-rank test is used). The deleted table was as follows.

(Table- xxx)The average base Cortisol serum levels the critical patients

The average base Cortisol serum levels	Normal amount	p-value
31.75	33	0.230

9. Please revise "Chi 2 tests".

This value has been presented as a percentage to assess the prevalence of adrenal insufficiency within the study population. Additionally, the data analysis section of the article has been revised, with the corresponding modifications whitened in red color within the data analysis and results sections.

10. Variable frequency of the sex of the patients is displayed!?

The relevant variables from Tables 1 and 6 have been incorporated into the body of the article.

11. The appropriate descriptive statistics for non-parametric tests are median (IQR). Revise it in the results section.

Thank you for your valuable feedback on our paper. We appreciate your suggestion regarding the appropriate descriptive statistics for non-parametric tests. In response to your comment, we have revised the results section to include the median (IQR) as the descriptive statistic for the non-parametric data.

Specifically, we have updated Table 2 to include the median column for both baseline cortisol and 60-minute serum cortisol levels. Additionally, we have modified the text in the results section to reflect these changes. The revised paragraph now presents the median values alongside the mean, standard deviation, minimum, and maximum values.

12. Report exact P-values in the text and tables.

We greatly appreciate your valuable comment. Detailed reporting of all p-values can be found in the manuscript's abstract, results, and discussion sections.

13. Remove Table 1.

Thank you very much for your helpful comment. This was done.

14. The variable frequency of Base Cortisol serum levels is shown If we consider COVID-19 patients similar to the normal population!?

The manuscript has been revised regarding Williams. As a result, we classified the studied patients as critical, eliminating all the tables we initially considered normal populations. It is important to note that studies have shown higher baseline cortisol

levels in patients with Covid-19 compared to the general population. Therefore, the patients were investigated according to the flowchart shown in Figure 1.

15. Remove Tables 2-4.

Thank you for your feedback. In response to your comment, Tables 3 and 4 have been removed from the article. Furthermore, Table 2 has been modified based on the flowchart presented in Figure 1 and has been retained in the text of the paper as it is deemed necessary for the study.

16. What do you mean by P>0.005?

The result and discussion of P-values values have been accurately modified and reported in the introduction section.

17. Where are the results of correlation tests, repeated measurement test and Kruskal-Wallis test?

We actually used the Mann-Whitney U test in the study. The Kruskal-Wallis test is commonly used to compare three or more independent groups when the data do not meet assumptions of normality. However, if we compare only two groups, the Mann-Whitney U test (also known as the Wilcoxon rank sum test) is more appropriate. The Mann-Whitney U test is designed to compare two independent groups when the data are not normally distributed. Therefore, using the Mann-Whitney U test is more appropriate instead of the Kruskal-Wallis test.

18. Reported findings are not adequate.

The results section includes Numerous results in Tables 3 to 7. These results have also been thoroughly discussed in the corresponding sections.

2 Revision 1

1 comment · 30 Jul 2023

Associate Editor

ACCEPT 30 Jul 2023

In this manuscript, the authors considered "Investigation of serum cortisol level and response to cosintropin test in covid 19 patients".

The authors of the article have made many of the requested corrections, but I think the title of the article should also be revised, as I mentioned in the first review.

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.

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Dear Associate Editors, Thanks for reviewing my paper titled " Adrenal insufficiency in patients with SARS-CoV-2". I appreciate your thoughtful comments, valuable suggestions, and constructive feedback. Your input has been instrumental in improving the quality of my work, and I am grateful for the opportunity to address your concerns

The sample size calculation is wrong:

The following text was added in the method section:

> Since, at the time of conducting the research, we did not find a similar study to determine the sample size; therefore, based on the experimental sample of our community and with the following formula, the number 60 was calculated and obtained.

(α=0.05, d=0.1, p=0.19)

$$n=\frac{Z^2_{1-\frac{\alpha}{2}} \times p(1-p)}{d^2}=59 \quad 60$$

2. Please revise “paired T-test (Wilcoxon)”:

Unpaired samples were compared using Student's t-test or Mann-Whitney U test as required

3. The appropriate descriptive statistics for non-parametric tests are median (IQR). Revise it in the results section:

We appreciate your suggestion regarding the appropriate descriptive statistics for non-parametric tests. In response to your comment, we have revised the results section to include the median (IQR) as the descriptive statistic for the non-parametric data. we have modified the text in the results section to reflect these changes.

4. Report exact P-values in the text and tables:

We greatly appreciate your valuable comment. Detailed reporting of all p-values can be found in the manuscript's abstract, results, and discussion sections.

5. Remove Table 1:

Thank you very much for your helpful comment. This was done.

6. Remove Tables 2-5:

Thank you for your feedback. In response to your comment, Tables 2-5 have been removed from the article.

7. P=0.00 is not true. Report as <0.001:

The result and discussion of P-values values have been accurately modified and reported in the introduction section.

8. Where are the results of the correlation and Kruskal-Wallis test?

You are right. We actually used the Mann-Whitney U test in the study. The Kruskal-Wallis test is commonly used to compare three or more independent groups when the data do not meet assumptions of normality. However, if we compare only two groups, the Mann-Whitney U test compares two independent groups when the data are not normally distributed.

9. Reported findings are not adequate.

Following your valuable suggestions, we proceeded to extract additional outcomes and results and subsequently documented them in accordance with Table 1. we incorporated these findings into the method, discussion, and results sections as appropriate.

Associate Editor 2:

The authors in this manuscript considered "Investigation of serum cortisol level and response to cosintropin test in covid 19 patients

The authors of the article have corrected many of the desired points... but I think the title of the article should also be revised, which I mentioned in the first review:

I greatly appreciate your invaluable guidance, which has led to the modification of the article's title as well. Your input has been truly valuable

3 Revision 2

0 comments

No public comments in this round.

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.

Associate Editor 1:
*In the sample size calculation, d must be 0.1*p=0.02, so you can’t justify the sample size using the current information:*

Dear Associate Editor, Thanks for reviewing my paper titled " Adrenal insufficiency in patients with SARS-CoV-2". I appreciate your thoughtful comments, valuable suggestions, and constructive feedback. Your input has been instrumental in improving the quality of my work. It is necessary to provide the following explanations regarding the calculation of the sample size. At the outset of our work, given that no similar articles were found based on the conducted investigations, and studies were limited to only a few case reports, we decided to examine patients through a census at a specific time. Due to the fact that the majority of patients had received corticosteroids during outpatient treatment, we couldn't include them in the study according to the exit criteria. Additionally, as the study progressed, in line with the new national guidelines, dexamethasone was introduced to improve pulmonary function in both outpatient and inpatient treatments for COVID-19 patients. Therefore, we terminated the study of patients because continuation did not provide additional benefit. This information was presented in the initial draft. Subsequently, based on the valuable feedback from the esteemed reviewer for improving the calculation method, we introduced the sample size formula and performed the calculations based on the reference provided below[1]. In the end, we were able to assess 60 patients within a three-month period who met the specified entry and exit criteria among all hospitalized patients with a confirmed diagnosis of COVID-19. We hope that the above reasons clarify the calculation of this number as the sample size in our study. Thank you very much for your attention.

1. Pourhoseingholi, M.A., M. Vahedi, and M. Rahimzadeh, Sample size calculation in medical studies. Gastroenterology and Hepatology from bed to bench, 2013. **6**(1): p. 14.

4 Revision 3

0 comments

No public comments in this round.