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OPEN PEER REVIEW

Investigation of the Effectiveness of Tocilizumab on COVID-19 Patients: A Retrospective Study

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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 · 5 Sep 2024 – 7 Sep 2024

Samaneh Naeimi Reviewer

MAJOR REVISION 5 Sep 2024

Greetings and respect
The following comments are provided to improve the quality of your article:

1) The time period of the fifth wave of the corona pandemic should be mentioned in the text of the article.
2) In the abstract, it is mentioned that "and the chi-square test was insignificant (p-value=0.64). Please mention that the chi-square test was not significant for the comparison of which parameters and in which groups?"
3) The translation of the article generally does not read naturally and needs to be re-evaluated.
4) Greater precision is needed when citing references so that each sentence has a specific reference. In paragraphs with several references grouped together at the end, it should be specified which reference supports each sentence.
This issue can be seen throughout the text of the article.
5) In the study design section, it is mentioned that "from among patients admitted to the ICU with severe COVID-19 infections who tested positive for SARS-CoV-2"
In this section, it should be mentioned how much time had elapsed since the participants tested positive.

6) The flow chart of the study procedure should display the breakdown of the number of participants, the number of people excluded based on the exit criteria, the number of people who died in each group, and other details in one chart.

7) The exclusion criteria are not the same as the entry criteria, and many confounding variables are not included in this study. The respected research team is requested to mention other ways of controlling confounding variables in this study with the help of other similar studies.

8) In the results section, the underlying diseases of the participants are not explained.
9) It is mentioned in the results section that "
The frequency of intubated patients was 3.5% in the TCZ group and 5.3% in the control group and no significant relationship was found in the two groups (P-value = 0.64). " Add a reference to table one in the text. References to the tables should be reviewed throughout the text.
10) In the results section, in addition to the percentage, the number of people who died in each group should also be mentioned and shown in the diagram.
11) In the results section, it is written that ". No significant relation was noted in these two groups." Please mention the p-value.

Referee 1 Reviewer

REJECT 7 Sep 2024

Greetings and respect
The title of the received article is repetitive and has been repeated a lot in past studies, so, in my opinion, it is not suitable for publication.

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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.

Dear editor in chief;

Once again, we appreciate your kindness in considering our article. We read the reviewer new comments and responded to them carefully. We hope that the reviewer will be satisfied with our answers to the questions.

Reviewers' Comments:

Reviewer 1:

Dear Professor

The topic of the proposed work is interesting but it should be taken into account some considerations and modifications, that could improve the quality of the research, in agreement with the aim and the prestige of Journal.

1. The manuscript requires revision for proper English. Furthermore, some sentences are not properly phrased. The English language must be corrected and improved by a native speaker. Please check your manuscript thoroughly and carefully to refine the language. There are some grammar and spelling mistakes in the paper, please correct them carefully.

A: We revised it.

Reviewer 2:
Greetings and respect
The following comments were mentioned to improve the quality of your article:
1) The time period of the fifth wave of the corona pandemic should be mentioned in the text of the article.

A: We revised it to (Investigation the Effectiveness of Tocilizumab on COVID-19 Patients; a Retrospective Study)**.**

2) In the abstract, it is mentioned that "and the chi-square test was insignificant (p-value=0.64). Please mention that the chi-square test was not significant for the comparison of which parameters and in which groups?".

A: The rate of intubation was observed to be 3.5% in the TCZ group compared to 5.3% in the control group, with no significant association detected between the two groups (p-value =0.64).

3) The translation of the article is generally not native and needs to be re-evaluated.

A: We revised it.

4) In the reference writing of the sentences, more precision should be used so that each sentence has a specific reference and in the paragraph at the end of which you have put several references together, it should be specified which reference each sentence had.
This issue can be seen in the entire text of the article.

A: We revised it.

5) In the design part of the study, it is mentioned that "from among patients admitted to the ICU with severe COVID-19 infections who tested positive for SARS-CoV-2"
In this section, it should be mentioned how much time has passed since the participants tested positive.
A: As mentioned in the method, all patients suspected of being diagnosed with COVID-19 infection were tested for COVID-19 upon admission and had a positive result were included in the study.

6) The flow chart of the working method in terms of dividing the number of participants, the number of people excluded based on the exit criteria, the number of people who died in each group and other details should be displayed in one chart.

A: we added it.

7) The exclusion criteria are not the same as the entry criteria, and many confounding variables are not included in this study. The respected research team is requested to mention other ways of controlling confounding variables in this study with the help of other similar studies.

A: Based on the provided inclusion criteria, the exclusion criteria for the study include the following: unvaccinated Patients, non-severe COVID-19 cases (patients diagnosed with mild

or moderate COVID-19 infections, as they do not meet the severity criteria), delayed treatment (patients who did not receive treatment within the first 24 hours of hospitalization), not transferred to ICU, underlying health conditions that could independently affect outcomes (e.g., terminal illnesses, end-stage organ failure), current participation in another clinical trial, patients below 18 years of age, pregnancy or lactation, inability to comply, historical medical conditions (any history of severe allergic reactions to vaccines or treatments used in the study).

8) In the results section, the underlying diseases of the participants are not explained.

A: we revised it for both the table and text.

9) It is mentioned in the results section that "The frequency of intubated patients was 3.5% in the TCZ group and 5.3% in the control group and no significant relationship was found in the two groups (P-value = 0.64). "Write in the text to refer to table one. In all the text, the references to the tables should be reviewed.
A: We revised them.

10) In the results section, in addition to the percentage, the number of people who died in each group should also be mentioned and shown in the diagram.
A: We revised it to (The frequency distribution of mortality was 47.4% (27 patients) in the TCZ group and 56.1% (32 patients) in the control group. No significant relation was noted in these two groups. In addition, the findings showed no difference between the distribution of the frequency of mortality in the two studied groups in patients under 60 years old (P-value = 0.8) (13 patients in TCZ group and 14 patients in control group). Although, in patients ≥ 60 years, the mortality rate was higher in the control group (19 patients) than in the TCZ group (13 patients)).

11) In the results section, it is written that ". No significant relation was noted in these two groups." Please mention the P value.
A: we added the p-value

Reviewer 3:
Greetings and respect
The title of the received article is repetitive and has been repeated a lot in past studies, so in my opinion it is not suitable for publication.

A: This study is considered suitable for publication for several reasons: Tocilizumab, an IL-6 inhibitor, has been explored as a treatment for severe COVID-19. Given the pandemic's global impact, studies evaluating potential treatments' effectiveness are timely and significant. Limited data or conflicting results regarding Tocilizumab's efficacy in COVID-19 patients exist. This study addresses existing gaps in the literature. Retrospective studies generally can provide valuable insights. A substantial number of patients enhance the validity of its findings and allow for more generalizable conclusions. Findings from the study could directly inform clinical practice and guidelines for treating COVID-19 patients, influencing treatment protocols and improving patient outcomes. Positive or negative findings regarding Tocilizumab’s effectiveness could significantly contribute to clinical understanding and management of COVID-19, making it a worthwhile addition to scientific literature. Furthermore, acknowledging the importance of the impact of TCZ in the timely treatment and outcome prediction for COVID-19 patients may aid healthcare authorities in their preparedness for future pandemics or unavoidable global crises.

Reviewer 4:
Dear Editor,
Thank you for sending me the manuscript titled “Investigation of Tocilizumab Efficacy on COVID-19 Patients during the Fifth Wave of the Pandemic; a Retrospective Study in North of Iran”.
After reading and analyzing the manuscript, some comments are provided to improve it.
First, I congratulate you on doing such a study and I hope you can provide better work by editing it.
1. Considering that the effectiveness of various cases of COVID-19 is mentioned in various articles, it is better to mention the effectiveness of this drug in the treatment of COVID-19 in the title according to the purpose of your study.

A: We revised it to (Investigation the Effectiveness of Tocilizumab on COVID-19 Patients; a Retrospective Study)**.**

2. I suggested deleting the name of the city and country in title. You can add these in the method of the abstract.

A: We revised it to (Investigation the Effectiveness of Tocilizumab on COVID-19 Patients; a Retrospective Study), and we add these in the method of the abstract.

3. Please check your keywords with Mesh.

A: We revised it **(**Keywords: Tocilizumab, COVID-19 pandemic, COVID-19 mortality rate, Interleukin-6 family).

4. In data collection, in Inclusion and Exclusion Criteria and matching the two groups, you did not pay attention to variables such as age, gender and the presence of underlying disease and etc., which can be effective in the mortality rate. Confounding variables should be identified so as not to cause problems in the process of results and comparison of two groups. Therefore, both groups should be matched in terms of variables that affect the final outcome (here, treatment and mortality). In table 1 and 2, you mentioned the comparison of variables in both groups, but in this part you should mention matching and write more explanations.

A: This type of experimental design requires fewer participants, the results may also be more accurate and the experiment may give more informed results. In this study, to achieve more accurate results by reducing the sampling error, we used group matching to match two groups based on the confounding variables of age and underlying diseases, the results of which are shown in the text. (In group matching, it is expected that the percentage of presence of underlying diseases in two groups will be completely similar to qualitative variables. Nevertheless, due to the small number of eligible patients at the time of the study, since this study was conducted in one center, we could not choose exactly the same amount of presence of underlying diseases in patients in the two groups. However, as you can see, there is no significant difference between the two groups in terms of underlying diseases.)

5. In ethics approval, please refer to the version of the “Declaration of Helsinki” that you used.

A: This research adhered to the principles outlined in the Declaration of Helsinki. Approval for the study was granted by the ethical committee at Golestan University of Medical Sciences under ethic number IR.GOUMS.REC.1401.447.

6. In discussion, there is no need to mention the results again in the first paragraph. Just point out the main results and discuss them.
Also, paragraph 5 is not really needed. This information is more useful in the introduction.
I think, you need more integrity in discussion. Make your writing coherent and avoid overwriting.

A: We revised them.

7. In references, some items are bolded and italicized. Check all the references based on the format of the journal.

A: We corrected all the references.

Please highlight all the amends in your manuscript or indicate them by using tracked changes.

Reviewer 5:
minor revision.
A: we answered all the questions and revised them all.

Best regards

2 Revision 1

1 comment · 28 Sep 2024

Samaneh Naeimi Reviewer

ACCEPT 28 Sep 2024

Greetings and respect
The comments provided by the reviewers have been addressed, and the article is acceptable.