OPEN PEER REVIEW

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Peer Review

Journal of Kermanshah University of Medical Sciences
Article DOI: https://doi.org/10.5812/jkums-126623
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Peer Review Report for "The Effect of Recombinant Erythropoietin on the Levels of Hemoglobin, Mean Corpuscular Volume, LDH, and Length of Stay at the Hospital in COVID-19 Patients"

Author(s): HamidReza Samimagham, Mehdi Hassani Azad, Dariush Hooshyar, Maryam Haddad, Mohsen Arabi, Mitra KazemiJahromi

Review Timeline:

Submit Date:	12 Apr 2022
Revised Date:	7 Jun 2022
Accepted Date:	14 Jun 2022

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Alireza Janbakhsh

Editor-in-chief, Journal of Kermanshah University of Medical Sciences

Dear Dr. Janbakhsh,

Thank you very much for your email dated 25-Apr-2022 regarding the second revision of our manuscript entitled "**Evaluation of the effect of recombinant erythropoietin on the improvement of COVID-19 patients** (**Manuscript ID: 126623)** and the opportunity to revise and resubmit the manuscript. We have complied with all reviewers' comments and answered each critique and comment separately, and hope that the manuscript is now suitable for publication in the **Journal of Kermanshah University of Medical Sciences**. Herewith, a revised version of the MS with a point-by-point response (R) to each comment (C) and all changes highlighted.

We are looking forward to hearing from you at your earliest convenience.

Sincerely,

Mitra KazemiJahromi, MD

Endocrinology and Metabolism Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
Phone: +989177912820
Email: mitra.kazemijahromi@gmail.com

Response (R) to reviewer comments (C)

Reviewer #1

Please consider the below comments and response them with address.

R: Thank you for your valuable critical comments. We have tried to revise and modify the content of the Manuscript appropriately based on your comments.

C1: Please edit the texts for typo and grammatical errors.

R: The manuscript has been edited for proper English language, grammar, punctuation, spelling, and overall style by one highly qualified subject-expert native English-speaking editor.

C2: Please reduce the abstract word counts less than 250 words. There is some of the unnecessary details in method section of the abstract for example.

R: Agreed. We have summarized the **Abstract section** and removed the unnecessary details from this section. The number of words in the **Abstract section** is now **238 words**.

C3: Please edit the references: 1- refs should be on the style of the briefland voncover. 2- the refs should be in English

R: Agreed. According to your comment, we have modified the **References list** style (Vancouver style) and its language (English Language)

C4: There is many un-referenced sentences in the introduction. Please edit them and add related refs

R: Thank you for your valuable comment. We have provided the proper related references for the "**Introduction Section**" contents**.**

C5: The introduction is very short. Please explain more in novelty, the gap with previous studies, etc.

R: Agreed. We revised and modified the **Introduction** section, focusing on the results of previous studies and the gap in knowledge on this topic. We also tried to provide an appropriate reference for the content of the **Introduction** section. The changes made in the **Introduction** section were highlighted **as follows:**

Page 2, Lines 27-34: "*The range of clinical spectrum of COVID-19 is variable from asymptomatic to fatal pneumonia (2). According to the severity of symptoms, COVID-19 has been classified into four levels, including mild, moderate, severe, and critical (3). The severe and critical levels of COVID-19 are characterized by various criteria, including dyspnea, oxygen saturation less than 93% in ambient air, respiratory system dysfunction, septic shock, and multiple organ abnormalities (3); therefore, the use of immediate and effective treatments to increase the immune response and strengthen the respiratory system of patients with severe or critical levels of COVID-19 is very vital to save its life (4)."*

Pages 2-3, Lines 47-57: "*In a brief review, Ehrenreich et al. have introduced erythropoietin as a potentially effective medication for relieving the major problems of severely affected COVID-19 patients (12). Also, Fishbane et al. reported that using erythropoiesis-stimulating agents (ESAs) treatment in hospitalized COVID-19 patients who have anemia may be a good idea, but in most cases, the efficacy of ESAs can be limited due to inflammation, so more research is needed to address the possible efficacy of these agents in these patients (13). Furthermore, in another study, it has been reported that antiviral treatment along with recombinant human erythropoietin may reduce respiratory distress syndrome and confront the severe acute respiratory syndrome in patients with COVID-19, however, it suggested that more well-organized clinical trials be conducted to assess the potential clinical benefits of erythropoietin with considering the possible its adverse effects in COVID-19 patients (14)."*

Page 3, and Lines 58-65: "*Despite the potential positive effect of ESAs on improving respiratory performance indicators based on the results of limited studies, there is still no sufficient and remarkable evidence based on relevant clinical trials on the significant efficacy of ESAs in critically ill COVID-19 patients in different populations. Also, the interventional studies investigating the possibility of erythropoietin side effects (such as increasing the patients' prothrombotic status and embolism) in COVID-19 patients are not yet convincing. Therefore, in the current study, we aimed to assess the immunity-induction and effectiveness of recombinant erythropoietin for patients with COVID-19 in a randomized two-armed study."*

C6: Please use the "participants" instead of "sample or subject"

R: We have used the term "participants" instead of "sample or subject" throughout the Manuscript.

C7: How did you have 20 participants? Please explain with reference

R: Thank you for your valuable comment. A structured summary of a study protocol for this randomized controlled trial has been published (**Ref***), which indicates a clear explanation of Trial registration, the study's sample size, randomization, blinding, outcomes measurements, and other protocol section of the study. It is worth mentioning that the sample size of the current study was small because of the multiplicity of exclusion criteria that had to be considered to avoid the side effects of erythropoietin and the possible hazards associated with its administration. So, we used the Census technique as a sampling method to select participants in the current study. We mentioned this limitation in the Manuscript **as follows:**

Page 9, Lines 193-195: *"This study was limited by the small sample size due to the multiplicity of exclusion criteria that had to be considered to avoid the side effects of erythropoietin and the possible hazards associated with its administration."*

Ref*: Samimagham HR, Azad MH, Hooshyar D, Haddad M, Arabi M, KazemiJahromi M. Evaluation of the efficacy and safety of recombinant erythropoietin on the improvement of hospitalised COVID-19 patients: A structured summary of a study protocol for a randomised controlled trial. Trials. 2021; 22(1):435

C8: Why did you use the Mann-Whitney U and Wilcoxon?

R: Thank you for your valuable comment. It is worth mentioning that, considering that the sample size of the current study is small (less than 30 individuals), nonparametric tests were used for study analysis. The Mann-Whitney U test was run to compare the quantitative data between the two groups, and the Wilcoxon test was performed to compare the quantitative data pre-and post-treatment. We have revised the "**Statistical analysis**" section **as follows:**

Page 5, Lines 98-104: *"The data were analyzed in SPSS 26. Baseline characteristics of subjects were expressed as mean ± SD continuous variables and percentage for qualitative variables. Considering that the sample size of the current study was small, nonparametric tests were used for our study analysis. The Mann-Whitney U test was run to compare the quantitative data between the two groups, and the Wilcoxon test was performed to compare the quantitative data pre-and post-treatment. The percentage of gender distribution between intervention and control groups was compared using Chi-square test. P-values <0.05 were considered statistically significant. "*

C9: Are the two study groups similar? Which statistical method did you use to examine the similarity of the two groups?

R: Thank you for your critical comment. In this study, we tried to select participants for the current study by considering different and multiple inclusion and exclusion criteria, who are similar in both groups in terms of possible effective characteristics on the study results, including confounding variables. In fact, in the current study, we controlled the possible effects of confounding factors in the design phase of the study (protocol of study), and so there was no need to control these confounding variables in the statistical analysis stage. The inclusion and exclusion criteria of our study are **as follows:**

Page 4, Lines 71-81: *"All patients (n=20 participants) with a definitive diagnosis of COVID-19 visiting Shahid Mohammadi Hospital (Bandar-e Abbas, Iran) with hemoglobin of ≥ 9 and having at least one severe COVID-19 symptom/sign (tachypnea: respiration rate > 30 per minute; hypoxemia: oxygen saturation ≤93; arterial oxygen partial pressure ratio ≤ 300; pulmonary infiltration: ≥50% of the pulmonary field in 24-48 hours; progressive lymphocytopenia, LDH>245 U/I, CRP>100) and lacking the exclusion criteria (a history of coagulation disorders, thrombosis, deep vein thrombosis, chronic pulmonary disease, diabetes mellitus, immunodeficiency, end-stage renal disease, hepatic disease, taking contraceptives, systolic blood pressure > 160 mmHg, diastolic blood pressure > 90 mmHg, age > 65 years, erythropoietin > 500, history of myocardial infarction or unstable angina, and a history of malignancies) were included"*

C10: Dear, you should add tables for your results included the 1- tables for demographic details, 2- table for compare the two groups for variables, 3- table for Mann Whitney, 4- table for Wilcoxon

R: Agreed. We have designed three tables for the presentation of the results of the study **as follows:**

Table 1. The characteristics of participants based on Intervention group and control group classification

Variable	Intervention group (n=10)	Control group (n=10)	P-Value*
Age (years), Mean ± SD	53.4 ± 11.7	52.9 ± 12.2	0.700
Sex, %			0.210
Men	60 %	70 %	
Women	40 %	30 %	

*P-value was determined using the Mann-Whitney U test.

Table 2. The change in hemoglobin and MCV levels of patients in the intervention group and the control group during the period of study

Nutritional variables	The study groups		P-Value [a]
	Intervention (n=10)	Control (n=10)	
	Mean± SD	Mean± SD	
Hemoglobin level (mg/dl)			**0.04**
Before	9.0 ± 0.8	9.0 ± 0.8	
After	10.1 ± 1.1	8.0 ± 0.7	
P-Value [b]	0.001	0.002	
MCV (fl)			
Before	73.0 ± 11.1	68.0 ± 8.0	0.017
After	73.0 ± 10.5	57.0 ± 6.0	
P-Value [b]	0.600	0.002	

Data are presented as mean ± standard deviation.
[a] Between-group P-value was determined using the Mann-Whitney U test.
[b] Within-group P-value was determined using the Wilcoxon test

Table 3. The change in mean length of stay at the hospital and LDH levels of participants based on Intervention and control groups during the period of study

Variable	Intervention group (n=10)	Control group (n=10)	P-Value*
length of stay at the hospital (day)	6 ± 2	9 ± 4	0.001
LDH level (u/l)	503 ± 264	725 ± 320	0.017

Data are presented as mean ± SD
*P-value was determined using the Mann-Whitney U test.

C11: You should add the below information before references: Funding, Data availability, Consent for publication, Authors' contributions, Competing interests, Ethical approval, and Acknowledgement

R: Thank you for your valuable comment. We have provided information for Funding, Data availability, Consent for publication, Authors' contributions, Competing interests, Ethical approval, and Acknowledgement in the Manuscript before the Reference list section on **Pages 9-10, Lines 199-223 as follows:**

"Ethics approval and consent to participate: *All participants filled out written informed consent. This study was conducted in conformance with good clinical practice standards and*

was performed according to the Declaration of Helsinki 1975, as subsequent amendments. Also, this study was approved by the Research Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.13 99.165) and registered in the Iranian Registry of Clinical Trials (IRCT20200509047364N1).

Consent for publication: *Not applicable.*

Availability of data and material: *The datasets generated and analyzed during the current study are not publicly available due to the Hormozgan University of Medical Sciences policies, but are available from the corresponding author on reasonable request.*

Competing interests: *The authors declared there is no conflict of interest.*

Funding: *The current research was funded by the Hormozgan University of Medical Sciences, Bandar-e-Abbas, Iran.*

Authors' contributions: *HR.S and MH.A: conceptualized and designed the study. HR.S, D.H, and M.KJ: drafted the initial manuscript; M.H and M.A: analyzed and interpreted the data; M.KJ: supervised the project; all authors have read and approved the final version of the manuscript.*

Acknowledgments: *We claim our appreciation to the Shahid Mohammadi Hospital participants for their generous cooperation and thank the Hormozgan University of Medical Sciences staff for their precious help.***"**

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Revision (1)

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Revision (2)

Reply to Reviewers

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You can read the authors' responses to the reviewers' comments in the next page.

Alireza Janbakhsh

Editor-in-chief, Journal of Kermanshah University of Medical Sciences

Dear Dr. Janbakhsh,

Thank you very much for your email dated 16-May-2022 regarding the second revision of our manuscript entitled "**The effect of recombinant erythropoietin on the levels of hemoglobin, mean corpuscular volume, LDH, and length of stay at the hospital in COVID-19 patients** (**Manuscript ID: 126623)** and the opportunity to revise and resubmit the manuscript. We have complied with all reviewers' comments and answered each critique and comment separately, and hope that the manuscript is now suitable for publication in the **Journal of Kermanshah University of Medical Sciences**. Herewith, a revised version of the MS with a point-by-point response (R) to each comment (C) and all changes highlighted.

We are looking forward to hearing from you at your earliest convenience.

Sincerely,

Mitra KazemiJahromi, MD

Endocrinology and Metabolism Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
Phone: +989177912820
Email: mitra.kazemijahromi@gmail.com

Response (R) to reviewer comments (C)

Reviewer #1

C1: You can reduce the word count more.

R: Agreed. We have summarized the **Abstract section** and removed the unnecessary details from this section as much as possible. Now the words number of the Abstract section is less than 200 words.

C2: You should use the statistical test to confirm the similarity between two groups. Such as chi-square/ Pearson, Spearman, etc. Please advise with statistical expert. You add some explain in table 1 but this is limited. Please tell the name of the test, please explain the reason for use of this test, and please add more variables if possible. If not possible please tell the reason.

R: Thank you for your critical comment. It is necessary to explain that the data of variables related to participants' general characteristics in two groups (except age and sex), including body mass index, socio-economic status, physical activity, and smoking, have not been measured or collected. Indeed, given that these variables were not potentially strong confounders to influence our results (the effect of erythropoietin intake on length of stay in the hospital and paraclinical measurements in patients with COVID-19), to save time and money, as well as the lack of suitable conditions for COVID-19 patients to cooperate in obtaining a lot of information about different variables, these measurements have not been performed. This limitation has been added to the Manuscript **as follows:**

Page 9, Lines 192-195: *"Also, in the current study, the information on some characteristics of participants, including body mass index, socioeconomic status, physical activity and smoking, have not been determined, which could allow for more analysis and stronger interpretation of the results."*

C3: Its OK, but please see the before comment. In addition, some terms in tables should be changed exp: table 2: baseline should change to before (please see tables in manuscript file

R: Thank you for your critical comment. As we explained in answer to the previous comment, data on some variables related to participants' general characteristics in two groups (except age and sex), such as body mass index, socioeconomic status, physical activity, and smoking, have not been measured or collected. Given that these variables were not potentially strong confounders to influence our results (the effect of erythropoietin intake on length of stay in the hospital and paraclinical measurements in patients with COVID-19), to save time and money, as well as the lack of suitable conditions for COVID-19 patients to cooperate in obtaining a lot of information about different variables, these measurements have not been performed. This limitation has been added to the Manuscript on **Page 9, Lines 192-195.** We have also revised briefly **Table 2.**

C4: there is a wrong in title. If you only examine the length of stay and LDH so please change the title in same. The term of "Improvement" has extend meaning so please change the title.

R: Agreed. We have revised the **Title of the Manuscript as follows:**

Title of Manuscript: "*The effect of recombinant erythropoietin on the levels of hemoglobin, mean corpuscular volume, LDH, and length of stay at the hospital in COVID-19 patients"*

OPEN PEER REVIEW

Revision (2)