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OPEN PEER REVIEW

Investigating the Effect of Expiratory Time Constant on Outcome in Intubated Patients with Acute Respiratory Failure Caused by COVID-19 in Critical Care Unit: A Research 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

3 comments · 30 Sep 2021 – 17 Oct 2021

Referee 1 Reviewer

MAJOR REVISION 30 Sep 2021

There were the following problems with the method:
1- Determine the severity of acute respiratory failure in patients (mild, moderate, and severe).
2- Calculate the patient's prognosis based on the APACHE score.
3- Calculate organ failure based on the SOFA score.
4- Determine the level of respiratory support in patients (Full support, Partial support, Spont.).
5- Explain more about the method of calculating compliance and resistance.
6- More suggested references need to be included, and the references should be updated.

Ata Mahmoodpoor Reviewer

REJECT 9 Oct 2021

I read the interesting manuscript about the relationship between the time constant and respiratory mechanical indices in patients with respiratory failure due to COVID-19, and the following are my recommendations:
1-The type of study should be defined in the title.
2-The keywords are not based on the MeSH database.
3-What was the formula for the sample size calculation in the study?
4-The exclusion criteria are not appropriate for the study.
5-The methodology of the study should be revised and completed.
6-Sentences related to the time constant should be transferred from the methods to the introduction.
7-How did the authors evaluate and eliminate the effects of confounding factors on the study outcomes?
8-What was the new finding of this study compared to previous studies in the field?
9-The discussion should be revised and improved based on the study results and comparisons with previous studies.
10-The text should be revised by a native English speaker.

Editor-in-Chief

MAJOR REVISION 17 Oct 2021

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.

Manuscript number: 119572

Manuscript title: Investigating the effect of expiratory time constant on outcome in intubated patients with acute respiratory failure caused by COVID-19 in critical care unit

Dear Editor-in-chief, Prof. Farnad Imani and reviewers

Our team appreciates the editor and the reviewers for their observations and comments on the manuscript. We have fulfilled their comments and suggestions and wish to submit a revised version of the manuscript for further consideration in the journal. Changes in the revised version of the manuscript are highlighted in yellow. Below, we also provide a point-by-point response explaining how we have addressed each of the reviewer and editors' comments. The responses is written in red.

Yours sincerely,

Dr. Mahzad Yousefian

Reviewer 1:
I read the interesting manuscript about the relationship of time constant and respiratory mechanic indices in patients with respiratory failure due to COVID-19 and the following are my recommendations:
1-The type of study should be defined in the title.

Response: Thank you for your comments. The type of study is now defined in the title.

2-Keywords are not based on MeSH database.

Response: Thank you for your comments. All keywords are now based on MeSH database.

3-What was the formula for sample size calculation in the study?

Response: Thank you for your comments. Sample size was determined according to the related papers.

4-Exclusion criteria are not appropriate for the study.

Response: Thank you for your comments. Exclusion criteria was written in a relevant manner.

5-Methodology of study should be revised and completed.

Response: Thank you for your comments. Methodology of study should be revised and completed.

6-sentences related to time constant should be transferred from method to introduction.

Response: Thank you for your comment. Time constant is now discussed in the introduction and discussion part.

7-How did the authors evaluate and omitted the effect of confounding factors on the study outcomes?

Response: Thank you for your comment. Inclusion criteria were patients hospitalized due to pulmonary causes, intubation, and underwent ventilator for more than 48 hours. Additionally, exclusion criteria included patients hospitalized for non-pulmonary causes and hospitalization for less than 48 hours. The SAT (Spontaneous Awakening Trial) and SBT (Spontaneous Breathing Trial) protocols were used to separate patients from the ventilator.

8-What was the new finding of this study compared to the previous studies in the field?

Response: Thank you for your comment. There are a wide variety of factors for determining the weaning process time and extubating. Although RCEXP can be used for a factor for successful prediction for weaning, but there is not any study on the determining the weaning process time. Considering the effect of importance of predicting successful weaning time in patients with COVID-19, and untimely separation of patients, in this study, we surveyed the effects of this factors on weaning time.

9-Discussion should be revised and improved based on the study results and compared to the previous studies.

Response: Thank you for your comments. Most parts of discussion is now rewrite to be relevant.

10-The text should be revised by a native person.

Reviewer 2:
In the method there were the following problems :
1- Determining the severity of acute respiratory failure in patients (mild , moderate and severe)

Response: Thank you for your comments. All patients were severe patients.

2- Calculate patient’s prognosis based on APACHE score

Response: Thank you for your comment. We did not calculate this score in the current study.

3- Calculate organ failure based on SOFA score

Response: Thank you for your comment. We did not calculate this score in the current study.

4- Determining the level of respiratory support in patients (Full support , Partial support , Spont.)

Response: Thank you for your comment. All patients require full mechanical respiratory support and long-term ventilator use.

5- Explain more about the method of calculating compliance and resistance

Response: Thank you for your comment. The method of calculating compliance and resistance is now added to the manuscript.

6- References need some more suggested references and should be up-date.

Response: Thank you for your comment. Several new references was added.

Associate Editor's Comments:

Associate Editor 1:
Dear EIC of Anesthesiology and Pain Medicine
My comments about the article are as follow:
Title:
The type of study should be mentioned in the title of the article. . And instead of the phrase "the effect of" expiratory time constant on … , it is better to use the word "correlation". The duration of mechanical ventilation is also better to eliminate from title.

Response: Thank you for your comments. The type of study is now mentioned in the title of the article. Also the effect is replaced with correlation and finally the "duration of mechanical ventilation" is eliminate from title.

Abstract:
- It is not necessary to mention the place of study in the summary of the article twice, only in the method section should the study setting be explained.

Response: Thank you for your comment. The place of study is now mention in the method section.

- It is better to mention the unit of measurement of compliance and resistance in the results section.

Response: Thank you for your comment. The unit of measurement of compliance and resistance is now added in the results section.

- The conclusion is not stated correctly. There was an inverse relationship between high resistance, low compliance and the amount of RCEXP and the result of successful weaning , not a significant difference!!

Response: Thank you for your comments. The significant difference in this section is corrected.

- Keywords should be selected from the MeSH system.

Response: Thank you for your comments. All keywords are now based on MeSH database.

Introduction:
- Parts of the introduction can be omitted, such as ARDS Physiopathology Lines 56-62

Response: Thank you for your comments. This part was omitted.

- The purpose of the study and its hypothesis are not clearly stated.

Response: Thank you for your comments. The purpose of the study and its hypothesis is now written in a relevant manner.

Methods:
- The method part is very incompletely written and important information is forgotten.
How to select patients and when to group and how to record the main variables of the study is unclear. Is the data collection prospective or retrospective? It is not known when the study grouping, which was based on the outcome of death or separation from the ventilator, occurred? In the text, apparently, the grouping was done first!! How are the study variables calculated and recorded for the dying patient?

Response: Thank you for your comments. The methods part is rewritten.

- Inclusion and exclusion criteria are written incomplete.

Response: Thank you for your comments. Inclusion and exclusion criteria are now completed.

- Define the main variables of study and explain the exact way of calculating them.

Response: Thank you for your comment. The main variables defined briefly in the manuscript.

- Confounding factors and variables and how to adjust their effect on the final result of the study have not been determined.

Response: Thank you for your comment. Confounding factors and variables determined in the text.

- What does means? "monitoring of susceptible position"

Response: Thank you for your comment. This phrase was removed in the text

Method of data analysis and statistical analysis
- Which statistical software is used?

Response: Thank you for your comment. We used SPSS version 16 software in this study.

Response: Thank you for your comment. The SPSS software was added.

- Statistical tests to investigate and eliminate the effect of confounding factors??

Results:
- Tables 1 and 2 do not exist in the uploaded file.

Response: The tables in the manuscript were corrected and added to the manuscript.

- Comparison of underlying disease history is a total of 40 patients, which probably belongs to one study group, and there is no news about the result of the other group. It is better to compare between the two study groups.

Response: Thank you for your comment. Underlying disease history compare between the two study groups.

- None of the unit numbers are measured.

Response: Thank you for your comment. The unit numbers are now measured.

- No results were reported regarding the duration of mechanical ventilation in two groups.

Response: Thank you for your comment. We did not report duration of mechanical ventilation in two groups, so the title changed to be relevant.

Discussion:
- The first paragraph was just a repetition of the raw results of the study, while it should be a summary of the important results.

Response: Thank you for your comment. This paragraph is rewritten.

- The contents of the second paragraph should have been discussed in the introduction of the article.

Response: Thank you for your comment. The contents of the second paragraph of discussion is now discussed in the introduction of the article.

- In line 161: “endotracheal contraction” ???

Response: Thank you for your comment. Endotracheal intubation is true.

- The results of studies 14 and 15 have been stated incompletely and incomprehensibly.

Response: Thank you for your comment. The results of studies 14 and 15 is now discussed comprehensibly.

- In line 176: CROP and RSBI ???

Response: Thank you for your comment. The abbreviations is defined in the text.

- Reference No. 20 (Basiri) is not in the list of references.

Response: Thank you for your comment. This reference is now added to the list.

- There is an incomplete discussion about generalizing the results of the study and proposing its practical use in the clinic.

Response: Thank you for your comment. Discussion section is now generalize the research findings.

- The limitations of the study have not been addressed completely, including the type of study, its non-randomness …

Response: Thank you for your comment. The limitations of the study have addressed completely.

- Who is Nawar? In Line 183

Response: The incorrect reference in the manuscript were corrected.

Statistical review is required also.

EIC Decision:

Major Revision

2 Revision 1

3 comments · 12 Nov 2021 – 12 Nov 2021

Referee 2 Reviewer

MINOR REVISION 12 Nov 2021

Dear Editor in Chief
Anesth Pain Med
I read with interest this revised format. My suggestions are as follows:
Remove the names of the city, university, and hospital from the abstract.
Keywords need correction based on MeSH (RCEXP, Separation from mechanical ventilation!!).
Mention the clinical trial code (the code mentioned was the ethics code).
The mean and SD should be presented as Mean±SD.
The introduction is too long and should be summarized.
Professional editing by a native English speaker is needed throughout (e.g. underwent or separation from mechanical ventilation!!).
Avoid duplicating data in the text and tables in the Results section.
Captions of tables need correction.
I recommend considering some more related references.
Sincerely

Associate Editor

MINOR REVISION 12 Nov 2021

Dear Editorials
Based on the reviewers' comments, this revised format needs some corrections before publication.
Final decision: Minor revision
Regards
AE

Editor-in-Chief

MINOR REVISION 12 Nov 2021

Minor Revision

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.

1. Dastan, F., et al., *Sitagliptin repositioning in SARS-CoV-2: effects on ACE-2, CD-26, and inflammatory cytokine storms in the lung.* Iranian Journal of Allergy, Asthma and Immunology, 2020: p. 10-12.
2. McLean, S.E., et al., *Improving adherence to a mechanical ventilation weaning protocol for critically ill adults: outcomes after an implementation program.* American Journal of Critical Care, 2006. **15**(3): p. 299-309.
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4. Madani, S.J., et al., *Validity of integrative weaning index of discontinuation from mechanical ventilation in Iranian ICUs.* Thrita, 2013. **2**(4): p. 62-8.
5. Delisle, S., et al., *Preliminary evaluation of a new index to predict the outcome of a spontaneous breathing trial.* Respiratory care, 2011. **56**(10): p. 1500-1505.
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12. Arnal, J.-M., et al., *Parameters for simulation of adult subjects during mechanical ventilation.* Respiratory care, 2018. **63**(2): p. 158-168.
13. Desai, J.P. and F. Moustarah, *Pulmonary compliance.* StatPearls [Internet], 2020.
14. Das, N., et al., *Estimating Airway Resistance from Forced Expiration in Spirometry.* Applied Sciences, 2019. **9**(14): p. 2842.
15. Schultz, K., et al., *Lung volumes and airway resistance in patients with a possible restrictive pattern on spirometry.* Jornal Brasileiro de Pneumologia, 2016. **42**: p. 341-347.
16. Yousefian, M., S.R.G.P. Sadegi, and M. Sakaki, *Vitamin D supplements' effect on expediting the weaning process in patients with the stroke.* Electronic Journal of General Medicine, 2019. **16**(2).
17. Okabe, Y., et al., *Lung-thorax compliance measured during a spontaneous breathing trial is a good index of extubation failure in the surgical intensive care unit: a retrospective cohort study.* Journal of intensive care, 2018. **6**(1): p. 1-9.
18. Čandik, P., et al., *Relationship Between Dynamic Expiratory Time Constant τedyn and Parameters of Breathing Cycle in Pressure Support Ventilation Mode.* Physiological research, 2018. **67**(6): p. 875.
19. Al-Rawas, N., et al., *Expiratory time constant for determinations of plateau pressure, respiratory system compliance, and total resistance.* Critical care, 2013. **17**(1): p. 1-11.
20. Ikeda et al. Reference value for expiratory time constant calculated from the maximal expiratory flow-volume curve. BMC Pulmonary Medicine, 2019. 19:208.

Manuscript number: 119572

Manuscript title: Investigating the effect of expiratory time constant on outcome in intubated patients with acute respiratory failure caused by COVID-19 in critical care unit

Dear Dr. ,

Pleased find enclosed our revised manuscript "**Investigating the correlation of expiratory time constant on outcome in intubated patients with acute respiratory failure caused by COVID-19 in critical care unit: A research study** ". We have first addressed the points raised by reviewer. We would like to express our gratitude for the comments made by you and the reviewers. We believe that the critiques on our initial manuscript have certainly improved the quality of our paper.

With best wishes,

Reviewer comments and responses:

Remove the name of City, University and Hospital from the abstract.

Response: Thank you for your comment. We entirely agree with this. We now remove the name of City, University and Hospital from the abstract.

Kay word need correction based on Mesh (RCEXP, Separation from mechanical ventilation!!)

Response: Thank you for your comment. We now corrected this mistake.

Mention Clinical trial code (mentioned code was Ethical code)

Response: Thank you for your comment. But this study was not clinical trial.

Mean and SD should be mention as Mean±SD

Response: Thank you for your comment. Mean and SD mentioned as Mean±SD.

Introduction is too long and should be summarized

Response: Thank you for your comment. As suggested by the reviewer, we have summarized

The introduction part.

Need professional native writing at all parts (e.g. underwent or separation from mechanical ventilation!!)

Avoid duplicating data in text and tables in Result section.

Response: Thank you for your comment. We have deleted the duplicated data in text and tables in Result section.

Captions of tables need correction.

Response: Thank you for your comment. We now corrected the caption of the tables.

Recommend to consider some more related references.

Response: Thank you for your comment. We now add a related reference.

3 Revision 2

1 comment · 20 Nov 2021

Editor-in-Chief

MINOR REVISION 20 Nov 2021

Dear Author,
Please consider the suggested references.

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

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With best wishes,

Response: Thank you for your comment. We entirely agree with this. We now add the recommended references to the manuscript.

4 Revision 3

1 comment · 21 Nov 2021

Editor-in-Chief

MINOR REVISION 21 Nov 2021

Please consider all suggested references.

5

Revision 4

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

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With best wishes,

Response: Thank you for your comment. We entirely agree with this. We now add the recommended references to the manuscript.

5 Revision 4

3 comments · 27 Nov 2021 – 27 Nov 2021

Referee 2 Reviewer

ACCEPT 27 Nov 2021

Dear Editor in Chief
I read article ID#119572 with interest. Fortunately, the authors were able to respond fully to all requested items. Therefore, it may now be appropriate for publication.
Sincerely

Associate Editor

ACCEPT 27 Nov 2021

Dear Editorial
Following the comments by the reviewer, this manuscript (ID#119572) may be useful for readers. Therefore, in my opinion, the paper is acceptable, but the final decision will be made by the editors.
Best wishes
Associate Editor

Editor-in-Chief

ACCEPT 27 Nov 2021

Accept