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Clinical prediction model for pulmonary thrombosis diagnosis in hospitalized patients with SARS-CoV-2 infection

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1st Editorial decision
10-Dec-2022

Ref.: Ms. No. JCTRes-D-22-00197
Clinical prediction model for pulmonary embolism diagnosis in hospitalized patients with SARS-CoV-2 infection
Journal of Clinical and Translational Research

Dear Dr. Franco-Moreno,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jan 09, 2023.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Authors describe the results of a retrospective analysis of computer tomography pulmonary angiograms performed in hospitalized COVID-19-patients (4704) to investigate the presence of pulmonary thrombosis/pulmonary embolism (PE).132 (48.7%) of 271 patients with the suspect of embolism were found to have pulmonary thrombosis.Those patients had higher heart rate,higher respiratory rate,higher CRP-serum level,higher D-dimer plasma level (>3000 ng/ml)The RALE-score was also higher (>4) in the patients with thrombosis.
From these markers the author generated a risk score for pulmonary thrombosis which could help to reduce the presence of pulmonary thormbosis and to avoid the invasive procedure.
Comments:
1.the title should delet pulmonary embolism and replace it with pulmonary thrombosis
2.introduction: line 50 confirms my comment to the title.
Line 54 microclot formations is accompained by extravasation of serum components into the alveolus (including fibrinogen and fibrin, as cleavage product, will constitute the hyaline membrane).The review,Ramadori GP Medical Sciences 2022) offers an alternative explanation fort he thrombosis of the capillaries.In fact as stated in line 57 D-dimer plasma levels are elvated also in absence of thrombosis (in this manuscript 51.3% had elevated D-dimer-plasma-levels
Line 58,61 and throughout the introduction the word PE should be deleted.
As stated in line 63 indication for CTPA should be expressed with much more caution.The changes observed at the CT-scan of the chest observed without comntrast should be mentioned and the characteristics for indication of the use of contrast,including heart size changes should be mentioned also in the introduction.It also should be said what would be the therapeutic consequences of a „temporary" thrombosis
3.Methods:line 90 how was pneumonia assessed (edema ARDS…)?
Line 94,95,see comment for line 54
Line 106:total results of the contrats CT-scan oft he cest should also be performed and reported.
4.Results
In Table 1 albumin serum level should be added
Median blood pressure, fever, administered drugs and pO2 at admission should be given for all patients.Some chest CT-scan (total) pictures should be presented .

5.discussion:the review published in Int J mol Sciences 2021,22(13),7126 should be used to discuss the increase of the D-Dimer plasma-levels and the pathophysiology (including reversibility) of thrombosis „edema and „ARDS" in COVID-19 patients.

Authors' response

We thank the reviewers for their thoughtful comments and efforts towards improving our manuscript. In the following, we highlight comments of reviewers and our effort to address them. The answer is shown in red.

Reviewer #1:

1. The title should delet pulmonary embolism and replace it with pulmonary thrombosis.
We have replaced pulmonary embolism with pulmonary thrombosis in the title. We thank the reviewer for this comment, that improve the understanding the manuscript.

2. Introduction:
Line 50 confirms my comment to the title.
See previous comment. Thanks.

Line 54 microclot formations is accompained by extravasation of serum components into the alveolus (including fibrinogen and fibrin, as cleavage product, will constitute the hyaline membrane). The review, Ramadori GP Medical Sciences 2022, offers an alternative explanation for the thrombosis of the capillaries. In fact as started in line 57 D-dimer plasma levels are elevated also in absence of thrombosis (in this manuscript 51.3% had elevated D-dimer-plasma-levels.
We have added **"In addition, microclot formations companies by exudative interstitial edema with a high protein content (including fibrinogen and fibrin) that rapidly fills the alveoli and is associated with the formation of hyaline membranes"**

- **Reference: Ramadori GP. SARS-CoV-2-Infection (COVID-19): Clinical Course, Viral Acute Respiratory Distress Syndrome (ARDS) and Cause(s) of Death. Med Sci (Basel). 2022 Oct 10;10(4):58. doi: 10.3390/medsci10040058.**

Line 58, 61 and throughout the introduction the word PE should be deleted.
We have replaced pulmonary embolism with pulmonary thrombosis (PT) in the introduction, Methods, results and discussion.

As started in line 63 indication for CTPA should be expressed with such more caution. The changes observed at the CT-scan of the chest observed without contrast should be mentioned.
Thank for the comment. We are unable to meet this reviewer's request since the pulmonary thrombosis studies on Covid use CT-scan with contrast.

The characteristics for indication of the use of contrast, including heart size changes should be mentioned also in the introduction.

We have added the sentence **"Computed Tomography Pulmonary Angiography (CTPA) is considered the first-line diagnostic technique in patients with suspected PE with sensitivity and specificity values between 96 and 100% and between 89 and 98%, respectively. In addition, CTPA provides others imaging parameters useful in diagnosing PE such as the ratio of the right ventricle (RV)/left ventricle (LV) >1, and the moving of the interventricular septum to LV"**

- **Reference: Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, et al. PIOPED II Investigators. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006 Jun 1;354(22):2317–27. doi: 10.1056/NEJMoa052367.**

It also should be said what would be the therapeutic consequences of a "temporary" thrombosis
We have added the sentence **"Per the CHEST Guideline and Expert Panel Report for COVID-19, patients with PT in the setting of COVID-19 are considered to have a provoking factor, the viral disease itself, and thus its recommended anticoagulation therapy for at least three months".**

- **Reference: Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, Diagnosis, and Treatment of VTE in Patients With Coronavirus Disease 2019: CHEST Guideline and Expert Panel Report. Chest. 2020 Sep;158(3):1143–63. doi: 10.1016/j.chest.2020.05.559.**

3. Methods:
Line 90 how was pneumonia assessed (edema ARDS…)?
We have added the sentence: **"The reticular pattern, ground-glass opacities and lung consolidations were the imaging findings evaluated on chest radiography"**

Line 94, 95, see comment for line 54.
We have addressed the comment on line 54

Line 106: total results of the contrats CT-scan of the chest should also be performed and reported.
We have added the sentence: **"Pulmonary lesions more often involved bilateral lungs with a peripheral distribution. Ground-glass opacity followed by ground-glass opacity plus consolidation or reticular pattern and consolidation were the findings in CTPA lung window. The pulmonary lobes most commonly involved were the right lower lobe (85.7%) and left lower lobe (80.3%)"**

4. Results:
In Table 1 albumin serum level should be added.
Albumin serum have been added in Table 1.

Median blood pressure, fever, administered drugs and pO2 at admission should be given for all patients.
Median blood pressure, fever and administered drugs have been added in Table 1.

pO2 at admission was not available in a high percentage of patients due to the absence of arterial blood gases, so we have incorporated the SaO2 value at admission. We regret that this data was not available.

Some chest CT-scan (total) pictures should be presented.
We have added the sentence: **In the PT group, the location of the thrombus was proximal (central or lobar) in 33.3% (44/132) patients, and peripheral (segmental or subsegmental) in 66.6% (88/132) patients (Fig. 2).**

We have presented some chest CT-scan pictures with PT (Figure 2).

5. Discussion:
The review published in Int J mol Sciences 2021,22(13),7126 should be used to discuss the increase of the D-Dimer plasma-levels and the pathophysiology (including reversibility) of thrombosis “edema and ARDS" in COVID-19 patients.
We have added the sentence: **“Dehydration in critically ill patients cause tissue ischemia. This mechanism could be responsible for the increased serum levels of D-dimer, the main marker of thromboembolism, in COVID-19. Albumin is responsible for 80% of the oncotic pressure in the vessels. In a recent study, the albumin administration induced a decrease in D-dimer plasma levels, not because of the hemodilution, but because of the reduction of the ischemic complications. Therefore, albumin infusion could be an “anticoagulant therapy” for critically ill patients with SARS-CoV-2 infection”**

- **Reference: Violi F, Cangemi R, Romiti GF, Ceccarelli G, Oliva A, Alessandri F, et al. Is Albumin Predictor of Mortality in COVID-19? Antioxid Redox Signal. 2021 Jul 10;35(2):139–42. doi: 10.1089/ars.2020.8142.**
- **Reference: Ramadori G. Albumin Infusion in Critically Ill COVID-19 Patients: Hemodilution and Anticoagulation. Int J Mol Sci. 2021 Jul 1;22(13):7126. doi: 10.3390/ijms22137126.**

2nd Editorial decision
17-Dec-2022

Ref.: Ms. No. JCTRes-D-22-00197R1
Clinical prediction model for pulmonary thrombosis diagnosis in hospitalized patients with SARS-CoV-2 infection
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use

the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Jan 16, 2023.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Thank you for submitting a revised draft.

I have perused over the requested modifications by the reviewer and the depth to which these changes were implemented in the revision, and have concluded that your manuscript has successfully passed peer review.

However, before we can proceed to publishing the paper, I must ask you to proofread the manuscript and deliver it in pristine linguistic state. I have taken the liberty to make modifications in some of the sections, however, the mistakes were too replete throughout the text so I was unable to finish the corrections due to time restraints. The modified manuscript is attached to this email and you are requested to complete the proofreading using the attached version.

If you are unable to complete this yourselves, it is recommended that you engage a native speaker versed in the field, a third party editing service, or contact the journal (m.heger@jctres.com) for assistance with the proofreading. The journal has dedicated editors who will conduct a deep dive for a fee (content appraisal and language polishing).

Good luck with finishing this important and timely paper.

Kindest regards,

Michal Heger
Editor

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

3rd Editorial decisión
12-Jan-2023

Ref.: Ms. No. JCTRes-D-22-00197R2
Clinical prediction model for pulmonary thrombosis diagnosis in hospitalized patients with SARS-CoV-2 infection
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.
Please notify our assistant editor/production editor when you receive the proofs if your article should belong to a special issue specifying the issue's title.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: