Jin-Lei Wang

Company Editor-in-Chief

World Journal of Clinical Cases

19th January, 2023

Dear Dr. Wang,

We are submitting our revised manuscript titled "**The Evolving Paradigm of Thrombolytics in Pulmonary Embolism: A Comprehensive Review of Clinical Manifestations, Indications, Contraindications, Recent Advances and Guidelines to Diagnosis and Management (Manuscript NO: 81868)**" for consideration for publication in the *World Journal of Clinical Cases.*

We appreciate the editorial and reviewer comments, all of which have been specifically addressed in this revised version of the paper. Please find below the reviewer comments in bold and the author responses in non-bold. We believe the revisions made have strengthened the quality of our manuscript and that you will find it suitable for publication in the journal.

All authors had access to all the study data, take responsibility for the accuracy of the analysis, and had authority over manuscript preparation and the decision to submit the manuscript for publication. The manuscript represents original work that has not been published and is not under consideration for publication in any other journal. All authors meet the criteria for authorship and instructions to the author were read. We accept all conditions and publication rights. We have no conflicts of interest to declare and no funding sources to declare.

Once again, thank you for this opportunity to submit our revised manuscript.

Thank you,

Yours sincerely,

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Editor's comments:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Ans. We have carefully read all the editors and reviewers comments and addressed them to the best of our ability. We hope our amendments will meet the editors' expectations.

Reviewers' comments:

Reviewer 1: The authors investigated the evolving Paradigm of thrombolysis in pulmonary embolism and performed a comprehensive review of clinical manifestations, indications, contraindications, recent advances and guidelines to diagnosis and management. It is impresseive and good. I have several questions for the authors： 1. I would suggest to revise thrombolytics to thrombolysis. 2. There is no doubt that patients with unstable hemodynamics require thrombolysis, but I insist that part of patients with sub-massive or intermediate-risk PE also required thrombolysis. The mortality for these patients still ranged from 3% to 15%. Do you find any evidence or literature to identify those patients with intermediate-riks PE would get benefit from thrombolysis? 3. Endovascular treatment, including CDT, MPT, or catheter aspiration with or without fragmentation is a promising method for high-risk PE, especially under the support of ECMO. I would suggest the authors to add it in the conclusion. 4. I would suggest to delete "Systemic thrombolytics are not recommended if the patient is hemodynamically stable. " in the conclusion section. 5. "Except in cases where there is a contraindication, systemic thrombolytics are recommended for high-risk and part intermediate-risk PE" is adviced in the conclusion.

Ans. We appreciate the reviewer's time and positive characterization of our manuscript. We have made the suggested changes to the best of our abilities.

1. Thrombolytics has been replaced with thrombolysis everywhere in the manuscript as recommended.
2. Thank you for addressing this important point. We have expanded upon the reasons behind the debatable utilization in the sub-section, indications of thrombolysis.

   "Although according to the statement by the American Heart Association, thrombolytic therapy should be administered to patients with sub-massive or

intermediate-risk PE, the utilization in such scenarios is debatable. These are defined by right ventricular dysfunction (RVD), including right ventricle (RV) hypokinesis, dilation, elevated brain natriuretic peptide (BNP), or cardiac injury defined by elevated troponin and without hypotension. The use of thrombolysis, though, has high efficacy, with a 30% reduction in mortality; however, the effect size on mortality of submassive PE patients is <1%. Furthermore, in patients with intermediate risk, none of the patients treated adjunctively with alteplase showed an increase in right ventricular systolic pressure on a 6-month follow-up."

3. The sentence "Endovascular treatment, including CDT, MPT, or catheter aspiration with or without fragmentation is a promising method for high-risk PE, especially under the support of ECMO" has been added to the conclusion.
4. The sentence "Systemic thrombolytics are not recommended if the patient is hemodynamically stable." has been removed from the conclusion.
5. The sentence "Except in cases where there is a contraindication, systemic thrombolytics are recommended for high-risk and part intermediate-risk PE" has been added to the conclusion.

Reviewer 2: This is an interesting review, but the Methods section is redundant here. It is needed if the review is systematic and done on the basis of accepted rules. This review, as I understand it, is literary, so this section is not needed here.

Ans. We appreciate the reviewer's time and positive characterization of our manuscript. As suggested, we have removed the Methods section. Thank you for the recommendation towards publication.