Response to Reviewers' comments

Reviewer #1:

Conclusion: Accept (High priority)

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Comments: Interesting title. Well designed study. Good work

Response: Thank you for your positive comments.

Reviewer #2:

Conclusion: Rejection

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Comments: The authors wanted to prove that their method of thrombus volume quantification can be reproduced in multiple centers using CTPA. My concern of this work is that if there is a well-defined protocol and procedure for the CTPA, it is difficult to understand why the method cannot be implemented in another center even using different CT scanners. The authors have to clearly define what issues and reasons they wanted to conduct such study and why the results are important. Otherwise, it is just a routine evaluation of the method proving it is practical. The publication value is therefore low.

Response: We wish to thank the reviewer for his comments/critique. Most imaging centers have well defined protocols for CTPA. They are however disparate across centers depending on the make/model of their CT scanner, contrast agent used and imaging acquisition and reconstruction protocols. In this study we wish to evaluate if measuring thrombus volume from data acquired using these different scanners/protocols is reproducible in a centralized analysis framework. We fell that this work is important for critically evaluating pulmonary embolism clot volume data obtained from CTPA scans in a multicenter study; for example, one evaluating the thrombolytic effect of a new drug in PE. It should be noted that measuring PE clot volume from CTPA data is not routinely used in clinical practice but is

especially important while evaluating the efficacy of a thrombolytic agent in a clinical trial setting.

Reviewer #3:

Conclusion: Major revision

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Comments: In this MS, the authors studied the reproducibility of thrombus volume quantification in multicenter computed tomography pulmonary angiography studies. Some problems existed. 1. The language needs to be improved because of some grammar and punctuation mistakes. 2. Use of tense: In the sections of Materials and Methods and Results, the tense of the sentences should be past tense because you did this study or these studies in the past. However, the authors used a lot of present tense. Please change the tense to the past tense. 3. Introduction: In this part, the authors said in the second paragraph that "the goal of this study is to evaluate the quantifiable metric of TTV in PE, especially as new drugs are being developed that aim to eliminate and reduce clot size.". Then, in the third paragraph, the authors restated that "The purpose of this study to evaluate the reproducibility of in vivo PE data obtained in a multicenter setting where the CT scanners vary by site, as do acquisition and -------". What are your purpose or your goals? Actually, when you gave the background information and pointed out the shortcomings and problems in the literature regarding this study in the introduction section, you should propose a hypothesis and then give your purpose in this study. Please rewrite this part. 4. Statistical analysis: In this section, you should give the P value. Is it less than 0.05? 5. In Fig.1, please indicate in the figure all the names of the part of the pulmonary vessels like MPA, RPA, TA, RILA etc. 6. The references seemed a little older with no citations in recent two years. 7. The authors did not say if they had obtained the ethics committee approval and if the patients had given the participation consent in written form.

Response: We wish to thank the reviewer for his/her comments and suggestions.

1. **We have tried to correct as many grammatical and spelling mistakes as we could that were alluded to by the reviewer.**
2. **We have updated the language the Materials and methods section to past tense to reflect that the work is already completed.**
3. **We have now clarified the goals of the study in the manuscript to reflect that we are evaluating the reproducibility of measuring total thrombus volume as a metric for evaluating PE from data obtained in a multicenter setting. Additionally, we also evaluate the reproducibility of analysis of other metrics such as the Qanadli scores.**

4. **We have added p-values to statistical tests wherever they are relevant.**
5. **Figure 1 has been corrected so that the entire vessel names are now visible. They were truncated in the previous submission.**
6. **The previous work in measuring clot volumes in PE was done many years ago. The semi-automated region growing algorithm is also based on methodology that has been available for many years. This is the reason the refences are not recent. We however feel that they are the appropriate references for this study.**
7. **Work performed in this study complied with all HIPAA and Institutional review board (IRB)/ Ethics committee guidelines. Ethics statement has now been added to the beginning of the materials and methods section.**

Reviewer #4:

Conclusion: Minor revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Comments: This manuscript describes a study that evaluated the reproducibility of embolism volume quantification in multicenter CT pulmonary angiography exams. It includes the analysis of data obtained from 23 patients at 18 sites using different site-specific imaging protocols. A semi-automatic seed-growing algorithm was used for embolism volume measurement that was performed by two experienced image analysts. Scoring evaluation were also conducted. The study found excellent inter- and intra-observer reproducibility in the emboli volume measurement suggesting that the image analysis method may be suitable for multicenter use. I have the following specific comments. 1) This study looks at the reproducibility of the emboli volume measurement, which has the value of demonstrating the reliability of the measurement in a given protocol setting. However, it does not address the potential variation in the sensitivity and accuracy of emboli volume measurement due to different imaging protocols used in multicenter clinical trials. For example, a small embolus may be seen on images with thin slices and small pitch size but missed on images with thick slices and large pitch size. This may affect emboli quantification in multicenter studies of drugs aimed to reduce and eliminate clot size. 2) As mentioned in the paper, the selection of cases and images from a site qualification visit prior to the start of a multicenter clinical trial of a thrombolytic agent may lead to bias in the study. Besides, the small population size of 23 is also a limitation of the study. What is the basis/criterion for the data selection? Minor comment: In the abstract, please state that the data were acquired from 18 sites (in addition to 23 scanners).

Response: We wish to thank the reviewer for his/her very useful comments/suggestions.

1. **The reviewer brings up a very valid point that this manuscript only addresses the reproducibility of the clot volume analysis and does not address potential variation in sensitivity and accuracy due to different protocols. We have recently published a paper addressing this issue (Reference # 24 in manuscript, PMID 29599936) that examines the effect of varying CTPA acquisition and reconstruction parameters on semi-automated volume quantification using our approach. We have shown that except for pitch of acquisition, none of the other imaging parameters have a significant impact on volume measurements in PE. This indicates that special attention needs to be paid to imaging data obtained with different pitches across sites in a multicenter setting.**
2. **We acknowledge that the small sample size and potential selection bias in our population. The criteria for data selection was dependent on the site where the data was received from. It was a CTPA scan acquired on their scanner using the standardized CTPA protocol at the center/scanner in the one week prior to an imaging site qualification visit for a multicenter study. We have now added the 18 sites/23 scanners statement to the abstract as requested.**

Reviewer #5:

Conclusion: Accept (General priority)

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Comments: The article is typical scientific article and therefore I fully agree with the conclusion, that semi-automated region growing algorithm for quantifying PE is a suitable method for image analysis in multicenter clinical trials. For everyday practice is however this algorithm useless. The statistical analysis is complex and good.

Response: Thank you for your comments. We feel that measurements of thrombus volume from CTPA data is not routinely used in clinical practice due to the time it takes to perform this assessment. If robust, fast and automated methodologies to evaluate PE volume become commonplace, it is possible that this may be adopted in routine clinical practice in the future.