

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Clinical Outcomes and Factors Associated with Pulmonary Infarction Following Acute Pulmonary Embolism: A Retrospective Observational Study at a US Academic Center
<b>AUTHORS</b>	Lio, Ka U; O'Corragain, Oisin; Bashir, Riyaz; Brosnahan, Shari; Cohen, Gary; Lakhter, Vladimir; Panaro, Joseph; Rivera-Lebron, B; Rali, Parth

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Adrish, Muhammad Baylor College of Medicine
<b>REVIEW RETURNED</b>	26-Sep-2022

<b>GENERAL COMMENTS</b>	<p>I read this study "Clinical Relevance of Pulmonary Infarction Following Acute Pulmonary Embolism" with great interest. In this study, authors performed a retrospective review of 496 adults patients with PE and reviewed characteristics and outcomes of patients with infarction. These are interesting findings, however, I have following observations for which I would like authors to provide more information.</p> <p>Major:</p> <p>Authors stated that "Cases of pulmonary infarction were identified by review of the final CT reports by board-certified thoracic radiologists". From this statement, seems like multiple radiologist interpreted these images. Did the authors note any variations in study interpretations or had to disagree with radiologist conclusion. I would also like the authors to describe features that were used to differentiate infarctions from consolidations. For example (Radiology. 2007 Sep;244(3):875-82. doi: 10.1148/radiol.2443060846. PMID: 17709834.)</p> <p>It is also noteworthy that "There were more patients with infarction who received antimicrobial therapy compared to those without infarction (15% vs 5%, p&lt;0.001). This creates further doubt whether the infarctions was diagnosed accurately, especially in these absence of histologic confirmation.</p> <p>Authors used BNP cut-off <math>\geq 100</math>pg/ml to describe. It is noteworthy that there are several factors that affect BNP value. Was there any adjustment? Int J Cardiol. 2014;176(3):611-617. doi:10.1016/j.ijcard.2014.08.007</p>
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	<p>Clin Chem Lab Med. 2014 Sep;52(9):1341-6. doi: 10.1515/cclm-2013-0791. PMID: 24781675.  <a href="https://doi.org/10.1053/ajkd.2003.50118">https://doi.org/10.1053/ajkd.2003.50118</a></p> <p>RV strain was diagnosed on CT images. Were there any old images that were reviewed to account for any pre-existing pulmonary hypertension in these patients?</p> <p>In this study, troponin elevation was less frequent in patients with infarction and RV strain was higher. One would expect a higher troponin in patients with RV strain. What was the reason for this discrepancy? Eur Respir J 2014; 44: Suppl. 58, 2407</p> <p>Authors noted increased RV strain in infarction patients on CT but no difference observed in echo. Were these studies done during the same admission. What was the mean/median time difference between the CT scans and the echo.</p> <p>Minor:  Authors stated that "Cases of acute PE diagnosed by other imaging modalities were excluded". For the completion of information, please state how many cases were excluded.</p>
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<b>REVIEWER</b>	Singer, Adam Stony Brook University Hospital, Emergency Medicine
<b>REVIEW RETURNED</b>	01-Nov-2022

<b>GENERAL COMMENTS</b>	<p><b>GENERAL COMMENTS</b></p> <p>In this study the authors performed a secondary analysis of a pulmonary embolism registry to describe the characteristics and outcomes of patient with pulmonary infarction. They found that patients with pulmonary infarction were younger and with less co morbidities than those without infarction. They also found that patients with infarction were more likely to have pleuritic chest pain and hemoptysis. However, most patient with pulmonary infarction had neither pleuritic chest pain nor hemoptysis. This point deserves greater emphasis in the text. Finally, patients with pulmonary infarction had similar outcomes as those without pulmonary infarction.</p> <p>This is the largest reported series of patients with PE and pulmonary infarction and therefore of interest to readers.</p> <p>The major limitation of the study is its observational and retrospective nature.</p> <p><b>SPECIFIC COMMENTS</b></p> <p><b>Abstract</b>  Page 4, Line 36. Add "s" to "infarction".  P4, L40. Change "higher" to "more common".  P4, L45. Change "readmission" to "readmissions".</p> <p><b>Methods</b>  P7, L36. Add "requirement" between "oxygen" and "on discharge".  P7, L49. Add "the" before "pulmonary artery".</p> <p><b>Results</b></p>
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	<p>Patient Characteristics. I would recommend starting by describing the overall population and then focusing on those patients with infarction.</p> <p>P10, L9. The authors found lower troponin levels in patients with infarction despite more evidence of RV strain on CT. How do the authors explain this discrepancy?</p> <p>Table 1. Since this was not a hypothesis testing study use of P values is not appropriate.</p> <p>Table 2. the sPESI score is ordinal and should not be summarize as means. Instead, the authors should present the percentages of patients with low vs non-low sPESI scores.</p> <p>P11, L10. Should read "...infarction occurred in the lower lobe (60%) and involved a single lobe..."</p> <p>P11, L22. Add "a" before "variety".</p> <p>P11, L24. Place a period after "post-discharge" and capitalize "Resolution".</p> <p>P13, L45. Why did presence of troponin decrease risk of infarction?</p> <p>Discussion</p> <p>P14, L18. Would emphasize that while patients with infarction were more likely to have pleuritic chest pain and hemoptysis, most didn't have either so the absence of these symptoms is not helpful in identifying infarction.</p> <p>P14, L30. Again, please try and explain why the presence of elevated troponins was associated with a reduced risk of pulmonary infarction.</p> <p>P15, L20. Add "the" before "absence".</p> <p>The authors suggest that the discrepancy between CT and echo presence of RV strain is likely due to the fact that the echo was delayed. Do the authors have data on when the echo was performed relative to presentation vs. timing of CT to support this notion?</p> <p>P16, L22. Change "performed" to "had".</p> <p>The authors should have a dedicated section for study limitations before the conclusion. Other limitations include inability to control for potential confounding factors and single center.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1Dr. Muhammad Adrish, Baylor College of Medicine

Comments to the Author:

I read this study "Clinical Relevance of Pulmonary Infarction Following Acute Pulmonary Embolism" with great interest. In this study, authors performed a retrospective review of 496 adults patients with PE and reviewed characteristics and outcomes of patients with infarction. These are interesting findings, however, I have following observations for which I would like authors to provide more information.

Major:

1. *Authors stated that "Cases of pulmonary infarction were identified by review of the final CT reports by board-certified thoracic radiologists". From this statement, seems like multiple radiologist interpreted these images. Did the authors note any variations in study interpretations or had to disagree with radiologist conclusion. I would also like the authors to describe features that were used to differentiate infarctions from consolidations. For example*

(*Radiology*. 2007 Sep;244(3):875-82. doi: 10.1148/radiol.2443060846. PMID: 17709834.)  
It is also noteworthy that "There were more patients with infarction who received antimicrobial therapy compared to those without infarction (15% vs 5%,  $p < 0.001$ ). This creates further doubt whether the infarctions were diagnosed accurately, especially in the absence of histologic confirmation.

Thank you for the suggestion. We have revised these sections and provide description about features that used to diagnose infarctions. Indeed, there are some distinct radiographic features described from previous studies that could help identify infarction from other causes of consolidation. For example, a central lucency within peripheral consolidation may indicate necrosis with secondary cavitation and such finding has a specificity of 98% and sensitivity of 46%.<sup>1</sup>

Regarding to the finding that more patients with infarction received antimicrobial therapy than those without infarction, we found that the most common reason for antimicrobial therapy is sepsis, either from a pulmonary or non-pulmonary source. We believe this may confound clinical management but not necessarily a misdiagnosis of infarction.

2. *Authors used BNP cut-off  $\geq 100$ pg/ml to describe. It is noteworthy that there are several factors that affect BNP value. Was there any adjustment?*  
*Int J Cardiol*. 2014;176(3):611-617. doi:10.1016/j.ijcard.2014.08.007  
*Clin Chem Lab Med*. 2014 Sep;52(9):1341-6. doi: 10.1515/cclm-2013-0791. PMID: 24781675.  
[https://urldefense.com/v3/https://doi.org/10.1053/ajkd.2003.50118;!!MigbTO58FHE1!!QOVP-qvDF-hKZL5rZ4ZEzk6w0Qef22IF5IZF3yVRe31RU-ZzITefmjV4jAQz5tQxY-zmzHm7AximgEgCY4-epgaoljhzrblYw\\$](https://urldefense.com/v3/https://doi.org/10.1053/ajkd.2003.50118;!!MigbTO58FHE1!!QOVP-qvDF-hKZL5rZ4ZEzk6w0Qef22IF5IZF3yVRe31RU-ZzITefmjV4jAQz5tQxY-zmzHm7AximgEgCY4-epgaoljhzrblYw$)

Thank you for the valuable suggestion and we read through the reference carefully. We acknowledge that there are various conditions that affect serum BNP concentrations, such as age, sex, body mass index, or pre-existing conditions including heart failure, CAD, pulmonary hypertension, and sepsis, which are conditions that are all relevant to this study. We did not make any adjustments to the cut-off levels at the time of the study.

We found a previous meta-analysis<sup>2</sup> that may be helpful in understanding our clinical reasoning in the design of the study. In summary, this meta-analysis included 13 studies that examined the role of BNP in predicting adverse outcomes in acute PE. Seven studies used BNP with four different cutoff levels: 75pg/ml, 89pg/ml, 90 pg/ml (3 studies), 100pg/ml (2 studies). Despite different cutoff levels, the prognostic value of BNP was consistent in all included studies.

In fact, we read through the guidelines from ESC<sup>1</sup>, CHEST<sup>3</sup>, and PERT<sup>4</sup>, and neither of those guidelines specifies the cutoff level of BNP, I believe this will be of particular interest for future study.

3. *RV strain was diagnosed on CT images. Were there any old images that were reviewed to account for any pre-existing pulmonary hypertension in these patients?*  
Thank you for the insightful comment. Patients with pre-existing pulmonary hypertension were documented as presence of "cardiac disease". We acknowledge that the presence of existing pulmonary hypertension could lead to parenchymal changes similar to RV strain caused by acute PE. In those scenarios, it would be technically difficult to differentiate whether these signs of RV strain are related to pre-existing pulmonary hypertension itself, or the combination. In response to this comment, we have revised the limitation of study part and included this as one of the study limitations.

4. *In this study, troponin elevation was less frequent in patients with infarction and RV strain was higher. One would expect a higher troponin in patients with RV strain. What was the reason for this discrepancy? Eur Respir J 2014; 44: Suppl. 58, 2407*

Thank you for the comment. In this study, patients without infarction were significantly older and associated with higher comorbidities including cardiac diseases, chronic kidney diseases, diabetes, and malignancy. While troponin elevation is indicative of RV strain, RV myocardium might not necessarily be its only source.<sup>5</sup> We believe a mismatch between oxygen demand and supply is secondary to underlying comorbidities and possibly a decrease in renal clearance.

We agree with the two reviewers that this is a relevant and validated question that warrants further clarification. In response to the comments, we have revised the related context in the discussion part.

5. *Authors noted increased RV strain in infarction patients on CT but no difference observed in echo. Were these studies done during the same admission. What was the mean/median time difference between the CT scans and the echo.*

Thank you for the comment. These echocardiograms were done during the same admission. The mean and median time lapse between the availability of CT results to echocardiogram results was 29 hours 40 minutes and 20 hours 11 minutes respectively. We agreed that the time lapse in test result can provide more evidence to support our hypothesis in explaining the discrepancy of RV strain between CT and echocardiogram. We have revised the related context in the discussion part.

Minor:

6. *Authors stated that "Cases of acute PE diagnosed by other imaging modalities were excluded". For the completion of information, please state how many cases were excluded.* We have revised the related context to include the information mentioned.

Reviewer: 2

Dr. Adam Singer, Stony Brook University Hospital

Comments to the Author:

GENERAL COMMENTS

In this study the authors performed a secondary analysis of a pulmonary embolism registry to describe the characteristics and outcomes of patient with pulmonary infarction. They found that patients with pulmonary infarction were younger and with less co morbidities than those without infarction. They also found that patients with infarction were more likely to have pleuritic chest pain and hemoptysis. However, most patient with pulmonary infarction had neither pleuritic chest pain nor hemoptysis. This point deserves greater emphasis in the text. Finally, patients with pulmonary infarction had similar outcomes as those without pulmonary infarction.

This is the largest reported series of patients with PE and pulmonary infarction and therefore of interest to readers.

The major limitation of the study is its observational and retrospective nature.

SPECIFIC COMMENTS

Abstract

7. *Page 4, Line 36. Add "s" to "infarction".*  
The sentence has been revised.
8. *P4, L40. Change "higher" to "more common".*  
The sentence has been revised.

9. *P4, L45. Change “readmission” to “readmissions”.*  
The sentence has been revised.

Methods

10. *P7, L36. Add “requirement” between “oxygen” and “on discharge”.*  
The sentence has been revised.
11. *P7, L49. Add “the” before “pulmonary artery”.*  
The sentence has been revised.

Results

12. *Patient Characteristics. I would recommend starting by describing the overall population and then focusing on those patients with infarction.*  
We agree with the reviewer’s recommendation and have revised the corresponding part.
13. *P10, L9. The authors found lower troponin levels in patients with infarction despite more evidence of RV strain on CT. How do the authors explain this discrepancy?*  
Indeed, both reviewers expressed similar comments. We agree with the reviewer that this needs to be addressed, please refer to No. 7 for our response. In case it is not available, please see the response below.

In this study, patients without infarction were significantly older and associated with higher comorbidities including cardiac diseases, chronic kidney diseases, diabetes, and malignancy. While troponin elevation is indicative of RV strain, RV myocardium might not necessarily be its only source.<sup>5</sup> We believe a mismatch between oxygen demand and supply is secondary to underlying comorbidities and possibly a decrease in renal clearance.

We agree with the two reviewers that this is a relevant and validated question that warrants further clarification. In response to the comments, we have revised the related context in the discussion part.

14. *Table 1. Since this was not a hypothesis testing study use of P values is not appropriate.*  
We believe the p-value may be relevant in the context of understanding the difference between PE patients with pulmonary infarction vs those without.
15. *Table 2. the sPESI score is ordinal and should not be summarized as means. Instead, the authors should present the percentages of patients with low vs non-low sPESI scores.*  
We agree with reviewer’s comment and have revised the corresponding part. We have revised the related context.
16. *P11, L10. Should read “...infarction occurred in the lower lobe (60%) and involved a single lobe...”*  
The sentence has been revised.
17. *P11, L22. Add “a” before “variety”.*  
The sentence has been revised.
18. *P11, L24. Place a period after “post-discharge” and capitalize “Resolution”.*  
The sentence has been revised.
19. *P13, L45. Why did presence of troponin decrease risk of infarction?*  
Please refer to No. 7 and 17 for our response.

Discussion

20. *P14, L18. Would emphasize that while patients with infarction were more likely to have pleuritic chest pain and hemoptysis, most didn’t have either so the absence of these symptoms is not helpful in identifying infarction.*  
We agree with the reviewer’s recommendation and have revised the corresponding part.
21. *P14, L30. Again, please try and explain why the presence of elevated troponins was associated with a reduced risk of pulmonary infarction.*  
Please refer to No. 7 and 17 for our response.
22. *P15, L20. Add “the” before “absence”.*  
The sentence has been revised.

23. *The authors suggest that the discrepancy between CT and echo presence of RV strain is likely due to the fact that the echo was delayed. Do the authors have data on when the echo was performed relative to presentation vs. timing of CT to support this notion?*

Thank you for the comment. Indeed, both reviewers also expressed similar comments.

The mean and median time lapse between the availability of CT results to echocardiogram results was 29 hours 40 minutes and 20 hours 11 minutes respectively. We agree that the time lapse in results will provide additional information to support our hypothesis for explaining the discrepancy of RV strain between CT and echocardiogram. This information has been added to the discussion part.

24. *P16, L22. Change “performed” to “had”.*

The sentence has been revised.

25. *The authors should have a dedicated section for study limitations before the conclusion. Other limitations include inability to control for potential confounding factors and single center.*

We agree with the reviewer’s recommendation and have revised the corresponding part.

Reviewer: 1

Competing interests of Reviewer: None

Reviewer: 2

Competing interests of Reviewer: None

#### References

1. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *European Heart Journal*. 2019;41(4):543-603.
2. Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. *Am J Respir Crit Care Med*. 2008;178(4):425-430.
3. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e419S-e496S.
4. Rivera-Lebron B, McDaniel M, Ahrar K, et al. Diagnosis, Treatment and Follow Up of Acute Pulmonary Embolism: Consensus Practice from the PERT Consortium. *Clinical and Applied Thrombosis/Hemostasis*. 2019;25:1076029619853037.
5. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation*. 2007;116(4):427-433.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Adrish, Muhammad Baylor College of Medicine
<b>REVIEW RETURNED</b>	18-Nov-2022

<b>GENERAL COMMENTS</b>	Authors have answered all my queries and I commend them for the extensive revisions which have greatly improved the quality of this manuscript. I would like the authors to edit Table 2 which has some duplications.
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<b>REVIEWER</b>	Singer, Adam Stony Brook University Hospital, Emergency Medicine
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<b>REVIEW RETURNED</b>	17-Nov-2022
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<b>GENERAL COMMENTS</b>	<p>Please make the following changes:</p> <p>Strengths and Limitations Line 36. Add “we are” before “unable to comment”.</p> <p>Page 32, line 6. Delete the word “a” before “generally accepted”. Add “shaped” to “wedge”.</p> <p>L 11. Add “and” before “air bronchogram”.</p> <p>Table 1. P values imply hypothesis testing. You could replace the p values with the mean difference and 95% CI if you want the readers to see if the differences between the groups are significant.</p> <p>Page 40, line 27. Should read “..that the majority did not have these symptoms may not be useful...”</p>
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## VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Adam Singer, Stony Brook University Hospital

Comments to the Author:

Please make the following changes:

1. Strengths and Limitations

Line 36. Add “we are” before “unable to comment”.

Thank you, the sentence has been revised.

2. Page 32, line 6. Delete the word “a” before “generally accepted”. Add “shaped” to “wedge”.

L 11. Add “and” before “air bronchogram”.

Thank you, the sentence has been revised.

3. Table 1. P values imply hypothesis testing. You could replace the p values with the mean difference and 95% CI if you want the readers to see if the differences between the groups are significant.

Page 40, line 27. Should read “..that the majority did not have these symptoms may not be useful...”

Thank you for the suggestion. The aim of the study is to investigate the clinical and radiographic characteristics of pulmonary infarction and to compare those with and without infarction. We would want to keep the p-values in the table, as all parameters were tested in univariate logistic regression



to establish a relation with pulmonary infarction. Any relevant parameters are represented as odds ratio with a confidence interval in Table 4.

Reviewer: 1

Dr. Muhammad Adrish, Baylor College of Medicine

Comments to the Author:

4. Authors have answered all my queries and I commend them for the extensive revisions which have greatly improved the quality of this manuscript. I would like the authors to edit Table 2 which has some duplications.

Thank you, the table has been revised.