

Peer review file

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Reviewer A

Comment 1: Definitions of the intervention..." section. What does PT abbreviation mean?

Reply 1: Apologies for the mistake. This abbreviation is wrong and we have corrected it. It is: PE (Pulmonary Embolism)

Changes in the text: we have modified our text. See change in Page 5, line 89

Comment 2: How many beds were in PE unit, ICU? pulmonary, cardiology unit? Please describe shortly the structure of this unit? It is not clear. Which specialists were involved?

Reply 2: Patients with high-intermediate-risk pulmonary embolism should be admitted to Units of Intensive Care (ICUs) or Respiratory Intermediate Care Units (RICUs) for hemodynamic monitoring. In our hospital, we have 24 ICU beds and the pulmonology service has one Respiratory Intermediate Care Unit with six monitored beds.

A detailed description of the care process is made in the attached material (Integrated care pathway)

Changes in the text: See attached file as supplementary material.

Comment 3: I cannot find supplementary materials!

Reply 3: The supplementary material was removed because it was not anonymized. We are attaching it now.

Changes in the text: See attached file as supplementary data.

Comment 4: "Results" section. How many patients were intermediate low, intermediate high and high risk. Please add to table 1. Have you got serum troponin level of PE patients?

Reply 4: Thank you very much for your comment. This classification has been added to Table 1. The difference observed in the number of intermediate-high risk patients

between the groups is probably due to the fact that prior to 2014, troponin determinations were not always carried out.

In our series of 1,142 patients, troponin detection was performed in 798 (69.9%). The normal range of our laboratory is 0-0.056 ng/mL. 29% of our patients had elevated troponin levels

Changes in the text: we have modified our table 1. See last row of table 1.

We have modified the manuscript. See Results: page 8, lines 143-144 and Discussion: page 10, lines 192-197.

Comment 5: "Results" section. Please look carefully on table 2. The table is not formatted properly. LMWH, DOACs n(%) are shifted

Reply 5: Thank you for this correction.

Changes in the text: we have modified the table 2 accordingly. Please check Table 2

Comment 6: It is really surprised that only 7.3% of APE patients after 2014 y were treated on DOACs. Please explain. According to the ESC guidelines DOACs are preferred against VKA. It is also surprised that almost 70% of patients were treated with VKA. Moreover 23.3% of APE patients were treated with LMWH after discharged. Please explain why and discuss.

Reply 6: The reason that most patients receive VKA treatment at discharge is that, although DOAC is offered as a first option, they are not funded by our national health system. VKAs are funded, and that is why they are the preference of the majority of our patients.

Through the Spanish scientific societies (SEPAR), we are trying to modify this funding due to the scientific evidence showing clear superiority of treatment with DOACs over VKA for the treatment of acute pulmonary embolism.

Changes in the text: we have modified our text. See Discussion, Page 11, lines 207-212.

Comment 7: Please cite interesting paper about influence of DOACs on hospitalization period in APE patients: "Paczyńska M, Kurnicka K, Lichodziejewska B, Goliszek S, Dzikowska-Diduch O, Sobieraj P, Burzyński Ł, Kostrubiec M, Pruszczyk P, Ciurzyński M. Acute pulmonary embolism: treatment with rivaroxaban results in shorter period of hospitalization compared to the standard therapy. An Academic Centre experience.

Kardiol Pol. 2016;74(7):650-6. doi: 10.5603/KP.a2015.0253. Epub 2016 Jan 18.”

Reply 7: Thank you for this citation (Paczyńska M et al.). This paper shows that, compared to standard therapy, use of DOACs (Rivaroxaban) has been associated with a significant reduction of the duration of hospital stay.

Following this comment, we have modified our text.

Changes in the text: See Discussion, Page 11, lines 207-212, and Reference 28.

Comment 8: Do creatinine or GFR were involved in uni and multivariable analysis?

Reply 8: We have the renal function of all our patients, in the screening carried out initially with the different variables, renal function was included, however it was not reflected in the tables due to not finding a significant association / effect (the same as with the hemoglobin levels, platelets etc.)

Comment 9: Table 3. “Edad” is not in English.

Reply 9: Thank you for this correction and apologies for the mistake.

Changes in the text: we have modified our table 3. Please check Table 3

Reviewer B

Thank you for submitting your report on a quasi-experimental study of whether the quality of care can be improved with establishment of a dedicated unit for pulmonary embolism (integrated care plan) at a tertiary university hospital, comparing 2015-2020 (n=612 patients) to 2010-2013 (n=510 patients). The result overall was finding reduced median LOS by -2 days, and reduced by -1 day time to start oral anticoagulant, but without statistically significant changes in hospital and 30d mortality.

The integrated care plan (ICP) and dedicated unit are not well defined methodologically - we are told there is a specific protocol for management and followup, designed by a multidisciplinary group, and referring to a supplementary material. Unfortunately, I do not find this supplementary material in the pdf or on the JTD website. One this protocol should be reviewed for JTD review, but also the actual protocol methods should be made explicit in the manuscript. PERT is mentioned - was this part of the protocol and

how does it interdigitate? (we are tangentially told it is "broader scope" than PERT but have no way to evaluate it). Were there any changes in the protocol over time? We are told the protocol was published internally in 2018 but need much more data to evaluate. What in Table 3 does "service of admission" mean if there is a dedicated Unit?

Comment 1: Specific protocol.

Reply 1: The Integrated care pathway (supplementary material) was removed because it was not anonymized. We attach it now.

Changes in the text: See attached file as supplementary data.

Comment 2: PERT

Reply 2: With regard to PERT, unfortunately in our hospital we do not have a rapid response team for pulmonary embolism. In our study, we tried to evaluate the impact of a care plan for lung embolism. In the text, we mean that an integrated care plan for pulmonary embolism (IPC) covers a broader field than a PERT, and we try to evaluate the impact of a IPC on the quality of care

Changes in the text: See Introduction, page 3, line 54 and supplementary data.

Comment 3: "service of admission"

Reply 3: Although in our hospital most of the patients with a diagnosis of pulmonary embolism are admitted to pulmonology, though in some occasions they are admitted to other services (mainly internal medicine), and we have taken advantage of this fact to assess whether differences exist when this occurs.

Changes in the text: See discussion page 11.

Comment 4: As authors note, despite inherent quasi-experimental design, it was a relatively large sample over many years.

Patients admitted to a critical care unit after the implementation of the ICP increased from 8.2% to 18.4% between periods. More patients received recanalization procedures - and this is a concern that PERTs increase utilization, and to date only historical control, like this series, are available. It is noteworthy on this point that a "similar number of patients were hemodynamically instable in the two periods" and I must vigorously disagree with the authors that this "reflects an improvement in the management of

patients with high-risk PE". There is zero data to support that contention and it should be removed. In fact, there is no randomized data in the PE field at all to support that more intervention is better and this is a major area of research in PE.

Reply 4: We fully agree with the reviewer that fibrinolysis treatment should not be performed outside of the strict indications of the clinical practice guidelines.

What we tried to highlight in our study is that, in the post-intervention period, patients who were admitted to our hospital with acute symptomatic high-risk pulmonary embolism (defined as: Need for cardiopulmonary resuscitation. Systolic blood pressure (BP) < 90 mmHg or vasopressors required to achieve a systolic BP \geq 90 mmHg despite adequate filling status. Systolic BP drop \geq 40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis) and without a contraindication for fibrinolysis, underwent this treatment. But only in this group of patients (high risk and without contraindications) which indicates that the implementation of specific healthcare processes improves adherence to clinical practice guidelines, unfortunately in our study this has not been accompanied by a significant decrease in mortality.

Changes in the text: See discussion page 13 line 271-273.

Comment 5: The decrease in LOS must be interpreted in context: please discuss the change in ambient LOS for the entire hospital in this series. Was the change motivated by hospital-wide changes or process improvements, cost concerns, etc? It is possible that earlier start of oral anticoagulation helped (as noted in prior studies), but that itself may be confounded by the growth in use of DOAC compared to VKA.

Reply 5: It is true that the use of DOAC is related to a decrease in LOS. However, in our study this decrease cannot be attributed to DOAC as they are rarely used. The reason is that, despite the fact that this treatment is offered to the patient, our national health system does not finance DOACs for pulmonary embolism. This is the reason that in the group post-intervention only 7.3% of the patients were treated with DOAC at discharge.

Changes in the text: See Discussion, Page 11, lines 207-212, and Reference 28.

Comment 6: Table 3 - fix "edad".

Reply 6: Thank you for this correction. Apologies for this mistake.

Changes in the text: we have modified our table 3. See changes in Table 3

Reviewer C

The report is nicely written and addresses an important subgroup of chest-pain patients that is commonly endangered to be underdiagnosed. However, there are several concerns remaining:

Comment 1: length of stay: how much influence do the authors predict to result from improved pathways? Per se, the general length of stay did reduce even without (e.g. due to NOAC therapy)

Reply 1: In fact, the use of DOAC is related to a decrease in LOS. However, in our study this decrease cannot be attributed to DOAC as they are rarely used.

The reason that most patients receive VKA treatment at discharge is that, although DOAC is offered as a first option, they are not funded by our national health system. VKAs are funded, and that is why they are the preference of the majority of our patients. This is the reason that in the group post-intervention only 7.3% of the patients were treated with DOAC at discharge.

Through the Spanish scientific societies (SEPAR), we are trying to modify this funding due to the scientific evidence showing clear superiority of treatment with DOACs over VKA for the treatment of acute pulmonary embolism.

Changes in the text: we have modified our text. See Discussion, Page 11, lines 207-212

Comment 2: Length of stay: how much dependence on the NOAC chosen for therapy (pre-treatment?)

Reply 2: Has been answered in comment 1. See Reply 1

Comment 3: risk groups: is there any difference in certain risk groups (e.g. intermediate-high)? Was this issue addressed to?

Reply 3: Thank you very much for your comment. The classification has been added to Table 1. The difference observed in the number of intermediate-high risk patients between the groups is probably due to the fact that prior to 2014, not as many

determinations of troponin levels were carried out.

The determination of markers of myocardial damage has made it possible to better classify hemodynamically stable patients who showed data of right ventricular dysfunction on imaging tests. After the intervention, a greater number of patients were admitted to monitoring units for hemodynamic surveillance (intermediate-high risk). It should be noted that this did not imply that these patients underwent more reperfusion treatment, since this treatment was only carried out when they presented hemodynamic instability (high risk).

Changes in the text: we have modified our table 1. See last row of table 1. We have also modified our text. See Results: page 8, lines 143-144 and Discussion: page 10, lines 192-197.

Comment 4: recanalization: this term is confusing - lysis? aspiration? surgical?

Reply 4: We agree with the reviewer that the most suitable term is reperfusion treatment. In our hospital, we perform two reperfusion treatments: systemic thrombolysis and percutaneous catheter-directed treatment, the latter is only performed in patients with high-risk pulmonary embolism (with hemodynamic instability) and who have an absolute contraindication for systemic fibrinolysis.

We attach the care pathway as attached material where the procedures and doses are detailed.

Changes in the text: We make the correction in the document and specify which reperfusion treatments we carry out. See page 6, line 109. Page 8, line 152. Page 11, line 225-226. Page 13, line 272

Comment 5: long-term: how can authors exclude a relevant effect of NOAC therapy instead of pathway improvements?

Reply 5: It is answered in comment 1. See reply 1.

Reviewer D

In this investigation, titled "Evaluation of the impact of an integrated care pathway for pulmonary embolism: a quasi-experimental pre-post study," the authors looked at the

impact of implementing a PERT on quality metrics, specifically LOS, mortality, bleeding, time to initiation of anti-coagulation, etc. The analysis showed a reduction in LOS, a non-significant reduction in mortality and increase in bleeding, and a faster time to initiation of anticoagulation post intervention. Strengths of the analysis are the sample size and multivariable logistic regression methodology. However, there are some limitations, which if addressed should help improve the paper:

Major Concerns:

Comment 1: In the introduction and the discussion, there is little mentioned as to other PERT pathways that have been studied. While not purely European studies, there have been at least 4-5 different manuscripts in the last 2-3 years that have looked at the impact of PERT on clinical outcomes. This is especially pertinent to the discussion, where paragraph 2 suggests that this has not been studied (references at the bottom). These should be incorporated, specifically citing consistencies or differences in this experience from the other previous studies.

Reply 1: With regard to PERT, unfortunately in our hospital we do not have a rapid response team for pulmonary embolism. In our study we tried to evaluate the impact of an integrated care pathway (ICP) for pulmonary embolism. In the text we mean that an integrated care plan for pulmonary embolism covers a broader field than a PERT, and we try to evaluate the impact of a IPC on the quality of care.

Changes in the text: Thank you very much for your suggestion. We have added the references to the bibliography (6-9) and we have modified the manuscript. See Introduction page 3, line 54.

See supplementary data (integrated care pathway)

Comment 2: In the methods, more information is needed in the “selection of Variables” subsection. First, it is organized together as “variables”, but likely should be broken up into outcomes of interest (first paragraph within this paper) and co-variables. Furthermore, more information is needed into defining “high risk PE” and “recanalization surgery”. While PESI score is a marker of risk and mortality, it is not criteria used to determine deployment of thrombolytics, recanalization or mechanical support. Were measures of RV size/function assessed? Were the hemodynamic parameters of sPESI better predictors of outcomes.

Reply 2: Thank you very much for your comment. The variables that we have described in the first place, have been the quality indicators used by our hospital to assess the quality of the care process. Subsequently, demographic parameters and finally scales commonly used in the management of PE. Unfortunately, we have not collected hemodynamic parameters, only the final report of RV dysfunction in echocardiography or final report of indirect signs of RV enlargement by CT angiography as an indicator of RV dysfunction.

- Following your comments, we have added Risk-adjusted management strategy for acute pulmonary embolism.

- We have changed in the document the term “recanalization” for a more suitable term: “reperfusion treatment”. In our hospital, we perform two reperfusion treatments: systemic thrombolysis and percutaneous catheter-directed treatment, the latter is only performed in patients with high-risk pulmonary embolism (with hemodynamic instability) and who have an absolute contraindication for systemic fibrinolysis.

- We have attached the care pathway as attached material where the procedures and doses are detailed.

Changes in the text:

See changes in table 1.

We have modified the manuscript. See Results page 8, lines 143-144, Discussion: page 10, lines 192-197.

See page 6, line 109. Page 8, line 152. Page 11, line 225-226. Page 13, line 272.

Comment 3: There are quite a few references to the institutions local practice that either require further clarification or omission as they may not be applicable to the broader audience. For example, the discussion in the 3rd paragraph of the Discussion heavily emphasizes the impact of their internal medicine service versus pulmonary or being admitted to a specific unit. These practice patterns (who is admitted to what team and level of service) vary heavily across institutions and makes it difficult for readers to truly understand what is the driver of individual outcomes.

Reply 3: Indeed, the local practices of each institution may be slightly different. There may be other alternative explanations that our study has not included, such as the doctor responsible for deciding the admission service. What we mean by our comment is that differences when entering one or another service may be due to greater adherence to

recommendations in the management of these patients. This is demonstrated in another study of our group in which we already said that this fact could be explained because the start of oral anticoagulation with vitamin K antagonists was started significantly earlier than in other services and that this could explain the shorter hospital stay.

Comment 4: The identification of patients in the methodology would need to be clarified (first section of the Methods). Initially, it suggested that this was a prospective cohort study, but then the search criteria suggested a retrospective cohort study.

Reply 4: This was a pre-post study assimilated to a quasi-experimental study. All patients were collected retrospectively and consecutively during the inclusion period comprised between 2010 and 2020. In 2014 the intervention was applied.

Following the reviewer's suggestion, we have added to the first paragraph that all information was collected from electronic health records where the patients were identified with the ICD-9 and ICD-10 diagnostic codes.

Changes in the text: See page 5, lines 73-75

Minor Concerns:

Comment 5: While Chi-square is a reasonable univariate analysis tool for comparing categorical variables between groups, continuous variables should have been assessed using t-test. Was this done?

Reply 5: Thanks for your correction, for the analysis of continuous variables, the t-student and the comparison of medians test were used, but it was not correctly reflected in the statistical analysis section.

Changes in the test: It is verified that the calculations have been carried out with the appropriate tests and the manuscript is modified.

See Statistical analysis, page 7, line 17.

Comment 6: Would recommend rephrasing the sentence starting in line 156 ("Although no significant differences were observed..."). It is okay to say a non-statistically significant reduction in mortality was observed or while there was a numerically reduced mortality rate, it did not reach statistical significance.

Reply 6: Thanks for the suggestion. It is modified in the document.

Changes in the text: See page 8, line 154-155

Comment 7: Median LOS should be compared and reported as opposed to mean. LOS is rarely a normally distributed variable, and therefore requires non-parametric analysis.

Reply 7: (See reply 5) Thanks for your correction, we comparison of medians test were used, but it was not correctly reflected in the statistical analysis section.

Changes in the test: It is verified that the calculations have been carried out with the appropriate tests and the manuscript is modified.

See Statistical analysis, page 7, line 17.

Comment 8: Discussion should include the higher rates of DOAC use (although not statistically significant) as a mechanism for reducing LOS.

Reply 8: Thank you very much for your comment. It is true that the use of DOAC is related to a decrease in LOS. However, in our study this decrease cannot be attributed to DOAC as they are rarely used. The reason is that, despite the fact that this treatment is offered to the patient, our national health system does not finance DOACs for pulmonary embolism. This is the reason that in the group post-intervention only 7.3% of the patients were treated with DOAC at discharge.

Changes in the text: See Discussion, Page 11, lines 207-212, and Reference 28.

Comment 9: Some minor grammatical errors (for example line 188: “EP” instead of “PE”)

Reply 9: Thank you for this correction.

Changes in the text: The change has been made, see Discussion, page 10, line 186.

Comment 10: While I commend the authors on improving quality in their institution to warrant SEPAR certification of excellence, this likely does not need to be added to the manuscript.

Reply 10: Thank you very much for your suggestion.

Changes in the text: We remove the comment from the manuscript. See page 12. Line 133-234.

Comment 11: Would avoid using non-standard abbreviations (i.e. – PTSD)

Reply 11: Thank you very much for your comment. Correction is made to the document.

Changes in the text: See page 7, line 120-121

PERT outcomes studies:

Jen WY, Kristanto W, Teo L, Phua J, Yip HS, MacLaren G, Teoh K, Sim TB, Loh J, Ong CC, Chee YL, Kojodjojo P. Assessing the Impact of a Pulmonary Embolism Response Team and Treatment Protocol on Patients Presenting With Acute Pulmonary Embolism. *Heart Lung Circ.* 2020 Mar;29(3):345-353. doi: 10.1016/j.hlc.2019.02.190. Epub 2019 Mar 12. PMID: 30910512.

Chaudhury P, Gadre SK, Schneider E, Renapurkar RD, Gomes M, Haddadin I, Heresi GA, Tong MZ, Bartholomew JR. Impact of Multidisciplinary Pulmonary Embolism Response Team Availability on Management and Outcomes. *Am J Cardiol.* 2019 Nov 1;124(9):1465-1469. doi: 10.1016/j.amjcard.2019.07.043. Epub 2019 Aug 7. PMID: 31495443.

Myc, L.A., Solanki, J.N., Barros, A.J. et al. Adoption of a dedicated multidisciplinary team is associated with improved survival in acute pulmonary embolism. *Respir Res* 21, 159 (2020). <https://doi.org/10.1186/s12931-020-01422-z>

Annabathula R, Dugan A, Bhalla V, Davis GA, Smyth SS, Gupta VA. Value-based assessment of implementing a Pulmonary Embolism Response Team (PERT). *J Thromb Thrombolysis.* 2021 Jan;51(1):217-225. doi: 10.1007/s11239-020-02188-3. PMID: 32542527.

Reviewer E

Comment: This is a large sample of PE patients pre and post a pathway for PE care and it demonstrated improved quality of care. This is a useful finding.

I remain unclear on the PE care pathway and whether these patients were in a specific unit.

Please specify what the internal protocol was exactly - and please specify whether these patients were taken care of on a specific unit and by whom. A flowchart for patient care delineating what types of patients were intervened upon, how were anticoagulation decisions made etc is necessary. In the discussion please elaborate on what aspects of the ICP you believe were different pre and post and what aspects you think contributed to the improvement in length of stay

Reply: We understand the questions of the reviewer. The document with the integrated healthcare process and diagrams has not been previously attached because it was not anonymized or translated. Attached now.

Changes in the text: See supplementary data (integrated care pathway)