PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Is pulmonary embolism recurrence linked with the severity of the first event ? A French retrospective cohort study.
AUTHORS	Ferrari, Emile; Fourrier, Etienne; Asarisi, Florian; Heme, Nathan; Redjimi, Nassim; Berkane, Nathalie; Labbaoui, Mohamed; Breittmayer, Jean Philippe; Bun, Sok Sithikun; MOCERI, Pamela; Squara, Fabien

VERSION 1 – REVIEW

REVIEWER	Anetta Undas Jagiellonian University, Institute of Cardiology
REVIEW RETURNED	13-May-2021

GENERAL COMMENTS	The current cohort study is the first to show that aftert 5 years since VTE, the recurrence rate was higher when the first PE was severe, which was driven by patients with provoked PE. The observation is interesting and might have practical implications if confirmed in an additional cohort. However the study design and data presentation require improvement. 1. In the Methods section, the definition of provoked and unprovoked VTE should be presented including data on additional important risk factors such as oral contraceptives. family history of VTE, chronic inflammatory diseases etc. Moreover, the medications used should be provided; for example statins as well as aspirin have been reported to reduce the risk of VTE. Data on the duration and quality of anticoagulant therapy (including the type of anticoagulants) should also be added. 2. More details on follow-up should be provided. Were the patients followed at outpatient clinics? Which definitions were used? Were the DVT episodes objectively confirmed in particular in subjects in whom they were found in the same leg. What does the term "non-normal D-dimer" mean? Did the authors use age-adjusted cut-offs or not? 3. I suggest performing aultivariable analysis to show whether the severity of acute PE represents an independent predictor of VTE recurrence. 4. Were the patients who required thrombolysis or invasive therapy eligible? If so, when excluded, were the intergroup differences still statistically significant? Minor comments All abbreviations used in tables should be spelled out below. Please double check the normal distribution of variables e.g. duration of follow-up appears non-normally distributed (please provide medians and IQR). The rate of proximal DVT should be shown.

REVIEWER	Pierre-Marie Roy University Hospital of Angers, Emergency Medicine I report personal fees and non-financial support from Aspen, Boehringer Ingelheim France, Bayer Health care, Bristol Myers Squibb and Pfizer, outside the submitted work and review.
REVIEW RETURNED	29-May-2021

GENERAL COMMENTS	The authors address an important issue, i.e., the link between the severity of acute PE and the risk of recurrence. Of a cohort of 1080 PE patients, they analyzed 417 (38.6%) patients for whom anticoagulant treatment was discontinued and who were followed at least 12 months. Using the Kaplan Meier method and the Log Rank test, they observed that the 5-year risk of VTE recurrence was higher in patients with an initial cardiac involvement (n=186) than in others (n=231). This difference was driven by patients with a provoked PE, no difference was found in the recurrence rate according to cardiac involvement in the subgroup of patients with an unprovoked PE. If confirmed, these results may help in decision making for long term anticoagulation of patients with a severe unprovoked PE with cardiac involvement. However, this study has important limitations that should at least be more addressed in the manuscript. Major comments: 1) The study is described as a prospective cohort study (l26-p5; l32-p8) or a case-control study (l28-p6). Case-control is not appropriate for this kind of study. Moreover, I wonder if this was a prospective study or a retrospective analysis of prospectively collected data from a regional registry. Please specified. 2) In this trial, a cardiac involvement was a risk factor of VTE recurrence as was the presence of DVT. Another well-known risk factors of recurrence are previous VTE and sex. A multivariate analysis involving all these factors should be performed to assess if cardiac involvement is an independent risk factor of recurrence. Detailed comments: - An IRB approval was obtained (l50-p6). More information will be helpful: the name of the ethical committee, the registration number, and the date of delivering. - In case of prospective study, could you provide the protocol? Was the subgroup analysis (provoked/unprovoked) prespecified? Was the trial registered prior the inclusion of the patients? - More details of the assessment of the patients will be helpful: o The delay between PE diagnosis and the echocardiography and the biomarkers measurement o The definition of provoked PE. Was it predefined in the protocol or left to the investigators' opinion? What were the exact provoking factors? o The assessment of concomitant DVT. Was a leg-vein compression ultrasonography systematically required? o Severity criteria. Could you provide description of the simplified PESI criteria? Rather than the troponin, BNP and RV/LV means,

	could you provide the rates of patient with abnormal results? The rate of patients with a cardiac involvement appears quite high. Could you comment? - Did an adjudication committee assess the possible recurrences and especially deaths to determine possible fatal-PE? - 72 patients had VTE recurrence, 63 (88%) had PE. Could you provide information of the severity of PE recurrence? Indeed, in addition to the rate of recurrence, the severity of recurrence and especially the risk of PE-related death may be considered to determine treatment duration. - Did you observed a correlation between PE severity, i.e., low risk, intermediate-low risk, intermediate-high risk, high risk PE and the rate of recurrence? - The sentence “the correlation between PE severity and risk of recurrence was stronger in cases of provoked PE” seems incorrect. It suggests the existence of a link between recurrence and severity in both subgroups but lower in patients with an unprovoked PE than in patients with a provoked PE. - For all the results and especially in the abstract, please provide the exact numbers of patients in addition to the percentages. - In the abstract conclusion, p values should be avoided.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Anetta Undas, Jagiellonian University

Comments to the Author:

The current cohort study is the first to show that aftert 5 years since VTE, the recurrence rate was higher when the first PE was severe, which was driven by patients with provoked PE. The observation is interesting and might have practical implications if confirmed in an additional cohort. However the study design and data presentation require improvement.
1. In the Methods section, the definition of provoked and unprovoked VTE should be presented including data on additional important risk factors such as oral contraceptives. family history of VTE, chronic inflammatory diseases etc.

> The definitions of provoked and unprovoked PE have been indicated on page 5 (ref 8 has been added). Family history of VTE as well as chronic inflammatory diseases and the data on treatment with Aspirin or Statins appears in table 1.

Moreover, the medications used should be provided; for example statins as well as aspirin have been reported to reduce the risk of VTE. Data on the duration and quality of anticoagulant therapy (including the type of anticoagulants) should also be added.

The medications used as well as the duration and quality of anticoagulant therapy are reported in the text on page 5.

Because anticoagulant treatments used were quite exclusively non Vit K antagonists oral anticoagulants, there was, as in our clinical practice, no control of the quality of anticoagulation treatment.

2. More details on follow-up should be provided. Were the patients followed at outpatient clinics?

This information has been added on page 6.

Indeed all patients were followed in our institution at 1, 3 or 6, then every 12 months.

Which definitions were used? Were the DVT episodes objectively confirmed in particular in subjects in whom they were found in the same leg. What does the term "non-normal D-dimer" mean? Did the authors use age-adjusted cut-offs or not?

Yes, the definition of recurrences have been specified in page 6.

The term « non-normal D-dimer » has also been modified on page 6.

Indeed we used age-adjusted values cut-offs. This has been notified on page 6.

3. I suggest performing multivariable analysis to show whether the severity of acute PE represents an independent predictor of VTE recurrence.

Multivariable analysis has been realized by introducing parameters such as sex, associated DVT, Duration of anticoagulation … results are reported in the abstract , in the text and also in a new table (Table 3)

This multivariate analysis confirms an independent link between PE severity and recurrence (Thanks to the reviewer for this query)

4. Were the patients who required thrombolysis or invasive therapy eligible? If so, when excluded, were the intergroup differences still statistically significant?

Yes, patients who underwent a thrombolysis were eligible.

This was noticed in the patient details on page 6 and in Table 1.

In this cohort, no patients received mechanical thrombolysis.

Minor comments

All abbreviations used in tables should be spelled out below.

The abbreviations have been spelt out.

Please double check the normal distribution of variables e.g. duration of follow-up appears non-normally distributed (please provide medians and IQR).
The rate of proximal DVT should be shown.

Distribution has been checked and medians and IQR are now provided for non normal distribution parameters

Reviewer: 2
Dr. Pierre-Marie Roy, University Hospital of Angers, Université d'angers, UFR Santé
Comments to the Author:
The authors address an important issue, i.e., the link between the severity of acute PE and the risk of recurrence. Of a cohort of 1080 PE patients, they analyzed 417 (38.6%) patients for whom anticoagulant treatment was discontinued and who were followed at least 12 months. Using the Kaplan Meier method and the Log Rank test, they observed that the 5-year risk of VTE recurrence was higher in patients with an initial cardiac involvement (n=186) than in others (n=231). This difference was driven by patients with a provoked PE, no difference was found in the recurrence rate according to cardiac involvement in the subgroup of patients with an unprovoked PE.
If confirmed, these results may help in decision making for long term anticoagulation of patients with a severe unprovoked PE with cardiac involvement.

However, this study has important limitations that should at least be more addressed in the manuscript.

Major comments:

1) The study is described as a prospective cohort study (l26-p5; l32-p8) or a case-control study (l28-p6). Case-control is not appropriate for this kind of study. Moreover, I wonder if this was a prospective study or a retrospective analysis of prospectively collected data from a regional registry. Please specified.

Indeed this study is a retrospective analysis of prospectively collected data (NCT04980924)
The terms retrospective analysis of prospectively collected data have been corrected throughout the article as In the title

2) In this trial, a cardiac involvement was a risk factor of VTE recurrence as was the presence of DVT. Another well-known risk factors of recurrence are previous VTE and sex. A multivariate analysis involving all these factors should be performed to assess if cardiac involvement is an independent risk factor of recurrence.

Multivariable analysis has been realized by introducing parameters such as sex, associated DVT, Duration of anticoagulation … results are reported in the abstract, in the text and also in a new table (Table 3)
This multivariate analysis confirms an independent link between PE severity and recurrence (Thanks to the reviewer for this query)

Detailed comments:

- An IRB approval was obtained (l50-p6). More information will be helpful: the name of the ethical committee, the registration number, and the date of delivering.

This study being a retrospective analysis of prospectively collected data it was not suitable for a partnering with patients, their careers, support networks, and the public. Our study is in accordance with law n78-17 « Information, technology and freedom » of 6th January 1978 (modified by the new act dated 6th August 2004) and with the EU 2016/679 European Parliament and the 27 April 2016 Council regulation, applicable from May 25th of 2018 (GDRP)

- In case of prospective study, could you provide the protocol? Was the subgroup analysis (provoked/unprovoked) prespecified? Was the trial registered prior the inclusion of the patients?

This study is a retrospective analysis of prospectively collected data however the definitions of provoked or unprovoked PE where used following consensual definitions.
This have been specified in the text. A ref have also been added.

- More details of the assessment of the patients will be helpful:
o The delay between PE diagnosis and the echocardiography and the biomarkers measurement

In our patients care, the first echocardiography is realised upon admission, as well as a biomarkers measurement. Biomarkers are repeated at H12, H24 and H48. This have been added in the text page 5

o The definition of provoked PE. Was it predefined in the protocol or left to the investigators' opinion? What were the exact provoking factors?

The definitions of provoked or unprovoked PE used are in accordance with consensual definitions.

This have been specified in the text. A ref (8) has also been added.
Furthermore, this classification is verified at the one month follow-up visit, because new elements, often provided by the family, could highlight unreported aetiologies during the hospitalization of patients.

o The assessment of concomitant DVT. Was a leg-vein compression ultrasonography systematically required?

A venous echo-doppler is always performed upon admission of the patient in the same time than echocardiography (this have been added page 5)

o Severity criteria. Could you provide description of the simplified PESI criteria? Rather than the troponin, BNP and RV/LV means, could you provide the rates of patient with abnormal results? The rate of patients with a cardiac involvement appears quite high. Could you comment?

The PESI score could not be used because we have excluded patients with active cancer and we aim to quantify the severity of PE rather than the risk of mortality even if both can be correlated.

We have used the criteria which, according to the ESC guidelines, allow the classifications in low-risk PE, intermediate-risk PE and high-risk PE.

The proportion of patients with a cardiac involvement i.e. 45% is usual in our recruitment.

- Did an adjudication committee assess the possible recurrences and especially deaths to determine possible fatal-PE?

Because our study is not randomized there has been no adjudication of the recurrences and the causes of deaths could not be specified. This have been reported page 6.

- 72 patients had VTE recurrence, 63 (88%) had PE. Could you provide information of the severity of PE recurrence? Indeed, in addition to the rate of recurrence, the severity of recurrence and especially the risk of PE-related death may be considered to determine treatment duration.

As the causes of death could not be specified, these information are lacking. This has been added in the text at the end of “method” paragraph.

- Did you observed a correlation between PE severity, i.e., low risk, intermediate-low risk, intermediate-high risk, high risk PE and the rate of recurrence?

As indicated in the flow chart Fig 1 page 17; Our study separated low-risk PE (without cardiac involvement) from intermediate and high-risk PE (with cardiac involvement). This has been precised in the chapter concerning the classification of the 2 groups of PE. The isolated group of high-risk PE (n=21) seemed too small for a statistical analysis.

- The sentence “the correlation between PE severity and risk of recurrence was stronger in cases of provoked PE” seems incorrect. It suggests the existence of a link between recurrence and severity in both subgroups but lower in patients with an unprovoked PE than in patients with a provoked PE.

We agree. The sentence has been modified on page 2 and in the conclusion of the main text.

- For all the results and especially in the abstract, please provide the exact numbers of patients in addition to the percentages.

The exact number has been specified on pages 1 and in the result chapter.

- In the abstract conclusion, p values should be avoided.

P values have been removed.

VERSION 2 – REVIEW

REVIEWER	Anetta Undas Jagiellonian University, Institute of Cardiology
REVIEW RETURNED	29-Aug-2021

GENERAL COMMENTS	The paper ha simproved however some issues should be addressed. 1. Study limiatations should be presented as a separate paragraph. The current version contains 2 sentences regarding the limitations of the study design. Other issues to be mentioned are among others: reporting of only symptomatic episodes, no data on potential changes in risk factors over time (e.g. obesity, smoking etc). 2. Some variables are most likely non-normally distributed for instance in Table 2, tp (ng/l) with large SDs. The variables should be shown as medians with interquartile range, Was the distribution of variables assessed? minor comments Family history of VTE was not presented in Table 1 or 2, but it appered in Table 3. Figures , X axis - instead "discontinuation anticoagulant" it should be "doscontinuation of anticoagulation" Doea the term"supra-ventricular arrthymia" (e.g. Fig. 1) mean "atrial fibrillation"? If not, this exclusion criterion is controversial.

REVIEWER	Pierre-Marie Roy University Hospital of Angers, Emergency Medicine I report personal fees and non-financial support from Aspen, Boehringer Ingelheim France, Bayer Health care, Bristol Myers Squibb and Pfizer, outside the submitted work and review.
REVIEW RETURNED	08-Sep-2021

GENERAL COMMENTS	I thank the authors for this important review. However, I was a little confused because the revised manuscript with marked changes differed from the final unmarked manuscript in several points as in the result of the multivariate analysis. I based my review on the unmarked final manuscript. Most of my comments have been taken into account in this version. I still have only a few remarks and suggestions. 1) To avoid misinterpretation, PE with cardiac involvement should be mentioned rather than severe PE along the paper. 2) Abstract: - Participants: a more precise definition of cardiac involvement should be mentioned: increased cardiac biomarker(s) and/or

	echocardiographic right ventricular dysfunction? - Results: the sentence “When the first PE was unprovoked, no difference is found (p=0.27)” could be delated or at least, reformulated. Indeed, in multivariate analysis cardiac involvement was an independent risk factors of recurrence whereas provoked PE was associated with a low risk of recurrence. - Conclusion: the rates of recurrences should be delated or replaced in the result paragraph. 3) Objective and methods: - In the following sentence “PE with no cardiac involvement when none of the above-mentioned criteria were present corresponding to low-risk PE according to the ESC classification”, the ESC guidelines severity risk classification seems partly incorrectly interpreted. Indeed, PE patients without cardiac involvement but with a simplified PESI ≥ 1 or PESI class III-V are classified as intermediate risk rather than low-risk PE. - How the items included in the multivariate analysis were chosen should be specified. It is unusual to assess “family history of PE” rather than “family history of VTE”. This patients’ characteristic should be mentioned in table 1. 4) Results - The results of the multivariate analysis could be presented in a less declarative way. Rather than “Multivariate analysis… demonstrates that…”, you can say “In the multivariate analysis including cardiac involvement, gender, family history of PE, psychotropic medication, unprovoked PE, associated DVT and duration of anticoagulation, cardiac involvement (HR…) and family history of VTE (…) were independent risk factors of recurrence…” 5) Discussion - Some other limitations of this retrospective trials may be mentioned: i. The used definition of PE severity (cardiac involvement) differed from the ESC guidelines and ACCP guidelines. ii. Patients with long term anticoagulation and with active cancer were excluded. iii. Some known risk factors of recurrence were not taken into account in the multivariate analysis as old age, high body mass index or high D-dimer level (cf. validated prediction models of recurrence as HERDOO2, Vienna prediction model, DASH…). 6) Strengths and limitations - The fourth sentence is poor informative. - Other limitations could be mentioned (see upper)

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Anetta Undas, Jagiellonian University Comments to the Author:

The paper ha simproved however some issues should be addressed.

1. Study limiatations should be presented as a separate paragraph. The current version contains 2 sentences regarding the limitations of the study design. Other issues to be mentioned are among others: reporting of only symptomatic episodes, no data on potential changes in risk factors over time (e.g. obesity, smoking etc).

Indeed we add several limitation points at the end of discussion paragraph taking into account also the 2nd reviewers queries addressing the same point.

The paragraph becomes: Our study was a retrospective analysis of prospectively collected data. There are possible limitations; we report only symptomatic episodes, potential changes in risk factors over time (e.g. obesity, smoking …) could not be taken into account. Some known risk factors of recurrence were not considered in the multivariate analysis as high body mass index or high D-dimer level. Our conclusions cannot be applied to cancer patients or those needing long-term treatment since these patients were excluded from the study. Our results deserves to be confirmed in a dedicated prospective study.

2. Some variables are most likely non-normally distributed for instance in Table 2, tp (ng/l) with large SDs. The variables should be shown as medians with interquartile range, Was the distribution of variables assessed?

Indeed Tp as BNP are not normally distributed there are now reported as mean ± SD (table 2). The statistical analysis paragraph has been update (page 7).

minor comments

Family history of VTE was not presented in Table 1 or 2, but it appered in Table 3.

Family history of VTE is now reported in table 2

Figures , X axis - instead "discontinuation anticoagulant" it should be "doscontinuation of anticoagulation"

Done In all figures

Doea the term"supra-ventricular arrthymia" (e.g. Fig. 1) mean "atrial fibrillation"? If not, this exclusion criterion is controversial.

Yes it does

Reviewer: 2

Dr. Pierre-Marie Roy, University Hospital of Angers, Université d'angers, UFR Santé Comments to the Author:

I thank the authors for this important review. However, I was a little confused because the revised manuscript with marked changes differed from the final unmarked manuscript in several points as in the result of the multivariate analysis. I based my review on the unmarked final manuscript.

Most of my comments have been taken into account in this version.

I still have only a few remarks and suggestions.

1) To avoid misinterpretation, PE with cardiac involvement should be mentioned rather than severe PE along the paper.

done.

2) Abstract:

- Participants: a more precise definition of cardiac involvement should be mentioned: increased cardiac biomarker(s) and/or echocardiographic right ventricular dysfunction?

Done as proposed:

those with associated cardiac involvement (increased cardiac biomarker(s) and/or echocardiographic right ventricular dysfunction) and those with no cardiac involvement

- Results: the sentence “When the first PE was unprovoked, no difference is found (p=0.27)” could be delated or at least, reformulated. Indeed, in multivariate analysis cardiac involvement was an independent risk factors of recurrence whereas provoked PE was associated with a low risk of recurrence.

Done (cancelled)

- Conclusion: the rates of recurrences should be delated or replaced in the result paragraph.

Done (cancelled)

3) Objective and methods:

- In the following sentence “PE with no cardiac involvement when none of the above-mentioned criteria were present corresponding to low-risk PE according to the ESC classification”, the ESC guidelines severity risk classification seems partly incorrectly interpreted. Indeed, PE patients without

cardiac involvement but with a simplified PESI ≥ 1 or PESI class III-V are classified as intermediate risk rather than low-risk PE.

I understand the concern of the reviewer and I agree. As previously mentioned, we excluded patients with cancer. As a consequence one of the major comorbidity item of the PESI score was not available. But, I agree, this point deserves to be indicated and I propose: “PE with no cardiac involvement when none of the above-mentioned criteria were present corresponding mainly to low-risk PE according to the ESC classification 9. “ page 6

- How the items included in the multivariate analysis were chosen should be specified. It is unusual to assess “family history of PE” rather than “family history of VTE”. This patients’ characteristic should be mentioned in table 1.

The items included in the multivariate analysis were those available in our register. Age has not been integrated because it was not significant in univariate analysis.

Indeed we meant family history of VTE. This has been added in table 2

4) Results

- The results of the multivariate analysis could be presented in a less declarative way. Rather than “Multivariate analysis… demonstrates that…”, you can say “In the multivariate analysis including cardiac involvement, gender, family history of PE, psychotropic medication, unprovoked PE, associated DVT and duration of anticoagulation, cardiac involvement (HR…) and family history of VTE (…) were independent risk factors of recurrence…”

Done. We used the proposed formulation.

5) Discussion

- Some other limitations of this retrospective trials may be mentioned:

i. The used definition of PE severity (cardiac involvement) differed from the ESC guidelines and ACCP guidelines.

ii. Patients with long term anticoagulation and with active cancer were excluded.

iii. Some known risk factors of recurrence were not taken into account in the multivariate analysis as old age, high body mass index or high D-dimer level (cf. validated prediction models of recurrence as HERDOO2, Vienna prediction model, DASH…).

Done: all these limitations were added at the end of the discussion. These modifications also took into account the reviewer 1 proposal.

6) Strengths and limitations

- The fourth sentence is poor informative.

Cancelled and replaced by one of the limitations added in the discussion and proposed by reviewer 1: Only symptomatic events were taken into account

- Other limitations could be mentioned (see upper) Only 5 items are required including the strengths of the study.

I thank the reviewers for their constructive remarks

VERSION 3 – REVIEW

REVIEWER	Anetta Undas Jagiellonian University, Institute of Cardiology
REVIEW RETURNED	15-Sep-2021

GENERAL COMMENTS	no further comments

REVIEWER	Pierre-Marie Roy University Hospital of Angers, Emergency Medicine I report personal fees and non-financial support from Aspen, Boehringer Ingelheim France, Bayer Health care, Bristol Myers Squibb and Pfizer, outside the submitted work and review.
REVIEW RETURNED	15-Sep-2021

GENERAL COMMENTS	I thank the authors to have taken into account all my remarks. I have no further comment.