Peer review file

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Reviewer A

This study was performed to investigate whether cardiovascular risk factors are risk factors for unprovoked PE and to establish the association with disease severity and prognosis.

Major comments

Comment 1: Several studies have investigated the association of cardiovascular risk factors with venous thromboembolism (VTE) for a large numbers of patients (Mahmoodi et al. Circulation 2017;135:7), although the data were controversial. A recent population-based study showed that older age, smoking, and adiposity were consistently associated with higher VTE risk (Gregson et al. JAMA Cardiology 2019;4:163). In this study, age and hypertension were independent risk factors for unprovoked PE. However, the numbers of subjects in this study were smaller, as compared with previous studies.

Reply 1: Thank you for this citation (Mahmoodi et al). This clearly shows that not always there is agreement when associating cardiovascular risk factors with an increase on the VTE. Following this comment, we have introduced the following modification at the beginning of the second paragraph of the discussion section: "*Though in a recent meta-analysis Mahmoodi et al did not find an association between traditional modifiable cardiovascular risk factors with an increase on the risk of VTE (Mahmoodi BK, Cushman M, Naess IA, et al. Association of Traditional Cardiovascular Risk Factors with Venous Thromboembolism: An Individual Participant Data Meta- analysis of Prospective* Studies. Circulation 2017;135:7-16), there is ….".

Regarding the citation by Gregson et al it is already included in the manuscript, and there is the following comment "*obesity, smoking and an advanced age are associated with a higher risk for VTE*".

Finally, we do agree with the comment regarding the limited sample size, and we have included a new paragraph in the discussion section highlighting the limitations and the fact that we have a relatively small sample size, particularly when assessing the effect of variables with a low frequency (such as diabetes or obesity).

Comment 2: Adjusted ORs (Table 3) and Ors (Table 4) may not be significantly different between 2 and ≥3 cumulative number of CRF, although p-values were not presented. Thus, other CRFs other than age and hypertension may not have an effect on Table 3 and 4. The importance of "cumulative number of CRF" would decline.

Reply 2: Thank you for this point. Tables 3 and 4 present different information and are not comparable. But it is true that the risks are not very different for 2 vs 3 risk factors in both tables. It is striking that we have not observed a relevant increase in the Ors of unprovoked PE when the accumulated number of risk factors turns from 2 to 3, but we have no explanation for this observation. Following your comment, we have also added the p-values in Table 3 and we have also added as a limitation (in the new paragraph showing the study limitations) that we have not measured all possible cardiovascular risk factors. We have included the p-values in Table 3. Please check the tracked changes version of the manuscript.

Comment 3: The severity of PE was presented by simplified PESI alone in this study. In addition to PESI or simplified PESI, RV dilation by CT scan or echocardiography, and blood biomarkers should be considered in risk stratification of PE. Thus, data regarding these parameters are needed.

Reply 3: Thank you for this comment. The reviewer is asking for different parameters that, of course, are very helpful regarding the risk stratification of PE. Nevertheless, the simplified PESI has

been developed and validated to determine the seriousness of PE (Jiménez D, et al. RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170:1383-9; Righini M et al. The Simplified Pulmonary Embolism Severity Index (PESI): validation of a clinical prognostic model for pulmonary embolism. J Thromb Haemost 2011;9:2115-7; Sam A, et al. The shock index and the simplified PESI for identification of low-risk patients with acute pulmonary embolism. Eur Respir J 2011;37:762-6). As with the original version of PESI, the strength of the Spesi lies in the reliable identification of patients at low risk for 30 day mortality. Furthermore, the prognostic performance of the Spesi has been confirmed in observational cohort studies (Elias A, et al. Prognostic models in acute pulmonary embolism: a systematic review and meta-analysis. BMJ Open 2016;6:e010324; Kohn CG, et al. Prognostic accuracy of clinical prediction rules for early post-pulmonary embolism allcause mortality: a bivariate meta-analysis. Chest 2015;147:1043-62). Therefore, we believe that Spesi is a reliable tool to assess PE seriousness and can be used in studies settled in daily clinical practice, such as ours. Nevertheless, we have included the lack of information highlighted by the reviewer in the paragraph addressing the study limitations.

Comment 4: The selection criteria of the CRFs (age, active smoking, and obesity) were not described.

Reply 4: The selection of CVRF from the REMOTEV study were taken as a reference (Ref 17: Gaertner S, Cordeanu E-M, Mirea C, et al. Increased risk and severity of unprovoked venous thromboembolism with clustering cardiovascular risk factors for atherosclerosis: Results of the REMOTEV registry. *Int J Cardiol*. 2018;252:169-174). Detailed information on each criteria such as age, smoking, and obesity, is described in the methods section (fifth paragraph).

Comment 5: The content of Table 4 was repeated in Figure 2. Thus, Table 4 or Figure 2 can be removed.

Reply 5: We do not believe that this information is repeated. Table 4 shows only information of provoked PE, while figure 2 gives information of both provoked and unprovoked PEs. Furthermore, figure 2 describes only patients with sPESI with a score higher or equal to 1, and this is the reason why PESI percentages are not the same between Table 4 and figure 2.

Comment 6: Text (result section) and Figure 3 are redundant data: mortality according to simplified PESI.

Reply 6: Thank you for this suggestion. We have deleted figure 3, as suggested.

Comment 7: In Discussion, paragraphs for study limitation and conclusions are needed.

Reply 7: We have included this information, following the aforementioned comments. Please check the tracked changes version of the manuscript.

Comment 8: Minor comments

I think that there are typos.

1. Line 144, 145, 182: EP to PE (pulmonary embolism). They are corrected in the manuscript

2. Line 204: PD to PE . It´s corrected

3. Line 219: presence or not of CRF-- presence or absence of CRF. It´s corrected

4. Line 228: OR with 95% confidence interval-- odds ratio (OR) with 95% confidence interval (CI) It´s corrected

5. Line 238: recurret to recurrent It´s corrected

6. Line 260: 95CI% to 95% CI, IC95% to 95% CI It´s corrected

7. Table 1

1) Obesidad to Obesity It´s corrected

2) Dyslipemia to Dyslipidemia. It´s corrected

3) Previus stroke to Previous stroke It´s corrected

4) Pulmonary embolism/deep vein thrombosis previus to Previous PE/DVT It´s corrected

5) In column 4 (p-value), remove each "p": for example, p=0.736 to 0.736 or p < 0.001 to <0.001 They are corrected in the manuscript

8. Table 2.

1) Lactate >2 to Lactate > 2 mmol/L It´s corrected

2) What does GSV mean? ESR, erythrocyte sedimentation rate (It´s corrected in the table 2)

3) In column 4 (p-value), remove each "p": for example, p=0.736 to 0.736 or p < 0.001 to <0.001 They are corrected in the manuscript

4) The raw OR of "thrombocytosis" needs to be corrected. 0,49 (0,34-0,56) (It´s corrected in the table

Reviewer B

Comment 1: In your manuscript, you performed a case control study that categorized into provoked and unprovoked pulmonary embolism and you choose the reference of 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism(Ref. 2).

But there is updated guidelines that published at 2019.

And the 2019 ESC guidelines don't recommend to categorize pulmonary embolism into "provoked "and "unprovoked".

The new ESC guidelines says as belows ;

Terminology such as 'provoked' vs. 'unprovoked' PE/VTE is no longer supported by the guidelines, as it is potentially misleading and not helpful for decision-making regarding the duration of anticoagulation.

Reference>

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). Eur Respir J. 2019;54(3):1901647. Published 2019 Oct 9. doi:10.1183/13993003.01647-2019

So I think that your manuscript would be not compatible with this updated 2019 ESC guidelines and there were previous studies that reveal the relationship of cardiovascular risk factor with the venous thromboembolism. Moreover, the 2019 ESC guidelines include theses risk factors.

What is the outstanding point of your manuscript?

I recommend to revise your manuscript according to the new guidelines.

Reply 1: Thank you for this comment. 2019 guidelines avoid the use of the terms “unprovoked” or “idiopathic” and use the terms “identifiable risk factor” (which can be classified in “transient/reversible” or “persistent” risk factor) and “no identifiable risk factor”. We think that this classification is much more precise. This discrepancy might be solved with a change in the terminology used in the new version of the manuscript. Therefore, “unprovoked PE” would be those corresponding to no identifiable risk factor, and provoked PE would be those termed “identifiable risk factor”, without differentiating transient or persistent. As it can be observed in Table 8.4 of these guidelines, the new terminology is used to establish recommendations for the regimen and duration of anticoagulation after pulmonary embolism in patients without cancer, and for that, they are based in references already used in the previous guideline where the terminology “unprovoked” and “provoked” was used. In any case, we think that this issue does not alter our conclusion that “A relationship was observed between CVRF and PE without identifiable risk factor, as the risk for PE without identifiable risk factor increased with the number of CVRF. In addition, the number of CVRF was associated with PE without identifiable risk factor severity, but not with prognosis”.

Regarding the affirmation that “and there were previous studies that reveal the relationship of cardiovascular risk factor with the venous thromboembolism”, it is true that in some studies this association has been obtained, but not in all studies, as in the one by Mahmoodi BK, et al. Association of Traditional Cardiovascular Risk Factors with Venous Thromboembolism: An Individual Participant Data Meta-analysis of Prospective Studies. Circulation 2017;135:7-16, which is now included in the new version.

Comment 2: I wonder that the population who used the aspirin, anticoagulation, and NOAC, etc before the occurrence of thromboembolism, especially in whom with cardiovascular disease.

Reference>

Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. The New England Journal of Medicine. 2012;(21):1979.

Reply 2: This is an interesting question, referring to reference number 16 of our paper. In our study, we are registering information on the long-term antithrombotic treatment following a first episode of confirmed PE.

Comment 3: I recommend to change the abbreviation of cardiovascular risk factor.

The ‘CRF’ may have the possibility of misleading that means ‘Chronic renal failure’

So ‘CVRF’ will be better and the article belows used the abbreviation.

Reference>

Gaertner S, Cordeanu EM, Mirea C, et al. Increased risk and severity of unprovoked venous thromboembolism with clustering cardiovascular risk factors for atherosclerosis: Results of the REMOTEV registry. Int J Cardiol. 2018;252:169-174. doi:10.1016/j.ijcard.2017.11.055

Reply 3: It’s corrected.

Comment 4: There are errors in abbreviation of text and commas in Table 2,4.

Reply 4: It’s corrected.