Peer review file

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Reviewer A

Comment 1: How the Authors differentiate pulmonary effusion due to pneumonia and APE pulmonary infraction? Please add to the "Methods" section.

Reply: Thanks for the reviewer's suggestion. There are many causes which lead to pleural effusion, including pneumonia, malignant diseases, tuberculosis, heart failure, etc. We added the related diagnostic criteria of parapneumonic pleural effusion in the section of Methods (Page 4). Thank you for your kind understanding.

Comment 2: Pulmonary embolism risk stratification is according clinical symptoms (BP), scales (PESI, sPESI), biomarkers (troponins, BNP/NT-proBNP) and imaging (echo/CT), not only sPESI. It is not correct to stratify patients only according sPESI scale (Methods section, table 1). Please provide the information about how many patients were high risk, intermediate high, intermediate low and low risk. Please cite the recent European APE guidelines. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ní Áinle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; ESC Scientific Document Group.Eur Heart J. 2020 Jan 21;41(4):543-603.

Reply: Thanks for your suggestion. We have cited the recent European APE guidelines to stratify patients with high risk, intermediate high, intermediate low and low risk, and re-analyze the data (Ref 14). The results are listed in Table 1.

Comment 3: It is surprising that mean hospital stay was 19.99 and 15.3 days. Why so long? Please cite the paper by Paczyńska et al and discuss (Paczyńska M, Kurnicka K, Lichodziejewska B, Goliszek S, Dzikowska-Diduch O, Sobieraj P, Burzyński Ł, Kostrubiec M, Pruszczyk P, Ciurzyński M.Kardiol Pol. 2016;74(7):650-6.). The hospital stay in Polish group was 6-8 days.

Reply: We agree with the reviewer that mean hospital stay was long in this study, we also cited the article with your recommendation (Ref 26). This may be explained by the extreme values of LOS in a subset of our cohort, which may have skewed the results; alternatively, as China is a developing country, hospitalized patients have high expectations for treatment, resulting in a relatively long LOS (Page 11). Thank you for your kind understanding.

Comment 4: Please add the data about pleural effusion according to risk stratification group: high risk, intermediate high, intermediate low and low risk.
Reply: Thank you for your comment. We have revised the manuscript with your suggestion, and the results were listed in Table 1.

Comment 5: Please add the most important echocardiographic data: RV/LV, TRPG.
Reply: Thank you for your kind suggestion, we have re-checked the medical record of included patients, and since this is a retrospective study and quite a lot data of RV/LV, TRPG were missing, we can't make a meaningful statistical analysis based on limited data, we will pay attention to this issue in our further study. Thank you again for your kind suggestion.

Reviewer B:

Comment 1: I am not sure that the right term is "incidence" rather than "prevalence" of pleural effusion
Reply: Thanks for your kind suggestion and we have replaced incidence with prevalence in the text.

Comment 2: The Authors report a number of statistical analyses showing differences between patients with and without pleural effusion. It should be made clear in the text that none of the analyses were predefined based on previous reports, and therefore must be considered only as post-hoc analysis

Reply: We agree with the reviewer that our study is a post-hoc analysis, and we have made it clear in “Statistical Analysis” section in the text (Page 6).

Comment 3: The word gender (table 4) should be changed to sex as the two terms are no longer considered synonyms

Reply: Thanks for your kind suggestion and we have replaced gender with sex in the Table 4.

Comment 4: Although the text is easy to understand, it would benefit from a further style and grammar check

Reply: Thanks. We have read through the manuscript, corrected the typos and changed some wording in the manuscript with the help of Charlesworth Author Service, and we uploaded certification of English editing into the submission system.

Reviewer C

The manuscript has many grammatical errors along with poor sentence formulation.

The study itself does not add much to existing literature regarding the presence of pleural effusions in patients presenting with acute pulmonary embolism. It is a retrospective study which did not show an increase in mortality in patients with APE and pleural effusion.

Reply: Thank you for your comment. We do admit that this study is a retrospective study, we think there are several improvements in our study. Firstly, the prevalence of pleural effusion in Chinese cohort of APE remain lack of data, we provide further data regarding on pleural effusion and APE; Secondly, after analysis, we get different results from previous studies and we find that pleural effusion is not an risk factor of 30day mortality for patients with APE, and we make a re-visitation on this issue. Thank you for your kind understanding.

Reviewer D

major concern

Comment 1: The authors mention pleural effusion as a risk for death at 30 day in-hospital mortality. It is important that management is mentioned eg were more patients in the effusion group given thrombolysis which may indicate increased clinical severity of that group and therefore be a reasonable explanation for death.

Reply: Thank you for your comment, we have investigated a number of factors which were may be related to 30 day in-hospital mortality, such as age, sex, congestive heart failure, heart rate, SPESI, and so on, as shown in the Table 4. However, after a multivariable analysis, we found pleural effusion is not a risk for death at 30 day in-hospital mortality. For thrombolysis treatment, only one patient received thrombolysis treatment, and there was no difference on severity regarding on SPESI criteria. Thus, the contribution to the mortality of patients with APE is so complex and need further studies to clarify this issue.

Comment 2: A Kaplan-Meier curve is presented to show increased risk of death. The absolute change in survival is small and the Log rank analysis reflects that. They do not mention absolute patient numbers in hospital at each of the points in each group. Presuming half of the control patients would have been discharged by about day 15, and half of those in the effusion group by day 20, these numbers are important and should be included in Figure 2.

Reply: Thank you for your kind suggestion. We have added the absolute patient numbers in hospital at each of the points in each group in revised Figure 2.

Comment 3: (1) 30 days is a very long length of hospital stay in patients with PE and the obvious question is whether a confounder is the explanation for that eg. did patients have longer LOS and higher mortality due to malignancy? This needs further discussion.

Reply: We do agree with the reviewer that 30 days is a very long length of hospital stay in patients with PE, and malignant pleural effusion were excluded from this study, This may be explained by the extreme values of LOS in a subset of our cohort, which may have skewed the results; alternatively, as China is a developing country,

hospitalized patients have high expectations for treatment, resulting in a relatively long LOS (Page 11). Thank you for your kind understanding.

(2) NT-proBNP is significantly higher in the effusion group than the control group, which indicates, (probably along with the echocardiogram evidence of RV/LV ratio) right heart strain and is a well-recognized indicator of risk in patients with PE. The authors should include a discussion of these features.

Reply: Thank you for your comment. NT-proBNP is a frequently cardiac biomarker for risk stratification in acute pulmonary embolism. Several studies have indicated that abnormal levels of NT-proBNP as an indicator of right ventricular dysfunction, which indicated an increased risk of adverse outcome. We have discussed this issue in the section of Discussion (Page 11).

Comment 4: The authors show NT-proBNP is a log power higher in the non-survivor group than the survivor group, with a P value <0.001 and yet the Cox regression shows a HR of only 1 (with 95%CI 1.0-1.0). This is intriguing and probably needs further explanation to add weight to it as a conclusion. It needs to be confirmed and discussed further.

Reply: Thank you for your comment, and we consulted the statisticians on this issue. Although NT-proBNP is increased in the non-survivor group than the survivor group, while during the course of multivariate Cox regression, other potential covariate of mortality like age, gender, etc were all considered, and after adjusted for these factors, the effect of NT-proBNP on mortality of patients of APE may be decreased. The result was generated by the software, thank you so much for your kind understanding.

Comment 5: These issues influence the conclusions that can be derived from the data. I'm not sure the K-M curve should be included as it is not significant and shows little absolute change in survival anyway. I think the strength of this paper lies more in the examination of clinical data and how this made differences in outcome, as opposed to the association between effusion and APE.

Reply: The K-M curve is well-known method of survival analysis. In this study, the K-M curve was used to study the relationship between survival time and outcome and pleural effusion, it found that pleural effusion may increase risk of death, while log-rank analysis found that the difference between the pleural effusion group and non-pleura effusion group had no statistical significance. We keep the figure of K-M curve and we also examined the potential association between other clinical data and outcomes. Thank you for your kind understanding.

Comment 6: Finally, the concluding paragraph should be rewritten to emphasize that the best that can be said for effusion in patients with APE from these data, is an association between them but it cannot imply causation, as the paragraph seems to suggest.

Reply: Thank you for your kind suggestion. We have rewritten the concluding paragraph of the paper in the revised version (Page 12).

Comment 7: Again, in order to make the results more generalizable, the long LOS must be addressed in the text or the article loses impact.

Reply: Thank you for your comment, we have revised the manuscript and discussed this issue on Page 11.

Minor concerns

Comment 1: There are many examples where language and syntax need to be corrected. Acknowledging the problems with English as a second language, a professional academic translation service may be of use. While I have been through the paper and corrected much of the language, it should be done prior to the reviewing stage.

P9, line 21. The percentage says 17363.4% (presumably this should be 63.4%).

P12, line 12-13 The sentence needs to be rewritten.

Reply: Thank you for your kind suggestion, we have improved the English written of this manuscript with the help of Charlesworth Author Service, and we uploaded

certification of English editing into the submission system.

Comment 2: In the discussion, the authors mention the need for further studies at the end of four paragraphs. This only needs to be mentioned once as a summary of the discussion and the other statements should be removed.

Reply: Thank you for your comment, we have removed this sentence with your suggestion.

Comment 3: It would strengthen the authors case to discuss some of the seemingly incongruous findings in the results section. An example might be to discuss the finding of higher rate of pleuritic chest pain in the survivor group vs non-survivors. Of course this may be due to central emboli vs peripheral emboli and the incidence of pulmonary infarct but this should be explored.

Reply: Thank you for your comment. In this study, we found higher rate of pleuritic chest pain in the survivor group than control group, which may be due to central emboli vs peripheral emboli and the incidence of pulmonary infarct. As we all know, pleuritic chest pain is one of the leading clinical manifestation of APE, whether it was associated with mortality still lack of data and should be explored in further study.

Comment 4: Similarly, did more patients with effusion receive thrombolysis due to increased clinical severity and therefore have increased risk of in-hospital bleeding? Also, the rate of effusion in association with APE is very high when compared to other studies. This should be discussed and possible explanations offered.

Reply: Thank you for your comment. There was only one thrombolytic patient in our study population, with no differences between the two groups. Patients with effusion who received thrombolysis may have increased risk of in-hospital bleeding, which needs more evidence.

We do agree with the reviewer that the rate of effusion in association with APE is very high when compared to other studies. However, it was reported that the prevalence of pleural effusion may be as high as 61% in patients with APE (Ref 18). There were

differences in patient populations and span of study, so the prevalence of pleural effusion in patients with APE exists differences accordingly. Thank you for your understanding.