Peer Review File

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Reviewer A

C. Dear Authors, I have received your manuscript entitled "Predictors of Chronic Thromboembolic Disease after Anticoagulation Monotherapy in Patients with Intermediate-Risk Pulmonary Thromboembolism". Overall, I deem this to be a well-written manuscript with interesting data, of course fitting this journal's aims. I would only recommend a few minor revisions to improve data presentation, particularly in the Discussion, where the level of English writing seems to be far less consistent and appropriate than in the rest of the manuscript.

R. Thank you for your comment. Based on the definition of chronic thromboembolic disease (CTED) and other reviewer's comments, we changed the word of "CTED" as the word of "residual pulmonary vascular obstruction (RPVO)" in title and main manuscript.

Results:

C1. Line 145: what do you mean with "whether the occurrence"?

R1. Thank you for your comment. To deliver the definite meaning of sentence, this sentence changed as the following sentence.

"We investigated the occurrence of RPVO during long-term follow-up to evaluate the

appropriateness of anticoagulation monotherapy" (page 12, line 197-198)

C2. Line 159: please anticipate the specification of backward elimination in the Methods section, namely in line 113/114.

R2. Thank you for your comment. Based on your comment, we changed original sentence as the following sentence in statistical analysis section.

"Logistic regression analyses using backward elimination were performed to identify the factors independently predicting RPVO occurrence.". (page 9, line 164-165)

Discussion:

C3. Lines 174/175: there is a bit of "logic void" between the indication of chronic lung disease and increased PA/Ao ratio as risk factors for CTED (as your results correctly show) and the attribution of "dyspnea" and "exercise limitation" as direct, consequences of these two conditions. Please specify.

R3. The reviewer's opinion is absolute correct. Based on reviewer's comment, we rewrote the discussion section. In addition, we changed the comment sentences as the following sentence.

"This study investigated whether anticoagulation monotherapy was appropriate in patients with intermediate risk PE, and the factors that independently predicted RPVO. Our results showed that almost 30% of patients undergoing anticoagulation monotherapy showed RPVO

on follow-up imaging. The occurrence of RPVO was higher among patients with underlying chronic lung disease and a P/A ratio > 1 on the chest CT scan obtained at initial presentation than in patients without these factors. Therefore, clinicians should pay close attention to differentiate between persistent dyspnea due to RPVO and dyspnea due to underlying disease in patients with chronic lung disease, particularly those with a P/A ratio > 1 on the initial chest CT scan. If patients have unexplained dyspnea, CTEPD should be considered and CTEPD patients should be treated to improve quality of life". (page 14, line 219-228)

C4. Lines 177/179: I would avoid any self-assessment, perhaps altogether eliminating this sentence.

C5. Lines 180/181: unclear. I would rephrase starting the paragraph from line 179, maybe as: "Most published studies on intermediate-risk PTE aimed to define an appropriate treatment for reducing mortality. Based on the results of these studies, risk stratification of acute PTE, as recommended by international guidelines, focuses on mortality due to acute PTE.

R4, 5. The reviewer's opinion is absolute correct. Based on the reviewer's comments, we eliminated self-assessment sentences and we changed the discussion section as the following sentences.

"Most studies on PE aimed to define an appropriate treatment for reducing mortality. Patients with PE were treated according to risk stratification based on the results of these studies[1-7]. In patients at intermediate risk, PE treatment was also decided based on the evaluation of bleeding risk and the likely benefit in terms of reducing mortality". (page 14, line 229-232)

C6. Line 185: grammatically incorrect, please rephrase.

R6. Thank you for your comment. Based on reviewer's comment, we deleted this sentence.

C7. Line 190: what do you mean by "lesion"?

C8. Line 191: if you say "this study" it seems you are referring to your work, not to a reference. Please identify it, here and in line 189, using the first author's name.

C9. Lines 202/203: the concept is clear but clumsily put, please rephrase.

R7, 8, 9. Thank you for your comment. To deliver the definite meaning of sentence, we changed original manuscript as the following sentence.

"Anticoagulation monotherapy in patients with intermediate risk PE is effective for reducing mortality when considering the risk-benefit ratio, but anticoagulation monotherapy did not seem to be a sufficient treatment for RPVO because almost 30% of patients with anticoagulation monotherapy showed RPVO on follow-up imaging. However, this result was similar to that of patients in our initial cohort who were first treated with systemic thrombolysis or catheter-based therapy instead of anticoagulation monotherapy (27.5% vs. 31.1%; p = 0.690, **Supplementary Figure 1**). Therefore, the type of initial treatment (anticoagulation alone vs. systemic thrombolysis or catheter-based therapy) did not affect the occurrence of RPVO, similar to previous studies. Also, in our study, 44% of patients with RPVO (11 of 25 patients) suffered from persistent dyspnea. Because almost 50% of intermediate-risk PE patients with RPVO suffered from persistent dyspnea, clinicians should

pay close attention to the presence of CTEPD in these patients. International guidelines only recommend follow-up imaging in patients with persistent symptoms due to PE. However, in clinical practice, it is difficult to differentiate between dyspnea due to PE and dyspnea due to comorbidities, particularly in elderly patients. To solve this problem, several examinations, such as cardiopulmonary exercise testing (CPET) and exercise right heart catheterization (ex-RHC), may be needed. Because clinicians cannot apply these examinations in all intermediate-risk PE patients, selecting patients at risk of RPVO is important. Previous studies have proposed a predictive model for CTEPH, we could not easily apply to intermediate-risk PE patients because of many variables in this model. In our study, patients with underlying chronic lung disease and a P/A ratio > 1 determined from the chest CT scan obtained at the initial presentation were at higher risk of RPVO than patients without these factors. These variables can be used to evaluate patients with RPVO, even by non-experts. Because we can easily predict RPVO on the day of admission, patients with risk factors for RPVO could be more carefully evaluated for persistent dyspnea through history-taking, CPET, and ex-RHC.

A mechanism explaining the associations of risk factors with RPVO has been suggested: chronic lung diseases are associated with systemic inflammation and the release of systemic inflammatory factors, such as C-reactive protein, fibrinogen, and tumor necrosis factor-α, which contribute to thrombotic events. In addition, pulmonary hypertension (PH) induced by chronic lung disease can impede the pulmonary circulation. A P/A ratio > 1 on the chest CT scan is an indicator of persistent PH, especially in patients with chronic lung disease. The RV/LV ratio > 0.9, interventricular septum flattening and paradoxical septal bowing on chest CT are an indicator of RV dysfunction, but these findings were not associated with RPVO in this study. Considering a P/A ratio > 1 on the chest CT is an indicator of persistent PH, persistent PH may be a better predictor of RPVO than transient RV dysfunction". (page 14,

line 235-240; page 15; page 16, line 264-270).

C10. Lines 230/231: unclear, please rephrase.

R10. We re-investigated respiratory symptoms after the termination of anticoagulation therapy and showed as the following sentence in revised manuscript.

"Among the patients diagnosed with RPVO, 11 (44%) suffered from persistent dyspnea" (page 11, line 193; page 12, line 194).

C11. Lines 233/235: I do not understand how a change in imaging routines (from V/Q scans to CTPA) could represent a limitation of your study. Please explain.

R11. Thank you for your comment. We changed original manuscript as the following sentence.

"Second, patients with PE or RPVO were diagnosed by chest CT. Although ventilation-perfusion scintigraphy is the most effective modality to diagnose PE and RPVO, chest CT is easier to perform because of the relatively low cost in the Republic of Korea (< $200). In addition, given that high-quality CT angiography is adequate for diagnosing proximal CTEPD (sensitivity = 99%, specificity = 97%), chest CT may also be valuable in the treatment of the disease" (page 16, line 276-281).

C12. Line 239: please do tone down your conclusions (given the small sample size and retrospective nature of your study) and write, for example "did not seem to be a sufficient treatment" instead of "was not".

C13. Lines 243/245: again, please avoid making recommendations about follow-up im aging at this early stage of investigation.

R12,13. The reviewer's opinion is absolute correct. As reviewer's comment, we changed original manuscript as the following sentence.

"In conclusion, anticoagulation monotherapy did not seem to be a sufficient treatment for RPVO, but the outcome was similar to that of patients treated with other therapies. Therefore, considering the risk-benefit ratio, we do not need to change the initial treatment as systemic thrombolytic therapy or catheter-based therapy in patient with intermediate risk PE. Underlying chronic lung disease and a P/A ratio > 1 on the initial chest CT scan predicted the occurrence of RPVO. Therefore, we should carefully assess persistent of dyspnea and exercise limitations using various methods in patients with these risk factors, to detect the occurrence of CTEPD earlier" (page 16, line 282-286; page 17, line 287-289).

C14. Figure 2: please rename the first column from "No" to "Zero Factor"

R14. Thank you for your comment. As reviewer's comment, we changed from "No" to "Zero Factor" in figure 2.

Reviewer B

This well-written manuscript describes a multicenter retrospective observational study of patients with intermediate-risk PE who were admitted to 3 hospitals during 5 years period. 91 patients were included, and predictors of chronic thromboembolic disease (CTED) were determined. CTED was documented in 27% of the population. It is concerning that 35% of the otherwise eligible population were excluded due to lack of follow up data.

My comments are included below.

R. Thank you for your comment. Based on the definition of chronic thromboembolic disease (CTED) and review's comments, we changed the word of "CTED" as the word of "residual pulmonary vascular obstruction (RPVO)"

C1. "Anticoagulation monotherapy in PTE patients at intermediate risk in terms of 26 CTED was not sufficient treatment". This conclusion is not accurate, as there is no evidence that CTED occurrence represents a failure of anticoagulation, but rather is an expected complication of acute PE. Moreover, escalation of anticoagulation therapy may confer an unacceptable balance of bleeding risk to benefit.

R1. Thank you for your comment. The focus of this study was not to treat with thrombolysis therapy for PTE patients with intermediate risk but to pay attention to detect the occurrence of CTED to improve the quality of life of patient. However, these sentences were not appropriate because these sentences may cause the confusion to reader. Therefore, we changed these sentences as the following sentences.

“In conclusion, anticoagulation monotherapy did not seem to be a sufficient treatment for RPVO, but the outcome was similar to that of patients treated with other therapies. Therefore, considering the risk-benefit ratio, we do not need to change the initial treatment as systemic thrombolytic therapy or catheter-based therapy in patient with intermediate risk PE. Underlying chronic lung disease and a P/A ratio > 1 on the initial chest CT scan predicted the occurrence of RPVO. Therefore, we should carefully assess persistent of dyspnea and exercise limitations using various methods in patients with these risk factors, to detect the occurrence of CTEPD earlier”. (page 16, line 282-286; page 17, line 287-289)

C2. In this retrospective cohort study, were consecutive patients included?

R2. Yes, the median follow-up in included patients was 30 months.

C3. “Acute PTE was defined as patients with initial symptoms (e.g., dyspnea) occurring within 15 days before diagnosis, with embolism in the pulmonary artery confirmed by chest CT”. Were patients in whom the diagnosis of PTE was made on ventilation perfusion scanning excluded, or were no patients diagnosed using this modality?

R3. In this study, there was no patients diagnosed with ventilation perfusion scanning because clinicians in this study preferred chest CT or echocardiography to ventilation perfusion scanning for the diagnosis of PTE. This is a limitation of this study. We changed original sentences to the following sentences.

“Second, patients with PE or RPVO were diagnosed by chest CT. Although ventilation-perfusion scintigraphy is the most effective modality to diagnose PE and RPVO, chest CT is easier to perform because of the relatively low cost in the Republic of Korea (< $200). In addition, given that high-quality CT angiography is adequate for diagnosing proximal CTEPD (sensitivity = 99%, specificity = 97%), chest CT may also be valuable in the treatment of the disease”. (page 16, line 276-281)

C4. In the methods, please provide additional detail on the definition of hemodynamic instability. Were guideline-recommended criteria applied? How was hypotension defined?

R4. Thank you for your comment. Based on the reviewer’s comment, we inserted the following sentences in method section.

″Hemodynamic instability was defined as the need for cardiopulmonary resuscitation, systolic BP < 90 mmHg with evidence of end-organ hypoperfusion, and vasopressors required to achieve BP > 90 mmHg despite adequate filling status with evidence of end-organ hypoperfusion” (page 8, line 136-139).

C5. In the methods, please provide additional detail on the definition of right ventricular dysfunction, in particular echocardiographic and CT criteria.

R5. Thank you for your comment. Based on the reviewer’s comment, we inserted the following sentences in method section.

“RV dysfunction on echocardiography was defined as an enlarged RV and flattened interventricular septum in the parasternal long axis view, dilated RV with a basal RV/LV ratio > 1.0 and McConnell sign on the four-chambered view, and decreased tricuspid annular plane systolic excursion measured in M-mode (< 16 mm)” (page 8, line 139-142)

C6. CTED was defined as persistent pulmonary vascular obstruction” was any persistent defect considered to define CTED? What imaging modality was utilized?

R6. In this study, CTED was defined as persistent pulmonary vascular obstruction by chest CT. However, recent guideline showed that CTED was defined as persistent pulmonary vascular obstruction with symptoms (e.g., dyspnea or exercise limitation). I agree this definition because only CTED with symptoms consider to be treated. Thus, to avoid reader’s confusion, we changed the word of "CTED" as the word of "residual pulmonary vascular obstruction (RPVO)".

C7. Of the 249 patients with intermediate-risk PE included, 71 had been treated with systemic thrombolysis or catheter-based therapy rather than anticoagulation monotherapy and 87 had no follow-up data”. The exclusion of 87/249 patients (35%) due to lack of follow up data is concerning, as it represents a major potential source of bias. How was this handled by the investigators?

R7. Thank you for your comment. Because international guidelines recommends that only pulmonary embolism patients with persistent dyspnea or exercise limitations were followed up imaging after the termination of pulmonary embolism therapy, patients with inclusion

criteria in this study were small. In addition, in the period of collected data (from 2012 to 2017), CTEPD was not an important clinical issue in patients with pulmonary embolism. Thus, clinicians decided whether the follow-up of imaging, based on not the severity of pulmonary embolism but the preference of clinicians. In addition, because this study focused to only patients with intermediate risk, the disease severity may not affect the decision of imaging follow-up. Therefore, authors believe that selection bias in a reviewer's comment may not affect the results of this study.

C8. What was the formal post-PE follow-up pathway during this time period for each of the hospitals, and how did this change during the course of the study?

R8. Because the clinical meaning of CTEPD was not clarified between 2012 to 2017, clinicians investigated only whether the presence of pulmonary hypertension. Patients without pulmonary hypertension were only follow-up whether the presence of pulmonary hypertension without any treatment.

C9. Given the large number of predictor variables included, was a Bonferroni correction (or similar) applied?

R9. We did not apply a Bonferroni correction to this analysis because of the comparison of only two groups (presence of CTED of not).

C10. It is surprising that such a high percentage of patients were anticoagulated long-term with warfarin: although the study commenced in 2012, higher DOAC use would have been predicted during the overall time course. Can the authors comment on whether financial (drug-reimbursement) factors or other considerations may have driven this finding?

R10. Thank you for your comment. Because clinician had more an experience about warfarin use than those about DOAC use between 2012 to 2017 and DOAC was more expensive compared with warfarin, many clinicians used warfarin for long term anticoagulation.

C11. It is surprising that there were no major bleeding events. Were patients specifically asked this question during follow-up or was the absence of bleeding determined by the lack of its being recorded in hospital notes?

R11. Because the issue of major bleeding is an important in patients with anticoagulation therapy, the record about bleeding was a relatively accurate. Considering the proportion of major bleeding was 3 % in other studies, patients in this study did not occur major bleeding events due to small number of included patients.

C12. "Multicenter retrospective observational study of patients at intermediate risk of PTE": this should state "diagnosed with intermediate-risk PTE.

R12. Thank you for your comment. Based on the reviewer's comment, we changed the

original sentences to the follow sentences.

“This was a multicenter retrospective observational study of patients with intermediate risk PE who were admitted to one of three university-affiliated hospitals in South Korea between January 2012 and December 2017” (page 7, line 99-101)

Reviewer C

This is a report of a retrospective study on predictors of chronic thromboembolic disease after anticoagulation monotherapy in patients with intermediate-risk pulmonary thromboembolism.

While the subject of the study is of interest, the study design unfortunately suffers from some flaws.

C1. The diagnosis of CTED only depend on CTPA is not accurate.

R1. The reviewer's comment is absolutely correct. Recent guideline showed that CTEPD was defined as a persistent pulmonary vascular obstruction with symptoms (e.g., dyspnea or exercise limitations). I agree this definition because only CTEPD patients with symptoms were considered to be treated. Thus, to avoid reader's confusion, the word of "CTED" in this study changed as the word of "residual pulmonary vascular obstruction (RPVO)".

C2. It is unable to draw the conclusion of "Anticoagulation monotherapy in PTE patients at intermediate risk in terms of CTED was not sufficient treatment" from the results, because the occurrence of CTED was similar to that of patients who were initially treated with systemic thrombolysis or catheter-based therapy instead of anticoagulation monotherapy.

R2. The reviewer's comment is absolutely correct. Based on the reviewer's comment, we changed original manuscript as the following sentence.

“In conclusion, anticoagulation monotherapy did not seem to be a sufficient treatment for RPVO, but the outcome was similar to that of patients treated with other therapies. Therefore, considering the risk-benefit ratio, we do not need to change the initial treatment as systemic thrombolytic therapy or catheter-based therapy in patient with intermediate risk PE. Underlying chronic lung disease and a P/A ratio > 1 on the initial chest CT scan predicted the occurrence of RPVO. Therefore, we should carefully assess persistent of dyspnea and exercise limitations using various methods in patients with these risk factors, to detect the occurrence of CTEPD earlier”. (page 16, line 282-286; page 17, line 287-289)

C3. Although this was a retrospective study, a sample size consideration is lacking because the data was only from patients at intermediate risk with anticoagulation monotherapy not including other patients. I suspect the current analysis is underpowered.

R3. Thank you for your comment. The meaning of this study was that the initial information of chest CT and clinical data could predict the RPVO and, in patients with RPVO, we should pay close attention to detect the occurrence of CTEPD using exercise test or close follow-up. Authors believe that these results will help the patients with intermediate risk to improve the quality of life.

C4. The use of words is insufficient and should be revised as necessary.

Moreover, the study lacks novelty.

R4. Thank you for your comment. Based on reviewer's comment, we rewrote the discussion.

Reviewer D

This manuscript was analyzed using statistical methods after collecting relevant data from clinical PTE patients to investigate whether single anticoagulation therapy is appropriate for intermediate-risk PTE patients and the independent risk elements that predict the development of chronic thromboembolic disease (CTED) in intermediate-risk PTE patients. The article's title has some clinical utility and guidance, but there are some suggestions:

C1. Many previously published articles have been explored the applicability of single anticoagulation therapy in patients with intermediate-risk PTE or the efficacy, safety, and long-term prognostic impact of thrombolytic therapy and anticoagulation in patients with intermediate-risk PTE, with relevant findings. Prognostic studies related to CTED and/or CTEPH have also been published in PTE studies. The angle of exploration of the selected topic in this paper, on the other hand, is not so novel.

R1. Thank you for your comment. In general, low-risk patients are treated with anticoagulation monotherapy, and high-risk patients are treated with systemic thrombolysis or surgical embolectomy. In patients at intermediate risk, anticoagulation monotherapy was shown to be effective in reducing mortality and is therefore recommended by current guidelines. However, clinicians are still concerned as to whether anticoagulation monotherapy is sufficient to reduce mortality in patients with a large embolic burden. Actually, some studies showed that systemic thrombolysis was needed in acute PE patients at intermediate risk. In addition, because large pulmonary arterial thrombi on chest CT and RV dysfunction on echocardiography is risk factors for CTEPH, clinician are still concerned as to

whether anticoagulation monotherapy is sufficient to resolve vascular obstruction. Therefore, studies for patients with intermediate risk is needed. As the reviewer's comments, there was some prognostic studies related to CTEPD and/or CTEPH. Based on international guideline, patients with symptoms at 3-6 months after the termination of treatment are checked echocardiography for CTEPH work up and patients without symptoms are evaluated risk factors for CTEPH. However, in elderly patients, it is not easy to differentiate between dyspnea caused by CTEPD and/or CTEPH and dyspnea caused by comorbidities. In addition, risk factors for CTEPH are obscured for applying in clinical field. In our study, the presence of lung disease and P/A ratio>1 on initial chest CT were risk factors for RPVO. Clinicians could easily acquire these data and could easily differentiate patient who is needed further examinations. Authors believe that these points were novelty in this study. To deliver the novelty in this study, we rewrote the discussion section.

C2. It is recommended to refine the inclusion and exclusion criteria and to create a detailed case record form, which should be as detailed and specific as possible and should have certain requirements for the mode of administration: dose, route of administration, and duration of treatment. The source of diagnostic criteria for confirming the diagnosis of PTE should also be clearly defined.

R2. Thank you for your comment. We inserted the following sentences in method section.

"The inclusion criteria were patients aged above 20 years diagnosed with an intermediate risk PE; these patients were treated with anticoagulation monotherapy. In addition, all included patients had follow-up images (e.g., chest CT or echocardiography) after 3–6 months of PE

therapy. The exclusion criteria were as follows: patients with acute PE who were at low or high risk of mortality; patients initially treated with anticoagulation therapy combined with thrombolytic therapy (e.g., systemic thrombolysis or catheter-based therapy); patients without a follow-up chest CT or follow-up echocardiography after 3–6 months of PE treatment; and patients with insufficient electronic medical records" (page 8, line 122-129)

"Anticoagulation monotherapy included initial heparin treatment (e.g., conventional heparin or low-molecular-weight heparin [LMWH] for 5 days, followed by warfarin or non-vitamin K antagonist oral anticoagulant (NOAC) for 3-6 months) and initial NOAC treatment (e.g., NOAC use from first day at admission to 3-6months). In patients using conventional heparin, we intravenously injected conventional heparin and titrated the dose to maintain an activated partial thromboplastin time of 60–80 sec. In patients using LMWH, we subcutaneously injected 1 mg/kg of LMWH every 12 hours. In patients using oral administration of warfarin or NOAC, the dose of warfarin was titrated to maintain an international normalized ratio of 2–2.5 and the NOAC dose was determined based on the manufacturer's recommendations" (page 7, line 104-113)

C3. The number of cases collected in the article is large, but the number of cases that finally meet the enrollment criteria is small, and further stratification of factors affecting efficacy, prognosis, and safety cannot be carried out, which lacks certain persuasive power.

R3. Thank you for your comment. The meaning of this study was that the initial information of chest CT and clinical data could predict the RPVO and, in patients with RPVO, we should pay close attention to detect the occurrence of CTEPD using exercise test or close follow-up.

Authors believe that these results will help the patients with intermediate risk to improve the quality of life.

C4. The article belongs to a multicenter retrospective case observation study analysis, and there is no randomized controlled clinical trial yet. It is recommended to carry out formal randomized controlled clinical trials or small-scale exploratory prospective randomized controlled clinical trials.

R4. The reviewer's comment is absolutely correct. We will hope to proceed using a randomized controlled clinical trial to validate our findings.

C5. Single anticoagulation therapy includes the use of different drugs in different treatment phases, and there are differences in the side effects and adverse reactions of different drugs, so it is recommended that routine laboratory tests for adverse drug reactions or side effects be included in the study analysis.

R5. Because this study was retrospective study and was collected data through the review of electric medical record, detailed all adverse reactions of drugs could not investigate. However, there was no specific adverse reactions of drugs within the limit of possibility of the review of electric medical record.

C6. It is recommended that all technical terms be expressed in full the first time they appear

in the article and that abbreviations be used later. Further, embellish the chart to make the classification and grouping clear. The cited literature can be updated with some more relevant recent publications.

R6. Thank you for your comment. We corrected this manuscript according to reviewer's comment.

Reviewer E

In this retrospective study it was tried to investigate whether anticoagulation monotherapy in 91 intermediate risk patients with venous thromboembolism (VTE) was associated with CTED and it was tried to identify predicting factors for the occurrence of CTED

The authors diagnosed 25 patients with what they called CTED during follow-up and described chronic lung disease and a P/A ratio >1.0 documented on a chest CT scan at presentation as significant independent predictors of CTED occurrence. Without these two factors the incidence of CTED was 9.7% and with the two factors 60%.

The authors conclude that anticoagulation monotherapy in intermediate risk VTE patients was not sufficient treatment for avoiding CTED. Obtained at initial presentation predicted the occurrence of CTED. They recommend in patients with dyspnea or exercise limitations and chronic lung disease and a P/A ratio >1 on the chest CT careful assessment, with follow-up imaging performed to detect the occurrence of CTED.

The topic is is promising and data could be interesting, however there is a big problem with your definition of CTED. CTED (or CTEPD =chronic thromboembolic pulmonary disease (CTEPD) as coined in the current ERS Statement on Chronic Thromboembolic Pulmonary Hypertension Eur Respir J 2020; in press) is more than persistent perfusion defects in imaging, the patient has to be symptomatic due to these obstructions. The presence of persisting perfusion defects in CT is frequent and has been described previously in 20-50 % of patients undergoing imaging after an acute VTE within the first year. Many of these patients are asymptomatic, and no routine follow-up CTPA imaging is needed in such patients treated for PE, (den Exter et al.). Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism. Thromb Haemost 2015;114:26 34.) as stated in the current ESC guidelines on VTE.

It is known that patients with signs of right heart strain at the time of VTE (e.g. P/A ratio >1.0 as described in the current manuscript) are at risk of CTEPH or already have CTEPH at the time of VTE diagnosis, (Guerin et al. Thromb Haemostasiol 2014). Persisting or deteriorating dyspnea, are frequently present 6 months to 3 years after an acute PE episode (Klok et al. The post-PE syndrome: a new concept for chronic complications of pulmonary embolism. Blood Rev 2014;28:221 226).

R. Thank you for your comment. Based on the definition of chronic thromboembolic disease (CTED) and review's comment, we changed the word of "CTED" as the word of "residual pulmonary vascular obstruction (RPVO)"

Specific comments:

C1. The abbreviation PTE is misleading, since it has been used for pulmonary thromboendartectomy in the CTEPH community, VTE (venous thromboembolism) as used in the current guidelines is better.

R1. Thank you for your comment. We changed the word of PTE to the word of PE to deliver the definite meaning of word.

C2. Please give a rationale for the indication of CT in your patients. Why did about 50% of your patients get a CT and 50% not, could there be a selection bias?

R2. Thank you for your comment. Because international guidelines recommends that only pulmonary embolism patients with persistent dyspnea or exercise limitations were followed up imaging after the termination of pulmonary embolism therapy, patients with inclusion criteria in this study were small. In addition, in the period of collected data (from 2012 to 2017), CTEPD was not an important clinical issue in patients with pulmonary embolism. Thus, clinicians decided whether the follow-up of imaging, based on not the severity of pulmonary embolism but the preference of clinicians. In addition, because this study focused to only patients with intermediate risk, the disease severity may not affect the decision of imaging follow-up. Therefore, authors believe that selection bias in a reviewer's comment may not affect the results of this study.

C3. How many of your patients with perfusion defects were symptomatic?

R3. Thank you for your comment. Eleven patients (44%) with perfusion defects suffered from persisted dyspnea after the termination of anticoagulation monotherapy.

We inserted this information to result section using the following sentence.

“Among the patients diagnosed with RPVO, 11 (44%) suffered from persistent dyspnea” (page 11, line 193; page 12, line 194)

C4. In how many patients did you diagnose CTEPH?

R4. Unfortunately, we checked only echocardiography in 11 CTEPD patients for the

diagnosis of CTEPH. Thus, these patients were not definitely diagnosed with CTEPH.

C5. What was the indication for thrombolysis in 71 patients with intermediate risk?

R5. Because this is a retrospective study, we do not definitely know why patients were applied thrombolysis. Probably, thrombolysis therapy may consider the possibility to apply to patients with large burden of pulmonary embolism and without the contraindication of thrombolysis.

C6. Right heart strain (e.g. P/A ratio >1.0) is a predictor of CTEPH, not CTEPD.

C7. There is an accepted CTEPH prediction score, which should be mentioned (Klok et al. Thromb Haemostasiol 2015.

R6,7. Thank you for your comment. The journal of reviewer's comment is that:

Table 3 Multivariable analysis and derivation of clinical prediction score

	Regression coefficient	95% CI	*P*-value	Points for score
Unprovoked PE	18	1.8 to > 100	0.011	+ 6
Known hypothyroidism	8.7	2.1–34	0.002	+ 3
Symptom onset > 2 weeks before PE diagnosis	6.9	2.5–19	< 0.001	+ 3
Right ventricular dysfunction on CT or echocardiography	5.9	1.8–19	0.003	+ 2
Known diabetes mellitus	Infinitely low		0.004	− 3
Thrombolytic therapy or embolectomy	Infinitely low		0.003	− 3

In this prediction model, the right ventricular dysfunction on CT was not P/A ratio >1.0 but RV/LV ratio >0.9. Most of previous studies showed that right ventricular dysfunction on CT were RV/LV ratio >0.9, interventricular septum flattening and paradoxical septal bowing. However, these findings were not associated with RVPO in our study. Considering a P/A ratio

> 1 on the chest CT is an indicator of persistent pulmonary hypertension, persistent pulmonary hypertension may be a better predictor of RPVO than transient RV dysfunction. Previous studies have proposed a predictive model for CTEPH, we could not easily apply to intermediate-risk PE patients because of many variables in this model. In our study, patients with underlying chronic lung disease and a P/A ratio > 1 determined from the chest CT scan obtained at the initial presentation were at higher risk of RPVO than patients without these factors. These variables can be used to evaluate patients with RPVO, even by non-experts. Because we can easily predict RPVO on the day of admission, patients with risk factors for RPVO could be more carefully evaluated for persistent dyspnea through history-taking, CPET, and ex-RHC. We believe that our results will help the patients with intermediate risk to improve the quality of life.

To deliver the meaning of our study, we inserted the following sentences in discussion section.

“International guidelines only recommend follow-up imaging in patients with persistent symptoms due to PE. However, in clinical practice, it is difficult to differentiate between dyspnea due to PE and dyspnea due to comorbidities, particularly in elderly patients. To solve this problem, several examinations, such as cardiopulmonary exercise testing (CPET) and exercise right heart catheterization (ex-RHC), may be needed. Because clinicians cannot apply these examinations in all intermediate-risk PE patients, selecting patients at risk of RPVO is important. Previous studies have proposed a predictive model for CTEPH, we could not easily apply to intermediate-risk PE patients because of many variables in this model. In our study, patients with underlying chronic lung disease and a P/A ratio > 1 determined from the chest CT scan obtained at the initial presentation were at higher risk of RPVO than patients without these factors. These variables can be used to evaluate patients with RPVO, even by non-experts. Because we can easily predict RPVO on the day of admission, patients

with risk factors for RPVO could be more carefully evaluated for persistent dyspnea through history-taking, CPET, and ex-RHC" (page 15, line 247-260).

"A mechanism explaining the associations of risk factors with RPVO has been suggested: chronic lung diseases are associated with systemic inflammation and the release of systemic inflammatory factors, such as C-reactive protein, fibrinogen, and tumor necrosis factor-α, which contribute to thrombotic events. In addition, pulmonary hypertension (PH) induced by chronic lung disease can impede the pulmonary circulation. A P/A ratio > 1 on the chest CT scan is an indicator of persistent PH, especially in patients with chronic lung disease. The RV/LV ratio > 0.9, interventricular septum flattening and paradoxical septal bowing on chest CT are an indicator of RV dysfunction, but these findings were not associated with RPVO in this study. Considering a P/A ratio > 1 on the chest CT is an indicator of persistent PH, persistent PH may be a better predictor of RPVO than transient RV dysfunction" (page 15, line 261-263; page 16, line 264-270)

C8. Page 12: "Though anticoagulation monotherapy in patients at intermediate risk is effective in reducing mortality, but whether it can reduce the long-term complications of PTE (e.g., CTED or CTEPH) is unclear because of limited data." What do you want to say by this? There are many data showing the incidence of CTEPH or persistent asymptomatic perfusion defects.

R8. Thank you for your comment. This sentence was removed in introduction based on reviewer's comment.

C9. page 13 “It is not clear how CTED patients should be treated” There are clear guidelines.

C10: “this was because the international guideline does not recommend follow-up imaging after treatment in patients with acute PTE” There are clear recommendations for follow up in the guidelines, and they don`t recommend CT scans for good reasons.

R9, 10. Thank you for your comment. Based on reviewer’s comment, we changed this sentence to the following sentence.

“According to previous studies, many patients treated with PE show residual pulmonary vascular obstruction (RPVO) on follow-up imaging after terminating PE therapy. Because RPVO is associated with the recurrence of PE and occurrence of chronic thromboembolic pulmonary disease (CTEPD), with or without pulmonary hypertension (PH), patients with RPVO have a lower quality of life than those without RPVO. In patients with RPVO, persistent dyspnea and exercise limitations due to dyspnea are important symptoms because they may indicate CTEPD or CTEPH. In addition, treating CTEPD and CTEPH improves quality of life. Thus, current guidelines recommend that clinicians confirm the presence of RPVO via follow-up imaging in patients with persistent dyspnea and exercise limitations after terminating PE therapy” (page 5, line 80-89)

“In conclusion, anticoagulation monotherapy did not seem to be a sufficient treatment for RPVO, but the outcome was similar to that of patients treated with other therapies. Therefore, considering the risk-benefit ratio, we do not need to change the initial treatment as systemic thrombolytic therapy or catheter-based therapy in patient with intermediate risk PE. Underlying chronic lung disease and a P/A ratio > 1 on the initial chest CT scan predicted the occurrence of RPVO. Therefore, we should carefully assess persistent of dyspnea and

exercise limitations using various methods in patients with these risk factors, to detect the occurrence of CTEPD earlier" (page 16, line 282-286; page 17, line 287-289)

C11. page 14 "CT angiography is the preferred imaging modality for evaluating the presence of CTED, since expertise in the interpretation of ventilation-perfusion lung scanning is waning ..." This is your own opinion and far away from all current guidelines on CTEPH or PE

R11. Thank you for your comment. Based on reviewer's comment, we changed this sentence to the following sentence in limitation section.

"Second, patients with PE or RPVO were diagnosed by chest CT. Although ventilation-perfusion scintigraphy is the most effective modality to diagnose PE and RPVO, chest CT is easier to perform because of the relatively low cost in the Republic of Korea (< $200). In addition, given that high-quality CT angiography is adequate for diagnosing proximal CTEPD (sensitivity = 99%, specificity = 97%), chest CT may also be valuable in the treatment of the disease" (page 16, line 276-281)

C12: page 15: "In conclusion, anticoagulation monotherapy in PTE patients at intermediate risk in terms of 238CTED was not sufficient treatment, but the outcome was similar to that of patients treated with other therapies." What is your alternative proposal, no anticoagulation??

R12. Thank you for your comment. To deliver definite meaning of sentence, we rewrote conclusion section.

“In conclusion, anticoagulation monotherapy did not seem to be a sufficient treatment for RPVO, but the outcome was similar to that of patients treated with other therapies. Therefore, considering the risk-benefit ratio, we do not need to change the initial treatment as systemic thrombolytic therapy or catheter-based therapy in patient with intermediate risk PE. Underlying chronic lung disease and a P/A ratio > 1 on the initial chest CT scan predicted the occurrence of RPVO. Therefore, we should carefully assess persistent of dyspnea and exercise limitations using various methods in patients with these risk factors, to detect the occurrence of CTEPD earlier” (page 16, line 282-286; page 17, line 287-289)