**Comparison of the severity and radiologic extent of pulmonary embolism at the time of recurrence compared with the previous event**

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**Abstract**

**Background**

Pulmonary embolism (PE) recurs in less than 5% of patients on anticoagulant therapy. However, the recurrence rate increases up to 30% after 10 years. Patients who are at a high risk of recurrence are recommended to maintain extended anticoagulation therapy. However, there is no data regarding the severity of PE recurrence, which may help to determine a more effective anticoagulation strategy.

**Methods**

This was a retrospective cohort study of consecutive patients with recurrent PE at a single tertiary center in Korea. The severity of PE was stratified according to the 2014 European Society of Cardiology (ESC) guideline, Pulmonary embolism severity index (PESI) and simplified PESI scores. The radiologic extent of PE was staged as limited, intermediate, and extensive depending on the extent of vessel involvement. The severity and radiologic extent were compared between the 1st PE event and its recurrence using a marginal homogeneity test.

**Results**

A total of 86 patients (median age 66.5 years, male 54.7%) were included. Compared with patients with provoked PE at the 1st event, unprovoked PE patients underwent longer duration of anticoagulation therapy (12.0 ± 20.3 vs. 4.8 ± 6.3 months, p<0.001), took a longer time for recurrence (36.5 ± 31.2 vs. 17.6 ± 26.6, p=0.003), and displayed fewer recurrences during the course of anticoagulation therapy (10.8 vs. 34.7%, p=0.011). The PESI score was significantly elevated at recurrence (94.5 ± 30.8 vs. 98.0 ± 30.0, p=0.032). However, the PESI score class (p=0.170), simplified PESI score (p=0.229) and ESC risk classification (p=0.707) of the recurred event were not significantly different from those at the 1st event. Similarly, the radiologic extent of PE was not significantly changed at recurrence (p=0.174).

**Conclusion**

Patients with recurred PE present similar clinical manifestations, especially in terms of the severity and radiologic extent, compared with the 1st event. Further, extensive prospective studies are needed to validate these findings.

**Introduction**

Pulmonary embolism (PE) recurs in less than 5% of patients on anticoagulant therapy. However, the recurrence rate increases up to 30% after 10 years (1). Due to the high recurrence rate of unprovoked as well as provoked PE with persistent risk factors, prolonged treatment with anticoagulation is recommended for these populations (2). However, it is difficult to maintain proper anticoagulation because patients with unprovoked PE show low compliance for treatments of indefinite duration. Additionally, patients with malignancies undergo challenging treatment regimens including subcutaneous injection of low molecular weight heparin (LMWH) until they are free of cancer, and have an increased risk of bleeding. Therefore, demonstrating risk factors of recurrent PE is of particular interest in order to identify groups at a high risk of recurrence, which require prolonged anticoagulation therapy. Based on this, there have been several well-designed studies regarding risk factors of recurrent PE (3, 4).

On the other hand, there are few studies describing the clinical manifestations of recurred PE in comparison with previous PE. Therefore, the current acute PE guidelines do not consider the severity of PE in determining the duration of anticoagulation therapy (2). One retrospective review examining the size of recurred PE compared with first PE in 63 patients revealed that the rates of massive PE at recurrence were low regardless of the size of the first PE (5). Although the radiologic extent was stable at recurrence, the clinical manifestation could not be deduced since the severity is not always consistent with radiological findings. If the severity of recurred PE can be predicted, it will help to determine an anticoagulation strategy in each patient. To the best of our knowledge, there are no published studies on the severity of recurred PE, so we designed this study to investigate the manifestation of recurred PE, with a focus on the severity.

**Material and methods**

This retrospective study included patients aged ≥ 18 years who were diagnosed with recurrent PE, from January 2010 to December 2017 at Asan Medical Center, a 2,700-bed university-affiliated tertiary referral center in Seoul, South Korea. PE was confirmed by spiral computed tomography (CT) and patients were diagnosed with provoked PE if they have one or more of the known risk factors for PE, including temporary risk factors (e.g., surgery, hospitalization due to acute illness, cesarean section within 3 months, estrogen therapy, pregnancy, or leg injury within 2 months), and persistent risk factors (cancer or inflammatory bowel disease) (6). All clinical, radiologic, echocardiographic and laboratory data were retrospectively collected from medical records.

This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the Institutional Review Board of Asan Medical Center (Approval number: 2015-0516), which waived the requirement for informed consent due to the retrospective nature of the study.

Risk groups based on early mortality rate were stratified according to the 2014 European Society of Cardiology (ESC) guidelines, Pulmonary embolism severity index (PESI) and simplified PESI scores (2, 7). Patients were classified as being at high-, intermediate-high-, intermediate-low-, or low-risk according to the ESC classification. Patients were classified numerically and/or by class from I to V (PESI alone) according to the PESI and simplified PESI scores. Risk-adjusted therapy was administered based on these risk classifications.

The radiologic extent of PE was graded into three groups according to a previous study (8) as follows: limited refers to involvement of 25% or less of the vasculature of a single lobe; intermediate refers to involvement of more than 25% of the vasculature of a single lobe or multiple lobes with involvement of 25% or less of the entire vasculature; and extensive refers to involvement of multiple lobes with 25% or more of the entire vasculature. Deep vein thrombosis (DVT) was evaluated by CT or doppler ultrasonography.

Categorical variables were reported as n (%) and compared using the chi-square test. Continuously measured parameters were reported as means ± standard deviation or median [interquartile range] and were compared using Student’s t-test or the Mann-Whitney U test. To compare the paired means for continuous data, paired t-test or Wilcoxon signed rank test was used. To compare paired categorical data, the test of marginal homogeneity was used. All statistical analyses were performed using SPSS 21.0 (IBM Corporation, Armonk, NY, USA) with statistical significance defined as a p-value <0.05.

**Results**

A total of 86 patients (median age 66.5 years, 54.7% of male sex) with recurred PE were included (Table1). 12.8% of patients had a chronic pulmonary disease and 3.5% had congestive heart failure. Patients with unprovoked PE were 43.0% of all the patients and the most common provoking factor was malignancy (39.5%).

Compared with the first event of PE, patients with recurrent PE showed similar vital signs, symptoms, rate of DVT and heart function (Table 2). Although the laboratory data in these patients were also similar, the hemoglobin levels were significantly lower at the time of recurrence compared with previous events (13.0 ± 2.3 vs. 13.5 ±2.3, p=0.013).

Table 3 shows characteristics of treatment and recurrence according to the category of PE at the first event. The patients with unprovoked PE at the first event underwent treatment for a longer duration (12.0 ± 20.3 vs. 4.8 ± 6.3 months, p<0.001), showed recurrence after a longer period of time (36.5 ± 31.2 vs. 17.6 ± 26.6 months, p=0.003), and recurred less frequently during anticoagulation therapy (10.8 vs. 34.7%, p=0.011). Importantly, 34 patients with provoked PE having persistent risk factors had the shortest treatment duration (median 2.0 months [1.0, 5.3]) and time to recur (median 4.0 months [2.0, 10.3]), and 16 (47.1%) patients showed recurrence during anticoagulation therapy. 83.8% of the unprovoked PE patients recurred as unprovoked PE, while the remaining 16.2% recurred as provoked PE. On the other hand, 14.3% of the provoked PE patients recurred as unprovoked PE, while the remaining 85.7% recurred as provoked PE.

17 of the patients who underwent anticoagulation therapy (Direct acting oral anticoagulant [DOAC] n=5; warfarin, n=3; LMWH, n=9) showed recurrence within 6 months of anticoagulation, whereas 4 patients showed recurrence during extended anticoagulation therapy of longer than 6 months. 3 of the latter group were unprovoked PE patients inappropriately anticoagulated with an International normalized ratio (INR) less than 1.5 (1.06, 1.38 and 1.15), and the other was a provoked PE patient who had active cancer with INR of 2.07. Among the 5 patients who underwent thrombolysis at the first event, only one patient received thrombolysis at the time of recurrence while none of the others needed thrombolysis. Thrombectomy was performed in one patient at the time of recurrence.

The PESI score was significantly increased at the time of recurrence compared with the previous event (98.0 ± 30.0 vs. 94.5 ± 30.8, p=0.032); however, the PESI class (p=0.170), simplified PESI score (p=0.229) and ESC risk classification (p=0.707) were not significantly different in each patient (Figure1). Similarly, the radiologic extent of recurred PE was not significantly changed from the extent of previous PE (p=0.174) (Figure 2).

The 3-months mortality rate of recurred PE was 15 (17.4%); of which only one patient had unprovoked PE at the first and recurred events, while the others had provoked PE with malignancy from the first episode. The unprovoked PE patients and one of the malignant PE patients died due to pulmonary embolism, while the others died due to the progression of cancer, pneumonia, stroke, combination of these causes, or unknown causes.

**Discussion**

Investigating which patients show severe manifestation at the time of recurred PE may help to determine an anticoagulation strategy, especially in those who need indefinite or extended treatment. This is the first study examining the severity of recurred PE compared with the first event. In this retrospective review of 68 patients, the severity and radiologic extent of recurred PE was not significantly different from those of the first PE, suggesting a need for extended anticoagulation in the high-risk patients.

Although the PESI score was significantly increased at the time of recurrence compared with the first PE, the PESI class, simplified PESI score, and ESC risk classification were not significantly changed in each patient. This indicates that the clinical severity classified on the basis of early mortality risk did not significantly change at the time of recurrence compared with the previous event. This finding is important in the determination of an anticoagulation strategy. Since the patients who presented with a severe manifestation during the first PE are prone to recur as high-risk PE, clinicians need to consider prescribing extended anticoagulation therapy and monitoring these patients closely for signs of recurrence. The current acute PE guideline recommends extended anticoagulation treatment in patients with unprovoked PE or active cancer but does not consider the severity of PE in determining the duration of anticoagulation (2). Further studies are needed to validate these findings and guide anticoagulation strategies.

The radiologic extent of recurred PE was also not significantly changed from the extent of previous PE. In one previous retrospective study, radiologic massive PE (RMPE) was defined as the presence of saddle embolus, bilateral main pulmonary artery involvement, or right ventricular (RV) strain, while the others were grouped as radiologic non-massive PE (RNMPE) (5). They found that patients with RNMPE and RMPE at the first event had a similar chance of RMPE at recurrence. This result is slightly different from our findings from a previous study which showed that although the first event may occur as a massive PE, it is prone to recur as a non-massive PE (5). This disparity could result from a difference in the definition of radiologic extent or other unknown causes. Despite the reason, we need to be cautious in translating these findings to real-world practice, since radiologic extent does not always coincide with clinical severity. Thus, it is necessary to focus more on the change in severity mentioned above, when clinicians decide anticoagulation strategy in each patient.

There was a high recurrence rate (47.1%) during anticoagulation with malignant PE. During the course of extended anticoagulation after 6 months, 4 patients showed recurrence, 3 of which were unprovoked PE patients inappropriately anticoagulated with INR less than 1.5, and the other was a malignant PE patient treated with appropriate anticoagulation. This finding suggests two important points. First, clinicians need to monitor INR cautiously when they decided to maintain anticoagulation indefinitely using warfarin. Secondly, active cancer not only increases the rate of recurrence, but also carries the risk of warfarin failure. Active cancer is a well-known risk factor for recurrence of PE in the early as well as late periods, and was an independent predictor of 6-month venous thromboembolism recurrence after controlling for heparin and warfarin therapy, suggesting a high rate of warfarin failure (9, 10). Therefore, it is important to recognize that there is a high risk of recurrence even with proper anticoagulation when treating malignant PE patients.

Among the 5 patients who underwent thrombolysis at the first event, only one patient received thrombolysis at the time of recurrence, while none of the other patients needed thrombolysis, and thrombectomy was needed in one recurred PE patient. Although it was a small number of patients, the need for invasive treatment was not higher following recurred PE.

There are several limitations. First, this was a small, retrospective, single-center study that is susceptible to bias in data selection and analysis. Second, we included patients who developed recurrence from 2010 to 2017, resulting in a difference of anticoagulation methods in each patient. Since the previous events were distributed from 2000 to 2017, some patients received treatment before the use of DOAC. Therefore, the interpretations regarding anticoagulation method or the duration of therapy should be done with caution. Further, extensive prospective studies are needed to validate these findings.

**Conclusion**

Recurrent PE patients present similar clinical manifestations, especially in severity and radiologic extent compared with the 1st event. Clinicians may consider these results while determining the anticoagulation strategy. Further, extensive prospective studies are needed to validate these findings and be reflected in the guidelines.

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**Table 1. Baseline characteristics of 86 patients at the first presentation of acute pulmonary embolism**

|  |  |
| --- | --- |
| **Characteristics** | **Values** |
| Age, years | 66.5 [58.5, 74.0] |
| Male sex | 47 (54.7) |
| Body mass index, kg/m2 | 24.4 ± 3.6 |
| Ever-smoker | 26 (30.2) |
| Comorbidities |  |
|  Hypertension | 35 (40.7) |
|  Chronic pulmonary disease | 11 (12.8) |
|  Diabetes mellitus | 10 (11.6) |
| Coronary artery disease | 6 (7.0) |
|  Congestive heart failure | 3 (3.5) |
|  Atrial fibrillation | 4 (4.7) |
| Chronic kidney disease | 2 (2.3) |
| Liver cirrhosis | 2 (2.3) |
| Category of pulmonary embolism |  |
|  Unprovoked | 37 (43.0) |
|  Provoked |  |
|  Persistent risk factor | 34 (39.5) |
|  Malignancy | 34 (39.5) |
|  Transient risk factor | 15 (17.4) |
|  Immobilization | 9 (10.5) |
|  Hospitalization due to acute medical illness | 4 (4.7) |
|  Surgery | 1 (1.2) |
|  Fracture of leg | 1 (1.2) |

All values are presented as n (%) or median [interquartile range] or mean ± standard deviation.

**Table2. Characteristics of recurred pulmonary embolism compared with the first event**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **1st event** | **Recurrence** | **p-value** |
| Vital signs |  |  |  |
|  Systolic BP, mmHg | 124.9 ± 20.0 | 125.1 ± 21.8 | 0.942 |
|  Diastolic BP, mmHg | 81.9 ± 14.1 | 78.6 ± 14.9 | 0.080 |
|  Heart rate, /min | 91.1 ± 19.2 | 92.9 ± 20.2 | 0.555 |
|  Respiratory rate, /min | 21.4 ± 4.7 | 21.7 ± 5.4 | 0.787 |
|  Body temperature, ℃ | 36.6 ± 0.5 | 36.7 ± 0.7 | 0.737 |
|  SpO2, % | 95.1 ± 4.2 | 95.5 ± 2.9 | 0.552 |
| Symptom onset, days | 5.5 [2.0, 10.0] | 3.5 [0.8, 7.0] | 0.103 |
| Symptom |  |  | 0.704 |
|  Dyspnea or chest pain | 40 (46.5) | 45 (52.3) |  |
|  Pain or swelling of leg | 14 (16.3) | 16 (18.6) |  |
|  Asymptomatic | 23 (26.7) | 19 (22.1) |  |
|  Etc. | 9 (10.5) | 6 (7.0) |  |
| DVT |  |  | 0.060 |
|  Proximal | 41 (47.7) | 36 (41.9) |  |
|  Isolated distal | 7 (8.1) | 2 (2.3) |  |
|  None | 26 (30.2) | 9 (10.5) |  |
|  Not evaluated | 12 (14.0) | 39 (45.3) |  |
| TTE |  |  |  |
|  Ejection fraction, % | 60.2 ± 6.0 | 61.2 ± 6.6 | 0.319 |
|  PGsys (RV-RA), mmHg | 37.9 ± 17.6 | 38.4 ±18.9 | 0.898 |
| RV dysfunction | 34 (39.5) | 32 (37.2) | 0.754 |
| Laboratory data |  |  |  |
|  WBC, /uL (n=68) | 9122.6 ± 3318.1 | 9251.5 ± 3160.3 | 0.801 |
|  Hemoglobin, g/dL (n=68) | 13.5 ±2.3 | 13.0 ± 2.3 | 0.013 |
|  Platelet, x10³/uL (n=68) | 206.4 ± 84.2 | 196.2 ± 73.3 | 0.211 |
| D-dimer, ug/ml FEU (n=67) | 11.1 ± 10.1 | 10.6 ± 9.3 | 0.702 |
|  Troponin-I, ng/mL (n=41) | 0.129 ± 0.189 | 0.501 ± 1.798 | 0.199 |
| CK-MB, ng/mL (n=36) | 2.7 ± 2.5 | 3.5 ± 4.2 | 0.310 |
| BNP, pg/mL (n=38) | 180.6 ± 369.5 | 139.4 ±219.3 | 0.274 |

All values are presented as n (%) or mean ± standard deviation.

BP, blood pressure; SpO2, saturation by pulse oximetry; DVT, deep vein thrombosis; TTE, transthoracic echocardiography; PGsys (RV-RA), systolic pressure gradient between right ventricle and right atrium; RV, right ventricle; WBC, white blood cell; FEU, fibrinogen equivalent unit; BNP, Brain natriuretic peptide

**Table 3. Characteristics of treatment and recurrence according to the category of pulmonary embolism at the first event**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Unprovoked (n=37) | Provoked (n=49) | P-value |
| Treatment duration (months) | 12.0 ± 20.3 | 4.8 ± 6.3 | <0.001 |
| Time to recurrence (months) | 36.5 ± 31.2 | 17.6 ± 26.6 | 0.003 |
| Treatment at the time of recurrence |  |  | 0.037 |
| Under anticoagulation | 4 (10.8) | 17 (34.7) | 0.011 |
|  Warfarin | 3 (8.1) | 4 (4.7) |  |
|  DOAC | 1 (2.7) | 4 (4.7) |  |
|  LMWH | 0 | 9 (10.5) |  |
| Under antiplatelet agent | 7 (18.9) | 6 (12.2) | 0.545 |
|  None | 26 (70.3) | 26 (53.1) | 0.124 |
| Category of recurrent PE |  |  | - |
|  Unprovoked | 31 (83.8) | 7 (14.3) |  |
|  Provoked | 6 (16.2) | 42 (85.7) |  |

All values are presented as n (%) or mean ± standard deviation.

DOAC, Direct acting oral anticoagulant; LMWH, low molecular weight heparin

**Figure1. The change of severity of pulmonary embolism at the time of recurrence compared with the first event**

PESI, Pulmonary embolism severity index; H, High; IH, Intermediate-high; IL, Intermediate-low; L, Low

**Figure2. The change of radiologic extent of pulmonary embolism at the time of recurrence compared with the first event**

L, Limited; I, Intermediate; E, Extensive