

Clinical Phenotype of a First Unprovoked Acute Pulmonary Embolism Associated with Antiphospholipid Antibody Syndrome

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Background: Antiphospholipid antibody syndrome (APS), an important cause of acquired thrombophilia, is diagnosed when vascular thrombosis or pregnancy morbidity occurs with persistently positive antiphospholipid antibodies (aPL). APS is a risk factor for unprovoked recurrence of pulmonary embolism (PE). Performing laboratory testing for aPL after a first unprovoked acute PE is controversial. We investigated if a specific phenotype existed in patients with unprovoked with acute PE, suggesting the need to evaluate them for APS.

Methods: We retrospectively reviewed patients with PE and APS (n=24) and those with unprovoked PE with aPL negative (n=44), evaluated 2006–2016 at the Asan Medical Center. We compared patient demographics, clinical manifestations, laboratory findings, and radiological findings between the groups.

Results: On multivariate logistic regression analysis, two models of independent risk factors for APS-PE were suggested. Model I included hemoptysis (odds ratio [OR], 12.897; 95% confidence interval [CI], 1.025–162.343), low PE severity index (OR, 0.948; 95% CI, 0.917–0.979), and activated partial thromboplastin time (aPTT; OR, 1.166; 95% CI, 1.040–1.307). Model II included age (OR, 0.930; 95% CI, 0.893–0.969) and aPTT (OR, 1.104; 95% CI, 1.000–1.217).

Conclusion: We conclude that patients with first unprovoked PE with hemoptysis and are age <40; have a low pulmonary embolism severity index, especially in risk class I–II; and/or prolonged aPTT (above 75th percentile of the reference interval), should be suspected of having APS, and undergo laboratory testing for aPL.

Keywords: Antiphospholipid Syndrome; Antibodies, Antiphospholipid; Pulmonary Embolism; Phenotype; Risk Factors

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Introduction

In patients with a first symptomatic pulmonary embolism (PE), clinicians should evaluate for predisposing factors. Unprovoked venous thromboembolism (VTE), for which there is the absence of a temporary or reversible risk factor within the 6 weeks to 3 months before diagnosis, has a moderately high risk of recurrence, which is estimated to be 10% within 1 year and 30% within 5 years¹⁻³. The following risk factors for recurrence in patients with an unprovoked PE may help to identify those at higher long-term relative risk of recurrence: (1) one or more previous episodes of VTE, (2) antiphospholipid antibody syndrome (APS), (3) hereditary thrombophilia, or (4) residual thrombosis in the proximal veins³⁻⁶.

One of those risk factors is APS, a systemic autoimmune

disease that is diagnosed when arterial and/or venous thrombosis, and recurrent fetal losses occurs in the presence of persistent antiphospholipid antibodies (aPL)⁷. APS tends to be more common in young to middle aged women. Estimates have indicated an incidence of around five new cases per 100,000 persons per year, with prevalence around 40–50 cases per 100,000 persons⁸. PE is the most common pulmonary manifestation and may be the first sign of APS^{9,10}. Patients with PE-associated APS are recommended to have extended anticoagulant therapy because of the risk of recurrent VTE¹¹. Prothrombotic states and impaired clot dissolution are believed to contribute to the occurrence of chronic thromboembolic pulmonary hypertension in APS¹².

aPL contributes to the pathogenesis of thrombosis¹³. Galli et al.¹⁴ reported that the odds ratios (OR) of aPL for cerebral stroke and deep vein thrombosis (DVT) ranged between 4.09 and 16.2, all with significant 95% confidence intervals (CI). Recently updated *British Journal of Haematology* guidelines on the investigation and management of APS recommend testing for aPL before stopping anticoagulation after unprovoked proximal DVT or PE, as a positive result favours long-term anticoagulation¹⁵. However, laboratory testing for aPL after a first symptomatic unprovoked PE remains controversial.

We hypothesized that there might be a specific clinical phenotype in patients with unprovoked acute PE indicating a need for evaluation for APS. This study investigated the clinical characteristics of PE in patients with and without APS who had unprovoked PE, looking for clinical predictors for APS.

Materials and Methods

1. Study design and patients

A retrospective descriptive study was conducted. All clinical, radiological, and laboratory data were retrospectively collected from medical records. We reviewed a total of 261 patients diagnosed as having had a first episode of PE between June 2006 and September 2016 at the Asan Medical Center, a 2,700-bed university-affiliated tertiary referral hospital in Seoul, Korea. PE was confirmed in all patients by pulmonary angiography or spiral computed tomography or ventilation-perfusion lung scan indicating a high probability of pulmonary embolism. We tested for aPL in patients with a first unprovoked PE. If results were positive for aPL, aPL test was performed again at least 12 weeks apart. Patient records were included if the PE was confirmed to be unprovoked (i.e., idiopathic) and if laboratory testing for aPL had been performed or the patient was known to have APS. We excluded those with provoked PE in the presence of temporary or reversible risk factors (e.g., surgery, trauma, immobilization, pregnancy, oral contraceptive use, or hormone replacement therapy) within the preceding 6 weeks to 3 months³.

The study was approved by the institutional review board (IRB) of Asan Medical Center (IRB No. 2015-0516). The need for informed consent was waived owing to the retrospective nature of the study.

2. Classification criteria for the antiphospholipid syndrome

According to the 2006 revised APS classification criteria, APS requires the combination of at least one clinical and one laboratory criterion. Clinical criteria include vascular thrombosis (arterial, venous, or small vessel thrombosis in any tissue or organ) and/or pregnancy morbidity (one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, or one or more premature births of a morphologically normal neonate before the 34th week of gestation because of severe pre-eclampsia/eclampsia, or recognized features of placental insufficiency, and/or three or more unexplained consecutive spontaneous abortions before the 10th week of gestation). Laboratory criteria include positive tests for circulating aPL (lupus anticoagulant [LA]; anticardiolipin antibody [ACA], IgG and/or IgM; anti- β_2 glycoprotein-I antibody [$\alpha\beta_2$ GPI], IgG and/or IgM) on two or more occasions at least 12 weeks apart⁷.

3. Laboratory diagnosis of APS

LA tests were determined according to the criteria of the Subcommittee for Standardization of LA¹⁶. The diluted Russell's Viper Venom Test (dRVVT) was performed using an ACL TOP 750 automated coagulometer (Instrumentation Laboratory, Milan, Italy) with a commercial assay (HemosIL, dRVVT screen; Instrumentation Laboratory, Milan, Italy). Samples with a prolonged dRVVT that was not corrected by mixing with a normal plasma pool were tested for confirmation using an excess of phospholipids (HemosIL, dRVVT confirm; Instrumentation Laboratory, Milan, Italy). A commercial silica clotting time (SCT) with low and high concentrations of synthetic phospholipids (HemosIL, SCT screen; Instrumentation Laboratory, Milan, Italy) was used as an activator in the coagulation test. The SCT was carried out on the ACL TOP 750 automated coagulometer (Instrumentation Laboratory, Milan, Italy). Samples with a prolonged SCT that was not corrected by mixing with a normal plasma pool were tested for confirmation using a high phospholipid concentration (HemosIL, SCT confirm; Instrumentation Laboratory, Milan, Italy). ACA (IgG and IgM) and $\alpha\beta_2$ GPI (IgG and IgM) were tested for using commercially assay kits (HemosIL; Instrumentation Laboratory, Bedford, MA, USA). Both tests were carried out on automated immunoassay, the HemosIL AcuStar (Instrumentation Laboratory, Bedford, MA, USA). All tests were performed according to the manufacturer's instructions.

4. Risk stratification

The pulmonary embolism severity index (PESI) is a clinical prediction rule for prognosis of PE developed by Aujesky et al.¹⁷ The PESI correlates with 30-day mortality^{3,17,18}. The risk of early mortality in patients with acute PE was classified as high, intermediate-high, intermediate-low, and low. Risk parameters and scores included shock or hypotension, PESI class III–V or a simplified PESI score ≥ 1 , signs of right ventricular (RV) dysfunction on an imaging test, and cardiac laboratory biomarkers. Risk-adjusted therapeutic strategies and algorithms are recommended on the basis of this risk classification³.

5. Statistical analysis

We compared patient demographics, clinical manifestations, laboratory findings, and radiological findings between patients with a PE associated with APS (APS-PE) and those with an unprovoked PE but who did not have APS (non-APS-PE). Results are expressed as means with standard deviations or median values with interquartile range (IQR) for continuous variables, and as percentages for categorical variables. For comparison of continuous variables between the APS-PE and non-APS-PE groups, parametric data were compared using independent Student's *t*-tests, and nonparametric data were compared using a Mann-Whitney *U* test. Categorical variables were compared using a chi-square or Fisher exact test. To evaluate the clinical predictors of APS-PE, univariate and multivariate logistic regression analysis was performed. Variables with a *p*-values of <0.05 as determined by univariate logistic

regression analysis in consideration of multicollinearity were entered into multivariate logistic regression analysis using a backward elimination method. Assessing goodness-of-fit in logistic regression models was performed by the Hosmer-Lemeshow goodness-of-fit test. Discrimination ability was assessed using the area under the receiver operating characteristic (ROC) curve.

All reported *p* values were two-sided, and a *p*-value of <0.05 was considered statistically significant. Statistical analysis was performed using the IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA).

Results

1. Patients

Among 261 patients diagnosed with a first episode of PE, 170 were excluded from analysis because they had a temporary or reversible risk factor (Figure 1). Of 67 patients with an unprovoked PE, 23 were not tested for aPL and were excluded. So, we compared with 44 patients testing negative for aPL and 24 diagnosed with APS, either primary ($n=17$) or in association with systemic lupus erythematosus ($n=7$).

2. Baseline characteristics

Table 1 shows a comparison of the baseline characteristics between the APS-PE and non-APS-PE groups. Individuals in the APS-PE group were significantly younger and had more

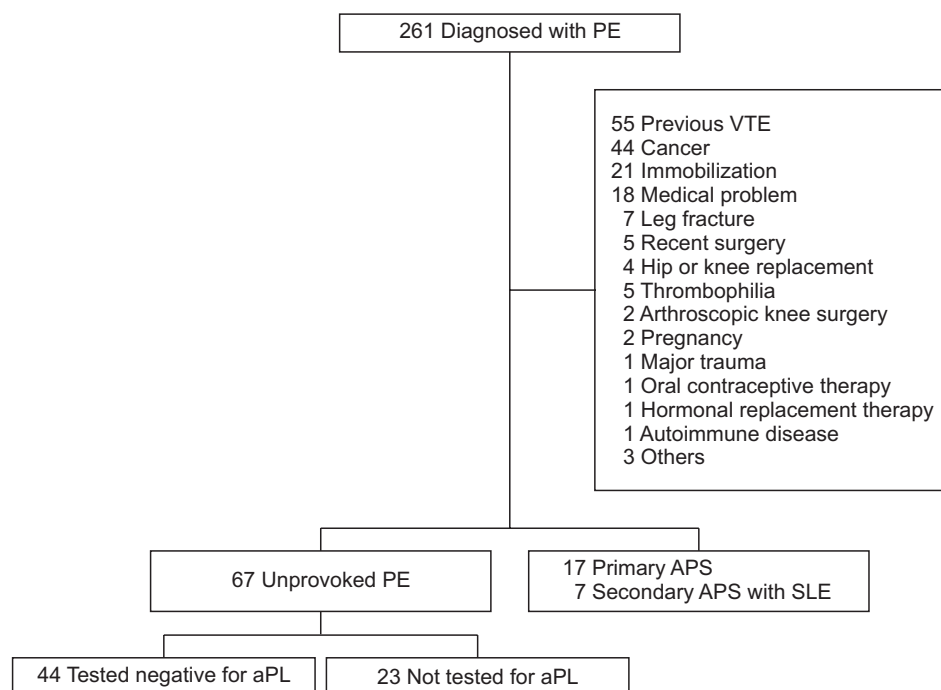


Figure 1. Flowchart of patient selection. One hundred seventy patients with predisposing factors were excluded. An additional 23 patients with unprovoked PE were excluded as they were not tested for APS. PE: pulmonary embolism; VTE: venous thromboembolism; APS: antiphospholipid antibody syndrome; SLE: systemic lupus erythematosus; aPL: antiphospholipid antibody.

Table 1. Baseline characteristics of patients with a first unprovoked PE

	APS-PE (n=24)	Non-APS-PE (n=44)	p-value
Age, yr	39.7±18.4	60.4±14.0	<0.001
Sex			0.492
Male	13 (54.2)	20 (45.5)	
Female	11 (45.8)	15 (54.5)	
Body mass index, kg/m ²	23.9 ± 4.4	25.5 ± 3.6	0.112
Deep vein thrombosis*	17 (70.8)	25 (56.8)	0.256
History of arterial thrombosis	3 (12.5)	0 (0)	0.017
History of pregnancy complications	1 (9.0)	0 (0)	0.176
Presentation			0.175
Acute signs or symptoms	20 (83.3)	42 (95.5)	
Incidental [†]	4 (16.7)	2 (4.5)	
Diagnostic modality			0.283
Computed tomography angiography	22 (91.7)	43 (97.7)	
Ventilation-perfusion scan	2 (8.3)	1 (2.3)	

Values are presented mean±standard deviation or number (%).

*Deep vein thrombosis was diagnosed by lower extremity compression ultrasonography or computed tomography venography.

[†]Incidental PE defined as the finding of PE in situations where it was not suspected.

PE: pulmonary embolism; APS: antiphospholipid antibody syndrome.

history of arterial thrombosis.

3. Radiological findings

The arteries involved by the modified Boyden classification¹⁹, involved lung lobes, and numbers of PEs by pulmonary computed tomography (CT) angiography were similar between the two groups (Table 2), but patients in the APS-PE group were more likely to have a pulmonary infarct than those in the non-APS-PE group.

4. Clinical and laboratory criteria in APS-PE group

As shown in Table 3, the types of aPL found in the APS-PE group included LA (in 58.3%), ACA IgM (in 25.0%), ACA IgG (in 29.2%), aβ2GPI IgM (in 20.8%), and aβ2GPI IgG (in 20.8%). A history of arterial thrombosis was found in three patients (12.5%): coronary artery disease history was found in two and cerebral infarction history in one. Among 11 female patients, one had had eclampsia. Of the 24 patients with APS, seven (29.2%) had systemic lupus erythematosus.

Table 2. Pulmonary CT angiography findings

	APS-PE (n=22)	Non-APS-PE (n=43)	p-value
Single-vessel PE	1 (4.5)	6 (14.0)	0.408
Multiple-vessel PE	21 (95.5)	37 (86.0)	0.408
Artery involved*			
Pulmonary trunk	2 (9.1)	2 (4.7)	0.599
Main pulmonary artery	10 (45.5)	16 (37.2)	0.521
Lobar pulmonary artery	15 (68.2)	34 (79.1)	0.335
Segmental pulmonary artery	19 (86.4)	33 (76.7)	0.516
Subsegmental pulmonary artery	8 (36.4)	12 (27.9)	0.485
Location in lung			
Right upper lobe	10 (45.5)	28 (65.1)	0.128
Right middle lobe	9 (40.9)	26 (60.5)	0.135
Right lower lobe	18 (81.8)	37 (86.0)	0.723
Left upper lobe	13 (59.1)	27 (62.8)	0.772
Left lower lobe	18 (81.8)	35 (81.4)	1.000
Pulmonary infarction [‡]	11 (50.0)	10 (23.3)	0.029

Values are presented as number (%).

*Location according to the modified Boyden classification¹⁹. [†]Defined as a wedge-shaped subpleural opacity on pulmonary CT angiography findings.

CT: computed tomography; APS: antiphospholipid antibody syndrome; PE: pulmonary embolism.

Table 3. Clinical and laboratory criteria in the APS-PE group

	APS-PE (n=24)
Antiphospholipid antibodies	
Lupus anticoagulants	14 (58.3)
Anticardiolipin antibody IgM	6 (25.0)
Anticardiolipin antibody IgG	7 (29.2)
Anti-β ₂ glycoprotein-I antibody IgM	5 (20.8)
Anti-β ₂ glycoprotein-I antibody IgG	5 (20.8)
Arterial thrombosis*	3 (12.5)
Pregnancy complications [†]	1 (9.0)
Secondary APS with SLE	7 (29.2)

Values are presented as number (%).

*Two patients had coronary artery disease. One patient had cerebral infarction. [†]One of eleven women in the APS-PE group had eclampsia.

APS: antiphospholipid antibody syndrome; PE: pulmonary embolism; SLE: systemic lupus erythematosus.

5. Clinical manifestations and laboratory findings

The clinical manifestations and laboratory findings of the two groups are summarized in Table 4. Patients in the APS-PE group had less dyspnea but significantly more hemoptysis, unilateral leg pain, and signs of DVT than the non-APS-PE group. In addition, the APS-PE group had a significantly higher creatinine clearance, prolonged activated partial thromboplastin time (aPTT), and lower aspartate transaminase levels.

6. Prognostic assessment

PESI and early mortality risk are shown in Table 5. The non-APS-PE group had significantly higher creatine kinase-MB (0.65, 0.30–1.60 vs. 1.85, 1.00–4.35; $p=0.003$), PESI, and PESI severity classification than the APS-PE group.

7. Clinical predictors for APS-PE

On univariate logistic regression analysis, significant clinical predictors for APS were age, pulmonary infarction, dyspnea, hemoptysis, unilateral leg pain, signs of DVT, PESI, aPTT, creatinine clearance, and C-reactive protein (CRP). The risk of having APS was 11-fold higher for patients with hemoptysis (OR, 11.316; 95% CI, 1.237–103.553) and 3-fold higher for patients with pulmonary infarction (OR, 3.400; 95% CI, 1.170–9.877), unilateral leg pain (OR, 3.400; 95% CI, 1.170–9.877), or signs of DVT (OR, 3.545; 95% CI, 1.236–10.170) (Table 6). The significant independent risk factors for having APS by multivariate logistic regression analysis for PESI, hemoptysis, signs of DVT, aPTT (model I) were hemoptysis (OR, 12.897; 95% CI, 1.025–162.343), a low PESI (OR, 0.948; 95% CI, 0.917–0.979), and aPTT (OR, 1.166; 95% CI, 1.040–1.307) (Table 7). When model I was applied to the validation data, the area under the ROC curve was 0.868 and the p -value for the Hosmer-Lemeshow

Table 4. Comparison of clinical manifestations and laboratory findings between the APS-PE and non-APS-PE groups

	APS-PE (n=24)	Non-APS-PE (n=44)	p-value
Clinical manifestations			
Dyspnea	14 (58.3)	37 (84.1)	0.019
Pleuritic chest pain	6 (25.0)	5 (11.4)	0.177
Cough	4 (16.7)	2 (4.5)	0.175
Substernal chest pain	5 (20.8)	9 (20.5)	1.000
Fever	3 (12.5)	1 (2.3)	0.122
Hemoptysis	5 (20.8)	1 (2.3)	0.018
Syncope	2 (8.3)	5 (11.4)	>0.990
Unilateral leg pain	12 (50.0)	10 (22.7)	0.022
Signs of deep vein thrombosis*	13 (54.2)	11 (25.0)	0.016
Hypotension [†]	1 (4.2)	4 (9.1)	0.649
Heart rate, beats per minute	90.3±14.9	94.1±18.3	0.396
Laboratory findings			
White blood cell count, / μ L	8,707±4,381	9,792±3,535	0.271
Platelet, $\times 10^3$ / μ L	190,125±102,075	205,090±62,744	0.518
Creatinine clearance, mL/min/1.73 m ²	114.4±25.1	82.9±26.2	<0.001
Prothrombin time, sec	11.8±1.2	11.5±1.3	0.366
International normalized ratio	1.05±0.11	1.03±0.11	0.398
Activated partial thromboplastin time, sec	31.8 (27.3–35.2)	27.1 (25.2–28.6)	<0.001
Aspartate transaminase, IU/L	22.0 (19.0–29.5)	28.0 (21.5–45.0)	0.029
Alanine transaminase, IU/L	20.5 (11.5–40.5)	27.0 (17.5–47.0)	0.152
C-reactive protein, mg/dL	1.17 (0.45–4.22)	0.55 (0.16–1.79)	0.051

Values are presented as number (%), mean±standard deviation, or median (interquartile range).

*A palpable cord reflecting a thrombosed vein, ipsilateral edema, warmth, and/or superficial venous dilation. [†]Defined as systolic blood pressure <90 mm Hg or a systolic pressure drop by ≥ 40 mm Hg for >15 minutes, if not caused by new-onset arrhythmia, hypovolemia or sepsis³. APS: antiphospholipid antibody syndrome; PE: pulmonary embolism.

show goodness-of-fit test was 0.656. Model II included age, hemoptysis, signs of DVT, aPTT, and CRP. The independent risk factors were age (OR, 0.930; 95% CI, 0.893–0.969) and aPTT (OR, 1.104; 95% CI, 1.000–1.217). When model II was applied to the validation data, the area under the ROC curve was 0.819 and the p-value for the Hosmer–Lemeshow goodness-of-fit test was 0.102.

Discussion

Our study shows which clinical factors in patients with unprovoked PE are predictive of APS, thereby suggesting which

patients need to be evaluated for APS. The factors we found to be associated with APS were (1) younger age, (2) the presence of a pulmonary infarct on CT pulmonary angiography, (3) the absence of dyspnea, (4) the presence of hemoptysis, (5) the presence of unilateral leg pain and signs of DVT, (6) a low PESI, (7) prolonged aPTT, and (8) high creatinine clearance and CRP. Among these factors, the most sensitive predictors for APS were younger age, the presence of hemoptysis, a low PESI, and prolonged aPTT.

The prevalence of APS is approximately 40–50 cases per 100,000 persons^{20,21}. APS usually occurs in young patients. Piette and Cacoub²² analyzed data on age at first thrombosis in patients with primary APS and found that the first event occurred in patients aged <50 years. This is in contrast to the risk for VTE in the general population which, as Anderson and

Table 5. PESI and early mortality risk

	APS-PE (n=24)	Non-APS-PE (n=44)	p-value
PESI			0.039
Class I (≤65 points)	14 (58.3)	11 (25.0)	
Class II (65–85 points)	7 (29.2)	13 (29.5)	
Class III (86–105 points)	3 (12.5)	14 (31.8)	
Class IV (106–125 points)	0 (0)	3 (6.8)	
Class V (>125 points)	0 (0)	3 (6.8)	
Average*	58.0±21.6	83.7±24.4	<0.001
Early mortality risk			0.072
High	1 (4.2)	4 (9.1)	
Intermediate–high	1 (4.2)	5 (11.4)	
Intermediate–low	7 (29.2)	22 (50.0)	
Low	15 (62.5)	13 (29.5)	

Values are presented as number (%) or mean±standard deviation. *Sum of points. PESI: pulmonary embolism severity index; APS: antiphospholipid antibody syndrome; PE: pulmonary embolism.

Table 6. Clinical predictors of APS on univariate logistic regression

Variable	OR (95% CI)	p-value
Age	0.929 (0.895–0.964)	<0.001
Pulmonary infarction	3.400 (1.170–9.877)	0.025
Dyspnea	0.265 (0.084–0.832)	0.023
Hemoptysis	11.316 (1.237–103.553)	0.032
Unilateral leg pain	3.400 (1.170–9.877)	0.025
Signs of DVT	3.545 (1.236–10.170)	0.019
PESI	0.950 (0.923–0.978)	0.001
aPTT	1.133 (1.025–1.253)	0.015
Creatinine clearance	1.057 (1.027–1.088)	<0.001
C-reactive protein	1.150 (1.004–1.318)	0.044

APS: antiphospholipid antibody syndrome; OR: odds ratio; CI: confidence interval; DVT: deep vein thrombosis; PESI: pulmonary embolism severity index; aPTT: activated partial thromboplastin time.

Table 7. Multivariate logistic regression model of independent risk factors for PE associated with APS

Variable	Model I*		Model II†	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	-	-	0.930 (0.893–0.969)	0.001
PESI	0.948 (0.917–0.979)	0.001	-	-
Hemoptysis	12.897 (1.025–162.343)	0.048	-	-
Signs of DVT	-	-	-	-
aPTT	1.166 (1.040–1.307)	0.008	1.104 (1.000–1.219)	0.050
C-reactive protein	-	-	-	-

*Multivariate logistic regression analysis for PESI, hemoptysis, signs of DVT, aPTT, and C-reactive protein. †Multivariate logistic regression analysis for age, hemoptysis, signs of DVT, aPTT, and C-reactive protein. PE: pulmonary embolism; APS: antiphospholipid antibody syndrome; OR: odds ratio; CI: confidence interval; PESI: pulmonary embolism severity index; DVT: deep vein thrombosis; aPTT: activated partial thromboplastin time.

Spencer²³ reported, increases in patients aged >40 years of age and approximately doubles with each subsequent decade. In this analysis, the mean age of the APS-PE group was 39.7 years, compared with 60.4 years in the non-APS-PE group. Therefore, if a patient aged <40 years presents with a first symptomatic unprovoked PE, we recommend testing for aPL.

The presenting symptoms and signs of PE are nonspecific. Our study showed that the APS-PE group had more hemoptysis and pulmonary infarction than the non-APS-PE group. The EMPEROR study reported that the most common presenting signs and symptoms of PE were dyspnea at rest (50.1%), pleuritic chest pain (39.4%), dyspnea on exertion (27%), extremity edema suggestive of DVT (23.5%), and cough without hemoptysis (22.9%). Cough with hemoptysis was present in only 7.6%²⁴. He et al.²⁵ reported that 32% patients with PE had pulmonary infarction. In our analysis, hemoptysis in the APS-PE group was present in 20.8% patients, and half the APS-PE group had pulmonary infarction in pulmonary CT angiography. Pulmonary infarction occurs more commonly in patients with peripheral than central pulmonary emboli due to the dual blood supply of the lung, i.e., with occlusion of pulmonary artery branches of ≤ 3 mm in diameter. A wedge-shaped subpleural opacity (“Hampton hump”) on X-ray has been thought by many to be diagnostic of pulmonary infarction^{25,26}. Miniati et al.²⁷ reported that hemoptysis in patients with pulmonary infarction was seen in 19 of 105 patients (18%) and was more frequent than in patients without pulmonary infarction. In patients with PE who had APS in our study, pulmonary infarction was more likely to occur, which may be accompanied by hemoptysis. APS is characterized by thrombophilia with systemic hypercoagulability. Because vascular thrombosis in APS involved at any level of the vascular trees, occlusions of pulmonary arteries and bronchial arteries can occur simultaneously, which can lead to pulmonary infarction²⁸. Therefore, hemoptysis and radiological evidence of pulmonary infarction in patients with unprovoked PE are important factors that should increase suspicion for APS.

The most common haematological manifestation in APS is thrombocytopenia, with an incidence ranging 22%–42% in different series. Thrombocytopenia in APS is rarely associated with haemorrhage^{29–32}. Many patients with APS have a prolonged aPTT because LA inhibits the formation of the prothrombinase complex³³. However, the presence of LA is strong risk factors for thrombosis, irrespective of the site and thrombosis type¹⁴ and not for bleeding. In this study, the most common aPL in the APS-PE group was LA, in 14 of 24 patients (58%). The median aPTT value in the APS-PE group was 31.8 seconds (IQR, 27.3–35.2), within the normal range. However, the median value was still significantly higher in the APS-PE than in the non-APS-PE group. On multivariate logistic regression analysis, aPTT was independently associated with APS. Thus, if patients with an unprovoked PE have an isolated prolonged aPTT above the 75th percentile of the reference inter-

val, screening for aPL, especially LA, should be considered.

PESI is an accurate and reproducible tool for risk stratification in acute PE and correlates with 30-day mortality. PESI and classification of early mortality risk may help identify appropriate candidates for outpatient management or hospitalization. In recently updated guidelines, patients with a confirmed PE in PESI class I–II or low early mortality risk are recommended to have early discharge and home treatment^{3,34,35}. Our study showed that the non-APS-PE group had a higher PESI, with a higher proportion of patients in risk classes III–V, than the APS-PE group. The distribution of early mortality risk between the APS-PE and non-APS-PE groups was not statistically significant, but 70.5% patients in the non-APS-PE group were at intermediate to high mortality risk compared with 37.5% in the APS-PE group. These patients in the non-APS-PE group were generally older than patients in the APS-PE group and had more signs of RV dysfunction. We recommend that laboratory testing for aPL should be considered for patients with unprovoked PE who have a low PESI, especially in risk class I or II.

Our study has limitations. First, it is a retrospective descriptive study from a single tertiary centre, with data collected from patients' medical records, making it susceptible to bias in data selection and analysis. Second, we did not perform a cost-effectiveness analysis of testing for aPL in patients with a first unprovoked PE. Auerbach et al.³⁶ reported that hypercoagulability testing followed by 24 months of anticoagulation was cost effective. Third, we did not analyze treatment outcomes after anticoagulation between the two groups. Fourth, the reason for the high prevalence of APS compared with recent study is unclear³⁷.

In conclusion, this study shows that patients with a first unprovoked PE who have hemoptysis, are aged <40 years, had a low PESI (risk class I or II), and/or prolonged aPTT (above the 75th percentile of the reference interval) should be suspected of having APS and should undergo laboratory testing for aPL. Further research requires cost-effectiveness analysis of testing for aPL in patients with a first unprovoked PE with these factors.

Authors' Contributions

Conceptualization: Oh YM, Lee SD, Lee JS. Methodology: Lee JS. Investigation: Na YS, Lee JS. Writing - original draft preparation: Na YS. Writing - review and editing: Jang S, Hong S. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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