



# Clinical and imaging risk factors for the persistence of thromboembolism following acute pulmonary embolism

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**Background:** Predicting the progression of acute pulmonary embolism to chronic pulmonary thromboembolism (CPTE) disease is essential to monitoring and improving the long-term prognosis of pulmonary embolism. We explored the risk factors for chronic persistence of thromboembolism after acute pulmonary embolism.

**Methods:** Cases with newly onset acute pulmonary embolism in the China-Japan Friendship Hospital from November 2016 to November 2019 were retrospectively analyzed. The clinical characteristics, serological examination results, and treatment strategies of acute pulmonary embolism patients were obtained through the electronic medical record system (Goodwill E-Health Info Co., Ltd.). Imaging parameters on computed tomography pulmonary angiography (CTPA) images at the onset of the acute pulmonary embolism were measured and counted. Notably, we propose a new parameter based on CTPA images: the ratio of  $S_d$  (sum of residual segmental pulmonary artery diameter) to  $MPA_d$  (the main pulmonary artery diameter) ( $S_d/MPA_d$ ). After 3 months of regular treatment for acute pulmonary embolism, patients were classified into a CPTE group or a non-CPTE group based on the presence of residual embolus. All data were compared between the CPTE group and non-CPTE group. Furthermore, logistic regression analysis was used to investigate risk factors for the progression of acute pulmonary embolism to CPTE.

**Results:** A total of 77 cases (male:female = 1:1.26) were included in the study. There were 43 cases (55.84%) in the CPTE group and 34 cases in the non-CPTE group (44.16%). The results of univariate analysis showed that there were statistically significant differences between the 2 groups in risk stratification ( $\chi^2=8.043$ ;  $P=0.005$ ), protein S activity ( $\chi^2=5.551$ ;  $P=0.018$ ), the ratio of sum of residual segmental pulmonary artery diameter to the main pulmonary artery diameter ( $S_d/MPA_d$ ;  $t=-2.103$ ;  $P=0.039$ ), Mastora score ( $U=362.500$ ;  $P<0.001$ ), and embolus location ( $\chi^2=16.969$ ;  $P<0.001$ ). However, there were no statistically significant differences between the 2 groups in treatment options ( $P=0.381$ ). According to multivariate logistic-regression analysis, protein S activity  $<55\%$  ( $P=0.025$ ),  $S_d/MPA_d \geq 1.97$  ( $P=0.011$ ), and an embolus being located in the central pulmonary artery ( $P<0.001$ ) were independent risk factors for chronic persistence of thromboembolism following acute pulmonary embolism.

**Conclusions:** The protein S activity, location of the embolus, and  $S_d/MPA_d$  on CTPA at the onset of acute pulmonary embolism may suggest the progression of acute pulmonary embolism to CPTE.

**Keywords:** Pulmonary embolism; chronic pulmonary thromboembolism disease (CPTE disease); computed tomography pulmonary angiography (CTPA); risk factors

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## Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) remains a major cause of chronic pulmonary hypertension, which can lead to right-sided heart failure and death (1,2). CTEPH is the ultimate consequence of hemodynamic compromise and persistent pulmonary perfusion defects that result from a failure to resolve pulmonary vascular obstructions after acute pulmonary embolism. Several pathophysiological mechanisms for thrombus resolution have been suggested based on the evidence derived from studies in patients with established CTEPH (3,4). Some risk factors, including high thrombus load, diagnostic delay, failure to achieve complete thrombus resolution, recurrent symptomatic pulmonary embolism (PE), and pulmonary hypertension or right ventricular compromise at the baseline, have been identified in the development of CTEPH (5,6). However, less is known about the pathophysiological mechanisms for thrombus resolution after acute PE occurs, which may be the precedent stage of CTEPH (6).

A few studies have reported that complete resolution may be achieved in 70–85% of all patients 6 to 12 months after the initial PE diagnosis, with partial resolution occurring in the majority of the remaining patients (7–10). In the study by Sanchez *et al.* (11), 29% of the patients had perfusion defects during follow-up, and the patients were more likely to have dyspnea, a higher systolic pulmonary arterial pressure, and shorter distance walked during the 6-minute walk test than patients without perfusion defects. The persistence of residual fibrotic blood clots after at least 3 months of effective anticoagulation is a sign of chronic pulmonary thromboembolism (CPTE) (5,6,12). Chronic thromboembolic disease (CTED) can be diagnosed in patients with CPTE if they present with exertional dyspnea [New York Heart Association class (NYHA) II, III, or IV], if they have normal pulmonary arterial pressure at rest, and if they have dead-space ventilation or pulmonary hypertension during exercise (13,14).

Computed tomography pulmonary angiography (CTPA) is increasingly used in the diagnosis of CPTE (15). While earlier trials comparing ventilation-perfusion (V/Q) scan and CT in the diagnosis of CPTE showed that V/Q was superior (16), more recent trials have shown comparable

sensitivity and specificity between the 2 modalities (17,18). CTED and CTEPH share similar imaging characteristics of CPTE on CTPA, such as eccentric filling defects or the formation of cords or webs in the vessel lumen, which shows partial recanalization of a vessel following thrombolysis (6,15). Currently, the early diagnosis of CTEPH remains a challenge, with a median time of 14 months between symptom onset and diagnosis in expert centers (19). Some predisposing factors have been identified for predicting CTEPH during imaging, including large pulmonary arterial thrombi and CTPA findings that suggest pre-existing CPTE (20,21). Although previous studies have mostly focused on predicting CTEPH, the risk factors for incomplete clot resolution after acute PE have not been thoroughly examined (5,22). Predicting the progression of acute pulmonary embolism (APE) to CPTE is essential to monitoring and improving the long-term prognosis of pulmonary embolism. Therefore, we aimed to identify those risk factors associated with the persistence of thromboembolism following APE (i.e., CPTE) to provide predictive information in a clinical setting. We present the following article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-21-753/rc>).

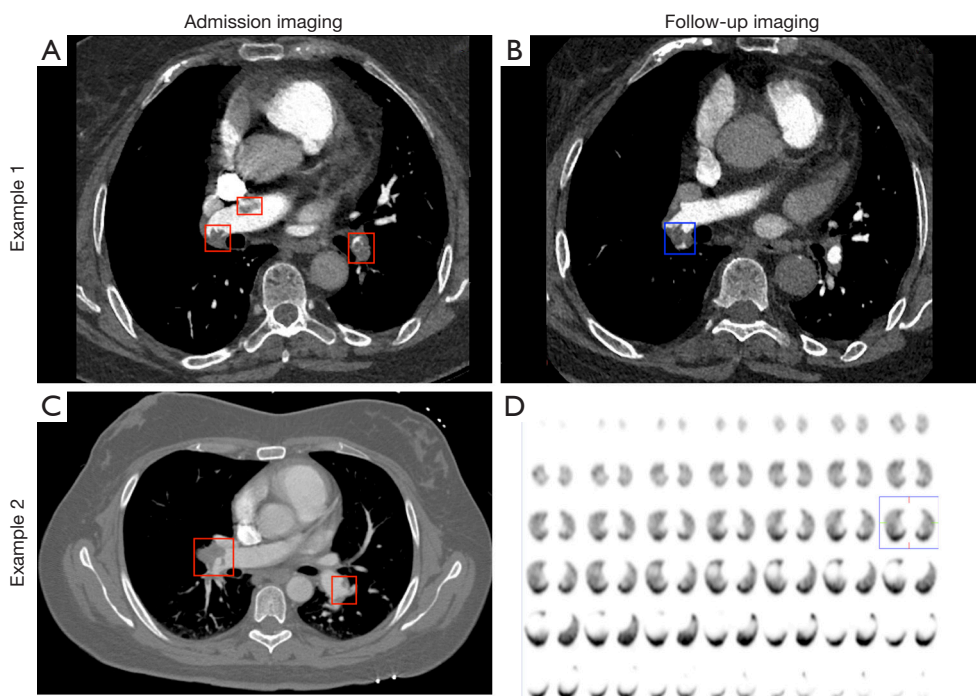
## Methods

### Study design

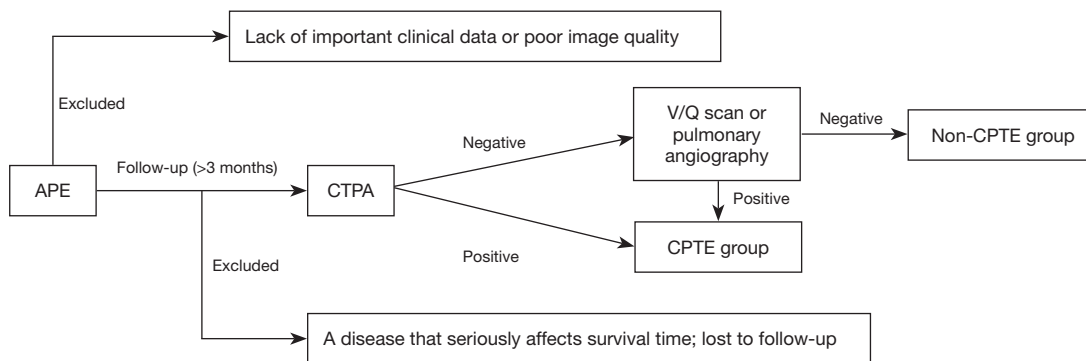
Patients with APE were classified into a CPTE group or a non-CPTE group according to follow-up results. Clinical characteristics, laboratory test results, imaging parameters, and treatment strategies of all APE patients were included in the analysis of the study.

### Study patients

Data from cases with newly onset APE in the China-Japan Friendship Hospital from November 2016 to November 2019 were retrospectively collected. The diagnostic criteria for APE were established according to the 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism (20). Subsequently, patients who had newly onset APE received three months of regular anticoagulation and were followed up for a minimum of



**Figure 1** CT images for cases with APE that developed CPTE. (A,B) The CTPA images of one patient with APE followed up for 3 months; (C,D) the images from another patient with APE followed up for 4 months. (A,C) The images of patients at admission. The red and blue boxes indicate emboli. CPTE, chronic pulmonary thromboembolism; CT, computed tomography; APE, acute pulmonary embolism; CTPA, computed tomography pulmonary angiogram.



**Figure 2** The diagnostic process of CPTE. APE, acute pulmonary embolism; CTPA, computed tomography pulmonary angiogram; V/Q scan, ventilation-perfusion lung scintigraphy; CPTE, chronic pulmonary thromboembolism.

3 months. A follow-up CTPA was performed to investigate the recanalization of the pulmonary vessels. Additional V/Q scintigraphy or pulmonary angiography was performed when the follow-up CTPA was negative (Figure 1). Patients with positive results on CTPA, V/Q scintigraphy or pulmonary angiography were classified into the CPTE group and others were in the non-CPTE group (Figure 2).

Exclusion criteria were as the follows: (I) the patient’s survival was affected by a disease other than pulmonary embolism during the follow-up, (II) there was a lack of important clinical data or poor image quality of CTPA, and/or (III) the patient was lost to follow-up. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the China-

Japan Friendship Hospital Institutional Review Board (Medical Ethics No. 2016-SSW-7), and individual consent for this retrospective analysis was waived.

### CTPA

CTPA was performed with a multi-slice CT scanner (Lightspeed VCT/64, GE Healthcare; Philips iCT/256) in the craniocaudal direction using a standard CTPA protocol. Scanning parameters were as follows: tube voltage 100–120 kVP, tube current 100–300 mAs, slice thickness 0.625–1 mm, table speed 39.37 mm/s, gantry rotation time 0.8 s, and reconstruction increment 1–1.25 mm. Soft tissue was used to reconstruct the nucleus. Lopromide (UV, 370 mg/mL) was intravenously injected with a mechanical syringe at a flow rate of 5.0 mL/s. To obtain the best intraluminal contrast enhancement, the automatic bolus-tracking technique positioned the region of interest at the level of the main pulmonary artery with a 100-Hu predefined threshold.

### Data collection

We obtained the patients' clinical data, serological results, and treatment strategy by searching the electronic medical record system (Goodwill E-Health Info Co., Ltd.). Clinical data included age, sex, etiology, risk stratification, presence of recurrent PE, and previous deep vein thrombosis. The etiology of APE includes secondary factors (including recent trauma, fracture, surgical intervention, hospitalization, pregnancy, active cancer, long term immobilization and the use of oral contraceptives or hormone-replacement therapy), primary factors (including deficiency of antithrombin, protein C, or protein S; coagulation factor abnormality; mutation in the factor V Leiden or prothrombin gene; the presence of lupus anticoagulants, and hyperhomocysteinemia), and idiopathic factors (i.e., pulmonary embolism of unknown cause). According to the 2019 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of acute pulmonary embolism (20) and the different treatment options, we divided patients with APE into a low-intermediate risk group and a high-intermediate risk group. The low-intermediate risk group comprised low-risk and intermediate-low risk patients, including those who had signs of right ventricle (RV) dysfunction on echocardiography or CTPA or elevated cardiac biomarkers. The high-intermediate risk group comprised (I) those at

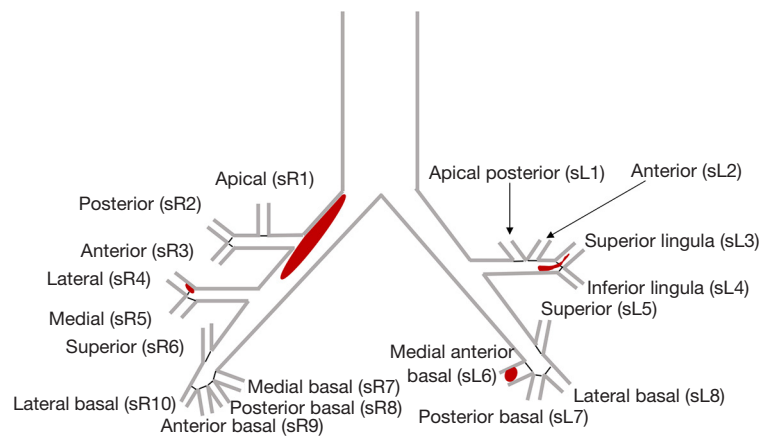
intermediate-high risk, including patients with evidence of both RV dysfunction and elevated cardiac biomarker levels in the circulation—particularly a positive cardiac troponin test—and (II) those at high risk, including patients with hemodynamic instability and/or RV dysfunction on echocardiography. In addition, we determined whether APE was recurrent either by outpatient clinic visits or by telephone contact.

Serological examinations consisted of prothrombin time (PT), prothrombin time activity (PTA), fibrinogen (Fbg), activated partial thromboplastin time (APTT), thrombin time (TT), antithrombin III, protein C (PC) activity, protein S (PS) activity, myoglobin (Myo), cardiac troponin-T (cTnT), N-terminal-pro-brain natriuretic peptide (NT-pro-BNP), creatine kinase isoenzyme (CK-MB), hematocrit (HCT), red cell distribution width (RDW), uric acid, creatinine (Cr), homocysteine, and blood type.

All patients underwent CTPA examination at the onset of APE. The CTPA images were independently evaluated using the Picture Archiving and Communication Systems by 2 radiologists with an experience of more than 5 years reading CTPA images. They observed and recorded the proximal location of the pulmonary embolus and categorized the location as the main (main pulmonary trunk, left or right pulmonary artery), lobar, segmental, or subsegmental artery. The presence of pulmonary infarction, pleural effusion, and pericardial effusion was also observed. Measurement and calculation of the parameters included the main pulmonary artery diameter ( $MPA_d$ ), the aorta diameter ( $Ao_d$ ), the ratio of  $MPA_d$  to  $Ao_d$  ( $MPA_d/Ao_d$ ), the sum of residual segmental pulmonary artery diameter ( $S_d$ ), the ratio of  $S_d$  to  $MPA_d$  ( $S_d/MPA_d$ ), the right ventricle maximum transverse diameter ( $RV_d$ ), the left ventricular maximum transverse diameter ( $LV_d$ ), the ratio of  $RV_d$  to  $LV_d$  ( $RV_d/LV_d$ ), and Mastora score (23).  $S_d$  referred to the sum of the residual patent diameters of all segmental pulmonary arteries where they branched from the lobar pulmonary artery, including the sum of the residual segmental pulmonary arterial diameters of the left lung ( $S_{Ld} = sL1_d + sL2_d + sL3_d + sL4_d + sL5_d + sL6_d + sL7_d + sL8_d$ ) and the right lung ( $S_{Rd} = sR1_d + sR2_d + sR3_d + sR4_d + sR5_d + sR6_d + sR7_d + sR8_d + sR9_d + sR10_d$ ), or  $S_d = S_{Ld} + S_{Rd}$  (d: diameter; Figure 3).

### Statistical analysis

Intraclass correlation coefficients (ICC) were used to evaluate the consistency of the measured results. Univariate



**Figure 3** The calculation diagram of  $S_d$ . The short black line represents the residual segmental pulmonary artery diameter. The red areas represent the embolus.  $S_d = s_{L,d} + s_{R,d}$ ,  $s_{L,d} = sL1_d + sL2_d + sL3_d + sL4_d + sL5_d + sL6_d + sL7_d + sL8_d$ ,  $s_{R,d} = sR1_d + sR2_d + sR3_d + sR4_d + sR5_d + sR6_d + sR7_d + sR8_d + sR9_d + sR10_d$  (d: diameter).

analysis was performed to detect differences between the CPTE group and the non-CPTE group. The *t* test was used for normally distributed data, the Mann-Whitney test was used for nonnormally distributed data, and the continuous corrected chi-square test (when  $N \geq 40$ , and  $1 \leq T < 5$ ) or Fisher's exact test (when  $n < 40$ , or  $T < 1$ ) were used for categorical variables. Following this, all variables with a univariate level of significance of less than 0.05 were included in a backward, stepwise multivariate logistic-regression model to detect the risk factors for the CPTE. All calculations were performed with the use of SPSS 20.0 (IBM Corp., Armonk, NY, USA).

## Results

A total of 77 patients with APE, including 34 males and 43 females (male:female = 1:1.26) were enrolled in this study, and their mean age was 60 years (range, 25–83 years) with the average follow-up time of 5 months (range, 3–7 months). According to the follow-up results, all APE patients were subsequently divided into the CPTE group (43 cases, 55.84%) and the non-CPTE group (34 cases, 44.16%); 16 patients (16/77, 20.78%) reported dyspnea at the follow-up, including 13 (13/77, 16.88%) in the CPTE group and 3 (3/77, 3.90%) in the non-CPTE group.

### Univariate analysis

#### Clinical and laboratory tests

The etiology, risk stratification, presence of recurrent PE,

and previous deep vein thrombosis were compared between the 2 groups (Table 1). We found that only risk stratification was statistically different between the 2 groups and that high-intermediate risk individuals with APE were more likely to progress to CPTE ( $\chi^2=8.043$ ;  $P=0.005$ ).

The comparison of serological examinations between the 2 groups is listed in Table 2. Results showed that only protein S activity was statistically different between the 2 groups. For the application in clinical practice, we chose the lower bound of the normal value (55%) as the cutoff value and found that APE patients with PS activity <55% were more likely to develop CPTE ( $\chi^2=5.551$ ;  $P=0.018$ ).

#### Measures on CTPA

The results of imaging parameters are listed in Table 3. The ICC between the 2 radiologists was 0.848 (95% CI: 0.713–0.920;  $P < 0.001$ ). Patients with APE and an increased  $S_d/MPA_d$  were more likely to progress to CPTE ( $t=-2.103$ ;  $P=0.039$ ). For the application in clinical practice, we took the mean value of  $S_d/MPA_d$  (1.97) as the cutoff value, and the difference between the two groups was statistically significant when it was  $\geq 1.97$  ( $\chi^2=3.970$ ;  $P=0.046$ ). The embolus was located in the main pulmonary artery in 18 cases (23.38%), in the lobar pulmonary artery in 29 cases (37.66%), in the segmental pulmonary artery in 27 cases (35.06%), and in the subsegmental pulmonary artery in 3 cases (3.90%). There was a statistically significant difference in the distribution of emboli and Mastora score between the 2 groups ( $P < 0.001$ ). In addition, 18 patients developed pulmonary infarction (23.38%). Pleural effusion was

**Table 1** Demographic and clinical characteristics of patients with APE

Risk factors	CPTE group (n=43)	Non-CPTE group (n=34)	P value
Age (year)	59.19±15.74	61.85±14.65	0.449
Male/female	23/20	11/23	0.064
Etiology, n (%)			0.921
Secondary PE	33 (76.74)	25 (73.53)	
Primary PE	5 (11.63)	4 (11.76)	
Idiopathic PE	5 (11.63)	5 (14.71)	
Recurrent PE, n (%)	10 (23.26)	5 (14.71)	0.347
Risk stratification			0.005
Low-intermediate risk	24 (55.81)	30 (88.24)	
High-intermediate risk	19 (44.19)	4 (11.76)	
Previous DVT, n (%)	22 (51.16)	17 (50.00)	0.919

APE, acute pulmonary embolism; CPTE, chronic pulmonary thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis.

**Table 2** Serological markers of patients with APE

Risk factors	CPTE group		Non-CPTE group		P value
	n	Values	n	Values	
PT (s)	43	14.06±2.73	34	14.63±1.86	0.298
PTA (%)	43	86.28±14.62	34	83.09±16.35	0.370
Fbg (g/L)	43	4.22±1.55	34	4.50±1.59	0.441
APTT (s)	43	45.31±9.91	34	42.40±13.79	0.285
TT (s)	43	27.59±35.87	34	19.89±19.16	0.262
D-D (mg/L)	42	3.20±3.02	34	3.16±3.80	0.952
Antithrombin III (%)	37	86.84±11.94	26	87.88±10.70	0.722
PC (<70%)	35	6	23	3	0.349
PS (<55%)	34	12	18	1	0.018
Myo (ng/mL)	31	53.76±64.17	27	32.74±34.36	0.134
cTnT (ng/mL)	34	0.03±0.04	25	0.04±0.09	0.751
NT-pro-BNP (pg/mL)	32	2,087±4,132	24	1,363±2,792	0.462
CK-MB (ng/mL)	38	2.54±3.95	30	1.38±1.45	0.131
Hct (%)	39	33.94±12.83	31	35.01±8.74	0.693
RDW (>15%)	40	3	31	5	0.500
Uric acid (μmol/L)	38	341.4±147.62	32	307.34±131.80	0.315
Homocysteine (μmol/L)	26	18.46±11.94	24	14.12±7.83	0.139
Cr (μmol/L)	39	75.48±25.56	32	70.84±27.17	0.462

APE, acute pulmonary embolism; CPTE, chronic pulmonary thromboembolism; PT, prothrombin time; PTA, prothrombin time activity; Fbg, fibrinogen; APTT, activated partial thromboplastin time; TT, thrombin time; D-D, D-dimer; PC, protein C; PS, protein S; Myo, myoglobin; cTnT, cardiac troponin-T; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; CK-MB, creatine kinase isoenzyme; Hct, hematocrit; RDW, red cell distribution width; Cr, creatinine.

**Table 3** Imaging findings for patients with APE

Risk factors	CPTE group (n=43)	Non-CPTE group (n=34)	P
MPA <sub>d</sub> (mm)	30.11±4.44	20.05±5.97	0.965
Ao <sub>d</sub> (mm)	33.44±5.49	33.12±5.07	0.797
MPA <sub>d</sub> /Ao <sub>d</sub>	0.92±0.16	0.91±0.13	0.822
S <sub>d</sub> /MPA <sub>d</sub>	2.05±0.34	1.89±0.30	0.039
S <sub>d</sub> /MPA <sub>d</sub> ≥1.97	25	12	0.046
RV <sub>d</sub> (mm)	39.03±5.68	37.44±7.40	0.288
LV <sub>d</sub> (mm)	43.49±8.44	41.08±5.51	0.155
RV <sub>d</sub> /LV <sub>d</sub>	0.93±0.22	0.91±0.13	0.706
Mastora score	43.86±29.46	19.79±21.11	<0.001
Location of embolism			<0.001
Subsegmental	0	3	
Segmental	8	19	
Lobar	19	10	
Main	16	2	
Pulmonary infarction	13	5	0.110
Pleural effusion	9	11	0.256
Pericardial effusion	4	7	0.281

APE, acute pulmonary embolism; CPTE, chronic pulmonary thromboembolism; MPA<sub>d</sub>, the main pulmonary artery diameter; Ao<sub>d</sub>, the aorta diameter; MPA<sub>d</sub>/Ao<sub>d</sub>, the ratio of MPA<sub>d</sub> to Ao<sub>d</sub>; S<sub>d</sub>, sum of residual segment pulmonary artery diameter; S<sub>d</sub>/MPA<sub>d</sub>, the ratio of S<sub>d</sub> to MPA<sub>d</sub>; RV<sub>d</sub>, the right ventricle maximum transverse diameter; LV<sub>d</sub>, the left ventricular maximum transverse diameter; RV<sub>d</sub>/LV<sub>d</sub>, the ratio of RV<sub>d</sub> to LV<sub>d</sub>.

**Table 4** Treatment strategies for patients with APE

Treatment	CPTE group (n=43), n (%)	Non-CPTE group (n=34), n (%)	P value
Oral anticoagulation	3 (7.0)	2 (5.9)	0.381
Intravenous anticoagulation	36 (83.7)	30 (88.2)	
Combined anticoagulation with thrombolysis	1 (2.3)	2 (5.9)	
Combined anticoagulation with interventional thrombolysis	3 (7.0)	0 (0.0)	

APE, acute pulmonary embolism; CPTE, chronic pulmonary thromboembolism.

found in 20 patients and pericardial effusion in 11 patients. However, there were no statistically significant differences between the 2 groups in pulmonary infarction (P=0.110), pericardial effusion (P=0.281), or pleural effusion (P=0.256).

### Therapy

All 77 patients received 3 months of uninterrupted anticoagulation therapy prior to repeat imaging. This included 4 treatment strategies: oral anticoagulation only (5

cases, 6.5%), intravenous anticoagulation (66 cases, 85.7%), combined anticoagulation with thrombolysis (3 cases, 3.9%), and combined anticoagulation with interventional thrombolysis (3 cases, 3.9%). However, there was no statistically significant difference between the 2 groups in treatment option (P=0.381; *Table 4*).

### Summary

Univariate analysis indicated the risk factors that may affect

**Table 5** Logistic-regression analysis of risk factors for CPTE

Risk factors	OR (95% CI)	P value
Protein S activity		
≥55%	1.00	
<55%	18.41 (1.45, 234.05)	0.025
S <sub>d</sub> /MPA <sub>d</sub>		
<1.97	1.00	
≥1.97	5.43 (1.47, 20.06)	0.011
Embolus location		
Peripheral	1.00	
Central	13.21 (3.43, 50.88)	<0.001

CPTE, chronic pulmonary thromboembolism; S<sub>d</sub>/MPA<sub>d</sub>, the ratio of sum of residual segmental pulmonary artery diameter to the main pulmonary artery diameter; OR, odds ratio.

the progression of APE to CPTE were as follows: (I) risk stratification—high-intermediate risk individuals with APE were more likely to progress to CPTE ( $\chi^2=8.043$ ;  $P=0.005$ ); (II) protein S activity—55% was selected as the cutoff value in this study, which found that APE patients with protein S activity <55% were more likely to develop CPTE ( $\chi^2=5.551$ ;  $P=0.018$ ); (III) S<sub>d</sub>/MPA<sub>d</sub>—APE patients with increased S<sub>d</sub>/MPAd were more likely to progress to CPTE ( $t=-2.103$ ;  $P=0.039$ ), and the difference between the 2 groups was statistically significant when it was  $\geq 1.97$  ( $\chi^2=3.970$ ;  $P=0.046$ ); (IV) Mastora score—patients with higher scores were more likely to progress to CPTE ( $U=362.500$ ;  $P<0.001$ ); and (V) embolus location—there was a statistically significant difference in the distribution of emboli between the 2 groups ( $\chi^2=16.969$ ;  $P<0.001$ ; *Tables 1-4*).

However, there were no statistically significant differences between the 2 groups in age, gender, etiology, or treatment options ( $P>0.05$ ).

### Multivariate regression analysis

Based on the results of the univariate analysis, variables were selected to perform multivariate logistic-regression analysis to determine the independent risk factors for progression to CPTE. The variables included were age at onset, etiology, risk stratification, protein S activity, S<sub>d</sub>/MPA<sub>d</sub>, Mastora score, embolus location, and therapeutic approaches. For convenience, the embolus location was simplified to be in the central pulmonary artery (main pulmonary trunk, left or right pulmonary artery or lobar artery; 35 cases in the

CPTE group and 12 cases in the non-CPTE group) and the peripheral pulmonary artery (segmental or subsegmental pulmonary artery; 8 cases in the CPTE group and 22 cases in the non-CPTE group).

We performed multivariable risk factor analysis and found that protein S activity <55%, S<sub>d</sub>/MPAd  $\geq 1.97$ , and the embolus being located in the central pulmonary artery were independent risk factors associated with the development of CPTE (*Table 5*).

### Discussion

In this retrospective study, the patients with APE were followed up and investigated to explore those risk factors associated with the persistence of thromboembolism after APE. We finally determined that PS activity <55%, S<sub>d</sub>/MPA<sub>d</sub>  $\geq 1.97$ , and the embolus being located in the central pulmonary artery were independent risk factors for the progression of APE to CPTE.

There exist a few studies regarding the risk factors for CTEPH development after APE (21,24). It is well known that CTEPH is an important long-term complication and cause of death in patients with pulmonary embolism. Although the pulmonary artery pressure of CPTE is normal, pulmonary artery remodeling and hemodynamic changes may occur (25). Therefore, patients with CPTE are suitable for strict surveillance and treatment to improve the prognosis of pulmonary embolism, and thus knowledge concerning the development of CPTE after APE is essential for clinical observation. Currently, the true incidence of CPTE is unknown, and the rate in this study was 55.84%, which was higher than the 15–30% reported in the literature (11,26). The difference may be attributed to the shorter interval of follow-up in our study relative to the 6–12 months used in prior studies. However, it is worth noting that the resolution of thrombi appears to reach a plateau phase after 3 months of adequate treatment, as the remaining clots have been remodeled into permanent fibrous scars (10,27,28).

To our knowledge, this is the first study to propose a new imaging quantitative parameter, S<sub>d</sub>/MPA<sub>d</sub>, for predicting persistent thromboemboli following APE. One noteworthy finding was that S<sub>d</sub>/MPA<sub>d</sub>  $\geq 1.97$  was an independent risk factor for CPTE. We have proposed the calculation of the parameter based on the pathophysiological mechanism of the pulmonary vascular obstruction, which is described in detail in the Methods section. S<sub>d</sub> was used to represent the total residual cross-sectional area of segmental vessels, and



$S_d/MPA_d$  was used in order to reduce individual differences as much as possible. According to Poiseuille's law, when the emboli block some of the pulmonary vessels, hypoxia, mechanical stimulation, and other factors that result from the pulmonary embolism cause vasoconstriction and decrease the total cross-sectional area, which leads to an increase in vascular resistance and a decrease in the regional blood flow. Blood stasis that results from vessel obstruction increases the release of tissue plasminogen activator and activates the fibrinolytic system, which are the accelerating factors for dissolving the thrombosis (29). Partially blocked vessels may not be able to thoroughly activate the fibrinolytic system, so they have more potential for residual thrombi. This also explains to some extent why the Mastora score was not an independent risk factor. It may be possible that thrombolysis is mainly determined by the hemodynamics-related activation of the fibrinolytic system rather than by the clot burden, so which should not be deemed as the counterpart of the Mastora score. The Mastora score is an index that shows obstruction, while  $S_d/MPA_d$  is suggestive of both residual lumens and secondary vessel reaction to the impaired hemodynamics. Overall, according to our results, an  $S_d/MPA_d \geq 1.97$  is an independent risk factor of incomplete resolution and organization of thrombus in patients following APE. However, this index should be widely tested in further research.

We also found that the embolus being located in the central pulmonary artery to be an independent risk factor of CPTE, which is consistent with findings by Guérin *et al.* (30). However, the results of previous studies on the effect of embolus location have been inconsistent. Yu *et al.* (31) reported that an embolus located in the segmental or subsegmental pulmonary arteries was more likely to be associated with an increased risk of CTEPH, while Tosun *et al.* (32) reported that embolus location had no effect on this risk. We speculate that an embolus located in the central pulmonary artery is usually overextended and is difficult to dissolve completely at some places, such as branching sites. Furthermore, in the univariate model, we found that  $RV_d/LV_d$  was not a risk factor for CPTE. Guérin *et al.* (30) reported that APE patients with increased  $RV_d/LV_d$  were more likely to develop CTEPH. Further research designed to explore the relationship between the above risk factors and the prognosis of APE is required.

As for serological markers, PS activity <55% was found to be an independent risk factor for CPTE in this study. A previous study showed there to be no association between

a deficiency of antithrombin, protein C, or protein S and CTEPH (33). PS, a vitamin K-dependent plasma protein, is an essential cofactor of the coagulation proteins involved in hemostasis and thrombosis. People with inherited disorders related to the production or function of PS may have a 10-fold risk for venous thrombosis (34-36). In a population-based study, Pintao *et al.* (37) demonstrated that patients at risk of venous thrombosis could be identified at levels <0.10th percentile of free protein S. During the short period after the onset of thrombosis or intaking warfarin, some patients show a decrease of PS activity due to consumption, with a variable extent and period. PS might regulate the process of thrombus dissolution via a series of cofactors (38,39). Therefore, it is worth investigating the role of reduced PS activity in the development of chronic embolus.

There were several limitations to this retrospective study. First, as  $S_d/MPA_d$  is a new risk factor for predicting CPTE, whether it is related to persistent functional impairment needs to be tested. Moreover, the sample size of this study was insufficient for a study of CTED, and thus a large, multicenter prospective study should be conducted to further verify the role of the imaging parameters. Second, the follow-up interval varied in this study although our patients underwent a standard anticoagulant therapy more than 3 months following APE. Recently, increasing attention has been paid to the need for follow-up care to recognize and prevent long-term sequelae. However, when and how best to screen and evaluate patients for post-PE syndrome remains an area of active research (5). Nonetheless, the difference in the follow-up interval might have had an impact on the grouping of CPTE patients. Third, the prognosis of CPTE is mainly related to the hemodynamic changes of pulmonary blood vessels, and persistent thromboemboli may not definitely represent hemodynamic impairments. However, our findings provide novel insights concerning the hemodynamic and pathophysiological effects on the treatment outcome.

In conclusion, the protein S activity,  $S_d/MPA_d$ , and the location of embolus at APE onset may suggest whether or not anticoagulant therapy can achieve a complete resolution of PE.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-21-753/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-21-753/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the China-Japan Friendship Institutional Review Board (Medical Ethics No. 2016-SSW-7), and individual consent for this retrospective analysis was waived.

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