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Usefulness of a refined computed tomography imaging method to assess the prevalence of residual pulmonary thrombi in patients 1 year after acute pulmonary embolism: The Nagoya PE study

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Abstract

Background: Post-pulmonary embolism (PE) syndrome is an important clinical condition that can affect the long-term prognosis after acute PE.

Objective: We aimed to evaluate the prevalence of residual pulmonary thrombi and the thrombotic burden 1 year after acute PE, by using our refined computed tomography (CT) imaging method.

Patients/Methods: In this prospective study, patients diagnosed with acute PE were recruited and examinations were conducted at 1 month, 6 months, and 1 year. Especially at 1 year, patients were evaluated multifacetedly, including by laboratory tests, quality-of-life, 6-min walking test, and enhanced CT.

Results: Fifty-two patients were enrolled. Two patients (3.8%) developed chronic thromboembolic pulmonary hypertension. A total of 43 patients completed evaluation at 1 year, among whom (74%) had residual thrombi, with a median modified CT obstruction index (mCTOI) of 10.7%. In multivariate analysis, residual thrombi at 1 month was the only factor significantly related to residual thrombi at 1 year (odds ratio, 103.4; 95% confidence interval, 4.2–2542.1). The tricuspid regurgitation pressure gradient ≥60 mmHg and left ventricular end-diastolic dimension at diagnosis were significantly related to mCTOI at 1 year ($\beta = 0.367$, $P = .003$; and $\beta = -0.435$, $P = .001$, respectively).

Conclusions: Using our improved CT imaging protocol, we found a high prevalence of residual thrombi 1 year after acute PE. Furthermore, right ventricular overload was related to the thrombotic burden. The long-term treatment strategy of acute PE could be modified to include precise CT imaging.

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1 | INTRODUCTION

Post-pulmonary embolism (PE) syndrome has recently been recognized as an important pathology in the chronic phase after acute PE.[1] Post-PE syndrome is defined to include persistent dyspnea, exercise limitation, and impaired quality of life (QOL) after acute PE. Previous studies reported that 41% of previously healthy patients had persistent cardiopulmonary problems within 6 months after first-time PE.[2] In another report, 45% of patients remained as New York Heart Association (NYHA) class 2 or higher, even at 3 years or more after acute PE.[3] Persistent perfusion defects are among the main components of post-PE syndrome.[1,4] In the SCOPE study, perfusion scans revealed residual pulmonary obstruction in 50.1% of patients 6 months after the index PE.[5] In the REVERSE cohort study, residual vascular obstruction detected by ventilation/perfusion scan after 5–7 months of anticoagulant therapy for the first episode of unprovoked PE was associated with significantly higher risk of recurrent venous thromboembolism (VTE).[6] In addition, residual PE after a mean of 9 months of anticoagulation therapy was detected in 15% of study patients who underwent multidetector computed tomography (MDCT) and in 28% of those who had lung perfusion scintigraphy.[7] Although the detection rate of residual thrombi evaluated by MDCT reportedly is inferior to that from lung perfusion scans, the resolution of MDCT has improved in recent years.[8] In fact, an enhanced computed tomography (CT) protocol for detecting pulmonary artery (PA) thrombi in patients with chronic thromboembolic pulmonary hypertension (CTEPH) has been reported.[9,10] Therefore, in this study, we applied a modified scanning protocol using fast MDCT to detect small thrombi up to the level of the subsegmental branches of the PA. Moreover, we combined our enhanced CT protocol with long-term multifaceted assessment and a modified index for scoring thrombotic burden to evaluate patients for residual pulmonary thrombi after acute symptomatic PE.

2 | METHODS

2.1 | Study population and diagnosis

This was a multicenter, prospective, observational study conducted at 46 hospitals in the Tokai area (Japan). Patients with acute symptomatic PE were recruited from April 2017 through August 2019 (Figure S1 in supporting information). This study was approved by the Human Research Ethics Committees of Nagoya University Hospital (no. 2016–0495) and was performed in accordance with the Declaration of Helsinki and the ethical standards of the institutional committee on human experimentation. Patients were eligible when

Essentials

- Long-term prognosis after acute pulmonary embolism (PE) is an important clinical issue.
- We evaluated the prevalence of residual thrombi and thrombotic burden 1 year after acute PE.
- Residual thrombi 1 year after acute PE were detected in 74% by refined computed tomography protocol.
- Right ventricular overload at diagnosis was related to the thrombotic burden at 1 year.

they were at least 16 years of age, demonstrated acute symptomatic PE, and provided signed informed consent. Patients were excluded when they were allergic to contrast media, had severe renal dysfunction, were pregnant, or had an estimated life expectancy of less than 1 year.

Post-PE was diagnosed when an intraluminal filling defect was noted on contrast-enhanced CT or lung perfusion scintigraphy images. The symptoms of acute PE were defined as the sudden onset of dyspnea, syncope, chest pain, cough, or hemoptysis. In addition, sudden abnormalities in vital signs, including decreased oxygen saturation, decreased blood pressure, and tachycardia, were considered symptomatic of acute PE.

The observational period was 1 year. Laboratory tests and echocardiography were performed at study entry and at 1 month, 6 months, and 1 year after acute PE. Contrast-enhanced CT was performed at 1 month and 1 year; all patients visited Nagoya University Hospital at the 1-year point to undergo our modified contrast-enhanced CT protocol. In addition, the 36-item Short-Form Health Survey (SF-36) and 6-min walking test (6 MWT) were performed at the 1-year visit.

2.2 | Study outcomes and definitions

The primary study outcome was the prevalence of residual pulmonary thrombi detected by applying our enhanced CT imaging method at 1 year after the onset of acute symptomatic PE. The secondary study outcomes were the prevalence of CTEPH, recurrent PE, all-cause death, cardiovascular death, and major bleeding. All the outcomes were strictly adjudicated by an independent endpoint evaluation committee in a blinded manner.

Chronic thromboembolic pulmonary hypertension was diagnosed when the patient had—in addition to pulmonary thrombi—persistent dyspnea or exercise limitation associated with a mean PA pressure of ≥25 mmHg and pulmonary capillary wedge pressure

of <15 mmHg according to right heart catheterization. Recurrent PE was defined as symptomatic PE with confirmation of new PA thrombi. Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis as bleeding associated with a ≥2 g/dl decrease in hemoglobin level, bleeding in a critical area or organ, or fatal bleeding.

We assessed the health-related QOL score using the validated SF-36 questionnaire; we calculated SF-36 component summary scores (physical component summary [PCS], mental component summary [MCS]) and scores for all subscales.[11,12]

Cutoff values for brain natriuretic peptide (BNP; >100 pg/ml) and N-terminal pro-brain natriuretic peptide (NT pro-BNP; >600 pg/ml) at diagnosis of acute PE were adopted from previous studies.[13,14] In addition, a tricuspid regurgitation pressure gradient (TRPG) cutoff value of ≥60 mmHg according to echocardiography was adopted for assessment of right ventricular pressure overload.[15] Exercise limitation was defined as a 6-min walking distance (6 MWD) of <330 m.[2]

2.3 | Computed tomography scanning and data reconstruction

Contrast-enhanced CT at diagnosis and at 1 month were performed at each registered institution. Although CT scanning and data reconstruction basically depended on the protocol for evaluating PE in each institution, CT scans were imaged in pulmonary arterial phase except in Nagoya University Hospital. Additionally in these institutions, CT images were reconstructed in slice thickness and increments of 3.3 ± 1.8 mm (range from 1 to 5 mm). Contrast-enhanced CT 1 year after acute PE was performed at Nagoya University Hospital using 128-slice dual-source CT (Somatom Definition Flash, Siemens Healthcare). Contrast medium (320 mg iodine/ml ioversol [patients ≤55 kg] or 370 mg iodine/ml iopamidol [patients >55 kg]) was injected at a rate of 4 ml/s for a total of 96 ml per injection, followed by 20 ml saline at the same rate. Using a bolus-tracking method, the pulmonary parenchymal phase with clear enhancement of both pulmonary arteries and veins was imaged (median of 24 s after injection of the contrast medium). CT images were reconstructed using a standard algorithm (I31f) and a high-spatial-frequency algorithm (I70f) at a 1-mm slice thickness and 1-mm increments.[16]

2.4 | Computed tomography image analysis

All CT images scanned at Nagoya University Hospital were transferred to an image archiving and communication system (Rapideye Core, Canon Medical Systems) and were evaluated by two radiologists including chest radiologist with 26 years of experience reading CT scans. The radiologists read the images including those reconstructed with standard algorithm (I31f) and high-spatial-frequency algorithm (I70f) by switching between two window settings (a window level of 150 and a width of 1500 or a window level of 80 and a width of 500) as needed.

The CT obstruction index (CTOI) was originally defined by Qanadli et al.;[17] CTOI is used to evaluate the presence of pulmonary emboli to the level of the segmentary arteries and to determine the degree of the composite lesion on CT images. We modified the CTOI (i.e., mCTOI) to accommodate emboli in subsegmental arteries. To define our mCTOI, the arterial tree of the right lung was regarded as having 10 segmental arteries—three to the upper lobes, two to the middle lobes, and five to the lower lobes—and 22 subsegmental arteries (Figure 1). The left lung arterial tree was regarded as having eight segmental arteries—two to the upper lobes, two to the lingula, and four to the lower lobes—and 20 subsegmental arteries. Each embolus in a subsegmental artery was scored as 1 point, and emboli in the most proximal arterial level were scored a value equal to the number of subsegmental arteries arising distally. An additional weighting factor was assigned according to the severity of arterial obstruction: 0, no thrombus was observed; 1, partial occlusion was present; or 2, the artery was completely obstructed. Thus, the maximal mCTOI score possible per patient was 84; the percentage of vascular obstruction (i.e., mCTOI) was calculated by dividing a patient's score by 84 (the maximal total score) and multiplying this result by 100%.
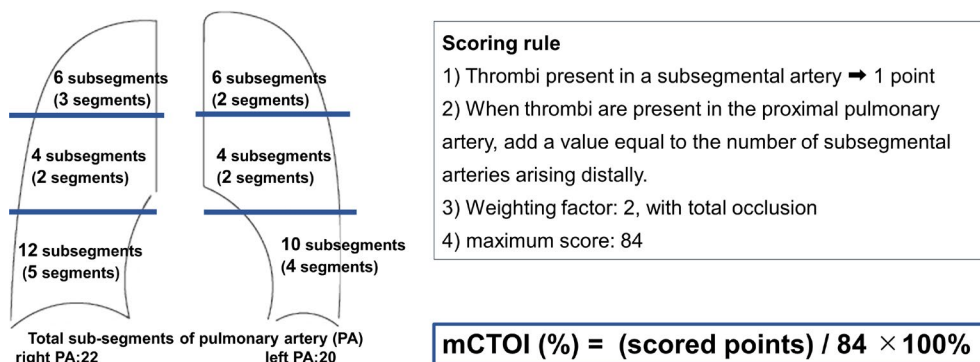

Scoring rule
1) Thrombi present in a subsegmental artery ➡ 1 point
2) When thrombi are present in the proximal pulmonary artery, add a value equal to the number of subsegmental arteries arising distally.
3) Weighting factor: 2, with total occlusion
4) maximum score: 84

6 subsegments (3 segments)
6 subsegments (2 segments)
4 subsegments (2 segments)
4 subsegments (2 segments)
12 subsegments (5 segments)
10 subsegments (4 segments)

Total sub-segments of pulmonary artery (PA)
right PA:22   left PA:20

$$\text{mCTOI (\%)} = \text{(scored points)} / 84 \times 100\%$$

FIGURE 1 Calculation of, and scoring rule for, our modified computed tomography obstruction index. mCTOI, modified computed tomography obstruction index

2.5 | Statistical analysis

Continuous variables are presented as means ± 1 standard deviation or as medians and interquartile range (IQR). Categorical variables are presented as numbers and percentages (%). Continuous variables were compared by using Student's *t*-test or the Mann–Whitney U-test, depending on the distribution of the data. Categorical variables were compared using Chi-square test or Fisher's exact test, depending on the distribution of the data. We performed multivariate logistic analysis using penalized maximum likelihood estimation proposed by Firth to evaluate which factors were related to the presence of residual pulmonary thrombi at 1 year. We also performed a stepwise multiple regression analysis to analyze factors related to mCTOI at 1 year. Independent variables among clinical and laboratory findings and echocardiographic parameters were selected according to their significance in the univariate analysis. In addition, because echocardiographic measurement at diagnosis was not obtained in one patient and BNP at diagnosis was not obtained in four patients, we imputed the missing values with the median value of the rest of the patients for multivariate analyses.

Statistical analyses were conducted using the SPSS statistical software program (version 24.0 for Windows; SPSS) or Stata version 17 (Stata Corp), and a *P*-value of <.05 was considered statistically significant.

3 | RESULTS

In total, 52 patients were enrolled in this study (Figure S1). However, seven patients were unable to visit our outpatient clinic at the 1-year point. In addition, two patients died (one from cancer and the other from a PE-related cause) during the observation period. Therefore, a total of 43 patients completed assessment at 1 year after acute PE.

Among these 43 patients, the mean age was 59.8 ± 16.2 years, and 56% were male. The study population included patients at high risk of thromboembolism: 19% had had a previous PE event, 9% had active cancer, and 12% had thrombophilia (Table 1). In contrast, two of the 43 patients had only transient major or reversible risk factors. At diagnosis of acute PE, 44% of the study population had BNP >100 pg/ml or NT pro-BNP >600 pg/ml, and 17% had TRPG ≥60 mmHg.

Among the 43 patients, 65% were initially treated with unfractionated heparin followed by oral anticoagulant. No major bleeding event occurred during the first month, and the anticoagulation therapy was continued in all 43 patients. Compared to the baseline, D-dimer levels significantly improved in all patients to median 0.6 µg/ml (IQR, 0.3–1.1) at 1 month. At 1 month, residual pulmonary thrombi were detected in 34 (79%) patients. Among them, 10 patients who were registered at our hospital underwent refined CT scanning, and residual pulmonary thrombi were detected in eight patients (80%) at 1 month. On the other hand, 33 patients underwent conventional CT scanning at 1 month in each registered institution other than our

TABLE 1 Characteristics of the 43 patients at baseline and 1 month

Age, years	59.8 ± 16.2
Male, *n* (%)	24 (56)
Recurrent pulmonary embolism, *n* (%)	8 (19)
Active cancer,[a] *n* (%)	4 (9)
Major transient or reversible risk factors only,[b] *n* (%)	2 (5)
Deep vein thrombosis, *n* (%)	33 (77)
Thrombophilia, *n* (%)	5 (12)
Body weight, kg	65.9 ± 14.7
Body mass index, kg/m²	25.0 ± 4.2
sPESI score (0/1/2/3), *n* (%)	28/10/3/2 (65/23/7/5)
Laboratory parameters at diagnosis	
Creatinine clearance,[c] ml/min	87.7 (58.0–103.3)
Hemoglobin, g/dl	13.8 ± 2.4
Platelets, ×10⁴	21.3 ± 8.4
D-dimer, µg/ml	7.5 (4.4–18.1)
Troponin T,[d] ng/ml	0.022 (0.008–0.0385)
BNP > 100 or NT proBNP > 600,[d] *n* (%)	17 (44)
Echocardiography at diagnosis[d]	
LVDd, mm	42.6 ± 5.9
LVEF, %	65.6 ± 8.0
TRPG, mmHg	31.0 (18.3–51.9)
TRPG ≥ 60 mmHg, *n* (%)	7 (17)
TAPSE, mm	18.2 ± 3.5
Initial anticoagulant used at diagnosis, *n* (%)	
Unfractionated heparin	28 (65)
Fondaparinux	2 (5)
Edoxaban	2 (5)
Apixaban	2 (5)
Rivaroxaban	9 (21)
Other treatment at diagnosis, *n* (%)	
IVC filter	9 (21)
Thrombolysis	2 (5)
Laboratory parameters at 1 month	
D-dimer, µg/ml	0.6 (0.3–1.1)
BNP,[d] pg/ml	14.6 (6.9–42.2)
Echocardiography at 1 month	
LVDd, mm	43.9 ± 6.8
LVEF, %	65.0 ± 7.6
TRPG, mmHg	22.1 (17.1–27.4)
TRPG ≥ 30, *n* (%)	8 (19)
TAPSE,[d] mm	19.3 ± 4.4
Computed tomography at 1 month	
Residual thrombi detected, *n* (%)	34 (79)

TABLE 1 (Continued)

Notes: Categorical variables are presented as numbers and percentages, and continuous variables are presented as means ± standard deviation or medians and interquartile range.

Abbreviations: BNP, brain natriuretic peptide; IVC, inferior vena cava; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT proBNP, N-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; sPESI, simplified pulmonary embolism severity index; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

[a]Active cancer was defined as any cancer, including locally recurrent, regionally advanced, or metastatic cancer, that had been diagnosed or treated in the 6 months before the diagnosis of PE.

[b]Major transient or reversible risk factors are as follows: surgery with general anesthesia for greater than 30 min, confined to bed in hospital for at least 3 days with illness, trauma with fractures, and Cesarean section.

[c]Creatinine clearance was calculated by using the Cockcroft–Gault equation.

[d]Limited number of participants due to missing data for each variable: Troponin T at baseline, $n = 31$; BNP > 100 or NT proBNP > 600 at baseline, $n = 39$; LVDd, LVEF, and TRPG at baseline, $n = 42$; TAPSE at baseline, $n = 34$; BNP at 1 month, $n = 39$; TAPSE at 1 month, $n = 38$.

hospital, and residual pulmonary thrombi were detected in 26 patients (79%) at 1 month.

At 1 year, 95% of patients were continuing to receive anticoagulation therapy; among them, 95% received a direct oral anticoagulant (DOAC; Table 2). Two patients received thrombolytic therapy during their initial treatment.

Compared to 79% at 1 month after acute symptomatic PE, 74% of study patients harbored residual pulmonary thrombi at 1 year (Table 3). In addition, the median mCTOI at 1 year was 10.7% (IQR, 0.6%–25.0%; Figure 2) and the median CTOI was 10.0% (IQR, 1.3%–25.0%) among all 43 patients (Table 2). Approximately 26% of patients were at NYHA class 2 or higher, and 10% had a 6 MWD of <330 m. Overall, major bleeding occurred in two patients (Table 3). No patients experienced recurrent symptomatic PE, but two patients were diagnosed with CTEPH.

To evaluate which factors influenced the presence of residual pulmonary thrombi at 1 year, we performed a logistic analysis (Table 4). Independent variables according to the univariate analysis were left ventricular end-diastolic diameter (LVDd) at baseline, TRPG at baseline, and residual thrombi detected by conventional enhanced CT at 1 month. In the multivariate logistic analysis, residual thrombi detected by conventional CT at 1 month was the only factor significantly associated with the presence of residual pulmonary thrombi at 1 year.

We then performed a regression analysis to analyze factors at baseline or 1 month that were related to mCTOI at 1 year. The independent variables that emerged from the single regression analysis were simplified pulmonary embolism severity index score (sPESI), hemoglobin concentration, BNP >100 pg/ml or NT pro-BNP >600 pg/ml, LVDd, and TRPG ≥60 mmHg at baseline. Multiple regression analysis indicated that TRPG ≥60 mmHg, LVDd, and sPESI at baseline were all significantly related to mCTOI at 1 year (Table 5).

TABLE 2 Results at 1 year after acute pulmonary embolism in 43 patients

Continuation of anticoagulant, *n* (%)	41 (95)
Warfarin	2 (5)
Apixaban	10 (24)
Edoxaban	16 (39)
Rivaroxaban	13 (32)
Laboratory	
D-dimer > 0.5 µg/ml, *n* (%)	5 (12)
Troponin T, ng/ml	0.008 (0.005–0.010)
Brain natriuretic peptide, pg/ml	11.2 (5.9–23.3)
Echocardiography	
LVDd, mm	45.4 ± 5.7
TRPG, mmHg	21.0 (17.3–24.4)
TRPG ≥ 30, *n* (%)	5 (12)
TAPSE, mm	19.7 ± 3.8
6-min walking test[a]	
Distance, m	474 (418–520)
Lowest SpO$_2$, %	92.5 ± 2.6
Maximum heart rate, bpm	112 ± 14
NYHA function class 1 or 2, *n* (%)	31/11 (74/26)
HR-QOL score	
Physical component score, %	43.5 ± 12.6
Mental component score, %	55.0 ± 11.4
Computed tomography	
Obstruction index, %	10.0 (1.3–25.0)
Modified obstruction index, %	10.7 (0.6–25.0)

Abbreviations: HR-QOL, health-related quality of life; LVDd, left ventricular end-diastolic diameter; NYHA, New York Heart Association; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

Notes: Categorical variables are presented as numbers and percentages, and continuous variables are presented as means ± 1 standard deviation or medians (interquartile range).

[a]Limited number of participants due to missing data for 6-min walking test, $n = 42$.

Furthermore, TRPG at 1 year was significantly correlated with mCTOI at 1 year (Figure S2 in supporting information).

To accurately assess patients' symptomatology, we used the SF-36 survey to assign health-related QOL (HR-QOL) scores. The PCS did not differ between patients at NYHA 1 and those at NYHA 2 ($P = .283$), but PCS was significantly correlated with 6 MWD ($R = 0.592$, $P < .001$).

4 | DISCUSSION

This prospective observational study yielded four main findings: (1) our enhanced CT imaging protocol disclosed residual pulmonary thrombi at 1 year in 74% of study patients, and 3.8% of patients

TABLE 3 Primary and secondary outcomes after pulmonary embolism

Primary outcome[a]	
Incidence of residual thrombi at 1 year, n (%)	32 (74)
Secondary outcomes[a]	
Chronic thromboembolic pulmonary hypertension, n (%)	2 (3.8)
Recurrent symptomatic pulmonary embolism,[b] n (%)	0 (0)
All-cause death, n (%)	2 (3.8)
Cardiovascular death	1 (1.9)
Major bleeding,[c] n (%)	2 (3.8)

Note: Categorical variables are presented as numbers and percentages.

[a]Outcome percentages were calculated according to the 43 patients who completed all testing at 1 year after acute symptomatic pulmonary embolism (PE, primary outcome) or all 52 patients enrolled in the study (secondary outcome).

[b]Recurrent pulmonary embolism was defined as newly diagnosed or exacerbated PE with symptoms, as confirmed by detection of new or exacerbated thrombus on imaging examination.

[c]Major bleeding was diagnosed when at least one of the following criteria of the International Society on Thrombosis and Haemostasis was met: bleeding associated with a decrease of ≥2 g/dl hemoglobin level, bleeding leading to ≥2 units of blood transfusion, symptomatic bleeding in a critical area or organ, or fatal bleeding.
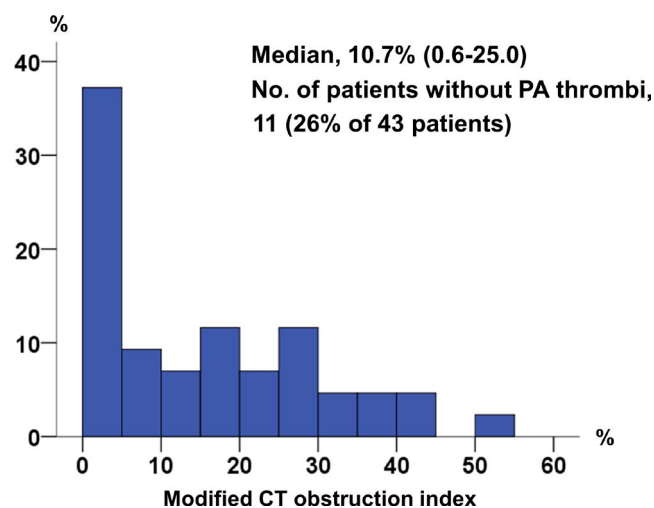
FIGURE 2 Distribution of modified computed tomography obstruction index values 1 year after acute pulmonary embolism. CT, computed tomography; PA, pulmonary artery

were diagnosed with CTEPH; (2) the median mCTOI at 1 year was 10.7% even though 95% of patients remained on anticoagulation therapy; (3) residual pulmonary thrombi at 1 month after acute PE evaluated by conventional CT protocol was significantly associated with residual pulmonary thrombi at 1 year evaluated by our modified CT scanning protocol; and (4) TRPG ≥60 mmHg, LVDd, and sPESI at diagnosis were all significantly related to mCTOI at 1 year after acute symptomatic PE.

In a previous systematic review, residual pulmonary thrombi (detected through either ventilation perfusion scanning or CT) were present in 68% of patients after 6 weeks, 57% after 6 months, and 52% after 11 months.[18] In another study, the rate of abnormal CTOI was 15.9% and that of perfusion vascular obstruction (according to perfusion scans) was 41% at 12 months after the index acute PE episode.[8] Therefore, in most of the previous studies, CT was inferior to lung perfusion scanning in the detection of residual pulmonary thrombi. Lung perfusion imaging is the gold standard for evaluating residual perfusion obstruction, but this methodology has several drawbacks. First, perfusion scanning does not detect residual thrombi directly but merely does so indirectly by evaluating perfusion deficits, thereby potentially false-positively detecting pulmonary disease in the absence of ventilation scans. However, here, our modified CT scanning protocol revealed residual pulmonary thrombi in as many as 74% of our patients 1 year after acute PE. In clinical practice, we use this same methodology to evaluate the chronic pulmonary thrombi in patients with CTEPH and now have applied it to patients after acute PE. We consider that this improved methodology is one of the main reasons underlying the high rate of detecting residual pulmonary thrombi in the current study; many of these thrombi likely would go undetected on conventional CT imaging. A previous prospective study from Netherlands reported that, after 6 months of anticoagulation treatment, the prevalence of residual thrombotic obstruction was 15.9%.[19] Furthermore, CTOI was reported as median 5.0% at follow-up, which was much lower than that of our patients with residual pulmonary thrombi (median 20%). In addition, in a previous meta-analysis, the risk of recurrent VTE and residual pulmonary obstruction after acute PE was reported.[20] They reported that the detection rate of residual pulmonary thrombi evaluated by CT after 6–12 months from acute PE was 10%–20% in the previous studies. Thus, a key difference from the conventional CT protocol was that our modified CT method was able to detect minimal abnormalities such as web lesions, a subtype of organized thrombi (Figure 3). In addition, unlike lung perfusion scanning, our modified CT protocol directly discerned residual pulmonary thrombi in PA regardless of whether they caused perfusion defects.

The CT scanning protocol we adopted has three innovations to detect small pulmonary thrombi. First, we used 1 mm thick sequential images by high-speed MDCT scanning, while conventional CT tends to scan with thicker slices, such as 5 mm. As a result, this improves spatial resolution. Second, we used a high-spatial-frequency algorithm in addition to the conventional standard algorithm for thin-section CT image reconstruction. The high-spatial-frequency enhancement function is used for mainly high-resolution CT reconstruction of lung fields and it can enhance the contrast between the thrombus and the contrast agent. Third, we used a bolus-tracking method to determine the scan timing of the pulmonary parenchymal phase when the pulmonary arteries were well enhanced. Because the pulmonary artery phase is very short, even slightly earlier scan timing results in a poor contrast enhancement in the PA.

During the 1-year observational period, two (3.8%) of the enrolled patients developed CTEPH. After receiving this diagnosis,

TABLE 4 Multivariate analysis of factors related to residual thrombi in pulmonary artery 1 year after pulmonary embolism in 43 patients

	Univariate		Multivariate	
	odds ratio (95%CI)	*P*	odds ratio (95%CI)	*P*
Baseline factor				
Age	0.99 (0.95–1.04)	.856		
Male	1.54 (0.38–6.33)	.546		
Body mass index	0.96 (0.82–1.13)	.652		
Recurrent pulmonary embolism	1.03 (0.18–6.10)	.967		
Active cancer	1.03 (0.10–11.11)	.978		
Concurrent deep vein thrombosis	1.34 (0.28–6.43)	.715		
Thrombophilia	1.43 (0.14–14.21)	.762		
sPESI score	0.57 (0.26–1.26)	.167		
Creatinine clearance	0.99 (0.96–1.01)	.191		
Hemoglobin	1.25 (0.93–1.68)	.132		
Platelets	1.01 (0.93–1.10)	.795		
D-dimer	0.96 (0.91–1.01)	.101		
Troponin T > 0.014 ng/ml	5.63 (0.92–34.57)	.062		
BNP > 100 pg/ml or NT proBNP >600 pg/ml	4.29 (0.77–23.75)	.096		
LVDd	0.80 (0.67–0.96)	.013	0.98 (0.76–1.26)	.861
TRPG	1.04 (1.00–1.08)	.047	1.01 (0.95–1.07)	.663
TAPSE	0.99 (0.80–1.24)	.957		
Anticoagulants	0.97 (0.50–1.91)	.937		
Factor at 1 month				
D-dimer >0.5 µg/ml	0.52 (0.12–2.34)	.394		
BNP	1.01 (0.98–1.03)	.677		
LVDd	0.91 (0.80–1.04)	.170		
TRPG	1.01 (0.96–1.08)	.644		
TAPSE	0.87 (0.70–1.10)	.874		
Residual thrombus in pulmonary artery detected by computed tomography	247.00 (10.89–5600.15)	.001	103.43 (4.21–2542.10)	.005

Abbreviations: BNP, brain natriuretic peptide; 95% CI, 95% confidence interval; LVDd, left ventricular end-diastolic diameter; NT proBNP: N-terminal pro-brain natriuretic peptide; sPESI, simplified pulmonary embolism severity index; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

one patient underwent pulmonary endarterectomy and the other received balloon pulmonary angioplasty. The prevalence of CTEPH after acute PE has been reported as 3.1% at 1 year and 3.8% at 2 years.[21] In a meta-analysis, the prevalence of CTEPH after acute PE was 0.56% overall and 3.2% in survivors.[22] In our study, because the estimated life expectancy was longer than 1 year, the study population was equivalent to survivors, except for one patient who died after acute PE. Therefore, our results are comparable to previous reports. A unique feature of our study is that more than 90% of patients were treated continuously with DOAC, whereas most previous patients received warfarin.

We not only evaluated the prevalence of residual pulmonary thrombi, we also used mCTOI to quantitatively assess the thrombotic burden. The original CTOI was defined 20 years ago to evaluate pulmonary thrombi to the level of segmental arteries.[17] In contrast, our enhanced CT imaging protocol and mCTOI enabled us to assess thrombi in subsegmental arteries and distally. In our patients, the median CTOI at 1 year was 10.0%, comparable to the values in previous reports. In addition, we noted a very strong positive correlation between CTOI and mCTOI (R = 0.995, P < .001, Figure S3 in supporting information). Now that balloon pulmonary angioplasty is an effective treatment for non-operable distal CTEPH, accurately localizing thrombi to subsegmental arteries is particularly important.[23-25]

As mentioned earlier, residual pulmonary thrombi are among the main causes of persistent cardiopulmonary problems after acute PE, but these two factors were unrelated in the SCOPE study.[7] Similarly, we here found no difference in right heart function as evaluated through echocardiography, exercise tolerance according to 6 MWD, and HR-QOL score between patients with residual pulmonary thrombi at 1 year and those without residual pulmonary thrombi. Furthermore, residual thrombi at 1 month was the only factor at baseline or 1 month that was predictive of residual pulmonary

TABLE 5 Multivariate regression analysis of baseline factors related to mCTOI at 1 year

	Univariate		Multivariate	
	Unstandardized β	P	Standardized β	P
Baseline factor				
Age	−0.225	.117		
Male	−1.849	.693		
Body mass index	0.317	.568		
Recurrent pulmonary embolism	9.059	.125		
Active cancer	−3.701	.644		
Concurrent deep vein thrombosis	1.419	.797		
Thrombophilia	2.963	.683		
sPESI score	−0.340	.026	−0.283	.018
Creatinine clearance	−0.025	.729		
Hemoglobin	2.531	.007		
Platelets	0.276	.323		
D-dimer	−0.304	.080		
Troponin T > 0.014 ng/ml	6.697	.245		
BNP >100 pg/ml or NT proBNP >600 pg/ml	11.229	.02		
LVDd	−1.329	<.001	−0.435	.001
TRPG ≥60 mmHg	21.176	<.001	0.367	.003
TAPSE	−0.194	.790		
Anticoagulants	−3.980	.075		
Factor at 1 month				
Troponin T > 0.014 ng/ml	−6.523	.285		
D-dimer >0.5 μg/ml	−0.860	.856		
BNP	−0.070	.321		
LVDd	−0.301	.381		
TRPG	0.381	.053		
TAPSE	−0.970	.096		

Abbreviations: BNP, brain natriuretic peptide; LVDd, left ventricular end-diastolic diameter; mCTOI, modified computed tomography obstruction index; NT proBNP: N-terminal pro-brain natriuretic peptide; sPESI, simplified pulmonary embolism severity index; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation pressure gradient.

thrombi at 1 year: 11 of our 43 patients had residual pulmonary thrombi at 1 month, and these thrombi dissolved in two patients only.

TRPG ≥60 mmHg and LVDd at the diagnosis of acute PE were predictive of the residual pulmonary thrombotic burden at 1 year; these two parameters are all reflective of acute-phase right ventricular overload. Although 81% of our study population was considered to have been diagnosed with their first episode of acute symptomatic PE, some patients might already have had chronic pulmonary thrombi prior to the acute symptomatic PE. In clinical practice, it is difficult to distinguish whether a particular PE event is an acute episode or indicative of chronic disease. In fact, the incidence of incidental diagnosis of PE on CT imaging reportedly is 3.6% in patients with cancer and 1.1% otherwise.[26] On the basis of that report, some patients previously might have had acute PE with few symptoms. Another possibility is underlying previous in

situ pulmonary thrombosis and pulmonary arteriopathy, which are hypothesized as potential etiologies of CTEPH.[27] Therefore, the elevated right ventricular overload at diagnosis of acute PE might be a predictor of chronic residual pulmonary thrombi, and discontinuation of anticoagulation therapy in such patients should be approached with caution.

We calculated the HR-QOL score to accurately assess patients' symptoms and the 6 MWD to evaluate exercise tolerance. Although PCS was significantly correlated with 6 MWD at 1 year ($R = 0.592$, $P < .001$), mCTOI was not correlated with either PCS or 6 MWD ($P = .224$ and $P = .480$, respectively, Table S1 in supporting information). Moreover, none of the measurements indicative of right ventricular overload (i.e., troponin T, BNP, TRPG) was correlated with either PCS or 6 MWD. These results support those of the ELOPE study, in which exercise limitation at 1 year after acute PE was unrelated to both PE clot burden at baseline and residual obstruction during follow-up

but likely mainly reflected a decline in lower-extremity strength.[8,28] Again, previous results and our current findings suggest that post-PE symptoms cannot be explained solely by the presence of residual thrombi but are affected by multiple factors.

This study had several limitations. First, despite this being a multicenter prospective study, the number of participants was limited because they needed to visit Nagoya University Hospital 1 year after acute PE. Therefore, the results of statistical analysis should be carefully interpreted. Nonetheless, our modified CT imaging protocol and evaluation of the thrombotic burden by using mCTOI enabled us to accurately evaluate the residual pulmonary thrombi. Second, to reduce the patients' radiation exposure, we did not obtain ventilation perfusion scans. Although we detected residual pulmonary thrombi more frequently than in previous studies, whether perfusion defects persist is uncertain. However, given the clear detection of residual pulmonary thrombi on CT, the results of a perfusion scan would not alter the diagnosis or treatment strategy. Third, because the improved CT protocol could be performed only at Nagoya University Hospital, we were able to evaluate our mCTOI only at 1 year after diagnosis of acute PE. We therefore evaluated the presence of residual pulmonary thrombi at 1 month using conventional CT protocols. Finally, most of our patients received one of three DOACs (apixaban, edoxaban, or rivaroxaban) for continuous anticoagulation therapy at 1 year. Because this study was not an interventional study, the treatment decision varied depending on the physician in charge. Therefore, therapeutic differences of each DOAC or warfarin might have occurred but could not be evaluated because of the limited number of participants. However, all three of these DOACs are known to be effective for the treatment of VTE, and none of our patients has had recurrent symptomatic PE.[29–31] Further study is needed to evaluate the efficacy of each DOAC for treating residual pulmonary thrombi, including those leading to CTEPH.

5 | CONCLUSIONS

Using our enhanced CT imaging protocol, we found a high incidence of residual pulmonary thrombi 1 year after acute PE. In addition, right ventricular overload was significantly related to the thrombotic burden. We suggest that the treatment strategy for acute PE should include the modified CT imaging protocol with mCTOI to accurately monitor residual pulmonary thrombotic burden.

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CONFLICTS OF INTEREST

AUTHOR CONTRIBUTIONS

FIGURE 3 Computed tomography images (axial view) of 5 patients scanned using our refined computed tomography imaging protocol: (A) 5 mm slice thickness with standard algorithm, (B) 1 mm slice thickness with standard algorithm (I31f), and (C) high-spatial-frequency algorithm (I70f) at a 1 mm slice thickness. The residual minimal lesions were more clearly visible using high-spatial-frequency algorithm (I70f) at a 1 mm slice thickness
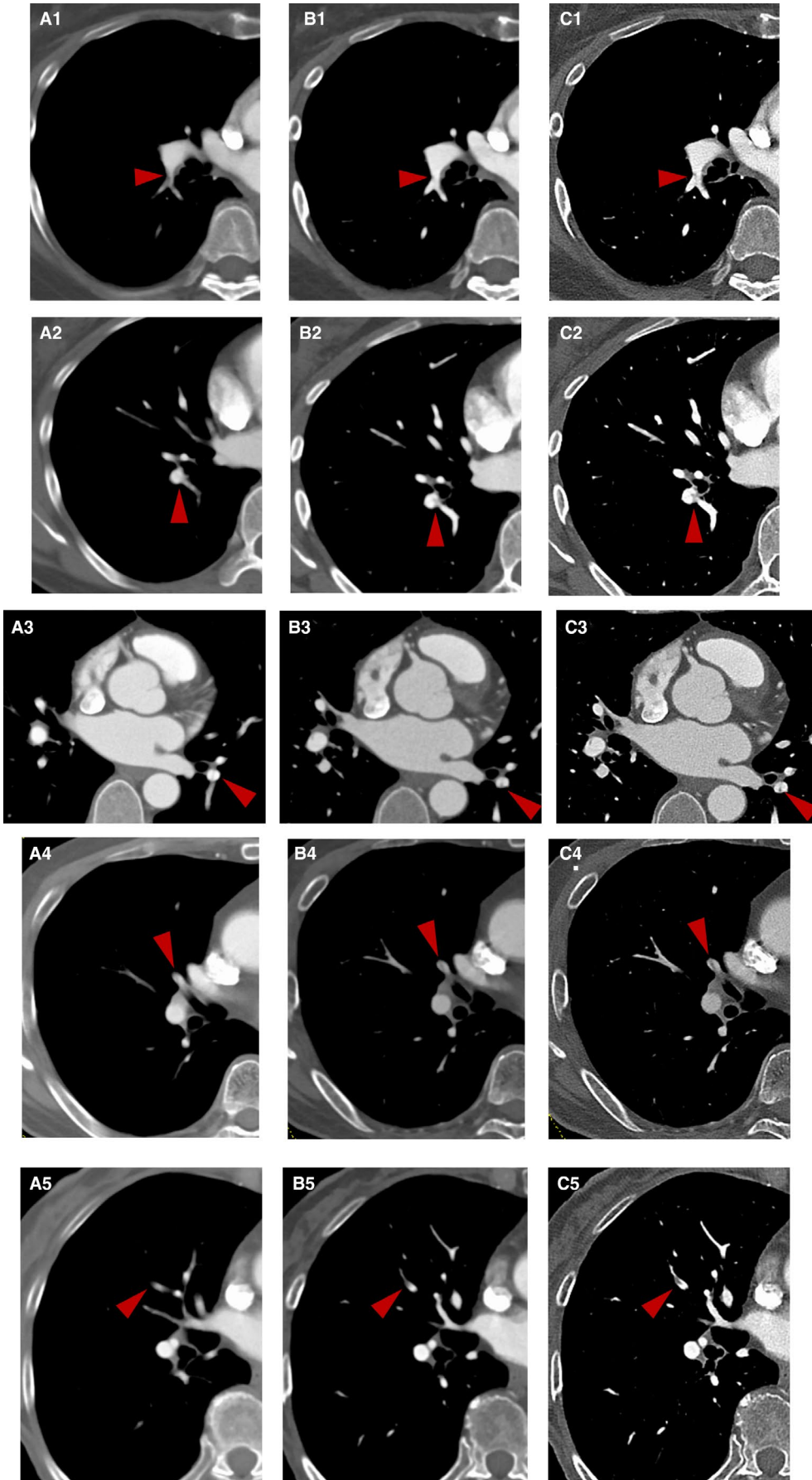
to drafting the manuscript, discussing the results, reviewing the manuscript, and approving the final manuscript.

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SUPPORTING INFORMATION
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