



# Residual pulmonary hypertension is associated with clinical outcomes in patients with acute pulmonary thromboembolism

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Received: 13 February 2019 / Accepted: 26 April 2019 / Published online: 2 May 2019  
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## Abstract

In patients with acute pulmonary thromboembolism (PTE), the influence of residual pulmonary hypertension (PH) has not been well investigated. The aim of this study was to compare clinical characteristics between patients with and without residual PH, and to investigate the association between residual PH and clinical outcomes after acute phase in acute PTE. We included acute PTE patients who underwent echocardiogram after acute phase between January 2009 and December 2016. These patients were divided into residual PH and non-residual PH groups according to the value of estimated right ventricular systolic pressure (eRVSP) by echocardiogram after acute phase (the residual PH group: eRVSP  $\geq$  40 mmHg, the non-residual PH group: eRVSP  $<$  40 mmHg). Kaplan–Meier survival curves were applied to investigate whether the residual PH were associated with PTE-related death or recurrent PTE in patients with acute PTE. A total of 49 patients with acute PTE were allocated into the residual PH group ( $n = 10$ ) and non-residual PH group ( $n = 39$ ). Median follow-up period for 49 patients was 7 months. The event-free survival rate was significantly lower in the residual PH group as compared with the non-residual PH group ( $p = 0.003$ ), whereas there was no statistical significance between two groups stratified by initial PH or not ( $p = 0.97$ ). Residual PH after acute phase was significantly associated with mid-term PTE-related death or recurrent PTE in patients with acute PTE.

**Keywords** Acute thromboembolism · Residual pulmonary hypertension · Pulmonary hypertension · Estimated right ventricular systolic pressure

## Introduction

Acute pulmonary thromboembolism (PTE) is a life-threatening disease, which is the third most cause of cardiovascular death following myocardial infarction and stroke in the present era [1]. The early death of acute PTE is mainly determined by acute right ventricular (RV) dysfunction on admission [2]. Such RV dysfunction is caused by RV pressure overload, which has resulted from pulmonary hypertension (PH) caused by acute thromboembolism [3]. Early studies reported that initial PH was associated with short-term clinical outcomes in patients with acute PTE [4].

On the other hand, long-term clinical outcomes in patients with acute PTE are influenced by multiple factors such as age, cancer, heart failure, and residual pulmonary obstruction [5–7]. Furthermore, persistent RV dysfunction at the timing of hospital discharge may be associated with long-term clinical outcomes [8]. While PH regresses by anticoagulation and thrombolytic therapy in acute phase, it sometimes persists despite appropriate management [9]. Therefore, as compared to initial PH, residual PH may be a better marker for outcomes after acute phase. The aim of this study was to compare clinical characteristics between patients with and without residual PH estimated by echocardiographic findings, and to investigate the association between residual PH and clinical outcomes after acute phase in acute PTE.

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## Methods

### Study design

We screened patients with acute PTE admitted to our hospital between January 2009 and December 2016. Only the patients who underwent echocardiogram during the hospital stay at least within 7 days before discharge or after 7 days or later on admission as well as at the timing of admission were investigated. The patients who were already diagnosed as chronic thromboembolic PH (CTEPH) before admission were excluded from this study. The period of “after acute phase” was defined as within 7 days before discharge or after 7 days or later on admission except for the day of hospitalization. Estimated right ventricular systolic pressure (eRVSP) measured by echocardiogram was calculated by the sum of peak RV-right atrium (RA) gradient and RA pressure estimated by diameter and respiratory change of inferior vena cava as previously reported [10]. High eRVSP was substituted for PH because right heart catheterization (RHC) was not performed in this study subjects. These patients were divided into the two groups according to the value of eRVSP measured by echocardiogram after acute phase (residual PH group: eRVSP  $\geq$  40 mmHg; non-residual PH group: eRVSP  $<$  40 mmHg).

### Diagnosis

The definitive diagnosis of acute PTE was established by findings of contrast computed tomography (CT).

### Risk stratification in acute phase

We classified the severity of acute PTE according to hemodynamics and the evidence of RV overload by echocardiogram for risk stratification as follows: (1) massive: acute PTE with shock or sustained hypotension; (2) sub-massive: acute PTE without systemic hypotension but with RV overload; and (3) non-massive: acute PTE without systemic hypotension and RV overload [11].

### Treatment strategy

In general, the initial treatment to acute PTE consisted of unfractionated heparin or fondaparinux in our hospital. Montepase administration was considered only for the patients with shock or hypotension. Either vitamin K antagonist or direct oral anticoagulant was used as the maintenance therapy.

### Follow-up

Clinical follow-up was performed via office visit. The follow-up period was until January 2018. The day when echocardiogram after acute phase was performed was defined as an index day. The primary end point in this study was the composite of PTE-related death (worsening of PTE or sudden death) and re-admission due to acute PTE. Either PTE related death or first readmission due to recurrent PTE were considered as the event. This study was approved by the institutional review board at our institution, and written informed consent was waived because of the retrospective study design.

### Statistical analysis

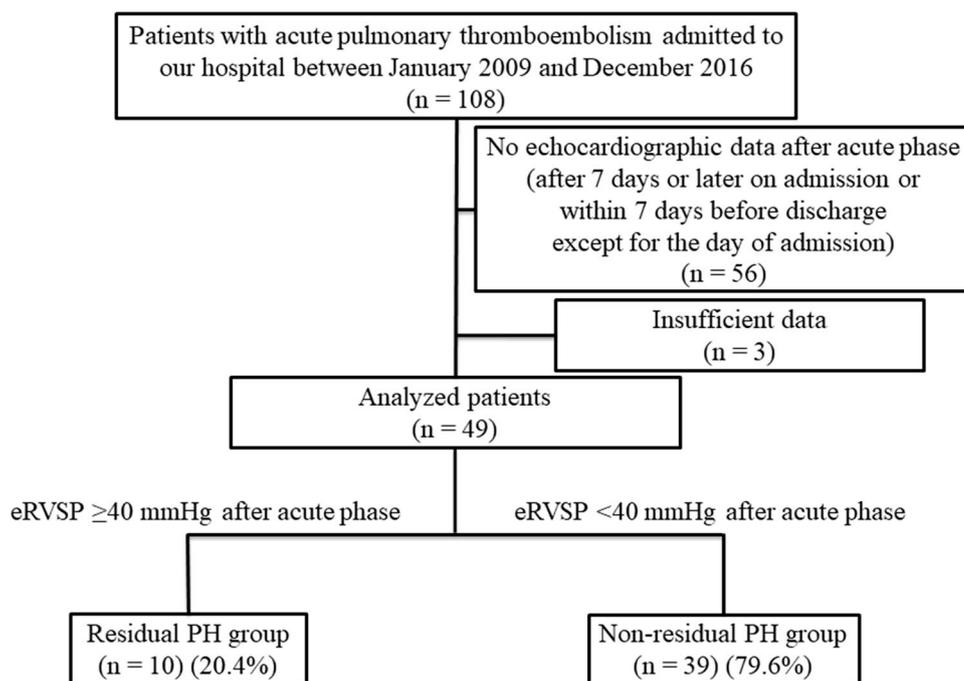
Continuous variables were calculated as mean  $\pm$  SD. Numerical data were analyzed using an independent *t* test. Comparisons of categorical data between the two groups were done by Chi-square test. The Kaplan–Meier curves stratified according to eRVSP were constructed, and these curves were compared by the log-rank test. Statistical analyses were performed using a statistical software, SPSS 19/Windows (SPSS Inc).

## Results

One hundred and eight patients were admitted to our hospital to treat acute PTE between January 2009 and December 2016. Fifty-six patients did not undergo echocardiogram after acute phase and 3 patients had insufficient data for echocardiogram. They were excluded from the study population. Finally, 49 patients with acute PTE were analyzed. The study patients were divided into the residual PH group ( $n = 10$ ) and non-residual PH group ( $n = 39$ ) according to the value of eRVSP. Study flow chart was shown in Fig. 1. Values of mean eRVSP after acute phase were  $54.1 \pm 10.7$  mmHg in the residual PH group and  $26.1 \pm 6.0$  mmHg in the non-residual PH group. Median follow-up period for 49 patients was 7 months. No patients were diagnosed as CTEPH between the follow-up period.

The comparison of clinical characteristics between the two groups is shown in Table 1. Age, sex, body mass index, and heart rate were similar between the two groups. The patients in residual PH group had higher rate of oxygen administration on admission without statistical significance ( $p = 0.06$ ). Only one patient required ventilation support in the non-residual PH group, whereas no patient required it in the residual PH group ( $p = 0.61$ ). Risk factors for venous thromboembolism (VTE) were comparable between the two groups. Majority of which

**Fig. 1** Patient enrollment. *eRVSP* estimated right ventricular systolic pressure, *PH* pulmonary hypertension



**Table 1** The clinical characteristics of the two groups

	Residual PH group (n = 10)	Non-residual PH group (n = 39)	p value
Age (years)	68.8 ± 10.9	61.5 ± 14.8	0.15
Male, n (%)	5 (50.0%)	23 (59.0%)	0.61
BMI (kg/m <sup>2</sup> )	22.9 ± 3.6	25.3 ± 4.4	0.12
Smoking, n (%)	3 (30.0%)	5 (12.8%)	0.19
Systolic BP on admission (mmHg) (n = 46)	144.3 ± 22.4 (n = 10)	127.9 ± 18.0 (n = 36)	0.02
Diastolic BP on admission (mmHg)	88.2 ± 13.7 (n = 10)	78.5 ± 13.2 (n = 36)	<0.05
HR on admission (beat/min) (n = 48)	100.7 ± 18.3 (n = 10)	89.5 ± 21.3 (n = 36)	0.13
SpO <sub>2</sub> on admission (%)	95.3 ± 4.0	96.5 ± 1.7	0.38
Oxygen administration on admission, n (%)	8 (80.0%)	18 (46.2%)	0.06
Need for ventilation, n (%)	0	1 (2.6%)	0.61
Risk factors for VTE			
Cancer, n (%)	3 (30.0%)	3 (7.7%)	0.30
Congenital coagulation disorder, n (%)	0	5 (12.8%)	
Trauma/fractures, n (%)	0	1 (2.6%)	
Psychiatric disease, n (%)	1 (10.0%)	5 (12.8%)	
Unknown, n (%)	6 (60.0%)	25 (64.1%)	
eRVSP on admission (mmHg) (n = 40)	69.7 ± 31.3 (n = 10)	48.5 ± 20.9 (n = 30)	0.02
eRVSP after acute phase (mmHg)	54.1 ± 10.7	26.1 ± 6.0	<0.001
Length of hospitalization (days)	12.6 ± 4.6	15.1 ± 7.2	0.31
Hypertension, n (%)	4 (40%)	13 (33.3%)	0.69
Diabetes mellitus, n (%)	2 (20%)	4 (10.3%)	0.40
Dyslipidemia, n (%)	2 (20%)	11 (28.2%)	0.60
Chronic kidney disease, n (%)	5 (50.0%)	13 (33.3%)	0.33
D-dimer on admission (µg/ml)	8.3 ± 4.8	15.1 ± 16.9	0.21
BNP on admission (pg/ml) (n = 33)	549.7 ± 315.0 (n = 7)	191.8 ± 265.4 (n = 26)	0.005

*PH* pulmonary hypertension, *BMI* body mass index, *BP* blood pressure, *HR* heart rate, *SpO<sub>2</sub>* percutaneous arterial oxygen saturation, *VTE* venous thromboembolism, *eRVSP* estimated right ventricle systolic pressure, *BNP* brain natriuretic peptide

was unknown cause in both groups. Mean eRVSP value on admission was significantly higher in the residual PH group ( $69.7 \pm 31.3$  mmHg) as compared with the non-residual PH group ( $48.5 \pm 20.9$  mmHg) ( $p = 0.02$ ). Length of hospitalization was not different between the residual PH group ( $12.6 \pm 4.6$  days) and the non-residual PH group ( $15.1 \pm 7.2$  days) ( $p = 0.31$ ).

The characteristics of VTE are shown in Table 2. PTE patients with DVT were significantly lower in the residual PH group compared with the non-residual PH group. Severity of PTE (such as massive, sub-massive, or non-massive) tended to be worse in the residual PH group as compared to the non-residual PH group ( $p = 0.10$ ). The type of PTE and DVT were also investigated. There was no statistical significance between the two groups. Although all patients in the residual PH group had bilateral PTE, the analysis whether location of PTE was bilateral or ipsilateral did not show significant difference in the two groups ( $p = 0.12$ ).

Table 3 shows clinical course of the two groups. Majority of initial treatments for acute PTE were unfractionated heparin in both groups. Monteplase administration tended to be higher in the residual PH group (30.0%) than in the non-residual PH group (5.1%). Majority of maintenance treatments in both groups were vitamin K antagonist. Direct oral anticoagulant was used about 10% of the patients in each group. Maintenance treatments for acute PTE did not show significant difference between the two groups. There was no statistical significance in the value of D-dimer after acute phase between the two groups, whereas  $\Delta$ D-dimer (D-dimer on admission – D-dimer after acute phase) tended to be small in the residual PH group as compared to the non-residual PH group ( $p = 0.07$ ).

Primary end points were observed in 6 patients (12.2%). The comparison of clinical events is shown in Table 4. Clinical characteristics, characteristics of VTE, and clinical courses between patients with and without primary

**Table 2** The characteristics of VTE between the two groups

	Residual PH group ( <i>n</i> = 10)	Non-residual PH group ( <i>n</i> = 39)	<i>p</i> value
<b>Diagnosis</b>			
PTE only, <i>n</i> (%)	5 (50.0%)	6 (15.4%)	0.02
PTE and DVT, <i>n</i> (%)	5 (50.0%)	33 (84.6%)	
<b>Severity of PTE (<i>n</i> = 48)</b>			
Massive, <i>n</i> (%)	1 (10.0%)	1 (2.6%)	0.10
Sub-massive, <i>n</i> (%)	8 (80.0%)	20 (51.3%)	
Non-massive, <i>n</i> (%)	1 (10.0%)	17 (43.6%)	
<b>Type of PTE</b>			
<b>Side</b>			
Left side, <i>n</i> (%)	0	2 (5.1%)	0.29
Right side, <i>n</i> (%)	0	6 (15.4%)	
Bilateral, <i>n</i> (%)	10 (100%)	31 (79.5%)	
<b>Location of thrombus</b>			
Pulmonary trunk, <i>n</i> (%)	0	0	0.25
Main pulmonary artery + lobar artery + segmental artery, <i>n</i> (%)	7 (70.0%)	18 (46.2%)	
Lobar artery + segmental artery, <i>n</i> (%)	3 (30.0%)	14 (35.9%)	
Segmental artery, <i>n</i> (%)	0	7 (17.9%)	
<b>Type of DVT (<i>n</i> = 38)</b>			
<b>Side</b>			
Left side, <i>n</i> (%)	2 (40.0%)	15 (45.5%)	0.91
Right side, <i>n</i> (%)	2 (40.0%)	10 (30.3%)	
Bilateral or inferior vena cava, <i>n</i> (%)	1 (20.0%)	8 (24.2%)	
<b>Location of thrombus</b>			
Below inferior vena cava, <i>n</i> (%)	0	3 (9.1%)	0.65
Below iliac vein, <i>n</i> (%)	0	5 (15.2%)	
Below femoral vein, <i>n</i> (%)	2 (40.0%)	12 (36.4%)	
Below popliteal vein, <i>n</i> (%)	3 (60.0%)	13 (39.4%)	

VTE venous thromboembolism, PH pulmonary hypertension, PTE pulmonary thromboembolism, DVT deep-vein thrombosis

**Table 3** Clinical course of the two groups

	Residual PH group ( <i>n</i> = 10)	Non-residual PH group ( <i>n</i> = 39)	<i>p</i> value
First treatment to acute PTE			
Unfractionated heparin, <i>n</i> (%)	6 (60.0%)	35 (89.7%)	0.05
Fondaparinux, <i>n</i> (%)	1 (10.0%)	2 (5.1%)	
Monteplase, <i>n</i> (%)	3 (30.0%)	2 (5.1%)	
Maintenance treatment to acute PTE			
Vitamin K antagonist, <i>n</i> (%)	9 (90.0%)	35 (89.7%)	0.98
DOAC, <i>n</i> (%)	1 (10.0%)	4 (10.3%)	
Left ventricular ejection fraction after acute phase (%) ( <i>n</i> = 43)	64.9 ± 11.9 ( <i>n</i> = 8)	59.9 ± 10.3 ( <i>n</i> = 35)	0.24
D-dimer after acute phase (µg/ml) ( <i>n</i> = 44)	8.7 ± 14.8 ( <i>n</i> = 10)	6.6 ± 9.6 ( <i>n</i> = 34)	0.59
ΔD-dimer <sup>a</sup> (µg/ml) ( <i>n</i> = 44)	− 0.5 ± 13.1 ( <i>n</i> = 10)	9.6 ± 15.2 ( <i>n</i> = 34)	0.07

PH pulmonary hypertension, PTE pulmonary thromboembolism, DOAC direct oral anticoagulant

<sup>a</sup>D-dimer on admission – D-dimer after acute phase

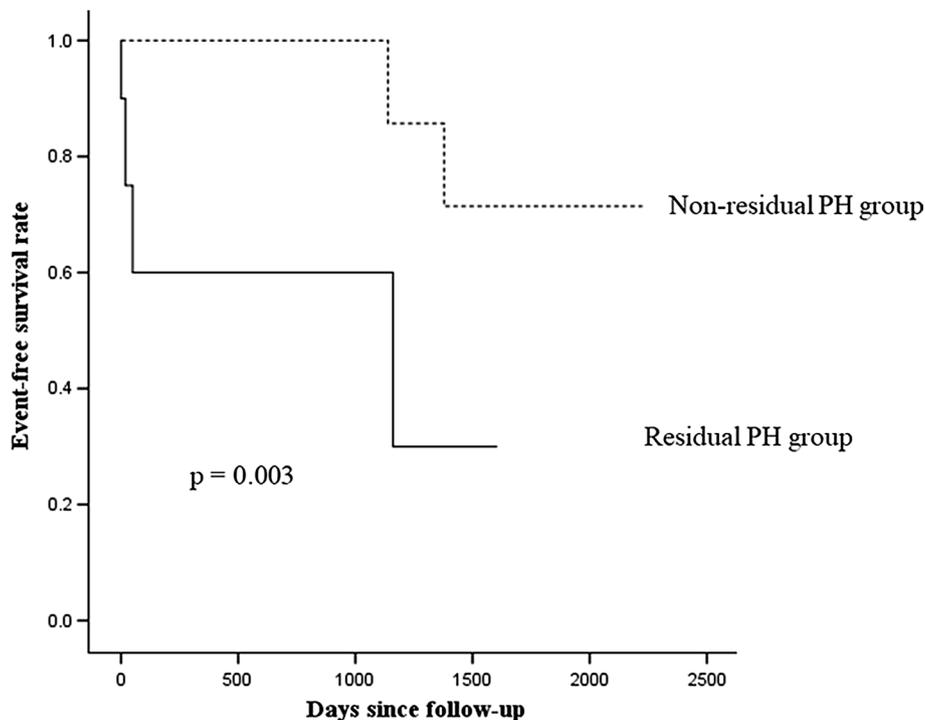
endpoints were also analyzed. Systolic and diastolic blood pressures were significantly higher in patients with primary endpoints as compared with patients without primary endpoints ( $p=0.03$ ), whereas other parameters did not show significant differences between the two groups. Kaplan–Meier curves for the primary endpoint stratified according to the two groups are shown in Fig. 2. Event-free survival rate was significantly lower in the residual PH group as compared to the non-residual PH group ( $p=0.003$ ). The comparison of event-free survival rate about the composite of all-cause death and recurrent PTE also showed similar

significant difference ( $p=0.039$ ) (Fig. 3). There was no statistical significance about the primary end points between the two groups stratified by initial PH (eRVSP on admission  $\geq 40$  mmHg) or not ( $p=0.97$ ) (Fig. 4).

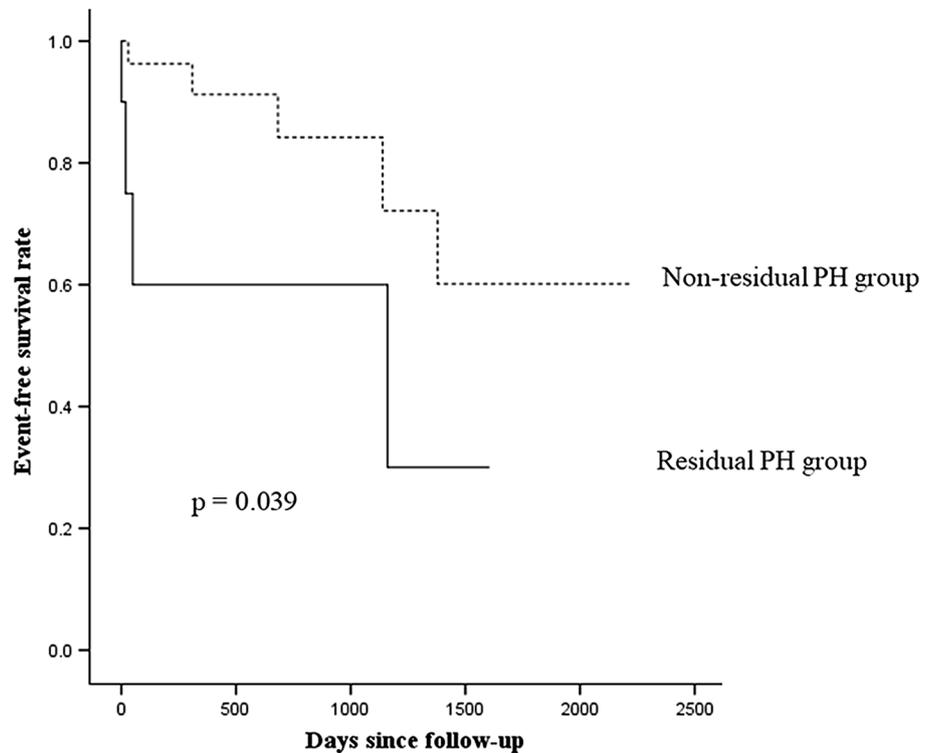
## Discussion

The present study included 49 acute PTE patients who were evaluated by the degree of PH by echocardiogram after acute phase, and investigated whether residual PH was associated

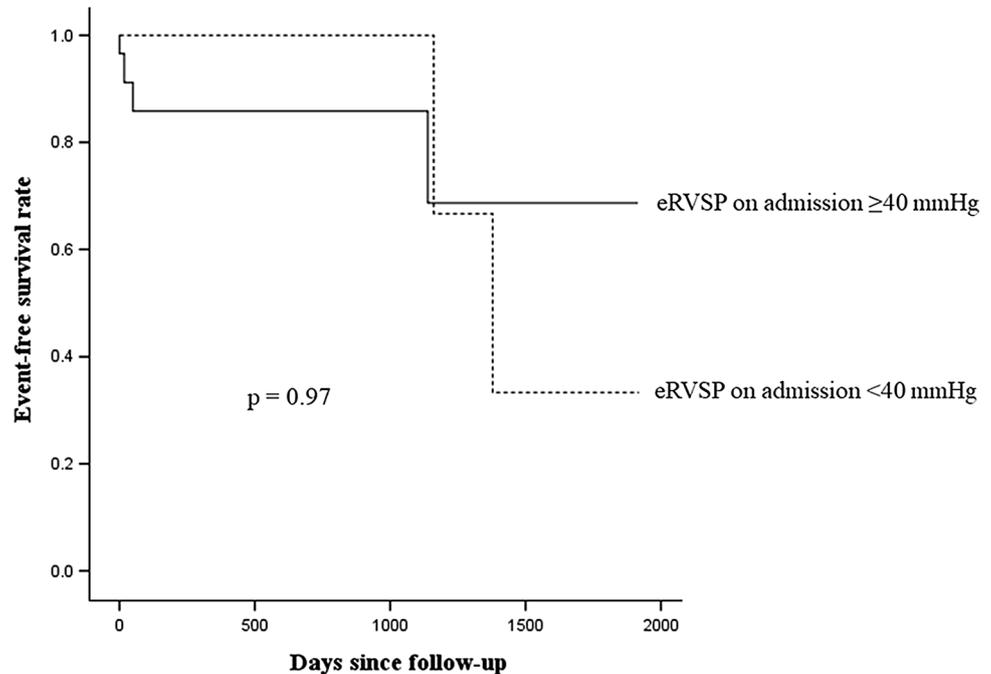
**Fig. 2** Kaplan–Meier curves for pulmonary thromboembolism (PTE) related death or recurrent PTE stratified according to the residual or non-residual pulmonary hypertension (PH) groups. The comparison of survival curves was performed by the log-rank test



**Fig. 3** Kaplan–Meier curves for all cause death or recurrent pulmonary thromboembolism stratified according to the residual or non-residual pulmonary hypertension (PH) groups. The comparison of survival curves was performed by the log-rank test



**Fig. 4** Kaplan–Meier curves for pulmonary thromboembolism (PTE) related death or recurrent PTE stratified according to initial pulmonary hypertension (estimated right ventricular systolic pressure (eRVSP) on admission  $\geq 40$  mmHg) or not. The comparison of survival curves was performed by the log-rank test



with PTE-related death or recurrent PTE after acute phase. As compared to the non-residual PH group, the residual PH group was significantly associated with adverse mid-term clinical events, which suggests the usefulness of residual PH as an indicator for clinical outcomes in patients with acute PTE.

Early study, which was reported over a decade ago, investigated the association between persistent RV dysfunction at hospital discharge and long-term outcomes [8]. In that study, RV dysfunction was defined as at least one of the following: RV dilation, paradoxical septal systolic motion, and/or PH (RV-RA gradient  $> 30$  mmHg). Our

**Table 4** End points

	Total ( <i>n</i> = 49)	Residual PH group ( <i>n</i> = 10)	Non-residual PH group ( <i>n</i> = 39)	<i>p</i> value
PTE-related death or recurrent PTE, <i>n</i> (%)	6 (12.2%)	4 (40.0%)	2 (5.1%)	0.003
All-cause death or recurrent PTE, <i>n</i> (%)	9 (18.4%)	4 (40.0%)	5 (12.8%)	<0.05
PTE-related death, <i>n</i> (%)	2 (4.1%)	2 (20.0%)	0	0.004
All-cause death, <i>n</i> (%)	5 (10.2%)	2 (20.0%)	3 (7.7%)	0.25
The causes of death				
Worsening of PTE, <i>n</i> (%)	1 (2.0%)	1 (10.0%)	0	0.12
Sudden death, <i>n</i> (%)	1 (2.0%)	1 (10.0%)	0	
Cerebral hemorrhage, <i>n</i> (%)	1 (2.0%)	0	1 (2.6%)	
Heart failure, <i>n</i> (%)	1 (2.0%)	0	1 (2.6%)	
Malignancy, <i>n</i> (%)	1 (2.0%)	0	1 (2.6%)	
Recurrent PTE, <i>n</i> (%)	4 (8.2%)	2 (20.0%)	2 (5.1%)	0.13

PH pulmonary hypertension, PTE pulmonary thromboembolism

study investigated only the relationship between residual PH itself and adverse outcomes, and we defined PH strictly as  $\geq 40$  mmHg of the sum of the values RV-RA gradient and RA pressure. Other previous study which investigated the prognosis of PTE in 1990s defined PH as eRVSP  $> 50$  mmHg [9], whereas we defined the PH using current echocardiographic guidelines [12, 13]. Furthermore, previous study included acute PTE patients diagnosed by the perfusion lung scan and/or by contrast CT, whereas our study only included patients who were diagnosed by contrast CT. Under the strict definition of acute PTE and PH, our result shows the usefulness of evaluating PH after acute phase as a predictor of adverse clinical events in present era.

Grifoni et al. emphasized that long-term prognosis in patients with acute PTE was determined by factors before discharge [8]. Indeed, our study showed the significant relationship between residual PH and mid-term clinical outcomes, whereas the relationship between initial PH and clinical outcomes was not significant. Our data may indicate the necessity of evaluating PH not only on admission but also after acute phase including just before discharge for better management for PTE.

The reason why residual PH was associated with adverse clinical events should be discussed. Our results suggest a hypothesis that the patients with poor response to initial treatment in acute phase results in worse mid-term clinical outcomes, because  $\Delta$ D-dimer tended to be small in the residual PH group as compared to the non-residual PH group. Although it is difficult to address the specific reason by our data, latent prothrombotic and poorer thrombolytic activities might contribute to poor response to initial treatment in acute PTE patients [14–16]. The answer for this issue requires more understanding for pathophysiology of acute PTE.

### Study limitations

This is a retrospective and small sample study in a single tertiary center. The patients who were hospitalized in our center might be highly selected. We might miss the important difference between the two groups, and there is a possibility of  $\beta$  error caused by the small sample size. PH was defined by only echocardiographic findings. Right heart catheterization (RHC) was not performed, because there was a potential risk of distal embolism caused by catheter manipulation in the acute phase. Therefore, we used eRVSP substituted for direct measurement of PH by RHC. However, high eRVSP measured by echocardiogram did not always indicate PH, and which would be different from real PH recorded by RHC. There were significant differences in clinical characteristics on admission such as systolic/diastolic blood pressure, eRVSP, and the value of BNP. Although these might affect the clinical outcomes for PTE, we did not develop a multivariate Cox regression analysis because of small sample size. There is a possibility of incomplete follow-up, because clinical follow-up was performed via office visit. We did not refer to the duration of anticoagulant therapy after discharge in this study. Although we showed the association between high eRVSP after acute phase and adverse clinical outcomes, follow-up data of eRVSP were not available. Although we excluded the patients who had been diagnosed or had been treated as CTEPH before the index admission, there was a possibility that undiagnosed CTEPH patients were included in the present study. Especially, there might be more patients with undiagnosed CTEPH in the residual PH group, because  $\Delta$ D-dimer (D-dimer on admission – D-dimer after acute phase) tended to be small in the residual PH group. However, we could not clearly distinguish whether the acute PTE was de novo or recurrent PTE in patients with CTEPH (acute on chronic PTE) in this study. Finally, we should mention

that residual PH after acute phase is not an only indicator for acute PTE. Further prospective large sample studies are warranted.

## Conclusions

Residual PH after acute phase was significantly associated with mid-term PTE-related death or recurrent PTE in patients with acute PTE.

## Compliance with ethical standards

**Conflict of interest** The authors declare that there is no conflict of interest.

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