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RESEARCH ARTICLE

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Impact of residual pulmonary hypertension on long-term outcomes after pulmonary endarterectomy in the modern era

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Abstract

Residual pulmonary hypertension (PH) negatively impacts long-term results following pulmonary endarterectomy (PEA) for chronic thromboembolic pulmonary hypertension (CTEPH). We sought to reveal whether modern PH therapy with PH-targeted medicine and balloon pulmonary angioplasty (BPA) improved long-term results of residual PH after PEA. Long-term findings of 80 patients who survived PEA between 2011 and 2019 were retrospectively investigated. One month after PEA, 30 patients developed residual PH defined as mean pulmonary artery pressure (mPAP) ≥25 mmHg, of whom 23 were treated by PH-targeted medicine and 9 by BPA. Patients with residual PH acquired considerably better functional status and exercise capacity after PEA, however, exhibited significantly worse survival rates than those without. Eleven patients died during follow-up: 8 patients with residual PH and 3 controls. Among patients with residual PH, the deceased had a significantly lower %decrease in mPAP from 1 month to 1 year following PEA (7.4 [−32.6 to 8.0] % vs. 10.4 [3.7−27.8] %, $p = 0.03$) and higher mPAP at 1 year following PEA (39.5 [33.25−42.5] vs. 27 [26−34] mmHg, $p < 0.01$) despite PH-targeted medicine than the survived. No patients passed away from right heart failure, and there was no difference between the groups in CTEPH-related mortality. Modern PH therapy was used to address the majority of residual PH. Long-term survival after PEA was negatively impacted by residual PH, but it appeared that long-term mortality was also correlated with unrelieved residual PH despite PH-targeted medicine. Modern PH therapy may have enhanced functional status and excercise capacity, and averted fatal right heart failure.

KEYWORDS
chronic thromboembolic pulmonary hypertension, pulmonary endarterectomy, residual pulmonary hypertension

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is associated with organized thrombus in the elastic pulmonary arteries and small vessel arteriopathy in the muscular pulmonary arteries and results in progressive pulmonary hypertension (PH), right heart failure, and ultimately death.[1] Pulmonary endarterectomy (PEA) is a potentially curative treatment improving pulmonary hemodynamics, symptoms, and long-term survival.[2–4]

Accumulated evidence indicate that residual PH following PEA was associated with poor long-term survival, and impaired symptoms and exercise capacity in addition to in-hospital mortality.[5–9] Residual PH is caused by residual thrombus in the distal segmental and subsegmental pulmonary arteries due to insufficient PEA and small vessel disease characterized by medial hypertrophy and intimal thickening with fibrous hyperplasia and cellular hyperplasia of the pulmonary muscular arteries and veins.[1,10]

For the treatment of residual PH and inoperable CTEPH, PH-targeted medicine and balloon pulmonary angioplasty (BPA) have recently been available. PH-targeted medicine has an effect on small vessel disease, and prospective randomized studies revealed that riociguat considerably improved exercise capacity and decreased pulmonary vascular resistance (PVR), while selexipag significantly decreased PVR.[11–14] Meanwhile, BPA dilates pulmonary arteries by shifting the residual thrombus to the wall in the distal pulmonary arteries to increase flow,[15] and promising results of BPA for residual and recurrent PH after PEA were demonstrated with improvements of pulmonary hemodynamics, symptoms, and exercise capacity.[16,17]

Despite the beneficial effects of PH-targeted medicine and additional BPA on residual PH, it is still unknown whether the modern PH therapy has benefited the long-term outcomes of patients with residual PH. We have shown that patients who developed residual PH before the widespread availability of the modern PH therapy had poor outcomes, and then treated aggressively residual PH by the modern PH therapy.[9] In the present study, we aimed to shed light on the long-term results of patients with residual PH who received modern PH therapy.

METHODS

Between December 2011 and November 2019, 85 patients had primary PEA at the Chiba University hospital, and 80 of those patients survived 1 month later. To determine the effects of residual PH on the long-term outcomes of survivors from PEA, 5 patients who passed away within 30 days of their PEA were omitted from further research. According to the definition of residual PH, patients were divided into two groups, and long-term outcomes were compared between the groups.

Ethical statements

The study was carried out in accordance with the Declaration of Helsinki and was approved by the institutional review board of Chiba University (approval number 2584).

A multidisciplinary CTEPH team evaluated surgical candidacy based on operability and the risk/benefit ratio according to the CTEPH treatment algorithm.[18,19] Surgical accessibility for thromboembolic disease, the balance between increased PVR and the quantity of thromboembolic disease, and major comorbidities that precluded cardiac surgery were used to determine operability. PEA was performed by the standard technique developed by Jamieson et al. under periods of deep hypothermic circulatory arrest in 62 patients, but multiple short periods of moderate hypothermic circulatory arrest in the remaining patients.[20,21]

Patients underwent right heart catheterization (RHC) at diagnosis, 1 month ($n = 77$), and 1 year following surgery ($n = 71$). Pulmonary artery pressure, right atrial pressure, and pulmonary artery wedge pressure were all recorded, and the thermodilution method was used to calculate cardiac output. Accordingly, PVR and cardiac index were calculated.

We defined residual PH as mean pulmonary artery pressure (mPAP) ≥25 mmHg and PVR > 300 dynes.s.cm^{-5} at 1 month after PEA,[11] and systolic PAP >40 mmHg on echocardiography for 3 patients who did not have RHC due to postoperative complications.

A CTEPH team decided how to treat residual PH based on pulmonary hemodynamics, residual symptoms, and a 6-minute walk distance (6MWD). The following treatment plan was used for residual PH. Patients with mPAP >30 mmHg at 1 month following PEA were treated by PH-targeted medicine. In the event that mPAP remained elevated at the follow-up RHC, additional PH-targeted medicine was administered, and BPA was indicated in the event that PH-targeted medicine insufficiently relieved PH. Patients with mPAP ≤30 mmHg were followed with anticoagulation therapy alone for 1 year following PEA. Patients who complained of residual symptoms during follow-up received PH-targeted medicine, and BPA was recommended if

PH-targeted medicine failed to relieve PH. With the exception of situations where mPAP surpassed 40 mmHg at the intensive care unit, we did not routinely administer PH-targeted medicine until the initial RHC. Regardless of the preoperative anticoagulant medications, warfarin was administered as an anticoagulation treatment to all patients.

Definition

CTEPH-related mortality included death from progressive right heart failure and recurrent pulmonary embolism (PE). Recurrent PE was diagnosed with an evidence of elevated pulmonary artery pressure and aggravation of pulmonary thrombus on enhanced CT scan. The cause of death was determined to be recurrent PE and CTEPH-related mortality for 1 patient who passed away within 30 days following re-PEA for recurrent PE.

Statistical analysis

Data analysis was conducted by using the Jump pro software version 16.1. Continuous variables are characterized as mean ± standard deviation and compared by Student's *t*-test if data were normally distributed, or median and interquartile range and compared by the Mann–Whitney *U* test, if not normally distributed. The χ^2 test or Fisher's exact test is used to compare categorical variables when they are given as the numbers (percentages). Continuous variables were compared using the Wilcoxon signed rank test. An analysis of variance test was used to evaluate changes over time. For post hoc multiple comparisons, Bonferroni's method was applied. The Kaplan–Meier method was used to estimate cumulative survival, and the log-rank test was used to compare patients with and without residual PH. % decrease in mPAP in patients with residual PH was calculated as follows: 100 x (mPAP at 1 month following PEA—mPAP at 1 year following PEA)/mPAP at 1 month after PEA. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Eighty patients who had primary PEA and survived 1 month later were divided into two groups based on how residual PH is defined: patients with residual PH ($n = 30$), and control patients ($n = 50$).

Patients with residual PH were significantly older, predominantly female, less likely in World Health Organization functional class (WHO FC) II, and had shorter 6MWD and Jamieson type III disease (Table 1). Patients with residual PH had significantly greater baseline mPAP and PVR than control patients (mPAP 49 [44–54] vs. 43 [36.5–49.5] mmHg, $p < 0.01$; PVR 774.5 [597.5–1085.1] vs. 689.4 [465.4–867.0] dynes.s.cm,$^{-5}$ $p = 0.01$).

Figure 1 contains a flowchart for the management of residual PH and Table 2 contains information on medications specifically designed to treat residual PH. Among 30 patients with residual PH, 23 patients (76.7%) were treated with PH-targeted medicine, and 19 of them (82.6%) were started on the medication based on the results of RHC at 1 month following PEA. A year or later after PEA, 10 control patients were initiated on PH-targeted medicine for residual symptoms, and 5 of them concurrently had elevated mPAP and PVR. Patients who got PH-targeted medicine after PEA were more likely to be received PH-targeted medicine before PEA than those who did not receive after PEA (93.9% vs. 66.0%, $p < 0.01$).

Nine patients with residual PH underwent BPA at 30.5 [14.6–66.5] months following PEA, while 5 control patients received BPA later at 50.1 [45.4–72.8] months primarily because of residual symptoms. The total number of sessions was 2 [2–4] and the number of the treated branches was 12 [4.8–18.3] with no significant difference between patients with and without residual PH.

Figure 2a,b show mPAP and PVR before and after surgery. One month following PEA, both groups' mPAP and PVR significantly decreased from baseline levels, but no further improvement was observed. In line with expectations, patients with residual PH had significantly higher mPAP and PVR values than control patients (mPAP 34 [29.3–39] vs. 20 [17–23] mmHg, $p < 0.0001$; PVR 489.7 [380.7–538.5] vs. 195.4 [148.0–257.7] dynes.s.cm,$^{-5}$ $p < 0.0001$). Patients with residual PH who underwent BPA during follow-up had significant improvement of pulmonary hemodynamics from 1 month after PEA to after BPA (37.8 [35–39.5] to 31.5 [24–34.3] mmHg, $p < 0.01$), while patients without residual PH had no significant hemodynamic improvement after BPA. It was determined that no patients had pulmonary thromboembolic disease, which precluded the use of BPA.

Figure 3a,b show pre and postoperative 6MWD and WHO FC. After PEA, patients with residual PH experienced a considerable improvement in their WHO FC: 81% of the patients were in WHO FC I or II at follow-up, compared to all of them being in FC III or IV preoperatively. 6MWD significantly increased 1 year after PEA compared to baseline and 1 month after PEA. Following PEA, control patients also saw a significant improvement in their 6MWD and WHO FC as well:

TABLE 1 Patient characteristics.

	Residual PH ($n = 30$)	Control ($n = 50$)	p Value
Age, years	68 [62.5–73.3]	62 [53–68]	0.01
Female, *n* (%)	28 (93.3)	30 (60)	<0.01
Time from symptom to PEA, months	25 [13.8–123]	36 [12.8–99]	0.76
History of APE, *n* (%)	14 (46.7)	30 (60.0)	0.25
History of DVT, *n* (%)	22 (78.6)	37 (74.0)	0.65
WHO FC, II/III/IV, *n*	0/27/3	9/39/2	<0.01
6MWD, m	359.6 ± 96.5	415.0 ± 96.8	<0.01
%VC, %	80.6 [72.5–96.0]	88.8 [69.6–98.8]	0.17
FEV1.0%, %	74.5 [69.5–86.1]	75.8 [68.8–82.5]	0.98
Coagulation abnormality, *n* (%)	10 (33.3)	18 (36.0)	0.81
Cancer, *n* (%)	4 (13.3)	3 (6.0)	0.27
COPD, *n* (%)	4 (13.3)	3 (6.0)	0.27
Mental disorders, *n* (%)	5 (16.7)	4 (8.0)	0.24
Thyroid dysfunction, *n* (%)	2 (6.7)	2 (4.0)	0.60
PH-targeted medicine, *n* (%)	27 (90.0)	35 (70.0)	0.03
Single, *n* (%)	17 (56.7)	25 (50.0)	
Double, *n* (%)	6 (20.0)	7 (14.0)	
Triple, *n* (%)	4 (13.3)	3 (6.0)	
Jamieson classification, I/II/III, *n*	12/8/10	25/20/5	0.04

Abbreviations: APE, pulmonary embolism; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; FEV, forced expiratory volume; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; VC, vital capacity; WHO, World Health Organization; WHO FC, World Health Organization functional class; 6MWD, 6-minute walk distance.

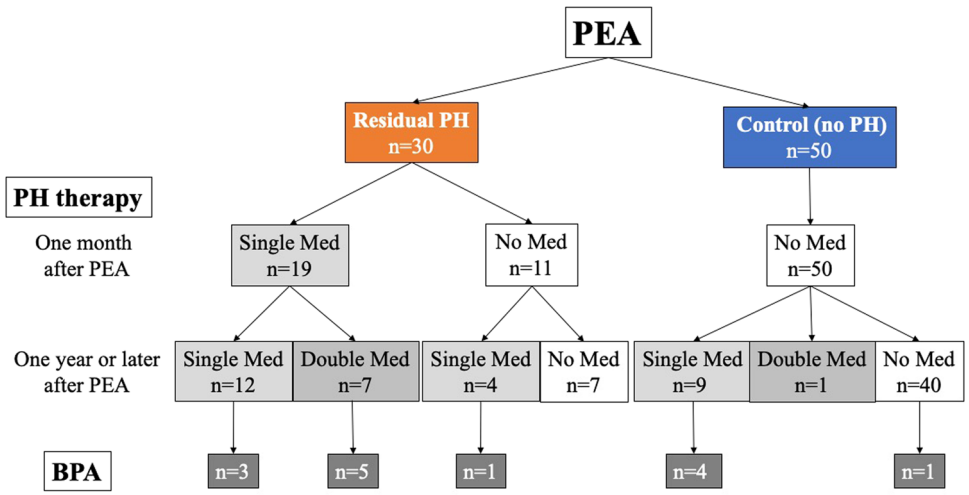

FIGURE 1 Flowchart for the management of residual PH. BPA, balloon pulmonary angioplasty; Med, medicine; PEA, pulmonary endarterectomy; PH, pulmonary hypertension.

72.3% of the patients were in FC I, and no patients were in FC III at follow-up, whereas 82% of the patients were in FC III or IV preoperatively. The overall survival including 30-day mortality (6.9%) was 86.2% at 3 years and 82.4% at 5 years. The survival rate of patients with residual PH was lower than those without (Figure 4a). Freedom from all-cause mortality at 3 and 5 years in patients with residual PH and control patients was 98%

and 93.7%, versus 86.7% and 82.9%, respectively ($p = 0.01$).

During a median follow-up of 66.9 [46.4–96.8] months, 11 patients died: 8 patients with residual PH and 3 control patients. It should be highlighted that neither group's patients experienced progressive right heart failure. Causes of death for patients with residual PH were interstitial pneumonia ($n = 1$), pneumonia ($n = 1$), subarachnoid hemorrhage ($n = 1$), cancer ($n = 1$), burn due to fire ($n = 1$), recurrent PE ($n = 1$), and unknown cause (sudden death) ($n = 2$). Five of these deceased patients received PH-targeted medicine, and 2 received additional BPA. Whereas 2 patients died from unknown cause (sudden death) and advanced cancer within 1 year, 6 patients underwent a follow-up RHC at 1 year following PEA and had significantly lower % decrease in mPAP (7.4 [−32.6 to 8.0] % vs. 10.4 [3.7–27.8] %, $p = 0.03$) and higher mPAP (39.5 [33.3–42.5] vs. 27 [25.3–33.8] mmHg, $p < 0.01$) than the survived patients with residual PH. Recurrent PE ($n = 2$) and cancer ($n = 1$) were the leading causes of mortality for control patients.

Patients with and without residual PH did not have different rates of CTEPH-related mortality (Figure 4b). Freedom from CTEPH-related mortality at 3 and 5 years, patients with residual PH and control patients experienced 98% and 96%, versus 93.2% and 89.2%, respectively ($p = 0.26$). Five patients passed away from CTEPH-related causes, and they all had coagulation abnormalities (antiphospholipid antibody syndrome for 4 patients and essential thrombocythemia for 1 patient).

TABLE 2 Treatment of residual PH.

	Residual PH	Control	*p* Value
PH-targeted medicine, *n* (%)	**23 (76.7)**	**10 (20)**	<0.01
Single, *n*			
sGCS, *n*	12	8	
PDE5i, *n*	4	1	
Double, *n*			
sGCS + ERA, *n*	5	1	
sGCS + PRA, *n*	1	0	
PDE5i + ERA, *n*	1	0	

Abbreviations: BPA, balloon pulmonary angioplasty; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase-5 inhibitor; PH, pulmonary hypertension; PRA, prostacyclin receptor agonist; sGCS, soluble guanylate cyclase stimulators.

DISCUSSION

The present study demonstrated the long-term outcomes of patients who underwent PEA and had residual PH during a time when PH-targeted medicine and BPA were widely accessible. A single or double PH-targeted medicine regimen was used to treat the majority of patients with residual PH. Although patients with residual PH had significantly worse survival than those without, it should be emphasized that the deceased patients' mPAP levels at 1 year following PEA were noticeably higher than those of the survivors despite receiving PH-targeted medicine. Additionally, aggressive PH therapy may have prevented residual PH from being connected with CTEPH-related mortality, while coagulation abnormalities appeared to be most likely to be responsible for CTEPH-related mortality.

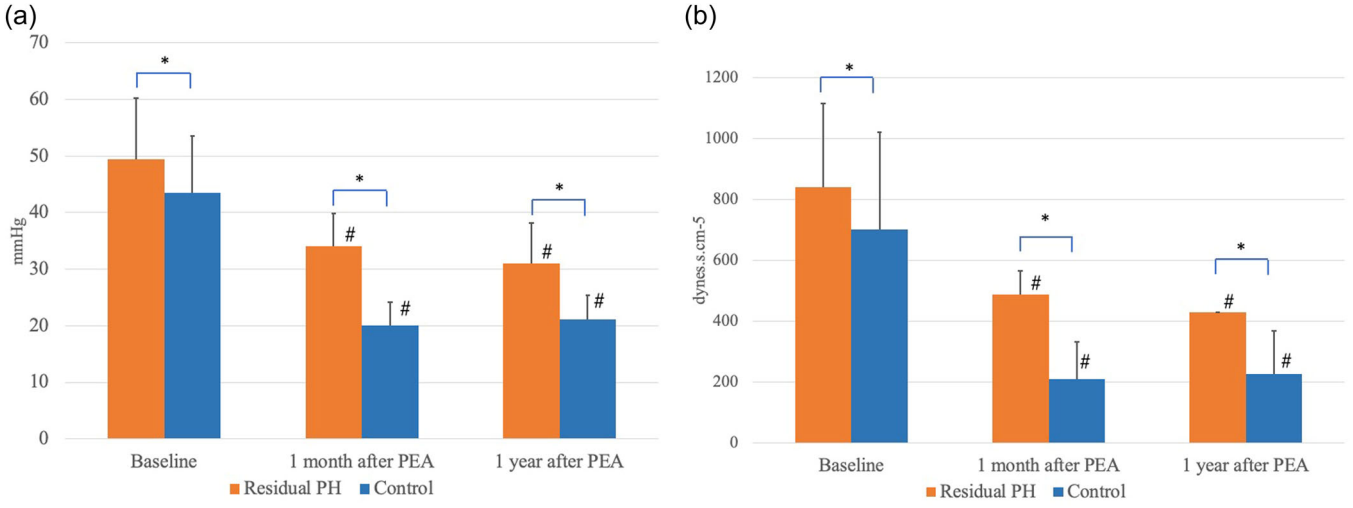

FIGURE 2 Pulmonary hemodynamics before and after pulmonary endarterectomy. (a) Mean pulmonary artery pressure. (b) Pulmonary vascular resistance. *$p < 0.05$ between the groups. #$p < 0.001$ versus preoperative.

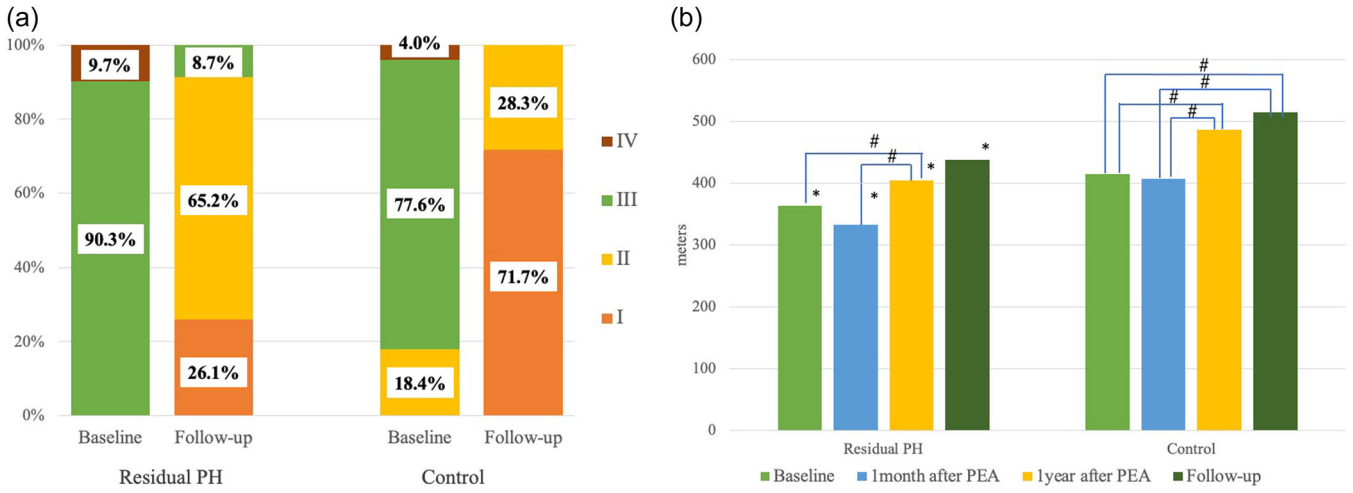

FIGURE 3 (a) Six-minute walk distance baseline and at follow-up. (b) WHO functional class. WHO, World Health Organization. *$p < 0.05$ between the groups. #$p < 0.001$.

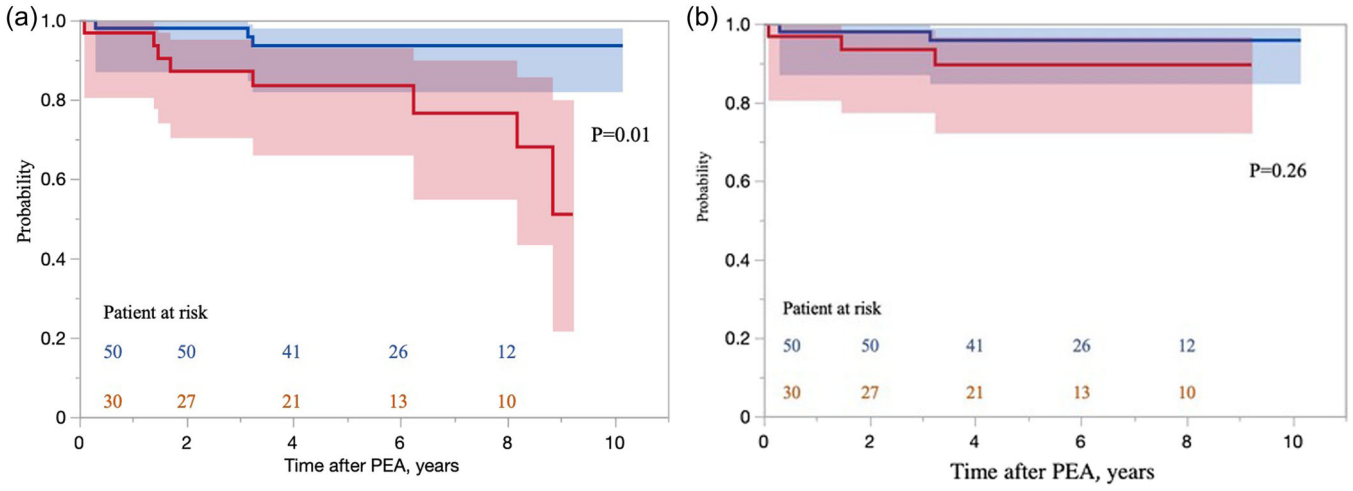

FIGURE 4 Event-free survival after PEA. (a) Event-free survival from all-cause mortality. (b) Event-free survival from CTEPH-related mortality. CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy.

The survival of inoperative CTEPH patients was enhanced by modern PH therapy using PH-targeted medicine and BPA. Miwa et al. demonstrated that the contemporary cohort treated with PH-targeted medicine and BPA had significantly improved event-free survival from CTEPH-related mortality than the historical cohort group.[22] In the present study, 76% of patients with residual PH were treated by PH-targeted medicine following PEA, which was higher than the previously reported rates ranging from 18% to 25% for those with mPAP >30 mmHg.[5,23]

The optimal treatment strategy of residual PH has not yet been determined and the guidelines advocated treating symptomatic patients with residual PH,[18,19] but we treated patients with residual PH primarily by PH-targeted therapy based on the pulmonary hemodynamic results of follow-up RHC. The UK national PEA cohort study showed that mPAP ≥30 mmHg predicted the initiation of PH targeted therapy, despite the fact that the threshold to begin PH therapy for residual PH has not been identified.[6] In our opinion, mPAP on follow-up RHC should be considered to initiate PH-targeted medicine and residual PH with mPAP >30 mmHg should be treated regardless of residual symptoms.

When PH-targeted medicine was insufficient to relieve PH, we also treated any remaining PH by additional BPA. BPA for residual PH was demonstrated to reduce mPAP from 43 to 26 mmHg, whereas riociguat decreased by 7 mmHg from baseline, suggesting that BPA was more successful in lowering mPAP than PH-targeted medicine.[17,24] Nevertheless, BPA for residual PH increases the risk of bleeding complications,[25] while

pretreatment by PH-targeted medicine before BPA decreases the risk of procedure-related complications.[26] Although the treatment interval of 37.5 months between PEA and BPA may be longer than earlier findings, our treatment strategy appeared to be fair in this regard.[25]

PEA offers superior long-term survival compared to medical treatment,[4,23] however it was demonstrated that residual PH adversely affected long-term survival after PEA. In-hospital mortality and poor long-term survival were both related to residual PH with mPAP ≥25 mmHg according to a multicenter registry study from Europe and Canada,[3,4] although other studies demonstrated that residual PH with mPAP >25 or 30 mmHg did not affect freedom from all-cause or CTEPH-related mortality in patients who survived PEA.[5,27]

The present study displayed that residual PH defined as mPAP ≥25 mmHg and PVR ≥ 300 dynes.s.cm^{-5} adversely affected late survival following PEA. However, it should be emphasized that the deceased patients had elevated mPAP of 39 mmHg at 1 year following PEA despite PH-targeted medicine. We previously showed that mPAP >34 mmHg was related to long-term adverse events,[9] and the UK national PEA cohort study revealed that mPAP ≥36 mmHg and PVR ≥ 416 dynes.s.cm^{-5} were significantly associated with all-cause mortality.[6] These findings suggested that intensive treatment should be given to patients who have residual PH with mPAP in the higher 30 mmHg range, since it is linked to poor long-term survival after PEA.

Meanwhile, the present study displayed no impact of residual PH on CTEPH-related mortality. Additionally, there was no mortality from progressive right heart failure, which was one of the primary causes of late CTEPH-related mortality.[4,23,28] In our prior study on long-term results of 77 patients who underwent PEA before approved PH-targeted medicine and BPA were regularly available, 4 out of 5 CTEPH-related mortality were attributed to progressive right heart failure.[9] These outcomes might indicate that PH-targeted medicine and additional BPA contributed to the prevention of death from progressive right heart failure.

One of the main reasons for late mortality following PEA is recurrent PE which may be related to coagulation abnormality. According to the UK national PEA cohort study, of the 356 patients who underwent PEA, 6 patients developed recurrent PE and 4 of them had antiphospholipid antibody syndrome.[6] All patients who required re-PEA had significant antiphospholipid antibody titers, according to another study on the long-term survival of patients with antiphospholipid antibodies.[29] In the present study, CTEPH-related mortality was attributed to recurrent PE and unknown causes (sudden death), and all of them had coagulation abnormalities. These findings indicate that patients with coagulation abnormality need to be closely monitored and given optimal anticoagulant management.

The present study demonstrated that that patients with residual PH as well as those without obtained significant improvement in symptoms and exercise capacity, in accordance with previous studies.[5,30] However, patients having residual PH were more symptomatically compromised and had less exercise capacity than those having no residual PH. Contrarily, 72% of patients without residual PH were asymptomatic at follow-up, and most of them were free from additional PH therapy. These outcomes revealed beneficial effects of PEA, although modern PH therapy may also have aided improve residual symptoms.

There are several limitations to the present study which are prone to bias and unmeasured confoundings, such as retrospective research design, single-center experience, and the small number of patients included. The number of our patients was quite low compared to experienced PEA centers in Europe and US, which may have had some influence on results after PEA because PEA is a technically challenging procedure with a steep learning curve. In the present study, most of the patients with residual PH were treated, thus it was challenging to assess the efficacy of our treatment strategy for residual PH. Furthermore, we treated some patients with mPAP <25 mmHg who complained of residual symptoms and had an elevation of mPAP by PH-targeted medicine and/or additional BPA, which might have contributed to avert adverse events. The treatment approach for those patients with mild residual PH was not standardized and further study is needed to establish an optimal treatment strategy.

In conclusion, PH-targeted medicine was administered to the majority of patients with residual PH, and additional BPA was used in cases where PH-targeted medicine was insufficient to relieve PH. Even though modern PH therapy may have helped to avert deadly progressive right heart failure associated with residual PH and improved functional status and exercise capacity, residual PH negatively impacted long-term survival after PEA. Poor survival after PEA appeared to be related to residual PH with higher mPAP despite PH-targeted medicine, and coagulation abnormalities were linked to CTEPH-related mortality. Patients with residual PH and coagulation abnormalities must be closely monitored, and patients whose residual PH is resistant to single PH-targeted medicine must receive aggressive treatment. However, further research is needed to determine optimal treatment strategy of residual PH after PEA.

AUTHOR CONTRIBUTIONS

Keiichi Ishida and Nobuyuki Tanabe conceived and designed the study. Keiichi Ishida, Hiroki Kohno, Kaoru Matsuura, Toshihiko Sugiura, Takayuki J. Sanada, Akira Naito, Ayako Shigeta, Rika Suda, Ayumi Sekine, and Seiichiro Sakao collected data. Toshihiko Sugiura, Takayuki J. Sanada, Akira Naito, and Nobuhiro Tanabe optimized methodology. Keiichi Ishida wrote the original manuscript. Masahisa Masuda, Seiichiro Sakao, Nobuhiro Tanabe, Koichiro Tatsumi, and Goro Matsumiya supervised the manuscript and revised critically for important intellectual content. All authors approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

Takayuki J. Sanada belongs to departments endowed by Nippon Shinyaku Co. Ltd. Akira Naito has received research grant support from Bayer Yakuhin. Ayumi Sekine has received research grant support from Jansen Pharmaceutical K. K. and Nippon Shinyaku Co, Ltd. Nobuhiro Tanabe has received remuneration from Nippon Shinyaku, Janssen Pharmaceutical K. K., Bayer Yakuhin, and belongs to departments endowed by Janssen Pharmaceutical K. K. and Nippon Shinyaku. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

IRB information: This retrospective, observational study protocol was approved by the institutional review board of Chiba University (approval number 2584).

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