Long-term survival outcome for pre-capillary pulmonary hypertension at a Japanese single center

Yoichi Sugiyama, Nobuhiro Tahara*, Munehisa Bekki, Atsuko Tahara, Akihiro Honda, Shoko Ogata-Maeda, Jiahui Sun, Sachiyo Igata, and Yoshihiro Fukumoto

Division of Cardiovascular Medicine, Department of Medicine, Kurume University School of Medicine

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Corresponding author: Nobuhiro Tahara (email: ntahara@med.kurume-u.ac.jp)

Abstract: In recent years, several treatment options for patients with pre-capillary pulmonary hypertension (PH) have improved the short-term prognosis. However, the long-term survival for pre-capillary PH has not been well investigated. This study sought to investigate the long-term survival for pre-capillary PH in Kurume University Hospital. A total of 144 patients with pre-capillary PH (110 women, mean age; 55.1 ±17.9 years) was enrolled. The maximal duration of follow-up was 15 years with a mean follow-up of 5.77 years. The 15-year survival was 59.1% for pre-capillary PH, 68.5 % for pulmonary arterial hypertension (PAH) and 44.3 % for chronic thromboembolic PH. The 5-year survival was 50.9% for PH due to lung disease (PH-LD) indicating the worst in the pre-capillary PH subgroups. The survival for portopulmonary hypertension was the lowest among PAH groups, and PAH associated with connective-tissue disease and congenital heart disease became to decrease 10 years after diagnosis. Six-minute walk distance and elevated brain natriuretic peptide were significantly associated with survival outcome in pre-capillary PH patients, and that diastolic pulmonary arterial pressure was related with survival for PH-LD. The survivals were different among pre-capillary PH groups in our hospital. Above all, the long-term survival was better than previous reports.

Introduction

Pulmonary hypertension (PH) is a multifactorial disease characterized leading to elevated pulmonary arterial pressure, right ventricular dysfunction, and ultimately heart failure and death (Galiè et al. 2015a). The classification system of PH underlying mechanisms contributes for understanding of pathophysiology and guiding treatment. The classification has been identified 5 forms as follows: Group 1, pulmonary arterial hypertension (PAH); group 2, PH associated with left heart disease (PH-LHD); group 3, PH associated with lung disease (PH-LD); group 4, chronic thromboembolic pulmonary hypertension (CTEPH); group 5, miscellaneous. Currently, there are several pulmonary vasodilator agents with approval for the medical management of PAH, including endothelin receptors antagonists, phosphodiesterase-5 (PDE-5) inhibitors, soluble guanylate cyclase stimulator, and prostanoids. These agents yield hemodynamic, functional, and outcome benefits for PAH patients. Also, pulmonary endarterectomy (PEA) promises a long-term survival in patients with CTEPH. For patients with recurrent or persistent PH after surgery and ineligible for PEA, medical treatment with soluble guanylate cyclase stimulator and percutaneous balloon pulmonary angioplasty (BPA) is beneficial.

Mortality associated with pre-capillary PH has decreased over the last 20 years due to increased recognition of these conditions, accurate diagnosis, risk stratification, and development of innovative treatment strategies (Barst et al. 1966; Galié et al. 2005; Galié et al. 2008a; Galié et al. 2008b; Galié et al. 2009; Ghofrani et al. 2013; Hiremath et al. 2010; Pulido et al. 2013; Sitbon et al. 2015). In fact, ASPIRE (Hurdman et al. 2012), French (Humbert et al. 2006), REVEAL (McGoon and Miller. 2012), and Japan PH (Tamura et al. 2017) registries have demonstrated short-term survivals and activities of daily living in patients with PH. However, there are limited cohorts comparing long-term outcomes in patients with each pre-capillary PH subgroup. Therefore, we sought to elucidate the long-term outcome and variables associated with survival in Japanese patients with pre-capillary PH.

Methods

Participants

All consecutive patients with pre-capillary PH were retrospectively enrolled who were evaluated by blood tests, electrocardiography, echocardiography, six-minute walking test, and right heart catheterization (RHC) between January 1986 and December 2017 in Kurume University Hospital. Pre-capillary PH was defined as a mean pulmonary

artery pressure (mPAP) ≥ 25mmHg, pulmonary artery wedge pressure ≤ 15mmHg, and pulmonary vascular resistance (PVR) ≥ 3 Wood units by RHC at rest. Diagnostic classification of PH was by standard criteria following by experienced cardiologists (Galiè N et al. 2015a).

Classification of pulmonary hypertension

The classification of PH was determined by a detailed medical history, physical examination, and standardized diagnostic approach for PH (Sanyal A.J. et al. 2008), (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. 2002). Pre-capillary PH associated with hereditary hemorrhagic telangiectasia (HHT) was not categorized in heritable PAH (HPAH). Pre-capillary PH after chemotherapy, which can cause pulmonary endothelial damage, for malignancies were defined as drug-induced PAH (McLaughlin et al. 2009). LD was diagnosed by pulmonologists based on detailed medical history, physical examination, and standardized diagnostic approach including lung function test, arterial blood gas analysis and high-resolution computed tomography (HRCT) (Galiè et al. 2015a). In particular, pre-capillary PH with HRCT findings for LD and predicted forced expiratory volume in 1-second ($FEV_{1.0\%}$) < 60% predicted and/or vital capacity (%VC) < 70%

predicted was defined as PH-LD (Tanabe N et al. 2015). Therefore, if having LD, pre-capillary PH associated with connective tissue disease (CTD) was excluded from CTD-PAH. Also, combined pulmonary fibrosis and emphysema (CPFE) with pre-capillary PH was categorized as PH-LD. CPFE was defined as UIP pattern with emphysema (Cottin et al. 2005). Pre-capillary PH with portal hypertension based on hemodynamic measure such as the gradient of free and wedged hepatic venous pressures > 5mmHg was diagnosed as portopulmonary hypertension (PoPH) (Sanyal et al. 2008). CTEPH was identified based on imaging findings of perfusion lung scintigraphy, multidetector computed tomographic pulmonary angiography, and pulmonary angiography (Sanyal et al. 2008), (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. 2002).

Data collection

Clinical and hemodynamic data including age, gender, medications, medical history, World Health Organization (WHO) functional class, laboratory findings, and RHC were collected on the patients with pre-capillary PH at the initial diagnosis. Blood samples for laboratory assays were drawn from the antecubital vein following overnight fasting in the morning to determine uric acid, and brain natriuretic peptide (BNP) or N-terminal pro-

brain natriuretic peptide (NT-pro-BNP). BNP ≥ 300pg/mL or NT-pro-BNP ≥ 1400pg/mL was considered to be an elevated level as high-risk patients (Galiè et al. 2015a). Ambulatory patients underwent a encouraged walk test using a standardized protocol (ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. 2002). Peripheral oxygen saturation (SpO_2) and heart rate were evaluated using a pulse oximeter with a finger probe. SpO_2, heart rate, blood pressure, and Borg dyspnea index were recorded at the beginning and the end of the test. Patients were instructed to walk as fast as possible for evaluation of total distance for 6 minutes. Hemodynamic variables were measured with a Swan-Ganz catheter (Baxter Healthcare Corporation, Santa Ana, CA, USA) in the recumbent position. Cardiac output (CO) was determined using the thermodilution or Fick's method. Cardiac index (CI) was derived by normalization of CO with the body surface area (BSA): CI = CO / BSA. PVR was calculated from the transpulmonary gradient and CO: PVR = 80 × [mPAP- PAWP] / CO. WHO functional class and exercise capacity using the 6-minute walking test were assessed closest to the date of RHC. Examinations were conducted according to physical status in patients with pre-capillary PH.

PH therapies

Therapeutic data such as PH-targeted drugs including prostacyclin and its analogues (beraprost, iloprost, epoprostenol, treprostinil), selective prostacyclin IP receptor agonist (selexipag), phosphodiesterase type 5 inhibitors (sildenafil, tadalafil), soluble guanylate cyclase stimulator (riociguat), and endothelin receptor antagonists (bosentan, ambrisentan, macitentan) and immunosuppressive agents, anti-fibrotic agent, oxygen therapy in patients with pre-capillary PH were collected at the last visit to our hospital. Upfront combination therapy was defined as receiving multiple types of PH-targeted drugs within 2 weeks without any hemodynamic evaluations by echocardiography or right heart catheterization.

Outcome measures

Endpoint for survival outcome included lung transplantation and all-cause of death. Survival status of the pre-capillary PH patients was ascertained by medical records and telephone interviews. The survival period was calculated from the day of first visit at our hospital to the endpoint or December in 2017. A Cox proportional hazards regression analysis with adjustment for age and gender was employed to obtain the variables associated with survival outcome.

Statistical analysis

Data were presented as mean ± standard deviation or medians with the interquartile range. Event-free survival from date of diagnosis was estimated using the Kaplan-Meier method with the comparison between groups performed by the log-rank test. The relationship between survival and selected variables was analyzed with the Cox proportional hazards model for all-cause mortality. The hazard ratios and 95% confidence intervals were defined. Values of $p < 0.05$ were considered to indicate statistical significance. All statistical analyses were performed with the use of the SPSS system (IBM, Chicago, IL, USA).

Results

Patient characteristics

A total of 144 patients with pre-capillary PH (110 females; mean age 55.1±17.9 years) was enrolled in this study. Clinical characteristics of our patients are presented in Table 1. There were 85 (59.0%) patients with PAH, 20 (13.9%) with PH-LD, 37 (25.7%) with CTEPH, and 2 (0.01%) with PH with unclear multifactorial mechanisms. At the time of first visit, 105 (72.9%) patients did not take any PAH-targeted drug. Forty-four patients were in WHO functional class I or II, 96 in class III or

IV, and 4 were unknown. PAP, CI, PVR, uric acid, and 6-minute walk distance (6MWD) were 42.8±14.8 mmHg, 2.55 L/min/m^2 (1.26-8.37 L/min/m^2), 9.33±5.44 Wood units, 6.12 mg/dL (1.73-10.78 mg/dL), and 352.0 m (70.0-650.0 m), respectively (Table 1). Plasma levels of BNP or NT-pro-BNP were elevated in 41 (31.1%) of 132 patients. During the follow-up period, 118 (81.9%) patients were receiving PAH-targeted drugs. Of these, approximately 60% of patients had combination therapy. During the follow-up period, 118 (81.9%) patients were receiving PAH-targeted drugs. Of these, approximately 60% of patients had combination therapy. About 8% of patients received upfront combination therapy after 2008 when it was commercially available to use 3 types of PH-targeted drugs in Japan. Also, 44.4% of pre-capillary PH patients underwent home oxygen therapy. All I/HPAH patients received PH-targeted drugs, and more than 70% of other PH patients except for PoPH were treated with the drugs. Half of PH-LD patients received PDE-5 inhibitors, and approximately 40% of CTEPH patients had riociguat (Table 3). Following for 0.08-15.0 years with a mean of 5.77 years, 31 patients died and no patients underwent lung transplantation. Thirty-one precapillary-PH patients died during the follow-up period. Of these, 24 patients died related to PH; 16 patients with right heart failure, 5 with alveolar hemorrhage, 2 with respiratory failure, and one with sudden unexpected death. On the other, 5 patients met

cancer-related death and 2 died from stroke. The 1-, 3-, 5-, 10-, and 15-year survivals for overall pre-capillary PH were 95.0%, 86.3%, 82.1%, 73.4%, and 59.1%, respectively (Fig. 1). The survival outcome for PH-LD was less than PAH and CTEPH (Fig. 2). There was no significant difference in the survival between PAH subgroups (Fig. 3). Cox proportional hazards regression analysis after adjustment for age and gender revealed that 6MWD (p=0.001) and elevated NT-pro-BNP/BNP (p=0.002) were significantly correlated with survival outcome in patients with pre-capillary PH (Table 2).

Pulmonary arterial hypertension (Group 1)

Of 85 patients with PAH, 24 (16.7%) patients were diagnosed as idiopathic PAH/HPAH and one as HHT-PAH. There were 22 (15.3%) patients with CTD-PAH, 28 (19.4%) with congenital heart disease-PAH (CHD-PAH), and 9 (6.3%) with PoPH (Table 2). There were 26 patients in functional class I or II, 57 patients in class III or IV, and 2 were unknown. During the follow-up period, 73 (85.9%) patients were receiving PAH-targeted drugs. Of these, 80.8% of the patients had combination therapy. The 1-, 3-, 5-, 10-, and 15-year survivals for PAH were 98.8%, 91.9%, 88.3%, 82.8%, and 68.5%, respectively (Fig. 2). The survival rate in PAH patients was much better than previous

studies (Hurdman et al. 2012; McGoon and Miller. 2012). Also, the 10-year survival for PAH was similar to CTEPH (p=0.200) (Fig. 2), which was different with a previous study (Hurdman et al. 2012).

Idiopathic and heritable pulmonary arterial hypertension

In patients with IPAH/HPAH, the mean age at diagnosis was 44.0±18.7 years with a female predominance of 75.0%. At the time of first visit, 9 of 24 patients presented WHO functional class I or II symptom and the other 15 in class III or IV. Approximately, 40% of the patients showed elevated levels of BNP or NT-pro-BNP. PAP, CI, PVR, uric acid, and 6MWD were 49.5±14.1 mmHg, 2.29 L/min/m^2 (1.53-4.12 L/min/m^2), 12.23±5.86 Wood units, 7.00 mg/dL (3.59-10.78 mg/dL), and 402.3 m (179.7-639.0 m), respectively.

Following for 0.83-13.80 years with a mean of 5.34 years, all patients received combination therapy with PAH-targeted drugs. Following for 0.83-13.80 years with a mean of 5.34 years, all patients received combination therapy with PAH-targeted drugs. Following for 0.83-13.80 years with a mean of 5.34 years, all patients received combination therapy with PAH-targeted drugs. During the follow-up period, 3 patients died from heart failure and alveolar hemorrhage in the 2000s, and one met cancer-

related death in the 2010s. The 1-, 3-, 5-, and 10-year survivals for IPAH/HPAH were 100.0%, 95.5%, 84.4%, and 72.3%, respectively (Fig. 3). Cox proportional hazards regression analysis after adjustment for age and gender showed that there was no significant variable related with survival, although P-value of mean PAP was 0.05 (Table 4). Typical IPAH patients diagnosed after 2008 were alive with benefit of PAH-targeted drugs for 3 pathways (Supplementary fig. 1A). The survival for typical IPAH was dependent on the initiation date of treatment.

Pulmonary arterial hypertension associated with connective tissue disease

CTD-PAH group consisted of 8 with systemic lupus erythematosus or mixed connective tissue disease, 3 with Sjogren syndrome, 7 with systemic scleroderma (SSc) and 4 with others. At diagnosis of CTD-PAH, the mean age of patients was 52.3±16.8 years and female predominance was observed (95.5%). There were 5 patients in functional class I or II and 17 patients in class III or IV. Eight (38.1%) patients showed high BNP/NT-pro-BNP levels. PAP, CI, PVR, uric acid, and 6MWD were 37.7±10.2 mmHg, 2.36 L/min/m^2 (1.71-4.33 L/min/m^2), 8.66±4.45 Wood units, 6.18 mg/dL (2.96-8.98 mg/dL), and 244.3 m (70.0-581.0 m), respectively (Table 2). Following for 0.17-15.00 years with a mean of 5.33 years, 5 of the patients received monotherapy and 16

with combination therapy. In CTD-PAH, 4 patients died during the follow-up period; 2 patients with heart failure, one with respiratory failure, and one with stroke. The 1-, 3-, 5-, 10-, and 15-year survivals for CTD-PAH were 100.0%, 95.0%, 89.7%, 89.7%, and 44.9%, respectively (Fig. 3). The survival rates except for SSc decreased over 10 years after first visit (Supplementary fig.2). On the other, the survival rate in SSc patients declined in early period (Supplementary figure 2). In Cox proportional hazards regression analysis, P-value of CI was 0.05, but no variable indicated statistical significance for survival outcome. (Table 4).

Drug-induced pulmonary arterial hypertension

In the study, there was one drug-induced PAH patient treated with dasatinib for chronic myelogenous leukemia. The patient is receiving oral combination therapy and alive after cessation of dasatinib with follow-up period of 9 months.

Pulmonary arterial hypertension associated with congenital heart disease

There were 23 (82.1%) patients with simple CHD such as atrial septal defect and ventricular septal defect, and the 5 others with repaired or unrepaired patients with moderate to severe CHD. At the first visit to our hospital, mean age was 45.4±17.0

years with 19 females (67.9%). At the time of diagnosis, 8 patients were in WHO functional class I or II, 18 in class III or IV, and 2 were unknown. Plasma levels of BNP/NT-pro-BNP were high in 6 (27.3%) of 22 patients. PAP, CI, PVR, uric acid, and 6MWD were 52.5±21.6 mmHg, 3.48 L/min/m^2 (1.70-7.55 L/min/m^2), 9.33±5.81 Wood units, 6.15mg/dL (2.71-8.42 mg/dL), and 369.0 m (160.0-508.2 m), respectively (Table 2). Over a mean follow-up of 10.51 years (range 0.17-15.00 years), 82.1% of the patients received monotherapy or combination therapy. During the follow-up period, 4 patients with CHD-PAH died; 2 patients with heart failure and one with alveolar hemorrhage. Also, one patient met cancer-related death. The 1-, 3-, 5-, 10-, and 15-year survivals for CHD-PAH were 96.4%, 96.4%, 92.2%, 92.2%, and 81.4%, respectively (Figure 3). No variable was observed to be significant for survival outcome.

Portopulmonary hypertension

In this study, autoimmune hepatitis, chronic hepatitis C, Immunoglobulin G-4 related disease, portal vein hypoplasia, multiple liver cysts, and peritoneal arteriovenous malformation were underlying conditions of PoPH. The mean age at diagnosis was 58.4±14.4 years without a female predominance. At the time of diagnosis, 3 patients presented class I or II symptom and 6 class III or IV symptom. PAP, CI, PVR, uric acid,

and 6MWD were 37.8±5.3 mmHg, 3.76 L/min/m^2 (2.50-8.37 L/min/m^2), 5.20±2.07 Wood units, 5.13 mg/dL (1.73-9.67 mg/dL), and 376.6 m (323.0-650.0 m), respectively (Table 2). During a mean follow-up of 3.45 years (range 0.42-12.17 years), 4 (44.4%) of PoPH patients received monotherapy or combination therapy with PAH-targeted drugs. Two patients with PoPH died from heart failure and cancer during the follow-up period. The 1-, 3-, 5-, 10-year survivals for PoPH were 100.0%, 75.0%, 75.0%, and 37.5%, respectively (Figure 3). There was no variable indicating statistical significance for survival outcome.

Pulmonary hypertension associated with lung disease (Group 3)

In patient with PH-LD, the mean age at diagnosis was 65.2±14.6 years and a female preponderance did not exist. At the time of diagnosis, majority of PH-LD patients had class II or III symptoms. Five (27.8%) of the patients showed elevated BNP/NT-pro-BNP levels. PAP, CI, PVR, uric acid, and 6MWD were 32.5±7.7 mmHg, 2.86 L/min/m^2 (1.82-4.39 L/min/m^2), 5.96±3.08 Wood units, 4.72 mg/dL (2.19-7.95 mg/dL), and 239.0 m (130.0-514.0 m), respectively (Table 1). There were 14 patients treated by PAH targeted drugs, 5 patients treated by anti-fibrotic agents, and 12 patients treated by home oxygen therapy in PH-LD in our study. Especially, all severe PH-LD received PAH

targeted drugs. Following for 0.08-6.50 years with a mean of 2.39 years, 8 patients died. Four patients died from heart failure, 1 from respiratory failure, 1 from alveolar hemorrhage, 1 from cancer, and 1 from stroke. The 1-, 3-, 5-year survivals for PH-LD were 66.0%, 59.4%, and 50.9%, respectively (Figure 2). Survival in PH-LD patients with mPAP ≥ 35 mmHg was inferior to those with mPAP < 35mmHg (**Supplementary figure 3**). Diastolic PAP was significantly correlated with survival outcome (p=0.045) (Table 4).

There were 5 PH-LD patients with mPAP ≥ 35mmHg which composed of 3 PH-ILD patients and 2 PH-CPFE patients in our study. Also, there were 15 PH-LD patients with mPAP < 35mmHg which composed of 4 COPD patients, 9 PH-ILD patients and 2 PH-CPFE patients. PVR and NT-pro-BNP/BNP were significantly different between the 2 subgroups. All PH-LD patients with mPAP ≥ 35mmHg received PH-targeted drugs. In those patients, 2 patients with mPAP ≥ 35mmHg have combination therapy. Four patients received PDE5-inhibitors, and one patient an endothelin receptor antagonist. On the other hand, 9 PH-LD patients with mPAP < 35mmHg received PH-targeted drugs. Three patients with mPAP < 35mmHg have combination therapy. Six patients received PDE5-inhibitors, 2 patients riociguat, and 5 patients endothelin receptor antagonists.

There were 4 PH-COPD, 12 PH-ILD, and 4 PH-CPFE patients in the PH-LD group. Two PH-COPD, 4 PH-ILD, and 2 PH-CPFE patients died during the follow-up period. In PH-COPD group, one died from heart failure, and another from cancer-related event. Each 4 patients with PH-ILD died from heart failure, respiratory failure, alveolar hemorrhage, and stroke. Both patients with PH-CPFE died from heart failure. The 1-, 3-, and 5-year survivals for PH-COPD were 100.0%, 66.7%, and 33.3%, respectively. The 1-, 3-, and 5-year survivals for PH-ILD were 59.5%, 59.5%, and 59.5%, respectively. The 1-, 3-, and 5-year survivals for PH-CPFE were 50.0%, 50.0%, and 50.0%, respectively. The survival for PH-ILD and PH-CPFE deteriorated within one year after the first visit at our hospital, although the survival for PH-COPD after 2 years. Furthermore, there was no significant difference for survival outcome among PH-COPD, PH-ILD, and PH-CPFE. No variable was observed to be significant for survival outcomes in each subgroup of PH-LD, even though mPAP ≥ 35mmHg and diastolic PAP were significant variables for survival in PH-LD.

Chronic thromboembolic pulmonary hypertension (Group 4)

In patients with CTEPH, the mean age was 65.5±12.6 years and female predominance was observed (94.6%). At the time of diagnosis, 14 patients were in class I or II and 23

in class III or IV. PAP, CI, PVR, uric acid, and 6MWD were 42.3±11.0 mmHg, 2.16 L/min/m^2 (1.26-5.10 L/min/m^2), 10.84±5.70 Wood units, 6.09 mg/dL (3.39-10.02 mg/dL), and 368.0 m (137.0-600.0 m), respectively (Table 1). Eight patients with CTEPH died during the follow-up period. There were 5 patients died from heart failure, 1 patient from death, and 2 from alveolar hemorrhage. In the CTEPH group, patients underwent PEA had an excellent long-term outcome (Supplementary fig. 4). In our hospital, BPA was officially initiated for ineligible patients for PEA from 2013, and was performed for 15 patients. Although one patient died due to hemoptysis 1 year after BPA procedure, the survival was ameliorated by BPA after 2013 (Supplementary fig. 5). Over a mean follow-up of 5.48 years (range 0.42-15.00 years), the 1-, 3-, 5-, 10, and 15-year survivals for CTEPH were 100.0%, 88.6%, 84.2%, 66.5%, and 44.3%, respectively (Fig. 2). Cox proportional hazards regression analysis indicated no significant variable correlated with survival outcome.

Pulmonary hypertension with unclear multifactorial mechanisms (Group 5)

There were only 2 pre-capillary PH patients with unclear multifactorial mechanisms (group 5) in this study. One patient with pulmonary tumor thrombotic microangiopathy

met cancer-related death., and the other with pulmonary lymphangioleiomyomatosis is alive without any PAH-targeted drug.

Discussion

In the present study, we report long-term survivals and variables related with the survival outcome in patients with pre-capillary PH. The novel findings of our study were [1] the much better the survival than 1900s era in PAH, especially IPAH/HPAH, [2] the poor prognosis in PH-LD group, and [3] the importance of PEA and BPA strategies for survival outcome in CTEPH.

In our study, the 15-year survival in pre-capillary PH was 59.1%. There were 96 (68.6%) patients in WHO functional class III or IV at the first visit to our hospital. This study demonstrated that the survival outcomes of each PH group were quite different and that the survival outcome of PAH, especially I/HPAH was better than a previous study (Hurdman et al. 2012). PH-targeted drugs might support the survival of PAH, because 85.7% of PAH patients received PH-targeted drugs in this study. Above all, patients with PH-LD and PoPH had poor prognosis (Figure 2, 3). In those patients, 70.0% of PH-LD patients and 44.4% of PoPH patients received PH-targeted drugs. Since it was difficult to use PH-targeted drugs for patients with PH-LD and PoPH due

to side effects and drug metabolisms, other therapeutic strategy was needed to improve the survival outcome of them. Early diagnosis and appropriate treatment such as combination therapy may be crucial to show much better long-term prognosis for precapillary PH (Humbert et al. 2011). Also, novel treatment is needed especially for patients with PoPH, PH-LD, and CTD-PAH due to SSc.

In the present study, a long-term survival outcome in IPAH/HPAH patients was superior to a previous study (Hurdman et al. 2012). Notably, only 4 of 24 patients with IPAH/HPAH died during the follow-up period. Especially, IPAH/HPAH patients diagnosed in the 2010s have gotten favorable outcomes (Supplementary fig. 1A). Actually, pulmonary hemodynamics were changed for the better by the 3-pathway drugs in patients with IPAH/HPAH (Table 3). The reason might be owing to amelioration of pulmonary hemodynamics by 3 pathway PAH-targeted drugs from the early stage. Recently, Japan PH registry has demonstrated an excellent outcome of short-term survival (3-year survival rate of 90.4%) in 105 patients with IPAH/HPAH treated by a number of PAH-targeted drugs (Tamura et al. 2017). A favorable long-term survival will be obtained in the Japan PH registry. In recent years, atypical type of IPAH has been increasing. When patients older than 65 years and having comorbidities with left heart disease and/or LD were defined as atypical IPAH (Tamura et al. 2017; Hurdman et al.

2012), 6 (25.0%) patients were ascertained as atypical IPAH in our study. Although it is difficult to treat for patients with atypical IPAH, the survival was comparable between typical and atypical types of IPAH in our study (Supplementary fig. 1).

In CTD-PAH group, 17 (77.3%) patients underwent medical treatments with PAH-targeted drugs and immunosuppressive agents, and 4 (18.2%) patients died during the follow-up period. The survival was better than a previous study (Chung L et al. 2010). Especially in patients with CTD-PAH except for SSc, intensive anti-inflammatory therapy may ameliorate pulmonary hemodynamics and the survival (Miyamachi-Yamamoto et al. 2011). However, the survival rate in CTD-PAH patients except for SSc deteriorated 10 years after the first visit at our hospital (Supplementary fig. 2). On the other, the survival for PAH associated with SSc declined 3 years after the first visit at our hospital (Supplementary fig. 2). Although we cannot explain the reason, we might have to initiate PAH-targeted drugs for PAH patients with SSc as soon as possible after diagnosis. Also, novel therapies are needed to show favorable the long-term survival for PAH associated with SSc.

PH-LD was known as a disease with poor prognosis (Hurdman et al. 2012.). Especially, the survival for severe PH-LD, defined as mPAP ≥ 35 mmHg (Galiè et al. 2015a) and pulmonary vascular lesions, was worse than mild to moderate PH-LD.

Therefore, PAH-targeted drugs including PDE-5 inhibitors may improve the survival of patients with severe PH-LD as previously reported (Tanabe et al. 2015). However, severe PH-LD had poor survival rate despite receiving PDE-5 inhibitors in our study. Survival in patients with PH-LD was independent on subgroup such as chronic obstructive pulmonary disease, interstitial pneumonia, and CPFE. The effects of PAH-targeted drugs might be insufficient in some patients with severe PH-LD. PEA brought better survival in CTEPH patients compared to those without PEA (Supplementary figure 4). Also, BPA was one of the helpful treatment strategies for ineligible CTEPH patients for PEA, because the mortality of CTEPH patients treated by BPA was 6.7% during 5 years in our study (Supplementary figure 5). Furthermore, there was a significant difference of survival between patients underwent BPA or PEA and those without underwent BPA and PEA in our study ($p=0.042$). BPA is a pivotal therapeutic strategy for survival in patients with CTEPH as well as PEA.

A multicenter cohort in Japan has demonstrated that BPA dramatically improved pulmonary hemodynamics and the survival for CTEPH (Ogawa et al. 2017). Recent guidelines (Galiè et al. 2015a) and the 5th World symposium on Pulmonary Hypertension (Kim NH et al. 2019) recommended BPA to ineligible CTEPH patients

for PEA. BPA to ineligible CTEPH patients for PEA is expected to spread all over the world.

6MWD has been shown to be a predictor for short-term survival in PAH (Galiè et al. 2015a). In the present study, these variables were associated with long-term survival outcome. Also, diastolic PAP, but not mean PAP was correlated with the survival in patients with PH-LD. Diastolic PAP has not been recognized as a survival predictor. Further longitudinal study with large-scale patients is needed to clarify whether these variables could be predictors for the long-term survival in patients with pre-capillary PH.

Limitations

Significant limitations should be mentioned in this study. First, this study was a single-center retrospective study. Therefore, possibility of selection bias and survivor bias could not be avoided. Our cohort involved 25.7% of prevalent cases, which might be a reason why survival could be better than previous reports (Hurdman et al. 2012), (McGoon M.D and Miller D.P. 2012). Also, the small number of patients may have limited the results of the present study. Second, RV function is an important parameter for survival in pre-capillary PH. However, the follow-up period of our study was too long to collect all data of the parameters of RV function. Third, it was difficult to

differentiate the subgroups of PH, especially in CTD. Patients with CTD have some types of PH such as PAH, PH-LD, and CTEPH (Galiè et al. 2015a). In the present study, the category in such patients was changed after first visit. Fourth, we did not evaluate the follow-up data for survival outcomes. A multi-center prospective study with serial evaluations is needed to confirm the follow-up variables for long-term survival.

In conclusion, long-term survival outcome for pre-capillary PH was better than previous studies. However, PH-LD showed poor prognosis as same as previous studies. Therefore, novel therapeutic strategy is required for improvement of survival especially in PH-LD.

Conflict of interest

The authors declare that there is no conflict of interest associated with this work.

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Figure legend

Fig. 1. Survival for pre-capillary PH

Fig. 2. Survivals for pre-capillary PH subgroups

Abbreviations as in Table 1

Fig. 3. Survivals for PAH subgroups

Abbreviations as in Table 1 and 2.

Supplementary fig. 1.

A: Survival for IPAH diagnosed after 2008

B: Survival for IPAH during all period

Abbreviations as in Table 1 and 2.

Supplementary fig. 2. Survival for CTD-PAH

Other abbreviations as in Table 1 and 2.

Supplementary fig. 3. Survival for PH-LD

Survival rate in PH-LD patients with < 35mmHg was significantly better than with ≥35mmHg (p=0.033).

Abbreviations as in Table 1

Supplementary fig. 4. Survival for CTEPH

Survival rate of CTEPH patients with PEA was significantly better than without PEA (p=0.020).

PEA, pulmonary endarterectomy. Other abbreviations as in Table 1.

Supplementary fig. 5. Survival for CTEPH treated by BPA after 2013

BPA, balloon pulmonary angioplasty; PEA, pulmonary endarterectomy. Other abbreviations as in Table 1

Fig. 1.

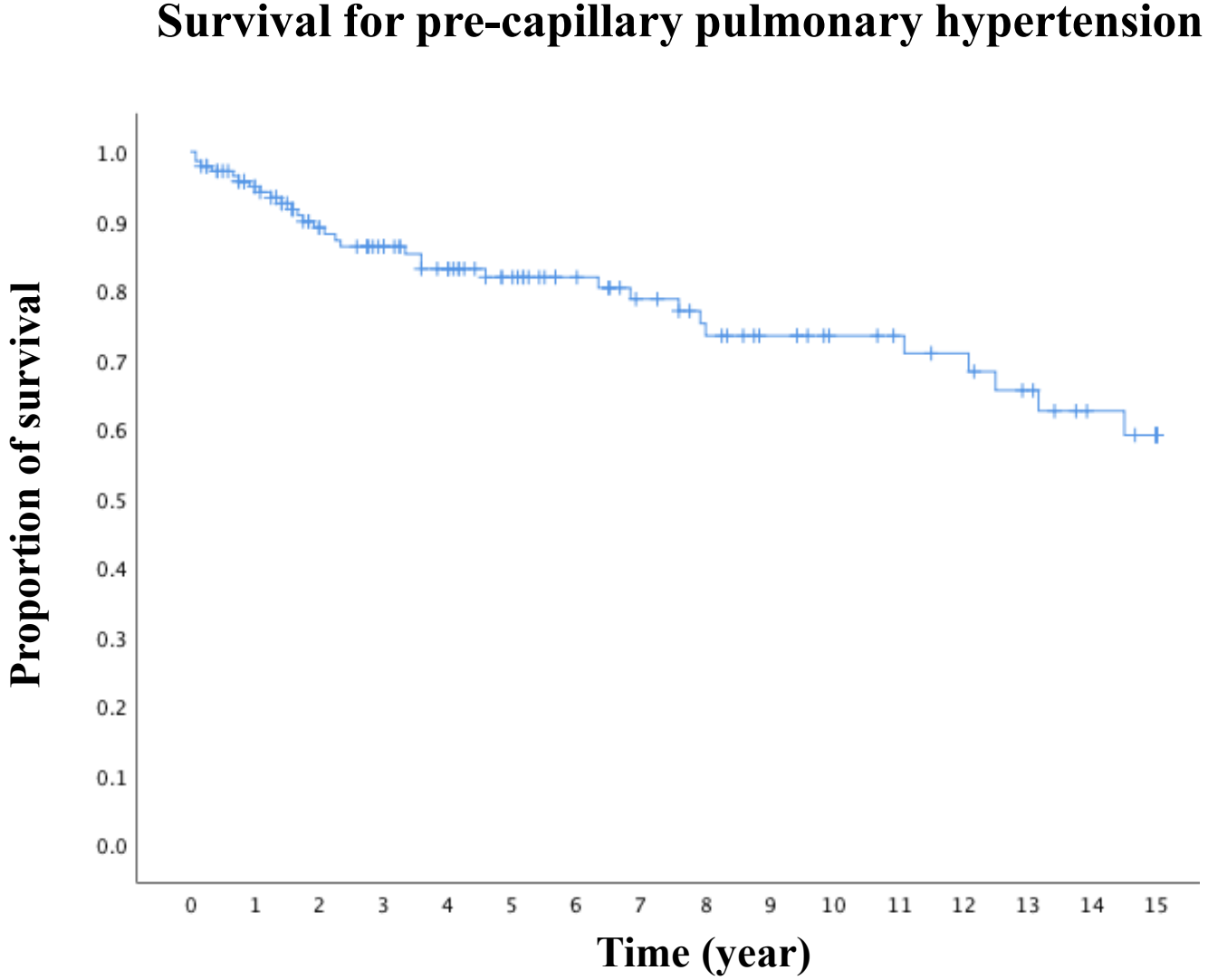
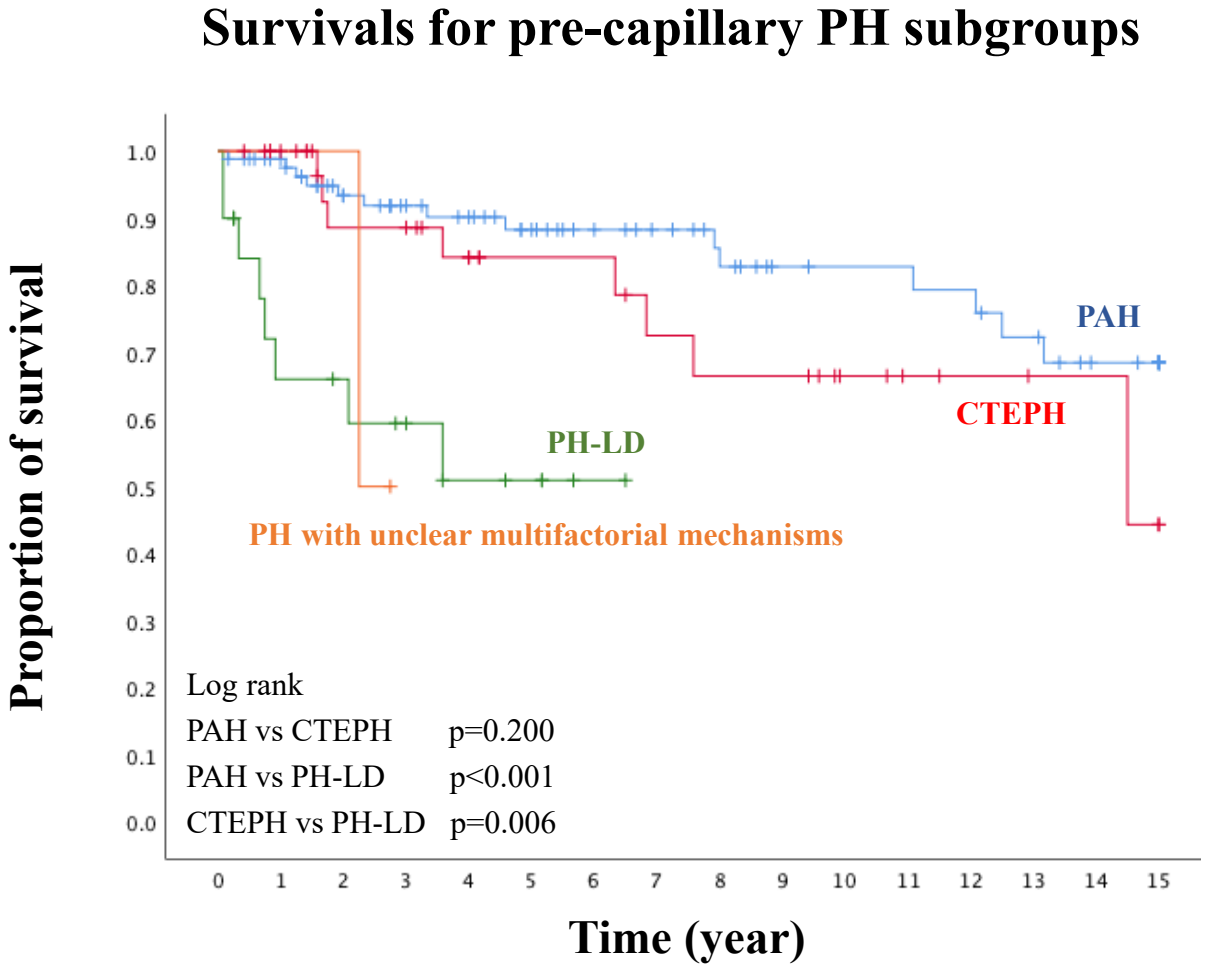

Survival for pre-capillary pulmonary hypertension
Proportion of survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time (year)
Patients at risk
144 121 97 86 75 63 54 47 41 36 31 29 27 23 18 15

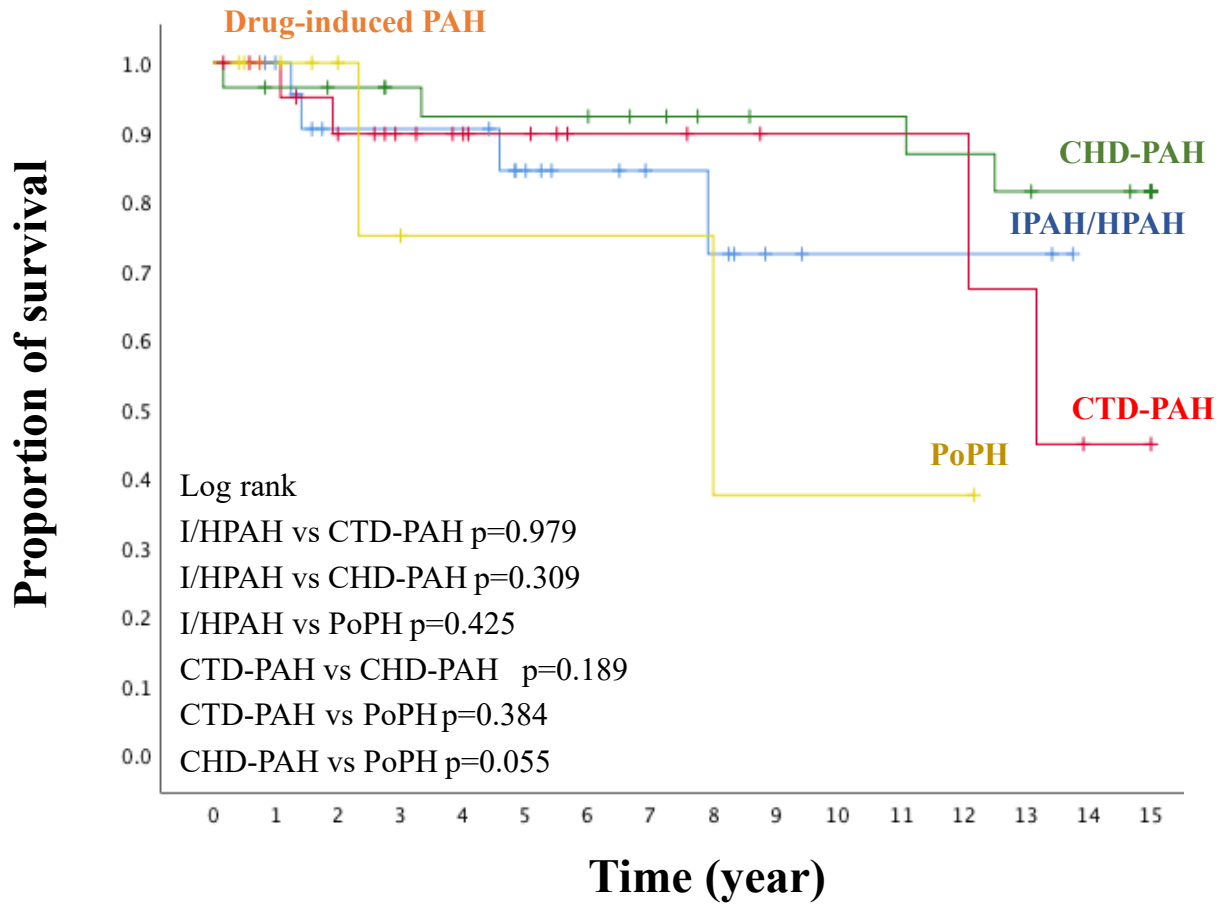
Fig. 2.



Patients at risk

PAH	85	76	63	55	51	44	38	35	30	25	24	24	23	20	15	13
CTEPH	37	31	23	22	18	15	15	12	11	11	7	5	4	3	3	1
PH-CLD	20	11	10	7	5	4	1									
PH with unclear multifactorial mechanisms	2	2	2													

Fig. 3.



Patients at risk

IPAH/HPAH	24	22	16	16	16	11	9	5	5	3	2	2	2	2		
CTD-PAH	22	20	16	13	10	9	6	6	5	4	4	4	4	3	1	1
CHD-PAH	28	26	25	25	23	23	23	20	18	17	17	17	16	15	14	12
Drug-induced	1															
PoPH	9	7	4	2	2	2	2	2	1	1	1	1	1			

Table 1.

Baseline characteristics in patients with pre-capillary pulmonary hypertension

Variables	Pre-capillary PH (Overall)	PAH	PH-LD	CTEPH	PH with unclear mechanism
Subjects, n (%)	144 (100%)	85 (59.0%)	20 (13.9%)	37 (25.7%)	2 (0.01%)
Follow-up period (range), year	5.77 (0.08-15.00)	6.77 (0.17-15.00)	2.39 (0.08-6.50)	5.48 (0.42-15.00)	2.50 (2.25-2.75)
Age, n	55.1 ± 17.9, 144	48.0 ± 17.5, 85	65.2 ± 14.6, 20	65.5 ± 12.6, 37	58.5 ± 6.4, 2
Female, n (%)	110 (76.4%)	63 (74.1%)	11 (55.0%)	35 (94.6%)	2 (100%)
WHO-FC I/II/III/IV (n)	4/40/88/8 (140)	3/23/52/5 (83)	1/2/14/1 (18)	0/14/21/2 (37)	0/1/1/0 (2)
mAoP, mmHg, n	87.9 ± 13.9, 134	87.3 ± 14.8, 80	87.0 ± 13.5, 18	89.6 ± 12.8, 34	91.0 ± 5.7, 2
Heart rate, beats per minute, n	74.8 ± 12.2, 129	75.1 ± 13.0, 75	75.9 ± 11.7, 18	73.9 ± 11.4, 34	71 ± 1.4, 2
PAWP*, mmHg, n	9.0 (2.0-19.0), 137	8.0 (3.0-19.0), 81	9.5 (5.0-14.0), 18	8.5 (2.0-16.0), 35	7.5 (4.0-11.0), 2
SvO_2, %, n	63.4 ± 9.5, 127	64.6 ± 9.5, 77	64.1 ± 7.8, 18	60.0 ± 10.0, 30	63.9 ± 0.07, 2
sPAP, mmHg, n	68.5 ± 22.9, 139	70.5 ± 24.2, 83	52.7 ± 16.2, 18	72.7 ± 19.8, 36	50.0 ± 2.8, 2
dPAP, mmHg, n	27.8 ± 11.6, 139	30.8 ± 13.0, 83	20.9 ± 4.8, 18	24.9 ± 7.9, 36	18.5 ± 2.1, 2
mPAP, mmHg, n	42.8 ± 15.0, 139	45.5 ± 16.7, 83	32.5 ± 7.7, 18	42.3 ± 11.0, 36	30.0 ± 2.8, 2
PVR, wood unit, n	9.33 ± 5.44, 138	9.47 ± 5.51, 82	5.96 ± 3.08, 18	10.84 ± 5.70, 36	7.00 ± 1.34, 2
CI*, $L/min/m^2$, n	2.55 (1.26-8.37), 138	2.70 (1.53-8.37), 82	2.86 (1.82-4.39), 18	2.16 (1.26-5.10), 36	2.51 (1.88-3.13), 2
RAP*, mmHg, n	6.0 (1-23), 136	6.0 (1.0-23.0), 80	5.0 (2.0-11.0), 18	5.5 (1.0-13.0), 34	3.5 (2.0-5.0), 2
6MWD*, m, n	352.0 (70-650), 120	352.0 (70.0-650.0), 68	239.0 (130.0-514.0), 16	368.0 (137.0-600.0), 32	279.0 (131.0-426.9), 2
Elevated BNP/NT-pro-BNP, n (%), n	41 (31.1%), 132	24 (31.2%), 77	5 (27.8%), 18	12 (34.3%), 35	0 (0.0%), 2
Uric acid*, mg/dL, n	6.12 (1.73-10.78), 132	6.27 (1.73-10.78), 61	4.72 (2.19-7.95), 18	6.09 (3.39-10.02), 34	4.30 (3.91-4.69), 2

Values are number (%), mean ± SD, or * median (interquartile range).

n, number; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PH-LD; pulmonary hypertension due to lung disease; CTEPH, chronic thromboembolic pulmonary hypertension; 5th, PH with unclear multifactorial mechanisms; WHO-FC, World Health Organization (WHO) functional class; mAoP, mean aortic pressure; PAWP, pulmonary artery wedge pressure; SvO_2, mixed venous oxygen saturation; sPAP, systolic pulmonary arterial pressure; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; CI, cardiac index; RAP, right arterial pressure; 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; NT-pro-BNP, N-terminal pro-brain natriuretic peptide.

Table 2.

Baseline characteristics in patients with pulmonary arterial hypertension

Variables	IPAH/HPAH	CTD-PAH	CHD-PAH	PoPH
Subjects, n (%)	24 (16.7%)	22 (15.3%)	28 (19.4%)	9 (6.3%)
Follow-up period, year (min-max)	5.34 (0.83-13.80)	5.33 (0.17-15.00)	10.51 (0.17-15.00)	3.45 (0.42-12.17)
Age, n	44.0 ± 18.7, 24	52.3 ± 16.8, 22	45.4 ± 17.0, 28	58.4 ± 14.4, 9
Female, n (%)	18 (75.0%)	21 (95.5%)	19 (67.9%)	4 (44.4%)
WHO-FC I/II/III/IV (n)	0/9/14/1 (24)	1/4/15/2 (22)	1/7/16/2 (26)	0/3/6/0 (9)
mAoP, mmHg, n	87.3 ± 11.7, 23	89.8 ± 19.3, 21	82.6 ± 11.3, 25	90.0 ± 15.9, 9
Heart rate, beats per minute, n	69.9 ± 13.8, 21	78.0 ± 11.8, 21	76.6 ± 11.5, 25	79.1 ± 14.7, 9
PAWP*, mmHg, n	8.0 (4.0-17.0), 24	8.0 (4.0-19.0), 22	9.5 (4.0-17.0), 24	8.0 (5.0-13.0), 9
SvO_2, %, n	64.2 ± 10.5, 22	61.8 ± 11.7, 21	66.4 ± 6.8, 24	68.2 ± 7.8, 9
sPAP, mmHg, n	78.5 ± 19.0, 24	59.5 ± 17.7, 22	78.5 ± 30.5, 26	60.0 ± 11.8, 9
dPAP, mmHg, n	33.6 ± 12.4, 24	24.5 ± 7.3, 22	36.5 ± 16.2, 26	25.1 ± 4.0, 9
mPAP, mmHg, n	49.5 ± 14.1, 24	37.7 ± 10.2, 22	52.5 ± 21.6, 26	37.8 ± 5.3, 9
PVR, wood unit, n	12.23 ± 5.86, 24	8.66 ± 4.45, 22	9.33 ± 5.81, 25	5.20 ± 2.07, 9
CI*, L/min/m^2, n	2.29 (1.53-4.12), 24	2.36 (1.71-4.33), 22	3.12 (1.70-7.55), 25	3.76 (2.50-8.37), 9
mRAP*, mmHg, n	6.0 (2.0-16.0), 24	4.5 (1.0-23.0), 22	6.0 (2.0-14.0), 25	6.0 (3.0-11.0), 9
6MWD*, m, n	402.3 (179.7-639.0), 22	244.3 (70.0-581.0), 22	369.0 (166.0-508.2),18	376.6 (323.0-650.0), 8
Elevated BNP/NT-pro-BNP, n (%), n	9 (39.1%), 23	8 (38.1%), 21	6 (27.3%), 22	1 (11.1%), 9
Uric acid*, mg/dL, n	7.00 (3.59-10.78), 23	6.18 (2.96-8.98), 22	6.15 (2.71-8.42), 22	5.13 (1.73-9.67), 9

Values are number (%), mean ± SD, or * median (interquartile range).
Abbreviations as in Table 1.

Table 3.

Characteristics of the PH treatment

	Pre-capillary PH (Overall)	IPAH/HPAH	CTD-PAH	CHD-PAH	PoPH	PH-LD	CTEPH
Subjects, n	144	24	22	28	9	20	37
PH-targeted drug use, n (%)	118 (81.9%)	24 (100.0%)	20 (90.9%)	23 (82.1%)	4 (44.4%)	14 (70.0%)	30 (81.1%)
Prostacyclin and its analogues							
Beraprost, n (%)	34 (23.6%)	4 (16.7%)	5 (22.7%)	7 (25.0%)	1 (11.1%)	2 (10.0%)	15 (40.5%)
Iloprost, n (%)	6 (4.1%)	4 (16.7%)	0	0	1 (11.1%)	1 (5.0%)	0
Epoprostenol, n (%)	7 (4.9%)	5 (20.8%)	0	1 (3.6%)	0	0	1 (2.7%)
Treprostinil, n (%)	4 (2.8%)	1 (4.2%)	0	2 (7.1%)	1 (11.1%)	0	0
Selective prostacyclin receptor agonist							
Selexipag, n (%)	29 (13.9%)	15 (62.5%)	6 (27.3%)	3 (10.7%)	0	1 (5.0%)	4 (10.8%)
Phosphodiesterase 5 inhibitors							
Sildenafil, n (%)	15 (10.4%)	2 (8.3%)	6 (27.3%)	3 (10.7%)	1 (11.1%)	2 (10.0%)	0
Tadalafil, n (%)	53 (36.8%)	19 (79.2%)	8 (36.4%)	12 (42.9%)	1 (11.1%)	8 (40.0%)	5 (13.5%)
Soluble guanylate cyclase stimulator							
Riociguat, n (%)	24 (16.7%)	2 (8.3%)	3 (13.6%)	1 (3.6%)	1 (11.1%)	2 (10.0%)	15 (40.5%)
Endothelin receptor antagonists							
Bosentan, n (%)	36 (25%)	6 (25.0%)	6 (27.3%)	9 (32.1%)	0	3 (15.0%)	12 (32.4%)
Ambrisentan, n (%)	6 (4.2%)	3 (12.5%)	1 (4.5%)	1 (3.6%)	0	0	1 (2.7%)
Macitentan, n (%)	39 (27.1%)	13 (54.2%)	9 (40.9%)	8 (28.5%)	1 (11.1%)	4 (20.0%)	3 (8.1%)
Combination therapy, n (%)	85 (59.0%)	24 (100.0%)	16 (72.7%)	17 (60.7%)	2 (22.2%)	7 (35.0%)	18 (48.6%)
Triple combination therapy, n (%)	43 (30.0%)	19 (79.2%)	8 (36.4%)	8 (28.5%)	0	2 (10.0%)	6 (16.2%)
Up front combination therapy, n (%)	12 (8.3%)	5 (20.8%)	1 (4.5%)	3 (10.7%)	2 (22.2%)	1 (5.0%)	0
Home oxygen therapy, n (%)	64 (44.4%)	16 (66.7%)	12 (54.5%)	8 (28.5%)	1 (11.1%)	12 (60.0%)	14 (37.8%)

Abbreviations as in Table 1.

Table 4.

Multivariate regression analyses using a Cox's proportional hazards model for each survival

Group	Variables	β	SE	Hazard Ratio (95%CI)	P-value
Pre-capillary PH	6MWD	-0.007	0.003	0.993 (0.988-0.998)	0.006

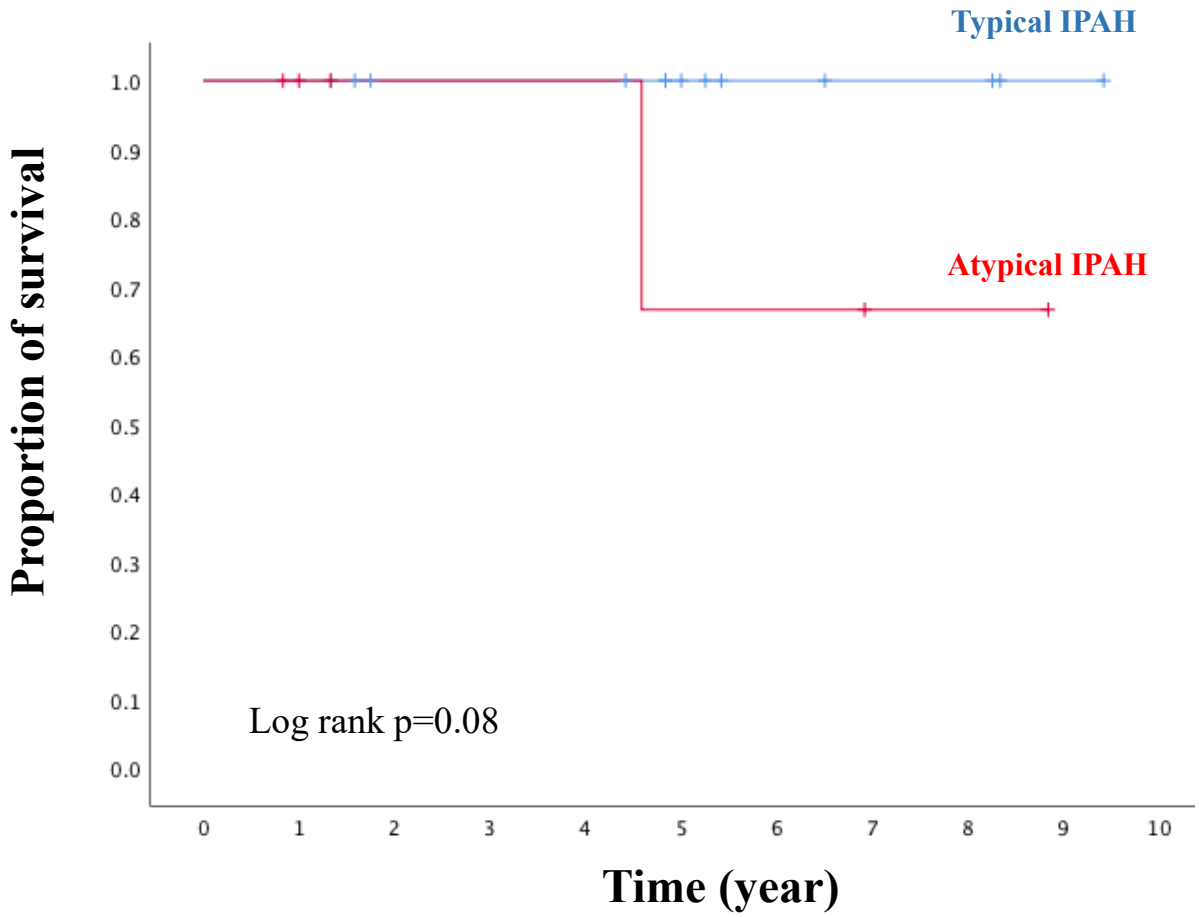
Univariate regression analyses using a Cox's proportional hazards model for each survival

Group	Variables	β	SE	Hazard Ratio (95%CI)	P-value
IPAH/HPAH	Mean PAP	0.277	0.141	1.319 (1.000-1.740)	0.050
CTD-PAH	CI	3.587	1.827	36.111 (1.005-1297.428)	0.050
PH-CLD	Diastolic PAP	0.677	0.337	1.968 (1.016-3.813)	0.045

Abbreviations as in Table 1.

Supplementary fig. 1.

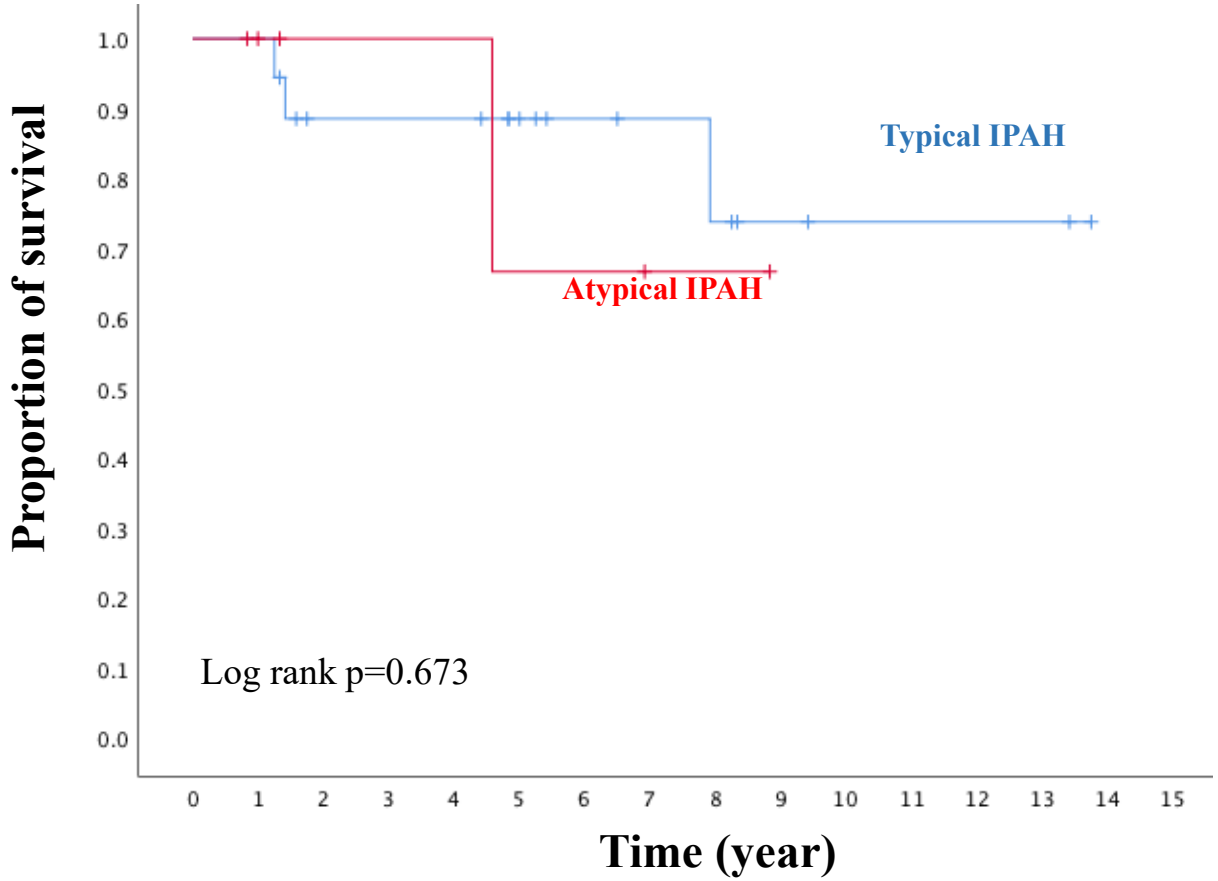
A. Survival for IPAH diagnosed after 2008



Patients at risk

Typical	13	13	10	10	10	6	4	3	3	1
Atypical	6	4	3	3	3	2	2	1	1	

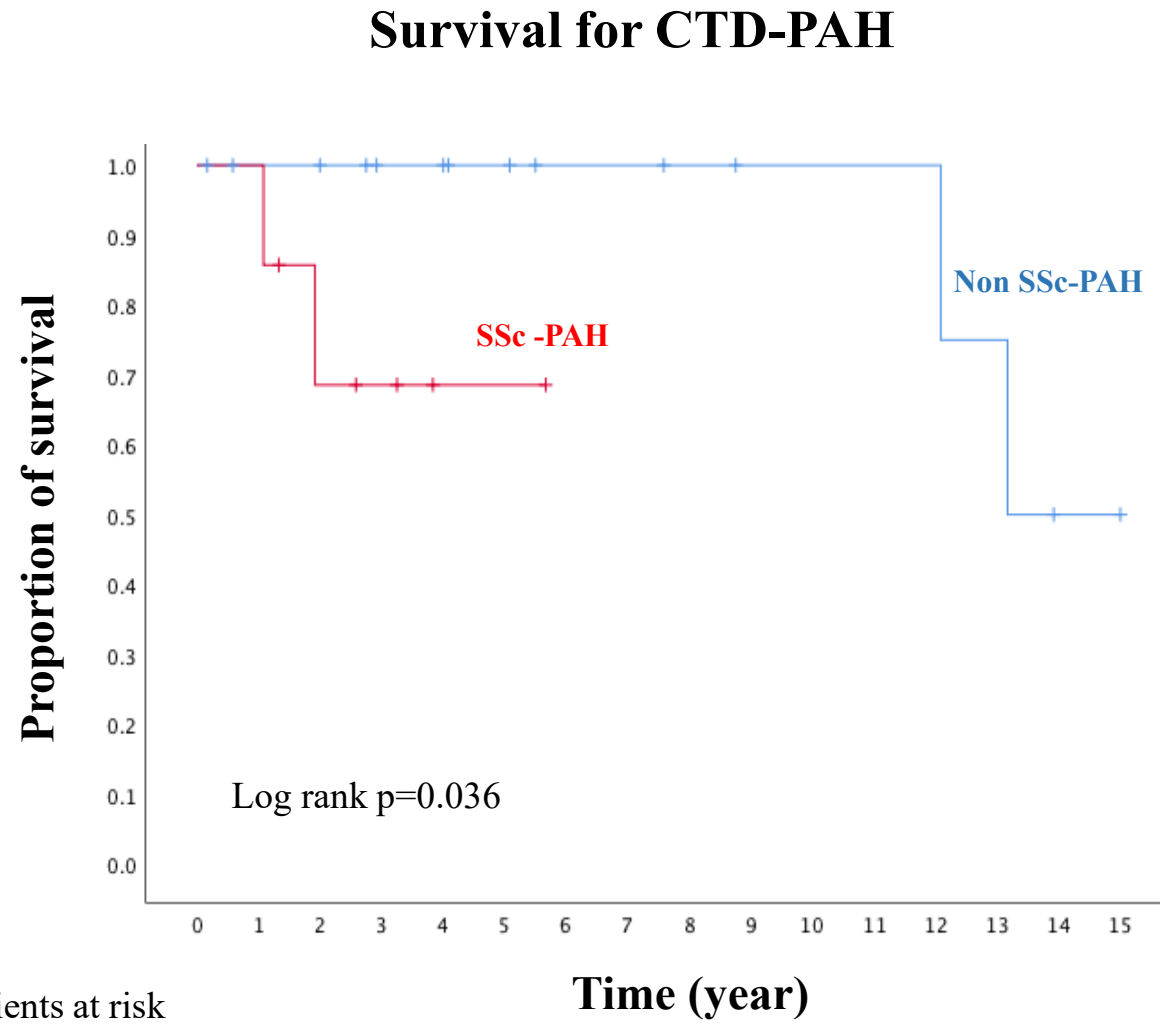
B. Survival for IPAH during all period



Patients at risk

Typical	18	18	13	13	13	9	7	6	5	3	2	2	2	2
Atypical	6	4	3	3	3	2	2	1	1					

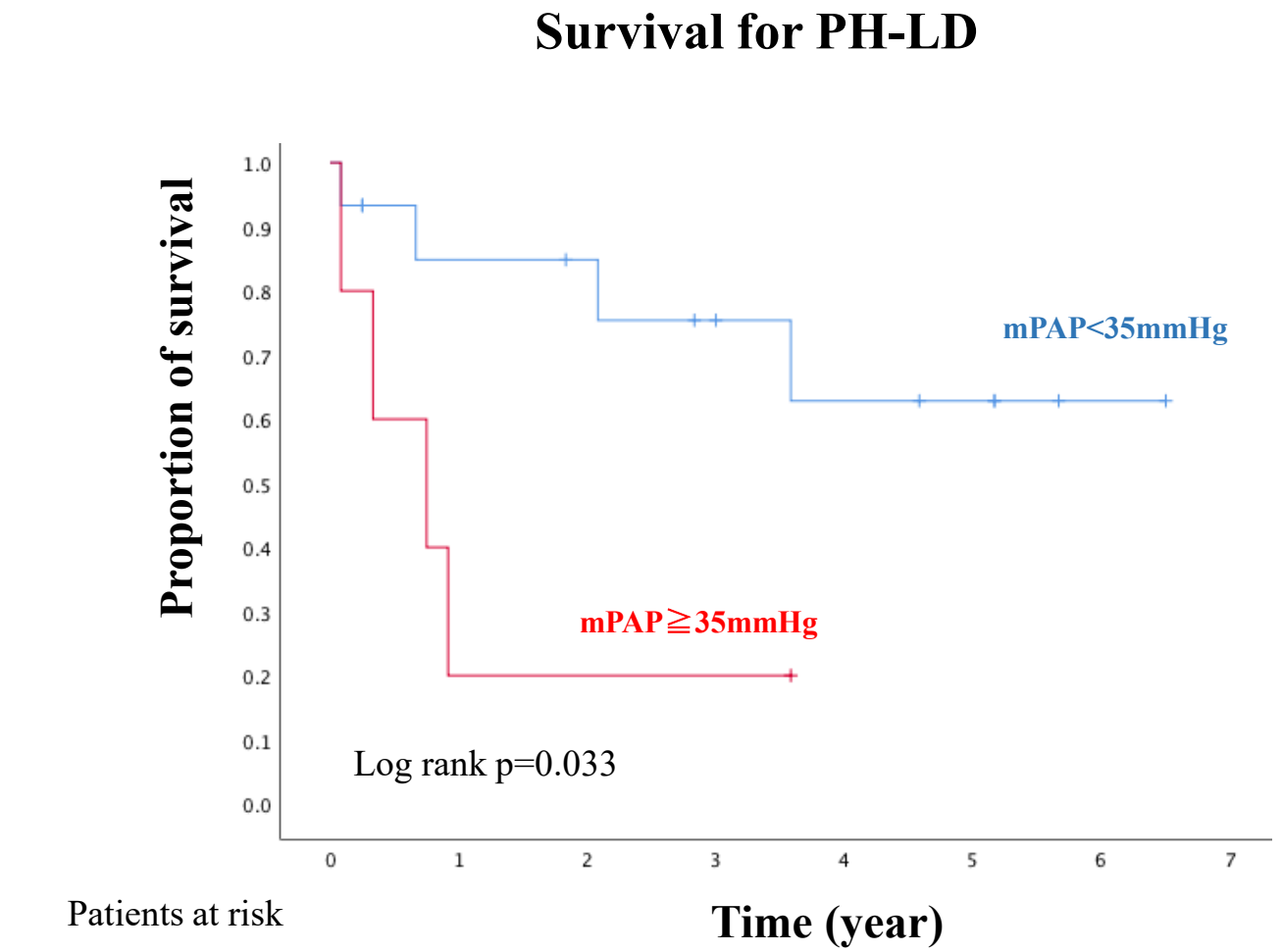
Supplementary fig. 2.



Patients at risk

Non SSc-PAH	15	13	12	10	9	8	6	6	5	4	4	4	4	3	1	0
SSc-PAH	7	7	4	3	1	1										

Supplementary fig. 3.



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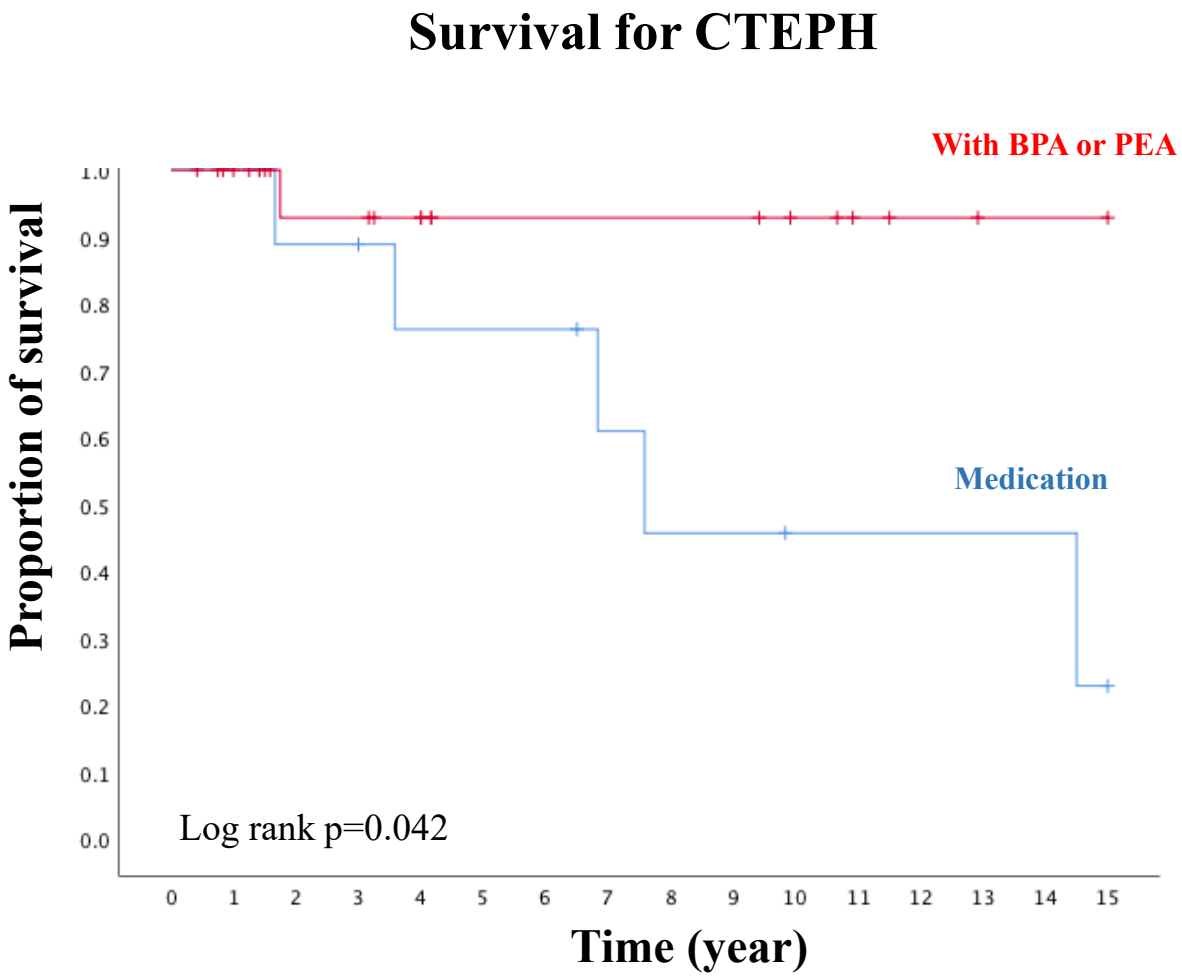

Patients at risk

BPA or PEA	24	18	13	13	10	7	7	7	7	7	5	3	2	1	1	0
Medication	10	10	8	7	6	6	6	4	3	3	2	2	2	2	2	0

Supplementary fig. 5.