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Portopulmonary hypertension in the current era of pulmonary hypertension management

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ABSTRACT

Background & Aims. Long-term outcomes in portopulmonary hypertension (PoPH) are poorly studied in the current management era of pulmonary hypertension. We analysed the effect of pulmonary arterial hypertension (PAH)-targeted therapies, the survival and the predictors of death in a large contemporary cohort of patients with PoPH.

Methods. Data from patients with PoPH consecutively enrolled in the French Pulmonary Hypertension Registry between 2007 and 2017 were collected. Effect of initial treatment strategies on functional class, exercise capacity and cardiopulmonary haemodynamics were analysed. Survival and its association with PAH- and hepatic-related characteristics were also examined.

Results. Six hundred and thirty-seven patients (mean age 55 ± 10 years; 58% male) were included. Fifty seven percent had mild cirrhosis, i.e. Child-Pugh (CP) stage A. The median MELD score was 11 (Q1-Q3; 9-15). Most patients ($n=474$; 74%) were initiated on monotherapy, either with a phosphodiesterase-5 inhibitor ($n=336$) or with an endothelin-receptor antagonist ($n=128$); 95 (15%) were initiated on double oral combination therapy and 5 (1%) on triple therapy. After a median treatment time of 4.5 months, there were significant improvements in functional class ($p<0.001$), 6-minute walk distance (6MWD) ($p<0.0001$) and pulmonary vascular resistance ($p<0.0001$). Overall survival rates were 84%, 69% and 51% at 1, 3 and 5 years, respectively. Baseline 6MWD, sex, age and MELD Score or CP stage were identified as independent prognostic factors. **Survival from PoPH diagnosis** was significantly better in the subgroup of patients who underwent liver transplantation (92%, 83% and 81% at 1, 3 and 5 years, respectively)

Conclusion. Survival of patients with PoPH is strongly associated with the severity of liver disease. Patients who underwent liver transplantation had the best long-term outcomes.

Lay Summary

Portopulmonary hypertension (PoPH) is defined by the presence of pulmonary arterial hypertension (PAH) in a context of chronic liver disease, and is characterized by progressive shortness of breath and exercise limitation. The presence of severe PAH in liver transplant candidates represents a contraindication for such a surgery. PAH-targeted medications are notably efficacious in PoPH allowing liver transplant candidates to undergo safe transplantation. The combination of PAH medications followed by liver transplantation are associated with a good survival in PoPH

INTRODUCTION

Portopulmonary hypertension (PoPH) is the concomitant presence of pulmonary arterial hypertension (PAH) and portal hypertension in patients with or without cirrhosis. PAH can develop in 2 to 6% of patients with portal hypertension and results from complex pathophysiological interactions between the portal and pulmonary circulation (1). Based on the high prevalence of cirrhosis, it is likely that PoPH remains underdiagnosed in many countries (2). In pulmonary hypertension (PH) registries, PoPH patients represent 5 to 15% of PAH patients (3–5). Survival and prognostic factors in PoPH remain controversial and are still poorly studied in the current era of PH management (3–5). Insights from previous PoPH registries are limited by the small number of patients enrolled, the historical nature of the data (ie, not from the current treatment era) and by the lack of information on the severity of the underlying disease (3–5).

The management of patients with PoPH is complex and must be based on a multidisciplinary approach, especially for liver transplant candidates (6). Although evidence supporting the use of PAH-targeted therapies in patients with PoPH is limited, the last joint European Society of Cardiology / European Respiratory Society (ESC/ERS) guidelines state that the algorithm for the management of PAH patients can be cautiously applied to patients with PoPH, taking into account the severity of the liver disease (7,8). The evidence for the use of PAH-targeted therapies in PoPH are scarce and mainly comes from retrospective experiences/analyses in/of small patient/case series. Recently, a dedicated randomized controlled trial demonstrated that, compared to placebo, a 12-week treatment with macitentan, a dual endothelin-receptor antagonist (ERA), significantly lowered pulmonary vascular resistance, without hepatic safety concerns (9). Finally, there is few information on the long-term use of PAH-targeted therapies in patients with PoPH.

With the development of efficacious PAH-targeted medications, the prognosis of patients with PoPH may have changed over the last decades. The current study was designed to evaluate the clinical and hemodynamic effect of PAH-targeted therapies and survival in a large contemporary cohort of patients with PoPH.

PATIENTS AND METHODS

Study population

The study population consisted in incident, treatment-naïve patients with PoPH who were prospectively enrolled in the French PH Network registry between January 2007 and January 2017 (Supplementary CTAT Table). Eligible patients had newly diagnosed precapillary PH associated with portal hypertension with or without cirrhosis, or congenital portosystemic shunts. Precapillary PH was defined as a resting mean pulmonary artery pressure (mPAP) ≥ 25 mmHg with pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units, measured by right heart catheterization (RHC) (7). The diagnosis of portal hypertension was based on hemodynamic measurement of a hepatic venous pressure gradient of more than 5 mmHg, or the combination of suggestive signs, including the presence of splenomegaly, thrombocytopenia and/or oesophageal varices, or clinical signs of portosystemic shunt. Cirrhosis was diagnosed by a documented historical liver biopsy or the presence of typical clinical and/or biological characteristics. Patients with extrahepatic portal hypertension (like portal vein thrombosis) or congenital portosystemic shunts who developed PAH were also classified as PoPH and eligible.

In line with the current guidelines, all patients with PH confirmed by RHC underwent extensive investigation to identify other causes or risk factors. Patients classified as group 2 (secondary to left heart disease), group 3 (due to lung disease or chronic hypoxemia), group 4

(chronic thromboembolic pulmonary hypertension) PH or group 5 (PH with unclear and/or multifactorial mechanisms), or with missing hemodynamic variables at enrollment in the PH registry were excluded from the study.

This study complied with the Declaration of Helsinki. Although French law does not require ethics committee approval or informed consent for retrospective data collection, the data collected were anonymized and complied with the requirements of the '*Commission Nationale Informatique et Libertés*', the organization dedicated to privacy, information technology and civil rights in France. The committee approved the methods used to collect and analyze the data on 24 May 2003 (approval number 842063).

Variables collected

Variables related to liver disease were assessed at time of PoPH diagnosis. Aetiology of portal hypertension was systematically reported. Severity of cirrhosis was assessed by Child-Pugh stage and/or Model for End-Stage Liver Disease (MELD) score which were calculated post-hoc based on the relevant available information. Liver transplant candidates were identified, and the date of transplantation was recorded if performed.

Variables related to PAH were assessed at baseline and at the first follow-up visit within 12 months of diagnosis. Modified New York Heart Association (NYHA) functional class, physical examination, routine blood tests, non-encouraged 6-min walk test and standard cardiopulmonary hemodynamic variables assessed by RHC were recorded.

Evaluation of initial PAH therapy

Patients were categorized according to the type and number of PAH-targeted therapy initiated within 6 months of diagnostic RHC: 1) monotherapy with an ERA, a phosphodiesterase type-5 inhibitor (PDE-5i), or a prostacyclin analogue; 2) double or 3) triple combination therapy.

Effect of the different initial treatment strategies on clinical status, exercise capacity and haemodynamics were analysed at the first follow-up visit within 12 months of diagnosis.

Statistical analysis

Continuous variables were expressed as mean \pm SD for normally distributed variables or median (first and third interquartile) for non-normally distributed variables. Categorical variables were expressed as number of patients and relative frequencies (percent). Differences in continuous variables were compared using the independent Student's t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Changes from baseline to follow-up were assessed using a paired Student's t test, Wilcoxon signed-rank test, or Chi-square test as appropriate. All comparisons were two sided with a p-value <0.05 considered significant.

Overall survival time was defined from the date of diagnostic RHC to death. Surviving patients were censored at the date of last clinical contact. Patients who underwent liver transplantation (LT) were not censored. The Kaplan-Meier method was used to estimate the proportion of patients surviving at each time point up to 5 years post-diagnosis. Survival curves were compared with log-rank test. Univariable analysis based on the Cox proportional hazards model was used to examine the relationship between survival and selected demographic, medical history and baseline variables. Multivariable analyses based on the Cox proportional hazards regression model were used to examine the independent effect of each variable on survival, controlling for possible confounding variables. Variables with a p-value ≤ 0.1 in the univariable analysis were eligible for entry into the multivariable models only if they were not highly correlated (absolute value of Pearson's or Spearman's $\rho < 0.6$) with other continuous variables and if $<25\%$ of individuals had missing values for that variable.

RESULTS

Study population

Patient disposition is shown in **Figure 1**. During the 10-year inclusion period, 4225 incident patients with PAH were enrolled in the French PH network registry. Of these, 742 patients had a diagnosis of portal hypertension (17.6%). After exclusion of patients with missing data or incompatible hemodynamic variables, study population comprised 637 patients with PoPH. Demographic and hepatic-related characteristics at PoPH diagnosis are shown in **Table 1**. The mean (\pm SD) age was 55 ± 10 years and the proportion of male was 58%. The majority of patients had alcohol cirrhosis. The proportion of patients with cirrhosis Child-Pugh stage B or C was 43% and that of patients with a MELD score ≥ 15 was 30%. PAH-related characteristics are shown in **Table 1**. The median (Q1, Q3) baseline 6-minute walk distance (6MWD) was 355 m (252, 425), and 63.4% of patients presented in NYHA functional class III or IV.

Effect of initial treatment strategies

Initial treatment strategy is shown in **Figure 1**. Ninety percent of patients received PAH-targeted therapy within 6 months of PoPH diagnosis. The proportion of patients in Child-Pugh class C who were not treated was 16% (9/57) versus 9% in the group of patients in Child-Pugh class A (30/333) and Child-Pugh class B (17/197) ($p=0.23$). The most frequently used strategy was initial oral monotherapy (74.4 %), with a PDE-5i (sildenafil, $n=239$; tadalafil, $n=97$) or an ERA (bosentan, $n=90$; ambrisentan, $n=36$; macitentan, $n=2$). Double combination was initiated in 95 patients (bosentan and sildenafil, $n=31$; bosentan and tadalafil, $n=15$; ambrisentan and sildenafil, $n=17$; ambrisentan and tadalafil, $n=24$; macitentan and tadalafil, $n=2$). Upfront triple combination therapy was used for only 5 patients (0.8 %). Comparison of patient characteristics who received initial oral monotherapy with an ERA, initial oral

monotherapy with a PDE-5i and double combination with an ERA and a PDE-5i is shown in **Table S1**.

Repeated clinical assessment was performed after a median (Q1, Q3) period of 4.5 (3.2, 7.4) months in 504 out of the 574 patients initiated on PAH-targeted therapy. RHC at the time of first follow-up was performed for 453 patients. Seventy patients were not reassessed within one year from diagnosis due to death (n=40) or loss to follow-up (n=30).

At the time of first follow-up, 264 out of 504 patients (52%) improved symptoms by at least one functional class. The median change (Q1, Q3) in 6MWD from baseline to first assessment was +40 meters (-9, +101). A significant effect of treatment on all hemodynamic variables was observed as well as a significant increase in the proportion of patients with normal level of brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) (**Table 2**).

Changes in PVR, mPAP, cardiac output (CO) and 6MWD observed with an ERA, a PDE-5i or the combination of both are illustrated in **Figure 2**. Changes in PVR and 6MWD at first follow-up were similar in patients treated with an ERA and those treated with a PDE-5i.

Despite a higher mean baseline PVR, patients treated with double oral combination had a significantly greater median change in PVR than patients initiated on monotherapy with either ERA (-64% vs -40%, $p < 0.0001$) or a PDE-5i (-64% vs -37%, $p < 0.0001$).

The effect of ERA or PDE-5i on PVR was consistent across different subgroups including age, gender, aetiology of cirrhosis, MELD score, Child-Pugh class, functional class, 6MWD and associated HIV infection (**Figure S1**).

Survival and prognostic factors

Over a median (Q1, Q3) follow-up period of 35 (15, 63) months, 136 (21%) patients needed treatment escalation with PAH-targeted medications. Three hundred and two patients (47%)

died during the observation period. Overall survival rates were 84%, 69% and 51% at 1, 3 and 5 years, respectively (**Figure 3A**). The median survival time was 60.9 months.

The univariable Cox regression analysis for the association of baseline characteristics and overall survival is shown in **Table 3**. In multivariable models, age, sex, 6MWD and MELD score (model A) or Child-Pugh stage (model B) were independently associated with survival. (**Table 3**). Overall survival according to the severity of the underlying liver disease is shown in **Figures 3B, 3C and 3D**.

Causes of death were recorded in 184/302 cases (61%) and reported in **Table S2**. The main causes of death differed according to the severity of the underlying disease. Patients with mild cirrhosis mainly died from PAH or cancers (hepatocarcinoma and extrahepatic cancers), while patients with more severe cirrhosis mainly died from liver disease.

Survival of liver transplantation recipients

PoPH was diagnosed during a pretransplant assessment in 117 patients. Of these, 63 (54%) underwent LT during the follow-up period. Most of them (n=60, 95%) received PAH-targeted therapy (46 on monotherapy, 12 on double combination and 2 on triple combination therapy) as a bridge to LT. **At the time of LT, 15 patients (24%) received intravenous epoprostenol that was initiated as first line therapy in 6 of them and as add-on therapy in the 9 remaining.**

Baseline characteristics of transplanted patients were compared to those of patients who had no indication for LT and those who had an indication for transplantation but who have not been transplanted (**Table S3**).

Overall survival of patients who underwent LT was 92%, 83% and 81% at 1, 3 and 5 years from PoPH diagnosis, respectively. In comparison, patients who had an indication for transplantation at time of PoPH diagnosis but did not undergo transplantation had a 1-, 3- and 5-year survival rate of 65%, 39% and 20%. Interestingly, survival from PoPH diagnosis was

also better in transplanted patients when compared to than that of patients who had no indication for transplantation (92%, 83%, 81% vs 85%, 70%, 50% survival at 1 or 3 or 5 years, respectively, $p < 0.0001$) (**Figure 4A**). Moreover, survival from PoPH diagnosis was better in all patients who underwent LT irrespective of Child-Pugh stage or MELD score when compared to patients who were not transplanted (**Figure 5**). Survival from LT was 88%, 85% and 78% at 1 or 3 or 5 years, respectively (**Figure 4B**). Twelve patients have died after LT including six deaths related to pulmonary arterial hypertension, all occurring within the first month following LT. Among survivors, PAH therapy was simplified from combination to monotherapy in 10 patients (16%), and discontinued in 14 (22%). Intravenous epoprostenol was weaned off after 1 to 23 months post-LT in the 12 survivors who received this treatment at the time of LT

.

DISCUSSION

This study describes the largest cohort of patients with PoPH to date. It provides a contemporary overview of long-term outcomes in patients with PoPH and identifies the main prognostic factors in the era of modern PAH management. In our study, the vast majority of patients received monotherapy with a PDE-5i or an ERA, both leading to similar clinical and hemodynamic improvement. Importantly, and as in other forms of PAH, double oral combination of these drugs led to a greater decrease in PVR than monotherapy. Survival was highly associated with the severity of the underlying liver disease. Other identified prognostic factors were age, gender and baseline 6MWD. The survival of patients who underwent LT was better than that of non-transplanted PoPH patients.

The proportion of PoPH patients in the French PH registry has progressively increased over the last decade, resulting in PoPH being today the third aetiology of incident PAH cases in the French PH registry. This is contrast with other registries and may be explained by the extensive collaboration between hepatologists and PAH expert centers in France, which is critical to improving detection and management of this condition (4,10–12). The differences in PoPH prevalence observed between countries may also be due to variability in health systems, screening approaches as well as in the prevalence of cirrhosis (1).

Despite the absence of PoPH patients in the main randomized controlled trials for PAH therapies, about 90% of our patients received PAH-targeted therapy according to current ERS/ESC guidelines (7). The vast majority of our patients was initiated on monotherapy. This is in line with the recent recommendations from the 6th World Symposium on PH which underline a residual role for monotherapy in subsets of patients, including those with PoPH (13). Most of these patients received initial therapy with a PDE-5i; this choice may have been

driven by the absence of hepatotoxicity with this class of drug. In our study, a significant proportion (35%) of patients also received an ERA either as monotherapy or in combination with a PDE-5i or a prostacyclin analogue. We previously observed that the safety profile of bosentan in patients with PoPH and cirrhosis Child-Pugh stage A or B was generally consistent with that observed in PAH patients without cirrhosis (14). Interestingly, the effect of monotherapy with a PDE-5i on clinical parameters and cardiopulmonary hemodynamic was similar to that of monotherapy with an ERA. Recently, the first randomized placebo-controlled trial dedicated to patients with PoPH (PORTICO) demonstrated that a 12-week treatment with macitentan led to a significant 35% decrease in PVR, with no hepatic safety concerns (9). As macitentan is not currently available in France, our cohort included a very small number of patients treated with macitentan (ie, patients enrolled in the PORTICO study). Nevertheless, in our study, monotherapy with an ERA led to a change in PVR that was similar to that observed in PORTICO.

Our data also support the use of initial combination therapy in selected PoPH patients. This treatment strategy was mainly used in patients with high PVR. With a mean decrease in PVR of about 60%, double combination therapy led to a better hemodynamic improvement than monotherapies, as observed in other forms of PAH (15). Overall, specific considerations, including hemodynamic profile and severity of the cirrhosis, must be taken into account in the management of PoPH patients. Fluid retention and/or worsening of portal hypertension induced by vasodilatation in the splanchnic circulation may occur with vasodilators (16–18). In addition, combination therapies must be used with caution to avoid high cardiac output, as the long-term effect of this condition on the pulmonary circulation and heart function is unknown.

Use of PAH-targeted therapies was also associated with a significant improvement in exercise capacity and functional class, irrespective of initial treatment strategy. In contrast, the

PORTICO trial with macitentan did not show significant effect on functional class and walk distance (9). However, it should be noted that PORTICO enrolled a relatively small number of patients who were predominantly prevalent, with most patients receiving background therapy with a PDE-5i.

Previous studies based on PoPH registries reported different survival rates, with 5-year survival rates ranging from 35% to 68% (3–5). More than 10 years ago, *Le Pavec et al.* showed, in a French series of 154 PoPH patients, that survival depended on the severity of both the pulmonary hypertension and the underlying liver disease (3). In contrast, in the UK PH registry, no clear prognostic factors were identified in 110 PoPH patients with hemodynamic and liver disease severity comparable to that of the French PoPH cohort described by Le Pavec et al. (5). Finally, data from the US REVEAL registry showed a worse survival for 174 PoPH patients as compared to patients with idiopathic PAH (4). It is important to note that the lack of information on the severity of the underlying liver disease in the REVEAL registry limits the interpretation of these results. In addition, the large periods of inclusion and the frequent missing information on the severity of the underlying liver disease may explain this broad range of survival rates. In our study, the 5-year survival was 51% and one of the main prognostic factors was the severity of the underlying liver disease. The large number of patients included in our study and the extent of the information available on the severity of the underlying liver disease allowed a robust analysis of prognostic factors in the era of modern PAH management. Interestingly, hemodynamic variables assessed at PoPH diagnosis were not independently associated with the risk of death. This could be due to a more aggressive therapeutic approach in patients with more severe haemodynamics at baseline.

The weight of liver disease severity on prognosis underlines the need for a multidisciplinary approach in the management of PoPH patients, including PAH experts and hepatologists. In our study, the main causes of death were complications of liver disease, in particular in patients with advanced cirrhosis. In contrast, the main causes of death in patients with mild cirrhosis were pulmonary hypertension and extrahepatic cancers.

Before the availability of PAH specific therapies, LT was usually contraindicated in most patients with PoPH because the hemodynamic severity was associated with an unacceptable risk of postoperative right heart failure (19). The International Liver Transplant Society Practice Guidelines recently underlined that “unlike hepatopulmonary syndrome, there are no data to support the concept that PoPH treated or not treated should be an indication for LT” (6). In the era of modern PAH therapies, we observed that survival of PoPH patients who underwent LT was better than non-transplanted patients, including those with mild cirrhosis. This observation likely results from a more aggressive management of the PoPH with PAH-targeted therapies as a bridge to LT to improve cardiopulmonary haemodynamics and reduce the risk of perioperative right heart failure. **It is interesting to underline that only 24% of transplanted patients were using intravenous epoprostenol as a bridge to LT. In the era of current PAH management, haemodynamic criteria allowing a safe transplantation can be reached with oral therapies in the majority of LT candidates. Moreover, the possibility to obtain a priority access to LT using an expert component (“MELD exception”) in this specific indication likely contributed to reduce the mortality on waiting list and to improve the overall survival from PoPH diagnosis of the subgroup of patients who were candidates for LT.** In addition, several studies have shown that stabilization, improvement or normalization of cardiopulmonary haemodynamics after LT is an attainable goal (20–23). The survival benefit

of LT in PoPH patients raises the question of whether LT should be considered in selected PoPH patients who do not have a liver transplant indication because of mild liver disease.

The main limitations of our study were its retrospective nature and the absence of collection of adverse events, such as hospitalization for PAH worsening, a major prognostic factor in PAH (24), and side effects related to therapies which are important to consider for the management of PoPH patients. We also want to underline that initial treatment strategy may explain the lack of independent association between baseline hemodynamics and outcomes, given that disease severity has likely influenced treatment decisions. Similar findings have been observed in idiopathic PAH or PAH associated with scleroderma (25–27). Finally, the better survival of transplanted patients may be driven by the selection of patients without severe comorbidities. Moreover, due to a systematic screening for PAH in liver transplant candidates, patients who were transplanted had less severe pulmonary hypertension at the time of PoPH diagnosis (**Table S3**).

In conclusion, our study confirms that PoPH is a devastating complication of portal hypertension, irrespective of the aetiology or the severity of the underlying liver disease. Our contemporary data from the largest cohort of PoPH patients to date confirm the effectiveness of PAH-targeted therapies on clinical, functional and hemodynamic variables without class effect. Prognostic factors are strongly related to the severity of cirrhosis. This underscores the need for a multidisciplinary approach including hepatologists and PAH experts for the management of PoPH patients. Finally, combination of PAH-targeted therapy and LT led to excellent long-term outcomes in selected PoPH patients.

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The authors acknowledge Laurence Rottat for her help in obtaining the data for this study and her hard work in managing data in the French PH Registry. They also thank all participants to the French PH Network and liver transplant centers : Fabrice Bauer (Rouen), Laurent Bertoletti (Saint Etienne), Philippe Bonniaud (Dijon), Philippe Brosset (Limoges), Arnaud Bourdin (Montpellier), Yvon Calmus (CHU La Pitié salpêtrière), Matthieu Canuet (Strasbourg), Claire Dauphin (Clermont-Ferrand), Claire Dromer (Bordeaux), Christophe Duvoux (CHU Henri Mondor), Odile Gorla (Rouen), Gilbert Habib (Marseille, La Timone), Pauline Houssel-Debry (Rennes), Etienne-Marie Jutant (Kremlin Bicêtre), Sylvie Leroy (Nice), Pierre Mauran (Reims), Jean-François Mornex (Lyon), Patrice Poubeau (La Réunion), François Picard (Bordeaux), Christophe Pison (Grenoble), Martine Reynaud-Gaubert (Marseille, Nord), Florence Parent (Kremlin Bicêtre), Pascal Roblot (Poitiers), Andrei Seferian (Kremlin Bicêtre)

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Table 1. Baseline characteristics

Variables	
Age, years	55±10
Male sex, n (%)	372 (58)
Body Mass Index, kg.m ⁻² (n=617)	27.2±6
Etiology of portal hypertension, n (%) (n=637)	
Cirrhosis	622 (97.6)
Alcohol	370 (58.1)
Viral hepatitis	83 (13)
Mixed viral and alcohol	100 (15.7)
Autoimmune	21 (3.3)
Dysmetabolic	22 (3.5)
Cryptogenic	15 (2.3)
Others	11 (1.7)
Extrahepatic portal hypertension	10 (1.6)
Congenital portosystemic shunt	5 (0.8)
Severity of cirrhosis	
Child-Pugh stage, n (%) (n=577)	
Stage A	328 (56.8)
Stage B	192 (33.3)
Stage C	57 (9.9)
MELD score (n=495)	
Median (Q1, Q3)	11 (9, 15)
MELD score ≥ 15, n (%)	148 (30)
Hepatocarcinoma, n (%)	76 (11.9)
HIV infection, n (%)	49 (7.7)
Indication for liver transplantation, n (%)	94 (14.7)
NYHA functional class, n (%) (n=636)	
I	34 (5.3)
II	199 (31.2)
III	342 (53.8)
IV	61 (9.6)
6-min walk distance, m (n=509)	355 (252, 425)
BNP <50 ng.L ⁻¹ or NT-proBNP <300 ng.L ⁻¹ , n (%) (n=498)	112 (22.5)
Hemodynamics variables	
Right atrial pressure, mmHg (n=610)	7 (5-11)
Mean pulmonary artery pressure, mmHg	47±11
Pulmonary artery wedge pressure, mmHg	9±3
Cardiac output, L.min ⁻¹	5.3±1.6
Cardiac index, L.min ⁻¹ per m ² (n=624)	2.8±0.8
Mixed venous oxygen saturation, % (n=332)	64±9
Pulmonary vascular resistance, Wood Units	7 (5.2-10)

Variables are expressed as median (interquartile range) or mean±SD as appropriate. Number of patients is 637 unless otherwise stated. *Abbreviations:* BNP, Brain Natriuretic Peptide; HIV, human immunodeficiency virus; MELD, model for end-stage liver disease; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-Brain Natriuretic Peptide.

Table 2. Change in clinical and hemodynamic variables at first follow-up visit in patients initiated with PAH-targeted therapy

	n	Baseline visit	First follow-up visit	P-value
NYHA functional class, n (%)	504			
I		24 (5)	73 (14)	<0.0001
II		154 (31)	313 (63)	
III		280 (55)	106 (21)	
IV		46 (9)	12 (2)	
6-minute walk distance, m	349	360 (270-430)	403 (329-462)	<0.0001
BNP <50 ng.L⁻¹ or NT-proBNP <300 ng.L⁻¹, n (%)	317	72 (23)	143 (45)	<0.0001
Hemodynamic variables	453			
Right atrial pressure, <i>mmHg</i>		7 (5-11)	6 (4-9)	<0.0001
Mean pulmonary artery pressure, <i>mmHg</i>		48±11	39±11	<0.0001
Pulmonary artery wedge pressure, <i>mmHg</i>		9±3	10±4	<0.0001
Cardiac output, <i>L.min⁻¹</i>		5.3±1.7	6.9±2.1	<0.0001
Cardiac index, <i>L.min⁻¹ per m²</i>		2.8±0.8	3.7±1	<0.0001
Pulmonary vascular resistance, <i>Wood Units</i>		7.1 (5.3-10.2)	4.1 (2.8-5.7)	<0.0001
Mixed venous oxygen saturation, %		64±9	71±7	<0.0001

Variables are expressed as mean ± SD or median (interquartile range) as appropriate. Comparisons made using a paired Student's t test, Wilcoxon signed-rank test, or Chi-square test as appropriate.

Abbreviations: BNP, Brain Natriuretic Peptide; NT-proBNP; N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAH, Pulmonary arterial hypertension.

Table 3. Univariate and multivariate analyses of baseline variables for overall survival

	Univariate analysis		Multivariate analysis (model A)		Multivariate analysis (model B)	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age (year)	1.022 (1.011-1.034)	0.0001	1.022 (1.002-1.041)	0.0302	1.022 (1.004-1.04)	0.0158
Female sex	0.801 (0.635-1.009)	0.0599	0.493 (0.332-0.733)	0.0005	0.616 (0.436-0.871)	0.0061
Body Mass Index (kg.m ⁻²)	0.995 (0.975-1.015)	0.6219				
NYHA-FC III-IV vs I-II	1.342 (1.055-1.716)	0.0168	1.164 (0.781-1.736)	0.4555	1.368 (0.958-1.955)	0.8480
6-minute walk distance (m)	0.998 (0.997-0.998)	<0.0001	0.997 (0.996-0.999)	0.0002	0.998 (0.997-0.999)	0.0007
Right atrial pressure (mmHg)	1.024 (1.007-1.042)	0.0063	1.005 (0.978-1.033)	0.7267	1.001 (0.977-1.026)	0.9233
mPAP (mmHg)	0.996 (0.986-1.006)	0.4097				
PAWP (mmHg)	0.988 (0.953-1.024)	0.5030				
Cardiac output (L.min ⁻¹)	1.004 (0.936-1.078)	0.9047				
Cardiac index (L.min ⁻¹ per m ²)	1.048 (0.911-1.205)	0.5150				
PVR (Wood unit)	0.990 (0.965-1.016)	0.4554				
SvO ₂ (%)	0.994 (0.977-1.011)	0.4589				
BNP <50 or NT-proBNP <300 ng/L	0.712 (0.512-0.99)	0.0433	0.956 (0.606-1.508)	0.8480	0.948 (0.630-1.426)	0.7975
Creatinine (µg/L)	1.003 (1.001-1.006)	0.0068				
Total bilirubin (µg/L)	1.006 (1.004-1.008)	<0.0001				
Extrahepatic PoH or congenital portosystemic shunt	0.351 (0.113-1.096)	0.0716				
MELD score (per unit)	1.081 (1.056-1.106)	<0.0001	1.062 (1.026-1.098)	0.0005		
Child-Pugh stage B/C vs A	2.451 (1.930-3.112)	<0.0001			1.924 (1.385-2.672)	<0.0001
Hepatocarcinoma, yes	1.429 (1.022-1.996)	0.0368	0.956 (0.568-1.608)	0.8640	0.965 (0.597-1.559)	0.8847
HIV infection	1.019 (0.654-1.589)	0.9330				
Initiation of PAH-targeted therapy, no	1.517 (1.083-2.126)	0.0153	1.503 (0.76-2.973)	0.2412	1.65 (0.965-2.823)	0.0674

Abbreviations: BNP: Brain Natriuretic Peptide; 95%CI: 95% confidence interval; HIV: Human immunodeficiency virus; HR: Hazard Ratio; MELD: Model for end-stage liver disease; mPAP: Mean pulmonary artery pressure; NT-proBNP: N-terminal proBNP; NYHA-FC: New York Heart Association Functional Class; PAWP: pulmonary artery wedge pressure; PoH: portal hypertension; PVR: pulmonary vascular resistance; SvO₂: Mixed venous oxygen saturation.

Figure Legends

Figure 1. Patient disposition

Abbreviations: ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PDE-5i, phosphodiesterase type-5 inhibitor; IV PCA, intravenous prostacyclin; PH, pulmonary hypertension; PoPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; RHC: right heart catheterization; WU, Wood unit.

Figure 2. Short-term effect of initial treatment strategy on cardiopulmonary haemodynamics and 6-minute walk distance

Changes from baseline (T0) to first follow-up (T1) were analysed using the paired Student's t-test or Wilcoxon signed-rank test, as appropriate: *** $p < 0.001$; **** $p < 0.0001$

Baseline values were compared using the unpaired Student's t-test or Mann-Whitney U test as appropriate: NS, non-significant; † $p < 0.05$; †† $p < 0.01$; ††† $p < 0.001$; †††† $p < 0.0001$

Changes in hemodynamic variables and 6-min walk distance were compared using the Mann-Whitney test: no significant difference between ERA and PDE-5i in monotherapy; significant differences between combination therapy and monotherapy (ERA or PDE-5i) (‡‡ $p < 0.01$, ‡‡‡‡ $p < 0.0001$).

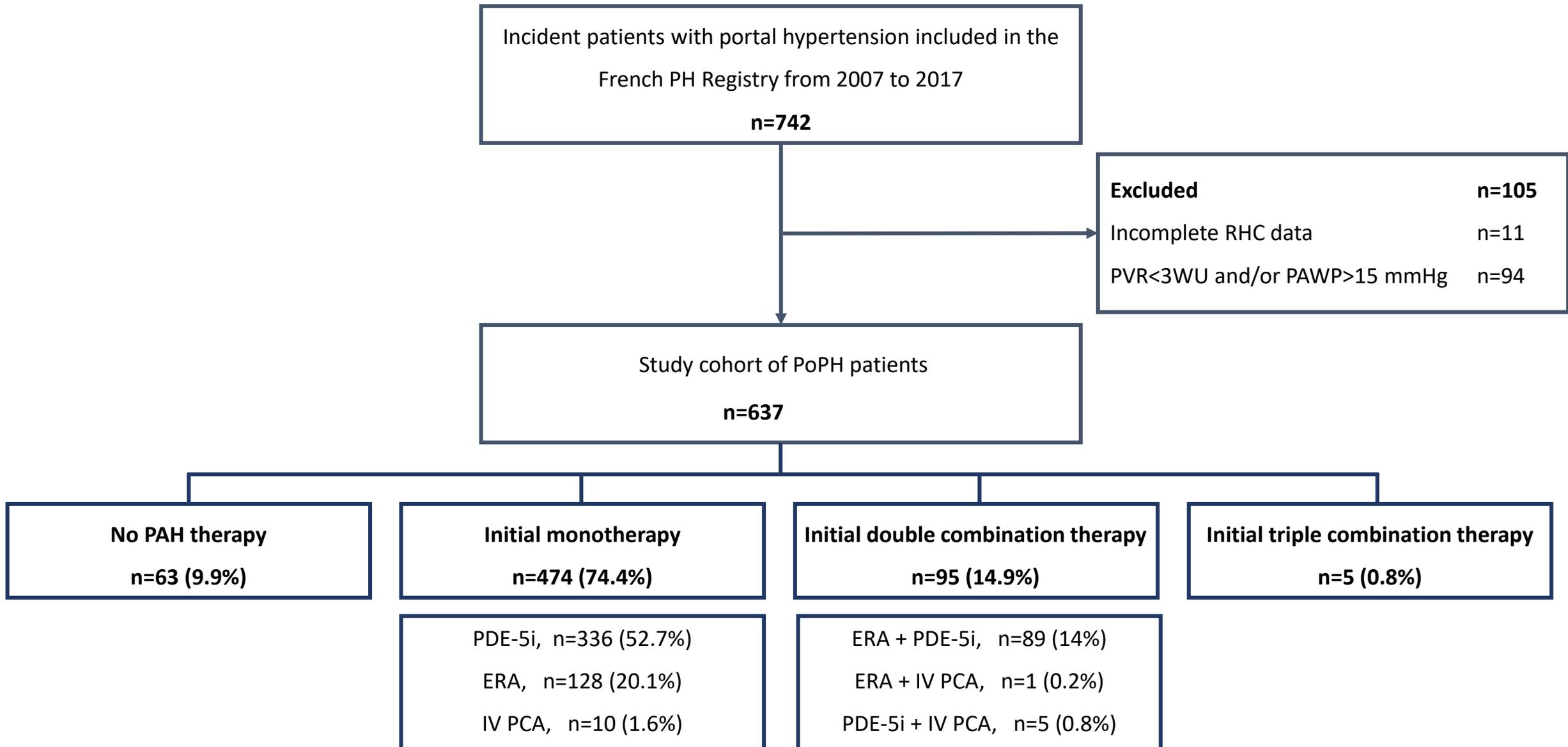
Abbreviations: 6MWD, 6-minute walk distance; CO, cardiac output; ERA, endothelin receptor antagonist; mPAP, mean pulmonary arterial pressure; PDE-5i, phosphodiesterase type-5 inhibitor; PVR, pulmonary vascular resistance

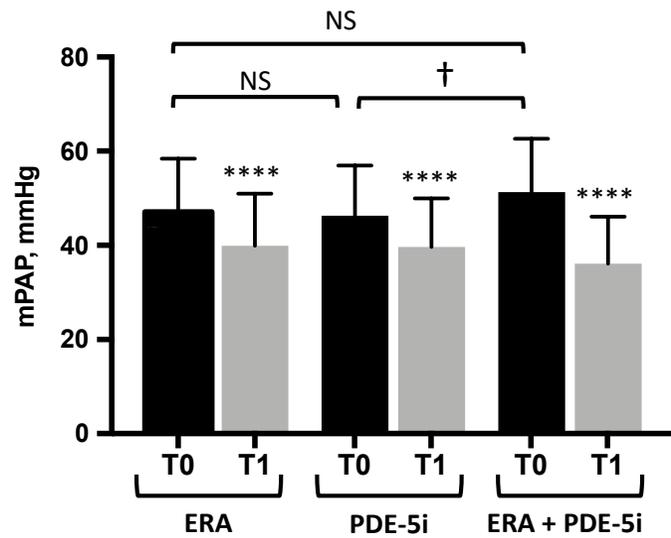
Figure 3. Outcomes of PoPH cohort. (A) Overall survival of the PoPH cohort; (B) Survival of patients with cirrhosis and of those with extrahepatic portal hypertension or congenital portosystemic shunt; (C) Survival according to Child-Pugh stage at the time of PoPH diagnosis; (D) Survival according to MELD score at the time of PoPH diagnosis.

Abbreviations: CP, Child-Pugh; CPS, congenital portosystemic shunt; MELD, Model for End-Stage Liver Disease; PoH, portal hypertension

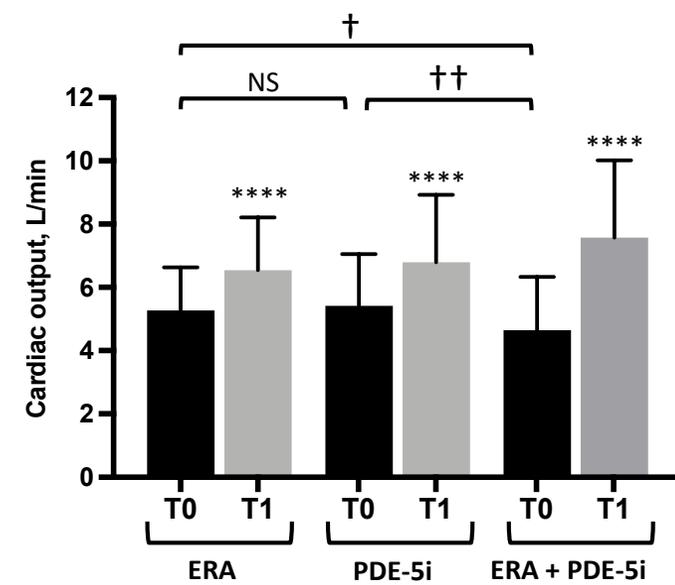
Figure 4. Outcomes of liver transplant candidates (A) Survival of PoPH patients by liver transplant status, (B) Survival of PoPH patients from liver transplantation

Figure 5. Survival of transplanted and non-transplanted patients according to Child-Pugh stage and MELD score

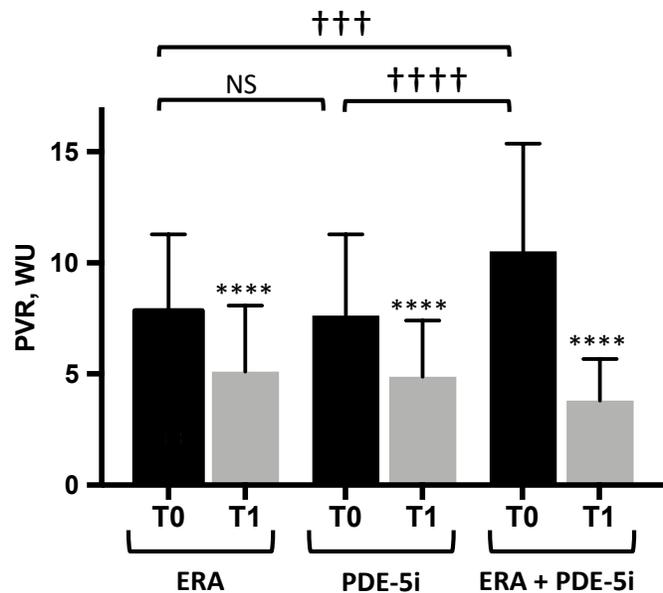




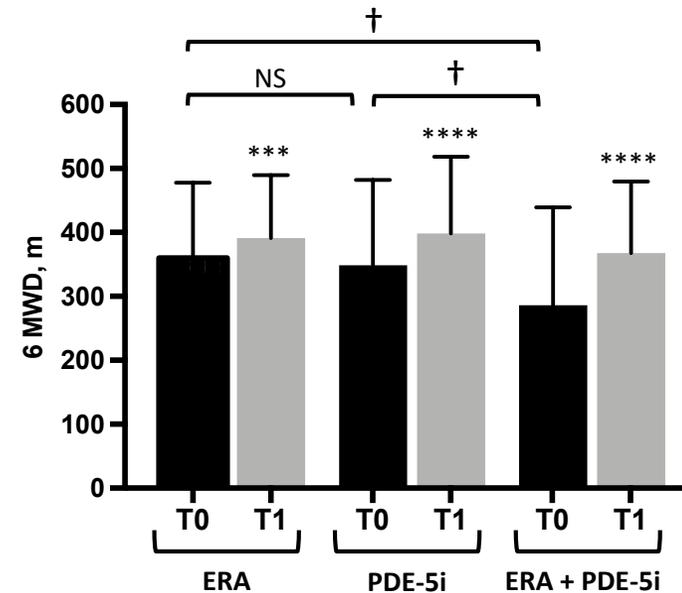
Median change in mPAP (Q1, Q3)	-7 mmHg (-2, -11)	-7 mmHg (-1, -12)	-15 mmHg (-6, -23) ^{****}
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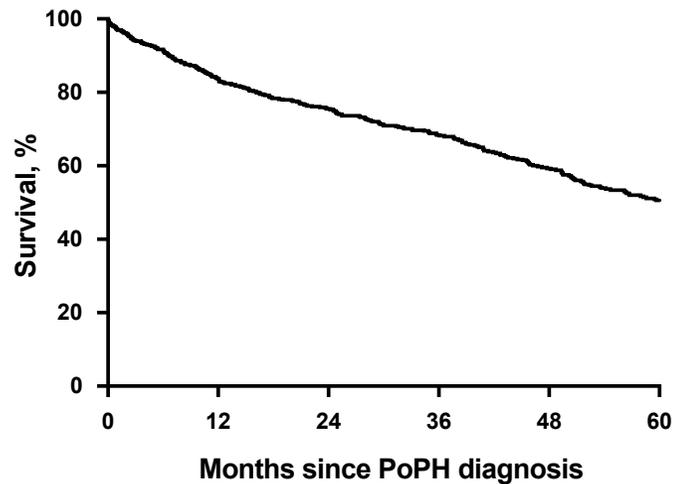
Median change in CO (Q1, Q3)	+1.2 L.min ⁻¹ (+0.4, +1.8)	+1.2 L.min ⁻¹ (+0.3, +2.2)	+2.8 L.min ⁻¹ (+1.6, +3.9) ^{****}
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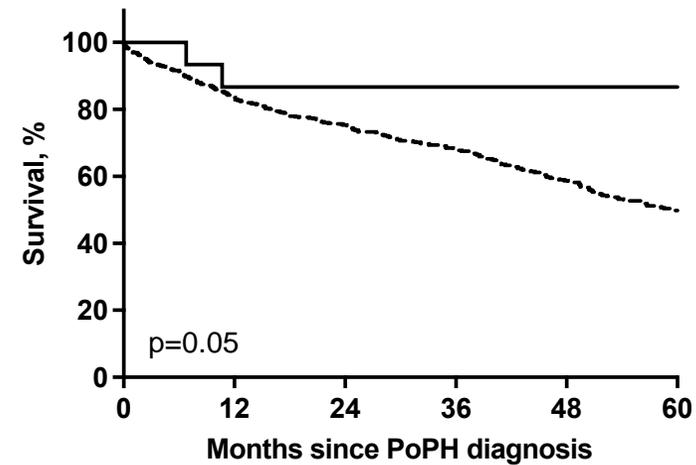
Median change in PVR (Q1, Q3)	-2.6 WU (-1.2, -3.9)	-2.2 WU (-1.1, -3.9)	-5.8 WU (-3.6, -8.3) ^{****}
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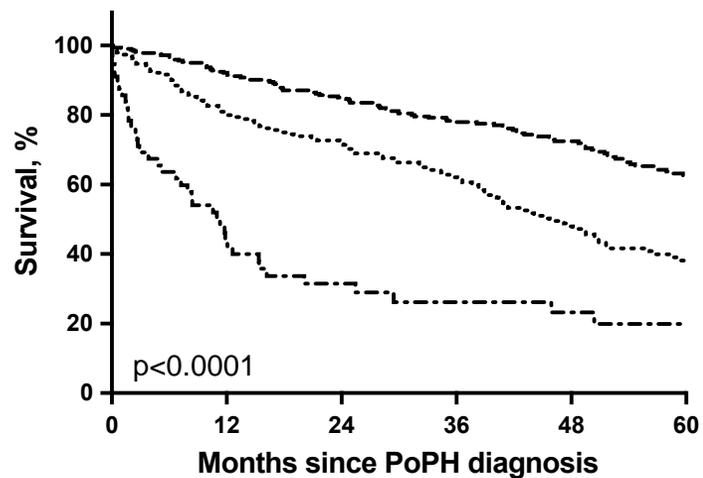
Median change in 6MWD (Q1, Q3)	+31 m (-7.5, +100)	+47 m (-7, +110)	+93 m (+26, +181) ^{††}
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A

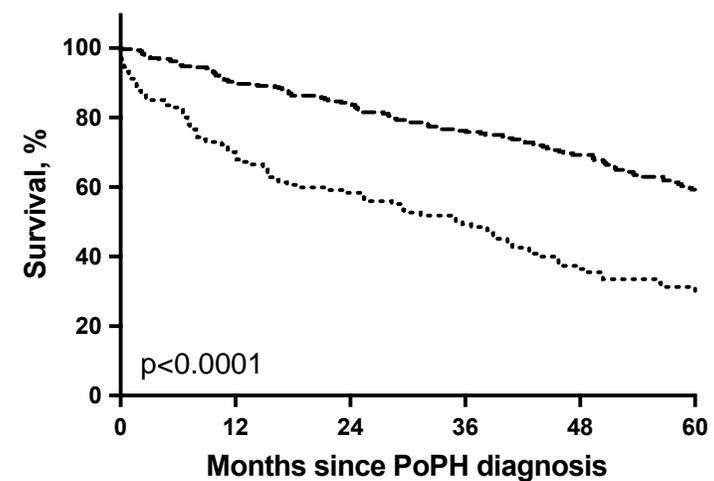
<i>Patients at risk</i>	637	501	396	309	240	174
<i>Overall survival</i>		84%	76%	69%	60%	51%

B

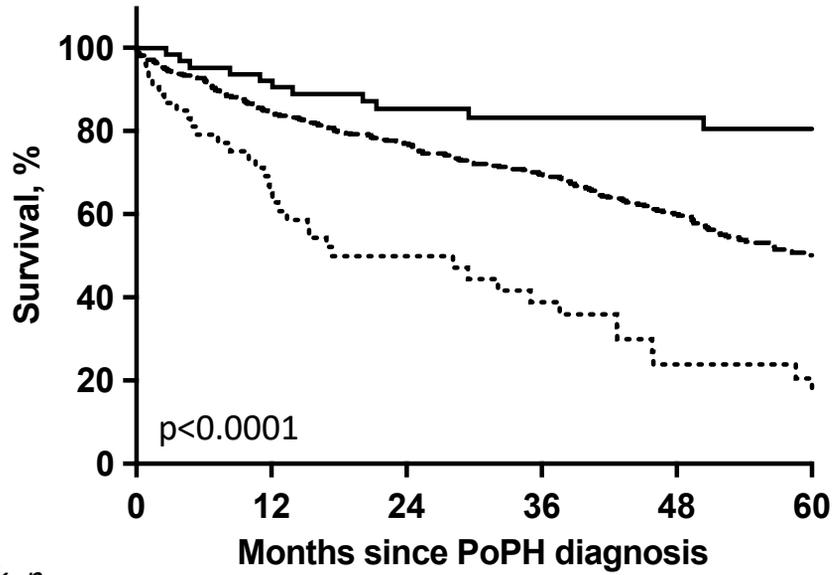
— <i>Cirrhosis</i>	15	14	11	10	8	6
- - - <i>Extrahepatic PoH and CPS</i>	622	488	387	300	234	170

C

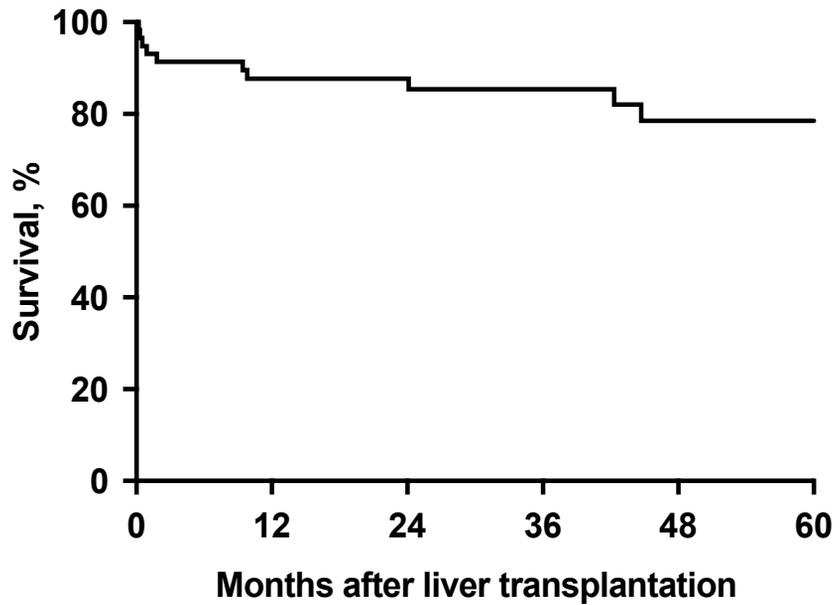
<i>Patients at risk, n</i>						
- - - <i>CP stage A</i>	328	286	235	182	149	115
- . . <i>CP stage B</i>	192	152	116	88	64	43
- . - <i>CP stage C</i>	57	23	14	10	9	3

D

<i>Patients at risk, n</i>						
- - - <i>MELD<15</i>	347	308	251	191	153	115
- . - <i>MELD\ge15</i>	148	100	77	62	43	28

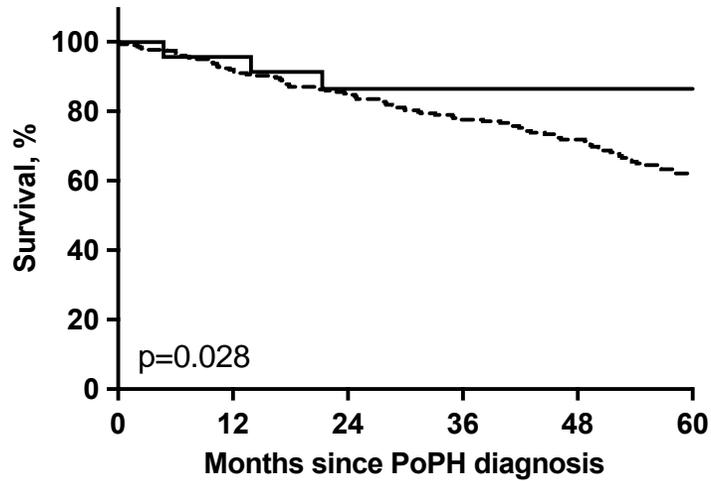
A*Patients at risk, n*

—	Transplanted patients	63	58	45	36	31	24
- - -	No indication for LT	520	412	332	259	201	144
.....	Indication for LT but not transplanted	54	31	19	14	8	6

B*Patients at risk, n*

63	49	38	33	21	17
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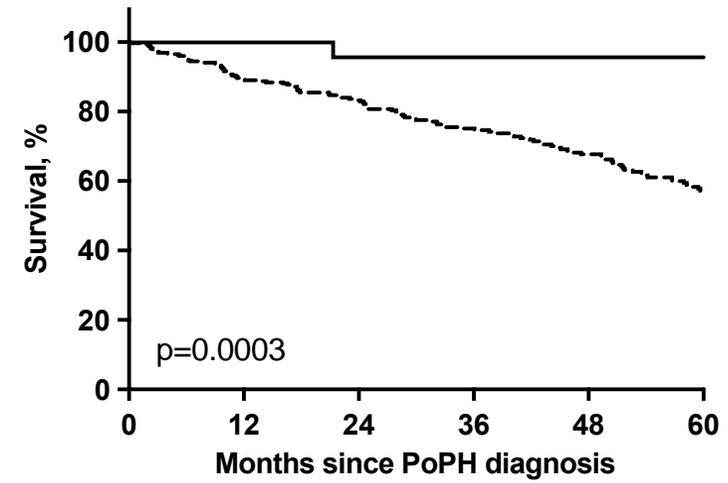
Child-Pugh Stage A



Patients at risk,

--- Non-transplanted	305	268	220	170	141	106
— Transplanted	23	22	17	14	10	10

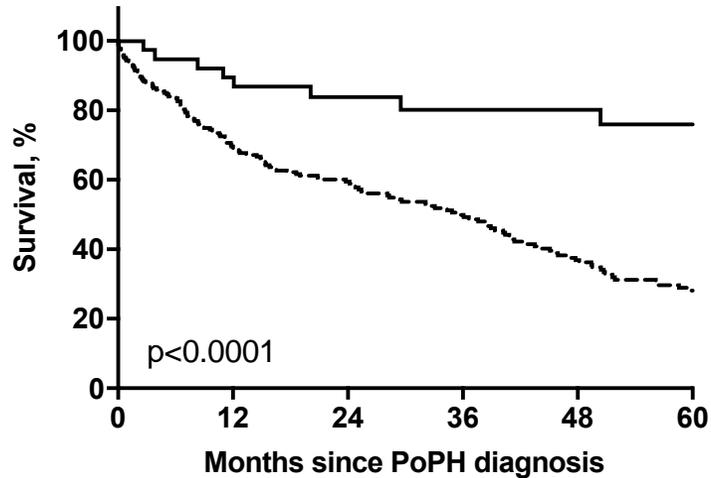
MELD score <15



Patients at risk,

--- Non-transplanted	320	281	229	172	139	102
— Transplanted	27	27	22	19	14	13

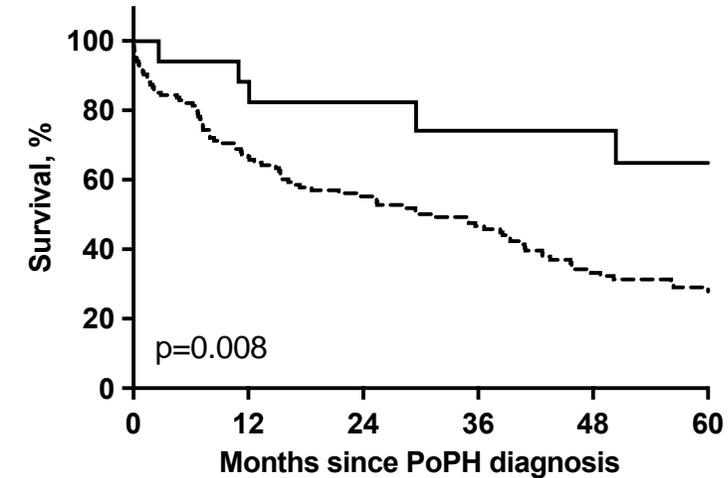
Child-Pugh Stage B and C



Patients at risk,

--- Non-transplanted	211	143	105	79	55	34
— Transplanted	38	34	26	20	19	12

MELD score ≥15



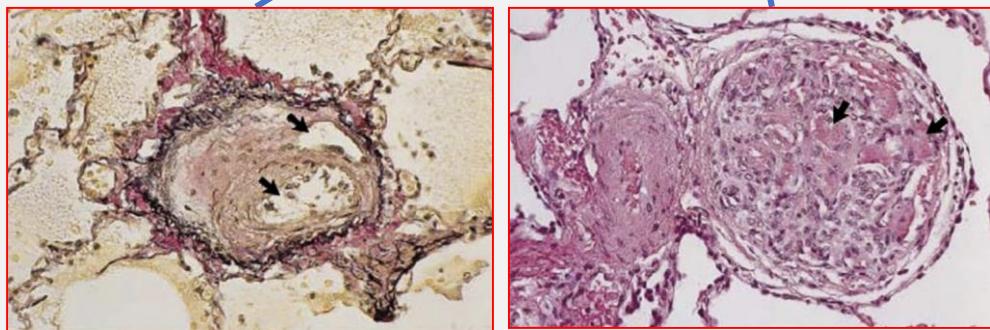
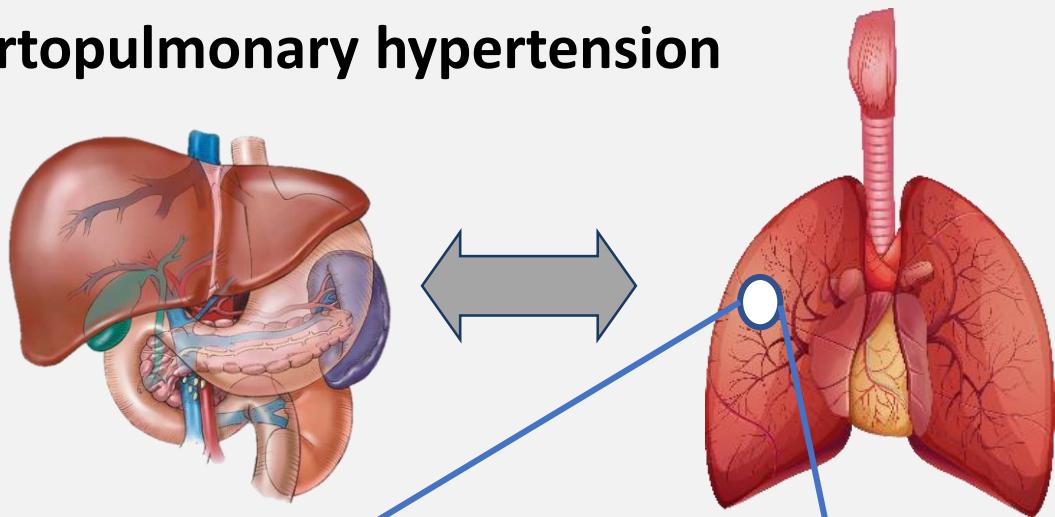
Patients at risk,

--- Non-transplanted	131	85	65	54	35	24
— Transplanted	17	15	12	8	8	4

Cohort of 637 patients with portopulmonary hypertension

Initial PAH therapy in 574 patients (90.1%)

Portopulmonary hypertension



Pulmonary vascular remodeling

Effect of oral PAH therapies on pulmonary vascular resistance

Endothelin receptor antagonist

-40%

Phosphodiesterase-5 inhibitors

-37%

Oral combination therapy

-64%

