EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Outcomes of cirrhotic patients with pre-capillary pulmonary hypertension and pulmonary vascular resistance between 2 and 3 Wood Units

Marie Caroline Certain, Audrey Baron, Matthieu Turpin, Nathan Ebstein, Athénaïs Boucly, Antoine Beurnier, Mitja Jevnikar, Anne Roche, Sophia Keddache, Sophie Bulifon, Andrei Seferian, Xavier Jaïs, David Montani, Marc Humbert, Olivier Sitbon, Laurent Savale

Please cite this article as: Certain MC, Baron A, Turpin M, *et al*. Outcomes of cirrhotic patients with pre-capillary pulmonary hypertension and pulmonary vascular resistance between 2 and 3 Wood Units. *Eur Respir J* 2022; in press (https://doi.org/10.1183/13993003.00107-2022).

Outcomes of cirrhotic patients with pre-capillary pulmonary hypertension and pulmonary vascular resistance between 2 and 3 Wood Units

Marie Caroline Certain[1,2,3], Audrey Baron[1,2,3], Matthieu Turpin[1,2,3], Nathan Ebstein[1,2,3], Athénaïs Boucly[1,2,3], Antoine Beurnier[1,2,3], Mitja Jevnikar[1,2,3], Anne Roche[1,2,3], Sophia Keddache[1,2,3], Sophie Bulifon[1,2,3], Andrei Seferian[1,2, 3], Xavier Jaïs[1,2,3], David Montani[1,2,3], Marc Humbert[1,2,3], Olivier Sitbon[1,2,3], Laurent Savale [1,2,3]

1- Université Paris-Saclay, School of Medicine, Le Kremlin-Bicêtre, France

2- INSERM UMR_S 999 «Pulmonary Hypertension: Pathophysiology and Novel Therapies», Hôpital Marie Lannelongue, Le Plessis-Robinson, France

3- Assistance Publique - Hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Center, Hôpital Bicêtre, Le Kremlin-Bicêtre, France.

Correspondence and reprint request:

Laurent Savale, MD, PhD

Service de Pneumologie et Soins Intensifs Respiratoires

Hôpital Bicêtre, 78, Rue du Général Leclerc, 94270 Le Kremlin-Bicêtre, France

Tel: +33.1.45.21.79.72; Fax: +33.1.45.21.79.71

E-mail: laurent.savale@aphp.fr

Portopulmonary hypertension (PoPH) is a subgroup of pulmonary arterial hypertension (PAH) complicating the course of portal hypertension [1, 2]. Similarly to other PAH causes, PoPH is characterized by a progressive structural and functional remodeling of small pulmonary arteries leading to pre-capillary pulmonary hypertension (PH) defined by a mean pulmonary artery pressure (mPAP) ≥25 mmHg, normal pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and raised pulmonary vascular resistance ≥ 3 Wood Units (WU) [1]. PoPH negatively impacts survival of patients with portal hypertension. Early detection of PoPH is of particular importance because it is treatable with PAH drugs and basic therapies such as diuretics [1, 3]. Moreover, beta-blockers often used in portal hypertension are contraindicated in these patients and PoPH should be screened prior to liver transplantation because it increases the risk of perioperative right heart failure and death in liver transplantation recipients [4–8]. Elevation of mPAP in cirrhotic patients can result from different pathophysiological mechanisms. High cardiac output (CO) and volume overload are frequently observed in cirrhotic patients and they may lead to mPAP elevation without increased PVR [2]. By contrast, remodeling of small pulmonary arteries in PoPH leads to progressive elevation of PVR. In the 2015 European PH guidelines, the cut-off value of PVR ≥3 wood units (WU) has been included in the definition of pre-capillary PH due to pulmonary vascular disease allowing discrimination from that due to other causes such as high CO or elevated PAWP [9]. However, large cohorts, systematic reviews and meta-analysis have shown that the upper limit of normal PVR is 2 WU [10]. Of note, this lower cut-off value is associated with clinical outcomes and mortality in patients referred for right heart catheterization [11]. Portal hypertension is usually associated with a hyperkinetic syndrome which lowers calculated PVR by increasing the denominator of calculated PVR (PVR= (mPAP – PAWP)/ CO) [2, 12]. A cut-off value of PVR ≥ 3 WU to define PAH in cirrhotic patients could thus be too high and wrongly exclude pulmonary vascular disease, thus delaying early PoPH diagnosis. In this study, we analyzed the outcomes of cirrhotic patients with mPAP ≥25 mmHg and PVR ranging from 2 to 3 WU, in order to study the natural history of mildly elevated PVR in PoPH.

In the French PH Registry, we identified consecutive patients referred between January 2007 and January 2017 who had portal hypertension and newly diagnosed mild pre-capillary PH defined by a mPAP ≥25 mmHg, PAWP ≤15 mmHg and PVR between > 2 and < 3 WU. 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. Hepatic- and PAH-related characteristics at baseline were analyzed. Continuous variables were expressed as the mean ± SD or median (interquartile range, 25% to 75% [IQR]) according to data distribution. Categorical variables were expressed as number of patients and relative frequencies (percent). The Kaplan-Meier method was used to estimate the proportion of patients developing PVR ≥ 3 WU at each time point up to five years after the first hemodynamic assessment. This retrospective study complied with the Declaration of Helsinki. Although French law does not require 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).

During the 10-year inclusion period, 742 incident patients with portal hypertension and pre-capillary PH were enrolled in the French PH registry [6]. Among them, 33 patients had PVR between 2 and 3 WU at baseline. A second right heart catheterization (RHC) was not available in 12 patients due to death (n=6) or lost to follow-up (n=6). The remaining 21 patients with at least one follow-up RHC were analysed **(Figure 1A)**. The median age was 55 (Q1-Q3; 49-59) years (76% male). Nine patients had a history of hypertension and one had diabetes. The etiologies of portal hypertension were alcohol-related cirrhosis, hepatitis C virus or both viral and alcohol cirrhosis (57%, 19% and 24%, respectively). The median value of

MELD score was 12 (Q1-Q3; 9-15). Ten patients were in New York Heart Association functional class (NYHA FC) I or II (48%) and 11 in NYHA FC III (52%). The median value of 6-minute walk distance (6MWD) was 420 (Q1-Q3; 359-476) meters. The mean PAP, PAWP and CI were respectively 32±5 mmHg, 9±3 mmHg and 4.2±1.0 L/min/m^2. The mean value of PVR was 2.6±0.2 WU. After first haemodynamic assessment, 5 patients received an off-label PAH therapy and 16 did not receive any PAH medication.

Patients who did not receive any PAH medication after first hemodynamic assessment (n=16) were followed-up during a median time of 56 (Q1-Q3, 25-82) months. The comparison of PAH-related characteristics at baseline and follow-up visit is detailed in **Figure 1B.** During the follow up period, 13 (81%) developed PVR >3 WU and the 1-, 3- and 5-years cumulative incidence of PVR >3 WU were 43%, 62%, and 77% at 1, 3 and 5 years, respectively. A liver transplantation was performed 5, 7, 9 and 18 months after the first hemodynamic assessment in 4 patients with pre-transplant PVR of 2.3, 2.4, 2.9 and 2.5 WU, respectively. None received PAH therapy as a bridge to transplantation. RHC performed 3 to 6 months after liver transplantation showed an increased PVR >3 WU in all patients and two developed severe right heart failure requiring initiation of PAH combination therapy after liver transplantation. In the 12 non-transplanted patients, 9 developed PVR >3 WU requiring the initiation of PAH therapies during follow-up in 6 of them. Among the 5 patients who received PAH therapy after first hemodynamic assessment, only one developed PVR >3 WU at follow-up **(Figure 1A)**.

The individual change in PVR between baseline and follow up visits are illustrated in **Figure 1C**. Eleven patients (52%) died during follow-up. The cause of death was cirrhosis in 5 cases, right heart failure, hepatocarcinoma and stroke (one case each). In 3 patients, the cause of death has not been identified.

Integration of PVR in the definition of PoPH is essential to distinguish a possible pulmonary vascular disease from passive causes of mPAP elevation in the absence of pulmonary arterial remodeling, such as high CO or hypervolemia. Indeed, cirrhosis is frequently associated with high CO and vasoreactivity

impairment leading to reduced systemic and pulmonary vascular resistance [12]. There is a risk of delayed diagnosis of overt pulmonary vascular disease in patients with PVR above the upper limit of normal but not meeting the current definition of pre-capillary PH. Our data support the concept that cirrhotic patients with pre-capillary PH, a high CO and PVR between 2 and 3 WU are likely to have early PoPH. Importantly, the most recent International Liver Transplant Society Practice Guidelines on Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension have suggested to consider a lower threshold of PVR to define PoPH in future clinical research [13]. This has a potential clinical impact, most specifically in liver transplantation candidates. Indeed, we previously reported that the evolution of PoPH after liver transplantation is often characterized by a transient worsening during the critical first six months after surgery requiring additional PAH therapy in some patients [5]. Our data indicate that cirrhotic patients with pre-capillary PH and PVR between 2 and 3 WU should be closely followed-up because they have a risk transient worsening of an underlying pulmonary vascular disease, as demonstrated in the four transplanted patients of our retrospective cohort. Other previous studies underlined the prognostic importance of PVR in the setting of liver transplantation. Indeed, DuBrock et al showed that pretransplant PVR was associated with waiting list mortality [14]. In addition, Jose et al reported that a pre-liver transplantation PVR of ≥1.6 WU may predict post-liver transplantation mortality [15].

In our study, five patients were treated after the first hemodynamic assessment. However, early use of PAH therapies in this population should be properly evaluated, considering the specificities of this subpopulation. Indeed, these patients have frequently a high cardiac output, especially when PVR are between 2 and 3 WU and we cannot exclude that the use of PAH therapies might lead to a worsening of the high cardiac output with potential short or long-term clinical consequences. However, our study shows that a screening of these patients is mandatory in order to follow them closely and adjust the management according to the clinical and hemodynamic evolution, especially after a liver transplantation.

Because these patients are at risk of pulmonary vascular diseases, a right heart catheterization should be proposed since the probability of pulmonary hypertension is intermediate on echocardiogram, whatever the symptomatology as underlined in the last guidelines [9].

Our study has limitations mainly due to its retrospective nature and the small number of patients. In addition, patients with mildly elevated mPAP ranging from 21 and 24 mmHg could not be studied in our Registry which mandates a mPAP ≥ 25 mmHg. Moreover, a control group with PVR below the upper limit of normal (2 WU) is lacking. However, these results are hypothesis-generating and support to reconsider the threshold of PVR that should be used to detect early forms of PoPH, as well as in other pulmonary vascular diseases.

In conclusion, our data suggest that PVR between 2 and 3 WU in patients with portal hypertension and pre-capillary PH could characterize early PoPH with clinical consequences, especially in candidates for liver transplantation. We propose to consider a lower cut-off PVR of 2 WU in the definition of PoPH.

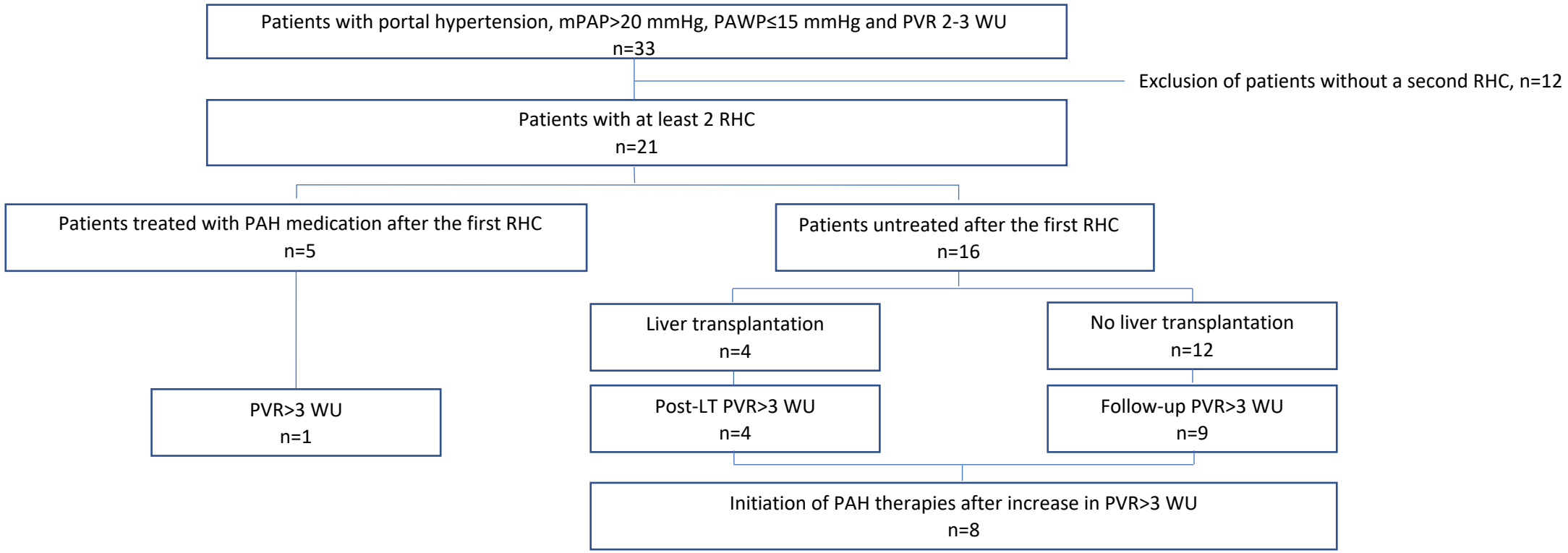
ACKNOWLEDGMENTS

We thank all physicians from the French Pulmonary Hypertension Network (PulmoTension)

Figure 1. **Flow chart and outcomes of patients (A), comparison of PAH-related characteristics at baseline and follow-up visits in untreated patients (B) and individual change in PVR in treated (plain line) and untreated patients (dotted line).**

Abbreviations: 6MWD, 6-minute walk distance; mPAP, mean pulmonary artery pressure; NYHA, New York Heart association; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RHC, Right Heart Catheterization.

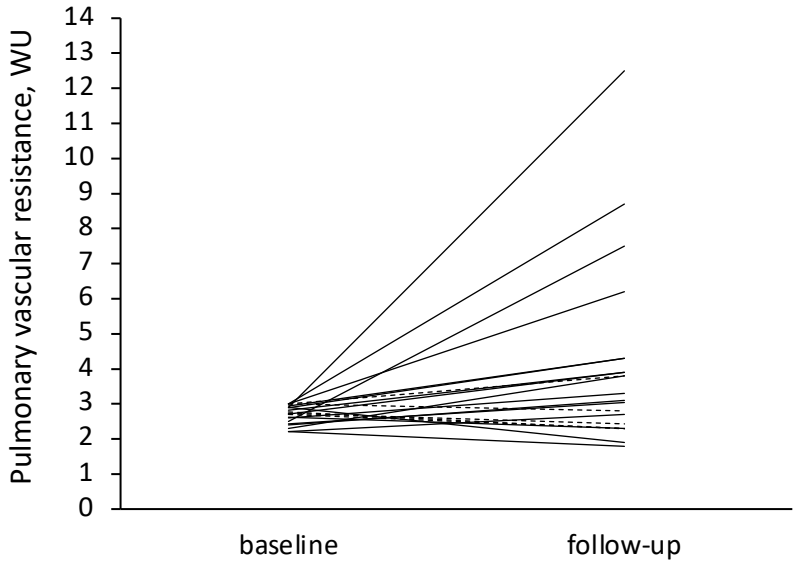
A



B

Untreated patients after first RHC (n=16)	Baseline visit	Follow-up visit	p value
NYHA Functional Class III-IV, n (%)	6 (37%)	8 (50%)	0.47
6MWD, meters, median (IQR)	451 (384-560)	440 (384-560)	0.08
Haemodynamics, mean±SD			
Mean Pulmonary Artery Pressure, mmHg	31±4	35±11	0.09
Pulmonary Artery Wedge Pressure, mmHg	9±3	10±5	0.6
Right Atrial Pressure, mmHg	6±3	8±4	0.01
Cardiac Index, L/min/m^2	4.4±0.9	3.3±0.9	0.001
Pulmonary Vascular Resistance, Wood units	2.7±0.3	4.6±2.9	0.001

C



References

1. Savale L, Watherald J, Sitbon O. Portopulmonary Hypertension. *Semin Respir Crit Care Med* 2017; 38: 651–661.

2. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur. Respir. J.* 2018; .

3. Galiè N, Channick RN, Frantz RP, Grünig E, Jing ZC, Moiseeva O, Preston IR, Pulido T, Safdar Z, Tamura Y, McLaughlin VV. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur. Respir. J.* 2018; .

4. Le Pavec J, Souza R, Herve P, Lebrec D, Savale L, Tcherakian C, Jaïs X, Yaïci A, Humbert M, Simonneau G, Sitbon O. Portopulmonary hypertension: survival and prognostic factors. *Am. J. Respir. Crit. Care Med.* 2008; 178: 637–643.

5. Savale L, Sattler C, Coilly A, Conti F, Renard S, Francoz C, Bouvaist H, Feray C, Borentain P, Jaïs X, Montani D, Parent F, O'Connell C, Hervé P, Humbert M, Simonneau G, Samuel D, Calmus Y, Duvoux C, Durand F, Duclos-Vallée JC, Sitbon O. Long-term outcome in liver transplantation candidates with portopulmonary hypertension. *Hepatology* 2017; 65: 1683–1692.

6. Savale L, Guimas M, Ebstein N, Fertin M, Jevnikar M, Renard S, Horeau-Langlard D, Tromeur C, Chabanne C, Prevot G, Chaouat A, Moceri P, Artaud-Macari É, Degano B, Tresorier R, Boissin C, Bouvaist H, Simon A-C, Riou M, Favrolt N, Palat S, Bourlier D, Magro P, Cottin V, Bergot E, Lamblin N, Jaïs X, Coilly A, Durand F, Francoz C, et al. Portopulmonary hypertension in the current era of pulmonary hypertension management. *J Hepatol* 2020; 73: 130–139.

7. Krowka MJ, Miller DP, Barst RJ, Taichman D, Dweik RA, Badesch DB, McGoon MD. Portopulmonary hypertension: a report from the US-based REVEAL Registry. *Chest* 2012; 141: 906–915.

8. Sithamparanathan S, Nair A, Thirugnanasothy L, Coghlan JG, Condliffe R, Dimopoulos K, Elliot CA, Fisher AJ, Gaine S, Gibbs JSR, Gatzoulis MA, E Handler C, Howard LS, Johnson M, Kiely DG, Lordan JL, Peacock AJ, Pepke-Zaba J, Schreiber BE, Sheares KKK, Wort SJ, Corris PA, National Pulmonary Hypertension Service Research Collaboration of the United Kingdom and Ireland. Survival in portopulmonary hypertension: Outcomes of the United Kingdom National Pulmonary Arterial Hypertension Registry. *J. Heart Lung Transplant.* 2017; 36: 770–779.

9. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur. Respir. J.* 2015; 46: 903–975.

10. Kovacs G, Olschewski A, Berghold A, Olschewski H. Pulmonary vascular resistances during

exercise in normal subjects: a systematic review. *Eur Respir J* 2012; 39: 319–328.

11. Maron BA, Brittain EL, Hess E, Waldo SW, Barón AE, Huang S, Goldstein RH, Assad T, Wertheim BM, Alba GA, Leopold JA, Olschewski H, Galiè N, Simonneau G, Kovacs G, Tedford RJ, Humbert M, Choudhary G. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. *Lancet Respir Med* 2020; 8: 873–884.

12. Herve P, Le Pavec J, Sztrymf B, Decante B, Savale L, Sitbon O. Pulmonary vascular abnormalities in cirrhosis. *Best Pract Res Clin Gastroenterol* 2007; 21: 141–159.

13. Krowka MJ, Fallon MB, Kawut SM, Fuhrmann V, Heimbach JK, Ramsay MAE, Sitbon O, Sokol RJ. International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension. *Transplantation* 2016; 100: 1440–1452.

14. DuBrock HM, Goldberg DS, Sussman NL, Bartolome SD, Kadry Z, Salgia RJ, Mulligan DC, Kremers WK, Kawut SM, Krowka MJ, Channick RN. Predictors of Waitlist Mortality in Portopulmonary Hypertension. *Transplantation* 2017; 101: 1609–1615.

15. Jose A, Shah SA, Anwar N, Jones CR, Sherman KE, Elwing JM. Pulmonary Vascular Resistance Predicts Mortality and Graft Failure in Transplantation Patients With Portopulmonary Hypertension. *Liver Transpl* 2021; 27: 1811–1823.