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

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To the Editor:

Portopulmonary hypertension (PoPH) is a subtype of pulmonary arterial hypertension (PAH) complicating the course of portal hypertension [1, 2]. Similar to other causes of PAH, PoPH is characterised by a progressive structural and functional remodelling of small pulmonary arteries leading to pre-capillary pulmonary hypertension defined by a mean pulmonary artery pressure (mPAP) ⩾25 mmHg, normal pulmonary artery wedge pressure (PAWP) ⩽15 mmHg and raised pulmonary vascular resistance (PVR) >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, β-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 may lead to mPAP elevation without increased PVR [2]. By contrast, remodelling of small pulmonary arteries in PoPH leads to progressive elevation of PVR. In the 2015 European pulmonary hypertension guidelines, the cut-off value of PVR >3 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 catheterisation (RHC) [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 analysed 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 pulmonary hypertension registry, we identified consecutive patients referred between January 2007 and January 2017 who had portal hypertension and newly diagnosed mild pre-capillary pulmonary hypertension defined by a mPAP ⩾25 mmHg, PAWP ⩽15 mmHg and PVR between >2 and <3 WU. The diagnosis of portal hypertension was based on haemodynamic measurement of a hepatic venous pressure gradient of >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 analysed. Continuous variables were expressed as the mean±SD or median (interquartile range (IQR)) according to data distribution. Categorical variables were expressed as number of patients and relative frequencies (%). The Kaplan–Meier method was used to estimate the proportion of patients developing PVR >3 WU at each time point up to 5 years after the first haemodynamic 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 anonymised and complied with the requirements of the Commission Nationale Informatique et Libertés, the organisation dedicated to privacy, information technology and civil

Shareable abstract (@ERSpublications)
Pulmonary vascular resistance between 2 and 3 Wood Units in patients with portal hypertension and pre-capillary pulmonary hypertension could characterise early portopulmonary hypertension with clinical consequences https://bit.ly/3PEFe79

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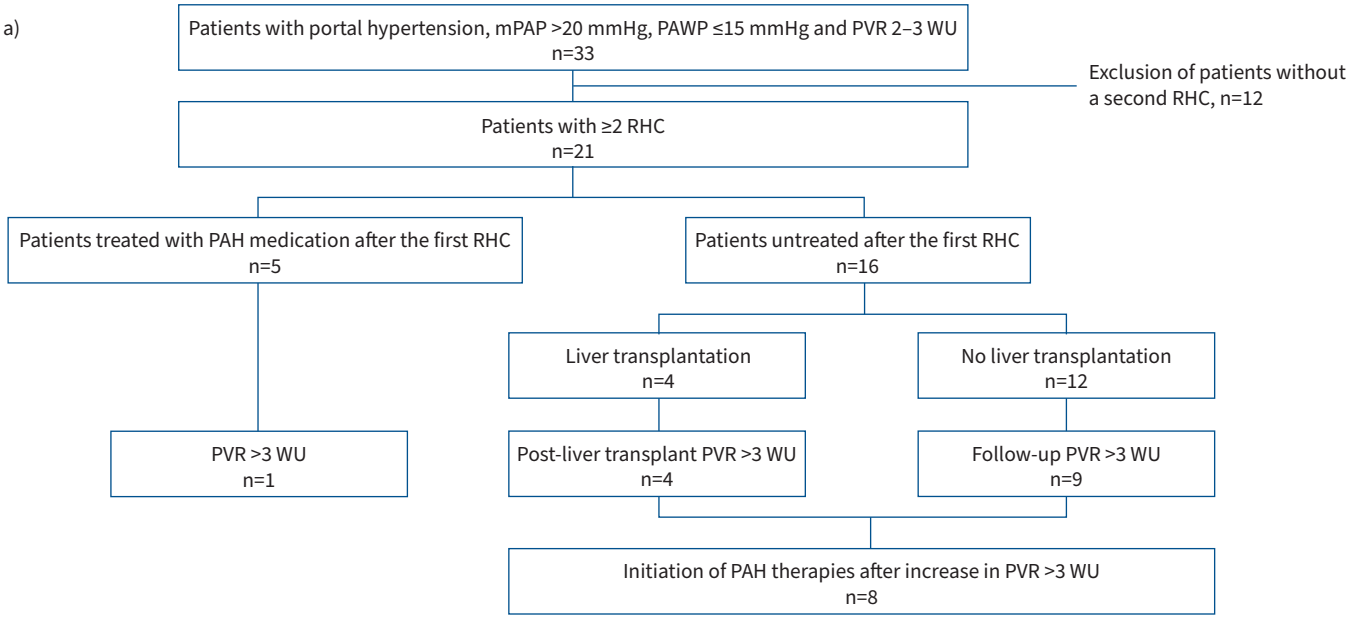
rights in France. The committee approved the methods used to collect and analyse the data on 24 May 2003 (approval number 842063).

During the 10-year inclusion period, 742 incident patients with portal hypertension and pre-capillary pulmonary hypertension were enrolled in the French pulmonary hypertension registry [6]. Among them, 33 patients had PVR between 2 and 3 WU at baseline. A second RHC was not available in 12 patients due to death (n=6) or loss to follow-up (n=6). The remaining 21 patients with at least one follow-up RHC were analysed (figure 1a). The median (IQR) age was 55 (49–59) years (76% male). Nine patients had a history of hypertension and one had diabetes. The aetiologies of portal hypertension were alcohol-related cirrhosis, hepatitis C virus or both viral and alcohol cirrhosis (57%, 19% and 24%, respectively). The median (IQR) Model for End-Stage Liver Disease score was 12 (9–15). 10 patients were in New York Heart Association functional class (NYHA FC) I or II (48%) and 11 in NYHA FC III (52%). The median (IQR) 6-min walk distance was 420 (359–476) m. The mean±SD PAP, PAWP and cardiac index were 32±5 mmHg, 9±3 mmHg and 4.2±1.0 $L \cdot min^{-1} \cdot m^{-2}$, respectively. The mean±SD PVR value was 2.6±0.2 WU. After first haemodynamic assessment, five patients received an off-label PAH therapy and 16 did not receive any PAH medication.

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, m, median (IQR)	451 (384–560)	440 (384–560)	0.08
Haemodynamics, mean±SD			
mPAP, mmHg	31±4	35±11	0.09
PAWP, mmHg	9±3	10±5	0.6
Right atrial pressure, mmHg	6±3	8±4	0.01
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	4.4±0.9	3.3±0.9	0.001
PVR, WU	2.7±0.3	4.6±2.9	0.001

c)

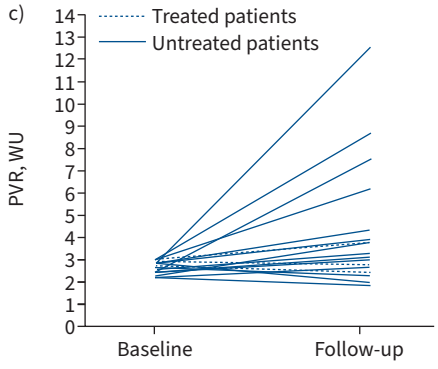


FIGURE 1 a) Flow chart and outcomes of patients; b) comparison of pulmonary arterial hypertension (PAH)-related characteristics at baseline and follow-up visits in untreated patients and c) individual change in pulmonary vascular resistance (PVR) in treated and untreated patients. mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; WU: Wood Units; RHC: right heart catheterisation; NYHA: New York Heart Association; 6MWD: 6-min walk distance; IQR: interquartile range.

Patients who did not receive any PAH medication after first haemodynamic assessment (n=16) were followed-up during a median (IQR) time of 56 (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-year cumulative incidences of PVR >3 WU were 43%, 62% and 77%, respectively. A liver transplantation was performed 5, 7, 9 and 18 months after the first haemodynamic assessment in four patients with pre-transplant PVRs of 2.3, 2.4, 2.9 and 2.5 WU, respectively. None received PAH therapy as a bridge to transplantation. RHC performed 3–6 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 nontransplanted patients, nine developed PVR >3 WU, requiring the initiation of PAH therapies during follow-up in six of them. Among the five patients who received PAH therapy after first haemodynamic 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. 11 (52%) patients died during follow-up. The cause of death was cirrhosis in five cases, right heart failure, hepatocarcinoma and stroke (one case each). In three patients, the cause of death was not identified.

Integration of PVR into 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 remodelling, such as high CO or hypervolaemia. 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 pulmonary hypertension. Our data support the concept that cirrhotic patients with pre-capillary pulmonary hypertension, 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 PoPH have suggested the consideration of 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 characterised by a transient worsening during the critical first 6 months after surgery requiring additional PAH therapy in some patients [5]. Our data indicate that cirrhotic patients with pre-capillary pulmonary hypertension 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.* [14] showed that pre-transplant PVR was associated with waiting list mortality. In addition, Jose *et al.* [15] reported that a pre-liver transplantation PVR of ⩾1.6 WU may predict post-liver transplantation mortality.

In our study, five patients were treated after the first haemodynamic 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 CO, 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 CO 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 haemodynamic evolution, especially after a liver transplantation. Because these patients are at risk of pulmonary vascular diseases, RHC should be proposed since the probability of pulmonary hypertension is intermediate on echocardiogram, whatever the symptomatology, as underlined in the latest 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 pulmonary hypertension could characterise early PoPH with clinical consequences, especially in candidates for liver transplantation. We propose the consideration of a lower cut-off PVR of 2 WU in the definition of PoPH.

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