Portopulmonary Hypertension: Prevalence, Clinical and Hemodynamic Features

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Abstract: Portopulmonary hypertension (PoPH) is a vascular complication of portal hypertension. This study aims to identify the prevalence and analyzing the clinical and hemodynamic features of patients with PoPH from a cohort of pulmonary arterial hypertension (PAH) patients. A retrospective transversal descriptive and analytical study. Patients with PoPH taken from a PAH cohort. We compare with those reported in the literature. We found prevalence of 6.1% of 244 consecutive patients with PAH, 11 females and 4 males. The mean age was 62 years and the main etiology of portal hypertension was primary biliary cirrhosis. Statistical differences were found in mean pulmonary arterial pressure, pulmonary vascular resistance, right atrial pressure; we found levels lower than reported. We found significant differences in clinical and hemodynamic characteristics such as older age and hemodynamic parameters of less severity in the group of patients analyzed compared with reported data. (Curr Probl Cardiol 2021;46:100747.)

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Introduction

Portopulmonary hypertension (PoPH) is one of the serious vascular complications of portal hypertension in patients with liver disease, it is associated with significant morbidity and can lead to right heart failure and death. It occurs most frequently in the context of end-stage liver disease, including candidates or submitted patients to liver transplantation (LTx), whit influence on the survival before, during and after LTx.[1,2] In the absence of liver transplant or pulmonary arterial hypertension (PAH) therapy, PoPH has been associated with a 5-year survival of 14%. Even in the modern PAH treatment era, PoPH has been associated with a 1-year survival of approximately 85%, 3-year survival varying between 38% and 68% and 5-year survival of 40%.[2,3]

The incidence and prevalence of PoPH are not well defined. In prospective studies, mainly in centers evaluating patients for LTx, have been shown a higher prevalence, between 5% and 8.5%.[2,4] In the context of patients with hepatic cirrhosis (HC) it is estimated that affects only 0.25%-4% of these patients.[5] Although, prevalence rates as high as 16% have been reported in patients with decompensated HC and refractory ascites.[5,6] In the REVEAL registry, a multicenter observational study of 3000 PAH patients, it was reported a frequency of PoPH de 5.1%.[1,7] The PoPH accounts for approximately 5%-10% of all patients with PAH in World Health Organization group 1.[8] Although HC is overwhelmingly the most common cause of PoPH, it can occur in patients with non-cirrhotic liver disease, approximately 10% of patients.[2] Female sex and autoimmune liver disease are associated with an increased risk of PoPH (odds ratios 4 and 9.8, respectively) while liver disease due to hepatitis C virus can be relatively protective of PoPH (odds ratio 0.2).[9]

The PoPH is characterized by PAH and may present with dyspnea or signs of right heart failure. The PoPH belongs to group 1 of the WHO of pulmonary hypertension[10,11] (Table 1) and is pathologically indistinguishable from other forms of PAH. However, the recognition of this specific form of PAH is imperative since it is associated with worse survival than its counterparts in group 1.[7,11-13] The transthoracic echocardiogram[9] is an important tool as a screening in these patients, the American Association for the Study of Liver Diseases and the European Society of Cardiology recommend to perform it in all symptomatic patients with liver disease and as part of LTx evaluation due to the high morbidity and mortality risk associated with performing LTx in patients with PoPH.[14,15]

The Model for End-Stage Liver Disease (MELD) exception scoring system is used to prioritize patients with PoPH for a liver transplant but is

TABLE1. Classification of pulmonary hypertension[10]

1. PAH
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.3 Drug and toxin induced PAH
   - 1.4 PAH associated with:
     - 1.4.1 Connective tissue disease
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart disease
     - 1.4.5 Schistosomiasis
   - 1.5 PAH long term responders to calcium channel blockers
   - 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
   - 1.7 Persistent PH of the newborn syndrome

2. PH due to left heart disease
   - 2.1 PH due to heart failure with preserved LVEF
   - 2.2 PH due to heart failure with reduced LVEF
   - 2.3 Valvular heart disease
   - 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH due to lung diseases and/or hypoxia
   - 3.1 Obstructive lung disease
   - 3.2 Restrictive lung disease
   - 3.3 Other lung disease with mixed restrictive/obstructive pattern
   - 3.4 Hypoxia without lung disease
   - 3.5 Developmental lung disorders

4. PH due to pulmonary artery obstructions
   - 4.1 Chronic thromboembolic PH
   - 4.2 Other pulmonary artery obstructions

5. PH with unclear and/or multifactorial mechanisms
   - 5.1 Haematological disorders
   - 5.2 Systemic and metabolic disorders
   - 5.3 Others
   - 5.4 Complex congenital heart disease

HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension. *Taken and modified of Simonneau G et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1).*

not known whether PoPH in the absence of significant liver disease should be an indication for a liver transplant.[16] The treatment of patients with PoPH usually follows the same as for the other PAH subgroups, however, patients with PoPH have been excluded in most randomized clinical trials (RCT) of PAH treatment. Cases and case series reports have suggested that treatments for PAH could benefit patients with PoPH as a bridge to LTx, by improving hemodynamic parameters. However, careful patient selection is required and this is not a generalized approach today.[16,17]

The understanding of the clinical behavior and the different outcomes in patients with PAH has been increasing in the last 20 years, the PoPH is

one of the PAH subgroups and it has been characterized by being one with the worst prognosis and high morbidity and mortality, due to what is important to know the clinical and hemodynamic characteristics of these patients in various cohorts. This study aims to identify the prevalence and analyzing the clinical and hemodynamic features of patients with PoPH from a cohort of PAH patients from a third level hospital.

Materials and Methods

Patients and Study Design

A retrospective transversal descriptive and analytical study. Patients with PoPH taken from the PAH cohort with right cardiac catheterization of the pulmonary circulation clinic of the General Hospital of México, between June 2016 and June 2020, of 244 consecutive patients. There were included patients ≥18 years old, and the patients were scored using the Child-Pugh classification and MELD score. PoPH was defined as pulmonary arterial hypertension associated with portal hypertension. The diagnosis criteria include (1) Portal hypertension (inferred from the presence of splenomegaly, thrombocytopenia portosystemic shunts, esophageal varices or portal vein abnormalities, or confirmed by hemodynamic measurements such hepatic venous pressure gradient (HVPG) >5 mm Hg[18]; and (2) PAH with mean pulmonary arterial pressure (mPAP) >20 mm Hg at rest, pulmonary capillary wedge pressure (PCWP) <15 mm Hg, and pulmonary vascular resistance (PVR) ≥3 Wood units (WU).[1,2,11,19]

Data Collection

Patient registry records were studied retrospectively and the following parameters recorded: gender, age, etiology of portal hypertension, Child-Pugh and MELD score, WHO functional class, brain natriuretic peptide (BNP), 6 minutes walk distance (6MWD), risk stratification of PAH, mPAP, PVR, right atrial pressure (RAP), right ventricle systolic pressure, right ventricle diastolic pressure, PCWP, cardiac index (CI), free hepatic venous pressure and wedged hepatic venous pressure, HVPG, the 3 last parameters only if they were available.

Risk Stratification

It was done based on the recommendations of the guidelines of the European Society of Cardiology/European Respiratory Society of

pulmonary hypertension[15] taking into account the following variables: clinical signs of right heart failure, progression of symptoms, syncope, WHO functional class, 6MWD, BNP plasma levels, echocardiography data: right atrium area or pericardial effusion, hemodynamic data: RAP, CI, or venous oxygen saturation. Each patient was classified based on the proposal of Sweden and Germany studies,[10,20] as low risk, intermediate risk or high risk by assigning a grade to each variable, where low risk = 1 point, intermediate-risk = 2 points and high risk = 3 points, and a mean score was calculated for each patient and rounded to the nearest integer.

Statistical Methods

The results were expressed as mean and standard deviation (SD) for continuous variables, and frequencies and percentages for categorical variables. We compare the findings of continuous variables (MELD score, BNP, 6MWD, mPAP, PVR, RAP, PCWP, and CI) with those reported in the literature using a one-sample *t* test (Shapiro-Wilk test reported a normal distribution). Significance in comparison of proportions with those of literature (for our categorical variables: gender, WHO functional class, etiology of portal hypertension, and Child-Pugh) were evaluated using chi-square with the goodness of fit analysis. We used the IBM SPSS Statistics software (version 25.0.0.1 IBM Corporation; Armonk, NY). Statistical significance considered a P-value < 0.05 (two-tailed).

Results

Of 244 consecutive patients with PAH between June 2016 and June 2020, 15 of them had a hemodynamic consistent diagnosis of PoPH (6.1%), of which 11 were females and 4 males, with a median age of 62 years (SD 7.88). The basic liver disease was in 7 cases (46.7%) due to primary biliary cirrhosis, followed by alcoholic liver failure in 4 cases (26.7%), 2 cases of autoimmune hepatitis (13.3%) and 2 cases of viral hepatitis cirrhosis type B (13.3%). The severity of liver failure due to Child-Pugh corresponded to grade A, 9 cases (60%), and grade B 6 cases (40%), there were no patients with grade C. In terms of the severity calculated by MELD, 8 patients (53.3%) were found with a score <10 points, 5 patients (33.3 %) between 10 and 19 points, and 2 patients (13.3%) with a higher score at 19. Seventy three percent of the patients were found in WHO I-II functional class and 26.7 % in WHO III-IV functional class. The main BNP was 438.67 pg/mL (SD 672.88). In the 6MWD, the main of the meters traveled was 305.69 m (SD 91.53) (Table 2).

TABLE 2. Demographic and clinical data

Characteristics	Data
Gender	Female 73%
Age, years	62.07 ± 7.88
Aetiology of portal hypertension	
Primary biliary cirrhosis	46.7%
Alcohol	26.7%
Autoimmune hepatitis	13.3%
Hepatitis B Infection	13.3%
Child-Pugh	
A	60%
B	40%
C	0
MELD Score	
<10 puntos	53.3%
10 a 19 puntos	33.3%
>19 puntos	13.3%
WHO Functional Class	
I	0
II	73.3%
III	26.7%
IV	0
Risk stratification, score	1.47 ± 0.23
Risk stratification of PAH	
Low	60 %
Intermediate	40 %
BNP, pg/mL	438.67 ± 672.88
6 min walk distance, m	305.69 ± 91.53
mPAP, mm Hg	39.67 ± 11.56
RAP, mm Hg	4.40 ± 3.58
RVSP, mmHg	65.2 ± 22.80
RVDP, mm Hg	3.73 ± 2.08
PCWP, mm Hg	7.73 ± 5.13
PVR, Wood Units	5.31 ±2.19
CI, L/min/m^2	4.07 ± 0.94
FHVP*, mm Hg	7.50 ± 2.99
WHVP*, mm Hg	16.10 ± 6.42
HVPG*, mm Hg	10.60 ± 5.64

BNP, brain natriuretic peptide; CI, cardiac index; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; MELD, Model for End Stage Liver Disease; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSP, right ventricle systolic pressure; RVDP, right ventricle diastolic pressure; WHO, World health organization; WHVP, hepatic venous pressure wedge.
*Data obtained in 10 patients.

Regarding hemodynamic data, mPAP 39.67 mm Hg (SD 11.56), RAP 4.40 mm Hg (SD 3.58), right ventricle systolic pressure 65.2 mm Hg (SD 22.80), right ventricle diastolic pressure 3.73 mm Hg (SD 2.08), PCWP 7.73 mm Hg (SD 5.13), PVR 5.31 WU (SD 2.19), CI 4.07 L/min/m^2 (SD

0.94). The hemodynamic liver data was obtained of ten patients, free hepatic venous pressure 7.50 mm Hg (SD 2.99), wedged hepatic venous pressure 16.1 mm Hg (SD 6.42), and HVPG 10.60 mm Hg (SD 5.64) (Table 2).

According to the severity classification of the international liver transplant society, 5 patients were found in mild (33.3 %), 5 in moderate (33.3%), and 5 in severe grade 33.3%). And the risk stratification of PAH, the mean of the risk stratification score was 1.47 (SD 0.23) and 9 patients (60 %) were classified in low risk and 6 patients (40 %) in intermediate-risk, there were no patients in high risk. All the patients had treatment with sildenafil, with a follow-up between 3 and 18 months, without reporting any deaths in our group of patients.

When we compared the data obtained from our court with data from PoPH patients by Le Pavec,[13] Krowka,[7] and Kawut.[9] We found statistically significance difference for chi-square in the following variables; gender, 73% women versus 43% reported by Le Pavec (chi-square 5.63 *P* 0.018); Functional class we found 73.3% in II and 26.7% in III versus 35% in II and 49% in III described by Krowka (chi-square 6.18 *P* 0.013); Regarding the etiology of portal hypertension, we compared that reported by Kawut, finding primary biliary cirrhosis in 46.7% versus 12%, for alcoholic liver disease we found 26.7% versus 41%, for autoimmune disease we found 13.3% versus 26%, and finally for hepatitis B infection we found 13.3% and the reported was 3%, (chi-square 9.03 *P* 0.029). Regarding the severity of liver disease, for the Child-Pugh classification when compared with that reported by Le Pavec, we did not find statistically significant differences (chi-square 0.045 *P* 0.833) (Table 3).

For hemodynamic, functional and continuous variables, we compared with the data reported by Krowka,[7], Kawut,[9] Goldberg,[19] and Le Pavec.[13]. Based on age, mPAP, IC, and BNP, Krowka et al reported 53 years, 49 mm Hg, 2.7 L/min/m^2, and 387 pg/mL, respectively, compared to our court of patient that had a mean of 62. 07 years, 39.67 mm Hg, 4.07 L/min/m^2, and 438.67 pg/mL with statistically significant difference for age, mPAP and CI. For PVR, RAP, and PCWP we found a mean of 5.31 WU, 4.40 mm Hg and 7.73 mm Hg, respectively and Kawut et al reported 8.7 WU, 10 mm Hg and 10 mm Hg, respectively and the *t* test was −5, 98 $P < 0.001$ (95% confidence interval [CI] −4.60 to −2.17), −6.05 $P < 0.001$ (95% CI −7.58 to −3.62), and −1.71 p 0.109 (95% CI −5.11 to 0.58), respectively; and for the MELD scores we found a mean of 13.3 points, and Goldberg et al reported 12 points, the *t* test was 0.436 *P* 0.669 (95% CI −5.22 to 7.89) (Table 4).

TABLE 3. Clinical features of patients with portopulmonary hypertension in comparison with reported data

Clinical characteristic	%	Comparison reported value %	χ^2*	*P*value	Author
Female	73	43	5.63	0.018	Le Pavec et al 2008[12]
WHO Functional Class					Krowka et al 2012[7]
II	73.3	35			
III	26.7	49	6.18	0.013	
Etiology of portal Hypertension					Kawut SM et al 2008[9]
Primary biliary	46.7	12			
cirrhosis	26.7	41			
Alcohol	13.3	26			
Autoimmune hepatitis	13.3	3	9.03	0.029	
Hepatitis B infection					
Child-Pugh					Le Pavec J et al, 2008[12]
A	60	51			
B	40	38	0.045	0.833	

WHO, world health organization.
* χ^2 goodness of fit.

The data found in the risk stratification of our patients were not compared because there were no publications of patients with PoPH that had these data.

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Discussion

This is the first study in our country that reports features of a group of patients with PoPH, the prevalence of PoPH found in our cohort of 244 patients with PAH, was 6.1%, similar at the reported by Krowka et al. in the REVEAL registry (5.1%).[7]

We present a summary of clinical characteristics and hemodynamic values, and their validation according to what is reported in the international literature. We also report risk stratification in our patient group, which has been suggested since 2015 to know the severity of the disease and response to treatment in patients with PAH, with noninvasive variables for risk stratification currently being recognized in these patients.[15,21] There was not a study to compare the stratification levels found in our patient group, 60% at low risk and 40% at moderate risk.

TABLE 4. Hemodynamic and quantitative features of patients with portopulmonary hypertension in comparison with reported data

Hemodynamic characteristics	Mean	S.D.	S.E. mean	Reported value	t*	*P* value	95% CI of the difference		Author
							Lower	Upper	
Age, years	62.07	7.88	2.04	53	4.45	0.001	4.70	13.43	Krowka et al[7]
mPAP, mm Hg	39.67	11.56	2.98	49	−3.13	0.007	−15.74	−2.93	Krowka et al[7]
CI, L/min/m^2	4.07	0.94	0.24	2.7	5.63	<0.001	0.85	1.89	Krowka et al[7]
PVR, mm Hg	5.31	2.19	0.56	8.7	−5.98	<0.001	−4.60	−2.17	Kawut SM et al[9]
RAP, mm Hg	4.40	3.58	0.92	10	−6.05	<0.001	−7.58	−3.62	Kawut SM et al[9]
PCWP, mm Hg	7.73	5.13	1. 32	10	−1.71	0.109	−5.11	0.58	Kawut SM et al[9]
BNP, pg/mL	438.67	672.88	179.83	387	0.287	0.778	−336.84	440.18	Krowka et al[7]
MELD score points	13.33	11.83	3.05	12	0.436	0.669	−5.22	7.89	Goldberg DS et al[18]
6-MWD, m	305.69	91.53	25.38	326	−0.800	0.439	−75.62	−35.00	Le Pavec et al 2008[12]

BNP, brain natriuretic peptide; CI, cardiac index; mPAP, mean pulmonary arterial pressure; MELD, Model for End Stage Liver Disease; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; 6-MWD, 6 minutes walking distance.
*One sample *t* test.

The average age in our patient group was 62.07 years, which is greater than reported in other cohorts, which is between 50 and 54 years of age.[3,9,13,19] For this case, we made the comparison analysis with reported data by Krowka et al finding a statistically significant difference (*P* 0.001, 95% CI 4.70-13.43).[7] Regarding the clinical characteristics such as age, gender, functional class, etiology of portal hypertension, and severity of liver disease due to MELD, significant differences were reported.[7,9,13,19] In hemodynamic parameters such as mPAP, PVR, RAP, and CI we found statistically significant differences, being the levels of mPAP, PVR, and RAP in our patients group lower, and the cardiac index was higher than reported.[7,9] Regarding the distance traveled in the 6-minute walk test, a statistically significant difference was not found, the meters covered by the patients in our group were similar than reported by Le Pavec.[13]

The pathogenesis of PoPH is not completely understood, result from a lack of hepatic clearance of vasoactive substances produced in the splanchnic territory occasionating pulmonary vascular remodeling and some degree of vasoconstriction.[2] The pulmonary vascular changes include intimal fibrosis, hypertrophy of the smooth muscle cells and fibroblasts, in situ thrombosis, and plexiform lesions resulting from intraluminal endothelization or microaneurysms within pulmonary arterioles. It has been proposed that the increased blood flow (high cardiac output) in chronic liver disease causes pulmonary vascular wall shear stress, which can trigger dysregulation of numerous vasoactive, proliferative and angiogenic mediators eventually leading to the characteristic arteriopathy changes mentioned, included endothelial dysfunction, mainly endothelin 1 as a potent vasoconstrictor found at elevated levels in cirrhotic patients and even at higher levels in those patients who also have ascites.[1,2,5,22]

The female sex and autoimmune disease have been identified as an important risk factor for POPH.[2] Also in a study to identify predictors of waitlist mortality in POPH it was found that the age, initial MELD score and initial PVR were the only significant univariate predictors of overall waitlist mortality.[3]

PoPH usually produces no symptoms or only has symptoms related to the underlying cirrhosis or portal hypertension. Dyspnea on exertion is the most common symptom, but these can be related to other conditions such as refractory ascites with mechanical thoracic impairment, hepatic hydrothorax, anemia, and sarcopenia or deconditioning. In advanced stages can appear oppressive chest discomfort, dyspnea at rest, syncope, and hemoptysis. The recognition of PoPH requires high clinical suspicion.[1,23]

The goals for management of PoPH are to provide symptomatic relief, improve quality of life and exercise capacity, and to facilitate successful LTx. At the respect of PAH-specific therapies, most of the evidence emerged from the subgroup of patients with idiopathic PAH and PH associated with connective tissue disorders, since PoPH patients were excluded earlier from randomized clinical trials. There is a lack of data regarding the overall efficacy.[1,22]

PATENT-1 was the first RCT that did not exclude patients with PoPH, and in a post hoc analysis they evaluated riociguat treatment in patients with PoPH included in PATENT 1 (3%), it was found improvement in 6MWD, WHO functional class, which It was maintained for 2 years in PATENT 2, and it was reported riociguat was well tolerated in this group of patients with a safety profile comparable to other PAH subgroups in PATENT-1 and PATENT-2.[24,25] More recently, PORTICO was the first RCT of PAH therapy specifically designed for patients with PoPH and its primary endpoint showed a 35% reduction of pulmonary vascular resistance at week 12 with macitentan versus placebo, also it was reported increases in cardiac index and decreases in mPAP and the treatment with macitentan was well-tolerated with no hepatic safety concerns.[26]

For moderate to severe PoPH, the LTx is not the definitive treatment, in some patients, it disappears several months after LTx, whereas in others it persists or even worsens over time. The pulmonary vasodilators should be used to lower mPAP <35 mm Hg, to minimize the risk of graft failure and improve the overall outcome (Figure).[2]

The international liver transplant society classifies the PoPH into 3 degrees: Mild with mPAP <35mm Hg, moderate with mPAP between 35 and 45 mm Hg and severe >45 mm Hg. This allows to guide the treatment in the patients with PoPH, mainly directed toward LTx, in such a way that mild patients can receive LTx, those of moderate degree can receive LTx if they are responders to the test of vascular reactivity and patients in severe grade are candidates for medical therapy.[23]

Our study has several limitations: first, is the small group of patients, the second is to be a retrospective description and the third is the lack of data regarding follow-up and evolution in the course of their disease.

The knowledge of the different clinical and hemodynamic aspects of PoPH presents great relevance for cardiologist, pulmonologists, gastroenterologists, and transplant surgeons, who are involved in the follow-up and management of this type of patients, so we believe that the presentation of our data may be useful to this community of experts during their clinical practice. PoPH has been recognized for its poor prognosis, although in this group of patients we find that the severity of PAH,

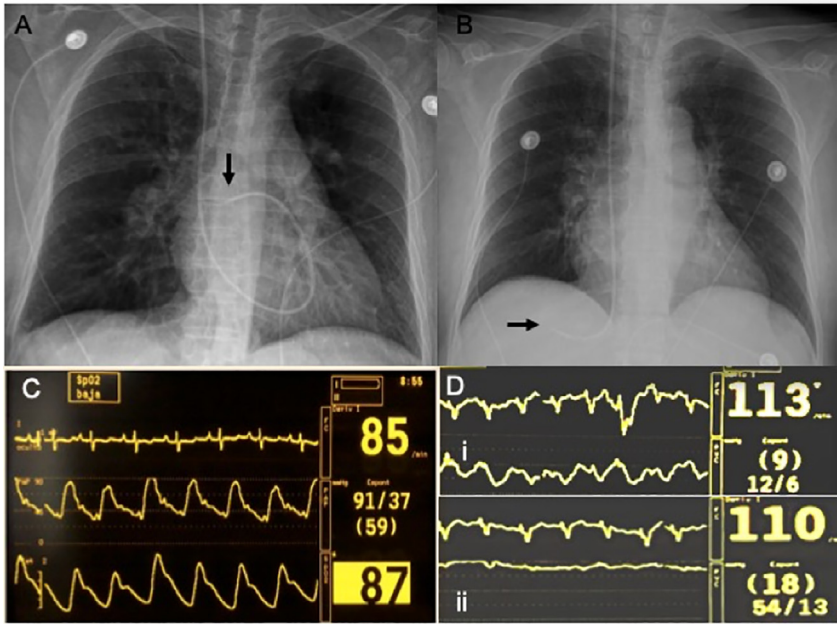

FIG. (A) Right heart catheterization (RHC) image, with catheter tip at the level of the pulmonary artery trunk (arrow). (B) Hepatic catheterization image, with catheter tip at the suprahepatic vein (arrow). (C) Hemodynamic traces during RHC, the middle one represents the pulmonary artery. (D) Hepatic hemodynamic traces, i. Measuring free hepatic venous pressure, ii. Measuring Wedged hepatic venous pressure.

measured by risk stratification, is low and intermediate. However, it is necessary to continue reporting cohorts of PoPH patients to better understand the evolution of these patients and the mechanisms of response to the targeted treatment, as well as the different outcomes in which they receive LTx or not.

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