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Pulmonary hypertension in antisynthetase syndrome: prevalence, etiology and survival.

Baptiste Hervier[1*] MD, Alain Meyer[2+] MD, Céline Dieval[3] MD, Yurdagul Uzunhan[4] MD, Hervé Devilliers[5] MD, David Launay[6] MD-PhD, Matthieu Canuet[2†] MD, Laurent Têtu[7] MD, Christian Agard[8] MD-PhD, Jean Sibilia[2+] MD-PhD, Mohamed Hamidou[8] MD-PhD, Zahir Amoura[1*] MD-PhD, Hilario Nunes[4] MD-PhD, Olivier Benveniste[1£] MD-PhD, Philippe Grenier[1#] MD-PhD, David Montani[9¥] MD-PhD, Eric Hachulla[6¥] MD-PhD.

1. Hôpital Pitié-Salpêtrière, APHP, Paris, France & University of Paris VI Pierre & Marie Curie; * Internal Medicine department 2 & INSERM UMRS-945, French Reference Center for Lupus; £ Internal Medicine department 1, French Reference Center for Neuromuscular Disorders, # Radiology department
2. Strasbourg university hospital, Strasbourg France, +Rheumatology department, French reference center for Systemic rare diseases, †Pneumology department
3. Internal Medicine & Infectious diseases department, St-André Hospital, University of Bordeaux, Bordeaux, France
4. University of Paris 13, Sorbonne Paris Cité, EA 2363; AP-HP, Department of Pneumology, Avicenne hospital, Bobigny, France
5. Internal Medicine & Systemic disease department, University hospital of Dijon, Dijon, France
6. Internal Medicine department, French National Center for Rare Systemic Auto-Immune Diseases (Scleroderma), Claude Huriez Hospital, Lille 2 University, Lille, France
7. Pneumology department, Larrey Hospital, Paul Sabatier university, Toulouse, France
8. Internal Medicine department, Hôtel Dieu, Nantes university, Nantes, France

9. Université Paris-Sud, Centre de Référence de l'Hypertension Pulmonaire Sévère, Service de Pneumologie et Réanimation Respiratoire, AP-HP, DHU Thorax Innovation, INSERM U999, Hôpital de Bicêtre, Le Kremlin-Bicêtre, F-94270, France

Corresponding author : Baptiste Hervier, Service de Médecine Interne 2, Centre National de référence du Lupus, 47-83 boulevard de l'hôpital, 75651 Paris cedex 13, France, tel : +33 1 42 17 80 40 ; fax : + 33 1 42 17 80 81 ; bhervier@yahoo.fr

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[¥] David Montani and Eric Hachulla contributed equally to the work.

KEY WORDS

Anti-tRNA-synthetase antibody, Myositis, Interstitial Lung disease, Pulmonary hypertension

ABSTRACT (199 words)

Antisynthetase syndrome (ASS) is characterized by the association of interstitial lung disease (ILD) and myositis with different anti-tRNA-synthetase antibodies. The occurrence, etiology and prognosis of pulmonary hypertension (PH) have not yet been evaluated.

Among 203 consecutive patients, echocardiography (TTE) and right heart catheterization (RHC) results were retrospectively analyzed in light of clinico-biological, morphological and functional parameters. Definitions of PH were based on the ESC/ERS 2009 guidelines, severe PH being defined by a mean pulmonary arterial pressure (mPAP) > 35 mmHg.

PH was suspected by TTE in 47 (23.2%) cases, corresponding to PH "possible" (n=27, 13.3%) or "likely" (n=20, 9.9%). RHC was performed in 21 patients, excluding PH in 5 and confirming pre-capillary PH in 16 (7.9%). Although related to ILD in all cases, pre-capillary PH was severe in 13 (81,3%) patients (mean mPAP: 46 ± 9 mmHg), frequently associated with low cardiac index (mean 2.3 ± 0.8 l/min/m²) and high FVC/DL_{CO} ratio (2.5 ± 0.6). PH was clearly associated with a lower survival ($p<0.001$), with a 3-year survival rate of 58%.

The occurrence of PH in ASS is significant and dramatically worsens the prognosis. Although systematically associated with ILD, PH was usually severe, suggesting a specific pulmonary vascular involvement.

INTRODUCTION

Antisynthetase syndrome (ASS) was first described in 1990 as a heterogeneous connective tissue disease, characterized by the association of an interstitial lung disease (ILD) and/or inflammatory myositis with the presence of anti-aminoacyl-tRNA-synthetase antibodies (anti-ARS) [1]. Different anti-ARS specificities have been described, anti-histidyl(Jo1)-tRNA-synthetase antibodies being the most common (20% of the polymyositis and dermatomyositis patients). The other antibody specificities, including anti-alanyl(PL12), anti-threonyl(PL7), anti-isoleucyl(OJ) and anti-glycyl(EJ)-tRNA-synthetase antibodies are less commonly found (each Ab being <5% of the of the polymyositis and dermatomyositis patients). Although the anti-ARS could be associated with other anti-extractable nuclear antigen Ab, including anti-Ro/SSA or anti-La/SSB Ab, they are mutually exclusive in most cases. Aside from myositis and ILD, other unspecific symptoms are quite commonly reported in ASS and include arthritis, Mechanic's hands, Raynaud's phenomenon. Associated symptoms of Sjögren Syndrome (SS) or Systemic Sclerosis (SSc) have also been reported in different proportions [1-4].

Pulmonary hypertension (PH) is by itself a severe life-threatening disorder, complicating with variable frequency connective tissue diseases [5;6], among which SSc is the most common [7;8]. In inflammatory myositis [9] and in ASS in particular, the occurrence of PH has never been systematically evaluated and its description rests only upon isolated case reports [10-12]. PH comprises many causes, including pulmonary arterial hypertension (PAH), left heart disease, chronic lung diseases, chronic thromboembolism and others [13]. However, although rarely reported, PH in ASS patients could be related to any of these etiologies, the most common of which would theoretically be PH due to ILD (PH-ILD) and PAH. Indeed, ILD is the most frequent manifestation of ASS and some patients with ASS may present signs of SSc

[1;2;14], which often causes PAH or PH-ILD [7;8;15;16]. Conversely, specific left heart dysfunction seems rare in myositis [17].

The knowledge of PH prevalence and its mechanism is important, as it implies different investigations, such as echocardiography for positive screening and right heart catheterization (RHC) for a precise positive and etiological diagnosis. Moreover, certain causes require specific treatments. These treatments could be essential since the long-term prognosis and the survival of patients with ASS, based on retrospective studies, showed a clear correlation with lung involvement [2;18-20]. However, the influence of cofactors associated with ILD, such as PH, has rarely been evaluated to date in large series. This led us to conduct this large multicenter study of 203 ASS patients, our aim being to evaluate the prevalence of PH in ASS and to describe more specifically patients with pre-capillary PH attested by a RHC, in order to identify both the causes of PH and the features associated with PH development.

PATIENTS & METHODS

Patients

This 2008-2012 retrospective study was conducted in nine French university hospitals. Identification of the patients (n=258) was performed in each center through the Laboratory of Immunology databases. We included 203 patients who met the following inclusion criteria: 1) two successive positive tests for anti-ARS, including LUMINEX-100 system (Luminex, Austin, TX, USA), ENA-LISA-kit (Biomedical diagnostics, Marne-la-vallée, France), and IMMUNO-DOT (Euroimmun AG, Lübeck, Germany or Diasorin, Saluggia, Italy); 2) clinical involvement in accordance with ASS, including ILD, muscle or rheumatic involvements [21]; 3) Realization of at least one echocardiography during the follow-up period. All patients were anonymously reported, and this study was approved by the institutional review board of each participating center.

Data collection

Demographic information, comorbidities, clinical history of ASS, imaging findings (including high thoracic resolution computed-tomography scan (HRCT) and echocardiography), pulmonary function tests, RHC, biological data and detailed medical treatment were collected. Data collection was compiled by BH, AM and CD using the same form.

Definitions

The onset of ASS was defined by the first occurrence of either pulmonary, muscular or rheumatic symptoms. ILD was defined by the results of HRCT and abnormal pulmonary function tests (forced vital capacity: FVC < 70% predicted and/or diffusing capacity of the lung for carbon monoxide: DLCO < 70% predicted). The characterization of the ILD pattern

was made by radiologists experienced in ILD assessment, and was based on the international consensus [22]. The HRCT of 15/16 patients with PH on RHC were retrospectively reviewed in consensus by BH, DL, DM, EH and PG. The extension of the ILD was evaluated by two different methods, as previously described [23;24]. In addition to the extension scores, a coarseness score was assigned where a reticular pattern was identified (Grade 1: fine intralobular fibrosis predominating; Grade 2: microcystic pattern with airspaces < 3 mm; Grade 3: large cysts > 3 mm. Scores were then summed, with a maximum score of 15).

Experienced cardiologists from each tertiary care center measured the echocardiographic parameters. PH was suspected on echocardiography and diagnosis was confirmed by RHC according to the judgement of each experienced physician in charge of the patient (on the basis of the European Respiratory Society and the European Society of Cardiology guidelines [25]). By echocardiography, PH was "possible" when systolic pulmonary artery pressure (PAP) was 37-50 mmHg, and/or tricuspid regurgitation velocity 2.8-3.4 m/sec. PH was "likely" when tricuspid regurgitation velocity was >3.4 m/s, and/or estimated systolic PAP was > 50 mmHg. By definition, the time of the diagnosis of PH was retrospectively based on the first positive echocardiographic screening.

Pre-capillary PH was defined during RHC as mean PAP ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg [25]. In the presence of an ILD and as previously described [16], pre-capillary PH was classified as PH-ILD. In patients with PH-ILD and a mean PAP ≥ 35 mmHg, the PH was considered severe, i.e. "out of proportion" [26]. Thromboembolic PH was defined by pre-capillary PH, past medical history of pulmonary embolism and positive 99Tc ventilation/perfusion scintigraphy (n=9) and/or angio-CT (n=7).

According to the American College of Rheumatology [27], signs and symptoms suggestive of associated SSc were: sclerodactyly, skin sclerosis and digital ulcers. Raynaud's phenomenon and ILD, as part of the ASS, were not considered as being SSc symptoms.

Statistical analysis

For the bivariate analysis, quantitative data were described as means (± standard deviation) and qualitative data as numbers and percentages. The Student or non-parametric Mann-Whitney tests were used for comparison of continuous variables while the χ^2 test was used for comparison of categorical variables. The Kaplan-Meyer method and log rank tests were used to compare survival between groups. A multivariate model using cox regression analysis was built to identify the variables independently associated with the survival. A *p*-value < .05 was considered significant. All the analyses were performed using SAS software (version 9.3, SAS Institute, Inc. Cary, NC).

RESULTS

Overall cohort description

Among the 203 patients, 150 were women and 53 were men (female/male ratio = 2.7). The medium age at onset was 49 ± 15.2 years and the mean follow-up was 78 ± 67 months. Over the course of the disease, ILD (86%, n=174) was the most common ASS manifestation, followed by inflammatory myositis (73%, n=148) and arthralgia/arthritis (60%, n=122). The immunological analyses of the patients' sera showed five different anti-ARS, anti-Jo1 being the most common (almost 66% of the patients), whereas anti-OJ and anti-EJ were exceptional in this population, which was mostly Caucasian (n=159, 78%)..

Prevalence of PH and pre-capillary PH in ASS

Of the included patients, 47 (23.2% of the whole cohort) were positively screened for PH (mean systolic PAP = 53 ± 16 mmHg), 27 (13.3%) patients being classified as PH "possible" and 20 (9.9%) as PH "likely" (Figure 1). Left ventricular ejection fraction was normal in 38 out of these 47 patients (81%). After echocardiographic screening of "possible or likely PH", RHC was performed in only 45% of the cases (n=21) and was mostly performed in patients who were classified as "PH likely" (55%). RHC confirmed the diagnosis of pre-capillary PH in 16 patients (7.9% of overall population) and was normal at rest in the 5 remaining cases. Then, among the patient with pre-capillary PH confirmed by RHC, 48% were screened by echocardiography as 'PH possible and 52% as 'PH likely'. Of note, on RHC, no patient had post-capillary PH (PCWP at rest < 15mmHg in all cases).

Comparisons of patients with pre-capillary PH and patients without PH on echocardiography

Clinico-biological features of patients with pre-capillary PH confirmed by RHC, were then compared to patients who were PH "unlikely" (based on normal echocardiographic screening). As shown in Table 1, arthralgia/arthritis were less common at diagnosis in patients developing pre-capillary PH than in patients without PH (38% *vs* 65%, p=0.028). This was the only phenotypic difference between the two groups of patients. Although systematic at the steady state of the disease in patients with pre-capillary PH, the occurrence of ILD was not significantly higher than in patients without PH (100% *vs* 81%, p=0.059). The ILD was not more severe clinically at diagnosis (NYHA functional class III or IV) in patients developing pre-capillary PH than in patients with ILD but without pre-capillary PH (n=127). However, the initial DL_{CO} as well as the FVC/DL_{CO} ratio were significantly different from those in patients without PH (38% ± 18 *vs* 53% ± 18 predicted, p=0.0015 and 2.1 ± 1.0 *vs* 1.4 ± 0.5, p=0.009, respectively). In contrast, FVC at the ASS diagnosis was similar in both groups. The distribution of the different ILD patterns on HRCT was statistically equivalent in patients without PH and in those with pre-capillary PH. The distribution of anti-ARS and other associated auto-Abs was similar in both groups.

Severity among patients with pre-capillary PH

The patients with pre-capillary PH confirmed by RHC (n=16) were mostly women (n=15, 94%) (Table 2). The diagnosis of pre-capillary PH was made 86 ± 60 months after the onset of ASS symptoms. At this time, nearly 69% (n=11) of the patients complained of severe dyspnea (NYHA functional class III/IV). Echocardiographic data are listed in Table 2. RHC showed increase in mean PAP (43.5 ± 10 mmHg) and normal PCWP (9 ± 4 mmHg). Acute

vasodilator testing with nitric oxide was performed in 10 patients and no acute response was observed.

All the patients with pre-capillary PH presented an ILD on HRCT and were diagnosed as "PH-ILD". However, one patient had a mixed PH (patient 9), with a possible chronic thomboembolic PH. No other cause of PH was found in the other patients.

Among these 16 patients, PH was considered as severe (mean PAP> 35 mmHg) in 13 cases (81%) with a mean PAP of 46 ± 9 mmHg. Moreover, the cardiac index (mean of 2.3 ± 0.8 L/min/m^2) of these patients was significantly decreased and pulmonary vascular resistance was dramatically increased (mean of 11.5 ± 19.2). These hemodynamic parameters contrasted with the mild severity of the parenchymal lung involvement. As shown in figure 2, the ILD pattern was a more or less fibrosing non-specific interstitial pneumonia in most patients (n=13, 81%) with a median coarseness score of 8 (ranging from 4 to 12). Although ILD was frequently extensive (n=13/14, 93%) [23], the median extension score [24] was 19% (3.5-45%). The decrease of the FVC (mean of 66% ± 13% predicted) and the DL_{CO}/VA ratio (mean of 53 ± 11%), were moderate, whereas the decrease of the DL_{CO} (mean of 28% ± 6%) was dramatically severe. Moreover, the FVC/DL_{CO} ratio was increased in these most severe patients (mean of 2.5 ± 0.6). Importantly, $PaCO_2$ was normal in all these cases at time of diagnosis of PH.

Management of patients with pre-capillary PH

The median follow-up of the 16 patients after PH diagnosis was 43 ± 50 months. PAH specific treatment was started in 13 out of the 16 patients (81%) with a mean of 23 ± 43 months after the PH diagnosis. As shown in Table 3, in all but two cases, a monotherapy was initiated. However, in seven cases, an initial (n=2) or sequential combined-therapy (n=5) was proposed. Specific PAH therapies included endothelin receptor antagonists (n=13),

phosphodiesterase 5 inhibitors (n=7) and prostanoid (n=3). Due to other symptoms of ASS and independently of the PH diagnosis, steroids and/or immunosuppressive drugs were also given to 15 patients (94%). During the follow-up period, one patient underwent lung transplantation and seven patients died due to acute or chronic respiratory or heart failure.

Survival analyses

When comparing survival from the onset of ASS between patients developing pre-capillary PH confirmed by RHC and patients without PH on echocardiography (n=156), pre-capillary PH was associated with a dramatically lower long-term survival rate (hazard ratio = 6.8, 95% confidence interval = 3.6-73.6, $p<0.001$). A similar result is also found in patients for whom the PH was only suspected by echocardiography (n=26, hazard ratio = 10.0, 95% confidence interval = 2.9-34.4, $p<0.001$). Since all the patients with pre-capillary PH presented an ILD, we also compared the survival rate of these patients to ASS patients displaying ILD without PH on echocardiography (n=127, Figure 3). As shown in Table 4, five parameters were associated with the survival, including severe dyspnea (NYHA III/IV) at diagnosis and pre-capillary PH confirmed by RHC. Importantly, the multivariate analysis showed that pre-capillary PH correlated independently of the other variables with a lower survival (hazard ratio of 5.7, $p=0.039$), suggesting that the occurrence of pre-capillary PH in patients with ILD was by itself a dramatic aggravating factor of ASS. Indeed, in the patients with pre-capillary PH confirmed by RHC, three-year survival rate after PH diagnosis was 58%.

DISCUSSION

Based on RHC, the prevalence of PH in this retrospective study is 7.9%. However, since 21% of the patients from this series were not screened for PH by TTE and since only 45% of the patients positively screened by echocardiography underwent a RHC to confirm the PH, this prevalence could have been underestimated. Nevertheless, these data suggest that - although rarely reported - occurrence of PH during ASS is not a rare complication. Furthermore, this prevalence is similar to other connective tissue diseases such as systemic lupus [5;6], but slightly lower than SSc [7;8]. Similarly to SSc, dyspnea in ASS has many causes, including ILD, PH or anemia. Moreover, in ASS, muscle involvement impacts both breathing and exercise capacity, leading to specific difficulties in diagnosing the dyspnea and its aetiology. According to these data, it could therefore be recommended to perform echocardiography in patients with ASS, particularly in presence of unexplained or severe dyspnea. Additionally, echocardiography should be repeated throughout the course of the disease, and especially when the severity of the dyspnea seems "out of proportion" to the severity of the ILD itself.

By comparing the patients without PH to the patients with pre-capillary PH as confirmed by RHC, the analysis showed how difficult it was to distinguish the patients at risk of developing pre-capillary PH. Indeed, only a few clinical and biological features present at diagnosis or during the course of the disease were associated with the occurrence of pre-capillary PH. These patients systematically showed an ILD and rarely complained of arthralgia/arthritis. It is therefore important to carefully analyze the HRCT (ILD pattern and extension) and pulmonary function test results, as the patients with pre-capillary PH lower DL_{CO} (or higher FVC/DL_{CO} ratio) upon first investigation. Furthermore, diagnosing PH in such a context is of

particular importance, since it could require specific management and could impact the patient outcome.

When analyzing the group of patients with pre-capillary PH confirmed by RHC, we observed that the time between ASS and PH onset was quite long (a mean of over 7 years). However, it is difficult to determine whether this delay -which is similar to what was found in series of SSc [15;28]- was caused by a late progression of the disease or a late diagnosis. However, since most of the patients were severe at PH diagnosis (based on the NYHA functional class and hemodynamic parameters), and since suspecting PH in the presence of ILD is very challenging, we could consider that the diagnosis of PH was delayed. These data should also encourage clinicians to perform echocardiographies early on and repeatedly over the course of the disease.

As the 16 patients with pre-capillary PH on RHC suffered from ILD, the retained mechanism of pre-capillary PH was PH-ILD. However, 81.3% of these patients with PH-ILD disclosed a severe PH (mPAP >35 mmHg), which could be considered "out-of-proportion" according to lung parenchymal involvement. Moreover, a FVC/DL_{CO} ratio > 1.8, a possible marker of pulmonary vascular disease in SSc [15], was frequently observed (n=14, 88% of the patients). These parameters suggest that ASS associated PH may be at least in part the consequence of a specific pulmonary vascular involvement. Furthermore, in the patients from the current series, pre-capillary PH was frequently associated with Raynaud's phenomenon, capillaroscopic abnormalities (data not shown) and dramatic increase in pulmonary vascular resistance. It is also of note that some have shown that sera from patients with anti-Jo1 Abs positive ASS can activate endothelial cells in vitro [29]. Altogether these data reinforce the hypothesis that in the context of ASS, PH-ILD may be associated with specific pulmonary vascular

involvement. In this series, most PH-ILD patients (n=10, 63%) displayed a low cardiac index (median 2.4, range 1-6), which is a classic hemodynamic parameter of severity in all forms of PH. Interestingly, the mean cardiac index was herein quite similar to the values previously reported in PH-ILD related to SSc [7;15]. In these patients with precapillary PH, no signs pointing to a left ventricular dysfunction (due to a specific inflammatory myocarditis and/or a proximal coronaropathy) was reported. This myocardial involvement could therefore be related to an involvement of the cardiac microvasculature leading to a worse cardiac adaptation to PH (as reported in SSc [30]).

Although some small retrospective studies suggested that specific PH therapy may be discussed in the presence of "out-of-proportion" due-to-lung-disease PH [16;25], the clinical benefit of this therapy still has not been rigorously demonstrated in this setting. Then, in regards to the current guidelines no specific treatment in PH related to any chronic lung disease, including ILD, is yet recommended. Nonetheless, most of the patients from the current series received specific PAH therapy because of the severity of the pre-capillary PH. As ILD was systematic and as both PH and ILD evolutions are closely linked, different immunosuppressive drugs were also given in association to PAH treatments. For these reasons and due to the retrospective nature of this study it was not possible to rigorously determine the impact of such treatments in these patients. Indeed, further prospective studies are needed to confirm the benefit/risk ratio of this strategy in ASS patients.

Similarly to what has been reported for idiopathic pulmonary fibrosis [31], or other underlying diseases [7;15;16;32], the survival analyses confirmed that PH in ASS worsened the prognosis, independently of its confirmation by RHC and of its supposed mechanism.

These data clearly show the need for a systematic PH screening by TTE and also for a RHC confirmation in all the suspected cases.

However, the three-year survival of the patients with PH confirmed by RHC (58%) could appear slightly better than previously reported in these diseases [16;31], but the diagnosis of PH in this study was based on the first positive echocardiography rather than on the RHC. Unlike what has been reported on SSc [15;32], we were not able to find individual factors associated with a poor outcome among patients with pre-capillary PH, due to the small number of patients. Larger series and series comparing the prognosis of ASS patients with patients suffering from other connective tissue diseases, such as SSc, or idiopathic pulmonary fibrosis with PH, would be of interest.

In summary, this series showed for the first time that pre-capillary PH is not a rare complication of ASS. PH is mainly related to ILD and associated with a poor outcome. Clinically diagnosing PH in this condition is particularly difficult but of importance. Altogether these data should encourage clinicians to perform a screening of PH by echocardiography in the context of ASS, to do so early on, more systematically and more regularly, and to rigorously confirm pre-capillary PH by RHC.

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TABLES AND LEGENDS

Table 1: Patient characteristics according to the diagnosis of pre-capillary PH.

Abs: antibodies; ILD: interstitial lung disease; sPAP: systolic pulmonary artery pressure; TTE: trans-thoracic echocardiography; pre-cap PH: pre-capillary pulmonary hypertension (mean pulmonary artery pressure ≥ 25 mmHg + pulmonary capillary wedge pressure ≤ 15 mmHg); RHC: right heart catheterization. DM: dermatomyositis; SSc: Systemic Sclerosis; UIP: usual interstitial pneumonia; NSIP: non specific interstitial pneumonia; OP: organizing pneumonia; FVC: mean forced vital capacity (% predicted); DL_{CO}: mean diffusing capacity of the lung for carbon monoxide (% predicted); ǂ: from the first pulmonary function tests after the ILD diagnosis; *: considering only patients with ILD. ** This included: sclerodactyly, skin sclerosis and digital ulcers.

		normal estimate sPAP on TTE (<37mmHg) (n=156)	pre-cap PH on RHC (n=16)	*p*-value
Demographic data	Mean Age at onset (years)	48.2 ± 15.2	50.8 ± 12.6	0.52
	Men	43 (28%)	1 (6%)	0.063
	Mean Follow-up (months)	72 ± 67	130 ± 65	**0.001**
Main Status	Myositis	113 (72%)	10 (63%)	0.40
	ILD	127 (81%)	16 (100%)	0.059
Phenotype at diagnosis	Muscle weakness	71 (46%)	5 (31%)	0.27
	Severe dyspnea (NYHA III/IV)	35 (22%)	7 (44%)	0.059
	Polyarthralgia	102 (65%)	6 (38%)	**0.028**
	Raynaud's phenomenon	66 (42%)	10 (63%)	0.12
	Mechanic's hands	29 (19%)	3 (19%)	0.99
	Cutaneous signs of DM	42 (27%)	3 (19%)	0.48
	Clinical signs of associated SSc**	43 (28%)	8 (50%)	0.061
Auto-Abs	Anti-Jo1	103 (66%)	8 (50%)	0.21
	Anti-PL7	17 (11%)	2 (13%)	0.85
	Anti-PL12	34 (22%)	5 (31%)	0.39
	Anti-OJ	1 (1%)	0	0.75
	Anti-EJ	1 (1%)	1 (6%)	0.27
	Anti-SSA-52 kDa	68 (44%)	6 (38%)	0.64
	Anti-SSA-60 kDa	33 (21%)	1 (6%)	0.41
	Anti-SSB	11 (7%)	0	0.27
	Anti-topoisomerase I/-Centromere	9 (5%)	1 (6%)	0.94
	Anti-RNP	3 (2%)	1 (6%)	0.27
	Anti-Sm/-Anti-DNA	3 (2%)	0 (0%)	0.58
		n=127	**n=16**	
ILD*	NSIP	103 (81%)	13 (81%)	1.00
	UIP	11 (9%)	3 (19%)	0.193
	OP	13 (10%))	0 (0%)	0.36
	FVC‡	70 ± 19	71 ± 24	0.86
	DLCO‡	53 ± 18	39 ± 18	**0.0015**
	FVC/DLCO‡	1.4 ± 0.5	2.1 ± 1.0	**0.009**

Table 2: Lung and heart evaluations of patients with pre-capillary pulmonary hypertension at first RHC.

ASS: antisynthetase syndrome; (m): months; RHC: right heart catheterization; PH: pulmonary hypertension; RP: Raynaud's phenomenon; BNP: brain natriuretic peptide; LV: left ventricular, AAN: antinuclear antibody titer (indirect fluorescence on Hep2 cells); sPAP: systolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; CI: cardiac index; PVR: pulmonary vascular resistance; ILD: interstitial lung disease; HRCT: thoracic high resolution computed tomography scan. N: normal; na: not applicable; nd: not determined; nr: normal range; w: woman, m: man; (m): months); (y): years; UIP: usual interstitial pneumonia, NSIP: non specific interstitial pneumonia. IVS: intra-ventricular septum; *: RHC was performed under specific PH treatment; [£]: all the investigations were performed at the tame time ± six months (with the exception of Patient 6's six minutes walk test). FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; TLC: total lung capacity; RV: residual volume; DL_{CO}: diffusing capacity of carbon monoxyde; AV: alveolar volume. IVS: inter-ventricular septum; L: liter; [+]: hospitalized in Intensive care Unit, for right heart failure, necessitating vassopressor drugs. The dilatation of the right ventricle lead to IVS and inhibited the left ventricle work. °: insufficient follow-up. $: 99Tc ventilation/perfusion scintigraphy was normal; ** : diaphragm dysfunction; ‡ according to Goh NS et al. classification [23];[++] according to McDonald SLS & al [24]. °°A coarseness score was assigned where a reticular pattern was identified, with a maximum score of 15. ¥ NSIP without fibrosis corresponded to the predominance of round-glass opacity, more or less associated fine reticulation without traction bronchiectasis or bronchiolectasis, without loss of lung volume and without honeycombing; NSIP with fibrosis corresponded to the predominance of reticular opacities, more or less associated with ground-glass opacities, traction bronchiectasis or

bronchiolectasis and with loss of lung volume, and absence of honeycombing; UIP: corresponded to the predominance of reticular pattern associated with honeycombing in the subpleural areas of the lung bases. PH diagnosis was based on the first positive echocardiography; pre-capillary PH was defined during RHC as mean pulmonary artery pressure (PAP) ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg. PH-ILD corresponded to pre-capillary PH associated ILD In case of severe PH-ILD with a mean PAP ≥ 35 mmHg, the PH was considered “out of proportion”. Thromboembolic(TE)-PH was defined by the association of pre-capillary PH, past medical history of pulmonary embolism and positive 99Tc ventilation/perfusion scintigraphy or angio-CT.

	1*	2	3	4**	5	6	7	8	9	10	11+	12	13	14	15	16
Gender, Age at ASS onset (y)	**w, 31**	**w, 53**	**w, 50**	**w, 44**	**w, 50**	**w, 44**	**w, 59**	**w, 63**	**w, 52**	**w, 33**	**w, 67**	**m, 65**	**w, 52**	**w, 40**	**w, 74**	**w, 34**
Time between onset of ASS & first positive echocardiography (m)	47	93	23	65	156	141	41	36	134	179	106	58	7	72	21	202
Time between first positive echocardiography & RHC (m)	182	5	0	0	16	0	26	0	3	1	0	1	5	2	0	16
NYHA functional class	II	II	II	II	III	III	III	III	III	III	III	III	III	III	II	III
Biological data£																
AAN, Cytoplasmic	1/1280, Cytoplasmic	none	1/160, negative	1/640, negative	1/160, negative	1/1280, negative	none, Cytoplasmic	1/160, Cytoplasmic	1/80, negative	1/80, Cytoplasmic	1/160, Cytoplasmic	1/320, Cytoplasmic	none	1/320, Cytoplasmic	none, Cytoplasmic	1/1280, Cytoplasmic
Ab Specificites	Jo1, SSA-52	Jo1, SSA-52	Jo1, SSA-52 & 60	PL12	Jo1	PL7, SSA-52, Scl-70	PL12	PL12	Jo1	Jo1, RNP	Jo1	EJ, SSA-52	PL12, SSA-52	PL12, SSA-52	PL7	Jo1, SSA-60
BNP or NT-pro-BNP	N	N	nd	4.8 x nr	nd	nd	nd	3 x nr	2 x nr	nd	nd	3.9 x nr	N	13 x nr	nd	17 x nr
Pa O2 (mmHg)	65	84	60	75	57	54	52	37	68	57	48	45	51	60	61	67
Pa CO2 (mmHg)	28	36	30	41	35	37	24	31	38	45	40	36	36	32	33	32
pH	7.45	7.43	7.43	7.42	7.41	7.46	7.54	7.55	7.2	7.45	7.38	7.52	7.48	7,44	7,5	7.47
Echocardiography£																
LV function (%)	76	>60	>60	>60	80	>60	60	82	35	65	<40+	>60%	>60%	62	54	75
Right Ventricle	N	Dilatation	Dilatation	Dilatation Paradoxal IVS	Dilatation	nd	N	Dilatation	Dilatation	Dilated	Dilatation Paradoxal IVS	Dilatation Paradoxal IVS	N	N	Dilated	Dilated
sPAP (mmHg)	52	45	60	87	45	46	56	96	50	87	86	85	95	57	80	85
Right Heart Catheterization£																
mPAP (mmHg)	45	33	42	44	41	36	39	47	33	51	71	45	28	37	55	49
PWP (mmHg)	10	10	8	5	11	14	4	8	9	6	15	11	1	11	15	8
Q (L/min)	4.9	2.8	8	2.9	2.3	5.9	4.6	3.9	2.2	4.7	1.7	4.6	9.7	3.7	2.2	2.7
CI (L/min/m2)	3.4	2.2	4.9	2.1	1.5	2.9	2.5	2.4	1.4	3	1	3	6	2.5	1.2	1.9
PVR (U Wood)	7.1	8.2	4.3	13.4	13.0	3.7	7.6	10.0	10.9	9.6	32.9+	7.4	2.8	7.1	18.2	15.2
Pulmonary Function Tests£																
FVC (% predicted)	67	102	61	36	62	70	74	81	61	47	85	65	38	70	67	67
FEV1 (% predicted)	69	106	62	42	68	46	74	70	65	55	91	69	47	72	66	60
TLC (% predicted)	59	106	48	56	56	90	59	97	80	50	81	58	43	68	67	55
RV/TLC (% predicted)	91	109	67	171	88	149	108	131	129	115	112	88	112	87	116	78
DLCO (% predicted)	25	35	30	nd	25	45	25	28	31	25	25	30	20	27	27	20
DLCO/AV (% predicted)	50	38	69	nd	39	nd	52	43	59	54	42	65	46	nd	67	52
FVC/DLCO	2.7	2.9	2.0	nd	2.5	1.6	3.0	2.9	2.0	1.9	3.4	2.2	1.9	2.6	2.5	3.4
6' walk test£																
distance (m/%predicted)	300/54%	273/52%	450/84%	330/65%	215/41%	211/40%	nd	315/69#	242/45%	470/88%	nd	234/49%	180/32%	370/83%	nd	nd
i/f SpO2 (%) & O2 output	99/87	96/93	93/nd	92/90 (2L/min)	nd/70	91/81	nd	96/80#	97/93	97/nd (2L/min)	nd	93/83 (2L/min)	93/70 (4L/min)	91/78	nd	nd
HRCT£																
ILD pattern¥	UIP	NSIP	NSIP	fibrosing NSIP	UIP	NSIP & Emphysema	fibrosing NSIP	fibrosing NSIP	fibrosing NSIP	fibrosing NSIP	UIP	fibrosing NSIP	fibrosing NSIP	fibrosing NSIP	fibrosing NSIP	fibrosing NSIP
ILD: % extension/ Coarseness score°°	22%/12	21%/4	3.5%/4	21%/10	16%/11	na	27%/5	45%/9	16%/6	12%/8	nd	13%/7	26%/6	26%/10	17%/8	11%/11
Extension of the ILD‡	**extensive**	**extensive**	**limited**	**extensive**	**extensive**	**na**	**extensive**	**extensive**	**extensive**	**extensive**	**nd**	**extensive**	**extensive**	**extensive**	**extensive**	**extensive**
Type of PH	**severe PH-ILD**	**PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**PH-ILD+chronic TE-PH**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**

Table 3: Treatments and outcomes of patients with pre-capillary PH

PH: Pulmonary Hypertension; ILD: Interstitial Lung disease; m: months; MMF: Mycophenolate Mophetyl; CYC: Cyclophophamide; MAb: monoclonal antibodies; IV: Intraveinous; Ig: immunoglobulins.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11[+]**	**12**	**13**	**14**	**15**	**16**
Type of PH	**severe PH-ILD**	**PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**PH-ILD + chronic TE-PH**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**PH-ILD**	**severe PH-ILD**	**severe PH-ILD**	**severe PH-ILD**
Follow-up after PH diagnosis (m)	209	36	58	26	60	15	86	29	12	18	0	2	17	55	62	9
Specific treatments (dose & duration: m)	**Sitaxentan** (100 mg/d; 155-191) **Sildenafil** (60 mg/d; 186-209) **Bosentan** (250 mg/d; 196-209)	none	**Bosentan** *(250 mg/d; 7-58)*	**Epoprostenol** *(<30 ng/kg/min; 0-26)* **Sildenafil** *(60 mg/d; 10-26)* **Bosentan** *(250 mg/d; 15-26)*	**Bosentan** (250 mg/d; 34-39)	**Bosentan** (250 mg/d; 12-15) **Sildenafil** (60 mg/d; 13-15)	**Bosentan** (250 mg/d; 28-86)	**Bosentan** (250 mg/d; 5-7) **Sildenafil** (60 mg/d; 7-29) **Treprostinil** (13,75 ng/kg/min; 5-29) **Prednisolone** (15 mg/d; 0-29)	**Bosentan** (250 mg/d; 0-12)	**Bosentan** (250 mg/d; 5-18)	none	**Iloprost** (nebulization; 1-2)	none	**Bosentan** (250 md/d; 0-53) **Sildenafil** (60 mg/d; 13-53)	**Sildenafil** (60 mg/d; 52-62) **Ambrisentan** (10 mg/d; 52-62)	**Sildenafil** (60 mg/d; 0-9) **Ambrisentan** (10 mg/d; 0-9)
Immunosuppressive treatments (dose & duration: m)	**Methotrexate** *(<10 mg/w; 0-201)* **Prednisone** *(<10 mg/d; 0-205)* **MMF** *(2g/d; 201-205)*	**Prednisone** *(5 mg/d; 0-36)*	**Methotrexate** *(15 mg/w; 0-16)* **Prednisone** *(10 mg/d; 0-58)* **MMF** *(2g/d; 16-58)*	**Prednisone** *(10 mg/d; 0-26)* **Azathioprine** *(100 mg/d; 0-26)*	**Methotrexate** (12.5 mg/w; 0-34) **Prednisone** (10 mg/d; 0-34) **MMF** (2g/d; 38-53) **Ciclosporine** (nd/38-53)	**Prednisone** (10 mg/d; 0-15)	**Prednisone** (<30 mg/d; 0-86) **IV CYC** (9x750 mg/m^2; 13-22)	**IV CYC** (3x500 mg/m2; 0-3) **AntiCD20 Mab** (375 mg/m^{2}x3; 4-5) **MMF** (1,5g/d; 0-29) **IV Ig** (2g/kg/m; 16-29)	**Prednisone** (<50mg/d; 0-12) **MMF** (1.5g/d; 4-5) **IV CYC** (6x500 mg/m^2, 6-12)	**Prednisone** (<15 mg/d; 0-18) **Methotrexate** (15 mg/d; 0-1) **Leflunomide** (10mg/d, 1-2) **IV CYC** (3x750 mg/m2; 3-5)	**Prednisone** (10 mg/d) **Azathioprine** (100 mg/d)	none	**MMF** (2g/d; 0-4) **IV CYC** (6x750 mg/m^2; 5-11) **Prednisone** (<30 mg/d; 0-17) **Methylprednisolone** (3x15 mg/kg; 4) **AntiCD20 Mab** (2x1g, 13-14)	**Prednisone** (<20 mg/d; 0-53) **IV CYC** (18x750 mg/m2; 1-19) **MMF** (2g/d, 20-53)	**Prednisone** (5mg/d; 0-125) **Azathioprine** (150 mg/d; 0-24)	**Prednisone** (<12.5mg/d; 0-9) **Azathioprine** (50 mg/d; 0-9)
Final Status	Alive	Alive	Alive	Death (Respiratory Failure)	Death (Respiratory failure)	Death (left heart failure)	Alive	Death (respiratory failure)	Alive	Death (nd)	Death (Right heart failure)	Alive	Alive	yes (2 months after lung transplantation)	Alive	Alive

Table 4: Survival analyses

Bivariate analysis: Log rank tests were used to compare survival between groups. Multivariate Regression analysis: the pertinent variables proposed to the model: Age at onset, Severe Dyspnea at diagnosis, pre-capillary PH on RHC and anti-PL7/12-antibodies.

DM : dermatomyositis ; CI: confidence interval; RHC: right heart catheterization; FVC: forced vital capacity; DL_{CO}: diffusing capacity of carbon monoxyde *: This included: sclerodactyly, skin sclerosis and digital ulcers.

		Bivariate analysis	**Multivariate regression analysis**		
		***p*-value**	Odds Ratio	95% CI	***p*-value**
	Age > 50 at ASS onset	**<0.001**	3.2	0.9 - 19.4	0.075
Main Status	Myositis	**0.011**	-	-	
	ILD	0.22			
Phenotype at diagnosis	Muscle weakness	**<0.001**	-	-	
	Severe dyspnea	**0.002**	3.1	0.8 – 11.1	0.090
	Polyarthralgia	0.082			
	Raynaud's phenomenon	0.99			
	Mechanic's hands	0.29			
	Clinical signs of Systemic sclerosis	0.46			
	Cutaneous signs of DM	0.72			
	initial FVC < 70%	0.47			
	initial DL_{CO} < 60%	0.76			
	pre-capillary PH on RHC	**0.0056**	5.1	1.1 - 24.9	**0.042**
	Anti-PL7/12	**0.015**	6.3	1.1 - 35.4	**0.038**
Auto-Abs	Anti-Ro/SSA-52 kDa	0.54			
	Anti-Ro/SSA-60 kDa	0.051			

Figure 1: Prevalence of pulmonary hypertension in the cohort of patients with ASS, according to echocardiography and RHC results.

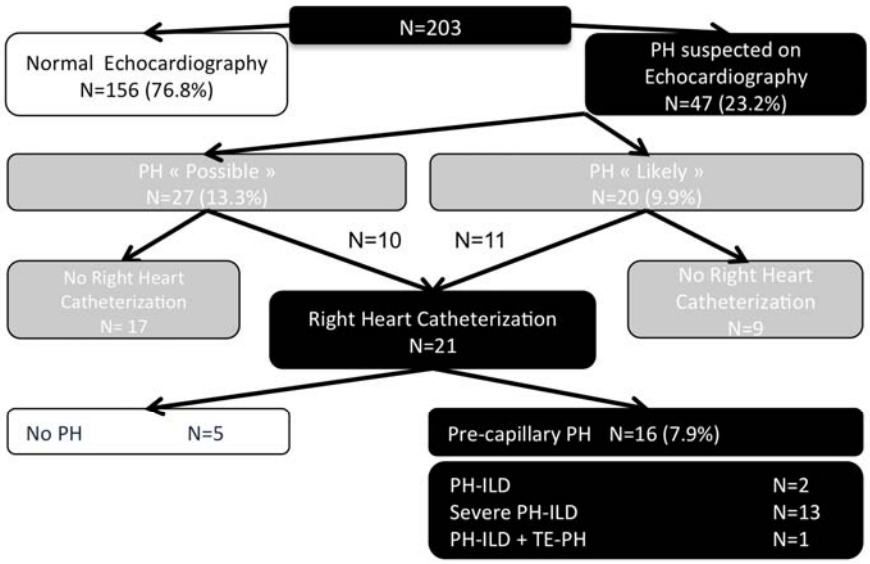

Figure 1: Prevalence of pulmonary hypertension in the cohort of patients with ASS, according to echocardiography and right heart catheterization results.

PH: pulmonary hypertension; pre-cap: pre-capillary; post-cap: post-capillary; PH-ILD: pre-capillary PH related to ILD; PAH: pulmonary arterial hypertension. Pre-capillary PH was defined during right heart catheterization as mean pulmonary artery pressure (PAP) ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg. PH-ILD corresponded to pre-capillary PH associated ILD on HRCT. Thromboembolic(TE)-PH was defined by the association of pre-capillary PH, past medical history of pulmonary embolism and positive 99Tc ventilation/perfusion scintigraphy or angio-CT.

PH: pulmonary hypertension; pre-cap: pre-capillary; post-cap: post-capillary; PH-ILD: pre-capillary PH related to ILD; PAH: pulmonary arterial hypertension. Pre-capillary PH was defined during RHC as mean pulmonary artery pressure (PAP) ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg. PH-ILD corresponded to pre-capillary PH associated ILD on HRCT. Thromboembolic(TE)-PH was defined by the association of pre-capillary PH, past medical history of pulmonary embolism and positive 99Tc ventilation/perfusion scintigraphy or angio-CT.

Figure 2: Representative thoracic-CT images of the ILD in patients with severe PH-ILD

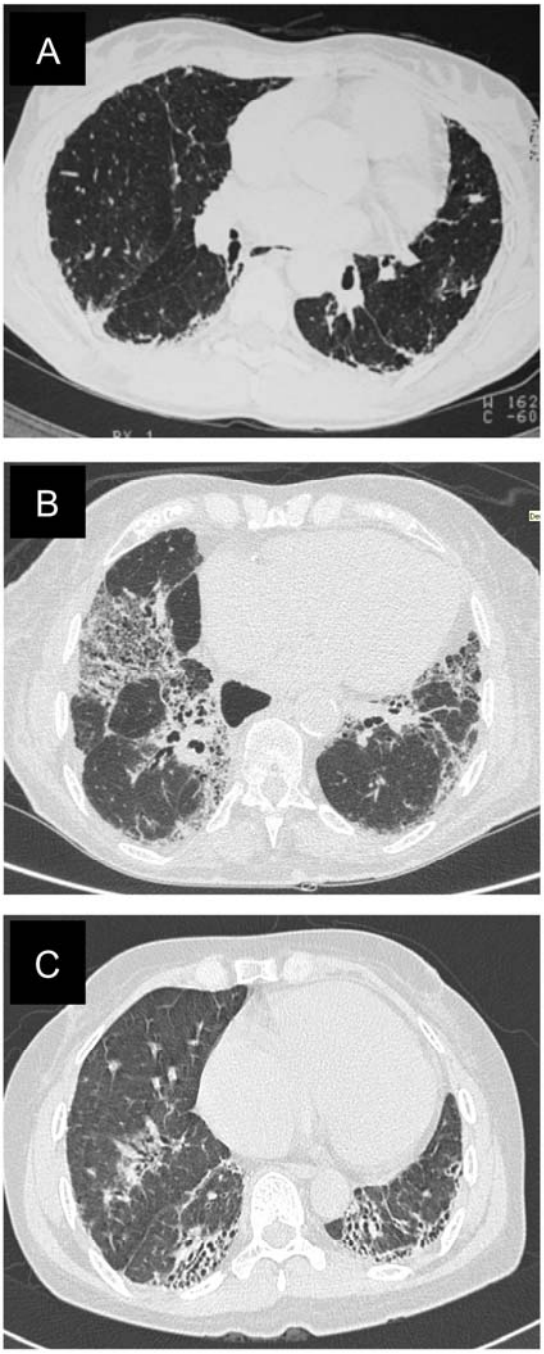

Figure 2: Representative thoracic-CT images of the ILD in patients with severe PH-ILD
HRCT images of the ILD in 3 different patients (A: patient 10, B: Patient 15, C: Patient 16), with a fibrosing non-specific interstitial pneumonia pattern, showing predominant reticular opacities more or less associated with ground glass opacities and traction bronciectasis or bronchio-lectasis. The lesions were bilateral and mainly localized to the posterior and basal areas of the lungs (lower lobes).

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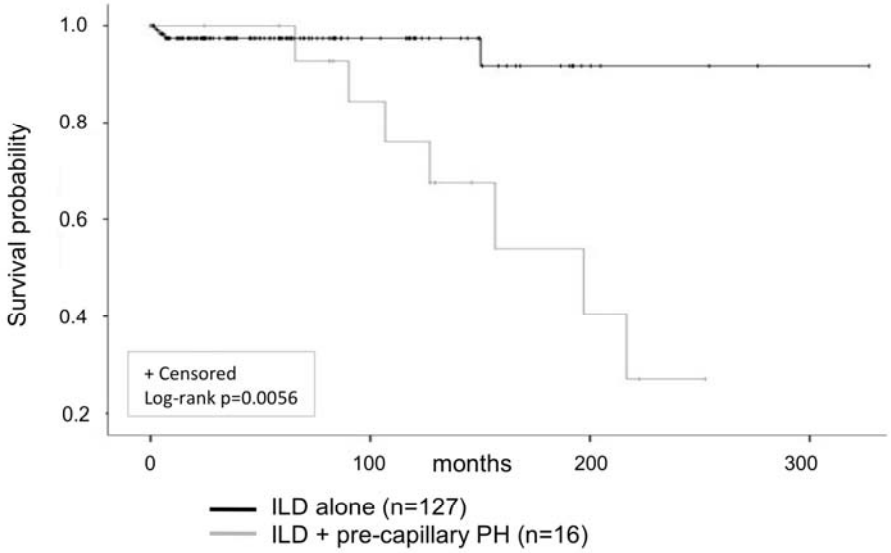
Figure 3: Kaplan-Meyer survival curve (from ASS diagnosis) comparing patients with ILD but without pulmonary hypertension (n=127, ILD alone, sPAP < 37 mmHg on TTE) to patients with pre-capillary pulmonary hypertension confirmed by RHC (n=16, all with ILD).



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Pre-capillary PH was defined during RHC as mean pulmonary artery pressure (PAP) ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg. ILD was defined by the results of HRCT and/or abnormal pulmonary function tests (Forced vital capacity: FVC < 70% predicted and/or diffusing capacity of the lung for carbon monoxide: DL_{CO} < 70% predicted). Log rank test was used to compare the survival rate between groups. TTE: transthoracic echocardiography.

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