Pulmonary hypertension in antisynthetase syndrome: prevalence, aetiology and survival

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ABSTRACT Antisynthetase syndrome is characterised by the association of interstitial lung disease and myositis with different anti-tRNA-synthetase antibodies. The occurrence, aetiology and prognosis of pulmonary hypertension have not yet been evaluated.

Among 203 consecutive patients, transthoracic echocardiogram and right heart catheterisation results were retrospectively analysed in the light of clinico-biological, morphological and functional parameters. Definitions of pulmonary hypertension were based on the European Society of Cardiology/European Respiratory Society 2009 guidelines, with severe pulmonary hypertension being defined by a mean pulmonary arterial pressure >35 mmHg.

Pulmonary hypertension was suspected by transthoracic echocardiogram in 47 (23.2%) cases, corresponding to pulmonary hypertension "possible" (n=27, 13.3%) or "likely" (n=20, 9.9%). Right heart catheterisation was performed in 21 patients, excluding pulmonary hypertension in five and confirming pre-capillary pulmonary hypertension in 16 (7.9%). Although related to interstitial lung disease in all cases, pre-capillary pulmonary hypertension was severe in 13 (81.3%) patients (mean±SD pulmonary arterial pressure 46±9 mmHg), frequently associated with low cardiac index (mean±SD 2.3±0.8 $L \cdot min^{-1} \cdot m^{-2}$) and high forced vital capacity/diffusing capacity of the lung for carbon monoxide ratio (2.5±0.6). Pulmonary hypertension was significantly associated with a lower survival rate ($p<0.001$), with a 3-year survival rate of 58%.

The occurrence of pulmonary hypertension in antisynthetase syndrome is significant and dramatically worsens the prognosis. Although systematically associated with interstitial lung disease, pulmonary hypertension was usually severe, suggesting a specific pulmonary vascular involvement.

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PH in antisynthetase syndrome significantly worsens the prognosis, suggesting a specific pulmonary vascular involvement http://ow.ly/okXyG

Introduction

Antisynthetase syndrome (ASS) was first described in 1990 as a heterogeneous connective tissue disease, characterised 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, with 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 antibody being <5% of the of the polymyositis and dermatomyositis patients). Although the anti-ARS could be associated with other anti-extractable nuclear antigen antibodies, including anti-Ro/SSA or anti-La/SSB antibodies, 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 and Raynaud's phenomenon. Associated symptoms of Sjögren's syndrome or systemic sclerosis (SSc) have also been reported in different proportions [1–4].

Pulmonary hypertension (PH) is, by itself, a severe life-threatening disorder, and is complicated with variable frequency with 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 aetiologies, 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 catheterisation (RHC) for a precise positive and aetiological diagnosis. Moreover, certain causes require specific treatments. These treatments could be essential, as 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, to date, the influence of cofactors associated with ILD, such as PH, has rarely been evaluated in large series. This led us to conduct this large multicentre 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 and methods

Patients

This 2008–2012 retrospective study was conducted in nine French university hospitals. Identification of the patients (n=258) was performed in each centre through the Laboratory of Immunology databases for each institution. 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]; and 3) realisation 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 centre.

Data collection

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

Definitions

The onset of ASS was defined by the first occurrence of pulmonary, muscular or rheumatic symptoms. ILD was defined by the results of HRCT and abnormal pulmonary function tests (forced vital capacity (FVC)

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<70% predicted and/or diffusing capacity of the lung for carbon monoxide (*D*LCO) <70% predicted). The characterisation of the ILD pattern was made by radiologists experienced in ILD assessment, and was based on the international consensus [22]. The HRCT scans of 15 out of 16 patients with PH on RHC were retrospectively reviewed in consensus by B. Hervier, D. Launay, D. Montani, E. Hachulla and P. Grenier. 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; and grade 3: large cysts >3 mm. Scores were then summed, with a maximum score of 15).

Experienced cardiologists from each tertiary care centre 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/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 $m \cdot s^{-1}$. PH was ''likely'' when tricuspid regurgitation velocity was >3.4 $m \cdot s^{-1}$, 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 (P_{pcw}) ⩽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 [26]. Thromboembolic PH was defined by pre-capillary PH, past medical history of pulmonary embolism and positive ^{99}Tc 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 are sclerodactyly, skin sclerosis and digital ulcers. Raynaud's phenomenon and ILD, as part of the ASS, were not considered to be SSc symptoms.

Statistical analysis

For the bivariate analysis, quantitative data were described as mean±SD and qualitative data as numbers and percentages. The t-test or nonparametric Mann–Whitney tests were used for comparison of continuous variables while the Chi-squared test was used for comparison of categorical variables. The Kaplan–Meier 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 <0.05 was considered significant. All the analyses were performed using SAS software (version 9.3; SAS Institute, Inc., Cary, NC, USA).

Results

Overall cohort description

Among the 203 patients, 150 were females and 53 were males (female/male ratio 2.7). The mean±SD age at onset was 49±15.2 years and the mean±SD follow-up was 78±67 months. Over the course of the disease, ILD (n=174, 86%) was the most common ASS manifestation, followed by inflammatory myositis (n=148, 73%) and arthralgia/arthritis (n=122, 60%). The immunological analyses of the patients' sera showed five different anti-ARS, anti-Jo1 being the most common (occurring in almost 66% of the patients), whereas anti-OJ and anti-EJ were unusual 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), with 27 (13.3%) patients being classified as PH ''possible'' and 20 (9.9%) as PH ''likely'' (fig. 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 21 (45%) of the cases 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 five remaining cases. Of note among the patient with pre-capillary PH confirmed by RHC, 48% were screened by echocardiography as PH ''possible'' and 52% as PH ''likely''. It is noteworthy that, on RHC, no patient had post-capillary PH (P_{pcw} at rest <15 mmHg 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 with 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 *versus* 65%; p=0.028). This was the only phenotypic difference between the two groups of

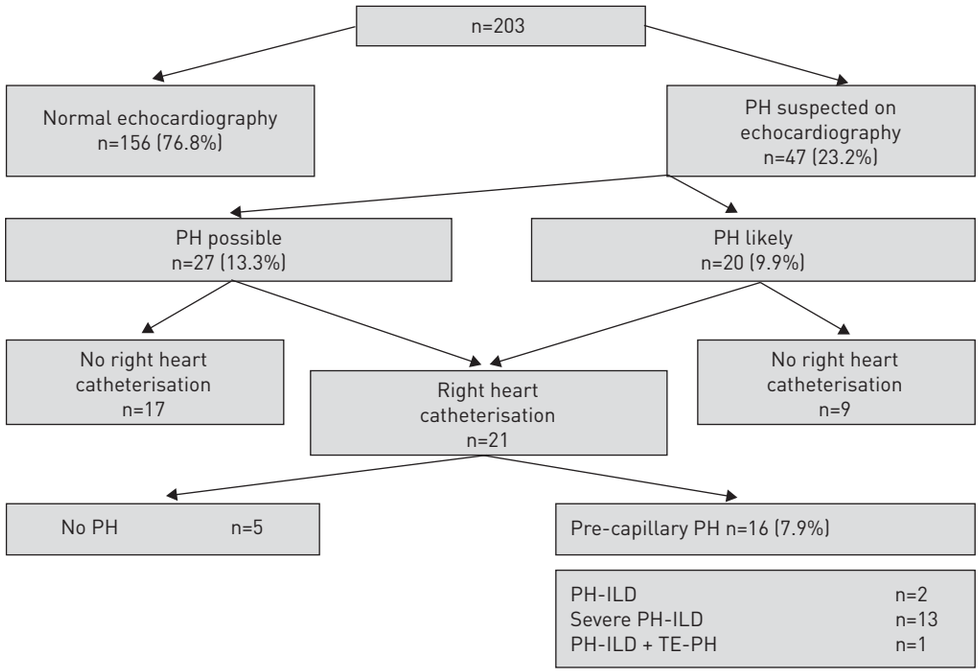

FIGURE 1 Prevalence of pulmonary hypertension (PH) in the cohort of patients with antisynthetase syndrome according to echocardiography and right heart catheterisation results. Pre-capillary PH was defined during right heart catheterisation as mean pulmonary artery pressure $\geqslant$25 mmHg and pulmonary capillary wedge pressure $\leqslant$15 mmHg. Pre-capillary PH related to interstitial lung disease (PH-ILD) was observed by high-resolution computed tomography. Thromboembolic (TE)-PH was defined by the association of pre-capillary PH, past medical history of pulmonary embolism and positive ^{99}Tc ventilation/perfusion scintigraphy or angio-computed tomography.

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 *versus* 81%; p=0.059). The ILD was clinically not more severe at diagnosis (New York Heart Association (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 D_{LCO} and the FVC/D_{LCO} ratio were significantly different from those in patients without PH (39$\pm$18% *versus* 53$\pm$18% predicted, p=0.0015, and 2.1$\pm$1.0 *versus* 1.4$\pm$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-antibodies 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 females (n=15, 94%) (table 2). The diagnosis of pre-capillary PH was made 86$\pm$60 months after the onset of ASS symptoms. At this time, nearly 69% (n=11) of the patients complained of severe dyspnoea (NYHA functional class III or IV). Echocardiographic data are listed in table 2. RHC showed an increase in mean PAP (43.5$\pm$10 mmHg) and normal P_{pcw} (9$\pm$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$\pm$9 mmHg. Moreover, the cardiac index (mean$\pm$SD 2.3$\pm$0.8 L·min^{-1}·m^{-2}) of these patients was significantly decreased and pulmonary vascular resistance was dramatically increased (mean$\pm$SD 11.5$\pm$19.2 Wood units). These haemodynamic 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 nonspecific 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

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TABLE 1 Patient characteristics according to the diagnosis of pre-capillary pulmonary hypertension (PH)

	Normal estimate sPAP on TTE (<37 mmHg)	Pre-capillary PH on RHC[#]	p-value
Subjects	156	16	
Demographic data			
Age at onset years	48.2±15.2	50.8±12.6	0.52
Males	43 (28)	1 (6)	0.063
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 dyspnoea (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-antibodies			
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
ILD[+]			
NSIP	103 (81)	13 (81)	1.00
UIP	11 (9)	3 (19)	0.193
OP	13 (10)	0 (0)	0.36
FVC[§] % pred	70±19	71±24	0.86
D_{LCO}[§] % pred	53±18	39±18	**0.0015**
FVC/D_{LCO}[§]	1.4±0.5	2.1±1.0	**0.009**

Data are presented as n, mean± SD or n (%), unless otherwise stated. sPAP: systolic pulmonary artery pressure; TTE: transthoracic echocardiography; RHC: right heart catheterisation; ILD: interstitial lung disease; NYHA: New York Heart Association; DM: dermatomyositis; SSc: systemic sclerosis; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; OP: organising pneumonia; FVC: forced vital capacity; % pred: % predicted; D_{LCO}: diffusing capacity of the lung for carbon monoxide. [#]: mean pulmonary artery pressure ⩾25 mmHg and pulmonary capillary wedge pressure ⩽15 mmHg; [¶]: this included sclerodactyly, skin sclerosis and digital ulcers; [+]: considering only patients with ILD; n=127 and n=16 for normal estimate sPAP on TTE (<37 mmHg) and pre-capillary PH on RHC, respectively; [§]: from the first pulmonary function tests after the ILD diagnosis.

score [24] was 19% (3.5–45%). The decrease of the FVC (mean± SD 66%±13% predicted) and the D_{LCO}/alveolar volume ratio (mean± SD 53±11%), were moderate, whereas the decrease of the $D_{L,CO}$ (mean± SD 28%±6%) was dramatically more severe. Moreover, the FVC/D_{LCO} ratio was increased in these most severe patients (mean± SD 2.5±0.6). Importantly, P_{aCO_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%) at 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.

TABLE 2 Lung and heart evaluations of patients with pre-capillary pulmonary hypertension (PH) at first right heart catheterisation (RHC)

Patient	1[#]	2	3	4[¶]	5	6	7	8	9	10	11[+]	12	13	14	15	16
Sex, age at ASS onset years	F, 31	F, 53	F, 50	F, 44	F, 50	F, 44	F, 59	F, 63	F, 52	F, 33	F, 67	M, 65	F, 52	F, 40	F, 74	F, 34
Time between onset of ASS and first positive echocardiography months	47	93	23	65	156	141	41	36	134	179	106	58	7	72	21	202
Time between first positive echocardiography and RHC months	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 Antibodies' specificites	1/1280, cytoplasmic Jo1, SSA-52	None Jo1, SSA-52	1/160, negative Jo1, SSA-52 & 60	1/640, negative PL12	1/160, negative Jo1	1/1280, negative PL7, SSA-52, Scl-70	None, cytoplasmic PL12	1/160, cytoplasmic PL12	1/80, negative Jo1	1/80, cytoplasmic Jo1, RNP	1/160, cytoplasmic Jo1	1/320, cytoplasmic EJ, SSA-52	None PL12, SSA-52	1/320, cytoplasmic PL12, SSA-52	None, cytoplasmic PL7	1/1280, cytoplasmic Jo1, SSA-60
BNP or NT-proBNP	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
P_{aO_2} mmHg	65	84	60	75	57	54	52	37	68	57	48	45	51	60	61	67
P_{aCO_2} 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
RHC[§]																
mPAP mmHg	45	33	42	44	41	36	39	47	33	51	71	45	28	37	55	49
P_{pcw} mmHg	10	10	8	5	11	14	4	8	9	6	15	11	1	11	15	8
Q' L·min^{-1}	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 Wood units	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 % pred	67	102	61	36	62	70	74	81	61	47	85	65	38	70	67	67
FEV_1 % pred	69	106	62	42	68	46	74	70	65	55	91	69	47	72	66	60
TLC % pred	59	106	48	56	56	90	59	97	80	50	81	58	43	68	67	55
RV/TLC % pred	91	109	67	171	88	149	108	131	129	115	112	88	112	87	116	78
D_{LCO} % pred	25	35	30	nd	25	45	25	28	31	25	25	30	20	27	27	20
D_{LCO}/AV % pred	50	38	69	nd	39	nd	52	43	59	54	42	65	46	nd	67	52
FVC/D_{LCO}	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-min walk test[§]																
Distance m/% pred	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 S_{pO_2} %/O_2 output	99/87	96/93	93/nd	92/90 (2 L·min^{-1})	nd/70	91/81	nd	96/80[#]	97/93	97/nd (2 L·min^{-1})	nd	93/83 (2 L·min^{-1})	93/70 (4 L·min^{-1})	91/78	nd	nd
HRCT[§]																
ILD pattern[f]	UIP	NSIP	NSIP	Fibrosing NSIP	UIP	NSIP and 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

ASS: antisynthetase syndrome; F: female; M: male; NYHA: New York Heart Association; AAN: antinuclear antibody titre (indirect fluorescence on Hep2 cells); BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; P_{aO_2}: arterial oxygen tension; P_{aCO_2}: arterial carbon dioxide tension; LV: left ventricular; sPAP: systolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; P_{pcw}: pulmonary capillary wedge pressure; Q': perfusion; CI: cardiac index; PVR: pulmonary vascular resistance; FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume; D_{LCO}: diffusing capacity of carbon monoxide; AV: alveolar volume; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; N: normal; nd: not determined; nr: normal range; IVS: intra-ventricular septum; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; na: not applicable; PH-ILD: pre-capillary PH associated with ILD; TE-PH: thromboembolic-PH; i/f: initial/final. [#]: RHC was performed under specific PH treatment; [¶]: diaphragm dysfunction; [+]: hospitalised in intensive care unit, for right heart failure, necessitating vasopressor drugs; the dilatation of the right ventricle led to IVS and inhibited the left ventricle work; [§]: all the investigations were performed at the same time±6 months (with the exception of the 6-min walk test of patient 6); [f]: NSIP without fibrosis corresponded to the predominance of ground-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 mPAP ⩾25 mmHg and P_{cwp} ⩽15 mmHg. In the case of severe PH-ILD with a mPAP ⩾35 mmHg, the PH was considered to be "out of proportion". TE-PH was defined by the association of pre-capillary PH, past medical history of pulmonary embolism and positive ^{99}Tc ventilation/perfusion scintigraphy or angio-computed tomography; [##]: according to McDonald *et al.* [24]; [¶¶]: a coarseness score was assigned where a reticular pattern was identified, with a maximum score of 15; [++]:according to the classification of Goh *et al.* [23].

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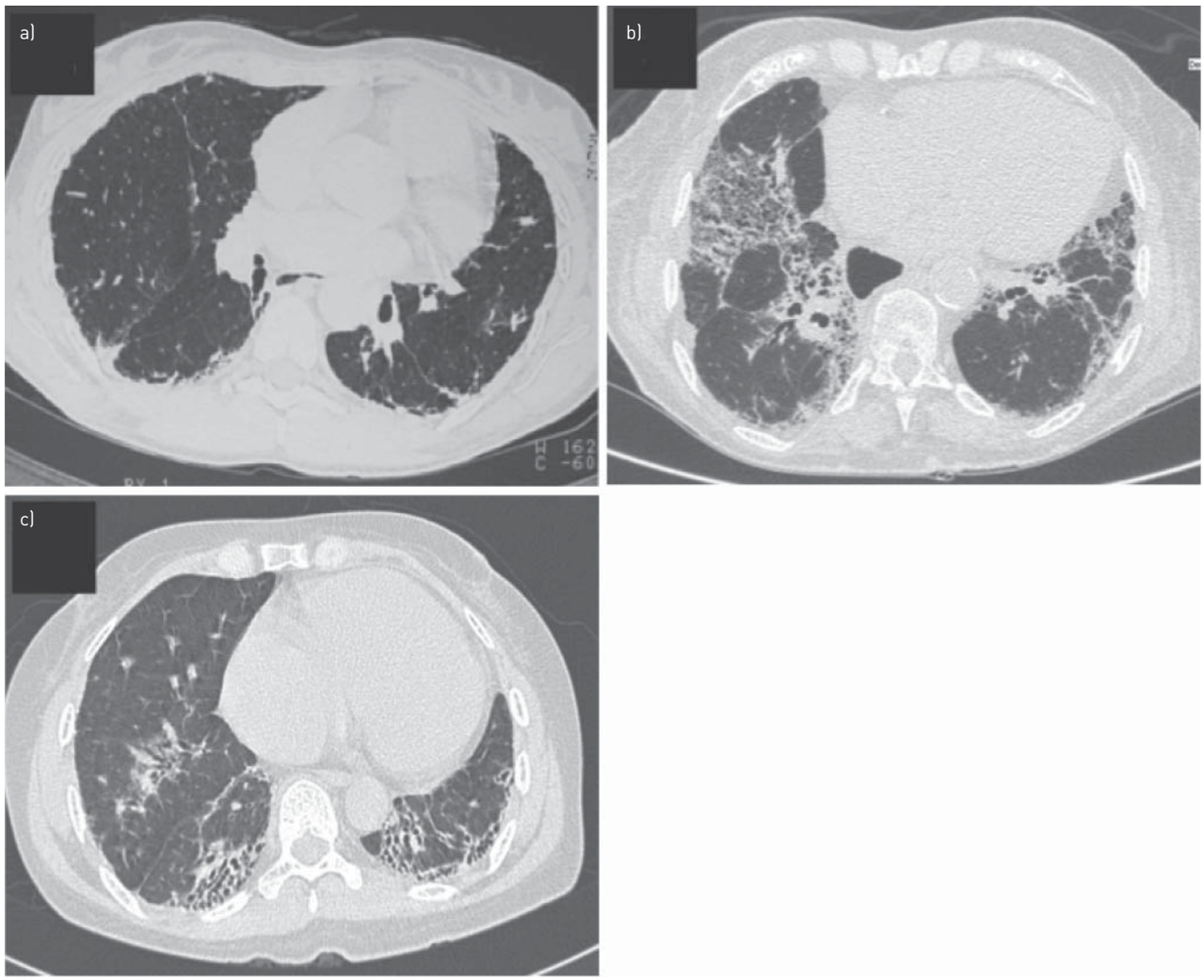

FIGURE 2 Representative thoracic computed tomography images of the interstitial lung disease (ILD) in patients with severe pulmonary hypertension associated with ILD. High-resolution computed tomography images of the ILD in three different patients, a) patient 10, b) patient 15, and c) patient 16, with a fibrosing nonspecific interstitial pneumonia pattern, showing predominant reticular opacities more or less associated with ground glass opacities and traction bronchiectasis or bronchiolectasis. The lesions were bilateral and mainly localised to the posterior and basal areas of the lungs (lower lobes).

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 when comparing patients for whom the PH was only suspected by echocardiography (n=26; hazard ratio 10.0, 95% confidence interval 2.9–34.4; $p<0.001$) with patients without PH on echocardiography. As all the patients with pre-capillary PH presented an ILD, we also compared the survival rate of these patients with ASS patients displaying ILD without PH on echocardiography (n=127) (fig. 3). As shown in table 4, five parameters were associated with the survival, including severe dyspnoea (NYHA III or 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 5.1, 95% confidence interval 1.1–24.9; p=0.042), 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, the 3-year survival rate after PH diagnosis was 58%.

Discussion

Based on RHC, the prevalence of PH in this retrospective study is 7.9%. However, as 21% of the patients from this series were not screened for PH by transthoracic echocardiography and as only 45% of the

TABLE 3 Treatments and outcomes of patients with pre-capillary pulmonary hypertension (PH)

Patient	1	2	3	4	5	6	7	8
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
Follow-up after PH diagnosis months	209	36	58	26	60	15	86	29
Specific treatments (dose and duration in months)	Sitaxentan (100 mg·day^{-1}; 155–191); sildenafil (60 mg·day^{-1}; 186–209); bosentan (250 mg·day^{-1}; 196–209)	None	Bosentan (250 mg·day^{-1}; 7–58)	Epoprostenol (<30 ng·kg^{-1}·min^{-1}; 0–26); sildenafil (60 mg·day^{-1}; 10–26); bosentan (250 mg·day^{-1}; 15–26)	Bosentan (250 mg·day^{-1}; 34–39)	Bosentan (250 mg·day^{-1}; 12–15); sildenafil (60 mg·day^{-1}; 13–15)	Bosentan (250 mg·day^{-1}; 28–86)	Bosentan (250 mg·day^{-1}; 5–7); sildenafil (60 mg·d^{-1}; 7–29); treprostinil (13.75 ng·kg^{-1}·min^{-1}; 5–29)
Immuno-suppressive treatments (dose and duration in months)	Methotrexate (<10 mg·week^{-1}; 0–201); prednisone (<10 mg·day^{-1}; 0–205); MMF (2 g·day^{-1}; 201–205)	Prednisone (5 mg·day^{-1}; 0–36)	Methotrexate (15 mg·week^{-1}; 0–16); prednisone (10 mg·day^{-1}; 0–58); MMF (2 g·day^{-1}; 16–58)	Prednisone (10 mg·day^{-1}; 0–26); azathioprine (100 mg·day^{-1}; 0–26)	Methotrexate (12.5 mg·week^{-1}; 0–34); prednisone (10 mg·day^{-1}; 0–34); MMF (2 g·day^{-1}; 38–53); cyclosporine (nd/38–53)	Prednisone (10 mg·day^{-1}: 0–15)	Prednisone (<30 mg·day^{-1}; 0–86); *i.v.* CYC (9 × 750 mg·min^{-2}; 13–22)	Prednisolone (15 mg·day^{-1}; 0–29); *i.v.* CYC (3 × 500 mg·m^{-2}; 0–3); anti-CD20 Mab (3 × 375 mg·m^{-2}; 4–5); MMF (1.5 g·day^{-1}; 0–29); *i.v.* Ig (2 g·kg^{-1}·min^{-1}; 16–29)
Final status	Alive	Alive	Alive	Death (respiratory failure)	Death (respiratory failure)	Death (left heart failure)	Alive	Death (respiratory failure)

Patient	9	10	11	12	13	14	15	16
Type of PH	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 months	12	18	0	2	17	55	62	9
Specific treatments (dose and duration in months)	Bosentan (250 mg·day^{-1}; 0–12)	Bosentan (250 mg·day^{-1}; 5–18)	None	Iloprosl (nebulisation; 1–2)	None	Bosentan (250 mg·day^{-1}; 0–53); sildenafil (60 mg·day^{-1}; 13–53)	Sildenafil (60 mg·day^{-1}; 52–62); ambrisentan (10 mg·day^{-1}; 52–62)	Sildenafil (60 mg·day^{-1}; 0–9); ambrisentan (10 mg·day^{-1}; 0–9)
Immuno-suppressive treatments (dose and duration in months)	Prednisone (<50 mg·day^{-1}; 0–12); MMF (1.5 g·day^{-1}; 4–5); *i.v.* CYC (6 × 500 mg·m^{-2}; 6–12)	Prednisone (<15 mg·day^{-1}; 0–18); methotrexate (15 mg·day^{-1}; 0–1); leflunomide (10 mg·day^{-1}. 1–2); *i.v.* CYC (3 × 750 mg·m^{-2}; 3–5)	Prednisone (10 mg·day^{-1}); azathioprine (100 mg·day^{-1})	None	MMF (2 g·day^{-1}; 0–4); *i.v.* CYC (6 × 750 mg·m^{-2}; 5–11); prednisone (<30 mg·day^{-1}; 0–17); methyl-prednisolone (3 × 15 mg·kg^{-1}; 4); antiCD20 Mab (2 × 1 g; 13–14)	Prednisone (<20 mg·day^{-1}; 0–53); *i.v.* CYC (18 × 750 mg·m^{-2}; 1–19); MMF (2 g·day^{-1}; 20–53)	Prednisone (5 mg·day^{-1}; 0–125); azathioprine (150 mg·day^{-1}; 0–24)	Prednisone (<12.5 mg·day^{-1}; 0–9); azathioprine (50 mg·day^{-1}; 0–9)
Final status	Alive	Death (nd)	Death (right heart failure)	Alive	Alive	Death (2 months after lung transplantation)	Alive	Alive

PH-ILD: pre-capillary PH associated with ILD; TE-PH: thromboembolic-PH; MMF: mycophenolate mophetyl; CYC: cyclophophamide; MAb: monoclonal antibodies; Ig: immunoglobulin; nd: not determined.

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 is slightly lower than SSc [7, 8]. Similarly to SSc, dyspnoea in ASS has many causes, including ILD, PH or anaemia. Moreover, in ASS, muscle involvement impacts on both breathing and exercise capacity, leading to specific difficulties in diagnosing dyspnoea and its aetiology. According to these data, it could be recommended to perform echocardiography in patients with ASS, particularly in the presence of unexplained or severe dyspnoea. Additionally, echocardiography should be repeated throughout the course of the disease, and especially when the severity of the dyspnoea seems to be ''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 which patients were 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 analyse the HRCT

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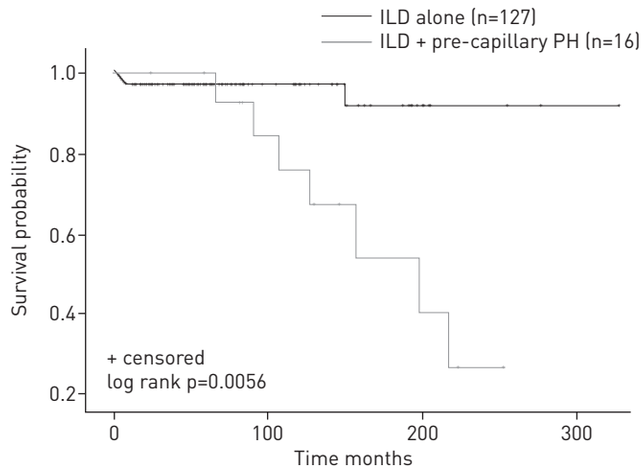

FIGURE 3 Kaplan–Meyer survival curve (from antisynthetase syndrome diagnosis) comparing patients with interstitial lung disease (ILD) but without pulmonary hypertension (PH) (n=127, ILD alone, systolic pulmonary arterial pressure (PAP) <37 mmHg on transthoracic echocardiogram) with patients with pre-capillary PH confirmed by right heart catheterisation (RHC) (n=16, all with ILD). Pre-capillary PH was defined during RHC as mean PAP ⩾25 mmHg and pulmonary capillary wedge pressure ⩽15 mmHg. ILD was defined by the results of high-resolution computed tomography and/or abnormal pulmonary function tests (forced vital capacity <70% predicted and/or diffusing capacity of the lung for carbon monoxide <70% predicted). Log rank test was used to compare the survival rate between groups.

(ILD pattern and extension) and pulmonary function test results, as the patients with pre-capillary PH had a lower *D*LCO (or higher FVC/*D*LCO ratio) upon first investigation. Furthermore, diagnosing PH in such a context is of particular importance, as it could require specific management and could impact on the patient outcome.

TABLE 4 Survival analyses

	Bivariate analysis[#] p-value	Multivariate regression analysis[¶]	
		Odds ratio (95% confidence interval)	p-value
Age >50 years 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 dyspnoea	**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 *D*LCO <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-antibodies			
Anti-Ro/SSA-52 kDa	0.54		
Anti-Ro/SSA-60 kDa	0.051		

ASS; antisynthetase syndrome; ILD: interstitial lung disease; DM: dermatomyositis; FVC: forced vital capacity; *D*LCO: diffusing capacity of carbon monoxide; PH: pulmonary hypertension; RHC: right heart catheterisation. [#]: log rank tests were used to compare survival between groups; [¶]: the pertinent variables proposed to the model were age at onset, severe dyspnoea at diagnosis, pre-capillary PH on RHC and anti-PL7/12-antibodies; [+]: this included sclerodactyly, skin sclerosis and digital ulcers. Bold indicates statistical significance.

When analysing 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 >7 years). However, it is difficult to determine whether this delay, which is similar to that found in series of SSc patients [15, 28], was caused by a late progression of the disease or a late diagnosis. However, as most of the patients were severe at PH diagnosis (based on the NYHA functional class and haemodynamic parameters), and because 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 (mean PAP >35 mmHg), which could be considered ''out of proportion'' according to lung parenchymal involvement. Moreover, a FVC/D_{LCO} 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 it has been 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 haemodynamic parameter of severity in all forms of PH. Interestingly, the mean cardiac index herein was quite similar to the values previously reported in PH-ILD related to SSc [7, 15]. In these patients with pre-capillary PH, no signs pointing to a left ventricular dysfunction (due to a specific inflammatory myocarditis and/or a proximal coronaropathy) were 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 as 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 with 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 both its confirmation by RHC and of its supposed mechanism. These data clearly show the need for a systematic PH screening by transthoracic echocardiography and also for a RHC confirmation in all the suspected cases.

However, the 3-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 echocardiograph rather than on the RHC. Unlike what has been reported for SSc [15, 32], we were unable 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 is associated with a poor outcome. Clinically diagnosing PH in this condition is particularly difficult, but is important. 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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