Pulmonary arterial hypertension associated with primary Sjögren's syndrome: a multicentre cohort study from China

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The prognosis of primary Sjögren's syndrome-associated pulmonary arterial hypertension might be improved by improving reserved cardiopulmonary function, by achieving a damage-free state and especially by achieving low-risk category https://bit.ly/3h7mZ9h

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ABSTRACT

Objectives: Primary Sjögren's syndrome (pSS) is an important cause of pulmonary arterial hypertension (PAH), which remains insufficiently studied and needs attention. This study aimed to investigate the clinical characteristics, risk factors, prognosis and risk assessment of pSS-PAH.

Methods: We established a multicentre cohort of pSS-PAH diagnosed by right heart catheterisation. The case–control study was conducted with pSS-non-PAH patients as a control group to identify the risk factors for PAH. In the cohort study, survival was calculated, and risk assessment was performed at both baseline and follow-up visits.

Results: In total, 103 patients with pSS-PAH were enrolled, with 526 pSS-non-PAH patients as controls. The presence of anti-SSB ($p<0.001$, OR 4.095) and anti-U1RNP antibodies ($p<0.001$, OR 29.518), the age of pSS onset ($p<0.001$, OR 0.651) and the positivity of corneal staining ($p=0.003$, OR 0.409) were identified as independent risk factors for PAH. The 1-, 3- and 5-year survival rates were 94.0%, 88.8% and 79.0%, respectively. Cardiac index ($p=0.010$, hazard ratio (HR) 0.161), pulmonary vascular resistance ($p=0.016$, HR 1.105) and Sjögren's syndrome disease damage index ($p=0.006$, HR 1.570) were identified as potential predictors of death in pSS-PAH. Long-term outcomes were improved in patients in the low-risk category at baseline ($p=0.002$) and follow-up ($p<0.0001$).

Conclusion: The routine screening of PAH is suggested in pSS patients with early onset and positivity for anti-SSB or anti-U1RNP antibodies. Patient prognosis might be improved by improving reserved cardiopulmonary function, by achieving a damage-free state and especially by achieving low-risk category, which supports the treat-to-target strategy for pSS-PAH.

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Introduction

Pulmonary arterial hypertension (PAH) is a clinical pathophysiological syndrome that is classified as group I pulmonary hypertension by the World Symposium on Pulmonary Hypertension [1]. PAH associated with connective tissue disease (CTD) makes up one quarter of all PAH diagnoses, second only to idiopathic PAH [2]. Several studies demonstrated that the prognosis of CTD-PAH patients was poorer than that of other PAH groups despite similar therapy, raising concern about inadequate response in these patients [3–7].

While systemic sclerosis (SSc) is the most common CTD-associated PAH in Western countries, it is noteworthy that the disease spectrum is different in Asians, with systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS) being the two most common diseases [8, 9]. Recently, new data focusing on SSc-PAH [10, 11] and SLE-PAH [12, 13] have been presented. However, pSS-PAH remains insufficiently studied. In addition, published studies have often suffered from small sample sizes or the fact that the diagnosis of PAH was not confirmed by right heart catheterisation (RHC) [14–16].

Periodic risk assessment with a multidimensional and comprehensive approach is recommended by current European guidelines [17]. It has been shown that risk stratification can be used to predict the outcome of patients with SSc-PAH [11, 18, 19], as has been demonstrated previously for idiopathic, heritable and drug-induced PAH [20]. However, the validity of risk assessment has not been studied in pSS-PAH specifically.

For a better understanding, a multicentre cohort study of pSS-PAH was conducted to explore the clinical characteristics, risk factors and long-term clinical outcomes of pSS-PAH, including mortality and potential prognostic predictors. A secondary objective was to evaluate the association between survival and risk assessment from baseline to follow-up.

Methods

Patients and controls

A multicentre cohort study of pSS-PAH was initiated in 2014 at Peking Union Medical College Hospital (Beijing, China) and eight other qualified referral CTD-PAH clinical centres. Patients who visited the clinical centres between 2005 and 2017 and fulfilled the inclusion criteria were recruited. The controls were defined as pSS patients without known PAH from 16 Chinese medical centres nationwide during the same time period. The cases and controls were recruited from the same catchment area, and the suspected PAH patients were transferred to the qualified referral CTD-PAH centres. This study was approved by the medical ethics committee of each centre, and written informed consent was obtained from all recruited patients.

Inclusion criteria

Primary Sjögren's syndrome was diagnosed in accordance with the classification criteria proposed by the American–European Consensus Group in 2002 [21] or American College of Rheumatology/European

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League Against Rheumatism (EULAR) in 2016 [22]. PAH was defined by RHC according to the 2015 guidelines of the European Society of Cardiology (ESC)/European Respiratory Society (ERS) [17]: mean pulmonary artery pressure ⩾25 mmHg at rest, pulmonary artery wedge pressure ⩽15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units.

The exclusion criteria of pSS-PAH were as follows. 1) Symptoms can be classified into other CTDs, such as SLE, SSc and mixed CTD; 2) evidence of congenital heart disease or left heart disease; 3) lung disease, which can cause pulmonary hypertension, confirmed by chest high-resolution computed tomography and/or pulmonary function tests; and 4) chronic thromboembolic disease confirmed by ventilation and perfusion scanning and/or computed tomographic pulmonary angiography.

In the case–control study, patients with pSS without PAH were recruited as controls. Patients with PAH-related symptoms, such as exertional dyspnoea, or evidence of pulmonary hypertension by transthoracic echocardiography were excluded.

Data collection

All clinical centres used the same evaluation table to collect information on patients. The data of patients enrolled before 2014 were collected retrospectively by reviewing the medial charts, and the data of those enrolled since 2014 were collected prospectively. The baseline was defined as the time PAH was confirmed by RHC. The demographic characteristics (age, sex and disease duration), clinical manifestations, laboratory and autoantibody profiles, echocardiography and RHC data and treatment were obtained at baseline. In addition, the EULAR primary Sjögren's syndrome disease activity index (ESSDAI) [23] and Sjögren's syndrome disease damage index (SSDDI) [24] were evaluated. If the patient was included retrospectively, the information was collected based on medical chart reviews and confirmed with patients during follow-up. All data were collected by a trained rheumatologist.

Risk assessment

The risk assessment was performed at baseline and at every follow-up, a method that was first recommended in the 2015 ESC/ERS guidelines [17] and further validated in various studies [6, 20, 25]. We used the four determinants: World Health Organization (WHO) functional class, 6-min walk distance (6MWD), brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) plasma levels and haemodynamics (right atrial pressure, cardiac index, mixed venous oxygen saturation (S_{vO_2})). Risk strata were defined as low risk (at least three low-risk determinants and no high-risk determinants), high risk (at least two high-risk determinants including S_{vO_2} or cardiac index) and intermediate risk (low- or high-risk criteria not fulfilled). Since repeated RHC was not available, we applied the noninvasive risk stratification strategy from Boucly *et al.* [20] and Hoeper *et al.* [25] in the follow-up risk assessments (low risk defined as meeting all three of the following criteria: WHO functional class I–II, BNP <50 ng·L^{-1} or NT-proBNP <300 ng·L^{-1}, and 6MWD >440 m).

Follow-up and outcome

The follow-up of the included patients was recorded at each clinical centre and was reported at least once a year. Evaluation included symptom questionnaires, WHO functional class, 6MWD, BNP or NT-proBNP plasma levels, echocardiography, parameters related to pSS and risk category. The follow-up interval was 3–6 months, depending on the patient's condition. The end-point was all-cause mortality. Those lost to follow-up were contacted by phone to confirm the survival status. Survival time was determined as the interval between the first RHC and the recorded date of death or confirmation. The censoring date was May 31, 2017. Survival status was confirmed for all patients within 3 months before the deadline.

Statistical analysis

The data were analysed using SPSS version 24.0 (Chicago, IL, USA). Continuous variables are described as the mean±SD or median (interquartile range), while categorical variables are described as percentages. The comparisons of continuous variables were conducted using the t-test or the Mann–Whitney U-test. Categorical variables, including proportions, were compared using the Chi-squared test or Fisher's exact test. Risk factors were identified by univariate and multivariate logistic regression analysis. Survival rates were determined by Kaplan–Meier curve analysis, and potential predictors of death were identified by univariate Cox proportional hazard regression analysis. The choice of variables included in multivariate models depended on the result of univariate analysis ($p<0.05$) and their clinical relevance. A p-value <0.05 was considered statistically significant.

TABLE 1 Demographic data of the primary Sjögren's syndrome (pSS)-pulmonary arterial hypertension (PAH) and pSS-non-PAH

	pSS-PAH	pSS-non-PAH	p-value
Subjects	103	526	
Female/male	101/2	507/19	1.000
Age at diagnosis of PAH years	43.2±12.7		<0.001
Age at onset of pSS years	37.4±13.1	44.1±13.1	<0.001
Duration of pSS months	46.0 (13.0–100.4)	33.1 (12.7–73.8)	0.186
Ocular symptoms	47 (45.6)	381 (72.4)	<0.001
Oral symptoms	62 (60.2)	480 (91.3)	<0.001
Schirmer test	70 (70.0)	329 (90.1)	<0.001
Ocular stain	31 (31.6)	200 (54.8)	<0.001
UWS	76 (75.2)	326 (62.0)	0.011
ESSDAI score	6±6	6±5	0.988
IgG elevation	64 (61.0)	329 (68.5)	0.379
Anti-SSA$^+$	95 (90.5)	439 (83.5)	0.069
Anti-SSB$^+$	47 (44.8)	88 (18.5)	<0.001
Anti-U1RNP$^+$	23 (22.1)	13 (3.0)	<0.001

Data are presented as n, mean±SD, median (interquartile range) or n (%), unless otherwise stated. UWS: unstimulated whole saliva flow rate; ESSDAI: European League Against Rheumatism primary Sjögren's syndrome disease activity index.

Results

Baseline characteristics of pSS-PAH

103 pSS-PAH patients were enrolled from the study centres, of whom 67 (65%) were recruited and followed-up prospectively, while 36 (35%) patients were included retrospectively and followed-up prospectively. The baseline characteristics are shown in tables 1 and 2. The majority were female, accounting for 98.0% of the study population, and the mean age was 43.2±12.7 years. The majority of patients were in WHO functional class I–II (58.2%). ~86.4% of patients received glucocorticoid therapy. The rates of high, moderate and low dosages were 42.7%, 25.2% and 18.4%, respectively. The usage rate of immunosuppressants was 84.5%, with cyclophosphamide being most commonly prescribed. The target therapy for PAH was given to 88.3% of patients, and 15.5% patients received two or more PAH therapies. Binary therapy was defined as the use of both immunosuppressant and PAH target therapy, and 80.6% of patients received binary therapy.

Case–control study

526 pSS patients without PAH from a multicentre study in China were included as controls [26]. The comparison between pSS-PAH and pSS-non-PAH is shown in table 1. There was no significant difference in pSS duration, ESSDAI or the elevation of IgG between the two groups. Based on the results of the univariate regression analysis and the variables' clinical relevance, four statistically significant variables were included in the multivariate analysis, and they were found to be associated with PAH in pSS patients (table 3). Anti-SSB ($p<0.001$, OR 4.095) and anti-U1RNP antibodies ($p<0.001$, OR 29.518) were identified as possible risk factors, while age at onset of pSS ($p<0.001$, OR 0.651) and positivity of corneal staining ($p=0.003$, OR 0.409) were identified as potential protective factors of PAH.

Survival analysis

All patients completed confirmation of survival state. The mean follow-up was 2.6 years, and the median follow-up was 1.6 years. 11 end-point events happened in our cohort. Eight deaths were attributed to right heart failure, two deaths were due to infection and haemorrhage and the cause of death could not be traced in one case. The pooled 1-, 3- and 5-year survival rates were 94.0%, 88.8% and 79.0%, respectively (figure 1). The results of the univariate Cox regression analysis are shown in table 4. Univariate analysis showed that SSDDI ($p=0.006$, hazard ratio (HR) 1.570), cardiac index ($p=0.010$, HR 0.161) and PVR ($p=0.016$, HR 1.105) may be potential predictors of mortality (table 4). Among these, PVR was related to cardiac index as it was calculated by a formula that contains the cardiac index. To confirm the impact of the predictors on mortality, a Kaplan–Meier curve analysis was conducted, and the difference was significant between subgroups. A cardiac index $\geqslant 2.5$ L·min^{-1}·m^{-2} suggested by the low-risk criteria and a SSDDI >3, which most pSS patients possessed, were defined as the cut-off values (figure 2). Multivariate analysis was not performed due to lack of end-point events.

TABLE 2 Clinical and haemodynamic data of patients with primary Sjögren's syndrome (pSS)-pulmonary arterial hypertension (PAH) at PAH diagnosis

Subjects	103
PAH duration months	12.0 (5.5–34.2)
Onset interval of pSS and PAH months	2.1 (0.0–59.9)
SSDDI score	2±1
WHO FC I–II	60 (58.2)
6MWD m	398±98.1
BNP ng·L^{-1}	239 (98–545)
NT-proBNP pg·mL^{-1}	822 (324–2100)
RHC	
mPAP mmHg	48.1±10.7
PAWP mmHg	8.4±2.9
PVR WU	11.5±5.3
Cardiac index L·min^{-1}·m^{-2}	2.6±0.9
RAP mmHg	6.4±4.6
TTE	
PASP mmHg	80.1±20.1
RV diameter mm	35.8±11.2
TAPSE mm	16.2±4.1
LVEF %	67.8±6.7
Pericardial effusion	37 (37.0)
Treatment regimen	
Glucocorticoids	89 (86.4)
Immunosuppressant	87 (84.5)
CYC	63 (61.2)
Initial PAH target therapy	91 (88.3)
ERA	34 (33.0)
PDEi	63 (61.2)
⩾2	16 (15.5)
Initial binary therapy[#]	83 (80.6)
Follow-up	
Sequential PAH therapy[¶]	8 (7.8)
Immunosuppression therapy alone	4 (3.9)

Data are presented as n, median (interquartile range), mean±SD or n (%). SSDDI: Sjögren's syndrome disease damage index; WHO FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal proBNP; RHC: right heart catheterisation; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood units; RAP: right atrial pressure; TTE: transthoracic echocardiography; PASP: pulmonary arterial systolic pressure; RV: right ventricle; TAPSE: tricuspid annular plane excursion; LVEF: left ventricle ejection fraction; CYC: cyclophosphamide; ERA: endothelin receptor antagonist; PDEi: phosphodiesterase inhibitor. [#]: combination of immunosuppressant and PAH target therapy at baseline; [¶]: initial immunosuppression therapy followed by sequential PAH therapy.

Risk assessment at baseline and follow-up

At baseline, the proportions of patients with low, intermediate and high risk were 26%, 61% and 13%, respectively (figure 3). Survival differed significantly between the different groups (p=0.002), and the 1-year mortality rates of the low-, intermediate- and high-risk groups were 0%, 6.9% and 14.9%, respectively. As this is a partly retrospective study, only 62 patients with complete data for risk assessment were included during follow-up analysis. The baseline data comparison between those included and those not included showed no difference in WHO functional class, 6MWD, BNP or NT-proBNP plasma level, RHC-related parameters and target therapy (supplementary table S1), although some variables such as age and pSS disease activity remained significantly different. Up to last follow-up visit, a total of 41 patients were in the low-risk category, 14 of whom were already in the low-risk category at baseline. The median time between baseline assessment and the last follow-up visit was 15.2 months. The 1-, 2- and 3-year pooled rates of achieving low-risk category were 56.4%, 74.5% and 80.9%, respectively. The survival rate of patients achieving low-risk category at follow-up was significantly higher than that of patients not achieving low-risk category (p<0.0001). The 1-, 3- and 5-year survival rates were 73.5%, 66.2% and 55.1%, respectively, among patients in the intermediate- or high-risk category during follow-up, compared with 100% among those in the low-risk category (figure 4a). Among those who achieved low-risk category during follow-up, 31 patients (75.6%) achieved low-risk category within 1 year after diagnosis of PAH, and 38 patients (92.7%) achieved low-risk category within 2 years. Based on the result of the risk assessment

TABLE 3 Possible risk factors of developing pulmonary arterial hypertension among primary Sjögren's syndrome (pSS) patients

	p-value	OR (95% CI)
Univariate		
Female	0.701	1.274 (0.370–4.386)
Age at onset of pSS years	**<0.001**	0.961 (0.944–0.977)
Duration of pSS months	0.845	1.000 (0.998–1.001)
Ocular stain	**<0.001**	0.382 (0.238–0.613)
ESSDAI score	0.262	1.022 (0.984–1.062)
Anti-SSB$^+$	**<0.001**	3.564 (2.275–5.583)
Anti-U1RNP$^+$	**<0.001**	9.327 (4.538–19.168)
Elevation of IgG	0.121	0.713 (0.465–1.094)
Multivariate		
Age at onset of pSS, 10 years	**<0.001**	0.651 (0.524–0.810)
Ocular stain	**0.003**	0.409 (0.229–0.732)
Anti-SSB$^+$	**<0.001**	4.095 (2.183–7.681)
Anti-U1RNP$^+$	**<0.001**	29.518 (6.026–144.600)

Bold type represents statistical significance. ESSDAI: European League Against Rheumatism primary Sjögren's syndrome disease activity index.

from the 1-year follow-up visit, the patients reaching low-risk category within 1 year had a better prognosis than those not reaching low-risk category within 1 year (p=0.01) (figure 4b).

Discussion

To our knowledge, this is the largest cohort study of pSS-PAH and the first to demonstrate the long-term prognosis with risk assessment. The main findings were as follows: 1) pSS-PAH patients tended to have low disease activity and damage; 2) several risk factors were identified, suggesting that pSS patients with young age, anti-SSB and anti-U1RNP antibodies, and negative results of corneal staining might have an increased risk of developing PAH; 3) the 1-, 3- and 5-year survival rates were 94.0%, 88.8% and 79.0%, respectively, with a low cardiac index and increased damage index being significantly and independently associated with survival; and 4) a risk assessment recommended by ESC/ERS guidelines helped modestly to predict future risk, and patients fulfilling low-risk criteria either at baseline or follow-up had a better prognosis.

It raised concerns that not all patients (88.3%) received PAH target therapy in our study. Since PAH is one of the organ manifestation of CTD, it is highly likely that immunological mechanisms are involved in its pathophysiology. According to the guidelines for treatment of pulmonary hypertension [27], immunosuppressive therapy is effective in a subset of patients with CTD-PAH. Therefore, based on the patient's situation, especially for mild PAH and active underlying CTD, clinicians might initially administer immunosuppressive treatment without immediately prescribing pulmonary vasodilators. In our

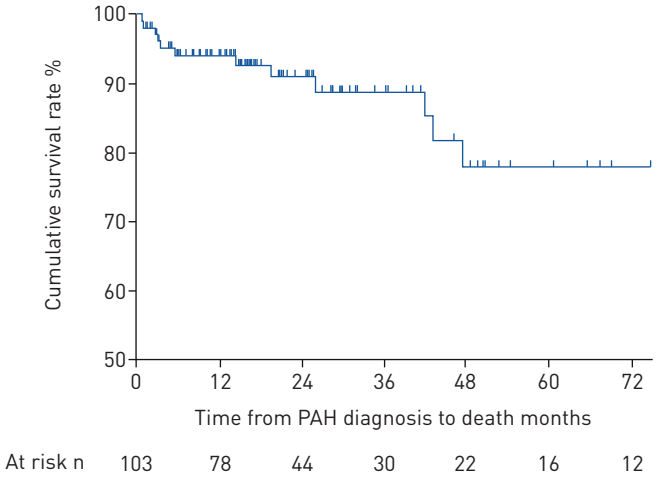


FIGURE 1 Cumulative survival rate of the whole primary Sjögren's syndrome-pulmonary arterial hypertension (PAH) population.

TABLE 4 Predictive factors of death in patients with primary Sjögren's syndrome (pSS)-pulmonary arterial hypertension (PAH)

	p-value	Hazard ratio (95% CI)
Age at onset of pSS years	0.961	0.999 (0.950–1.050)
Age diagnosis of PAH years	0.320	1.024 (0.978–1.072)
Duration of pSS months	0.056	1.005 (1.000–1.011)
PAH duration months	0.839	0.998 (0.977–1.019)
Ocular/oral symptoms	0.109	3.511 (0.755–16.323)
Schirmer/ocular stain^{+}	0.961	1.039 (0.222–4.853)
Raynaud's phenomenon	0.119	2.570 (0.784–8.428)
ESSDAI score	0.384	1.034 (0.959–1.116)
SSDDI score	**0.006**	1.570 (1.135–2.172)
Anti-SSB^{+}	0.252	2.171 (0.576–8.188)
Anti-U1RNP^{+}	0.823	1.191 (0.257–5.526)
WHO FC III–IV	0.064	3.522 (0.930–13.332)
6MWD m	0.123	0.995 (0.988–1.001)
NT-proBNP pg·mL^{-1}	0.397	1.000 (1.000–1.001)
RHC		
mPAP mmHg	0.776	1.008 (0.956–1.063)
PVR WU	**0.016**	1.105 (1.019–1.199)
Cardiac index L·min^{-1}·m^{-2}	**0.010**	0.161 (0.040–0.645)
RAP mmHg	0.770	0.979 (0.849–1.129)
TTE		
RV diameter mm	0.468	0.975 (0.911–1.044)
LVEF %	0.906	1.006 (0.917–1.103)
Pericardial effusion	0.723	1.240 (0.377–4.074)
Immunosuppressant	0.071	0.323 (0.094–1.103)
Target therapy for PAH	0.734	0.764 (0.161–3.625)
Binary therapy$^{\#}$	0.577	0.685 (0.181–2.591)

Bold type represents statistical significance. ESSDAI: European League Against Rheumatism primary Sjögren's syndrome disease activity index; SSDDI: Sjögren's syndrome disease damage index; WHO FC: World Health Organization functional class; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; RHC: right heart catheterisation; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; WU: Wood unit; RAP: right atrial pressure; TTE: transthoracic echocardiography; RV: right ventricle; LVEF: left ventricle ejection fraction. $^{\#}$: combination of immunosuppressant and PAH target therapy.

cohort, there were 12 patients not receiving PAH therapy at baseline and only four remaining on immunosuppression therapy alone during follow-up (table 2). However, PAH target therapy was not identified as a potential prognostic factor in analysis (table 4).

The ESSDAI was shown to have large sensitivity and good construct validity for evaluating disease activity [28, 29]. Our study showed a low to moderate activity level [30] among pSS-PAH patients, consistent with SLE-PAH [12, 31]. A low SSDDI suggested a tendency to have solitary pulmonary system involvement except in the exocrine gland. The evaluation of pSS suggests that the development of PAH may not be parallel to disease activity and damage, and a clinically quiescent patient still has the risk of developing PAH. By contrast, pSS should be carefully ruled out in a patient diagnosed with idiopathic PAH due to its nonspecific and quiescent manifestation.

Our study identified that the onset age of pSS and positivity of corneal staining were potential protective factors for PAH, which was consistent with our clinical observation. The pSS-PAH patients were younger than the common pSS population, and the sicca manifestation was not as prominent. Anti-U1RNP and anti-SSB antibodies were identified as possible risk factors for developing PAH. The positivity of these two antibodies in our cohort was similar to that of Hachulla et al. [12]. Anti-U1RNP antibody was proven to be a predictor for SLE-PAH in different studies, and a meta-analysis confirmed this [31–33]. *In vitro*, the study found that the anti-U1RNP antibody can upregulate adhesion molecules and histocompatibility complex class II molecules on human pulmonary arterial endothelial cells, suggesting that it plays an important role in proliferative pulmonary vasculopathy [34]. In addition, Hachulla *et al.* [12] demonstrated a higher frequency of anti-SSB antibodies in SLE-PAH patients. The basic study revealed that the titre of anti-SSB antibody was correlated with the level of signal transducer and activator of transcription-5 (STAT-5) in B cells and monocytes in pSS patients [35]. STAT-5 has been reported to be

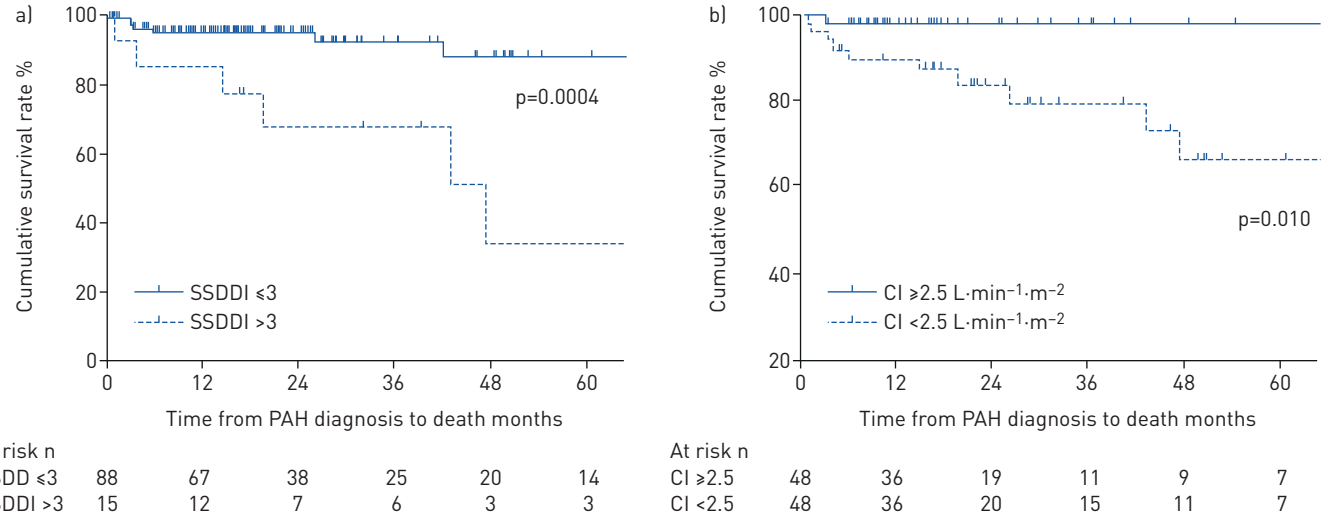


FIGURE 2 Kaplan–Meier analysis of survival according to a) Sjögren's syndrome disease damage index (SSDDI) and b) cardiac index (CI). PAH: pulmonary arterial hypertension.

associated with Golgi dysfunction [36], which is a common feature in idiopathic pulmonary hypertension [37]. Further research is needed to explore the role that these auto-antibodies play in the pathogenesis of PAH.

Overall, the 1-, 3- and 5-year survival rates of patients with pSS-PAH in our cohort were 94.0%, 88.8% and 79.0%, respectively, similar to a previous study showing that the 1-, 3- and 5-year survival rates were 92.1%, 84.8% and 72.9%, respectively, in SLE-PAH patients [13], but different from a study showing 87%, 55% and 35% survival, respectively, in SSc-PAH patients [11]. The prognosis of SSc-PAH has indeed been shown to be poorer than that of other CTD-PAH [10, 38–41]. Our research suggested that the prognosis of pSS-PAH might be the same as that of SLE-PAH and better than that of SSc-PAH, especially with prolonged follow-up.

The cardiac index was identified as a potential predictor of death in pSS-PAH patients. The same results were reported for idiopathic and SSc-associated PAH [42–44], which was in accordance with the risk assessment. A decrease in cardiac index suggests that PAH has progressed into the decompensation state, suggesting that preserved cardiopulmonary function is crucial for PAH patients. Furthermore, our study showed that SSDDI might be a predictive factor of death. SSDDI is an instrument that objectively measures disease damage in pSS patients [24]. Most pSS patients already had an SSDDI of 3 when diagnosed with pSS due to damage to the exocrine glands. Thus, an SSDDI >3 means that patients have other systems involved in addition to the exocrine gland, and patients with multisystem damage have a poorer prognosis.

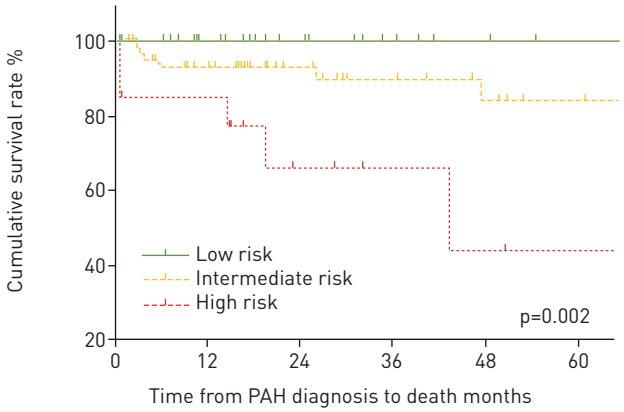
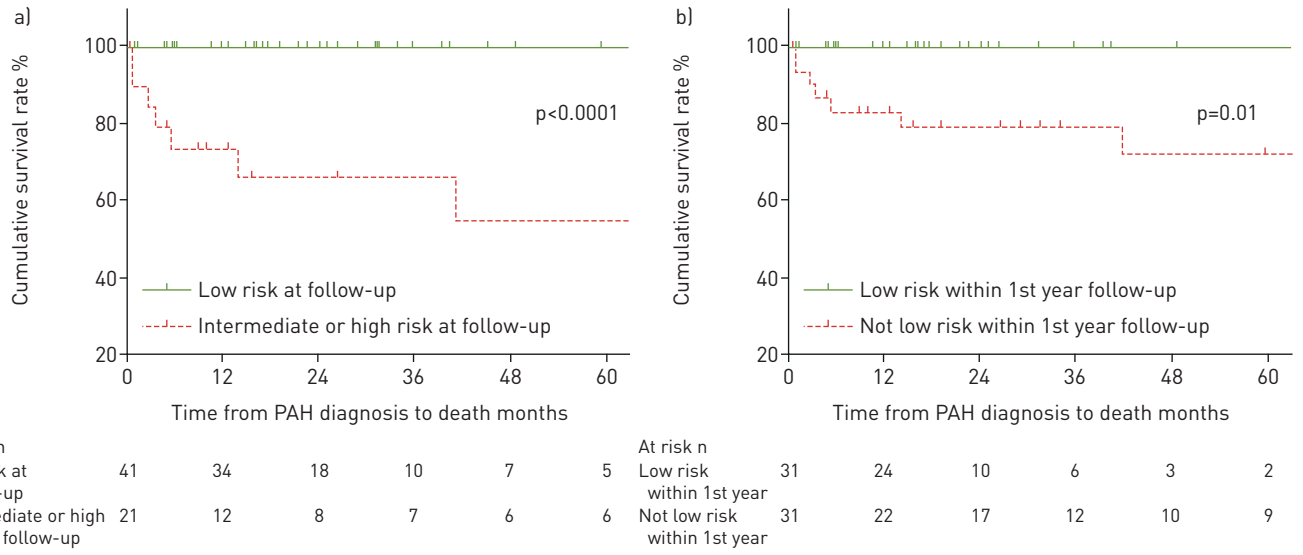


FIGURE 3 Comparison of the cumulative survival rate of patients with different risk category at baseline. PAH: pulmonary arterial hypertension.



At risk n						
Low risk at follow-up	41	34	18	10	7	5
Intermediate or high risk at follow-up	21	12	8	7	6	6

At risk n						
Low risk within 1st year	31	24	10	6	3	2
Not low risk within 1st year	31	22	17	12	10	9

FIGURE 4 Comparison of the cumulative survival rate of patients with different risk category a) during whole follow-up period and b) within first-year follow-up visit. PAH: pulmonary arterial hypertension.

We confirmed that the ESC/ERS risk stratification, now validated in five prior studies [6, 11, 18, 20, 45], also applied to the pSS-PAH subgroup, a less recognised complication in Western countries. In the CTD-PAH subgroup, where SSc-PAH was mostly studied, we extended the validation of risk assessment to pSS-PAH. The results corresponded to estimates from guidelines with a 1-year mortality rate <5% in the low-risk group, 5–10% in the intermediate-risk group, and >10% in the high-risk group [17]. In addition, we confirmed the noninvasive risk stratification strategy from Boucly *et al.* [20] and Hoeper *et al.* [25] in the follow-up visits of our cohort. The patients achieving low-risk category either at baseline or follow-up had an obviously better outcome than those who did not. This suggests that risk assessment could be used not only as an evaluation tool but also as a treatment target. The treat-to-target strategy of PAH was originally promoted by Hoeper *et al.* [46] in 2005 and has evolved since then. Treatment based on this strategy has improved patients' prognosis [47, 48]. Recently, a study that focused on SLE-PAH [13] applied the low-risk criteria as a treatment goal and found that patients achieving this goal had a better prognosis than those who did not achieve this goal. Our study supported this approach, which suggested that a treat-to-target strategy might be a beneficial treatment management strategy for pSS-PAH patients. However, further research is needed.

There are several limitations to this study. First, this was a partly retrospective cohort study, and second, it was a case–control study. Since there were no follow-up data in the control group, those who developed PAH later might also be included. Third, there were missing follow-up data which entailed a risk of selection bias with respect to the follow-up cohort. Fourth, the survival time was calculated from diagnosis to death in follow-up risk assessment analysis, which might introduce survival time bias. Fifth, repeated RHC was not performed. However, a recent study showed that a risk assessment strategy containing noninvasive parameters still had a good predictive value during follow-up [25], although further validation is needed. Finally, since there were only 11 end-point events in the survival analysis, the multivariate Cox analysis cannot be performed until more follow-up time is accrued. The result of the univariate Cox model need to be interpreted carefully. We hope to improve these data in the future.

Conclusion

This study is currently the largest prognostic cohort consisting of patients with pSS-associated PAH based on an RHC algorithm. PAH is a rare complication of pSS, and routine screening of PAH is recommended in pSS patients with an early onset of pSS and positive anti-SSB and anti-U1RNP antibodies. The exclusion of pSS as a possible diagnosis is needed before a diagnosis of idiopathic PAH can be made. The overall 5-year survival rate of pSS-PAH was 79.0%, and the prognosis might be improved by optimising cardiopulmonary function and achieving a damage-free state. Periodic risk assessment is recommended as low-risk category is associated with better long-term outcomes and could be applied as a therapy goal. Future studies should clarify whether a treat-to-target strategy might be beneficial in the management of CTD-PAH patients.

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