Is it possible to apply the treat-to-target strategy in primary Sjögren's syndrome-associated pulmonary arterial hypertension?

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Abstract

The treat-to-target (T2T) strategy improved long-term survival of patients with pulmonary arterial hypertension (PAH). Little was known about applying the T2T strategy in primary Sjögren's syndrome-associated PAH (pSS-PAH). We investigated how to identify patients who are more likely to reach the treatment goals in a cohort of pSS-PAH. In this way, we explored the possibility of implementing T2T in pSS-PAH. Data were retrospectively collected from patients visiting our center between 2007 and 2017. PAH was confirmed by right heart catheterization (RHC). Patients were treated following the T2T strategy. PAH treatment goals were defined by the 5th World Symposium on Pulmonary Hypertension. The primary end point was reaching the PAH treatment goals. Of the 62 patients enrolled, 98.4% were female, with a mean age of 38.9 ± 9.1 years at the diagnostic RHC. The median disease duration of pSS was 46 months (0–365), while the median disease duration of PAH was 12 months (0–149). Following the T2T strategy, 32 (50%) patients achieved the treatment goals. The 1-, 3-, and 5- year cumulative rates of reaching the goals were 40.6, 67.4, and 73.9%, respectively. Predictive factors included using immunosuppressants (HR 4.715, 95% CI 1.101–20.192, $p = 0.037$) and right ventricular anterior-posterior diameter (RV-APD) > 30 mm at baseline (HR 0.426, 95% CI 0.188–0.968, $p = 0.042$). The results provide strong evidence that patients who received immunosuppressants are more likely to reach the treatment goals. In contrast, impaired RV structure correlates to worse treatment response. The T2T strategy is effective in pSS-PAH.

Keywords Predictive factor · Primary Sjögren's syndrome · Pulmonary arterial hypertension · Treat-to-target

Introduction

Pulmonary arterial hypertension (PAH) is a rare and severe complication of connective tissue disease (CTD). Compared with idiopathic PAH (IPAH), CTD-PAH has worse response

to the PAH therapies and poorer prognosis [1, 2]. In Western populations, the prevalence of systemic sclerosis-associated PAH (SSc-PAH) was higher than other types of CTD-PAH [2–4]. In Asian populations, however, a different distribution of underlying CTDs was reported. Data from Korea and Japan identified systemic lupus erythematosus (SLE) as the most common underlying disease [5, 6] and primary Sjögren's syndrome (pSS) as one major associated CTD [6]. Peking Union Medical College Hospital (PUMCH) established the cohort of CTD-PAH in 2006 [7]. In our published cohort, the most common underlying CTD was SLE (58.4%), followed by SSc (26.3%) and pSS (15.3%) [7]. This trend remained consistent in two other Chinese cohorts [8, 9]. Preliminary survival analysis revealed that pSS-PAH had better prognosis than SSc-PAH, whereas worse than SLE-PAH [7]. However, little was known about pSS-PAH due to the limited data.

The treat-to-target (T2T) strategy of PAH was originally promoted by Hoeper et al. in 2005 [10]. The essential idea of T2T is that PAH requires regular monitoring and treatment escalation if the treatment goals are not met. Since then,

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researches have focused on optimizing the treatment approaches for PAH, and the long-term survival of PAH was improved under this strategy [11, 12]. However, challenges are met in the subgroup of pSS-PAH. Cohorts of pSS-PAH are rare. Few case series reported the clinical manifestations and outcomes of pSS-PAH [13–15]; however, most were limited by lacking the diagnostic right heart catheterization (RHC). The physiopathology and clinical features of PAH in pSS still await much investigation. In addition, there is no specific guideline for the treatment in pSS-PAH. No previous study, to our knowledge, has reported the therapeutic response or pertinent clinical markers in patients with pSS-PAH. We aimed to investigate how to identify the patients who are more likely to reach the treatment goals following the T2T strategy. In this way, we explored the possibility of applying the T2T strategy in pSS-PAH.

Methods

Study population

Patients with pSS-PAH visiting the Department of Rheumatology, PUMCH, during August 2007 and May 2017 were enrolled in this study. The baseline was defined as the date of the diagnostic RHC. Patients were followed up every 3 to 6 months at the Rheumatology clinic of PUMCH. This study was approved by the Medical Ethics Committee of PUMCH. All patients entering the cohort signed the written informed consent.

The diagnosis of pSS was confirmed with the revised classification criteria proposed by the American-European Consensus Group in 2002 [16]. The evaluation of pSS was achieved through SS patient activity index (ESSDAI) and SS disease damage index (SSDDI). ESSDAI evaluates the number, importance, and severity of the involved organs [17, 18]. SSDDI evaluates the irreversible damage of the disease [19]. According to the guidelines of 2015 European Society of Cardiology/European Respiratory Society, PAH was defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 3 Wood units, as evaluated by RHC. Exclusion criteria included (1) fulfilling the classification criteria of other CTDs such as SLE, SSc, and mixed connective tissue disease (MCTD); (2) evidence of cardiac structural abnormality that can cause PAH; (3) chronic thromboembolic disease confirmed by ventilation and perfusion scanning and/or computed tomographic pulmonary angiography; (4) severe interstitial lung disease (ILD) revealed by chest high-resolution computed tomography (HRCT) and pulmonary function test (PFT). Patients were excluded if the total lung capacity (TLC) was $< 60\%$ of predicted and were included if the TLC was $> 70\%$ of predicted. Patients with TLC

between 60 and 70% of predicted were included if the HRCT revealed only minimal interstitial fibrosis.

Data collection

All data were collected in a protocol-directed method by well-trained rheumatologists. A uniform evaluation chart was designed to collect patients' baseline demographics, clinical manifestations, major comorbid conditions, laboratory tests, autoantibody results, hemodynamics data, and treatment regimens. Extra-glandular, extra-thoracic manifestations included (1) non-erosive arthritis; (2) purpura; (3) peripheral neuropathy; (4) hepatic involvement; (5) renal involvement; (6) hematological involvement: hemocytopenia, hyperglobulinemia, hypocomplementemia, and lymphoma. Laboratory tests included complete blood count, liver function test, renal function panel, urine analysis, erythrocyte sedimentation rate (ESR), hypersensitive C-reactive protein (hsCRP), immunoglobulin, and complement. All tests were conducted by the Laboratory Department of PUMCH. The evaluation of PAH included transthoracic echocardiography (TTE), modified New York Heart Association functional classification (NYHA FC), PFT, 6-min walking distance (6MWD) [20], serum brain natriuretic peptide (BNP), and N terminal-pro BNP (NT-proBNP). All patients conducted RHC; pertinent parameters included right atrial pressure (RAP), mPAP, PAWP, PVR, cardiac output (CO), and cardiac index (defined as CO divided by body surface area). To evaluate ILD, all patients performed HRCT and PFT. PFT examined forced vital capacity (FVC), TLC, and diffusing capacity for carbon monoxide (DLCO). For the treatment regimens, glucocorticoids and immunosuppressants were documented for the dosage and administration route. Immunosuppressants included cyclophosphamide, mycophenolate mofetil, methotrexate, leflunomide, and tacrolimus. Basic treatment for PAH was given as needed, such as diuretics, digoxin, anticoagulant therapy, and oxygen. PAH-targeted therapies were recorded and analyzed, including endothelial receptor antagonists (ERAs), phosphodiesterase type5 (PDE5) inhibitors, and prostacyclin derivatives. Combination therapy was defined as immunosuppressive treatment combining with PAH-specific therapies.

Follow-up and outcome

All patients were followed up every 3 to 6 months at the Department of Rheumatology, PUMCH. The primary endpoint was reaching the treatment goals of PAH. The composite treatment goals were defined according to the 5th World Symposium on Pulmonary Hypertension [21] as follows: (1) modified NYHA FC I or II; (2) normal or near-normalized structure and function of right ventricle (RV) demonstrated by TTE or cardiac MR: RV anterior-posterior diameter (RV-APD) < 30 mm, or RV transverse diameter (RV-TD) < 40 mm;

(3) 6MWD of > 380 to 440 m; (5) normal BNP levels: BNP < 50 pg/ml, or NT-proBNP < 300 pg/ml; (4) the repeated RHC was not mandatory. If applying, normal RV function showed by hemodynamic parameters: RAP < 8 mmHg and cardiac index > 2.5 L/min/m². Cardiopulmonary exercise testing was not involved in the treatment goals because it is not routinely performed in our center.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 24.0 (Chicago, IL, USA) was used for data processing and analysis. Continuous variables were presented as mean and standard deviations (SD) or medium (range) and were compared by independent sample *t* test or Mann-Whitney U test. Category variables were presented as frequencies and were compared by Pearson chi-squared test. One-, 3-, 5-year cumulative rates of goal reaching were calculated. Univariate and multivariate Cox proportional regression analysis was used to identify predictive factors among age, disease duration, clinical manifestations, lab tests, TTE, PFT, 6MWD, modified NYHA FC, RHC data, and the treatment regimens (glucocorticoids, immunosuppressants, and PAH-targeted therapies). Results were presented as odds ratios and 95% confidence intervals (CIs). A two-tailed *p* value of less than 0.05 was considered statistically significant.

Results

Study population

Overall, 64 patients with pSS-PAH fulfilled the criteria. Two patients failed to continue follow-up and were removed from the cohort. Of the 62 patients enrolled, 61 (98.4%) were female. The mean age at the diagnostic RHC was 38.9 ± 9.1 years with the range of (26–62). The median disease duration of pSS was 46 months (0–365). In 51.6% of the patients, PAH was the initial manifestation. PAH was confirmed 12 months (0–149) later than its onset (Table 1).

Information pertinent to the diagnosis of pSS is also shown in Table 1. Overall, 43 patients had positive Schirmer test among 58 patients who completed the test (74.1%). All of the 17 patients who performed labial salivary biopsy reported positive results (100%). Anti-SSA/SSB antibodies were detected in 55 out of 61 patients (90.2%). Raynaud phenomenon was found in 20 (32.3%) patients. Among 61 patients who were detected for anti-U1RNP antibodies, 12 (19.7%) were positive. However, no patient in this cohort had “puffy finger,” arthritis, myositis, or esophageal disease supporting the diagnosis of MCTD. Anti-centromere antibody, anti-Scl70 antibody, and anti-phospholipid antibodies were negative in all patients.

Table 1 Description of demographic and clinical characteristics in patients with pSS-PAH

Patients	<i>n</i> = 62
Demographics	
Age, year, mean ± SD	38.9 ± 9.1
Female, <i>n</i> (%)	61 (98.4)
Time since onset of pSS, months, medium (range)	46 (0–365)
Time since onset of PAH, months, medium (range)	12 (0–149)
Newly diagnosed pSS, <i>n</i> (%)	42 (67.7)
PAH as the initial manifestation, <i>n</i> (%)	32 (51.6)
Diagnosis of pSS	
Ocular symptoms ^a , <i>n</i> (%)	33/62 (54.1)
Oral symptoms ^b , <i>n</i> (%)	21/61 (34.4)
Schirmer test + (≤ 5 mm in 5 min), <i>n</i> (%)	43/58 (74.1)
Ocular staining + ^c , <i>n</i> (%)	23/56 (41.1)
Labial salivary biopsy +, <i>n</i> (%)	17/17 (100)
WUSF + (≤ 1.5 ml in 15 min), <i>n</i> (%)	48/55 (87.3)
Parotid sialography + ^d , <i>n</i> (%)	42/53 (79.2)
Anti-SSA or Anti-SSB +, <i>n</i> (%)	55/61 (90.2)
Clinical manifestations and assessment of the disease	
Saprodonia, <i>n</i> (%)	14 (22.6)
Parotid enlargement, <i>n</i> (%)	9/61 (14.8)
Non-erosive arthritis, <i>n</i> (%)	1 (1.6)
Purpura, <i>n</i> (%)	4 (6.5)
Hepatic involvement, <i>n</i> (%)	5 (8.1)
Renal involvement, <i>n</i> (%)	4 (6.6)
Peripheral neuropathy, <i>n</i> (%)	1 (1.6)
Hemocytopenia	32 (51.6)
Hypocomplementemia, <i>n</i> (%)	11/56 (19.6)
Hyperglobulinemia, <i>n</i> (%)	35/58 (60.3)
Raynaud's phenomenon, <i>n</i> (%)	20 (32.3)
Mild interstitial lung disease ^e , <i>n</i> (%)	5 (8.1)
ESSDAI, medium (range)	3 (0–29)
SSDDI, medium (range)	2 (0–7)
Autoantibodies	
ANA, <i>n</i> (%)	58/60 (96.7)
Anti-centromere, <i>n</i> (%)	0
Anti-Scl70, <i>n</i> (%)	0
Anti-phospholipid, <i>n</i> (%)	0
Anti-RNP, <i>n</i> (%)	12/61 (19.7)
ANCA, <i>n</i> (%)	1/42 (2.3)
Major comorbid conditions	
Arterial hypertension	4 (6.5)
Diabetes mellitus	1 (1.6)
Chronic kidney disease	2 (3.2)

pSS primary Sjögren's syndrome, PAH pulmonary arterial hypertension, WUSF whole unstimulated salivary flow, ESSDAI EULAR Sjögren's syndrome disease activity index, SSDDI Sjögren's syndrome disease damage index, ANCA anti-neutrophil cytoplasmic antibodies

^a Ocular symptoms: persistent dry eyes for more than 3 months, or recurrent sensation of sand in the eyes, or use tear substitutes more than 3 times a day

^b Oral symptoms: feeling of dry mouth for more than 3 months, or have recurrently swollen salivary glands as an adult, or frequently drink liquids to aid in swallowing dry food

^c Ocular staining positive: ≥ 4 according to van Bijsterveld scoring system

^d Parotid sialography positive: showing the presence of diffuse sialectasias (punctate, cavitory, or destructive pattern), without evidence of obstruction in major ducts

^e Mild interstitial lung diseases: patients with TLC between 60 and 70% of predicted were included, and only minimal interstitial fibrosis was showed in HRCT

The extra-glandular, extra-thoracic manifestations were analyzed: non-erosive arthritis (1.6%), purpura (6.5%), hepatic involvement (8.1%), renal involvement (6.5%), peripheral neurology (1.6%), hemocytopenia (51.6%), hypocomplementemia (19.6%), and hyperglobulinemia (60.3%). Major comorbid conditions included arterial hypertension (6.5%), diabetes mellitus (1.6%), and chronic kidney disease (3.2%). No arterial vascular events or malignancy was found in this cohort (Table 1).

PAH evaluation and treatment regimens of pSS-PAH

Nearly half of the patients (45.2%) were assessed as NYHA FC III to IV at baseline (Table 2). The mean 6MWD was 418 ± 106 m. According to HRCT, 5 (8.1%) patients presented with the evidence of ILD. However, the extent of disease on the image was minimal and was without clinical significance. The pulmonary function was normal or only slightly impaired: mean FVC was $85.9 \pm 9.6\%$ of predicted, and mean DLCO was $59.8 \pm 11.9\%$ of predicted. In hemodynamic profile, mPAP was 49.5 ± 9.4 mmHg, PVR was 11.6 ± 5.1 WU, and cardiac index was 2.5 ± 0.7 L/min/m².

The treatment regimens involved the treatment for both pSS and PAH. Almost all patients (56, 90.3%) received glucocorticoids, and 44 (71.0%) patients had mid-dose glucocorticoids or higher (prednisone ≥ 0.5 mg/kg/day). Among the 49 patients who received immunosuppressants, 45 (72.6%) received cyclophosphamide, 1 (1.6%) received methotrexate, 1 (1.6%) received leflunomide, 1 (1.6%) used Tacrolimus, and 1 (1.6%) used mycophenolate mofetil. On diagnosis of PAH, 93.5% patients were administrated with at least one PAH-targeted therapies, including sildenafil (30.6%), tadalafil (33.9%), bosentan (24.2%), ambrisentan (6.5%), or other medications (8.1%). Forty-two (74.2%) patients received combination therapy, which was defined as immunosuppressive treatment combining with PAH-specific therapies.

For patients who received immunosuppressants, the level of IgG was significantly lower 3 months after treatment than at baseline (12.1 ± 3.9 vs. 20.2 ± 8.4 g/L, $p < 0.001$), while the level of C3 was comparable before and after treatment (1.02 ± 0.22 vs. 1.00 ± 0.27 g/L, $p = 0.326$). Comparing the patients who received immunosuppressants with those who did not use immunosuppressant, the level of IgG after treatment also differed significantly (12.1 ± 3.9 vs. 16.6 ± 3.0 g/L, $p = 0.007$).

Predictive factors of achieving the PAH treatment goals

Thirty-one patients (50%) in this cohort achieved the composite PAH treatment goals. The 1-, 3-, and 5-year cumulative rates of reaching the goals were 40.6, 67.3, and 73.9%, respectively. The median time to reaching the goals was 15.2 months (1–57.1). Table 3 shows the comparison of baseline

Table 2 Evaluation of PAH and treatment regimens for pSS-PAH

Patients	<i>n</i> = 62
NYHA FC III-IV, <i>n</i> (%)	28 (45.2)
Hemodynamics	
mPAP, mm Hg	49.5 ± 9.4
RAP, mm Hg	6.6 ± 4.8
Cardiac index, L/min/m ²	2.5 ± 0.7
PVR, Wood units	11.6 ± 5.1
Echocardiography	
PASP, mm Hg	83.7 ± 17.9
Pericardial effusion, <i>n</i> (%)	16/59 (27.1)
RV-APD, mm	31.7 ± 6.9
RV-TD, mm	44.4 ± 8.2
Pulmonary function tests	
FVC, %predicted	85.9 ± 9.6
DLCO, %predicted	59.8 ± 11.9
6WMD, m	418 ± 106
BNP, pg/ml	387.2 ± 415.9
NT-proBNP, pg/ml	1261.2 ± 1180.9
Glucocorticoids, <i>n</i> (%)	56 (90.3)
Immunosuppressants, <i>n</i> (%)	49 (79.0)
PAH-specific therapy	
ERAs, <i>n</i> (%)	22/58 (37.9)
PDE5 inhibitors, <i>n</i> (%)	41/58 (70.7)
ERAs + PDE5 inhibitors, <i>n</i> (%)	10 (16.1)
Others medications ^a , <i>n</i> (%)	5/58 (8.6)
None, <i>n</i> (%)	4 (6.5)
Combination therapy ^b , <i>n</i> (%)	46 (74.2)

pSS primary Sjögren's syndrome, PAH pulmonary arterial hypertension, NYHA FC New York Heart Association functional class, mPAP mean pulmonary arterial pressure, RAP right atrial pressure, PVR pulmonary vascular resistance, PASP pulmonary artery systolic pressure, RV-APD right ventricular anterior-posterior diameter, RV-TD right ventricular transverse diameter, 6MWD 6-minute walk distance, FVC forced vital capacity, DLCO diffusing capacity for carbon monoxide, NT-proBNP N-terminal pro-brain natriuretic peptide, ERA endothelin receptor antagonist, PDE5 phosphodiesterase type 5

^a Other medications: inhaled iloprost, subcutaneous treprostinil, and selexipag

^b Combination therapy: immunosuppressive therapy combining with PAH-specific medications

demographics, clinical characteristics, and treatment regimens between two groups of patients: patients who reached the treatment goals were classified into group 1, and patients who failed to meet the goals into group 2. The time between onset of pSS and the diagnostic RHC was shorter in group 1 than that in group 2 (47.7 ± 49.9 vs. 87.9 ± 89.6 months, $p = 0.034$). Patients in group 1 seemed to have a better hemodynamic profile with a lower RAP (5.2 ± 3.6 vs. 8.4 ± 5.8 mmHg, $p = 0.023$). Consistently, mPAP was also lower in group 1, though not significantly. Markedly

Table 3 Comparing the demographic and clinical characteristics by group

	Patients who met the treatment goals (group 1)	Patients who failed to meet the treatment goals (group 2)	<i>p</i> value
Patients, <i>n</i>	31	31	
Age, year	38.0 ± 9.8	38.0 ± 9.8	0.465
Female gender, <i>n</i> (%)	31 (100)	30 (96.8)	0.313
Time since onset of pSS, months	47.7 ± 49.9	87.9 ± 89.6	0.034
Time since onset of PAH, months	19.3 ± 21.0	29.1 ± 36.0	0.196
PAH as the initial manifestation, <i>n</i> (%)	16 (51.6)	16 (51.6)	1.000
Newly diagnosed pSS, <i>n</i> (%)	25 (80.6)	17 (54.8)	0.030
Xerophthalmia, <i>n</i> (%)	13 (41.9)	14 (45.2)	0.798
Parotid enlargement, <i>n</i> (%)	4 (12.9)	5 (16.1)	0.679
Raynaud's phenomenon, <i>n</i> (%)	11 (35.5)	9 (29.0)	0.587
Hematopoietic involvement, <i>n</i> (%)	23 (74.2)	23 (74.2)	0.823
Mild interstitial lung disease ^a , <i>n</i> (%)	0	5 (16.1)	0.020
hsCRP, mg/L	2.6 ± 3.4	6.5 ± 7.5	0.031
NT-proBNP, pg/ml	1081.9 ± 1008.3	1440.4 ± 1330.9	0.320
Ro52, <i>n</i> (%)	23 (74.2)	22 (71.0)	0.677
Anti-RNP, <i>n</i> (%)	7 (22.6)	5 (16.1)	0.561
NYHA FC III-IV, <i>n</i> (%)	12 (38.7)	16 (51.6)	0.307
6WMD, m, mean ± SD	428.8 ± 103.4	408.3 ± 109.5	0.580
Pulmonary function tests			
FVC, %predicted	86.6 ± 9.6	85.3 ± 9.9	0.698
DLCO, %predicted	58.8 ± 9.5	60.9 ± 14.1	0.601
Echocardiography			
PASP, mmHg	79.6 ± 15.5	87.7 ± 19.4	0.076
RV-APD, mm	30.2 ± 6.5	33.2 ± 7.1	0.102
LV-EDD, mm	39.9 ± 4.6	35.3 ± 5.5	0.001
Hemodynamics			
RAP, mmHg	5.2 ± 3.6	8.4 ± 5.8	0.023
mPAP, mmHg	47.4 ± 9.0	51.6 ± 9.5	0.079
Cardiac Index, L/min/m ²	2.6 ± 0.8	2.4 ± 0.7	0.187
PVR, Wood units	10.6 ± 4.0	12.6 ± 5.9	0.131
Glucocorticoids, <i>n</i> (%)	29 (93.5)	27 (87.1)	0.390
Immunosuppressants, <i>n</i> (%)	30 (96.7)	24 (77.4)	0.023
PAH-specific medication			
ERAs, <i>n</i> (%)	14 (45.2)	8 (25.8)	0.156
PDE5 inhibitors, <i>n</i> (%)	19 (61.1)	22 (71.0)	0.203
ERAs + PDE5 inhibitors, <i>n</i> (%)	4 (12.9)	6 (19.4)	0.490
Other medications ^b , <i>n</i> (%)	1 (3.2)	4 (12.9)	0.138
Combination therapy, <i>n</i> (%)	25 (80.6)	25 (80.6)	0.785

pSS primary Sjögren's syndrome, PAH pulmonary arterial hypertension, hsCRP hypersensitive C-reactive protein, NT-proBNP N-terminal pro-brain natriuretic peptide, 6MWD 6-minute walk distance, NYHA FC New York Heart Association functional class, FVC forced vital capacity, DLCO diffusing capacity for carbon monoxide, PASP pulmonary artery systolic pressure, RV-APD right ventricular anterior-posterior diameter, LV-EDD left ventricular end diastolic diameter, mPAP mean pulmonary arterial pressure, RAP right atrial pressure, PVR pulmonary vascular resistance, ERA endothelin receptor antagonist, PDE5 phosphodiesterase type 5. *Italics* indicate statistical significance

^a Mild interstitial lung disease: patients with TLC between 60 and 70% of predicted were included, and only minimal interstitial fibrosis was showed in HRCT

^b Other medications: inhaled iloprost, subcutaneous treprostinil, and selexipag

more patients in group 1 received immunosuppressants (30 vs 24, $p = 0.023$). The two groups did not differ significantly in terms of NYHA FC, 6MWD, or treatment regimens with PAH-targeted therapies.

Univariate Cox regression analysis identified that the predictors of reaching the treatment goals included baseline RV-APD > 30 mm (HR 0.355, 95% CI 0.166–0.795, $p = 0.008$), LV-EDD < 35 mm (HR 0.302, 95% CI 0.122–0.744, $p = 0.004$), mPAP per 10 mmHg (HR 0.760, 95% CI 0.607–0.951, $p = 0.017$), and RAP $\geq$ 8 mmHg (HR 0.285, 95% CI 0.084–0.971, $p = 0.045$). In contrast, using immunosuppressants (HR 5.482, 95% CI 1.305–23.026, $p = 0.020$) and combination therapy (HR 3.761, 95% CI 1.142–12.389, $p = 0.029$) were protective factors of achieving the treatment goals (Table 4). Multivariate Cox regression analysis confirmed that the independent predictive factors of reaching the goals were using immunosuppressants (HR 4.715, 95% CI 1.101–20.192, $p = 0.037$) and baseline RV-APD > 30 mm (HR 0.426, 95% CI 0.188–0.968, $p = 0.042$) (Table 5).

Table 4 Predictive factors of achieving the PAH treatment goals in patients with pSS-PAH

Variables	Univariate Cox regression analysis	
	HR (95%CI)	<i>p</i> value
Age	1.004 (0.965–1.045)	0.844
Time since onset of pSS	0.997 (0.991–1.004)	0.416
Newly diagnosed pSS	1.993 (0.815–4.872)	0.131
Xerophthalmia	1.353 (0.657–2.790)	0.412
Raynaud's phenomenon	1.222 (0.561–2.664)	0.614
Mild interstitial lung disease	0.042 (0.000–8.966)	0.274
ESSDAI	0.990 (0.882–1.111)	0.863
SSDDI	0.855 (0.628–1.164)	0.319
Anti-RNP	1.795 (0.753–4.280)	0.187
NYHA FC III-IV	0.713 (0.346–1.471)	0.360
RV-APD > 30 mm	0.355 (0.166–0.759)	0.008
LV-EDD < 35 mm	0.302 (0.122–0.744)	0.009
PSAP, per 10 mmHg	0.712 (0.547–0.927)	0.012
mPAP, per 10 mmHg	0.760 (0.607–0.951)	0.017
RAP $\geq$ 8 mmHg	0.285 (0.084–0.971)	0.045
Cardiac Index < 2.5 L/min/m ²	0.808 (0.383–1.704)	0.575
PAH-specific therapy	1.781 (0.239–13.250)	0.573
Immunosuppressants	5.482 (1.305–23.026)	0.020
Combination therapy	3.761 (1.142–12.389)	0.029

pSS primary Sjögren's syndrome, *PAH* pulmonary arterial hypertension, *6MWD* 6-min walk distance, *ESSDAI* EULAR Sjögren's syndrome disease activity index, *SSDDI* Sjögren's syndrome disease damage index, *NYHA FC* New York Heart Association functional class, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *RV-APD* right ventricular anterior-posterior diameter, *LV-EDD* left ventricular end diastolic diameter, *PASP* pulmonary arterial systolic pressure, *mPAP* mean pulmonary arterial pressure, *RAP* right atrial pressure. *Italics* indicate statistical significance

Table 5 Independent predictive factors of achieving the PAH treatment goals in patients with pSS-PAH

Variables	Multivariate Cox regression analysis	
	HR (95%CI)	<i>p</i> value
RV-APD > 30 mm	0.426 (0.188–0.968)	0.042
mPAP, per 10 mmHg	0.991 (0.706–1.176)	0.474
Immunosuppressants	4.715 (1.101–20.192)	0.037

pSS primary Sjögren's syndrome, *PAH* pulmonary arterial hypertension, *RV-APD* right ventricular anterior-posterior diameter, *mPAP* mean pulmonary arterial pressure. *Italics* indicate statistical significance

To confirm the impact of immunosuppressants and baseline RV-APD, we evaluated the cumulative rates of achieving the treatment goals. The 1-, 3-, and 5-year rates of reaching the goals were 48.8, 78.4, and 83.8%, respectively, for patients who received immunosuppressant; 10.0, 21.2, and 21.2% respectively for patients who did not (Fig. 1a). The 1-, 3-, and 5-year rates of reaching the goals were 63.3, 75.5, and 75.5% respectively for patients who had baseline RV-APD $\leq$ 30 mm; 30.5, 54.4, and 63.5% respectively for patients who had RV-APD > 30 mm at baseline (Fig. 1b).

Discussion

This study focused on applying the treat-to-target (T2T) strategy in patients with pSS-PAH. We presented the largest cohort of pSS-PAH confirmed by RHC. Our results showed that patients who received immunosuppressants were more likely to reach the PAH treatment goals, subsequently to obtain a better prognosis. In contrast, patients with RV-APD larger than 30 mm at baseline tended to have worse response to treatment. Our study is the first to report the predictive factors of achieving the treatment goals in patients with pSS-PAH. We also confirm that T2T strategy is effective in pSS-PAH.

The last decade was marked by therapeutic advances in PAH with the T2T strategy. Historically, escalating treatment for PAH was mainly based on clinical deterioration. Promoted by Hoeper et al. in 2005 [10], the T2T strategy uses known prognostic indicators of PAH as the goals of treatment. Guided by T2T, patients with PAH have achieved better survival. However, PAH encompasses heterogeneous subgroups. In CTD-PAH, the most investigated underlying disease is SSc. Cohort studies and meta-analyses reported that the parameters classically associated with the severity of IPAH, including 6MWD, mPAP, cardiac index, and RAP, were also prognostic factors in SSc-PAH [22–25]. For pSS-PAH, however, it is still difficult to identify the patients who may benefit from the treatment more than others due to a paucity of data.

Fig. 1 Kaplan–Meier analysis of reaching the treatment goals in patients with pSS-PAH. **a** Curves of reaching the goals based on the use of immunosuppressants. **b** Curves of reaching the goals according to the

right ventricular anterior-posterior diameters. pSS primary Sjögren's syndrome, PAH pulmonary arterial hypertension, RV-APD right ventricular anterior-posterior diameter

The 1-, 3-, and 5-year cumulative rates of achieving the PAH treatment goals in our cohort of pSS-PAH were 40.6, 67.3, and 73.9%, respectively. These rates indicate that most patients reached the goals within 1 year after the treatment started. Previous studies on PAH have confirmed that achieving the treatment goals is associated with better clinical outcomes [26, 27]. Consistently, two sets of recently published guidelines also provided evidence-based recommendations for comprehensive prognostic evaluation and achieving PAH treatment goals [28, 29]. The data from our study reinforced the importance of early, active intervention following the T2T strategy in patients with pSS-PAH in order to achieve better prognosis.

We found that using immunosuppressants is independently predictive to reaching the treatment goals. Similarly, a Japanese cohort indicated that intensive immunosuppressive therapy could improve the hemodynamic profiles in patients with CTD-PAH. Thirteen patients were recruited, among which 4 had pSS. Six patients achieved nearly normal mPAP that maintained for at least 12 months after treatment [30]. In our cohort, since 45 out of 49 patients received cyclophosphamide, we also involved cyclophosphamide in multivariate analysis, but the result was not significant (HR 1.841, 95% CI 0.528–6.419, $p = 0.338$). Limited by the size of the cohort, it was difficult to inspect which specific immunosuppressive agent would have an impact on achieving the treatment goals. Currently, there is no specific guideline for the management of patients with pSS-PAH. We propose that immunosuppressants should be introduced as a part of standardized treatment

approach for pSS-PAH. Moreover, our finding also gives clue to the pathogenesis. pSS is characteristic of lymphocytic infiltration of the salivary glands. Abnormally activated B cells promote plasma cell secretion of immunoglobulins and various autoantibodies [31, 32]. The role of T-cells was with divergent conclusions, especially about the regulatory T-cells and T-helper 17 cells [33]. However, the T cell activation was confirmed. On the other hand, the mechanisms of PAH in pSS have not been well elucidated. PAH in CTD is not homogenous but intertwines the dysregulation in autoimmune and the remodeling of pulmonary vasculature. Histopathology study showed that SSc/MCTD-PAH was generally accompanied with fibrosis, whereas fibrosis in SLE-PAH was rare and mild [34]. Hypotheses on mechanism included endothelial dysfunction, immune complex accumulation, necrotizing vasculitis, and imbalances of endothelial vasoactive molecules [35–37]. In pSS-PAH, little was known due to the lack of data. The results of our study highlighted the essential role of autoimmune process in the pathogenesis of pSS-PAH, providing evidence for future studies.

We also identified that patients with RV-APD larger than 30 mm at baseline are less likely to achieve the PAH treatment goals. Similarly, Ghio et al. found that an increased RV diameter is prognostic to poor survival in patients with IPAH [38]. It is well established that an elevated RVSP or PASP by echocardiography is neither sensitive nor specific to diagnose PAH [39]. However, the structure of RV is reliable to evaluate the severity of PAH. Noninvasive echocardiography is widely available to provide information about RV function and can

estimate RV pressures [40]. Noticeably, RV failure is the main cause of mortality in PAH. Decreased RV ejection has been proved to strongly associate with poor survival in IPAH [41]. Although cardiac magnetic resonance remains the gold standard for evaluating RV volumes, it is expensive and less accessible. Therefore, echocardiography remains an important tool for screening to detect PAH and for assessment during follow-up [28, 42]. Given the relatively higher prevalence and greater mortality of SS-PAH, SS is now the only CTD with recommended screening guidelines [28]. The present study shows that echocardiography provides additional information other than detecting PAH in pSS. An impaired RV morphology at baseline helps identify patients with pSS-PAH who may not respond well to the initial treatment and may need particular attention. This is the practical implication that can help physicians to manage the patients with pSS-PAH more efficiently.

There are several limitations of this study. First, PUMCH is a tertiary center, and there is a possibility of referral bias. Some patients enrolled in this study were referred from local hospitals or cardiologists and have never undergone screening for PAH. Therefore, patients in this study appeared to have severe PAH, based on the RHC performance. An approach of early detection is required to recognize the patients in the early stage of PAH. Second, this study is single centered and was limited by size. Future multicenter cohorts are in need to explore independent prognostic factors of pSS-PAH and to further validate the T2T strategy.

In conclusion, we characterize the largest cohort of pSS-PAH confirmed by RHC. This is the first study to describe predictive factors of achieving the PAH treatment goals in pSS-PAH following the T2T strategy. We provide strong evidence that patients who received immunosuppressants are more likely to reach the treatment goals. In contrast, an impaired RV structure correlates to worse treatment response. We also confirm that the T2T strategy is effective in pSS-PAH. Future studies are required to optimize the therapeutic strategies for pSS-PAH in order to further shift the survival curve to the right.

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Compliance with ethical standards

Statement of ethics This study was approved by the Medical Ethics Committee of PUMCH. All patients entering the cohort signed their informed consent prior to their inclusion in the study.

Disclosures None.

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References

1. Rhee RL, Gabler NB, Sangani S, Praestgaard A, Merkel PA, Kawut SM (2015) Comparison of treatment response in idiopathic and connective tissue disease-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med* 192(9):1111–1117. <https://doi.org/10.1164/rccm.201507-1456OC>
2. Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, Miller DP, Nicolls MR, Zamanian RT (2010) Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest* 138(6):1383–1394. <https://doi.org/10.1378/chest.10-0260>
3. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, Vrani F, Das C, Elliot CA, Johnson M, DeSoyza J, Torpy C, Goldsmith K, Hodgkins D, Hughes RJ, Pepke-Zaba J, Coghlan JG (2009) Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* 179(2):151–157. <https://doi.org/10.1164/rccm.200806-953OC>
4. Ngian GS, Stevens W, Prior D, Gabbay E, Roddy J, Tran A, Minson R, Hill C, Chow K, Sahhar J, Proudman S, Nikpour M (2012) Predictors of mortality in connective tissue disease-associated pulmonary arterial hypertension: a cohort study. *Arthritis Res Ther* 14(5):R213. <https://doi.org/10.1186/ar4051>
5. Chung WJ, Park YB, Jeon CH, Jung JW, Ko KP, Choi SJ, Seo HS, Lee JS, Jung HO (2015) Baseline characteristics of the Korean Registry of Pulmonary Arterial Hypertension. *J Korean Med Sci* 30(10):1429–1438. <https://doi.org/10.3346/jkms.2015.30.10.1429>
6. Shirai Y, Yasuoka H, Okano Y, Takeuchi T, Satoh T, Kuwana M (2012) Clinical characteristics and survival of Japanese patients with connective tissue disease and pulmonary arterial hypertension: a single-centre cohort. *Rheumatology* 51(10):1846–1854. <https://doi.org/10.1093/rheumatology/kes140>
7. Zhao J, Wang Q, Liu Y, Tian Z, Guo X, Wang H, Lai J, Huang C, Yang X, Li M, Zeng X (2017) Clinical characteristics and survival of pulmonary arterial hypertension associated with three major connective tissue diseases: a cohort study in China. *Int J Cardiol* 236:432–437. <https://doi.org/10.1016/j.ijcard.2017.01.097>
8. Hao YJ, Jiang X, Zhou W, Wang Y, Gao L, Wang Y, Li GT, Hong T, Huo Y, Jing ZC, Zhang ZL (2014) Connective tissue disease-associated pulmonary arterial hypertension in Chinese patients. *Eur Respir J* 44(4):963–972. <https://doi.org/10.1183/09031936.00182813>
9. Zhang R, Dai LZ, Xie WP, Yu ZX, Wu BX, Pan L, Yuan P, Jiang X, He J, Humbert M, Jing ZC (2011) Survival of Chinese patients with pulmonary arterial hypertension in the modern treatment era. *Chest* 140(2):301–309. <https://doi.org/10.1378/chest.10-2327>
10. Hoeper MM, Markevych I, Spiekeroetter E, Welte T, Niedermeyer J (2005) Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 26(5):858–863. <https://doi.org/10.1183/09031936.05.00075305>
11. Sitbon O, Galie N (2010) Treat-to-target strategies in pulmonary arterial hypertension: the importance of using multiple

- goals. *Eur Respir Rev* 19(118):272–278. <https://doi.org/10.1183/09059180.00008210>
12. Hill NS, Cawley MJ, Heggen-Peay CL (2016) New therapeutic paradigms and guidelines in the management of pulmonary arterial hypertension. *J Manag Care Special Pharm* 22(3 Suppl A):S3–S21. <https://doi.org/10.18553/jmcp.2016.22.3-a.s3>
13. Launay D, Hachulla E, Hatron PY, Jais X, Simonneau G, Humbert M (2007) Pulmonary arterial hypertension: a rare complication of primary Sjogren syndrome: report of 9 new cases and review of the literature. *Medicine* 86(5):299–315. <https://doi.org/10.1097/MD.0b013e3181579781>
14. Chen CH, Chen HA, Yang KY, Yu WC, Liao HT, Huang DF (2006) Clinical features and endothelin receptor antagonist in primary Sjogren's syndrome with pulmonary arterial hypertension. *Scand J Rheumatol* 35(3):245–247. <https://doi.org/10.1080/03009740600765032>
15. Nakagawa N, Osanai S, Ide H, Nishigaki Y, Takahashi S, Nakano H, Ohsaki Y, Kikuchi K, Tokusashi Y, Obata H (2003) Severe pulmonary hypertension associated with primary Sjogren's syndrome. *Intern Med* 42(12):1248–1252
16. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH (2002) Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 61(6):554–558
17. Seror R, Bowman SJ, Brito-Zeron P, Theander E, Bootsma H, Tzioufas A, Gottenberg JE, Ramos-Casals M, Dornier T, Ravaud P, Vitali C, Mariette X, Asmussen K, Jacobsen S, Bartoloni E, Gerli R, Bijlsma JW, Kruize AA, Bombardieri S, Bookman A, Kallenberg C, Meiners P, Brun JG, Jonsson R, Caporali R, Carsons S, De Vita S, Del Papa N, Devauchelle V, Saraux A, Fauchais AL, Sibilia J, Hachulla E, Illei G, Isenberg D, Jones A, Manoussakis M, Mandl T, Jacobsson L, Demoulin F, Montecucco C, Ng WF, Nishiyama S, Omdal R, Parke A, Praprotnik S, Tomsic M, Price E, Scofield H, K LS, Smolen J, Laque RS, Steinfeld S, Sutcliffe N, Sumida T, Valesini G, Valim V, Vivino FB, Vollenweider C (2015) EULAR Sjogren's syndrome disease activity index (ESSDAI): a user guide. *RMD Open* 1(1):e000022. <https://doi.org/10.1136/rmdopen-2014-000022>
18. Seror R, Bootsma H, Saraux A, Bowman SJ, Theander E, Brun JG, Baron G, Le Guern V, Devauchelle-Pensec V, Ramos-Casals M, Valim V, Dornier T, Tzioufas A, Gottenberg JE, Solans Laque R, Mandl T, Hachulla E, Sivils KL, Ng WF, Fauchais AL, Bombardieri S, Priori R, Bartoloni E, Goeb V, Praprotnik S, Sumida T, Nishiyama S, Caporali R, Kruize AA, Vollenweider C, Ravaud P, Meiners P, Brito-Zeron P, Vitali C, Mariette X (2016) Defining disease activity states and clinically meaningful improvement in primary Sjogren's syndrome with EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). *Ann Rheum Dis* 75(2):382–389. <https://doi.org/10.1136/annrheumdis-2014-206008>
19. Vitali C, Palombi G, Baldini C, Benucci M, Bombardieri S, Covelli M, Del Papa N, De Vita S, Epis O, Franceschini F, Gerli R, Govoni M, Bonghi SM, Maglione W, Migliarese S, Montecucco C, Orefice M, Priori R, Tavoni A, Valesini G (2007) Sjogren's syndrome disease damage index and disease activity index: scoring systems for the assessment of disease damage and disease activity in Sjogren's syndrome, derived from an analysis of a cohort of Italian patients. *Arthritis Rheum* 56(7):2223–2231. <https://doi.org/10.1002/art.22658>
20. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002) ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 166(1):111–117. <https://doi.org/10.1164/ajrccm.166.1.atl102>
21. McLaughlin VV, Gaine SP, Howard LS, Leuchte HH, Mathier MA, Mehta S, Palazzini M, Park MH, Tapson VF, Sitbon O (2013) Treatment goals of pulmonary hypertension. *J Am Coll Cardiol* 62(25 Suppl):D73–D81. <https://doi.org/10.1016/j.jacc.2013.10.034>
22. Lefevre G, Dauchet L, Hachulla E, Montani D, Sobanski V, Lambert M, Hatron PY, Humbert M, Launay D (2013) Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. *Arthritis Rheum* 65(9):2412–2423. <https://doi.org/10.1002/art.38029>
23. Chung L, Farber HW, Benza R, Miller DP, Parsons L, Hassoun PM, McGoon M, Nicolls MR, Zamanian RT (2014) Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. *Chest* 146(6):1494–1504. <https://doi.org/10.1378/chest.13-3014>
24. Johnson SR, Swiston JR, Granton JT (2008) Prognostic factors for survival in scleroderma associated pulmonary arterial hypertension. *J Rheumatol* 35(8):1584–1590
25. Gadre A, Ghattas C, Han X, Wang X, Minai O, Highland KB (2017) Six-minute walk test as a predictor of diagnosis, disease severity, and clinical outcomes in scleroderma-associated pulmonary hypertension: the DIBOSA study. *Lung* 195(5):529–536. <https://doi.org/10.1007/s00408-017-0034-1>
26. Galie N, Palazzini M, Manes A (2010) Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses. *Eur Heart J* 31(17):2080–2086. <https://doi.org/10.1093/eurheartj/ehq152>
27. Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, Welte T, Hoeper MM (2012) The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 39(3):589–596. <https://doi.org/10.1183/09031936.00092311>
28. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barbera J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol C, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Voller H, Luis Zamorano J (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 37(1):67–119. <https://doi.org/10.1093/eurheartj/ehv317>
29. Taichman DB, Ornelas J, Chung L, Klinger JR, Lewis S, Mandel J, Palevsky HI, Rich S, Sood N, Rosenzweig EB, Trow TK, Yung R, Elliott CG, Badesch DB (2014) Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. *Chest* 146(2):449–475. <https://doi.org/10.1378/chest.14-0793>
30. Miyamichi-Yamamoto S, Fukumoto Y, Sugimura K, Ishii T, Satoh K, Miura Y, Tatebe S, Nochioka K, Aoki T, Do EZ, Shimokawa H (2011) Intensive immunosuppressive therapy improves pulmonary hemodynamics and long-term prognosis in patients with pulmonary arterial hypertension associated with connective tissue disease. *Circ J* 75(11):2668–2674
31. Cornec D, Devauchelle-Pensec V, Tobon GJ, Pers JO, Jousse-Joulin S, Saraux A (2012) B cells in Sjogren's syndrome: from

- pathophysiology to diagnosis and treatment. *J Autoimmun* 39(3): 161–167. <https://doi.org/10.1016/j.jaut.2012.05.014>
32. Miceli-Richard C, Wang-Renault SF, Boudaoud S, Busato F, Lallemand C, Bethune K, Belkhir R, Nocturne G, Mariette X, Tost J (2016) Overlap between differentially methylated DNA regions in blood B lymphocytes and genetic at-risk loci in primary Sjogren's syndrome. *Ann Rheum Dis* 75(5):933–940. <https://doi.org/10.1136/annrheumdis-2014-206998>
 33. Matsui K, Sano H (2017) T helper 17 cells in primary Sjogren's syndrome. *J Clin Med* 6(7):E65. <https://doi.org/10.3390/jcm6070065>
 34. Sasaki N, Kamataki A, Sawai T (2011) A histopathological study of pulmonary hypertension in connective tissue disease. *Allergol Int* 60(4):411–417. <https://doi.org/10.2332/allergolint.11-RAI-0337>
 35. Humbert M, Montani D, Perros F, Dorfmüller P, Adnot S, Eddahibi S (2008) Endothelial cell dysfunction and cross talk between endothelium and smooth muscle cells in pulmonary arterial hypertension. *Vasc Pharmacol* 49(4–6):113–118. <https://doi.org/10.1016/j.vph.2008.06.003>
 36. Perros F, Dorfmüller P, Humbert M (2005) Current insights on the pathogenesis of pulmonary arterial hypertension. *Semin Respir Crit Care Med* 26(4):355–364. <https://doi.org/10.1055/s-2005-916149>
 37. Aithala R, Alex AG, Danda D (2017) Pulmonary hypertension in connective tissue diseases: an update. *Int J Rheum Dis* 20(1):5–24. <https://doi.org/10.1111/1756-185x.13001>
 38. Ghio S, Pazzano AS, Klersy C, Scelsi L, Raineri C, Camporotondo R, D'Armini A, Visconti LO (2011) Clinical and prognostic relevance of echocardiographic evaluation of right ventricular geometry in patients with idiopathic pulmonary arterial hypertension. *Am J Cardiol* 107(4):628–632. <https://doi.org/10.1016/j.amjcard.2010.10.027>
 39. Finkelhor RS, Lewis SA, Pillai D (2015) Limitations and strengths of doppler/echo pulmonary artery systolic pressure-right heart catheterization correlations: a systematic literature review. *Echocardiography* 32(1):10–18. <https://doi.org/10.1111/echo.12594>
 40. Crowe T, Jayasekera G, Peacock AJ (2018) Non-invasive imaging of global and regional cardiac function in pulmonary hypertension. *Pulm Circ* 8(1):2045893217742000. <https://doi.org/10.1177/2045893217742000>
 41. Baggen VJ, Leiner T, Post MC, van Dijk AP, Roos-Hesselink JW, Boersma E, Habets J, Sieswerda GT (2016) Cardiac magnetic resonance findings predicting mortality in patients with pulmonary arterial hypertension: a systematic review and meta-analysis. *Eur Radiol* 26(11):3771–3780. <https://doi.org/10.1007/s00330-016-4217-6>
 42. Methia N, Latreche S, Ait Mokhtar O, Monsuez JJ, Benkhedda S (2016) Assessment for pulmonary artery hypertension using clinical and echocardiographic criteria in patients with systemic sclerosis. *Am J Med Sci* 352(4):343–347. <https://doi.org/10.1016/j.amjms.2016.07.007>