EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Pulmonary arterial hypertension associated with primary Sjogren's syndrome: a multi-centre cohort study from China

Jieying Wang, Mengtao Li, Qian Wang, Xiao Zhang, Junyan Qian, Jiuliang Zhao, Dong Xu, Zhuang Tian, Wei Wei, Xiaoxia Zuo, Miaojia Zhang, Ping Zhu, Shuang Ye, Wei Zhang, Yi Zheng, Wufang Qi, Yang Li, Zhuoli Zhang, Feng Ding, Jieruo Gu, Yi Liu, Yanhong Wang, Yan Zhao, Xiaofeng Zeng

Please cite this article as: Wang J, Li M, Wang Q, *et al*. Pulmonary arterial hypertension associated with primary Sjogren's syndrome: a multi-centre cohort study from China. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.02157-2019).

Title

Pulmonary arterial hypertension associated with primary Sjogren's syndrome: a multi-centre cohort study from China

Running title

Cohort study in patients with pSS-PAH

Authors and affiliations

Jieying Wang, MD[1,2*]; Mengtao Li, MD[1*,#]; Qian Wang, MD[1*,#], Xiao Zhang, MD[2*]; Junyan Qian, MD[1]; Jiuliang Zhao, MD[1]; Dong Xu, MD[1]; Zhuang Tian, MD[3]; Wei Wei, MD[4]; XiaoxiaZuo, MD[5]; Miaojia Zhang, MD[6]; Ping Zhu,MD[7]; Shuang Ye, MD[8]; Wei Zhang, MD[9]; Yi Zheng, MD[10]; Wufang Qi, MD[11]; Yang Li, MD[12]; Zhuoli Zhang, MD[13]; Feng Ding, MD[14]; JieruoGu, MD[15]; Yi Liu, MD[16]; Yanhong Wang, PhD[17]; Yan Zhao, MD[1]and Xiaofeng Zeng, MD[1#].

[1]Department of Rheumatology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Beijing, China

[2]Department of Rheumatology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

[3]Department of Cardiology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China

[4] Department of Rheumatology, Tianjin Medical University General Hospital, Tianjin, China

[5]Department of Rheumatology, Xiangya Hospital, Central South University, Changsha, China

[6]Department of Rheumatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

[7]Department of Clinical Immunology, PLA Specialized Research Institute of Rheumatology & Immunology, Xijing Hospital, Fourth Military Medical University, Xi'an, China

[8]Department of Rheumatology, Ren Ji Hospital South Campus, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

[9]Department of Rheumatology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

[10]Department of Rheumatology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

[11]Department of Rheumatology, the First Central Hospital, Tianjin, China

[12]Department of Rheumatology, the Second Affiliated Hospital of Harbin Medical University, Harbin, China

[13]Department of Rheumatology and Clinical Immunology, Peking University First Hospital, Beijing, China

[14]Department of Rheumatology, Qilu Hospital of Shandong University, Jinan, China

[15]Department of Rheumatology, the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

[16]Department of Rheumatology and Immunology, West China Hospital, Sichuan University, Chengdu, China

[17]Department of Epidemiology and Bio-statistics, Institute of Basic Medical Sciences, China Academy of Medical Sciences & Peking Union Medical College, Beijing, China

*J. Wang, M. Li, Q. Wang and X. Zhang contributed equally to this study.

#**Corresponding author**: Department of Rheumatology,Peking Union Medical College Hospital, No.1 Shuaifuyuan, Beijing 100730, China.

Dr. M. Li, mengtao.li@cstar.org.cn,

Dr. X. Zeng, zengxfpumc@163.com.

Author contributions: X. Z. is the guarantor of this article. J. W., M. L., X. Z., J. Q., J. Z., Q. W. and X. Z. contributed to the study design and data analysis and interpretation. All authors contributed to the data collection. J. W., J. Z., and Y. W. contributed to the statistical analysis. J. W., M. L. and X. Z. contributed to manuscript preparation. All authors gave their final approval of the manuscript.

Abstract

Objectives: Primary Sjogren'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 catheterization (RHC). 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, HR=0.161), pulmonary vascular resistance (p=0.016, HR=1.105) and Sjogren's syndrome disease damage index (SSDDI, 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. Patients' 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.

Key words： pulmonary arterial hypertension; primary Sjogren's syndrome; risk factor; survival; risk assessment.

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(WSPH)[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 Sjogren's syndrome (pSS) being the two most common diseases[8; 9]. Recently, some 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 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 multi-centre cohort study of pSS-PAH was initiated in 2014 at Peking Union Medical College Hospital and eight other qualified referral CTD-PAH clinical centres. Patients who visited the clinical centres from 2005 to 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 consents were obtained from all recruited patients.

Inclusion criteria

Primary Sjogren's syndrome was diagnosed in accordance with the classification criteria proposed by the American-European Consensus Group in 2002[21] or ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) in 2016[22]. PAH was defined by right heart catheterization (RHC) according to the 2015 guidelines of the European Society of Cardiology/European Respiratory Society (ESC/ERS)[17]: mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest, pulmonary artery wedge pressure (PAWP) ≤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 systemic lupus erythematosus, systemic sclerosis, and mixed connective tissue

disease; 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 (HRCT) and/or pulmonary function tests; and 4) chronic thromboembolic disease confirmed by ventilation and perfusion scanning and/or computed tomographic pulmonary angiography (CTPA).

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 enrolled patients before 2014 were retrospectively collected by reviewing the medial charts and since 2014 the data 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 Sjogren's syndrome disease activity index(ESSDAI)[23] and Sjogren'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 by the 2015 ESC/ERS guidelines[17] and further validated in various studies[6; 20; 25]. We used the four determinants: WHO functional class, 6-min walking distance, BNP or NT-proBNP plasma levels and hemodynamics (right atrial pressure, RAP; cardiac index, CI; mixed venous oxygen saturation, SvO_2). Risk strata were defined as follows: Low risk= at least 3 low-risk determinants and no high-risk determinants; High risk= at least 2 high-risk determinants including SvO_2 or CI; Intermediate risk= low or high risk criteria are not fulfilled. Since repeated RHC were not available, we applied the non-invasive risk stratification strategy from Boucly[20] and Hoeper[25] in the follow-up risk assessments (low risk defined as meeting all three criteria: WHO functional class I-II, BNP <50 ng/L or NTproBNP < 300 ng/L, 6-min walking distance >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, 6-min walking distance, 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 endpoint was all-cause mortality. Those lost to follow-up were contacted by phone to confirm the survival status. Survival status 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 three months before the deadline.

Statistical analysis

The data were analysed using SPSS version 24.0(Chicago, IL, USA). Continuous variables are described as the means ± standard deviation or median (interquartile range), while categorical variables are described as percentages. The comparisons of continuous variables were conducted using Student's t test or the Mann-Whitney U test. Categorical variables, including the 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 less than 0.05 was considered statistically significant.

Result

Baseline characteristics of pSS-associated PAH

A total of 103 pSS-PAH patients were enrolled from the study centres. Among which, 67 patients (65%) were recruited and followed-up prospectively, while 36 patients (35%) 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. More patients were in WHO functional class I-II (58.2%). Approximately 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% 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% patients received binary therapy.

Case-control study

There were 526 pSS patients without PAH from a multi-centre study in China included as controls[26].The comparison between pSS-PAH and pSS-nonPAH 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 the 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 survival-state confirmation. The mean follow-up was 2.6 years, and the median follow-up was 1.6 years. Eleven endpoint 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. 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, HR=1.570), CI (p=0.010, HR=0.161) and PVR (p=0.016, HR=1.105) may be potential predictors of mortality (Table 4). Among which, PVR was related to CI as it was calculated by a formula that contains CI. To confirm the impact of the predictors on mortality, a Kaplan-Meier curve analysis was conducted, and the difference was significant between subgroups. A CI≥2.5L/min/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). The multivariate analysis was not performed due to lack of endpoint events.

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 1), although some variables such as age and pSS disease activity remained significantly different. Up to last follow-up visit, a total of forty-one patients achieved low-risk category, 14 of whom were already in 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% among patients in intermediate- or high-risk category during follow-up, respectively, compared with 100% among those in low-risk category (Figure 4A). Among those who achieved low-risk category during follow-up, 31 patients (75.6%) achieved low-risk category within one year after diagnosis of PAH, and 38 patients (92.7%) achieved low-risk category within two years. Based on the result of the risk assessment from the one-year follow-up visit, the patients reaching low-risk category within one year had a better prognosis than those not reaching low-risk category within one 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 patients' situation, especially for the mild PAH and active underlying CTD, clinician might initially administer immunosuppressive treatment without immediately prescribing pulmonary vasodilators. In our cohort, there were 12 patients not receiving PAH therapy at baseline and only 4 remaining immunosuppression therapy alone during follow-up (Table 4). 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 Launay's study[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-U1 RNP 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]. Hachulla[12] also 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 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 the 1-, 3- and 5-year survival rates were 92.1%, 84.8% and 72.9% in SLE-PAH patients[13], respectively, and however different from a study showing 87%, 55% and 35% survival in SSc-PAH patients[11], respectively. 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 (CI) was identified as an 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 CI suggests that PAH has progressed into the decompensation state, suggesting that preserved cardiopulmonary function is crucial for PAH patients. Our study also 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 greater than 3 means that patients have other systems

involved in addition to the exocrine gland, and patients with multi-system damage have a poorer prognosis.

We confirmed that the ESC/ERS risk stratification, now validated in 5 previous studies[6; 11; 18; 20; 45], also applied to the pSS-PAH subgroup, a less recognized 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 lower than 5% in the low-risk group, between 5% and 10% in the intermediate-risk group, and more than 10% in the high-risk group[17]. We also confirmed the non-invasive risk stratification strategy from Boucly[20] and Hoeper[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. in 2005[46] 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 also supported this approach, which suggested that a treat-to-target strategy might be a beneficial treatment management strategy for pSS-PAH patients. Further research, however, is needed.

There are several limitations in this study. First, this was a partly retrospective cohort study. Second, in case-control study. Since there were no follow-up data in 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. A recent study, however, showed that a risk assessment strategy containing non-invasive parameters still had a good predictive value during follow-up[25], although further validation is needed. Finally, since there were only 11 endpoint events in survival analysis, the multivariate Cox analysis could not 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 optimizing 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.

Funding

This work was supported by the Chinese National Key Research R&D Program (grant number 2017YFC0907601, 2017YFC0907602, 2017YFC0907605, 2008BAI59B02) and the Chinese National High Technology Research and Development Program, Ministry of Science and Technology (grant number 2012AA02A513).

Conflict of interest: The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

The following investigators were collaborators in the CSTAR-PAH study: Huang C, Yang X, Xu D (Rheumatology), Liu Y, Guo X, Wang H, Lai J (Cardiology): Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences; Zhang N, Yang K, Liu Y (Rheumatology), Dong S (Cardiology): Tianjin Medical University General Hospital; Lei Y, Feng Y (Rheumatology): Guangdong General Hospital; Li Y, Zhou Y (Rheumatology): Xiangya Hospital, Central South University; Wang Q (Rheumatology): The First Affiliated Hospital of Nanjing Medical University; Jia J, Han Q (Rheumatology): Xijing Hospital, Fourth Military Medical University; Guo L, Chen J (Rheumatology): Ren Ji Hospital, Shanghai Jiao Tong University; Zhang Y, Liu Y (Rheumatology): Beijing Chao-Yang Hospital, Capital Medical University; Xu H (Rheumatology): The First Central Hospital, Tianjin; Sun Y (Rheumatology): The Second Affiliated Hospital of Harbin Medical University; Hao Y, Fan Y (Rheumatology): Peking University First Hospital; Shu Q, Wang Y (Rheumatology): Qilu Hospital of Shandong University; Lin Z (Rheumatology): The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou; Qing P (Rheumatology): West China Hospital, Sichuan University.

References

1. Simonneau G., Montani D., Celermajer D. S., Denton C. P., Gatzoulis M. A., Krowka M., Williams P. G., Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension[J]. *Eur Respir J*, 2019,53(1).

2. Badesch D. B., Raskob G. E., Elliott C. G., Krichman A. M., Farber H. W., Frost A. E., Barst R. J., Benza R. L., Liou T. G., Turner M., Giles S., Feldkircher K., Miller D. P., Mcgoon M. D. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry[J]. *Chest*, 2010,137(2):376-87.

3. Benza R. L., Miller D. P., Barst R. J., Badesch D. B., Frost A. E., Mcgoon M. D. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry[J]. *Chest*, 2012,142(2):448-56.

4. Launay D., Sitbon O., Le Pavec J., Savale L., Tcherakian C., Yaici A., Achouh L., Parent F., Jais X., Simonneau G., Humbert M. Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil[J]. *Rheumatology (Oxford)*, 2010,49(3):490-500.

5. Fisher M. R., Mathai S. C., Champion H. C., Girgis R. E., Housten-Harris T., Hummers L., Krishnan J. A., Wigley F., Hassoun P. M. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension[J]. *Arthritis Rheum*, 2006,54(9):3043-50.

6. Kylhammar D., Kjellstrom B., Hjalmarsson C., Jansson K., Nisell M., Soderberg S., Wikstrom G., Radegran G. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension[J]. *Eur Heart J*, 2018,39(47):4175-4181.

7. Ramjug S., Hussain N., Hurdman J., Billings C., Charalampopoulos A., Elliot C. A., Kiely D. G., Sabroe I., Rajaram S., Swift A. J., Condliffe R. Idiopathic and Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: A Comparison of Demographic, Hemodynamic, and MRI Characteristics and Outcomes[J]. *Chest*, 2017,152(1):92-102.

8. Hao Y. J., Jiang X., Zhou W., Wang Y., Gao L., Wang Y., Li G. T., Hong T., Huo Y., Jing Z. C., Zhang Z. L. Connective tissue disease-associated pulmonary arterial hypertension in Chinese patients[J]. *Eur Respir J*, 2014,44(4):963-72.

9. Jeon C. H., Chai J. Y., Seo Y. I., Jun J. B., Koh E. M., Lee S. K. Pulmonary hypertension associated with rheumatic diseases: baseline characteristics from the Korean registry[J]. *Int J Rheum Dis*, 2012,15(5):e80-9.

10. Kolstad K. D., Li S., Steen V., Chung L., Investigators Pharos. Long-Term Outcomes in Systemic Sclerosis-Associated Pulmonary Arterial Hypertension From the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry (PHAROS)[J]. *Chest*, 2018.

11. Weatherald J., Boucly A., Launay D., Cottin V., Prevot G., Bourlier D., Dauphin C., Chaouat A., Savale L., Jais X., Jevnikar M., Traclet J., De Groote P., Simonneau G., Hachulla E., Mouthon L., Montani D., Humbert M., Sitbon O. Haemodynamics and serial risk assessment in systemic sclerosis associated pulmonary arterial hypertension[J]. *Eur Respir J*, 2018,52(4).

12. Hachulla E., Jais X., Cinquetti G., Clerson P., Rottat L., Launay D., Cottin V., Habib G., Prevot G., Chabanne C., Fois E., Amoura Z., Mouthon L., Le Guern V., Montani D., Simonneau G., Humbert M., Sobanski V., Sitbon O., French Collaborators Recruiting Members. Pulmonary Arterial Hypertension Associated With Systemic Lupus Erythematosus: Results From the French Pulmonary Hypertension Registry[J]. *Chest*, 2018,153(1):143-151.

13. Qian J., Li M., Zhang X., Wang Q., Zhao J., Tian Z., Wei W., Zuo X., Zhang M., Zhu P., Ye S., Zhang W., Zheng Y., Qi W., Li Y., Zhang Z., Ding F., Gu J., Liu Y., Wang Y., Zeng X. Long-Term Prognosis of Patients with Systemic Lupus Erythematosus-Associated Pulmonary Arterial Hypertension: CSTAR-PAH Cohort Study[J]. *Eur Respir J*, 2019.

14. Kobak S., Kalkan S., Kirilmaz B., Orman M., Ercan E. Pulmonary Arterial Hypertension in Patients with Primary Sjogren's Syndrome[J]. *Autoimmune Dis*, 2014,2014:710401.

15. Liu Z., Yang X., Tian Z., Qian J., Wang Q., Zhao J., Huang C., Liu Y., Guo X., Wang H., Lai J., Li M., Zhao Y., Zeng X. The prognosis of pulmonary arterial hypertension associated with primary Sjogren's syndrome: a cohort study[J]. *Lupus*, 2018,27(7):1072-1080.

16. Liu Z., Wang J., Lai J., Wang Q., Zhao J., Huang C., Yang X., Qian J., Wang H., Guo X., Liu Y., Tian Z., Li M., Zhao Y., Zeng X. Is it possible to apply the treat-to-target strategy in primary Sjogren's syndrome-associated pulmonary arterial hypertension?[J]. *Clin Rheumatol*, 2018,37(11):2989-2998.

17. Galie N., Humbert M., Vachiery J. L., Gibbs S., Lang I., Torbicki A., Simonneau G., Peacock A., Vonk Noordegraaf A., Beghetti M., Ghofrani A., Gomez Sanchez M. A., Hansmann G., Klepetko W., Lancellotti P., Matucci M., Mcdonagh T., Pierard L. A., Trindade P. T., Zompatori M., Hoeper M. 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)[J]. *Eur Respir J*, 2015,46(4):903-75.

18. Mercurio V., Diab N., Peloquin G., Housten-Harris T., Damico R., Kolb T. M., Mathai S. C., Hassoun P. M. Risk assessment in scleroderma patients with newly diagnosed pulmonary arterial hypertension: application of the ESC/ERS risk prediction model[J]. *Eur Respir J*, 2018,52(4).

19. Olsson K. M., Hoeper M. M. Risk assessment in patients with systemic sclerosis and pulmonary arterial hypertension[J]. *Eur Respir J*, 2018,52(4).

20. Boucly A., Weatherald J., Savale L., Jais X., Cottin V., Prevot G., Picard F., De Groote P., Jevnikar M., Bergot E., Chaouat A., Chabanne C., Bourdin A., Parent F., Montani D., Simonneau G., Humbert M., Sitbon O. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension[J]. *Eur Respir J*, 2017,50(2).

21. Vitali C., Bombardieri S., Jonsson R., Moutsopoulos H. M., Alexander E. L., Carsons S. E., Daniels T. E., Fox P. C., Fox R. I., Kassan S. S., Pillemer S. R., Talal N., Weisman M. H., European Study Group on Classification Criteria for Sjogren's Syndrome. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group[J]. *Ann Rheum Dis*, 2002,61(6):554-8.

22. Shiboski C. H., Shiboski S. C., Seror R., Criswell L. A., Labetoulle M., Lietman T. M., Rasmussen A., Scofield H., Vitali C., Bowman S. J., Mariette X., International Sjogren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: A consensus and data-driven methodology involving three international patient cohorts[J]. *Ann Rheum Dis*, 2017,76(1):9-16.

23. Seror R., Ravaud P., Bowman S. J., Baron G., Tzioufas A., Theander E., Gottenberg J. E., Bootsma H., Mariette X., Vitali C., Force Eular Sjogren's Task. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome[J]. *Ann Rheum Dis*, 2010,69(6):1103-9.

24. 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., Bongi S. M., Maglione W., Migliaresi S., Montecucco C., Orefice M., Priori R., Tavoni A., Valesini G. 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[J]. *Arthritis Rheum*, 2007,56(7):2223-31.

25. Hoeper M. M., Pittrow D., Opitz C., Gibbs J. S. R., Rosenkranz S., Grunig E., Olsson K. M., Huscher D. Risk assessment in pulmonary arterial hypertension[J]. *Eur Respir J*, 2018,51(3).

26. Zhao Y., Li Y., Wang L., Li X. F., Huang C. B., Wang G. C., Zhang X. W., Zhang Z. L., Zhang X., Xiao W. G., Dai L., Wang Y. F., Hu S. X., Li H. B., Gong L., Liu B., Sun L. Y., Zhang M. J., Zhang X., Li Y. Z., Du D. S., Zhang S. H., Sun Y. Y., Zhang F. C. Primary Sjogren syndrome in Han Chinese: clinical and immunological characteristics of 483 patients[J]. *Medicine (Baltimore)*, 2015,94(16):e667.

27. Fukuda K., Date H., Doi S., Fukumoto Y., Fukushima N., Hatano M., Ito H., Kuwana M., Matsubara H., Momomura S. I., Nishimura M., Ogino H., Satoh T., Shimokawa H., Yamauchi-Takihara K., Tatsumi K., Ishibashi-Ueda H., Yamada N., Yoshida S., Abe K., Ogawa A., Ogo T., Kasai T., Kataoka M., Kawakami T., Kogaki S., Nakamura M., Nakayama T., Nishizaki M., Sugimura K., Tanabe N., Tsujino I., Yao A., Akasaka T., Ando M., Kimura T., Kuriyama T., Nakanishi N., Nakanishi T., Tsutsui H., Japanese Circulation Society, The Japanese Pulmonary Circulation, Pulmonary Hypertension Society Joint Working Group. Guidelines for the Treatment of Pulmonary Hypertension (JCS 2017/JPCPHS 2017)[J]. *Circ J*, 2019,83(4):842-945.

28. Seror R., Mariette X., Bowman S., Baron G., Gottenberg J. E., Bootsma H., Theander E., Tzioufas A., Vitali C., Ravaud P., European League against Rheumatism Sjogren's Task Force. Accurate detection of changes in disease activity in primary Sjogren's syndrome by the European League Against Rheumatism Sjogren's Syndrome Disease Activity Index[J].

Arthritis Care Res (Hoboken), 2010,62(4):551-8.

29. Seror R., Theander E., Brun J. G., Ramos-Casals M., Valim V., Dorner T., Bootsma H., Tzioufas A., Solans-Laque R., Mandl T., Gottenberg J. E., Hachulla E., Sivils K. L., Ng W. F., Fauchais A. L., Bombardieri S., Valesini G., Bartoloni E., Saraux A., Tomsic M., Sumida T., Nishiyama S., Caporali R., Kruize A. A., Vollenweider C., Ravaud P., Vitali C., Mariette X., Bowman S. J., Force Eular Sjogren's Task. Validation of EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI)[J]. *Ann Rheum Dis*, 2015,74(5):859-66.

30. Seror R., Bootsma H., Saraux A., Bowman S. J., Theander E., Brun J. G., Baron G., Le Guern V., Devauchelle-Pensec V., Ramos-Casals M., Valim V., Dorner T., Tzioufas A., Gottenberg J. E., Solans Laque R., Mandl T., Hachulla E., Sivils K. L., Ng W. F., Fauchais A. L., Bombardieri S., Priori R., Bartoloni E., Goeb V., Praprotnik S., Sumida T., Nishiyama S., Caporali R., Kruize A. A., Vollenweider C., Ravaud P., Meiners P., Brito-Zeron P., Vitali C., Mariette X., Force Eular Sjogren's Task. 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)[J]. *Ann Rheum Dis*, 2016,75(2):382-9.

31. Huang C., Li M., Liu Y., Wang Q., Guo X., Zhao J., Lai J., Tian Z., Zhao Y., Zeng X. Baseline Characteristics and Risk Factors of Pulmonary Arterial Hypertension in Systemic Lupus Erythematosus Patients[J]. *Medicine (Baltimore)*, 2016,95(10):e2761.

32. Lian F., Chen D., Wang Y., Ye Y., Wang X., Zhan Z., Xu H., Liang L., Yang X. Clinical features and independent predictors of pulmonary arterial hypertension in systemic lupus erythematosus[J]. *Rheumatol Int*, 2012,32(6):1727-31.

33. Wang J., Qian J., Wang Y., Zhao J., Wang Q., Tian Z., Li M., Zeng X. Serological biomarkers as risk factors of SLE-associated pulmonary arterial hypertension: a systematic review and meta-analysis[J]. *Lupus*, 2017,26(13):1390-1400.

34. Okawa-Takatsuji M., Aotsuka S., Fujinami M., Uwatoko S., Kinoshita M., Sumiya M. Up-regulation of intercellular adhesion molecule-1 (ICAM-1), endothelial leucocyte adhesion molecule-1 (ELAM-1) and class II MHC molecules on pulmonary artery endothelial cells by antibodies against U1-ribonucleoprotein[J]. *Clin Exp Immunol*, 1999,116(1):174-80.

35. Pertovaara M., Silvennoinen O., Isomaki P. STAT-5 is activated constitutively in T cells, B cells and monocytes from patients with primary Sjogren's syndrome[J]. *Clin Exp Immunol*, 2015,181(1):29-38.

36. Lee J. E., Yang Y. M., Liang F. X., Gough D. J., Levy D. E., Sehgal P. B. Nongenomic STAT5-dependent effects on Golgi apparatus and endoplasmic reticulum structure and function[J]. *Am J Physiol Cell Physiol*, 2012,302(5):C804-20.

37. Sehgal P. B., Mukhopadhyay S., Patel K., Xu F., Almodovar S., Tuder R. M., Flores S. C. Golgi dysfunction is a common feature in idiopathic human pulmonary hypertension and vascular lesions in SHIV-nef-infected macaques[J]. *Am J Physiol Lung Cell Mol Physiol*, 2009,297(4):L729-37.

38. Zhao J., Wang Q., Liu Y., Tian Z., Guo X., Wang H., Lai J., Huang C., Yang X., Li M., Zeng X. Clinical characteristics and survival of pulmonary arterial hypertension associated with three major connective tissue diseases: A cohort study in China[J]. *Int J Cardiol*, 2017,236:432-437.

39. Chung L., Domsic R. T., Lingala B., Alkassab F., Bolster M., Csuka M. E., Derk C., Fischer A., Frech T., Furst D. E., Gomberg-Maitland M., Hinchcliff M., Hsu V., Hummers L. K., Khanna D., Medsger T. A., Jr., Molitor J. A., Preston I. R., Schiopu E., Shapiro L., Silver R., Simms R., Varga J., Gordon J. K., Steen V. D. Survival and predictors of mortality in systemic sclerosis-associated pulmonary arterial hypertension: outcomes from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry[J]. *Arthritis Care Res (Hoboken)*, 2014,66(3):489-95.

40. Campo A., Mathai S. C., Le Pavec J., Zaiman A. L., Hummers L. K., Boyce D., Housten T., Champion H. C., Lechtzin N., Wigley F. M., Girgis R. E., Hassoun P. M. Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension[J]. *Am J Respir Crit Care Med*, 2010,182(2):252-60.

41. Sobanski V., Giovannelli J., Denton C. P., Coghlan J. G. Reply[J]. *Arthritis Rheumatol*, 2016,68(7):1789-90.

42. Lefevre G., Dauchet L., Hachulla E., Montani D., Sobanski V., Lambert M., Hatron P. Y., Humbert M., Launay D. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis[J]. *Arthritis Rheum*,

2013,65(9):2412-23.

43. Swiston J. R., Johnson S. R., Granton J. T. Factors that prognosticate mortality in idiopathic pulmonary arterial hypertension: a systematic review of the literature[J]. *Respir Med*, 2010,104(11):1588-607.

44. D'alonzo G. E., Barst R. J., Ayres S. M., Bergofsky E. H., Brundage B. H., Detre K. M., Fishman A. P., Goldring R. M., Groves B. M., Kernis J. T., Et Al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry[J]. *Ann Intern Med*, 1991,115(5):343-9.

45. Hoeper M. M., Kramer T., Pan Z., Eichstaedt C. A., Spiesshoefer J., Benjamin N., Olsson K. M., Meyer K., Vizza C. D., Vonk-Noordegraaf A., Distler O., Opitz C., Gibbs J. S. R., Delcroix M., Ghofrani H. A., Huscher D., Pittrow D., Rosenkranz S., Grunig E. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model[J]. *Eur Respir J*, 2017,50(2).

46. Hoeper M. M., Markevych I., Spiekerkoetter E., Welte T., Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension[J]. *Eur Respir J*, 2005,26(5):858-63.

47. Sitbon O., Galie N. Treat-to-target strategies in pulmonary arterial hypertension: the importance of using multiple goals[J]. *Eur Respir Rev*, 2010,19(118):272-8.

48. Galie N., Corris P. A., Frost A., Girgis R. E., Granton J., Jing Z. C., Klepetko W., Mcgoon M. D., Mclaughlin V. V., Preston I. R., Rubin L. J., Sandoval J., Seeger W., Keogh A. [Updated treatment algorithm of pulmonary arterial hypertension][J]. *Turk Kardiyol Dern Ars*, 2014,42 Suppl 1:78-94.

Table 1. Demographic Data of the pSS-PAH and pSS-non PAH

Characteristics	**pSS-PAH n=103**	**pSS-nonPAH n=526**	***P***
Gender (F/M)	101/2	507/19	1.000
Age at diagnosis of PAH, yr	43.2±12.7	-	<0.001
Age at onset of pSS, yr	37.4±13.1	44.1±13.1	<0.001
pSS duration, mth	46.0[13.0, 100.4]	33.1[12.7, 73.8]	0.186
Ocular symptoms, no	47（45.6%）	381（72.4%）	＜0.001
Oral symptoms, no	62（60.2%）	480（91.3%）	＜0.001
Schirmer test (+), no	70（70.0%）	329（90.1%）	＜0.001
Ocular stain, no	31（31.6%）	200（54.8%）	＜0.001
UWS, no	76（75.2%）	326（62.0%）	0.011
ESSDAI, score	6±6	6±5	0.988
Elevation of IgG	64（61.0%）	329（68.5%）	0.379
Anti-SSA(+), no	95（90.5%）	439（83.5%）	0.069
Anti-SSB(+), no	47（44.8%）	88（18.5%）	＜0.001
Anti-U1RNP(+), no	23（22.1%）	13（3.0%）	＜0.001

UWS=unstimulated whole saliva flow rate, ESSDAI=EULAR primary Sjogren's syndrome disease activity index.

Table 2. Clinical and Hemodynamic Data of patients with pSS-PAH at PAH Diagnosis

Characteristics	**pSS-PAH (n=103)**
PAH duration, month	12.0[5.5, 34.2]
Onset interval of pSS and PAH, month	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	239[98, 545]
NT-proBNP, pg/ml	822[324, 2100]
RHC	
mPAP, mmHg	48.1±10.7
PAWP, mmHg	8.4±2.9
PVR, WU	11.5±5.3
CI, L/min/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, no	37(37.0%)
Treatment regimen	
Glucocorticoids, no	89(86.4%)
Immunosuppressant, no	87 (84.5%)
CYC	63(61.2%)
Initial PAH Target therapy, no	91(88.3%)
ERA	34(33.0%)
PDE-I	63(61.2%)
≥2	16(15.5%)
Initial binary therapy[a]	83(80.6%)
Follow-up	
Sequential PAH therapy[b]	8(7.8%)
Immunosuppression therapy alone	4(3.9%)

SSDDI=Sjogren's syndrome disease damage index, WHO Fc = WHO functional class, 6MWD = 6 minutes walking distance, BNP = brain natriuretic peptide, NT-proBNP = N-terminal pro-brain natriuretic peptide, RHC = right heart catheterization, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, PVR = pulmonary vascular resistance, CI = cardiac index, RAP=right atrial pressure, TTE=transthoracic echocardiography, PASP = pulmonary arterial systolic pressure, RV = right ventricle, LVEF=left ventricle ejection fraction, CYC = cyclophosphamide, ERA = endothelin receptor antagonist, PDE-I = phosphodiesterase inhibitor.

[a] combination of immunosuppressant and PAH target therapy at baseline.

[b] Initial immunosuppression therapy followed by sequential PAH therapy.

Table 3. Possible Risk Factors of Developing PAH among pSS Patients

Variables	***P***	**OR**	**95% CI**	
Univariate				
Female, no	0.701	1.274	0.370	4.386
Age at onset of pSS, yrs	**＜0.001**	0.961	0.944	0.977
pSS duration, mth	0.845	1.000	0.998	1.001
Ocular stain, no	**＜0.001**	0.382	0.238	0.613
ESSDAI, score	0.262	1.022	0.984	1.062
Anti-SSB(+), no	**＜0.001**	3.564	2.275	5.583
Anti-U1RNP(+), no	**＜0.001**	9.327	4.538	19.168
Elevation of IgG, no	0.121	0.713	0.465	1.094
Multivariate				
Age at onset of pSS, 10yrs	**＜0.001**	0.651	0.524	0.810
Ocular stain, no	**0.003**	0.409	0.229	0.732
Anti-SSB(+), no	**＜0.001**	4.095	2.183	7.681
Anti-U1RNP(+), no	**＜0.001**	29.518	6.026	144.600

OR = odds ratio, CI = confidence interval, ESSDAI=EULAR primary Sjogren's syndrome disease activity index.

Table 4. Predictive Factors of Death in Patients With pSS-PAH

Variables	***P***	**HR**	**95% CI**	
Age at onset of pSS, yr	0.961	0.999	0.950	1.050
Age diagnosis of PAH, yr	0.320	1.024	0.978	1.072
pSS duration, mth	0.056	1.005	1.000	1.011
PAH duration, mth	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	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
CI, L/min/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[a]	0.577	0.685	0.181	2.591

ESSDAI=EULAR primary Sjogren's syndrome disease activity index, SSDDI=Sjogren's syndrome disease damage index, WHO Fc = WHO functional class, 6MWD = 6 minutes walking distance, NT-proBNP = N-terminal pro-brain natriuretic peptide, RHC = right heart catheterization, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, PVR = pulmonary vascular resistance, CI = cardiac index, RAP=right atrial pressure, TTE=transthoracic echocardiography, RV = right ventricle, LVEF=left ventricle ejection fraction. OR=odds ratio, CI=confidence interval.

[a] combination of immunosuppressant and PAH target therapy.

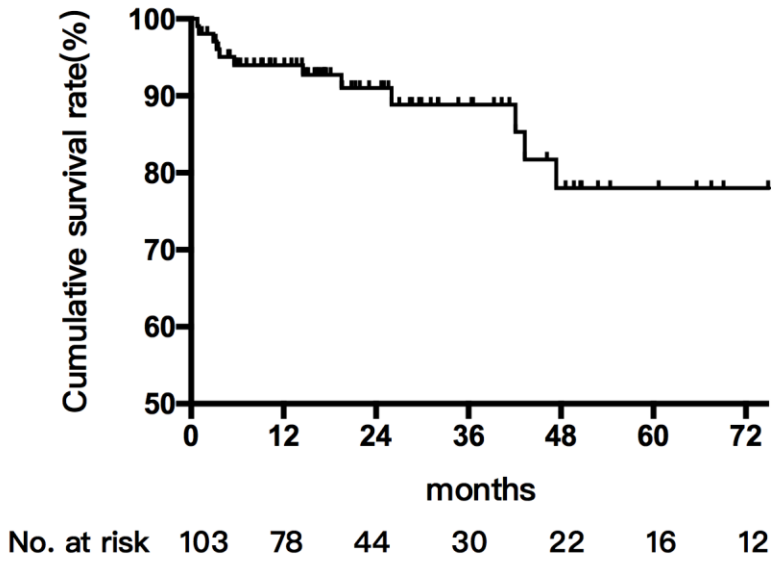
Figure legend

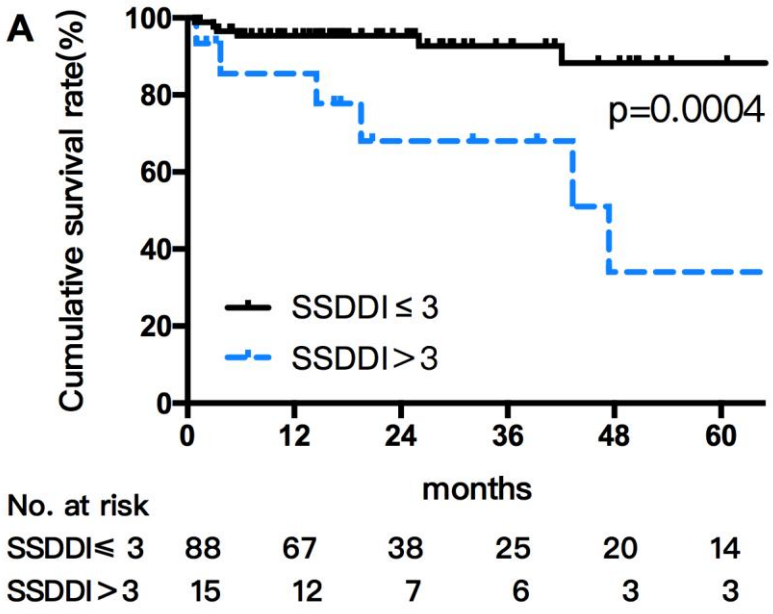
Fig.1. Cumulative survival rate of the whole pSS-PAH population. x axis = time from PAH diagnosis to death.

Fig.2. Kaplan-Meier analysis of survival according to A. SSDDI (Sjogren's syndrome disease damage index) and B. cardiac index(CI). x axis = time from PAH diagnosis to death.

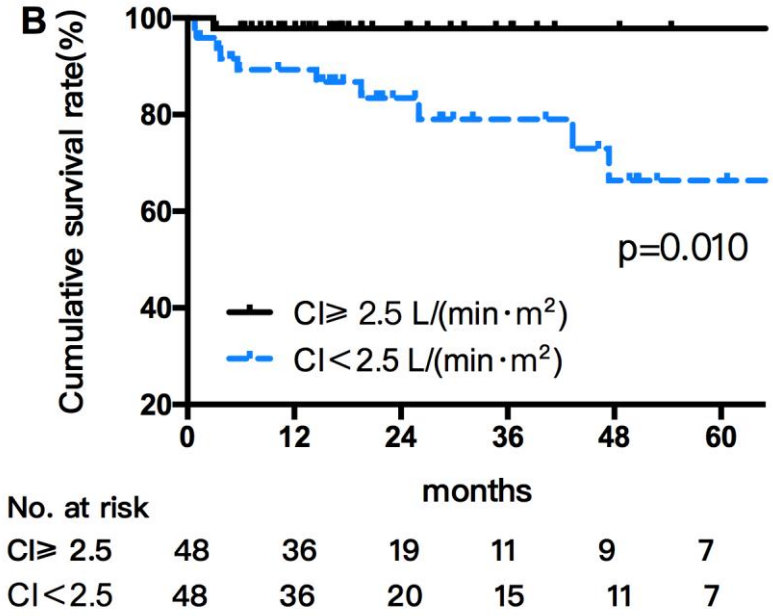
Fig.3. Comparison of the cumulative survival rate of patients with different risk category at baseline. x axis = time from PAH diagnosis to death.

Fig.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. x axis = time from PAH diagnosis to death.

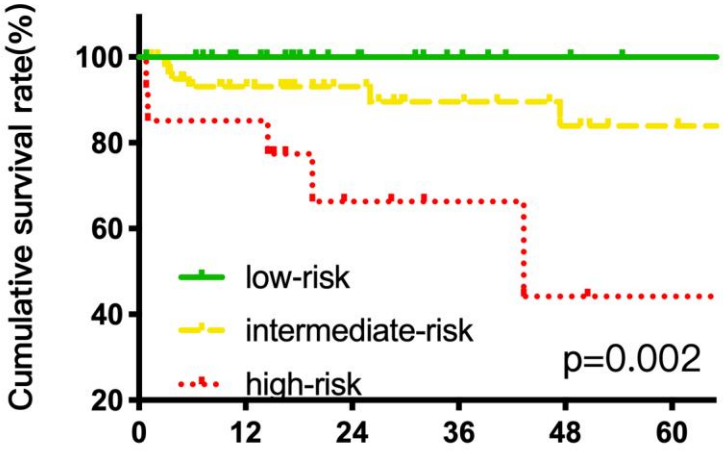

Cumulative survival rate(%)
100
90
80
70
60
50
0
12
24
36
48
60
72
months
No. at risk 103 78 44 30 22 16 12



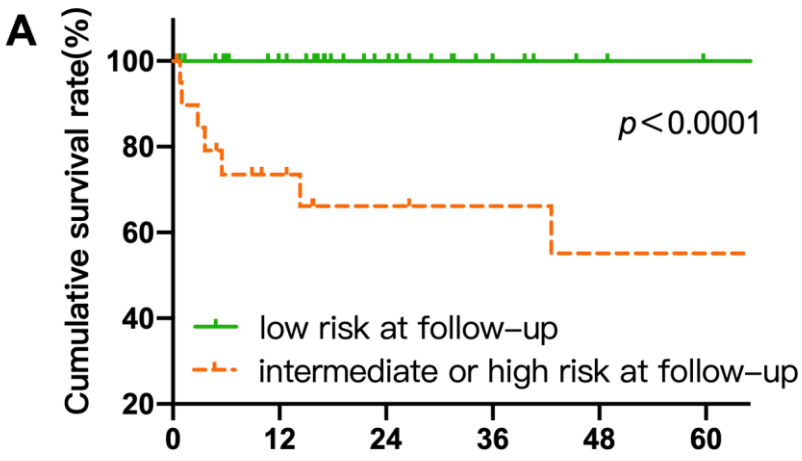
No. at risk						
SSDDI≤ 3	88	67	38	25	20	14
SSDDI > 3	15	12	7	6	3	3



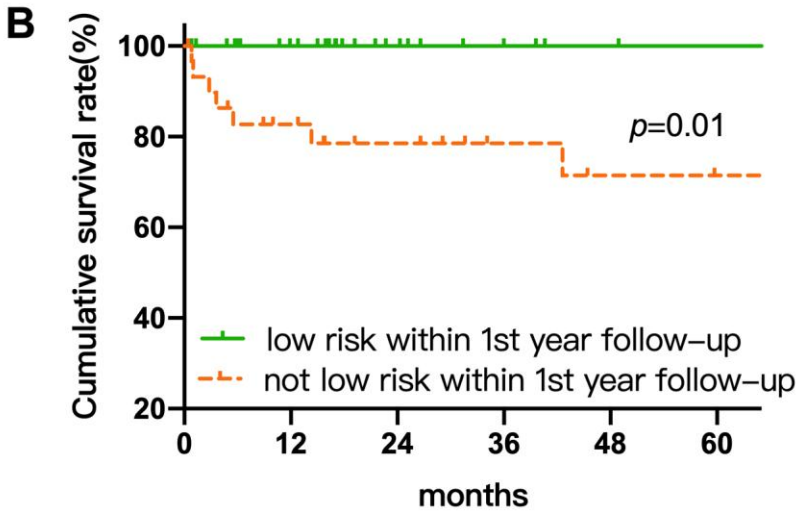
No. at risk						
CI≥ 2.5	48	36	19	11	9	7
CI < 2.5	48	36	20	15	11	7



No. at risk						
low–risk	27	22	13	8	5	3
intermediate-risk	62	46	27	20	16	13
high–risk	14	12	6	4	3	2



No. ar risk						
low risk at follow-up	41	34	18	10	7	5
intermediate or high risk at follow-up	21	12	8	7	6	6



No. ar risk						
low risk within 1st year	31	24	10	6	3	2
not low risk within 1st year	31	22	17	12	10	9

Title

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

Authors and affiliations

Jieying Wang, MD; Mengtao Li, MD; Xiao Zhang, MD; Junyan Qian, MD; Qian Wang, MD1; Jiuliang Zhao, MD; Zhuang Tian, MD; Wei Wei, MD; Xiaoxia Zuo, MD; Miaojia Zhang, MD; Ping Zhu,MD; Shuang Ye, MD; Wei Zhang, MD; Yi Zheng, MD; Wufang Qi, MD; Yang Li, MD; Zhuoli Zhang, MD; Feng Ding, MD; Jieruo Gu, MD; Yi Liu, MD; Yanhong Wang, PhD; Yan Zhao, MDand Xiaofeng Zeng, MD.

Online Data Supplement

Supplementary Table 1. Baseline data comparison between patients included in follow-up risk assessment and those not included.

	Risk assessment included n=62	Risk assessment not included n=41	*P*
Gender (F/M)	61/1	39/2	0.566
Age at recruitment, yr	38.8±9.1	49.5±14.5	**＜0.001**
PAH duration, mth	12.0[6.0, 29.0]	12.5[2.8, 45.9]	0.789
pSS duration, mth	46.0[12.7, 96.7]	46.6[14.2, 110.3]	0.677
Onset interval of pSS and PAH, mth	0.0[0.0, 55.2]	2.1[0.0, 105.6]	0.743
ESSDAI, score	3.7±4.3	9.7±7.5	**＜0.001**
SSDDI, score	2.0±1.3	2.3±1.6	0.217
WHO Fc I-II	34(54.8%)	25(60.5%)	0.567
6MWD, m	418.0±105.6	372.9±83.4	0.071
BNP, ng/L	239[106, 501]	275[77, 643]	0.854
NT-proBNP, pg/ml	846[292, 2114]	810[329, 2070]	0.957
RHC			
mPAP, mmHg	49.5±9.4	46.0±12.0	0.102
PAWP, mmHg	8.0±3.0	9.3±2.6	**0.050**
PVR, WU	11.6±5.1	11.3±5.8	0.795
CI, L/min/m^2	2.5±0.7	2.6±1.0	0.542
RAP, mmHg	6.6±4.8	6.6±4.3	0.972
TTE			
PASP, mmHg	83.7±17.9	74.8±22.1	**0.027**
LVEF, %	68.2±7.1	67.2±5.9	0.478
Pericardial effusion, no	16(27.1%)	21(51.2%)	**0.014**
Treatment regimen			
Glucocorticoids, no	56(90.3%)	35(85.4%)	0.276
Immunosuppressant, no	54(87.1%)	35(85.4%)	0.365
Target therapy for PAH, no	58(93.5%)	33(80.5%)	0.191
≥2	11(17.7%)	5(12.3%)	0.391
Binary therapy[a]	57(91.9%)	27(65.1%)	**0.001**

ESSDAI=EULAR primary Sjogren's syndrome disease activityindex. SSDDI = Sjogren's syndrome disease damage index, WHO Fc = WHO functional class, 6MWD = 6 minutes walking distance, BNP = brain natriuretic peptide, NT-proBNP = N-terminal pro-brain natriuretic peptide, RHC = right heart catheterization, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, PVR = pulmonary vascular resistance, CI = cardiac index, RAP=right atrial pressure, TTE=transthoracic echocardiography, PASP = pulmonary arterial systolic pressure, LVEF=left ventricle ejection fraction.

[a] combination of immunosuppressant and PAH target therapy.