ERJ Express. Published on January 11, 2019 as doi: 10.1183/13993003.00081-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Qian J, Li M, Zhang X, *et al*. Long-Term Prognosis of Patients with Systemic Lupus Erythematosus-Associated Pulmonary Arterial Hypertension: CSTAR-PAH Cohort Study. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00081-2018).

Title

Long-Term Prognosis of Patients with Systemic Lupus Erythematosus-Associated Pulmonary Arterial Hypertension: CSTAR-PAH Cohort Study

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Abstract

Aims: This study aimed to identify the long-term clinical outcomes and prognostic factors of patients with SLE-associated PAH confirmed by right heart catheterization.

Methods and Results: A multicenter prospective cohort of SLE-associated PAH was established. Baseline and follow-up records were collected. The primary end point was death. The secondary exploratory end point was treatment goal achievement (TGA), defined as an integrated outcome. In total, 310 patients were enrolled from 14 PAH centers. The 1-, 3- and 5-year survival rates were 92.1%, 84.8% and 72.9%, respectively. The 1-, 3- and 5-year TGA rates were 31.5%, 53.6% and 62.7%, respectively. Baseline serositis, 6-minute walking distance > 380 m and cardiac index ≥ 2.5 L/min×m^2 were identified as independent prognostic factors of TGA. Patients with baseline serositis were more likely to reach TGA after intensive immunosuppressive therapy. TGA was identified as a positive predictor of survival in

patients with SLE-associated PAH.

Conclusion: TGA was associated with long-term survival, which supports the treat-to-target strategy in SLE-associated PAH. Baseline heart function predicted both survival and treatment goal achievement in patients with SLE-associated PAH. Patients with serositis at baseline tended to benefit from intensive immunosuppressive therapy and have a better clinical outcome.

Keywords: Systemic lupus erythematosus; pulmonary arterial hypertension; multicenter study; prognosis; treatment goal.

Introduction

Connective tissue disease (CTD) is a major cause of pulmonary arterial hypertension (PAH) and causes 25.3% of PAH and 50.7% of associated PAH [1]. However, the underlying CTD varies between different populations. Although systemic sclerosis (SSc) is widely recognized as the major underlying cause of CTD-associated PAH in the Western world [2, 3], systemic lupus erythematosus (SLE)-associated PAH is most commonly reported in Asian countries [4, 5], especially in China, due to its higher prevalence of SLE than that in other ethnicities [6]. Notably, according to a meta-analysis of studies from the US [2, 7], UK [8], Japan [9] and China [4], the 5-year pooled survival rate was 68% for patients with SLE-associated PAH [10]. Compared with the 5-year survival rate for patients with SLE (92–94%) [11, 12], the clinical outcome of SLE patients is dramatically worsened after developing PAH [13]. However, only three studies (including 124 patients) meeting the eligible criteria were utilized to calculate the 5-year pooled survival rate with a huge heterogeneity (I^2 = 52.7%) [10]. Thus, a large, multicenter study is required to determine the long-term prognosis of patients with SLE-associated PAH.

The Chinese SLE Treatment and Research Group (CSTAR) was established in 2009 to collect data from Chinese patients with SLE and was further extended with the formation of the Chinese Rheumatism Data Center (CRDC), which is directed by the National Health and Family Planning Commission of the People's Republic of China [14, 15]. Based on the CSTAR registry, we determined the prevalence of PAH among Chinese patients with SLE [16]. Herein, we identified the long-term clinical outcomes, including mortality and treatment goal achievement (TGA), and related prognostic factors of patients with SLE-associated PAH confirmed by right heart catheterization (RHC) and also demonstrated the association between mortality and TGA.

Methods

CSTAR-PAH cohort

The CSTAR registry is a nationwide registry involving 104 rheumatology centers covering 30 provinces in China [15]. In total, 14 referral centers of CTD-associated PAH were qualified as patients enrollment centers (supplementary). Patients who visited the referral centers from November 2006 to May 2016 and met the following criteria were enrolled in the CSTAR-PAH cohort. The eligible criteria included the diagnosis of SLE confirmed by the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria [17] and the diagnosis of PAH based on RHC defined as the mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg at rest, pulmonary arterial wedge pressure (PAWP) $\leq$ 15 mmHg, and pulmonary vascular resistance (PVR) > 3 Wood units [18]. Patients with other types of pulmonary hypertension revealed by a pulmonary function test (PFT) showing total lung capacity (TLC) < 60% and ventilation perfusion scintigraphy (V/Q) or computed tomographic pulmonary angiography (CTPA) showing pulmonary thromboembolism were excluded. Patients with overlapping CTD, such as SSc, or

other CTDs were also excluded. Application of PAH guidelines [18, 19] and a census-based SLE-associated PAH treatment regimen [20] were as well required as inclusion criteria. This study was approved by the institutional review board, and we obtained informed consent from each patient.

Data collection

The time of recruitment (baseline) was defined as the time of SLE-associated PAH diagnosis confirmed by RHC. At baseline, we collected demographic information and medical history and performed the physical examination, laboratory evaluations, and transthoracic echocardiography (TTE). Data collected at baseline included age; gender; onset of SLE and PAH; organ involvement; SLE Disease Activity Index (SLEDAI) [21]; WHO functional class (WHO FC); 6-minute walking distance (6MWD); levels of serum brain natriuretic peptide (BNP) and N terminal-pro brain natriuretic peptide (NT-proBNP); anti-U1RNP status; antiphospholipid antibody status; TTE and RHC parameters (which were reviewed by independent cardiologists), including mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP), pulmonary vascular resistance (PVR), cardiac output (CO), cardiac index (CI), and right atrial pressure (RAP); and treatment regimen. The duration of SLE was defined as the time span from the diagnosis of SLE to the diagnosis of SLE-associated PAH by RHC (baseline). Serositis was defined as pleuritis/pleural effusion and/or pericarditis/pericardial effusion detected by TTE, chest X-ray or chest computerized tomography scan [17].

Follow-up

A comprehensive follow-up evaluation of every patient was recorded and reported at least once a year. These measures included WHO FC, 6MWD, serum BNP, serum NT-proBNP, and TTE. Treatment

regimens were also recorded. Death, causes of death, hospitalization due to disease deterioration, disease-related transplantation or atrial septostomy were also recorded and reported to the database.

Outcomes

The primary end point was death from any cause. Mortality was ascertained from PAH center records and the national population tracking system. The exploratory experimental end point was achieving the integrated treatment goal recommended by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) [19]. Treatment goal was defined as achieved when all of the following four aspects were reached, including: 1) clinical symptoms: no signs of right heart failure, syncope or progression; 2) WHO FC I or II, or 6MWD > 380–440 m; 3) serology: BNP < 50 ng/L or NT-proBNP < 300 ng/L; and 4) cardiac imaging: normal right atrial area according to echocardiography. For socioeconomic reasons in our country, hemodynamic parameters were not available in every follow-up visit and therefore were not included in evaluating TGA in our study. TGA was ascertained according to the follow-up date reported by each PAH center prior to the course of data analysis.

Statistical Analyses

Quantitative data are described as the means and standard deviations. Non-quantitative data are described as counts and percentages. Cumulative probabilities of survival and not achieving the treatment goal were calculated with the Kaplan-Meier estimator. Further comparisons were performed with a log-rank test. The Kaplan-Meier survival curves comparing patients with TGA and without TGA were plotted by the method proposed by Simon and Makuch [22] for time-dependent covariates. All-cause mortality was used in survival statistics. Follow-up time was calculated from the date of initial diagnostic RHC. Baseline

characteristics between patients with and without clinical outcomes (death and TGA) were compared. Baseline factors with clinical significance, including age at recruitment, gender, clinical features, RHC parameters, TTE parameters and treatment selection were analyzed by univariate Cox regressions. The cutting-offs of CI and 6MWD were based on the previous studies and guidelines [18, 19]. Considered that there is no widely recognized cutting-off of PVR, we did an outcome-oriented statistical analysis for cut-point determination by the method proposed by Contal and O'Quigley [23], and used 12 WU as the cutoff in our study. Other parameters, including NT-proBNP, BNP and RAP were firstly dichotomized according to tertiles, and then used in the Cox regression. As TGA was a time-dependent covariate, we used time-dependent Cox regression, in order to avoid immortal time bias. Variables with clinical relevance selected by univariate analysis, including age, gender, and others, were further subjected to multivariate analysis. The proportional hazard assumption based on the Schoenfeld residuals was tested. *P* values < 0.05 were considered significant. Data analyses were conducted with SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and R software (www.r-project.org).

Results

Baseline characteristics of patients with SLE-associated PAH

In total, 310 patients with RHC-confirmed SLE-associated PAH were enrolled in our study (Table 1). The mean duration of SLE was 4.4 ± 5.4 years. A total of 51.7% patients were WHO FC I or II, and the mean mPAP was 46.5 ± 12.1 mmHg. 99.4% and 92.6% patients were treated with glucocorticoid and immunosuppressant therapy, respectively. A total of 69.4% of patients were receiving PAH medication: 56.7% received endothelin receptor antagonists (ERA), 58.1% received phosphodiesterase inhibitors (PDE5-I), and 7.0% received prostacyclin analogues (PG). Among the 310 recruited patients, 282 patients

with confirmed mortality statuses were included in the survival analysis, and 263 patients with full follow-up data were included in the TGA study (Figure 1). The maximum follow-up duration was 107.5 months, and the median follow-up was 24.0 months.

Survival and predictors of mortality for patients with SLE-associated PAH

During the follow-up, 42 (14.9%) deaths occurred. No PAH-related transplantations or atrial septostomies occurred. The 1-, 3- and 5-year survival rates for patients with SLE-associated PAH were 92.1%, 84.8% and 72.9%, respectively (Figure 2A). The mean survival time was 7.0 years.

Baseline characteristics between survivors and non-survivors were compared (Supplementary Table 1). According to the univariate COX analysis, the following baseline factors were associated with mortality (Table 2): 6MWD ≤ 380 m; WHO FC III-IV; NT-proBNP > 1695.0 pg/ml; high mPAP; CI < 2.5 L/min×m^2 (Figure 2B); PVR > 12 WU; and enlarged right ventricular (RV) diameter. According to the multivariate Cox regression analysis adjusting sex and age, CI < 2.5 L/min×m^2 (HR = 2.62, 95% CI: 1.33 to 5.18, P = 0.006) was identified as an independent predictor of mortality for patients with SLE-associated PAH.

Relationship between TGA and death

TGA was identified as a factor positively associated with survival in univariate time-dependent Cox regression (HR = 0.18, 95% CI: 0.05 to 0.59, P = 0.005). We then compared the cumulative survival rates between patients who achieved the treatment goal and patients who did not (Figure 3). The cumulative survival rate was significantly higher for patients who achieved TGA (P = 0.002).

TGA and prognostic factors of TGA for patients with SLE-associated PAH

As the secondary exploratory end point of our study, we identified the TGA status of individual patient according to the follow-up data. Among them, 115 (43.7%) patients achieved the treatment goal, and their 1-, 3- and 5-year TGA rates were 31.5%, 53.6% and 62.7%, respectively (Figure 4A). The median time from baseline to TGA was 2.5 years. Baseline characteristics were compared between patients who reached the treatment goals and patients who did not (Supplementary Table 2). To investigate the predictors of TGA, univariate cox regression was conducted. Characteristics at baseline, including serositis (Figure 4B), 6MWD > 380 m (Figure 4C), low mPAP, BNP >339.3 ng/L, CI ≥ 2.5 L/min×m^2, PVR ≤ 12 WU and a smaller RV diameter were associated with TGA (Table 3). After adjusting for the effects of multiple covariates, baseline serositis (HR = 1.99, 95% CI: 1.27 to 3.11, *P* = 0.003), 6MWD > 380 m (HR = 2.12, 95% CI: 1.22 to 3.68, *P* = 0.008) and CI ≥ 2.5 L/min×m^2 (HR = 2.14, 95% CI: 1.26 to 3.62, *P* = 0.005) were identified as independent prognostic factors of TGA (Table 3).

Patients with serositis at baseline had better TGA after intensive immunosuppressive therapy

We hypothesized that patients with serositis at baseline would respond better to intensive immunosuppressive therapy (IST), defined as the therapy with one or more immunosuppressants, including cyclophosphamide, mycophenolate mofetil, cyclosporine A and tacrolimus, than those without serositis at baseline. There were no significant differences in baseline characteristics between patients on IST and those on only hydroxychloroquine (HCQ) therapy when stratified by baseline serositis (Supplementary Table 3). Notably, when comparing TGA between the two therapeutic groups, patients with baseline serositis were more likely to reach TGA after IST compared to non-IST recipients (HR = 2.47, 95% CI: 1.21 to 4.17, *P* = 0.013), which was not seen in those without baseline serositis (Figure 5).

Discussion

We identified the prognostic factors for patients with SLE-associated PAH based on a multicenter cohort with RHC-based diagnoses. All-cause mortality and TGA were set as the long-term and medium-term clinical end-points, respectively. The 1-, 3- and 5-year survival rates of patients with SLE-associated PAH were 92.1%, 84.8% and 72.9%, respectively. The 1, 3, and 5-year survival rates of 1494 SLE patients recruited during the same time period were 98.3%, 96.9% and 95.7% respectively in China (unpublished data). The survival rates of SLE-associated PAH are higher than those calculated in the previous meta-analysis (1-year 88%, 3-year 81%, 5-year 68%) [10]. In a recent French cohort, the 1-, 3- and 5-year survival rates were 94.1%, 89.4% and 83.9% [24]. There may be a population difference regarding prognosis; however, time-lead bias, disease severity, therapeutic strategy, and the study design should also be considered. According to univariate and multivariate analyses, baseline CI < 2.5 L/min×m^2 was an independent predictor of mortality. Our study, consistent with the conclusions of studies on idiopathic PAH and SSc-associated PAH, confirmed that heart function, represented by CI, is critical to the clinical outcomes of patients with SLE-associated PAH [25-27]. Preservation or improvement of heart function may become the priority of clinicians in the management of SLE-associated PAH, which will need to be proven in future studies.

Treat-to-target, defined as a therapeutic strategy aiming to treat patients to a goal and improve disease outcome, is increasingly accepted in disease management. A treat-to-target strategy of SLE has been recommended by an international task force, which asserted that complete remission is the main target of SLE [28]. With regard to the heterogeneity of SLE, the treatment goal may vary in situations with different organ involvement [29]. An integrated criterion with multiple parameters, including WHO functional class,

symptom, serological, echocardiographic and RHC parameters, was recommended as treatment goals for patients with PAH by ESC/ERS [19]. Although the goal-orientated treatment approach has not been fully validated, several studies have shown recently that PAH patients in a “low-risk” group showed a decreased mortality risk [30-32]. Although RHC is a relatively direct and accurate way of evaluating PAH, RHC cannot be performed at every follow-up visit due to its invasive nature and to socioeconomic factors in our country. Thus, TGA without RHC parameters was defined as the exploratory secondary end point in our study, and it was favorably associated with survival among patients with SLE-associated PAH. Our study demonstrated that TGA was associated with the long-term survival and that TGA could be a target in the management of SLE-associated PAH. The long-term survival of patients meeting different numbers of treatment goal at specific time points need to be further compared. The 1-, 3- and 5-year TGA rates were 31.5%, 53.6% and 62.7%, respectively. Baseline 6MWD $\geq$ 380 m and CI $\geq$ 2.5 L/min×m^2 were identified as predictors of TGA among patients with SLE-associated PAH in our study, indicating that heart function is also crucial in the response to treatment and to even achieving the treatment goal.

Notably, baseline serositis was newly identified to predict TGA in our study. It has been reported in our previous study that SLE disease activity scores were significantly higher in patients with serositis, and pulmonary arterial hypertension was significantly associated with serositis in patients with SLE [33]. Here, we found that indicators of heart failure, such as WHO FC, CI and RAP, had no significant differences in SLE-associated PAH patients with vs. without serositis (data not shown), indicating that inflammation may be the major mechanism leading to serositis in patients with SLE-associated PAH in our study. This result raised the question of whether patients with high SLE disease activity, indicated by baseline serositis, could benefit from immunosuppressive therapy and achieve better clinical outcomes. Therefore, a further

stratification analysis was conducted. It showed that patients with baseline serositis were more likely to reach TGA after intensive immunosuppressive therapy (IST) than those without IST, while the same phenomenon was not shown in patients without baseline serositis. This result suggests that, in developing future treatment strategies, that baseline serositis may be treated as an indicator for clinicians to initiate intensive IST for patients with SLE-associated PAH. Although the literature is limited, this result concurs with a recent case report finding that a patient with SLE-associated PAH and high disease activity has totally recovered after methylprednisolone pulse therapy [34]. In another recent study, the use of immunosuppressants was an independent predictor of a short-term response in patients with CTD-associated PAH [35]. The potential clinical significance still needs further investigation and evidence from randomized clinical trials.

This study has several limitations. First, 310 patients were initially enrolled in our study, and patients without information about death or TGA were excluded from the prognosis analyses. Fortunately, there was no significant difference in the baseline characteristics of patients included and excluded in the prognosis analyses (data not shown), indicating the lack of the outcome data was random. Second, we included both the incident and prevalent populations. Patients with incident PAH have poorer survival rates than patients with prevalent disease, according to both the French registry and the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) studies [7, 36]. Thus, the incident cohort and prevalent cohort need to be studied separately in future studies. Also, we reported that 69.4% patients in our cohort received PAH target medications at baseline, explained by socioeconomic reasons. Thus, the effect of different treatment regimens needs to be further studied. Lastly, there were 31.6% missing value of RAP in our cohort explained by the reason that RAP was not a routinely

reported value in some PAH centers. However, it showed some a tendency of predicting death even without significant significance. Future studies need to collect complete information on this value and prove its prognostic significance.

This study is for now the largest prognostic cohort consisting of patients with SLE-associated PAH based on a RHC algorithm. It reported the 1-, 3- and 5-year survival rates of patients with SLE-associated PAH and further identified CI as a predictor of mortality. We reported for the first time the 1-, 3- and 5-year rates of achieving treatment goals. CI, 6MWD and serositis were prognostic factors of TGA. TGA was associated with long-term survival, the first evidence supporting the treat-to target strategy in SLE-associated PAH. Baseline heart function predicted both survival and TGA in patients with SLE-associated PAH. Patients with serositis at baseline tended to benefit from intensive immunosuppressive therapy and to have better clinical outcomes. Further investigation on the therapeutic strategy specific for SLE-associated PAH is urgently needed.

Funding

This work was supported by the Chinese National Key Research R&D Program (grant number 2017YFC0907601, 2017YFC0907602, 2017YFC0907603, 2008BAI59B02) and the Chinese National High Technology Research and Development Program, Ministry of Science and Technology (grant number 2012AA02A513).

Acknowledgments

We appreciate Yang Ding, PhD, Center for Bioinformatics, School of Life Sciences, Peking University,

Beijing, China, for his kind technical support during data analysis. We also appreciate the comments and editing of our manuscript by Dr. Andrea Ballmer and her medical team from Actelion.

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Tables

Table 1 Baseline characteristics of patients with SLE-associated PAH

Characteristics	**SLE-associated PAH (n = 310)**
Age at recruitment, yr	35.0 ± 10.1
Female sex, %	99.4
Duration of SLE from diagnosis, yr	4.4 ± 5.4
Clinical features	
WHO FC	
I, %	5.6
II, %	46.1
III, %	44.6
IV, %	3.7
6MWD, m	408.6 ± 98.0
BNP, ng/L	600.4 ± 1328.2
NT-proBNP, pg/ml	1660.5 ± 2275.1
Acute rash, %	32.9
Serositis, %	35.2
Lupus nephritis, %	33.5
Neuropsychiatric lupus, %	3.9
Thrombocytopenia, %	45.2
Hypocomplementemia, %	63.2
Anti-dsDNA, %	51.5

Anti-Sm,%	34.2
Anti-U1 RNP	59.0
APL, %	12.9
SLEDAI	6.1 ± 5.5
RHC	
mPAP, mmHg	46.5 ± 12.1
PAWP, mmHg	7.9 ± 4.0
PVR, WU	11.0 ± 5.5
CI, L/min × m^2	2.8 ± 0.9
RAP, mmHg	5.6 ± 5.5
UCG	
PASP, mmHg	77.3 ± 21.5
RV diameter, mm	36.9 ± 12.5
Treatment	
Glucocorticoid, %	99.4
Immunosuppressant, %	92.6
CYC, %	61.7
≥ 2, %	44.3
PAH medication, %	69.4
ERA, %	56.7
PDE5-I, %	58.1
PG, %	7.0

≥ 2, %	19.5

WHO FC = WHO functional class, 6MWD = 6-minute walking distance, BNP = brain natriuretic peptide, NT-proBNP = N-terminal-pro BNP, APL = antiphospholipid, SLEDAI = SLE disease activity index, 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, UCG = echocardiography, PASP = pulmonary arterial systolic pressure, RV = right ventricular, CYC = cyclophosphamide, ERA = endothelin receptor antagonist, PDE5-I = phosphodiesterase inhibitor, PG = prostacyclin analogue.

Table 2 Predictors of mortality for patients with SLE-associated PAH

	Univariate analysis		**Multivariate analysis**	
Baseline variables	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
6MWD ≤ 380 m	4.56 (2.05, 10.18)	< 0.001**		
WHO FC III-IV	2.51 (1.24, 5.09)	0.010**		
NT-proBNP †				
< 536.3 pg/ml	Reference			
536.3- 1695.0 pg/ml	1.26 (0.38, 4.15)	0.704		
>1695.0 pg/ml	4.78 (1.73, 13.25)	0.003**		
mPAP, mmHg	1.04 (1.02, 1.06)	0.001**		
CI < 2.5 L/min × m^2	2.82 (1.43, 5.55)	0.003**	2.62 (1.33, 5.18)	0.006*
PVR > 12 WU	3.12 (1.51, 6.43)	0.002**		
RAP†				
<3mmHg	Reference			
3-7mmHg	0.78 (0.29, 2.04)	0.61		
>7mmHg	1.29 (0.52, 3.18)	0.58		
Missing‡	1.36 (0.62, 3.00)	0.45		

RV diameter, mm	1.04 (1.01, 1.07)	0.019*
Anti-U1 RNP positivity	1.46 (0.76, 2.81)	0.260
APL antibody positivity	0.69 (0.27, 1.79)	0.449
SLEDAI	0.97 (0.91, 1.03)	0.251

6MWD = 6-minute walking distance, WHO FC = WHO functional class, NT-proBNP = N-terminal-pro brain natriuretic peptide, mPAP = mean pulmonary arterial pressure, CI = cardiac index, PVR = pulmonary vascular resistance, RAP = right atrial pressure, RV = right ventricular, APL = antiphospholipid, SLEDAI = SLE disease activity index. * $P \leq 0.05$. ** $P \leq 0.01$.

† Variables grouped where appropriate into tertiles

‡ 30% patients with missing data

Table 3 Predictors of TGA for patients with SLE-associated PAH

	Univariate analysis		**Multivariate regression**	
Baseline variables	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Serositis	1.55 (1.07, 2.23)	0.021*	1.99 (1.27, 3.11)	0.003**
6MWD > 380 m	1.49 (1.16, 1.92)	0.002**	2.12(1.22, 3.68)	0.008**
BNP†				
< 105.3 ng/L	Reference			
105.3- 339.3 ng/L	0.83 (0.48, 1.43)	0.50		
>339.3 ng/L	0.29 (0.15, 0.57)	<0.001**		
mPAP, mmHg	0.97 (0.96, 0.99)	< 0.001**		
CI ≥ 2.5 L/min × m^2	1.97 (1.29, 3.01)	0.002**	2.14 (1.26, 3.62)	0.005**
PVR ≤ 12 WU	1.98 (1.27, 3.10)	0.003**		

RAP[†]		
<3mmHg	Reference	
3-7mmHg	0.76 (0.48, 1.22)	0.25
>7mmHg	0.45 (0.26, 0.78)	0.004**
Missing[‡]	0.29 (0.17, 0.50)	<0.001**

6MWD = 6-minute walking distance, BNP = brain natriuretic peptide, mPAP = mean pulmonary arterial pressure, CI = cardiac index, PVR = pulmonary vascular resistance, RAP = right atrial pressure, RV = right ventricular. * $P \leq 0.05$. ** $P \leq 0.01$.

[†] Variables grouped where appropriate into tertiles.

[‡] 30% patients with missing data

Figure legends

Figure 1 Study flow diagram.

Figure 2 Cumulative survival rates for patients with SLE-associated PAH.

(A) All patients with SLE-associated PAH. (B) Comparison between patients with CI ≥ 2.5 L/min × m^2 and CI < 2.5 L/min × m^2.

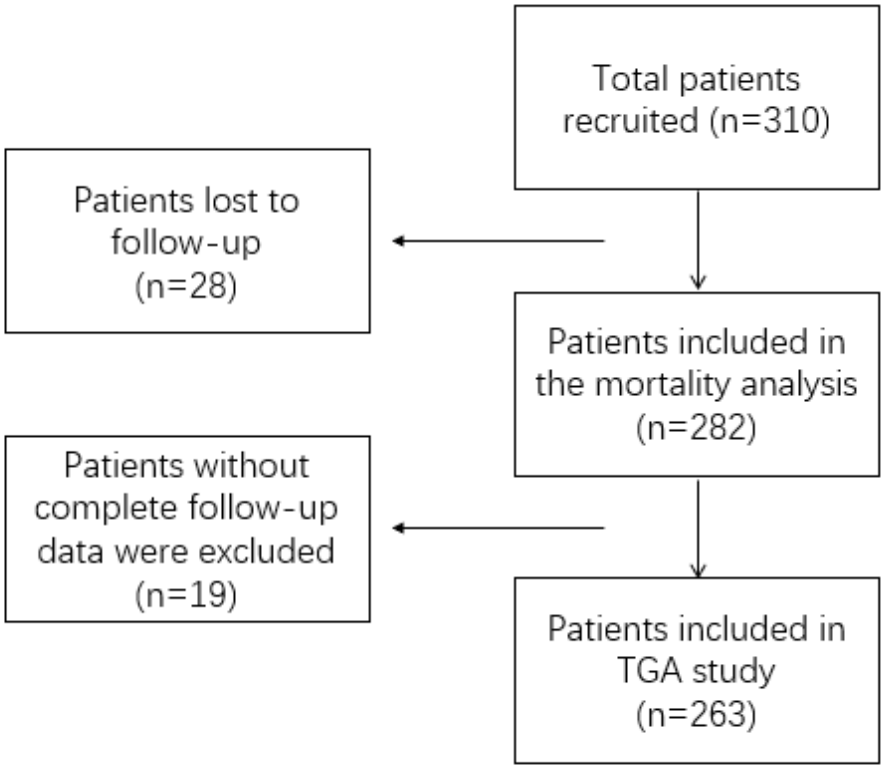
Figure 3 Comparison of the cumulative survival rates in patients with and without TGA.

Figure 4 Cumulative rates of not achieving treatment goals for patients with SLE-associated PAH.

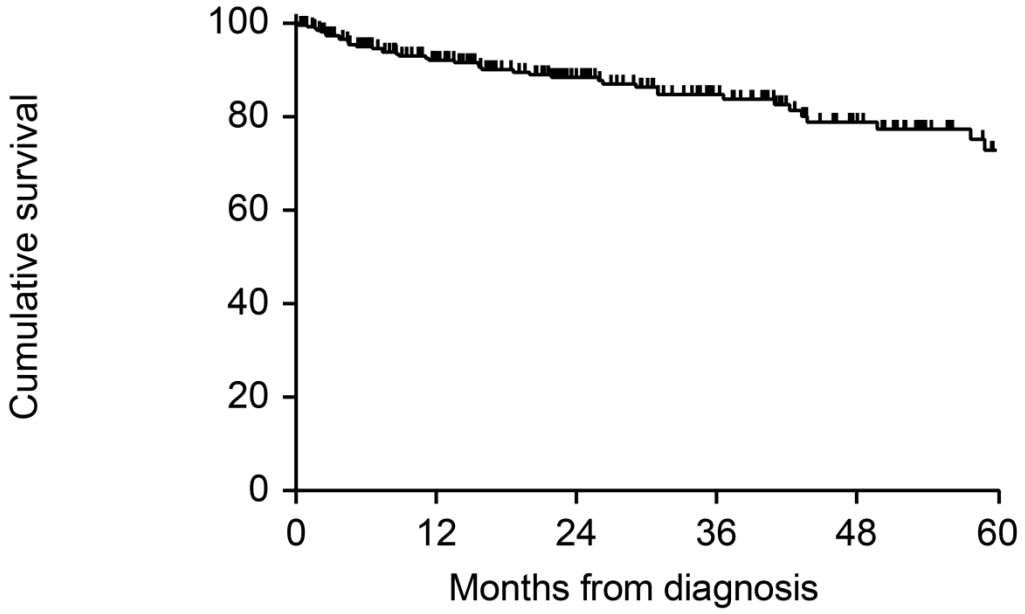
(A) The cumulative non-TGA rates for all patients with SLE-associated PAH. (B) Comparison between patients with and without baseline serositis. (C) Comparison between patients with 6MWD ≥ 380 m and 6MWD < 380 m.

Figure 5 Cumulative rates of not achieving treatment goals for patients with SLE-associated PAH.

(A) Comparison between patients with IST and patients with HCQ only among those without baseline serositis. (B) Comparison between patients with IST and patients with HCQ only among those with baseline serositis.

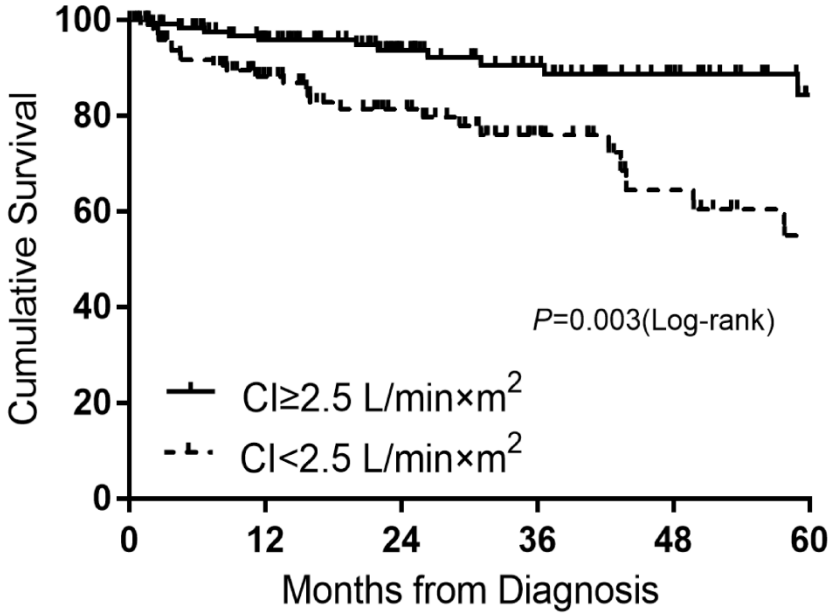

Total patients recruited (n=310)
Patients lost to follow-up (n=28)
Patients included in the mortality analysis (n=282)
Patients without complete follow-up data were excluded (n=19)
Patients included in TGA study (n=263)

a)

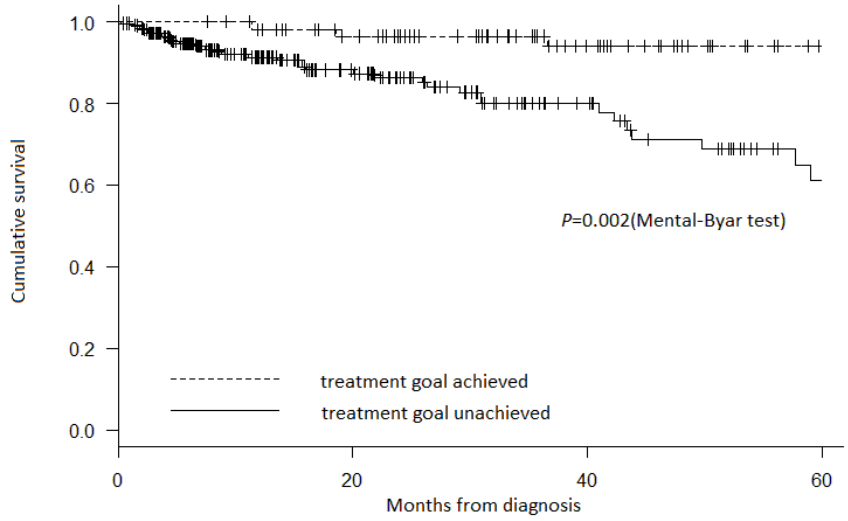


No. at risk	282	200	142	89	57	31

b)

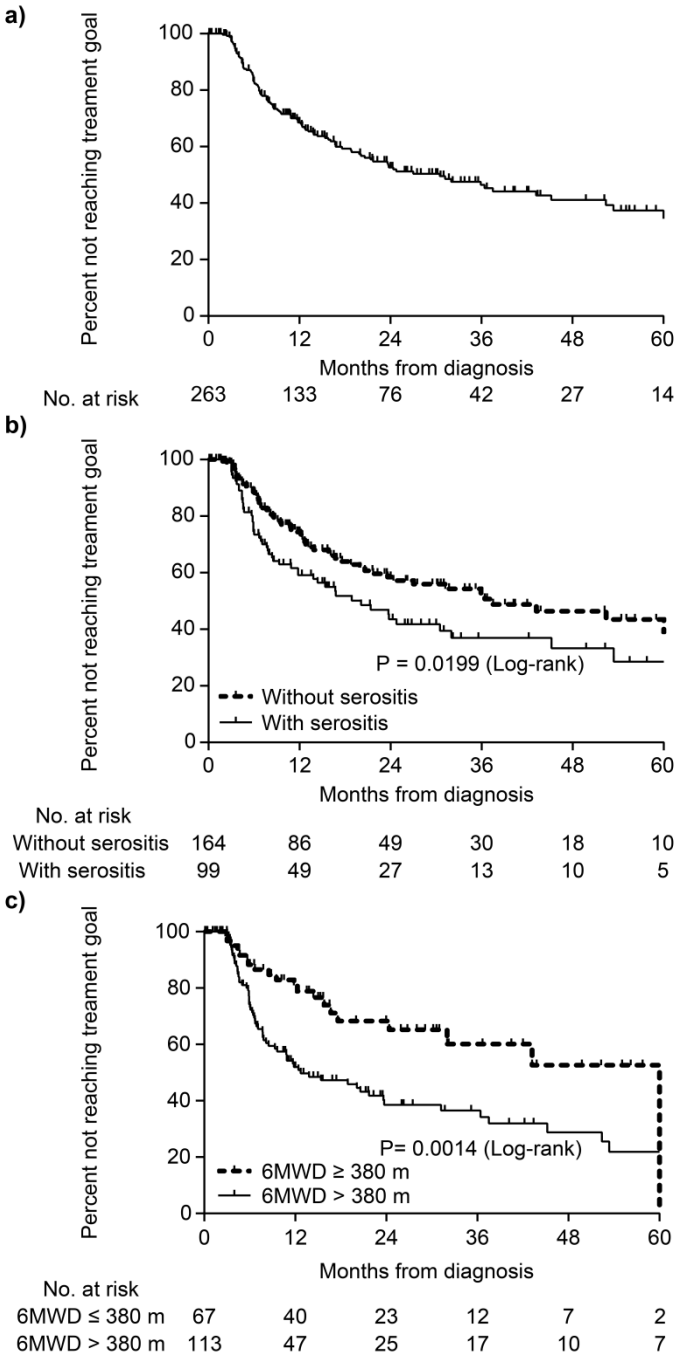


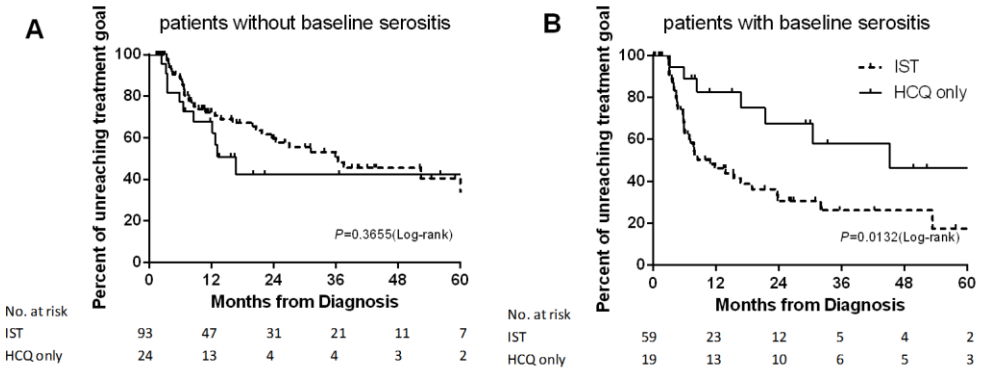
No. at risk						
CI ⩾2.5 L/min×m²	140	107	74	51	35	18
CI< 2.5 L/min×m²	102	72	52	29	17	11



Number at risk

treatment goal achieved	263	99	42	16
treatment goal unachieved	0	59	33	14


a)
Percent not reaching treament goal
100
80
60
40
20
0
0
12
24
36
48
60
Months from diagnosis
No. at risk 263 133 76 42 27 14
b)
Percent not reaching treament goal
P = 0.0199 (Log-rank)
Without serositis
With serositis
Months from diagnosis
No. at risk
Without serositis 164 86 49 30 18 10
With serositis 99 49 27 13 10 5
c)
Percent not reaching treament goal
P= 0.0014 (Log-rank)
6MWD ≥ 380 m
6MWD > 380 m
Months from diagnosis
No. at risk
6MWD ≤ 380 m 67 40 23 12 7 2
6MWD > 380 m 113 47 25 17 10 7


A
patients without baseline serositis
Percent of unreaching treatment goal
100
80
60
40
20
0
0
12
24
36
48
60
Months from Diagnosis
P=0.3655(Log-rank)
No. at risk
IST 93 47 31 21 11 7
HCQ only 24 13 4 4 3 2
B
patients with baseline serositis
IST
HCQ only
P=0.0132(Log-rank)
No. at risk
IST 59 23 12 5 4 2
HCQ only 19 13 10 6 5 3

Supplementary

Supplementary table 1

Comparison of baseline characteristics between survivors and non-survivors

Characteristics	Non-survivors (n = 42)	Survivors (n = 240)	*P* value
Age at recruitment, yr	36.2 ± 12.0	34.9 ± 10.0	0.439
Female sex, %	100.0	99.2	1.000
Lupus duration, yr	3.3 ± 4.3	4.5 ± 5.5	0.176
Clinical features			
WHO FC I-II, %	29.7	53.8	0.007**
6MWD, m	347.1 ± 81.3	414.4 ± 98.2	0.001**
Raynaud's phenomenon, %	59.5	50.4	0.276
Acute rash, %	35.7	32.9	0.723
Serositis, %	40.5	36.3	0.600
Lupus nephritis, %	38.1	34.6	0.660
Neuropsychiatric lupus, %	2.4	4.2	0.905
Thrombocytopenia, %	40.5	46.3	0.488
Hypocomplementemia, %	59.5	64.2	0.564
Anti-dsDNA, %	35.7	35.3	0.961
Anti-Sm,%	31.0	36.7	0.476
Anti-U1 RNP, %	69.0	59.4	0.238
APL, %	12.8	13.1	0.961
SLEDAI	5.2 ± 3.8	6.5 ± 5.9	0.067
RHC			
mPAP, mmHg	52.6 ± 11.8	45.4 ± 11.9	0.001**
PVR, WU	13.9 ± 5.8	10.4 ± 5.2	0.001**
CI < 2.5 L/min×m^2, %	64.9	38.0	0.003**
RAP mmHg, %	5.9 ± 4.5	5.6 ± 5.8	0.849
Treatment			
Glucocorticoids	100.0	99.2	1.000

Immunosuppressants	95.2	92.5	0.524
PAH-targeted medications	76.2	69.2	0.358

WHO FC = WHO functional class, 6MWD = 6-minute walking distance, APL = antiphospholipid, SLEDAI = systemic lupus erythematosus disease activity index, RHC = right heart catheterization, mPAP = mean pulmonary arterial pressure, PVR = pulmonary vascular resistance, CI = cardiac index, RAP = right atrial pressure

Supplementary table 2

Comparison of baseline characteristics between patients who achieved or did not achieve their treatment goals

Characteristics	Achieved treatment goal (n = 115)	Did not achieve treatment goal (n = 148)	*P* value
Age at recruitment, yr	34.7 ± 9.6	35.2 ± 10.8	0.676
Female sex, %	99.1	99.3	1.000
Lupus duration, yr	4.9 ± 5.8	3.7 ± 4.6	0.082
Clinical features			
WHO FC I-II, %	53.6	45.5	0.217
6MWD, m	428.2 ± 93.0	376.0 ± 99.4	< 0.001**
Raynaud's phenomenon, %	56.5	47.3	0.138
Acute rash, %	33.0	33.1	0.991
Serositis, %	46.1	31.1	0.013*
Lupus nephritis, %	40.9	33.1	0.195
Neuropsychiatric lupus, %	6.1	2.7	0.174
Thrombocytopenia, %	53.0	43.9	0.142
Hypocomplementemia, %	70.4	60.1	0.083
Anti-dsDNA, %	37.2	31.7	0.360
Anti-Sm,%	36.5	35.1	0.816
Anti-U1 RNP, %	67.0	56.9	0.105

APL, %	13.1	13.0	0.973
SLEDAI	6.5 ± 6.7	6.0 ± 4.8	0.484
RHC			
mPAP, mmHg	43.7 ± 11.3	49.5 ± 12.6	< 0.001**
PVR, WU	9.7 ± 4.3	12.5 ± 6.0	< 0.001**
CI < 2.5 L/min×m^2, %	27.8	55.5	0.001**
RAP, mmHg	5.0 ± 6.3	6.2 ± 5.0	0.182
Treatment			
Glucocorticoids	99.1	99.3	1.000
Immunosuppressants	92.2	92.6	0.905
PAH-targeted medications	60.0	77.0	0.003**

WHO FC = WHO functional class, 6MWD = 6-minute walking distance, APL = antiphospholipid, SLEDAI = systemic lupus erythematosus disease activity index, RHC = right heart catheterization, mPAP = mean pulmonary arterial pressure, PVR = pulmonary vascular resistance, CI = cardiac index, RAP = right atrial pressure

Supplementary table 3

Baseline characteristics between intensive immunosuppressant (IST) group and the HCQ only group stratified by baseline serositis

	Baseline serositis			Without baseline serositis		
	IST n = 64	HCQ only n = 20	P value	IST n = 113	HCQ only n = 31	P value
Age at recruitment, yr	33.4 ± 8.2	35.7 ± 9.6	0.292	35.8 ± 10.4	36.1 ± 12.8	0.874
Female sex, %	100	100	-	98.2	100	0.456
WHO FC I-II, %	43.5	42.1	0.912	53.8	65.4	0.295
6 MWD > 380 m, %	59.6	42.9	0.400	76.1	59.1	0.121
CI ⩾ 2.5 L/min×m^2, %	35.9	60.0	0.057	35.5	48.4	0.191

WHO FC = WHO functional class, 6MWD = 6-minute walking distance, CI = cardiac index

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