Research Article

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Systemic lupus erythematosus-associated pulmonary hypertension: clinical variables and survival outcome

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Aim: Compare systemic lupus erythematosus (SLE) patients with pulmonary hypertension (PH) versus SLE without PH, to study the variables associated with PH. **Methods:** Case–control cross-sectional study of SLE patients from 2006 to 2011. PH was diagnosed by echocardiogram or cardiac catheterization. Controls were randomly selected from SLE patients with no PH. PH cases: controls ratio was 39:69, matching for age and gender. Clinical, serologic profiles and outcome were analyzed. **Results:** We identified 39 PH patients. Anti-ribonucleoprotein was positively associated with PH; malar rash was negatively associated. The 3-year survival of SLE-PH patients was 87.2%. **Conclusion:** The differences associated with SLE-PH may aid early recognition and treatment. We suggest a lower threshold for screening or even routine screening of PH in patients with anti-ribonucleoprotein positivity and negative malar rash.

Keywords: anti-RNP • Chinese • connective tissue diseases • echocardiogram • malar rash • pulmonary arterial hypertension • pulmonary hypertension • systemic lupus erythematosus • systolic pulmonary arterial pressure

Pulmonary hypertension (PH) is associated with connective tissue diseases (CTDs). PH is classified into five subgroups as following [1]:

- Group 1: pulmonary arterial hypertension (PAH);
- Group 2: PH due to left heart disease;
- Group 3: PH due to lung disease or hypoxia;
- Group 4: chronic thromboembolic pulmonary hypertension (CTEPH);
- Group 5: PH with unclear or multifactorial mechanisms.

According to the REVEAL Registry [2], approximately 25.3% of all PAH (group 1) was associated with CTDs which represented the second largest group in PAH patients, while 46.2% were idiopathic PAH. The REVEAL Registry is the largest and most comprehensive registry of group I PAH reported to date which included 2967 PAH patients. Besides groups 1 PAH, PH in CTD such as systemic lupus erythematosus (SLE) may also be secondary to CTE (group 4) associated with antiphospholipid syndrome or cardiopulmonary complications like interstitial lung diseases (group 3). Therefore, different forms of PH can be found in SLE. PH is under-recognized in lupus, especially when compared with systemic sclerosis (SSc), with an estimated prevalence of 4–14% [3,4]. Historically, CTD-associated PH carries a poor prognosis [5,6]. With emerging therapies, early detection and prompt treatment may improve the outcome of PH in SLE.

Recent data regarding PH in SLE is scanty [7]. This cross-sectional case–control study was conducted to delineate the clinical profiles associated with PH; with an attempt to explore factors that may aid identification of SLE patients who develop PH. We also tried to assess the survival outcome.

Methodology

SLE patients who had been attending our rheumatology clinic or admitted into our

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hospital for care from 2006 to 2011 were retrieved using Clinical Data Analysis & Reporting System. Two hundred and sixty six SLE patients have had echocardiograms or cardiac catheterization performed and were included in the analysis. All patients fulfilled the revised American College of Rheumatology (ACR) classification criteria [8] of SLE with no clinical features suggestive of other overlapping CTDs. Patients in PH group were identified by echocardiogram (systolic pulmonary artery pressure of ≥40 mmHg) or cardiac catheterization (mean pulmonary artery pressure ≥25 mmHg at rest). Control group was randomly selected from the rest of SLE patients with echocardiogram showing no PH. Both groups were matched for age and gender as far as availability allowed (Table 1). PH: Control ratio was roughly 1:2 with sample size of 39:69 patients. Data including demographics, clinical features, serologic profiles, echocardiograms, right heart catheterization findings and survival outcome of SLE patients with and without PH were analyzed. Continuous variables were compared by *t*-test and nonparametric variables by Mann-Whitney U test whereas categorical variables were compared by chi-square test.

Materials & definitions

Demographical & clinical parameters

Demographical parameters were collected. Clinical parameters consisted of SLE disease duration, classification criteria of SLE met by patients, SLE activity and damage gauged by Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) [9] and Systemic Lupus International Collaborating Clinics Damage Index (SLICC damage index) [10], respectively. The SLEDAI and SLICC damage index were captured in follow-up episode nearest to the time of final data analysis.

Laboratory parameters

Hematological, biochemical blood, urine test results and serological activities were extracted at presentation of SLE and at time nearest to the point of final data analysis. Autoantibody profiles were analyzed.

Echocardiogram & right heart catheterization

Transthoracic echocardiogram (TTE) plays a pivotal role in identifying SLE patients with PH. Though right heart catheterization (RHC) remains the gold standard in diagnosis of PH, it carries risk of serious complications of around 1% and is an expensive procedure that is not widely accessible in many healthcare centers. On the contrary, TTE is noninvasive, inexpensive and widely available investigation to measure systolic pulmonary artery pressure (sPAP) and other hemodynamic parameters. Various studies reported statistically significant correlations between TTE and RHC values [11–13]. sPAP is considered equal to right ventricular systolic pressure (RVSP) in the absence of outflow tract obstruction. An estimate of RVSP can be obtained using Doppler echocardiography by calculating the right ventricular/right atrial pressure (RAP) gradient during systole, approximated by the modified Bernoulli equation as $4v^2$, in which v is the velocity of the tricuspid jet. RVSP is derived by adding the right atrial pressure (RAP) to the gradient.

in other words, RVSP (or sPAP) = $4v^2$ + RAP

The RAP that is used in this calculation is either a standardized value or an estimated value based on echocardiographic characteristics of the inferior vena cava, or the vertical height of the jugular venous pulse on physical examination.

Echocardiographic criteria to detect PH have been established and were included in the last updated European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of PH [14], and was endorsed by the International Society of Heart and Lung Transplantation. In the ESC guidelines, it was suggested that PH is possible when sPAP is ≥37 mmHg with/without additional echocardiographic variables suggestive of PH. Furthermore, another trial published in

Table 1. Age and gender of pulmonary hypertension and control groups.

Age group (years)	SLE			
	Controls = 69		PH cases = 39	
	Male	Female	Male	Female
21–30	0	6	0	3
31–40	1	14	0	6
41–50	1	18	1	10
51–60	2	16	1	8
61–70	2	5	1	3
71–80	0	3	1	4
81–85	0	1	0	1

Rheumatology 2004 also selected RVSP of 40 mmHg as the cut-off value for diagnosis of PH [15]. Therefore, we used sPAP or RVSP ≥40 mmHg in echocardiogram to define PH in our study, which was also the usual cut off adopted by the cardiac team in our hospital.

Other significant echocardiographic findings captured in the analysis included significant right or left heart valvular lesions, left ventricular systolic function measured by left ventricular ejection fraction (LVEF) and also evidence of right heart failure as evidenced by right atrial or ventricular dilatation. This is because significant left heart disease may lead to PH and is one of the confounding factors in studying SLE-related PH. On the other hand, right heart failure is an ominous sign in PH.

All of the 266 SLE patients included in the study had TTE done regardless of whether they were symptomatic of PH or not. All patients in both PH and control groups had undergone at least one TTE or even RHC. The reasons for doing TTE were listed in Figure 1.

For right heart catheterization (RHC), PH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest [16–18]. RHC remained the gold standard to confirm diagnosis of PH, to assess the severity of the hemodynamic impairment and to test the vasoreactivity of the pulmonary circulation in response to vasodilators like calcium channel blockers (CCB).

Results

Number of PH patients & demographics

Among the 266 SLE patients in our study, 39 of them were identified to have PH.

For PH patients, the mean age at SLE diagnosis was 41.5 ± 15.5 (mean ± SD) versus 36.6 ± 11.4 years old in control patients (p = 0.15). At final data analysis, the mean disease duration of SLE was 10.5 ± 8.2 years in PH group and 11.7 ± 8.4 years in control group (p = 0.48). Concerning the disease duration of SLE when PH was diagnosed in the 39 cases, the mean was 7.5 ± 8.3 years and the median was 5 years.

Past medical history including significant infections leading to hospitalization; cardiovascular diseases namely ischemic heart disease, congestive heart failure; significant metabolic diseases namely hyperlipidemia, diabetes mellitus were also compared in PH and control groups. The percentages in two groups were not significantly different.

Classification criteria & clinical features

For the 11 classification features according to the revised ACR classification criteria of SLE [8], all features were studied and compared between two groups. Other clinical features like interstitial lung disease (ILD), which was diagnosed by chest radiograph (CXR) or computed tomography, or even by biopsy, as well as Raynaud's phenomenon (RP) and dependence on renal replacement therapy (RRT), were also analyzed and compared (Table 2).

Compared with controls, significantly more PH patients had pericardial effusion (43.6 vs 15.9%), pleural effusion (43.6 vs 13%), psychosis (12.8 vs 1.4%), interstitial lung disease (25.6 vs 8.7%), hemolytic anemia (38.5 vs 14.5%) and proteinuria of more than 0.5 g/day (76.9 vs 53.6%). On the contrary, significantly fewer PH patients had malar rash (46.2 vs 79.7%) and photosensitivity (7.7 vs 39.1%). Concerning CT thorax, it was done more in PH group (64.1%) than in control group (36.2%). None of the CT scans showed esophageal dilatation. The number of lupus patients on dialysis was too small to allow meaningful statistic comparison. There were five PH patients on either hemodialysis or peritoneal dialysis, whereas only three patients in control group were on dialysis.

Autoantibody profile

Besides ANA and anti-ds DNA, auto-antibodies included in the analysis were rheumatoid factor (RF) and anti-extractible nuclear antigens (anti-ENA) consisting of anti-ribonucleoprotein (RNP), anti-Ro, anti-La, anti-Sm, anti-Scl 70 and anti-Jo1. But only the first four types of anti-ENA were focused as they were more related to lupus.

Significantly, more PH patients had anti-RNP positivity than controls (22 out of 38, 57.9% vs 19 out of 69, 27.5% with p = 0.004 and OR = 3.62). The occurrences of anti-Ro, anti-La and anti-Sm were not significantly different between two groups (Table 2).

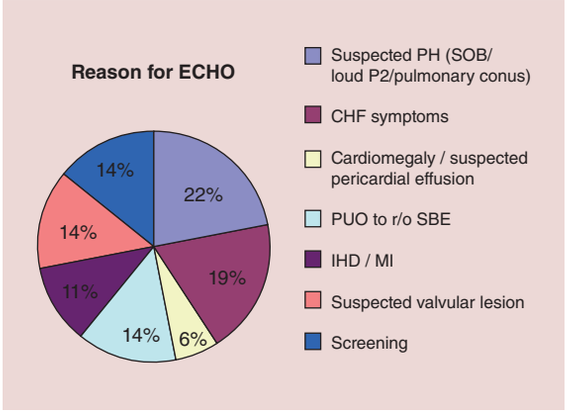


Figure 1. Indications for performing echocardiograms.
CHF: Congestive heart failure; IHD: Ischemic heart disease; MI: Myocardial infarction; P2: Pulmonic valve closure part of second heart sound; PUO: Prexia of unknown origin; SBE: Subacute bacterial endocarditis.

Table 2. Clinical features and autoantibodies in pulmonary hypertension cases and controls.

	Cases, n (%)	Controls, n (%)	p-value	OR
SLE criteria/features				
Photosensitivity	3/39 (7.7)	27/69 (39.1)	***<0.001***	***0.13***
Malar rash	18/39 (46.2)	55/69 (79.7)	***0.001***	***0.22***
Oral ulcer	13/39 (33.3)	24/69 (34.8)	1.00	
Discoid	2/39 (5.1)	7/69 (10.1)	0.48	
Arthritis	34/39 (87.2)	57/69 (82.6)	0.73	
Pleural effusion	17/39 (43.6)	9/69 (13.0)	***0.001***	***5.15***
Pericardial effusion	17/39 (43.6)	11/69 (15.9)	***0.003***	***4.07***
Seizure	3/39 (7.7)	4/69 (5.8)	0.70	
Psychosis	5/39 (12.8)	1/69 (1.4)	***0.02***	***10.00***
Proteinuria	30/39 (76.9)	37/69 (53.6)	***0.03***	***2.88***
Urinary casts	7/39 (17.9)	10/66 (15.2)	0.92	
RRT (PD)	1/39 (2.6)	0/69 (0)	0.36	
RRT (HD)	5/39 (12.8)	3/69 (4.3)	0.13	
Hemolytic anemia	15/39 (38.5)	10/69 (14.5)	***0.01***	***3.69***
Leucopenia	15/39 (38.5)	35/69 (50.7)	0.31	
Lymphopenia	34/39 (87.2)	60/69 (87.0)	1.00	
Thrombocytopenia	13/39 (33.3)	28/68 (40.6)	0.59	
Elevated anti-ds DNA	35/39 (89.7)	51/69 (73.9)	0.80	
Anti cardiolipin +ve	12/37 (32.4)	22/59 (37.3)	0.79	
Lupus anticoagulant +ve	8/17 (47.1)	7/27 (25.9)	0.27	
ANA +ve	39/39 (100)	68/69 (98.6)	1.00	
Other clinical features				
Raynaud's phenomenon	18/39 (46.2)	22/69 (31.9)	0.21	
Interstitial lung disease	10/39 (25.6)	6/69 (8.7)	***0.04***	***3.62***
PE confirmed by imaging	1/25 (4.0)	0/24 (0)	1.00	
Restrictive lung defect	4/13 (30.8%)	1/9 (11.1%)	0.36	
Diffusion capacity impairment	7/10 (70%)	2/7 (28.6%)	0.23	
Deceased	5/39 (12.8)	7/69 (10.1)	0.45	
Autoantibodies				
RF	7/22 (31.8)	6/46 (13.0)	0.13	
Anti-RNP	22/38 (57.9)	19/69 (27.5)	***0.004***	***3.62***
Anti-Ro	17/38 (44.7)	40/69 (58)	0.27	
Anti-La	4/38 (10.5)	11/69 (15.9)	0.63	
Anti-Sm	6/38 (15.8)	9/69 (13)	0.92	

HD: Hemodialysis; PD: Peritoneal dialysis; PE: pulmonary embolism; RNP: Ribonucleoprotein; RRT: Renal replacement therapy.

Laboratory parameters at presentation & time of final data analysis

Hemoglobin level at presentation of SLE was significantly lower in PH group than in controls. Starting hemoglobin level was 10.5 ± 2.5 g/dl in cases versus 11.8 ± 2.0 g/dl in controls (p = 0.004). Anti-ds DNA level at presentation was significantly higher in PH group than controls (242.8 ± 204.1 vs 166.0 ± 121.6 IU/ml with p = 0.02; normal range: <50 IU/ml). Other parameters at presentation were not significantly different between two groups.

In the follow-up episode nearest to final analysis, creatinine level was significantly worse in PH cases than controls (180.7 ± 236.6 vs 105.2 ± 98.8 umol/l

and p = 0.01). Furthermore, proteinuria was also significantly more in PH group (0.61 ± 1.02 g/day vs 0.34 ± 0.73 g/day). The worst creatinine level during the study was significantly higher in PH patients than in controls (256.4 ± 288.2 vs 172.4 ± 172.9 umol/l with p = 0.04).

Disease activity & disease damage

SLEDAI at time of final data analysis was significantly higher in PH group (median 4.0 vs 2.0, p = 0.03). This showed that PH patients had more severe disease and active disease or associated with more systemic involvement in SLE. This also echoed with our findings that PH patients had more proteinuria, pleurisy, pericarditis and anti-ds DNA level, etc. There was not much data in previous literature addressing the association of disease activity with PH.

SLICC damage index at time of final data analysis was also significantly higher in PH group (median 2.0 vs 1.0, p < 0.001). However, as PH was by default an item counted in SLICC damage index; all patients in PH group would have one mark more in SLICC damage index than controls. In order to eliminate the confounding effect of PH, in PH group we excluded the PH score from the initial SLICC damage index; whereas in control group, we also minus one point from the original SLICC damage index. After analysis, the modified SLICC damage indexes were not significantly different between two groups with both groups having median of 1 (Table 3).

Table 3. Laboratory parameters at presentation of systemic lupus erythematosus and time of final data analysis, disease activity and damage in pulmonary hypertension cases and controls.

	Cases (mean ± SD)	Controls (mean ± SD)	p-value
Parameters at presentation			
Hemoglobin (g/dl)	10.5 ± 2.5	11.8 ± 2.0	***0.004***
WCC (× 10 ^{9}/l)	5.7 ± 3.4	5.4 ± 3.1	0.43
ANC (× 10 ^{9}/l)	4.2 ± 3.0	3.7 ± 2.9	0.09
Lymphocyte (× 10 ^{9}/l)	1.1 ± 1.0	1.1 ± 0.6	0.56
Platelet count (× 10 ^{9}/l)	217.9 ± 128.0	202.3 ± 94.1	0.42
Creatinine (umol/l)	109.6 ± 139.8	81.6 ± 50.1	0.22
Proteinuria (g/day)	2.27 ± 3.72	1.93 ± 2.31	0.97
Anti-ds DNA (IU/ml)	242.8 ± 204.1	166.0 ± 121.6	***0.02***
C3 (g/l)	0.67 ± 0.36	0.70 ± 0.30	0.31
Parameters at final analysis			
Hemoglobin (g/dl)	11.0 ± 2.3	12.2 ± 1.8	0.09
WCC (× 10 ^{9}/l)	6.6 ± 3.8	6.6 ± 3.0	0.80
ANC (× 10 ^{9}/l)	4.8 ± 3.3	5.0 ± 3.1	0.65
Lymphocyte (× 10 ^{9}/l)	1.0 ± 0.5	1.2 ± 0.6	0.22
Platelet count (× 10 ^{9}/l)	205.6 ± 105.3	200.5 ± 86.2	0.47
Creatinine (umol/l)	180.7 ± 236.6	105.2 ± 98.8	***0.01***
Proteinuria (g/day)	0.61 ± 1.02	0.34 ± 0.73	***0.04***
Anti-ds DNA (IU/ml)	109.2 ± 175.3	83.8 ± 98.4	0.73
C3 (g/l)	0.90 ± 0.27	0.94 ± 0.31	0.47
Worst creatinine (umol/l)	256.4 ± 288.2	172.4 ± 172.9	***0.04***
Other parameters	**Cases: median (IR)**	**Controls: median (IR)**	**p-value**
SLEDAI-2K	4.0 (2.0–6.0)	2.0 (0–4.0)	***0.03***
SLICC Damage Index	2.0 (2.0–3.0)	1.0 (0–2.0)	***<0.001***
Modified SLICC Damage Index	1.0 (1.0–2.0)	1.0 (0–2.0)	0.12

ANC: Absolute neutrophil count; IR: Interquartile Range; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC Damage Index: Systemic Lupus Erythematosus International Collaborating Clinics Damage Score; WCC: White cell count.

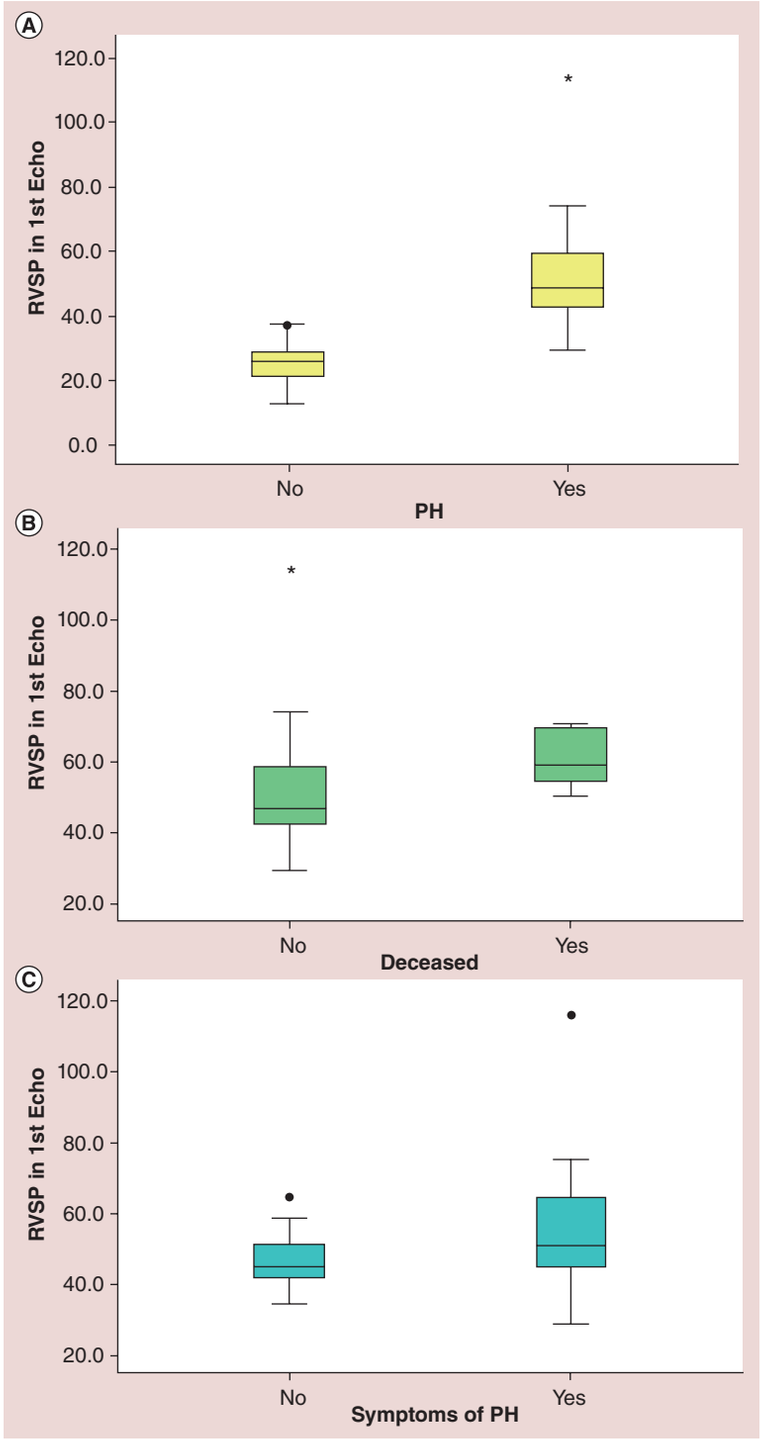


Figure 2. Comparison of right ventricular systolic pressure in respective patient groups. (A) Right ventricular systolic pressure in PH and control groups (p = <0.001). **(B)** Right ventricular systolic pressure and survival status (p = 0.03). **(C)** Right ventricular systolic pressure with symptoms of PH (p = 0.20). Asterisk or dot above bars are outliers.PH: Pulmonary hypertension.

Echocardiogram findings

PH group had higher RVSP than control group. In PH patients, the mean ± SD RVSP was 51.7 ± 15.4 mmHg versus 25.3 ± 5.2 mmHg in controls (p <0.001) (Figure 2A). In PH group, deceased patients had significantly higher RVSP. The mean ± SD RVSP was 60.4 ± 8.9 mmHg; while surviving patients had a reading of 50.4 ± 15.9 mmHg with a p-value of 0.03 (Figure 2B). There was no significant difference in RVSP among those who were symptomatic of PH and those who were asymptomatic (p = 0.20) (Figure 2C). These were similar to the findings in a paper of local population [7].

More PH patients were shown to have significant right heart valvular lesions and right heart failure as evidenced by right atrial or ventricular dilatation than controls (Table 4). This is not hard to understand as elevated RVSP would inevitably cause tricuspid regurgitation. The higher the RVSP, the more likely it would cause severe tricuspid regurgitation or even right heart failure. There was no significant difference in proportion of patients having LVEF impairment and significant left valvular lesions between PH and control groups. This was important as significant left heart lesions might lead to PH, that is why we would like to eliminate the confounding effect of significant left heart disease.

Right heart catheterization

Although RHC is the gold standard for diagnosing PH, only 5 out of 39 patients in PH group had RHC done because many patients refused the procedure. The mean mPAP was 41 mmHg. Two out of five patients had positive response to vasodilator as demonstrated by RHC.

Survival status

Five out of 39 (12.8%) PH patients passed away during study period; while 7 out of 69 (10.1%) control patients were deceased (p = 0.45). In PH patients who died, 60% died of sepsis, 20% died of cardiovascular causes, 0% of malignancy and 20% were due to other causes. In control group patients who died, 72% died of sepsis, 14% of cardiovascular causes and 14% died of malignancy.

Survival curve for PH group after PH onset was plotted and it showed that all death tolls occurred within the first 3 years of PH diagnosis, and most patients died in second to third year after PH (Figure 3).

Possible factors associated with PH

As revealed from the above univariate analysis, various factors were significantly different between PH and control groups. Factors there were more commonly found in PH group included pleural effusion, pericardial effusion, psychosis, proteinuria of more than 0.5 g/day, hemolytic anemia, anti-RNP positivity, ILD, higher worst creatinine level, lower hemoglobin level

Table 4. Echocardiographic findings in pulmonary hypertension cases and controls.

Echocardiographic findings	Cases, n (%)	Controls, n (%)	p-value	OR
LVEF impairment	7/39 (17.9%)	4/69 (5.8%)	0.09	
Significant L heart valves lesion	5/39 (12.8%)	7/69 (10.1%)	0.75	
Significant R heart valves lesion	22/39 (56.4%)	3/69 (4.3%)	***<0.001***	***28.47***
Features of R heart failure	9/39 (23.1%)	1/69 (1.4%)	***<0.001***	***20.40***

at presentation of SLE, higher anti-ds DNA level at presentation, higher proteinuria and creatinine level at the end of study and also higher SLEDAI and SLICC damage index at the end of study. But as SLICC damage index was potentially confounded by PH, it was not taken for further analysis. Factors that were negatively associated with PH group included photosensitivity and malar rash. To look for factors that may predict PH in SLE, logistic regression of the above factors was performed.

After multiple logistic regressions, only malar rash and anti-RNP positivity were statistically significant (Table 5). Anti-RNP positivity was an important risk factor for PH (p = 0.03), while malar rash was negatively associated with PH in SLE (p = 0.03). The Exp (B) gave the odds ratios for PH. SLE patients having anti-RNP positivity were 4.8-times more likely to have PH (OR: 4.81; 95% CI: 1.19–19.41); and patients having malar rash were 82% less likely to have PH (OR: 0.18; 95% CI: 0.04–0.81).

Discussion

Prevalence & treatment of PAH

Concerning the prevalence of PH in Chinese SLE population, two different studies revealed the figures between 4 and 11% [7,13]. The wide range of in prevalence could be due to multiple factors. Early studies relied on detection of clinical symptoms, which might lead to under-recognition of SLE-PH. Furthermore, previous studies might have used different cut offs for diagnosis of PH [19,20]. In this case controlled study, among 266 SLE patients with echocardiogram or even RHC performed, 39 of them were identified to have PH. Because a small proportion of patients in our SLE cohort had never had echocardiogram performed, in order to more accurately estimate the prevalence of PH in SLE, further study should be carried on to do echocardiogram in all SLE patients.

Rate of pulmonary hypertension (PH) in whom echo was done for screening is 7.7% (3 out of 39) while the rate in whom echo was done for other reasons is 92.3% (36 out of 39). Therefore, at least a small percentage of patients with possible PH would be missed as they were only identified by screening leading to certain percentage of under recognition. Historically, there had been more literature addressing PH-associated systemic sclerosis. PH associated with SLE was less commonly studied and hence was under-recognized compared with systemic sclerosis.

Previous studies [21,22] mentioned SLE-PH as a disease modality which is more responsive to immunosuppressants than other CTD-related PH like SSc. Concerning PH-specific treatments, general measures include O2 supplement for patients with hypoxemia, diuretics for right heart failure, anticoagulants [23] in selected cases CCB, which is a vasodilator, should be used in patients with positive vasoreactivity demonstrated in RHC [24]. Newer treatments for PAH (group I PH) are mainly divided into three classes:

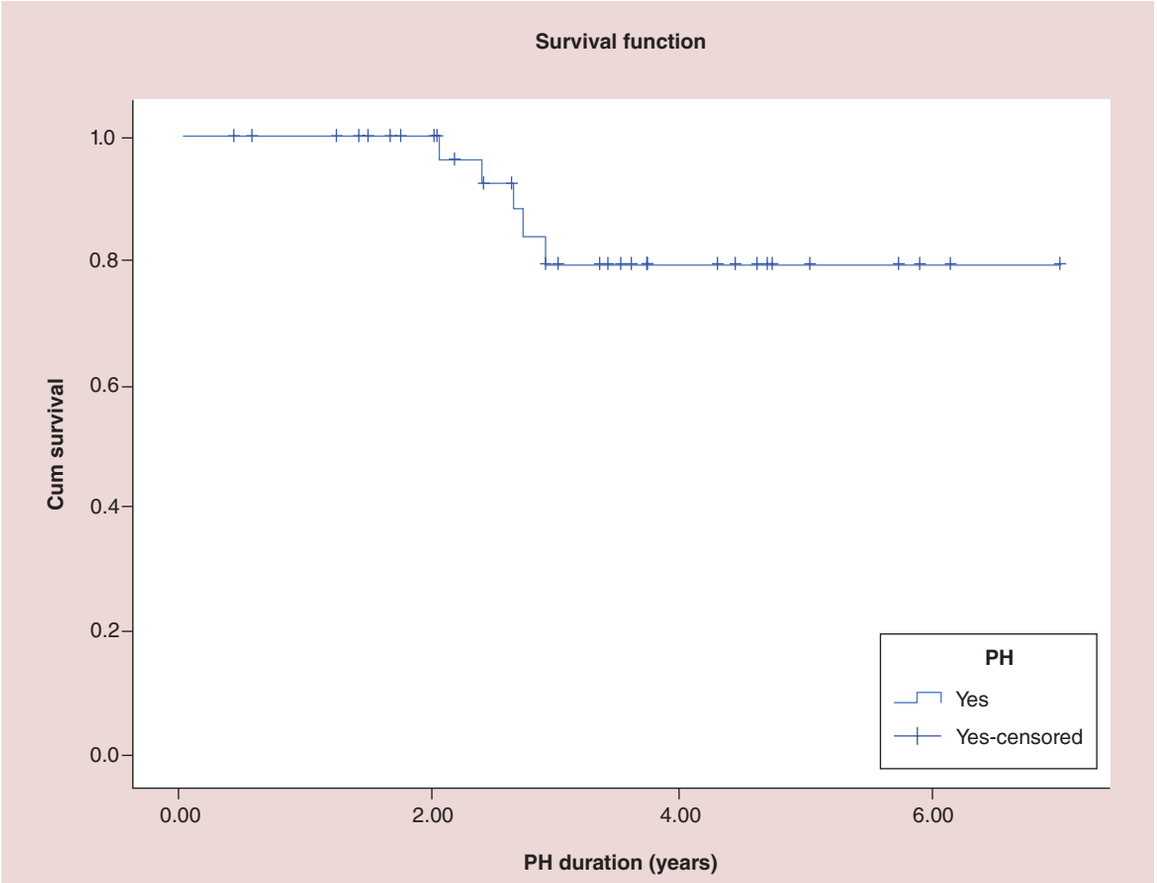
- Prostacyclin derivatives : epoprostenol, iloprost, treprostinil [25–27];
- Endothelin receptor blockers (ERB) : bosentan, ambrisentan [28,29];
- Phosphodiesterase 5 inhibitors (PDE-5 I) : sildenafil, tadalafil [30–32].

All these medications are recommended and included in the 2009 European Society of Cardiology for treatment of PH [14].

For other forms of PH, like group 4 PH secondary to chronic thromboembolism, anticoagulant should be implemented; while for group 3 PH associated with ILD, immunosuppressants according to histology of ILD and symptoms should be considered.

Survival

CTD-associated PH historically had a poor prognosis. One-year survival rate before availability of modern treatment was only around 45% inSSc [5]. In SLE, the estimated survival of PH patients was quoted to be better than SSc, but still, it was worse than those with idiopathic PH [33]. The emergence of various treat-



Years of FU	0	1	2	3	4	5	6
Remaining cases (n)	39	37	27	16	10	4	1
Deceased (n)	0	0	1	5	5	5	5

Figure 3. Survival curve of patients after diagnosis of pulmonary hypertension.
FU: Follow-up; PAH: Pulmonary arterial hypertension.

ment modalities seemed to improve the management of CTD associated PH. Recent study has shown that the 1- and 3-year survival rates of SLE-associated PH have improved to 78 and 74%, respectively [34].

We tried to determine the contribution of PH to mortality but it was difficult as the follow-up duration was hard to define. This was mainly because we could not ascertain the onset of PH if only to be taken from the date of echo; and we could not simply count all the follow-up duration of the comparative arm of lupus patients without PH. The Kaplan Meier curve aimed to show the mortality of PH group due to any causes after diagnosis of PH, not the mortality due to PH. In our study, 5 out of 39 PH patients were deceased, all within the first 3 years of PH symptoms or diagnosis. Hence, 3-year survival after diagnosis of PH was approximately 87.2%.

Possible factors associated with PH

After multiple logistic regression, only anti-RNP positivity was significant predictor for PH, while malar rash was significant negative predictor. If a patient was having both anti-RNP positivity but no malar rash, the likelihood of having PH would be the highest. After further analysis by comparing patients with anti-RNP but no malar rash with others, we found the OR to be 5.60.

The association of PH with anti-RNP positivity was quite commonly seen in previous studies [35,36], though the underlying mechanisms remained to be further clarified. One of the more recent studies published in 2014 [37] also demonstrated that anti-RNP positivity is associated with PH in SLE. This study [37] suggested there may be some associations between specific autoantibodies and clinical manifestations. On the other

Table 5. Multiple logistic regression analysis.

	p-values	Exp (B)	95% CI for Exp (B)
Photosensitivty	0.32	0.38	0.06–2.49
Malar rash	***0.03***	***0.18***	***0.04–0.81***
Pericardial effusion	0.71	0.71	0.12–4.19
Pleural effusion	0.16	3.68	0.60–22.53
Psychosis	0.13	20.58	0.39–1079.41
Proteinuria >0.5 g/day	0.95	1.06	0.21–5.26
Hemolytic anemia	0.30	2.18	0.50–9.41
Interstitial lung disease	0.08	4.86	0.84–28.12
Anti-RNP +	***0.03***	***4.81***	***1.19–19.41***
Hemoglobin at presentation	0.64	0.93	0.67–1.28
Anti-ds DNA at presentation	0.12	1.01	1.00–1.01
Worst creatinine	0.57	1.00	0.99–1.00
SLEDAI-2K	0.26	1.10	0.93–1.30
Creatinine at the end of the study	0.17	1.01	1.00–1.01
Proteinuria at the end of the study	0.37	0.65	0.25–1.68

SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

hand from our study, the negative association of malar rash with PH was a relatively new finding which was not commonly reported in previous literature. The underlying reason for this negative association may be related to prognostically distinct clinical patterns of SLE [38]. In SLE three distinct groups of patients were identified according to clinical manifestations [38]. Cluster 1 was characterized predominantly by mucocutaneous manifestations and arthritis but lowest prevalence of serositis, hematologic manifestations and nephritis. Patients in cluster 2 presented with mainly serositis, hematologic involvement and renal lupus; but lowest prevalence of mucocutaneous manifestations. Both pulmonary manifestations (pulmonary hypertension and pulmonary fibrosis) and gastrointestinal manifestations (protein losing gastroenteropathy, mesenteric vasculitis and colitis) were significantly more common in cluster 2. Cluster 3 had the most heterogeneous features. So the negative association of cutaneous manifestations and PH in our study could be explained by cluster 2 pattern. Also, cluster 2 features included hematologic and renal involvement which might explain the association of hemolytic anemia, proteinuria and worse creatinine level with PH observed in our study. From the findings of this paper [38] and our study, the mucocutaneous features were seemingly negatively associated with more visceral involvement like PH or nephritis or gastroenteropathy. However, the underlying mechanism is not clear.

We acknowledged that the lack of comprehensive RHC data as the limitation of this study, and hence we were not able to classify the subgroups of PH and tell whether it was PAH (group 1) or due to ILD (group 3) or even chronic thromboembolism (group 4). This is because many patients in our cohort refused to proceed to RHC which was perceived as invasive procedure. Also, echocardiographic criteria to detect PH have been established and were included in the 2009 updated ESC guidelines for diagnosis and treatment of PH [14], therefore we tried to use echocardiogram to study SLE-associated PH from a broader perspective regardless of the subgroups.

Our study identified factors that are associated with PH in SLE, and reinforced that certain autoantibodies and clinical features may help us to predict specific organ complication. Screening echocardiogram should be arranged for SLE patients at risk of PH to allow early recognition and specific treatment, especially those with positive anti-RNP but without malar rash.

Conclusion

SLE-associated PH is a more treatable subset with better prognosis among various CTDs. Also, the treatment of SLE-PH is advancing in recent years. This cross-sectional case–control study described PH among SLE patients, delineated the clinical profiles associated with PH, provided an outlook on the survival of SLE-PH patients, with an endeavor to look for factors that may aid early identification and prompt treatment of PH in SLE. This study showed that anti-RNP was positively associated with PH; malar rash was negatively associated. We suggest a lower thresh-

old for screening or even routine screening of PH in patients with anti-RNP positivity and negative malar rash.

Future perspective

With advancement of diagnostic modalities like more sophisticated echocardiogram, it is likely that PH can be detected earlier in future. Historically, CTD-associated PH had poor prognosis, but since the innovation of newer treatment including newer immunosuppressants and PH-specific drugs like endothelin receptor blockers, phosphodiesterase 5 inhibitors and guanylate cyclase stimulant; the initially gloomy future of these patients is more lucid. Therefore, further study about screening for PH and identification of PH-associated factors is worthwhile to capture lupus patients with PH in their early disease phase.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Background

- Pulmonary hypertension (PH) is associated with connective tissue diseases. PH in systemic lupus erythematosus (SLE) was under-recognized, especially when compared with systemic sclerosis.
- PH in SLE is a more treatable subset. With new therapies, early detection and treatment may further improve the outcome of SLE-PH.
- This cross-sectional case–control study was conducted to delineate the clinical profiles associated with SLE-PH, to look for factors that may aid early identification; and to assess survival.

Patients & methods

- We reviewed a cohort of 266 SLE patients who fulfilled revised American College of Rheumatology classification criteria and had echocardiogram or cardiac catheterization performed.
- PH was diagnosed by echocardiogram or cardiac catheterization. Controls were randomly selected from SLE patients with no PH, matching for age and gender.
- Echocardiographic criteria to detect PH were according to the ESC guidelines.
- Clinical, laboratory and serologic profiles were analyzed and compared between PH and control groups.

Results &conclusion

- Thirty nine PH patients were identified among 266 SLE patients.
- The mean disease duration of SLE upon PH diagnosis was 7.5 ± 8.3 years.
- With treatment, the 3-year survival of SLE-PH patients was 87.2%.
- Anti-RNP-positive lupus patients without malar rash have higher risk of developing PH. Screening echocardiogram may be performed early in the disease course in this subset of SLE patients to allow early recognition and specific treatment.

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