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ORIGINAL ARTICLE

Clinical Features and Risk Factors of Pulmonary Hypertension in Chinese Patients With Systemic Lupus Erythematosus

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ABSTRACT

Objectives: This study aims to evaluate the systemic lupus erythematosus (SLE) frequency, clinical characteristics, and laboratory features of pulmonary hypertension (PH) in a Chinese population with SLE and to evaluate the risk factors contributing in early diagnosis.

Patients and methods: A total of 39 patients (2 males, 37 females; mean age 38.2±14.9 years; range, 16 to 71 years) with combined SLE and PH and 407 patients (43 males, 364 females; mean age 34.8±14.0 years; range, 7 to 73 years) with SLE but without PH (NonPH) were enrolled and categorized into two groups, namely, PH and NonPH groups. The demographic and clinical characteristics of all patients, including disease duration, comorbidity, malar rash, epilepsy, arthritis, oral ulcer, photosensitivity, Raynaud's phenomenon, serositis, dyspnea, and visceral damage, were recorded. Laboratory parameters, including blood and urine routine, biochemical markers, 24-hour proteinuria, plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), immunoglobulin, complement 3 and 4, and autoantibodies, were tested. Inflammatory indexes, such as erythrocyte sedimentation rate and C-reactive protein level, were collected. Disease activity was assessed with systemic lupus erythematosus disease activity index score. Organ damage was assessed with the use of Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SLICC/ACR-DI; SDI). Pulmonary arterial systolic pressure was measured using echocardiography.

Results: Pulmonary hypertension frequency in our Chinese population with SLE was 8.74%. Statistical differences in neuropsychological symptoms, epilepsy, serositis, Raynaud's phenomenon, tachypnea, albumin, creatinine, abnormal electrocardiograph, urine protein, urine red blood cell rate, NT-proBNP, body mass index, SDI and duration of SLE were found between SLE patients with or without PH. Multivariate logistic regression revealed that Raynaud's phenomenon, serositis, tachypnea, epilepsy, and positive anti-U1 small nuclear ribonucleoprotein (U1RNP) were significant risk factors for PH in SLE.

Conclusion: Chinese patients with SLE are at high risk for PH if they present with epilepsy, Raynaud's phenomenon, serositis, tachypnea, and positive anti-U1RNP. Echocardiography is highly recommended to be performed on Chinese patients with SLE for the screening of PH.

Keywords: Hypertension; lupus erythematosus; pulmonary; risk factors; systemic.

Pulmonary hypertension (PH) is a serious condition that may ultimately lead to death if left untreated. In 2013, PH was classified into five groups at the Fifth World Symposium on PH held in Nice, France.[1] Connective tissue disease-associated pulmonary arterial hypertension (CTD-APAH) belongs to group 1. Given the epidemiological difference in connective tissue diseases (CTDs) between China and Western countries, systemic lupus erythematosus (SLE) acquires the largest portion of CTD-APAH in China, whereas systemic sclerosis constitutes the major portion of CTD-APAH in Western countries.[2,3] PH is a serious complication of SLE; however, this condition is rarely reported. Although the prevalence of PH in SLE was estimated to be different worldwide because of the lack of a uniform PH definition or different diagnostic approaches,[4] patients with combined SLE and PH exhibit lower one-year

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survival rate and quality of life than those of idiopathic patients,[5] particularly for Chinese people with increased prevalence rate. Early diagnosis and treatment are necessary to improve abnormal pulmonary and cardiac functions[6] and even decrease morbidity and mortality of patients with SLE and PH.[7] Factors involved in the pathogenesis of SLE-associated PH are genetic predisposition, environmental stimuli, and immune system dysfunction,[4] which make prognosis during progression possible.

Right heart catheterization (RHC) is the gold standard for the diagnosis of PH, but adverse events may exist after catheterization.[8] Hence, as a kind of noninvasive procedure, echocardiography is of considerable value for PH in clinical practice. Echocardiography provides an estimate of right ventricular function and pulmonary artery pressure and is useful in ruling out secondary causes of PH, such as left heart disease and congenital heart disease.[9] Pulmonary arterial systolic pressure (PASP) values of ≥40 mmHg by echocardiogram were recommended for screening patients with SLE, who have suspected PH.[10]

In this study, we aimed to evaluate the SLE frequency, clinical characteristics, and laboratory features of PH in a Chinese population with SLE and to evaluate the risk factors contributing in early diagnosis.

PATIENTS AND METHODS

Medical records of 446 patients (46 males, 400 females; mean age 35.1±14.1 years; range, 7 to 73 years) with SLE were collected in the Department of Rheumatology, Fujian Medical University Union Hospital between January 2013 and March 2017 according to Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria.[11] Among them, 39 patients (2 males, 37 females; mean age 38.2±14.9 years; range, 16 to 71 years) passed the SLICC 2012 classification criteria of SLE and the PH criteria previously described and were recruited as test subjects (PH group), while the remaining 407 patients (43 males, 364 females; mean age 34.8±14.0 years; range, 7 to 73 years) were recruited as controls (NonPH group). The PH group consisted of patients with PASP of ≥40 mmHg by echocardiography,[10,12] while the NonPH group consisted of patients with PASP of <40 mmHg. Patients with SLE were excluded if they suffered from diseases that could affect pulmonary artery pressure, including overlapping syndrome, interstitial lung disease, chronic thromboembolic PH, congenital heart diseases, significant valvular disease, chronic obstructive pulmonary disease, and pregnancy. The study protocol was approved by the Fujian Medical University Union Hospital Ethics Committee (No.2018KY015). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

We recorded the demographic and clinical characteristics of all patients, including disease duration, comorbidity, malar rash, epilepsy, arthritis, oral ulcer, photosensitivity, Raynaud's phenomenon, serositis, dyspnea, and visceral damage. We also tested laboratory parameters, such as blood and urine routine, biochemical markers, 24-hour proteinuria, plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), immunoglobulin, complement 3 and 4, and autoantibodies (such as anti-double-stranded deoxyribonucleic acid, anti-Sjögren's syndrome type A (anti-SSA), anti-Sjögren's syndrome type B (anti-SSB), anti-Sm, anti-U1 small nuclear ribonucleoprotein (U1RNP), anti-cardiolipin antibodies, and β2-glycoprotein I). Inflammatory indices, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, were also obtained. Disease activity was assessed using systemic lupus erythematosus disease activity index (SLEDAI) score,[13] and organ damage was evaluated with Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SLICC/ACR-DI; SDI).[14] All laboratory data were measured in the Department of Laboratory Medicine, Fujian Medical University Union Hospital. PASP was measured by specialized echocardiographers in the Department of Cardiology of the same hospital using GE Vivid E9 Ultrasound System (General Electric Company, Horten, Norway). Confirmation of PASP by a designated echocardiographer was required if the initial PASP was ≥40 mmHg.

Statistical analysis

Data distribution was tested by Shapiro-Wilk method. Results were reported as mean ± standard deviation or number (percentage). Non-normally distributed data or ranked data were compared between groups using the Mann-Whitney U test. Categorical data were compared with Chi-square test or Fisher's exact test. Multivariate logistic regression was adopted to report the correlation between the variables and PH in all patients with SLE. Data analysis was performed using PASW version 17.0 for Windows (SPSS Inc., Chicago. IL. USA). A difference was considered significant if the two-side *p* value was less than 0.05.

RESULTS

In terms of demographic data (age, sex), no significant difference was found between the two groups except body mass index (BMI). The PH group showed significantly increased frequencies of neuropsychological symptom, epilepsy, serositis, Raynaud's phenomenon, BMI, and tachypnea, as well as extended illness duration and increased SDI in clinical features (Table 1). In particular, more patients from the PH group manifested abnormal electrocardiography (Table 2). In the laboratory test, the PH group exhibited decreased albumin level and increased creatinine level, positive proteinuria rate, positive urine red blood cell rate, and NT-proBNP ratio.

Table 1. Demographic and clinical characteristics in systemic lupus erythematosus with or without pulmonary hypertension

Characteristics	SLE-PH (n=39)			SLE-NonPH (n=407)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			38.2±14.0			34.8±14.0	0.234
Gender Female	37	94.9		363	89.2		0.401
Body mass index (kg/m^2)			23.5±4.3			21.5±3.4	0.043
Systemic lupus erythematosus duration (year)			5.7±7.0			3.5±5.0	0.042
Pulmonary arterial systolic pressure (mmHg)			54.2±18.2			27.5±5.8	<0.001
Malar rash	17	43.6		170	42.0		0.845
Epilepsy	3	7.9		7	1.7		0.046
Fever	13	33.3		136	33.6		0.975
Arthritis	19	48.7		221	54.4		0.494
Photosensitivity	4	10.3		55	13.6		0.559
Serositis	26	66.7		121	29.9		<0.001
Psychiatricsymptoms	5	12.8		12	3.0		0.009
Myalgia/myasthenia	1	2.6		6	1.5		0.477
Xerostomia/xeroma	3	7.7		30	7.5		1.000
Oral ulcer	6	15.4		44	10.9		0.561
Raynaud's phenomenon	12	30.8		38	9.4		<0.001
Alopecia	6	15.8		49	12.3		0.722
Fingertip vasculitis	2	5.1		14	3.5		0.932
Peripheral neuritis	1	2.6		4	1		0.371
Erythra	15	38.5		125	30.9		0.329
Tachypnea	19	52.8		52	13.2		<0.001
Livedo reticularis	0	0		3	0.7		-
SLEDAI			10.9±7.1			7.8±5.3	0.050
SDI			2.5±1.9			0.6±0.8	<0.001

SLE: Systemic lupus erythematosus; PH: Pulmonary hypertension; SD: Standard deviation; SLEDAI: Systemic lupus erythematosus disease activity index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Table 2. Laboratory findings in systemic lupus erythematosus with or without pulmonary hypertension

Characteristics	SLE-PH (n=39)			SLE-NonPH (n=407)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Anti-dsDNA Ab			35.3±36.6			30.6±35.2	0.729
ANCA	1	4.2		7	2.5		0.491
RF	9	50.0		86	35.7		0.224
ANA	33	100		364	99.2		-
Spot nucleus	22	66.7		229	64.9		0.836
Anti-U1RNP Ab	21	63.6		174	47.8		0.081
Anti-SM Ab	13	39.4		123	33.6		0.502
Anti-SSA Ab	18	54.5		251	68.2		0.110
Anti-SSB Ab	8	24.2		92	25.1		0.910
Anti-SCL-70 Ab	0	0		4	1.4		-
Anti-PM-SCL Ab	2	6.1		12	3.3		1.000
Anti-JO-1 Ab	0			0			-
Anti-Centromere Ab	1	3.0		11	3.1		1.000
Anti-Proliferation Ab	0			9	2.5		-
Anti-Nucleosomes Ab	20	60.6		185	50.5		0.268
Anti-Histone Ab	16	48.5		141	39.0		0.278
Anti-rRNP Ab	14	42.4		146	39.9		0.776
Anti-Mitochondrial Ab	3	9.4		58	15.9		0.970
Anti-Cardiolipin IgM Ab	1	3.4		21	6.7		0.778
Anti-Cardiolipin IgG Ab	5	17.9		67	21.4		0.659
Anti-β2-GP1 Ab	3	10.7		54	17.7		0.498
Abnormal ECG	25	75.8		216	57.6		0.042
Leukopenia	13	36.1		151	37.8		0.846
Anemia	26	72.2		247	61.9		0.220
Thrombocytopenia	10	27.8		102	25.6		0.778
Urine protein	35	92.1		259	66.7		0.001
Urine RBC	23	60.5		149	39.5		0.009
ALB (g/L)			26.0±6.9			30.9±7.6	<0.001
GLB (g/L)			33.3±10.5			34.9±8.8	0.145
CRE (umol/L)			166.1±219.7			69.6±74.6	<0.001
LDH (IU/L)			307.7±256.5			265.1±186.4	0.116
IgG (g/L)			15.5±8.5			17.2±7.9	0.051
IgM (g/L)			1.1±0.7			1.3±1.0	0.064
IgA (g/L)			2.5±1.3			2.8±1.4	0.241
C3 (g/L)			0.5±0.3			0.5±0.3	0.953
C4 (g/L)			0.1±0.1			0.1±0.1	0.136
ESR (mm/h)			54.9±35.4			50.5±39.9	0.266
CRP	14	54.8		98	28.7		0.055
NT-proBNP	15	93.8		21	53.8		0.005

SLE: Systemic lupus erythematosus; PH: Pulmonary hypertension; SD: Standard deviation; Anti-dsDNA: Anti-double-stranded deoxyribonucleic acid; Ab: Antibody; ANCA: Antineutrophil cytoplasmic antibodies; RF: Rheumatoid factor; ANA: Antinuclear antibody; Anti-U1RNP: Anti-U1 small nuclear ribonucleoprotein; Anti-SM: Anti-Smith; Anti-SSA: anti-Sjögren's syndrome type A; Anti-SSB: Anti-Sjögren's syndrome type B; Anti-SCL-70: Anti-topoisomerase; Anti-PM-SCL: Anti- polymyositis-sclerosis; Anti-JO-1: Anti-histidyl-tRNA synthetase; Anti-rRNP: Anti- ribosomal ribonucleoprotein; Anti-β2-GP1: Anti-β2-glycoprotein I; ECG: Echocardiography; RBC: Red blood cell; ALB: Albumin; GLB: Globulin; CRE: Creatinine; LDH: Lactate dehydrogenase; Ig: Immunoglobulin; C: Complement: ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Table 3. Significant factors for pulmonary hypertension in systemic lupus erythematosus observed in multivariate logistic regression

Variables	Odds ratio	95% CI	*p*
Raynaud's phenomenon	39.208	6.143-250.244	<0.001
Serositis	10.144	1.771-58.108	0.009
Tachypnea	12.539	2.996-53.019	0.001
Epilepsy	21.353	1.725-264.342	0.017
Anti-U1RNP	6.117	1.390-26.921	0.017

CI: Confidence interval; U1RNP: Nuclear ribonucleoprotein.

No significant difference was found in items related to anti-double-stranded deoxyribonucleic acid antibody, ESR, CRP, immunoglobulin M, immunoglobulin G, complement 3, hemogram test, anti-U1RNP antibody, anti-SM antibody, anti-SSA antibody, anti-SSB antibody, antineutrophil cytoplasmic antibodies, or SLEDAI (Table 2).

Multivariate logistic regression method was used to determine the correlation between SLE-associated PH and the factors, such as serositis, Raynaud's phenomenon, tachypnea, anti-U1RNP, duration of SLE, and epilepsy. Among the above factors, Raynaud's phenomenon, serositis, tachypnea, epilepsy, and positive anti-U1RNP were significantly associated with the occurrence of PH in SLE (Table 3).

DISCUSSION

Pulmonary hypertension prevalence in SLE varied widely between 0.5% and 17.5%.[4] In 2014, PH prevalence in Chinese patients with SLE was 3.8% according to the Chinese SLE Treatment and Research (CSTAR) group registry.[15] The accuracy limitation of echocardiography and small sampling size may be responsible for the increased frequency in this study.[16,17] SLE-associated PH belongs to the CTD-APAH category,[1,18] because SLE is a common underlying CTD with PH complication as the Registry to Evaluate Early and Long-term (REVEAL) Pulmonary Arterial Hypertension Disease Management had reported.[19] Patients with SLE were extremely young at the time of PH diagnosis.[2] Therefore, an in-depth investigation of the features of SLE-associated PH is extremely important.

Consistent with findings in previous reports, increased positive percentages of serositis and Raynaud's phenomenon concurrent with extended illness duration and increased SDI score in PH group were observed in our study.[20,21] Multiple organs were injured during the course of SLE progression. Thus, increased pulmonary vascular resistance (PVR) plays an important role in PH development.[22] Numerous factors, such as extensive endothelial, adventitial, and smooth muscle dysfunction, vasodilator and vasoconstrictor imbalance, inflammatory and uncontrolled immune response, and an imbalance between proliferation and apoptosis, are involved to result in the increased PVR in patients with SLE.[23,24] Increased pulmonary capillary resistance and hypoxia causes PVR increase when the lung is injured. Pulmonary arterial vasoconstriction, which is caused by general vascular disorder, occurs when extensive connective tissues are invaded in patients with SLE. Raynaud's phenomenon and increased anti-U1RNP and anti-SSA levels are clearly observed.[4,20,25] However, anti-SSA levels showed no significant difference between PH and NonPH groups possibly because of sampling error and small sample size.

Owing to autoimmunity, renal function is impaired when kidneys are involved in SLE.[26] As a common comorbidity and independent risk factor for poor outcome in SLE, the damage is intensified by PH.[27] Impaired renal function and increased NT-proBNP are indicative that the right heart function is affected. Certain researchers believed that deterioration of these factors is related to the progression of cardiopulmonary involvement resulting from PH.[28,29] Increased PVR aggravated cardiac preload in PH and electrical activity of the heart consequently changed.[30] Data

from this study also confirmed that the injury to kidneys and heart is more serious in the PH group compared with the NonPH group.

Several researchers presented that disease duration, Raynaud's phenomenon, pleuritis, positive anti-U1RNP antibody, positive anti-SSA antibody, and positive anti-cardiolipin antibodies are independent predictors of PH in SLE.[15,21] We found that tachypnea, which has been rarely investigated, is an important marker relevant to PH in SLE. Dyspnea is one of the cardinal clinical manifestations of PH. No difference in dyspnea percentage was observed between idiopathic PAH and SLE-APAH.[30] Considering the exclusion of the lung and heart diseases affecting pulmonary artery pressure in our study, tachypnea was considered as an excellent indicator of SLE-associated PH that consumes short time and is assessed and observed easily in the early phase.

Although PH is a major cause of mortality in SLE, more than 40% of patients with SLE combined with early PH were asymptomatic or slightly symptomatic; thus, PH is frequently neglected.[1,25] The gold standard for PH diagnosis is mean pulmonary artery pressure at rest ≥25 mmHg by RHC. However, RHC is not commonly practiced in the rheumatology departments of numerous Chinese hospitals because of its high cost, lack of medical equipment, poor awareness of PH, and fear of severe complications or discomfort from the invasive procedure. Hence, no RHC data were collected in this retrospective study. However, as a non-invasive procedure, regular echocardiography provides information on not only the estimation of pulmonary hemodynamics but also the function of the right atrium.[31,32] Echocardiography can be used in preliminary screening,[10] and patients with SLE and with PASP ≥40 mmHg should undergo RHC for proper diagnosis. The combination of six-minute walk test, NT-proBNP, clinical findings, and monitoring of pulmonary pressure can aid in the early diagnosis and monitoring of treatment response to treatment.[33]

Patients with SLE benefit considerably if the SLE-associated PH markers are determined effectively. Immune inflammatory factors are involved in the pathogenesis of combined SLE and PH in addition to vascular medial smooth muscle hypertrophy, intimal proliferation and fibrosis, and adventitial thickening.[21,34] Inflammation plays an important role in the pathogenesis of PH in patients with SLE. The use of immunosuppressants, including intravenous cyclophosphamide and glucocorticoids, can achieve improved outcomes for SLE-PH patients.[35]

Immunosuppression and vasodilators produce significant improvement in SLE-APAH within a six-month period.[36] Prompt treatment of PAH with newer PAH therapy as well as immunosuppression can reduce morbidity and prolong survival.[34] Therefore, PAH-targeted treatment, such as prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, and immunosuppressive therapies should be considered.

The limitation of this retrospective study was that there was no RHC data. Hence, patients with SLE along with suspected PAH screened by echocardiography needs to be undergo RHC.

In conclusion, in this study, we investigated the frequency and risk factors of SLE-associated PH in Chinese population to obtain the convenient and simple test items, which can provide evidence for early diagnosis. Patients with SLE who manifest tachypnea, Raynaud's phenomenon, serositis, epilepsy and positive anti-U1RNP are at high risk of PH complication. These patients should be given regular examination through echocardiography in addition to monitoring of lupus disease activity, especially for SLE survivors with high SDI score, to decrease the probability of developing cardiovascular diseases, including PH, and improve survival rate and quality of life.

Declaration of conflicting interests

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