Risk factors of pulmonary arterial hypertension in patients with systemic lupus erythematosus

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Research

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Abstract

Introduction

: Pulmonary arterial hypertension (PAH) symptoms in systemic lupus erythematosus (SLE) patients are non-specific and early diagnosis and intervention are challenging. It remains essential to explore risk factors for PAH in SLE patients to identify high risk patients and allow intensive monitoring.

Methods

From January 2010 to December 2018, 84 patients with SLE and PAH and 160 patients with SLE but without PAH were enrolled. Clinical manifestations and laboratory test results were compared between the two groups to identify predictors of PAH. Candidate PAH risk factors were further compared among SLE-PAH patients with different characteristics.

Results

Among collected patient characteristics, Raynaud's phenomenon (OR 2.32, 95% CI: 1.17–4.61), digital vasculitis (OR 4.12, 95% CI: 1.48–11.49), pericardial effusion, pulmonary interstitial lesions, positive anti-U1RNP antibodies, and positive ACA-IgG were associated with significantly higher risk of PAH in SLE patients. Among these candidate risk factors, positive anti-U1RNP antibody was independently associated with severe PAH and more active disease. Digital vasculitis was independently associated with SLE alleviation, while pericardial effusion was associated with SLE deterioration. Pericardial effusion was associated with longer PAH duration.

Discussion

The significant association between studied clinical and laboratory indicators and risk of PAH, PAH and SLE characteristics suggested that these factors can be used to identify patients at higher risk of PAH and adverse outcomes. Close monitoring may be indicated in patients with these risk factors, especially with more than one risk factor.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex chronic autoimmune disease involving multi-system, a wide spectrum of manifestations, and overabundance of immunological and laboratory abnormalities [1]. Among all the complications, pulmonary arterial hypertension (PAH) is a major contributor of SLE related death [2, 3]. PAH is characterized by vascular proliferation and remodeling [4, 5], which results in progressively increase pulmonary vascular resistance and right ventricular failure and death [6]. The prevalence of PAH in SLE is estimated to be 0.5–17.5% [7]. The prevalence of SLE-related PAH in Chinese

population is around 3.8%, which is the third leading cause of death in patients with SLE after mental lupus and lupus nephritis [8].

Most of the early symptoms of PAH, such as dyspnea and fatigue, can be mild and non-specific. Symptoms of PAH in lupus can also be caused by other conditions such as interstitial lung disease, all make early diagnosis challenging. Recent novel therapies, especially therapies that targets abnormalities in prostacyclin, endothelin, and nitric oxides pathways have been shown to improve patients' functional status, pulmonary hemodynamics, and a potential to slow disease progression [9]. However, prevention PAH progression is extremely challenged and rarely achieved, especially for patients with connective tissue disease-related PAH [10]. For SLE-associated PAH, immunosuppressive treatment may benefit patients with relatively mild disease at baseline, but limited benefit for patients with severe PAH [11–13]. Early diagnosis and intervention are essential to improve patient outcomes.

Some clinical manifestations and immunologic test have been shown to predict PAH in SLE patients [14, 15]. However, PAH is a complex condition, risk factors may have different association for certain disease characteristics. In the current study, we aimed to identify early clinical and laboratory predictor for SLE associated PAH and other SLE characteristics to help early diagnosis and identify higher risk population and allow for more intensive monitoring and intervention if necessary.

2. Methods

2.1 Participants

Patients diagnosed with SLE in the Department of Rheumatology and Immunology of Guangdong General Hospital and Guangdong Academy of Medical Sciences from January 2010 to December 2018 were eligible for the study. A total of 84 patients who were diagnosed with SLE and PAH were included as the case group, and 160 patients who were diagnosed with SLE but did not have PAH were included as the control group. The study was approved by the Guangdong General Hospital and Guangdong Academy of Medical Sciences. Informed consent was obtained.

2.2 Diagnosis

Diagnosis of SLE was made in accordance with the SLE classification established by the American College of Rheumatology (ACR) in 1997 ¹⁶. PAH was diagnosed by pulmonary artery systolic pressure (PASP) ≥ 30 mmHg using the color Doppler echocardiography [17]. Patients with PAH caused by lung diseases, cardiomyopathy, structural heart disease, myocardial infarction, or other diseases were excluded. PAH severity was classified as mild: PASP 30–40 mmHg; moderate: PASP 41–70 mmHg; and severe: PASP > 71 mmHg. Mild and moderate PAH were grouped into mild to moderate PAH group. Disease activity was classified according to the SLE disease activity index (SLEDAI) [18], with SLEDAI ≥ 8 defined as disease being active.

2.3 Variables of interest

Clinical manifestations and laboratory test results at enrollment were collected and analyzed. Clinical manifestations, including lupus nephritis, skin and mucosa manifestations, Raynaud's phenomenon, pericardial effusion, serositis, digital vasculitis, arthritis, mental symptoms, and pulmonary interstitial lesions were included. Laboratory test including erythrocyte sedimentation rate (ESR), platelet count, C-reactive protein (CRP) level, complement 3 (C3), serum creatinine, urine protein, anti-double stranded DNA (anti-dsDNA) antibodies, antinuclear antibody (anti-ANA), anticardiolipin antibodies immunoglobulin G (ACA-IgG), ACA immunoglobulin M (ACA-IgM), anti-u1 ribonucleoprotein (anti-U1RNP) antibodies, anti-Sjögren's-syndrome-related antigen A (anti-SSA) antibodies, and anti-Sjögren's-syndrome-related antigen B (anti-SSB) antibodies. Indicators were compared between the case group and the control group using bivariate logistic regression. Indicators that were statistically significant were labeled as candidate SLE-PAH risk factors. Among the 84 cases with SLE-PAH, patients were grouped according to PAH severity (mild to moderate versus severe), SLE disease activity (SLEDAI < 8 points versus SLEDAI $\geq$ 8 points), treatment status (remission, stable, and deterioration), and duration of PAH (< 1 year and $\geq$ 1 year). Remission was defined as remaining in low risk status in accordance to the 2015 European pulmonary hypertension guidelines [19]. Stable was defined as the same risk status for 6 months (excluding high risk status). Deterioration was defined as moving from lower risk status to higher risk status (low risk status to intermediate/high risk status, intermediate risk status to high risk status, or high risk status with worsening indicators).

2.4 Statistical analysis

Data were analyzed using SPSS version 19.0 statistical software (SPSS Inc, Chicago, Illinois). Continuous variables were expressed as mean (standard deviation, SD) if following normal distribution, and median (interquartile range, IQR) if not. Categorical variables were expressed as count (percentage). Between groups comparison was performed using student t-test for continuous variables and chi-square test for categorical variables. Logistic regression was used for risk factor analysis. Associations between candidate SLE-PAH risk factors and different classification group were compared using logistic regression to identify risk factors for different PAH prognostic outcomes. $P < 0.05$ indicated that the difference is statistically significant.

3. Results

A total of 84 patients with SLE and PAH and 160 patients with SLE but without PAH were included. On average, cases were 36.2 (10.7) years old (range, 22–53) and 89.3% were female. In the control group, the mean (SD) age was 34.8 (11.5) years old (range, 24–55) and 88.1% were female. No statistically significant difference in age and sex were observed in the two groups ($p > 0.05$ for both).

3.1 Comparison of clinical manifestations between case group and control group

Compared to SLE patients without PAH, higher proportion of patients with PAH were presented with Raynaud's phenomenon (42.9% vs 25.6%, Table 1), pericardial effusion (60.7% vs 25.0%), digital vasculitis (26.2% vs 15.0%), and pulmonary interstitial lesions (21.4% vs 7.5%). No statistically significant differences were observed in lupus nephritis, skin and mucosa manifestations, serositis, arthritis, or mental symptoms ($p > 0.05$ for all).

Table 1
Clinical manifestations in the case group and the control group.

	Cases (n = 84)	Controls(n = 160)	<i>P value</i>
Lupus nephritis	41(48.8%)	74(46.3%)	0.704
Skin and mucosa manifestations	33(39.3%)	65(40.6%)	0.839
Raynaud's phenomenon	36(42.9%)	41(25.6%)	0.006
Pericardial effusion	51(60.7%)	40(25.0%)	< 0.001
Serositis	27(32.1%)	35(21.9%)	0.080
Digital vasculitis	22(26.2%)	24(15.0%)	0.034
Arthritis	45(53.6%)	87(54.4%)	0.905
Mental symptoms	5(6.0%)	10(6.3%)	0.927
Pulmonary interstitial lesions	18(21.4%)	12(7.5%)	0.002

3.2 Comparison of laboratory results between case group and control group

Compared to SLE patients without PAH, higher proportion of patients with PAH had ACA-IgG (40.5% vs 23.8%, Table 2) and anti-U1RNP antibodies (53.6% vs 17.5%). No statistically significant differences were observed in anti-dsDNA antibodies, anti-ANA, ACA-IgM, Anti-Sm, Anti-SSA, or Anti-SSB ($p > 0.05$ for all). No significant in other laboratory results demonstrated in Table 2 were observed between the two groups.

Table 2
Laboratory results in the case group and the control group.

	Cases (n = 84)	Controls(n = 160)	<i>P value</i>
Anti dsDNA antibodies(+)	30(35.7%)	65(40.6%)	0.455
Anti-ANA(+)	79(94.0%)	146(91.3%)	0.438
ACA-IgG(+)	34(40.5%)	38(23.8%)	0.006
ACA-IgM(+)	32(38.1%)	50(31.3%)	0.282
Anti- U1RNP(+)	45(53.6%)	28(17.5%)	< 0.001
Anti-Sm(+)	20(23.8%)	51(31.9%)	0.188
Anti-SSA(+)	50(59.5%)	91(56.9%)	0.691
Anti-SSB(+)	9(10.7%)	23(14.4%)	0.421
Elevated ESA	51(60.7%)	93(58.1%)	0.696
Elevated CRP	28(33.3%)	50(31.3%)	0.740
Decreased C3	53(63.1%)	104(65.0%)	0.768
Decreased platelets	26(31.0%)	36(22.5%)	0.150
Elevated serum creatinine	8(9.5%)	14(8.8%)	0.841
Elevated urine protein	48(57.1%)	99(61.9%)	0.473

3.3 Associations between candidate risk factors and PAH in SLE patients

Among collected patient characteristics, Raynaud's phenomenon, digital vasculitis, pericardial effusion, pulmonary interstitial lesions, positive anti-U1RNP antibodies, and positive ACA-IgG were associated with significantly higher risk of PAH in SLE patients (Table 3). Among them, digital vasculitis had the stronger association with PAH in SLE patients (OR 4.12, 95% CI: 1.48–11.49), followed by pulmonary interstitial lesions (OR 3.10, 95% CI: 1.55–6.21).

Table 3
Association between candidate risk factors and PAH in SLE patients.

	<i>P</i> value	<i>OR</i>	95% Confidence interval (<i>CI</i>)
Raynaud's phenomenon	0.016	2.32	1.17–4.62
Digital vasculitis	0.007	4.12	1.48–11.49
Pericardial effusion	0.000	2.79	1.57–4.98
Pulmonary interstitial lesions	0.001	3.10	1.55–6.21
Anti- U1RNP(+)	0.015	1.77	1.12–2.82
ACA-IgG(+)	0.003	1.96	1.25–3.06

3.4 Associations between candidate risk factors and PAH severity

Putting all candidate risk factors in the model, anti-U1RNP antibodies was associated with significantly higher risk of severe PAH (45.9% in mild to moderate PAH vs 73.9% in severe PAH group, Table 4). No significant differences in other candidate risk factors were observed between mild to moderate group and severe group ($p > 0.05$ for all).

Table 4
Association between candidate risk factors and SLE-PAH severity.

	Mild to moderate PAH(n = 61)	Severe PAH(n = 23)	<i>P</i> value
Raynaud's phenomenon	25(41.0%)	11(47.8%)	0.572
Digital vasculitis	15(24.6%)	7(30.4%)	0.587
Pericardial effusion	36(59.0%)	15(65.2%)	0.604
Pulmonary interstitial lesions	12(19.7%)	5(21.7%)	0.925
Anti- U1RNP(+)	28(45.9%)	17(73.9%)	0.022
ACA-IgG(+)	29(47.5%)	9(39.1%)	0.490

3.5 Associations between candidate risk factors and SLE activity

Comparing patients with SLEDAI < 8 versus those with SLEDAI $\geq$ 8, patients with higher SLE activity were more likely to have digital vasculitis (5.0% vs 32.8%, Table 5). Interestingly, patients with higher SLE activity were less likely to have anti-U1RNP antibodies (75.0% vs 46.9%). No significant differences were observed in other candidate risk factors.

Table 5
Association between candidate risk factors and SLE activity.

	SLEDAI < 8(n = 20)	SLEDAI ≥ 8(n = 64)	P value
Raynaud's phenomenon	9(45.0%)	27(42.2%)	0.824
Digital vasculitis	1(5.0%)	21(32.8%)	0.014
Pericardial effusion	13(65.0%)	38(59.4%)	0.653
Pulmonary interstitial lesions	5(25.0%)	12(18.8%)	0.773
Anti- U1RNP(+)	15(75.0%)	30(46.9%)	0.028
ACA-IgG(+)	9(45.0%)	29(45.3%)	0.980

3.6 Associations between candidate risk factors and treatment status

Among the 84 cases enrolled, 33 (39.3%) were at remission, 40 (47.6%) were at stable, and 11 (13.1%) were at deterioration. Checking the distribution of candidate risk factors across groups, digital vasculitis was most prevalent in remission group (42.4%), followed by stable group (17.5%) and deterioration group (9.1%, $p = 0.021$, Table 6). On contrary, pericardial effusion was most commonly observed in deterioration group (90.9%), while least common in the remission group (39.4%, $p = 0.003$). No significant differences were observed in other characteristics.

Table 6
Association between candidate risk factors and SLE treatment status.

	Remission(n = 33)	Stable(n = 40)	Deterioration (n = 11)	P value
Raynaud's phenomenon	13(39.4%)	18(45.0%)	5(45.5%)	0.875
Digital vasculitis	14(42.4%)	7(17.5%)	1(9.1%)	0.021
Pericardial effusion	13(39.4%)	28(70.0%)	10(90.9%)	0.003
Pulmonary interstitial lesions	6(18.2%)	8(20.0%)	3(27.3%)	0.809
Anti- U1RNP(+)	17(51.5%)	22(55.0%)	6(54.5%)	0.955
ACA-IgG(+)	15(45.5%)	17(42.5%)	6(54.5%)	0.776

3.7 Associations between candidate risk factors and PAH duration

Forty-one (48.8%) patients had PAH duration longer than 1 year. Compared to patients with PAH less than 1 year, these patients were more likely to have pericardial effusion (75.6% vs 46.5%, Table 7). No

significant differences were observed in other characteristics.

Table 7
Association between candidate risk factors and PAH duration.

	PAH < 1year(n = 43)	PAH ≥ 1 year (n = 41)	P value
Raynaud's phenomenon	19(44.2%)	17(41.5%)	0.801
Digital vasculitis	12(27.9%)	10(24.4%)	0.714
Pericardial effusion	20(46.5%)	31(75.6%)	0.006
Pulmonary interstitial lesions	8(18.6%)	9(22.0%)	0.703
Anti- U1RNP(+)	22(51.2%)	23(56.1%)	0.650
ACA-IgG(+)	22(51.2%)	16(39.0%)	0.264

4. Discussion

We found that clinical manifestations including Raynaud's phenomenon, digital vasculitis, pericardial effusion, and pulmonary interstitial lesions, and immunologic abnormalities including anti-U1RNP positive and ACA-IgG positive were predictors for SLE associated PAH. Among the risk factors, positive anti-U1RNP was independently associated with severe PAH and more active disease. Digital vasculitis was independently associated with SLE alleviation, while pericardial effusion was associated with deterioration. Pericardial effusion was associated with longer PAH duration.

Our findings were consistent with previous studies. In a study involving 41 SLE patients with PAH and 106 SLE patients without PAH, serositis, Raynaud's phenomenon, anticardiolipin antibodies, and anti-U1RNP were associated with higher risk of SLE-PAH [15]. In another cross-sectional study, Raynaud's phenomenon was associated with elevated pulmonary artery systolic pressure [20]. Luo et al found that pleural effusions frequently accumulate in patients with PAH associated with CTD [21]. Wang et al observed in a large SLE-PAH cohort that, pericarditis, pleuritis and anti-RNP positivity are associated with higher SLE activity and vasculopathy, suggesting that higher disease activity and vasculopathy may contribute to PAH development in SLE [8]. Study from the same cohort confirmed that long SLE duration and interstitial lung disease et al were associated with higher risk of PAH in SLE patients [2]. In addition, anti-U1RNP and antiphospholipid antibodies were associated with higher risk of PAH [2]. Consistent with our results, anti-U1RNP is associated higher risk of PAH [2, 8, 22]. Antiphospholipid antibodies, including ACA in our work, also is a strong predictor of PAH in SLE patients [2, 23, 24].

Consistently observed in various population and studies, anti-U1RNP antibody was associated with higher disease activity and more severe PAH. Anti-U1RNP antibody is a specific antibody for mixed connective tissue disease but also present in SLE patients [25]. Anti-U1RNP antibody can up-regulate the expression of adhesion molecules (CAM) and major histocompatibility complex II (MHC II) molecules on

pulmonary artery endothelial cells, which play important roles in the development of PAH [26]. In our work, positive anti-U1RNP antibody was associated with more severe PAH, suggesting that vascular lesion involving anti-U1RNP antibody may be involved in PAH development and positive U1RNP antibody indicates worse prognosis among PAH patients. Together with previous studies, our results suggest that among patients with SLE and patients with mild to moderate SLE-PAH, those with anti-U1RNP antibody are at higher risk of developing PAH, especially severe PAH. These patients should be more closely monitored. At the same time, positive anti-U1RNP antibody also is associated with higher disease activity in our study. Annual PAH screening is recommended by some researchers, especially for SLE patients with other risk factors [8].

Thrombosis has been suggested as one mechanism of PAH in patients with connective tissue disease [7]. Studies have found that anti-phospholipid antibodies are associated with PAH in SLE and suggested that thrombosis involves in PAH pathogenesis [8, 14, 23]. Though it is worth noted that some studies found negative results between antiphospholipid antibodies and PAH [27]. In our work, positive ACA- IgG was associated with PAH, but not associated severity of PAH. Thromboembolic disease, pulmonary vasculitis, and hypoxia and fibrosis from interstitial lung disease all have been suggested to involve in PAH in SLE patients [28]. It is possible that antiphospholipid antibodies is only involved in a certain pathways and that explains the heterogeneous associations observed.

Our study has several strengths. First, we have relatively large sample size. Second, we assessed the association between risk factors and different SLE, and SLE-PAH characteristics. As observed, different factors may predict different characteristics, which may be a result of various underlying mechanisms involved. Our study also has several limitations. First of all, our study is a cross-sectional study. It is difficult to interpret some of the observed associations with cross-sectional data. For example, pericardial effusion was more commonly observed in patients with PAH longer than 1 year. However, it is not clear whether patients with pericardial effusion shared certain risk factors with earlier onset of PAH, or the observed association is solely a result of longer SLE duration. Longitudinal data that is able to differentiate the temporal relationship between risk factors and PAH development and progression are needed to elucidate the associations. Second, our results are based on single center data. As a tertiary hospital, it is possible we are seeing patients with more severe SLE and more advanced PAH. Multicenter data involving patients at different stage are needed to test the generalizability of these results.

Conclusions

In summary, we confirmed several risk factors that are associated with PAH in SLE patients, and identified different risk factors for PAH and SLE characteristics. Specifically, Raynaud's phenomenon, digital vasculitis, pericardial effusion, and pulmonary interstitial lesions, and immunologic abnormalities including anti-U1RNP positive and ACA-IgG positive were predictors for SLE associated PAH. Positive anti-U1RNP was independently associated with severe PAH and more active disease. Our study suggested that for patients with above risk factors, more intensive monitoring and interventions if necessary should be given to improve these patients' prognosis.

Declarations

Ethics approval and consent to participate

The study was approved by the Guangdong General Hospital and Guangdong Academy of Medical Sciences. Informed consent was obtained.

Consent for publication:

Not applicable.

Availability of data and material:

Not applicable.

Competing interests:

There are no potential conflicts of interest to disclose.

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None.

Author Contributions

Yunxia Lei is responsible for the guarantor of integrity of the entire study, study concepts, definition of intellectual content, literature research, clinical studies, data analysis, statistical analysis, manuscript review; Xiao Zhang is responsible for the study design; Yuan Feng is responsible for the data acquisition & analysis, statistical analysis, manuscript preparation & editing & review; Jieying Wang is responsible for the experimental studies, data analysis, statistical analysis, manuscript preparation & editing & review; Riqiang Luo is responsible for the literature research, clinical studies.

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