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Pulmonary arterial hypertension in systemic lupus erythematosus: identification of risk factors and haemodynamics characteristics in a multicentre retrospective cohort

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ABSTRACT

Objectives The aim of our work was to identify specific patterns in clinical features and nailfold capillary changes that may help in screening for pulmonary arterial hypertension (PAH) in patients with systemic lupus erythematosus (SLE).

Methods We identified patients with SLE and type I PAH (n=20) without other connective tissue diseases and collected demographic, clinical and laboratory features. We selected as controls patients with SLE who underwent cardiopulmonary screening to exclude PAH (n=87): we collected demographic, clinical and laboratory features and performed nailfold videocapillaroscopy (NVC).

Results All patients with SLE-PAH were women; age and disease duration were not different from patients with SLE without PAH. Lupus anticoagulant (LAC)+and anti-ribonucleoprotein (RNP)+were more prevalent in patients with SLE-PAH (respectively, PAH 45.0% vs no-PAH 20.5%, p=0.042; PAH 45.0% vs no-PAH 19.5%, p=0.035). No differences were observed for anti-Sm, anti-Ro, anti-La and anti-cardiolipin and anti-beta2GPI antibodies. Among clinical features, mucocutaneous and central nervous system involvement were more prevalent in patients with SLE-PAH than in SLE controls (respectively, PAH 65.0% vs no-PAH 34.5%, p=0.024; PAH 25.0% vs no-PAH 8.0%, p=0.046). Raynaud's phenomenon (RP) was more prevalent in patients with SLE-PAH than in SLE controls (PAH 60.0% vs no-PAH 13.8%, p<0.001). RP was a predictor of PAH in patients with SLE (OR 3.8 (0.9–14.8)). We performed NVC on nine patients with PAH and on controls: we observed a significantly higher prevalence of scleroderma pattern at NVC in SLE-PAH than controls (PAH 66.7% vs no-PAH 9.2%, p<0.001). Patients with SLE-PAH showed a lower number of capillary density and a higher frequency of giant capillaries.

Conclusions Our data showed that LAC+, RNP+, RP and a scleroderma pattern at NVC was indicative for patients with SLE-PAH. Our results pointed to generalised microvascular involvement and a hypercoagulation state in patients with SLE-PAH. The variables we identified could be used to implement a screening algorithm to identify patients with SLE at risk of developing PAH.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pulmonary arterial hypertension (PAH) is a rare but severe complication of systemic lupus erythematosus (SLE). No screening algorithms have been validated yet to identify patients at high risk of developing PAH.

WHAT THIS STUDY ADDS

⇒ We identified that the presence of Raynaud's phenomenon can be predictors of PAH in patients with SLE. We also observed an association of lupus anticoagulant (LAC) positivity, anti-ribonucleoprotein (RNP) positivity and a scleroderma pattern at nailfold videocapillaroscopy with PAH in SLE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings underscore the importance of nailfold videocapillaroscopy (NVC) assessment and Raynaud's phenomenon in patients with SLE, potentially identifying a high-risk group for PAH development. While there is no recommendation for PAH screening in patients with SLE due to its low prevalence compared with systemic sclerosis, our study suggests using NVC as a non-invasive and cost-effective screening method for patients with SLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by the production of autoantibodies and multiple organ involvement.[1] Among the different visceral involvements of SLE, pulmonary hypertension (PH) strongly impacts the prognosis of the affected patients.[2] PH is a clinical syndrome defined by haemodynamic criteria.[3] Increased pulmonary vascular resistance of the pulmonary circulation can result from multiple mechanisms in patients with SLE, as, for example, hypoxia due to parenchymal lung disease, pulmonary venous hypertension due to left heart disease, pulmonary thromboembolisms and pulmonary veno-occlusive disease.[4] WHO group I PH, also known as pulmonary arterial hypertension (PAH), is characterised by increased pulmonary resistance without lung parenchyma and left heart involvement and without signs of thromboembolism.[3] PAH has an autoimmune component and is frequently associated with connective tissue diseases, such as SLE and systemic sclerosis (SSc). In the context of SLE, PAH presents unique challenges in terms of diagnosis, management and prognosis. The clinical presentation of PAH in SLE can be non-specific and variable, ranging from mild exertional dyspnoea to severe right heart failure and death.[5] However, these symptoms are often overlooked or attributed to other causes, delaying the diagnosis of PAH and contributing to poor outcomes. The diagnosis of PAH in SLE requires a high index of suspicion and a systematic approach. Initial evaluation typically includes a thorough medical history, physical examination, laboratory tests and non-invasive imaging studies such as echocardiography. The definitive diagnosis of PAH requires performing right heart catheterisation to confirm the presence of elevated pulmonary arterial pressures and to assess the severity of pulmonary vascular resistance.[3] The management of PAH in SLE is challenging and requires a multidisciplinary approach involving rheumatologists, pulmonologists, cardiologists and specialised PAH centres. Treatment strategies aim to control symptoms, delay disease progression and improve survival. Thus, an early diagnosis and prompt initiation of treatment are key to improving long-term outcomes of patients with SLE with PAH. Certain SLE manifestations and immunological abnormalities have been identified as predictors of PAH in observational cohort studies: Raynaud's phenomenon, active renal disease, cutaneous vasculitic manifestations, anti-U1-ribonucleoprotein (RNP) positivity and antiphospholipid antibodies positivity were shown to predict PAH development.[6–8] The development of screening and prognostic algorithm is crucial to identify high-risk patients who should undergo clinical and instrumental screening for PAH[9] (similarly to the DETECT algorithm for SSc[10]), and also for optimised disease monitoring and stratification. We set out to analyse clinical, immunological and capillaroscopy features in patients with SLE-PAH.

METHODS

Patients and study design

We designed a multicentre, cross-sectional, retrospective case–control study involving eight centres across Europe to address the features of patients with SLE with PAH in comparison to those without PAH (figure 1). All enclosed patients

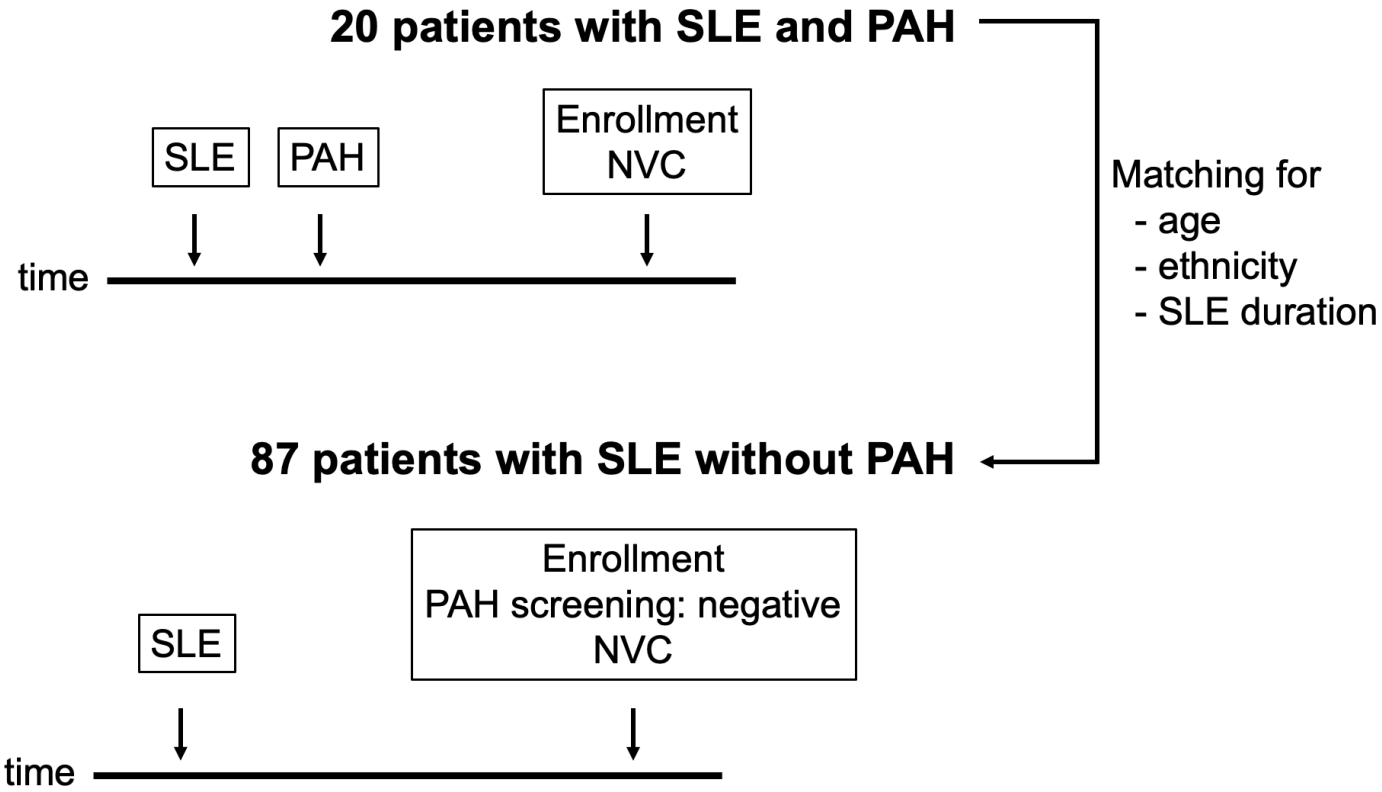

Figure 1 Diagram illustrating the study design. NVC, nailfold videocapillaroscopy; PAH, pulmonary arterial hypertension; SLE, systemic lupus erythematosus.

met the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for SLE.[11] We excluded patients with mixed connective tissue disease (patients did not fulfil Sharp's[12] and Alarcon-Segovia's[13] criteria) or with another connective tissue disease in overlap with SLE, except for Sjogren's syndrome. The diagnosis of PAH in all cases was made after performing right heart catheterisation (RHC) according to the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines.[14] Only patients with SLE with group I PAH were included. We planned to enclose four controls for every case. Cases were identified retrospectively through the revision of clinical records of every centre, whereas controls were enrolled consecutively between 01 January 2019 and 31 December 2022. Controls were enrolled in three participating centres, where physicians expert in PAH were available to participate (online supplemental table 1). To be included as controls, patients with SLE should have a recent (no more than 6 months before the inclusion) cardiopulmonary testing with Doppler echocardiography and pulmonary function tests plus diffusing capacity of the lungs for carbon monoxide (DLCO): patients were enrolled in the study if no signs of suspicion for PAH (ie, increased estimate of pulmonary arterial pressures (PAPs) at Doppler echocardiography or DLCO reduction) were observed.

Demographic and clinical data were retrospectively collected from patients' medical records. The following variables were taken into account: age at disease onset, follow-up length, gender, ACR/EULAR classification criteria for SLE satisfied items at time of enrolment, disease activity measured with Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) at baseline and at time of enrolment, complement levels, autoantibody profile, immunosuppressive therapy at enrolment and use of cyclophosphamide (CYC) in history, pulmonary vasodilator therapy for the SLE-PAH group. Patients were actively questioned about the presence of Raynaud's phenomenon, both currently and in the past. We recorded RHC parameters at diagnosis of PAH and at last cardiologic follow-up. Nailfold videocapillaroscopy (NVC) images were collected in centres with the availability of nailfold capillaroscopy. NVC images for patients with PAH-SLE were obtained 20.3 (IQR 6–146) months after the diagnosis of PAH. NVC images were centrally reviewed by a trained and blinded rheumatologist (VC).

Vasculitic and non-vasculitic PAH

Sun *et al* proposed the differentiation of patients with PAH and LES into two types: vasculitic and non-vasculitic.[15] To further explore the clinical applicability of this classification, we assessed the validity of the Sun score in identifying patients with distinct clinical features within our cohort of patients with SLE-PAH. The score was calculated based on two variables as described by Sun and colleagues: the time interval between diagnosis of SLE and PAH (time interval<2 years and≥2 years between SLE diagnosis and PAH diagnosis assigned, respectively, 1 and 0 point) and SLEDAI-2K at time of PAH diagnosis (an SLEDAI-2K>9, between 5 and 9 and<5 assigned, respectively, 2, 1, 0 point). A weighted score≥2 was proposed to identify patients with vasculitic PAH subtype. All the variables to calculate Sun's score were retrospectively collected at the time of PAH diagnosis.

Nailfold videocapillaroscopy

NVC was performed in five centres using various instruments (Videocap V.3.0 software, DS Medica; Zeiss, Stemi 2000-C) equipped with a 100 or 200× optical probe, after patients had acclimated to a comfortable temperature of 22–25°C for 20 min. A drop of immersion oil was applied to the nail fold to maximise the translucency of the keratin layer, and the fingers from the second to the fifth of both hands were examined. All measurements were performed over 1 mm. The following capillaroscopic variables were evaluated: giant capillaries (normally homogeneous, enlarged capillaries with limb diameter≥50 µm); microhaemorrhages (presence of one or more dark red masses characterised by haemosiderin deposits due to capillary injury or thrombosis); branching capillaries (branched, bushy, interconnected capillaries originating from a single capillary); number of capillaries per linear mm; number of giant capillaries per linear mm; avascular area (intercapillary distance>500 µm). The presence or absence of the scleroderma pattern (SD pattern), defined as an alteration of the microvascular network of the nailfold characterised by giant capillaries, capillary loss, microhaemorrhages and architectural disorganisation, was evaluated according to a published algorithm.[16]

Statistical analysis

Quantitative data were presented as median and IQR, while categorical data as absolute numbers and percentages. Proportions were compared using Fisher's exact test. Comparisons between groups were performed using the Mann-Whitney U test. A p value<0.05 was considered significant. Multiple correspondence analysis (MCA) was performed on categorical clinical and laboratory variables with the package FactoMineR. Logistic regression was used to assess associations between clinical and laboratory variables and the occurrence of PAH in patients with SLE. Multicollinearity was evaluated using correlation plots and variance inflation factors; highly collinear variables (antiphospholipid syndrome (APS) diagnosis and antiphospholipid antibodies) were excluded. A full model was built and refined using backward stepwise selection based on the Akaike Information Criterion, iteratively removing the least informative predictors to yield the most parsimonious model. All statistical analyses were performed using R (V.4.0.3).

RESULTS

Overall clinical characteristics of enclosed patients and groups comparison

A total of 107 patients was included in the study, 20 (18.5%) with PAH and 87 (81.5%) without PAH. The

demographic, clinical and laboratory characteristics of patients stratified for group are described in table 1. The median (IQR) age at SLE diagnosis was 42.3 (34.3–49.7) and 45.5 (34.2–54.6) years, respectively, for patients with SLE-PAH and patients with SLE without PAH. The median (IQR) follow-up was 13.4 (6.7–19.7) and 13.4 (6.4–20.3) years, respectively, for patients with SLE-PAH and patients with SLE without PAH. Among the study participants, 5 patients with SLE-PAH (25%) and 15 patients with SLE without PAH (17%) had a paediatric onset of the disease. The age at SLE diagnosis and the length of the follow-up were not different between SLE patients with and without PAH (respectively, p=0.21 and p=0.82). The majority of patients were women (84, 78.5%), which is lower than the female predominance typically reported in SLE cohorts. No male patients were observed in the SLE-PAH group. Most patients were Caucasian (100, 93.5%), 7 patients were of not Caucasian origin, without ethnicity differences between SLE-PAH and not PAH groups (p=0.36). Of the 20 identified patients with SLE-PAH, 2 died from non-SLE-related causes and 2 were lost to follow-up after 13.4 (±1.5 SD) and 6.8 (±1.5 SD) years, respectively. All patients with SLE referring to the control group were on active follow-up at the time of the inclusion.

Focusing on the comparison between groups, we observed a higher frequency of anti-RNP and LAC positivity in the SLE-PAH group; whereas, the frequency of patients positive for anti-Sm, anti-Ro, anti-La, anti-cardiolipin IgG and IgM, and anti-beta2GPI IgG and IgM antibodies was similar between the two groups. The frequency of APS was similar between the two groups (SLE-PAH 27.8%, SLE without PAH 16%, p=0.3). Of note, patients with SLE with PAH and with antiphospholipid antibodies had no signs of pulmonary thromboembolisms on imaging.

Baseline median (IQR) SLEDAI-2K score was 2 (0–2), with no differences between the two groups (SLE-PAH 2.00 (0.00–4.00), SLE without PAH 2.00 (0.00–2.00), p=0.469). Regarding the ACR/EULAR classification criteria domains, mucocutaneous (p=0.024) and central nervous system involvement (p=0.046) was more prevalent among patients with SLE-PAH; frequency of arthritis (p=0.96), serositis (p=0.1) and renal involvement (p=0.28) was not different (table 1). The frequency of patients with Raynaud's phenomenon was significantly higher among patients with SLE-PAH (p<0.001). The use of various immunosuppressants was similar between the two groups of patients, except for CYC which was more frequently used in patients with SLE-PAH (table 1). Interestingly, of the 13 patients treated with CYC, five received treatment 6.9 (1.4–8.3) years before the diagnosis of PAH. For three patients, CYC was started at the time of PAH diagnosis. The remaining five patients received CYC 1.4 (1.3–2.9) years after the diagnosis of PAH. After excluding male patients from the SLE without PAH group, a comparison restricted to female patients yielded similar results (data not shown).

PAH haemodynamics and treatment in patients with SLE-PAH

All enrolled patients with SLE-PAH had received a PAH diagnosis after undergoing RHC. The haemodynamic characteristics of patients with PAH are reported in table 2. Enrolled patients had precapillary PAH characterised by a median mPAP (mean PAP) of 53.00 (45.00–62.00) mm Hg, increased pulmonary vascular resistance (8.45 (5.80–16.96) WU (Woods Unit)) and a pulmonary wedge pressure of 11.00 (9.00–11.00) mm Hg. The cardiac index was 2.90 (2.28–3.23) L/min/m^2 (table 2). All patients at the last follow-up visit were being treated with at least one pulmonary vasodilator medication (online supplemental table 2). Twelve patients (60%) were on single pulmonary vasodilator medication, while six (30%) and two patients (10%) were in combination therapy with two or three medications, respectively. We also collected the results of RHC at the last cardiologic assessment performed at a median (IQR) of 55.1 (29.8–85.4) months after the first RHC: the haemodynamic parameters improved, with an observed significant reduction in mPAP (table 2).

We separated patients with SLE-PAH in our cohort into the vasculitic and non-vasculitic groups according to the proposed score:[15] no significant differences were found between the two groups of patients (online supplemental table 3).

Capillaroscopy features in patients with SLE and PAH

NVC was performed in 9 patients with SLE-PAH and in all the 87 SLE patients without PAH (online supplemental table 1). The SD pattern was detected in 66.7% of patients with SLE-PAH and in 9.2% of patients with SLE without PAH (p<0.001) (table 3). Both groups exhibited mostly an early SD pattern; only a minority of patients showed an active SD pattern (one patient with SLE-PAH and two patients with SLE without PAH). No late SD patterns were observed in either population. The majority of patients with SLE without PAH (75.9%) exhibited a normal pattern, while 13 patients (14.9%) presented with an unspecific pattern. Unspecific patterns were characterised by the presence of tortuous and/or serpentine capillaries and occasional microhaemorrhages. The number of capillaries per mm was significantly reduced in patients with PAH (respectively for SLE-PAH and SLE without PAH 7.48±1.09 and 8.86±1.38; p=0.004). The frequency of giant capillaries was significantly higher in patients with SLE-PAH compared with those without PAH (p<0.001). No significant differences were observed in the frequency of dilated capillaries or microhaemorrhages between the two groups (table 3).

Predictors of PAH in patients with SLE

We assessed if patients with SLE-PAH showed significant clinical differences from patients with SLE without PAH. To this end, we performed an MCA (online supplemental table 4). The aim of this analysis was to reduce the dimensionality of the complex data to a few variables without losing information. The first four dimensions of MCA explained 49.2% of the total variance.

Table 1 Demographic and clinical characteristics of patients with SLE without PAH (SLE no PAH) and with SLE and associated PAH (SLE PAH) at enrolment

	SLE no PAH n=87	SLE PAH n=20	P value
Female sex, n (%)*	64 (74.0)	20 (100.0)	–
Age, years (median (IQR))	45.5 (34.2–54.6)	42.3 (34.3– 49.7)	0.211
Ethnicity, n (%)†			0.363
African	1 (1.1)	1 (5)	
Asian	2 (2.3)	1 (5)	
Caucasian	83 (95.4)	17 (85)	
Hispanic	1 (1.1)	1 (5)	
Disease duration, years (median (IQR))	13.4 (6.4–20.3)	13.4 (6.7–19.7)	0.820
SLEDAI-2K (median (IQR)) at enrolment	2.00 (0.00–2.00)	2.00 (0.00–4.00)	0.469
Autoantibody profile			
anti-Sm, n (%)	18 (20.5)	6 (30.0)	0.529
anti-RNP, n (%)	17 (19.5)	9 (45.0)	0.035
anti-Ro, n (%)	38 (43.2)	10 (50.0)	0.721
anti-La, n (%)	7 (8.0)	3 (15.0)	0.591
LAC, n (%)	18 (20.5)	9 (45.0)	0.042
anti-beta2GPI, n (%)	17 (19.5)	2 (10.0)	0.495
anti-cardiolipin, n (%)	20 (23.0)	6 (30.0)	0.711
Clinical features at enrolment			
Mucocutaneous, n (%)	30 (34.5)	13 (65.0)	0.024
Serositis, n (%)	14 (16.1)	7 (35.0)	0.108
Haematological, n (%)	43 (49.4)	15 (75.0)	0.069
Musculoskeletal, n (%)	38 (43.7)	9 (47.4)	0.969
Neurological, n (%)	7 (8.0)	5 (25.0)	0.046
Kidney, n (%)	18 (20.7)	7 (35.0)	0.284
Lupus nephritis class, n (%)			0.068
I–II	4 (4.6)	4 (20.0)	
III–IV	12 (13.8)	2 (10.0)	
V	1 (1.1)	1 (5.0)	
APS diagnosis, n (%)	14 (15.9)	5 (27.8)	0.309
Raynaud's phenomenon, n (%)	12 (13.8)	12 (60.0)	<0.001
Current medications, n (%)			
Antimalarials	61 (70.1)	15 (75.0)	0.872
MMF	22 (25.3)	10 (50.0)	0.057
MTX	6 (6.9)	0 (0.0)	0.591
AZA	6 (6.9)	3 (15.0)	0.364
CsA	2 (2.3)	0 (0.0)	1
Belimumab	7 (8.0)	1 (5.0)	1
B cell depletion	2‡ (2.3)	2 (10.1)	0.158
Documented past use of CYC, n (%)	22 (25.3)	13 (65.0)	0.002

*Not tested.
†Missing three values for patients with SLE-PAH.
‡One patient was treated with rituximab and one patient with ofatumumab.
APS, antiphospholipid syndrome; AZA, azathioprine; beta2GPI, beta-2-Glycoprotein I; CsA, cyclosporine; CYC, cyclophosphamide; LAC, lupus anticoagulant; MMF, mycophenolate mofetil; MTX, methotrexate; PAH, pulmonary arterial hypertension; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Table 2 WHO functional class and RHC parameters in patients with SLE-PAH

	At PAH diagnosis	Last follow-up	P value
WHO functional class, n (%)*			0.177†
I	6 (33.3)	9 (47.4)	
II	4 (22.2)	8 (42.1)	
III	8 (44.4)	2 (10.5)	
IV	0 (0)	0 (0)	
Haemodynamic parameters on RHC			
mPAP, mm Hg (median (IQR))	53.00 (45.00–62.00)	36.00 (26.50–50.00)	0.014‡
PAWP, mm Hg (median (IQR))	11.00 (9.00–11.00)	9.50 (6.50–10.00)	0.176‡
PVR, Woods Unit/m^2 (median (IQR))	8.45 (5.80–16.96)	5.46 (2.48–8.93)	0.179‡
Cardiac Index, L/min/m^2 (median (IQR))	2.90 (2.28–3.23)	3.02 (2.50–3.41)	0.531‡

*Two missing values at PAH diagnosis and one missing value at last follow-up.
†χ^2 test.
‡Paired t-test.
mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, Pulmonary Artery Wedge Pressure; PVR, Pulmonary Vascular Resistance; RHC, right heart catheterisation; SLE, systemic lupus erythematosus.

The first dimension accounted for 17.0% of variance, and it was mostly driven by the antiphospholipid autoantibodies profile and presence of APS; the second dimension accounted for 13.2% of the variance and it was mostly driven by presence of Raynaud's phenomenon, anti-RNP autoantibody positivity and presence of haematological and serosal manifestations. Patients with SLE-PAH distributed differently from patients with SLE without PAH along the first two dimensions of MCA (figure 2A). Values of both first and second dimensions were significantly higher in patients with PAH than in patients without PAH (figure 2B). Thus, the MCA analysis showed that patients with SLE with PAH presented with different clinical and immunological features from patients with SLE without PAH.

A logistic regression analysis with the presence of PAH in SLE as the dependent variable was performed to assess the association between PAH and clinical features of SLE. Candidate variables for the full model were selected based on the results presented in table 1, including clinical and laboratory variables with a p value<0.2 and anti-Sm, anti-Ro, anti-La autoantibodies (all variables are listed in online supplemental table 4). In the final logistic multivariable analysis, after backward selection of variables, Raynaud's phenomenon remained significantly associated with PAH (OR 10.52 (0.98–14.8), p=0.0004), whereas anti-RNP positivity almost reached significance (OR 3.8 (2.8–38.9), p=0.052) (table 4). The McFadden's R-squared for the model was 0.33. Additionally, the model showed good

Table 3 Nailfold capillaroscopy findings in patients with SLE without PAH (SLE no PAH) and with SLE and associated PAH (SLE PAH)

	SLE no PAH n=87	SLE PAH n=9	P value
SD pattern, n (%)	8 (9.2)	6 (66.7)	<0.001
Early SD pattern, n (%)	6 (6.9)	5 (55.6)	
Active SD pattern, n (%)	2 (2.3)	1 (11.1)	
Unspecific findings, n (%)	14 (16.1)	1 (11.1)	1.000
Capillaroscopic parameters			
Capillary density, n capillaries/mm (mean (SD))	8.86 (1.38)	7.48 (1.09)	0.004
Giant capillaries, n (%)	7 (8.0)	6 (66.7)	<0.001
Dilated capillaries, n (%)	32 (36.8)	2 (22.2)	0.615
Neoangiogenesis, n (%)	18 (20.7)	0 (0.0)	0.287
Microhaemorrhages, n (%)	12 (13.8)	2 (22.2)	0.852
Avascular areas, n (%)	0 (0)	0 (0)	–

PAH, pulmonary arterial hypertension; SD pattern, scleroderma pattern; SLE, systemic lupus erythematosus.

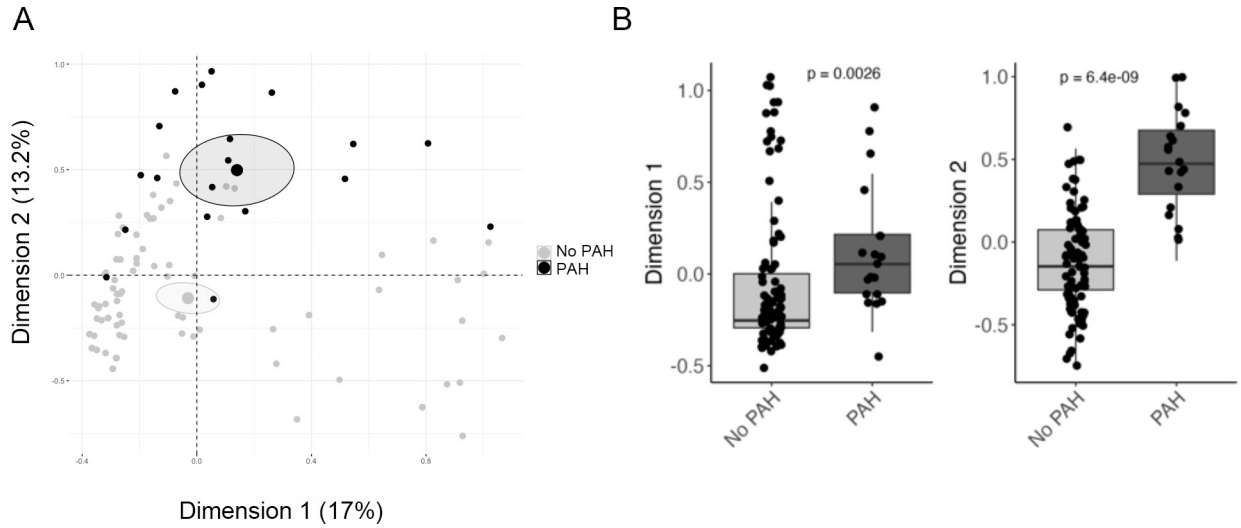

Figure 2 MCA of patients with SLE-PAH and patients with SLE without PAH (SLE – no PAH): plot showing the distribution of patients along dimension 1 and 2 (A). Boxplot showing the loadings of dimension 1 and dimension 2 for the two groups of patients (B). In A, each dot represents a single subject, big dots represent epicentres of distributions and ellipses indicate 95% CIs. In B, data are shown as box and whisker plots; horizontal lines at the centre of the boxes indicate medians. MCA, multiple correspondence analysis; PAH, pulmonary arterial hypertension; SLE, systemic lupus erythematosus.

discriminatory power, with an area under the curve of 0.86.

DISCUSSION

PAH is a severe complication of SLE, which can lead to right ventricular dysfunction and, consequently, death. Several studies have suggested that PAH associated with SLE can be a heterogeneous entity with different possible causes (left heart disease, lung parenchyma disease, etc) and variable treatment response.[5 17] Identifying risk factors can contribute to improving screening, early diagnosis and optimising treatment management. We showed that patients with SLE-PAH had a higher frequency of anti-RNP positivity, LAC positivity, Raynaud's phenomenon, mucocutaneous and neurological involvement than patients with SLE without PAH. An MCA analysis confirmed that patients with SLE with PAH had distinct clinical and laboratory features compared to patients with SLE without PAH. Analysis of NVC findings revealed a significantly higher prevalence of the SD pattern in patients with SLE-PAH with significantly reduced capillary density and increased frequency of giant capillaries. Logistic regression analysis identified Raynaud's phenomenon as an independent predictor of PAH in patients with SLE, with anti-RNP positivity showing a trend towards significance.

The pathogenesis of PAH is characterised by the involvement of multiple pathways, including an imbalance between mediators promoting vasodilation and vasoconstriction in the pulmonary circulation, smooth muscle and endothelial cell proliferation, and pulmonary vascular remodelling, resulting in increased pulmonary resistances.[5] Our capillaroscopy results suggest the presence of a peripheral microangiopathy observed at the nailfold bed of patients with SLE-PAH, which may parallel the microangiopathy occurring in the pulmonary vascular bed in PAH. Further confirming the role of systemic microcirculatory reactivity in the development of PAH, we established that the presence of Raynaud's phenomenon was a predictor of PAH in patients with SLE. The role of pulmonary bed vasospasm in raising the pressure in the pulmonary bed has been proposed in SSc.[18 19] However,

Table 4 Results from multivariate logistic regression model predicting PAH in patients with SLE

Predictor	OR (95% CI)	Z value	P value
anti-RNP positivity	3.82 (0.9 to 14.8)	1.936	0.0529
LAC positivity	1.72 (0.4 to 6.6)	0.790	0.4293
Mucocutaneous	2.70 (0.7 to 9.9)	1.492	0.1357
Neurological	5.29 (0.7 to 39)	1.620	0.1052
Serositis	1.24 (0.3 to 5.4)	0.290	0.7719
Haematological	2.77 (0.6 to 11.8)	1.373	0.1697
Raynaud's phenomenon	10.52 (2.8 to 38.9)	3.524	0.0004

LAC, lupus anticoagulant; PAH, pulmonary arterial hypertension; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus.

more than a causative association between Raynaud's phenomenon and increased pulmonary arterial pressures, the two may both represent a common endothelial dysfunction,[20] explaining the predictive value of Raynaud's phenomenon for PAH in SLE.

NVC is a non-invasive, low-cost technique useful for analysing microvascular abnormalities in peripheral circulation and for the early diagnosis of SSc.[16] The SD pattern occurs in up to 98% of patients with SSc and can be found in 2–15% of patients with SLE.[21 22] In patients with SSc, capillaroscopic abnormalities are associated with more severe visceral involvement and digital ulcers.[23 24] Studies on NVC in patients with SSc revealed a reduced capillary density among patients with PAH compared with those without PAH.[25 26] Riccieri *et al* observed a greater reduction in capillary density and a higher frequency of active and late SD patterns among patients with PAH compared with those without PAH.[27] Furthermore, more severe capillaroscopic abnormalities, such as a higher avascular score and lower capillary density, were associated with higher mPAP, suggesting an association between pulmonary arterial disease and the degree of abnormalities in NVC.[25 27] Interestingly, Hofstee *et al* observed an inverse correlation between pulmonary arterial pressure and capillary density among patients with PAH, whether idiopathic or secondary to SSc.[25] These data underscore the importance of NVC in risk stratification for developing PAH in patients with SSc, and a possible role as a screening tool in SLE. In our cohort, approximately 10% of patients with SLE without signs of PAH had an SD pattern in NVC (a frequency consistent with literature data for patients with SLE).[22 28] It is worth noting that about 50% of these patients had significant active cutaneous involvement at the time of NVC. In patients with SLE-PAH and SD pattern, no cutaneous disease activity was present instead. Additionally, capillary density appeared significantly reduced in patients with ongoing PAH in the context of SLE compared with patients with SLE without PAH. There is only one single-centre study analysing capillaroscopic alterations in 65 patients with SLE, including 21 with PAH.[29] This study showed that patients with an SD pattern in NVC had a 6.3 times greater risk of developing PAH than patients without an SD pattern, supporting the findings of our study. Our data, consistent with literature, confirm that the presence of SD pattern in NVC may be associated with the development of PAH, especially in the absence of concomitant active cutaneous disease. Moreover, the presence of giant capillaries and reduced capillary density appeared to be the type of capillaroscopic alterations mostly associated with the appearance of SLE-PAH. Thus, our data indicate that patients with SLE and PAH exhibit capillary alterations detectable by NVC and highlight the need for future studies to explore the potential of NVC as a screening tool in at-risk populations.

Anti-RNP antibodies and antiphospholipid antibodies have been associated with an increased risk of PAH among patients with SLE.[7 30–32] Several autoantibodies may cause endothelial damage, vasoconstriction, immune complex formation, and may deposit on the pulmonary arterial wall.[30] In a study on individuals of Asian origin, anti-RNP and anti-cardiolipin antibodies were independent predictors of PAH in patients with SLE, with ORs of 5.3 and 3.7, respectively.[7] A systematic literature review conducted on Asian cohorts reported a higher frequency of anti-RNP antibodies (51.5%) and anti-cardiolipin antibodies (46.6%) in patients with SLE-PAH.[31] While some studies have found a higher prevalence of anti-RNP antibodies among patients with SLE and PAH, others have not confirmed this data.[33 34] In our study, a trend towards a higher frequency of anti-RNP antibodies and LAC (but not anti-cardiolipin and anti-beta2GPI antibodies) was observed in patients with PAH.

Antiphospholipid antibodies are classically associated with APS and a higher risk of arterial or venous thrombosis and recurrent miscarriages. Cefle *et al* found a higher frequency of antiphospholipid antibodies among patients with suspected echocardiographic diagnosis of PAH compared with those without signs of PAH.[30] However, other studies failed to confirm this association.[33–36]

Multiple molecular pathways may be involved in the pathogenesis of PAH in SLE, including: endothelial activation, inflammation and autoantibodies.[5 37] It is not yet clear the contribution of each single pathway in different patients. The main implication of this hypothesis is that multimodal treatment strategies, employing both immunomodulators and pulmonary vasodilators to act on multiple converging pathophysiological pathways, would be more advantageous in PAH treatment in the context of SLE. Several retrospective studies have demonstrated the positive effect of CYC therapy on haemodynamic parameters and WHO functional class in patients with SLE and PAH.[38–41] In CYC-responsive patients factors associated with a good response were the presence of a less severe form of PAH at diagnosis from both a clinical and haemodynamical standpoint.[38 40] This data would indicate that in the early stages of PAH, there may be greater responsiveness to immunosuppressive therapy, emphasising the importance of early diagnosis and the need to develop screening tools for PAH in patients with SLE. However, it is also interesting to observe that the previous use of CYC did not prevent the occurrence of PAH in some of our patients.

Sun and colleagues proposed a clinical score that stratifies patients with SLE-PAH into two groups: vasculitic and non-vasculitic.[15] They demonstrated that patients with vasculitic PAH have a higher mortality rate compared with those with non-vasculitic PAH. However, Qian and colleagues applied the score developed by Sun to their cohort of patients with SLE-PAH and obtained contrasting results: patients with vasculitic PAH had a better survival rate and a lower rate of adverse events than those with non-vasculitic PAH.[42] We tried to assess the ability of the score proposed by Sun *et al* in our cohort of patients with SLE-PAH; however, we did not observe any statistically significant differences between the vasculitic and non-vasculitic PAH groups in terms of pulmonary

haemodynamic profile and clinical features, once again questioning the role of this score for patient stratification and prognosis.

Our study has several limitations, including a small number of patients with SLE-PAH and a retrospective nature. In addition, patients with SLE without PAH were not enrolled uniformly across all participating centre, as cardiopulmonary screening to exclude PAH was a limiting factor. This poses a possible selection bias related to centre-specific recruitment strategies, which may have influenced the distribution of key clinical features—particularly Raynaud's phenomenon, whose prevalence is known to vary geographically. As such, this limitation should be considered when interpreting the findings related to the potential predictive value of clinical features and NVC. The higher proportion of males in our overall cohort, compared with the 90% female predominance reported in historical adult-onset SLE cohorts, may be explained by the inclusion of a significant number of patients with paediatric-onset SLE, in whom the female-to-male ratio is typically lower, thus representing a potential confounder that requires further investigation in future studies. Our study exclusively included patients with confirmed PAH via RHC, considered the gold standard for diagnosis and prognostic analysis and selected a homogeneous group of patients with only type I PAH, excluding all other forms of PAH. While our study emphasises the importance of NVC evaluation and the presence of Raynaud's phenomenon in potentially identifying patients with SLE at high risk of developing PAH, prospective multicentre studies are needed to further elucidate the role of NVC in assessing PAH risk in patients with SLE.

In conclusion, our study highlights the increased prevalence of an SD pattern in NVC among patients with SLE with PAH compared with those without PAH, particularly concerning the presence of giant capillaries and reduced capillary density. Additionally, Raynaud's phenomenon emerged as a predictor of PAH in patients with SLE, suggesting that it may help identify a subset of patients with SLE at increased risk. These findings support the potential role of active screening for PAH in patients with SLE with Raynaud's phenomenon, which could improve early detection of this complication. Currently, routine PAH screening is not recommended in SLE due to its lower prevalence compared with SSc. However, our study suggests that a combined approach using NVC and clinical features could serve as a non-invasive and cost-effective screening tool for patients with high-risk SLE. Prospective multicentre studies are needed to further explore the role of NVC in PAH risk stratification among patients with SLE.

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