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Nailfold capillaroscopy as a risk factor for pulmonary arterial hypertension in systemic lupus erythematosus patients

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Abstract

Background: Pulmonary arterial hypertension (PAH) is a rare and severe complication of systemic lupus erythematosus (SLE). This study aimed to evaluate clinical and laboratory risk factors associated with PAH in SLE patients.

Methods: This was a retrospective case-control study in which patients with SLE with PAH (SLE-PAH) confirmed by right heart catheterization (RHC) were compared with SLE patients without PAH. Clinical and demographic variables related to SLE and PAH and nailfold capillaroscopy were evaluated by reviewing the medical records of the patients.

Results: Twenty-one patients with SLE-PAH and 44 patients with SLE without PAH matched for sex and disease duration were included. The scleroderma (SD) pattern on nailfold capillaroscopy was more frequently found in patients with SLE-PAH than in those without PAH (56.3% versus 15.9%, respectively, $p = 0.002$). By univariate analysis, Raynaud's phenomenon, history of abortion, and SD pattern on capillaroscopy were associated with PAH. Arthritis was a protective factor for PAH development. Multivariate analysis showed that the SD pattern on capillaroscopy was the only variable associated with a significantly higher risk of PAH, with an odds ratio of 6.393 (95% confidence interval, 1.530–26.716; $p = 0.011$).

Conclusion: In this study, SD pattern was associated with a 6.3-fold increased risk for PAH development in SLE patients, suggesting that nailfold capillaroscopy might be useful as a screening method to identify SLE patients with a high risk of developing this severe complication.

Keywords: Systemic lupus erythematosus, Pulmonary arterial hypertension, Risk factors, Nailfold capillaroscopy

Background

Systemic lupus erythematosus (SLE) is a rare chronic autoimmune disease of multifactorial etiology. Symptoms are heterogeneous and vary from mild to severe and potentially fatal systemic manifestations [1].

Pulmonary hypertension (PH) is a complex condition defined as an elevation of the mean pulmonary artery pressure (MPAP) (≥ 25 mmHg) at rest on right heart catheterization (RHC). The term pulmonary arterial hypertension (PAH) is used to designate a group of patients with pulmonary hypertension hemodynamically defined by precapillary PH, with pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg and an increase in the pulmonary vascular resistance (PVR) [2, 3].

PAH associated with autoimmune rheumatic diseases represent 30% of all adult PAH cases [4–6]. Among the rheumatic diseases associated with PAH, systemic sclerosis (SSc) and SLE are the most common [7, 8]. The prevalence of PAH among SLE patients varies from 0.5 to 14% according to the analyzed population [9–13]. Such wide variation is mainly attributed to the diagnostic methods used. Indeed, many studies were based on estimates of the right ventricular systolic pressure

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measured on transthoracic echocardiogram, using a variety of cutoff points (> 30 to 45 mmHg) to define PAH. Moreover, although PAH is the most frequent etiology of PH, it can be associated with other aetiologies, including pulmonary veno-occlusive disease, and pulmonary fibrosis and the differential diagnosis is not always simple [7].

Among patients with SLE, PAH is associated with high morbidity and mortality [14, 15]. Despite advances in the treatment of PAH in recent decades, patients with associated autoimmune rheumatic diseases exhibit a more severe form of disease and a poorer prognosis than do patients with other forms of PAH [8, 16]. According to reports in the literature, the 1- and 3-year survival rates for patients with SLE and PAH are 78 and 74%, respectively [17]. However, in a recent cohort study of 2967 patients with PAH at various American centers, the 1-year survival rate for patients with SLE was 94% [8].

Several risk factors have been associated with the development of PAH among SLE patients, including the presence of Raynaud's phenomenon (RP), anti-ribonucleoprotein (anti-RNP) and anti-cardiolipin antibodies, digital vasculitis, livedo reticularis, serositis, and high serum endothelin-1 levels [14, 16, 18–20]. However, most studies employed echocardiography for the diagnosis of PAH, which is a substantial limitation given its low accuracy.

Nailfold capillaroscopy (NC) is a noninvasive method that is widely used in the investigation of patients with RP. Patients with RP secondary to SSc and SSc spectrum disorders exhibit a classic microangiopathy pattern known as the scleroderma (SD) pattern, which is characterized by loss of capillary loops, capillary dilatation, and disorganization of the capillary structure [21]. Some studies of patients with SSc have found an association between NC abnormalities and the presence and severity of PAH, which suggests that changes in the microcirculation might play a role in the development or pathogenesis of PAH [22–25].

The aim of the present study was to identify risk factors for the development of PAH among SLE patients by analyzing clinical aspects and complementary tests, with an emphasis on NC as a possible method for the identification of patients with SLE and PAH.

Materials and methods

Patients and study design

In the present single-center, retrospective, case-control study conducted from 2013 to 2015, risk factors for PAH were investigated among SLE patients who developed PAH (SLE-PAH) or who did not (SLE-nPAH). Both groups were matched for sex and duration of disease (up to the outcome in group SLE-PAH) at a 2:1 ratio.

For the SLE-PAH group, the diagnosis of PAH met established criteria, especially confirmation on RHC [2]. Patients were identified through a review of medical records and via the database of PH patients of the Pulmonary Circulation Service, of the Pneumology Department of the Federal University of São Paulo.

Patients with SLE and without known diagnosed PAH (SLE-nPAH) were randomly selected from the SLE outpatient clinic, and those with SLE-PAH were also followed-up at the pulmonary outpatient clinic at the Federal University of São Paulo Medical School Hospital. The inclusion criteria were as follows: age of 18 years old or older; fulfilling the American College of Rheumatology (ACR) 1997 revised criteria for the classification of SLE [26]; and availability of clinical and laboratory data in the medical records at the time of inclusion. Patients with SSc overlap syndrome, rheumatoid arthritis, or polymyositis/dermatomyositis were excluded. The study was approved by the local research ethics committee (no. 503,630).

Thirty patients with PAH were identified. Five of them had not performed RHC for diagnosis and thus did not meet the inclusion criteria. Four patients had missing data in their medical records and had been subjected to one single outpatient evaluation; therefore, they could not be included in the study. As a result, the study sample comprised 21 SLE-PAH and 44 SLE-nPAH patients.

Right heart catheterization

RHC was indicated for patients with clinical suspicion of PAH and pulmonary artery pressure (PAP) ≥ 35 mmHg on Doppler echocardiogram. PAH was defined as MPAP ≥25 mmHg at rest, PCWP ≤15 mmHg, and an elevated PVR (> 3 Wood units-WU). The following parameters were analyzed on RHC at the time of PAH diagnosis: MPAP, cardiac index (CI), PCWP, and PVR index (PVRI). All exams were performed at the hemodynamics service of São Paulo Medical School Hospital. Interstitial lung disease, chronic thromboembolic pulmonary hypertension, congenital heart disease, significant valvular heart disease, chronic obstructive pulmonary disease, portal hypertension, schistosomiasis, immunodeficiency virus, and thyroid disorders had been previously ruled out.

Clinical and laboratory data

All the analyzed data were extracted from the patients' medical records. Attention was paid to the following variables: age, sex, ACR classification criteria for SLE, time since diagnosis of SLE and PAH, smoking, obstetric history, presence of RP and livedo reticularis, laboratory data, NC data, thrombotic events, and deaths in the SLE-PAH group. SLE activity was analyzed for all patients based on their score on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [27].

Laboratory tests included the detection of antinuclear (ANA) and anti-dsDNA antibodies by indirect immunofluorescence using HEp-2 cells and *Crithidia luciliae* as the substrate, respectively. Anti-Sm, anti-RNP, anti-Ro, and anti-La were investigated based on double immunodiffusion. Complement fractions (C2 and C100) were measured with radial immune hemolysis. Anti-cardiolipin antibodies (anti-aCL IgG and IgM) were detected using an enzyme-linked immunosorbent assay (ELISA). Serum creatinine levels, complete blood counts, C-reactive protein (CRP) levels, and 24-h urine protein levels, were also evaluated in all subjects.

NC was performed with a stereomicroscope (SZ40, Olympus) at 10-25x magnification. The NC parameters considered in the analysis were as follows: SD, normal or unspecific pattern, number of loops per mm, avascular score, number of giant and enlarged capillaries, and microhemorrhages [28]. The avascular score was determined semiquantitatively on a scale from 0 to 3 as previously described [29]. The mean score for each parameter was calculated from the analysis of all fingers except the thumbs.

Patients with PAH were also evaluated based on the New York Heart Association (NYHA) functional classification [30], distance walked in the 6-min walk test (6MWT), forced vital capacity (FVC) and carbon monoxide diffusing capacity (Dco) on pulmonary function tests, and echocardiogram at the time of PAH diagnosis. The echocardiogram parameters considered were as follows: PAP, right ventricular size, tricuspid regurgitation velocity (TRV), and presence of pericardial effusion.

Clinical and demographic data were collected at the time of diagnosis. The data on SLEDAI and current or previous SLE treatment were obtained at the time of inclusion in the study. For the SLE-PAH group, clinical and laboratory data on PAH were collected at the time of PAH diagnosis.

Statistical analysis

The data are presented as the mean and standard deviation and as absolute and relative frequencies in the case of categorical variables. The Shapiro-Wilk test was used to investigate the normality of the variable distribution. Continuous variables were compared between groups using Student's t-test or the Mann-Whitney test. Categorical data were analyzed using the chi-square or Fisher's exact test. The significance level was set at $p < 0.05$. To identify risk factors in the SLEP-PAH group, uni- and multivariate logistic regression analyses were performed, and the odds ratio (OR) for each factor was calculated with the corresponding 95% confidence interval (95% CI) relative to the SLE-nPAH group. All variables with $p < 0.10$ in the univariate analysis were included in the multivariate analysis. Statistical analyses were performed using *SPSS* software for Windows version 19.0 (Chicago, IL).

Results

The clinical, demographic, and laboratory characteristics of the 21 patients with SLE-PAH and the 44 SLE-nPAH patients are described in Table 1. The mean age at the time of SLE onset was 28.8 and 31.2 years in the SLE-PAH and SLE-nPAH groups, respectively. Female patients predominated in both groups. The mean duration of SLE at the time of PAH diagnosis was 6.7 ± 6.4 years in the SLE-PAH group. Regarding the ACR criteria, arthritis and photosensitivity were more frequent in the SLE-nPAH group (93.2 and 79.5%, respectively) than in the SLE-PAH group (70 and 55%, respectively). The SLEDAI score was not significant different between the groups; 29% of the patients in the SLE-nPAH group and 19% of those in the SLE-PAH group exhibited active disease (SLEDAI ≥4). Forty-two patients (64.6%) exhibited RP, with a trend toward a higher frequency in the SLE-PAH group than in the SLE-nPAH group (81% versus 56.8%, respectively; $p = 0.057$).

Forty patients (61.5%) had been pregnant at least once, without a significant difference between the groups. Only one patient in the SLE-PAH group had become pregnant after the diagnosis of PAH, and the outcome was a preterm birth. Ten patients (15.4%) had at least one miscarriage, with a significantly higher frequency in the SLE-PAH group than in the SLE-nPAH group (28.6% versus 9.1%, respectively; $p = 0.042$) (Table 1). Secondary antiphospholipid syndrome was diagnosed in two patients in the SLE-PAH group and in five patients in the SLE-nPAH group.

Nailfold capillaroscopy was performed in 16 patients in the SLE-PAH group and 44 patients in the SLE-nPAH group. The SD pattern was detected in 56.3% of the SLE-PAH patients. Most patients (84.1%) in the SLE-nPAH group exhibited a normal or unspecific pattern on capillaroscopy, and only 15.9% exhibited the SD pattern ($p = 0.002$). The number of dilated capillaries and the avascular score were significantly higher in the SLE-PAH group ($p = 0.027$ and $p = 0.010$, respectively) (Table 2).

The mean RHC findings for the SLE-PAH group were as follows: MPAP 48.9 ± 11.7 mmHg, CI 2.47 ± 0.7 L/min/m^2, and PVRI 10.9 ± 8.8 WU/m^2 (Table 3). The most frequent functional class (NYHA) at the time of diagnosis was functional class III (47.6%), followed by class II (33.3%); two patients (9.5%) were categorized as class I and another two (9.5%) as class IV. The mean distance walked in the 6MWT was 416.6 ± 80.6 m. The mean FVC was 79.6 ± 15.2%, and the mean Dco was 47.4 ± 18.9%. Regarding the echocardiography parameters, the mean PAP was 63.1 ± 14.1 mmHg, the mean TRV was 3.71 ± 0.41 m/s, and the mean right ventricular

Table 1 Clinical and demographic characteristics of patients with SLE associated with PAH (SLE-PAH) or not associated with PAH (SLE-nPAH)

	SLE-nPAH $n = 44$	SLE-PAH $n = 21$	*P*-value
Age at SLE diagnosis (years)	31.2 ± 12.3	28.8 ± 10.2	0.411
Age at PAH diagnosis (years)	–	35.5 ± 11.8	–
Duration of disease at recruitment (years)	5.6 ± 3.2	6.7 ± 6.4	0.437
Female sex, n (%)	42 (95.5)	20 (95.2)	0.969
Smoker, n (%)	0 (0)	1 (4.8)	0.145
Ex-smoker, n (%)	4 (9.1)	1 (4.8)	0.295
ACR SLE criteria, n (%)			
Malar rash	34 (77.3)	13 (65)	0.303
Photosensitivity	35 (79.5)	11 (55)	0.043
Discoid rash	3 (6.8)	0 (0)	0.232
Oral ulcers	7 (15.9)	4 (20)	0. 688
Arthritis	41 (93.2)	14 (70)	0.013
Serositis	2 (40%)	12 (60)	0.112
Hematologic involvement	27 (61.4)	14 (70)	0.504
Renal involvement	18 (40.9)	7 (35)	0.635
Neuropsychiatric involvement	8 (18.2)	4 (20)	0.863
ANA	44(100)	19 (90.4)	0.189
Anti-dsDNA, anti-Sm, or antiphospholipid	25 (56.8)	11 (57.9)	0.937
Raynaud's phenomenon, n (%)	25 (56.8)	17 (81)	0.057
Livedo reticularis, n (%)	0 (0)	1 (4.8)	0.145
Arterial thrombosis, n (%)	0 (0)	1 (4.8)	0.145
Venous thrombosis, n (%)	7 (15.9)	5 (23.8)	0.443
SLEDAI	1.91 ± 3.16	2.56 ± 3.79	0.559
Pregnancy, n (%)	26 (59.1)	14 (66.7)	0.557
Miscarriage, n (%)	4 (9.1)	6 (28.6)	0.042
Anti-SM, n (%)	10 (22.7)	4 (23.5)	0.947
Anti-RNP, n (%)	19 (43.2)	11 (64.7)	0.132
Anti-Ro, n (%)	11 (25)	5 (29.4)	0.725
Anti-La, n (%)	5 (11.4)	2 (11.8)	0.965
Positive anti- aCL IgM, n (%)	3 (7)	2 (11.1)	0.591
Positive anti- aCL IgG, n (%)	7 (16.3)	3 (16.7)	0.970
Positive anti-dsDNA, n (%)	15 (34.1)	3 (17.6)	0.207
C2 (mg/dL)	91.4 ± 25.7	86.9 ± 29.8	0.690
CH100 (mg/dL)	91.5 ± 24.8	89.4 ± 30.2	0.957
Hemoglobin (g/dL)	12.5 ± 1.3	13.2 ± 1.5	0.138
Leukocytes (/mm^3)	6.317 ± 3.120	6.149 ± 3.766	0.977
Lymphocytes (/mm^3)	1.643 ± 899	1.477 ± 675	0.617
Platelets (/mm^3)	251.295 ± 101.691	197.500 ± 68.534	0.028
Creatinine (mg/dL)	0.73 ± 0.23	0.86 ± 0.36	0.077
CRP (mg/dL)	9.02 ± 14.3	12.10 ± 37.32	0.314
24-h urine protein (mg/kg/24 h)	0.36 ± 0.52	0.26 ± 0.25	0.785

Data are expressed as the mean ± standard deviation or n (%). *ACR* American College of Rheumatology, *ANA* antinuclear antibodies, *anti-aCL* anticardiolipin, *CRP* C-reactive protein, *nPAH* no PAH, *PAH* pulmonary arterial hypertension, *SLE* systemic lupus erythematosus, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index

Table 2 Abnormalities on nailfold capillaroscopy among patients with SLE associated with PAH (SLE-PAH) or not associated with PAH (SLE-nPAH)

	SLE-PAH $n = 16$	SLE-nPAH $n = 44$	*P*-value
Capillaroscopy pattern			
SD, n (%)	9 (56.3)	7 (15.9)	0.002
Normal or unspecific, n (%)	7 (43.7)	37 (84.1)	
Number of loops/mm	8.63 ± 1.28	9.18 ± 1.77	0.081
Microhemorrhages	1.03 ± 1.67	0.3 ± 0.52	0.134
Dilated capillaries	1.39 ± 1.46	0.85 ± 1.72	0.027
Giant capillaries	0.04 ± 0.11	0.03 ± 0.44	0.468
Avascular score	0.45 ± 0.63	0.12 ± 0.28	0.010

Data are expressed as the mean ± standard deviation or n (%). *NC* nailfold capillaroscopy, *nPAH* no PAH, *PAH* pulmonary arterial hypertension, *SD* scleroderma pattern, *SLE* systemic lupus erythematosus

area was 26.2 ± 5.5 cm^2. Pericardial effusion was detected in 9.5% of the patients.

Among the medications for the treatment of SLE, current or previous use of corticosteroids and antimalarial agents was significantly more frequent in the SLE-nPAH group than in the SLE-PAH group (100% versus 85%, respectively, for both medications; $p = 0.009$). Mycophenolate and cyclophosphamide was also significantly more frequently used in the SLE-nPAH group than in the SLE-PAH group (29.5% versus 5%, respectively, $p = 0.028$; 56.8% versus 15%, respectively, $p = 0.002$) (Table 4). A higher proportion of patients used contraceptives in the SLE-PAH group than in the SLE-nPAH group (52.6% versus 22.7%, respectively; $p = 0.019$). Regarding the medications used for the treatment of PAH, 57.1% of the participants used sildenafil and 47.6% bosentan; five patients (23.8%) received combined therapy. Ten patients (47.6%) had received intravenous cyclophosphamide pulse therapy and eight (38.1%) intravenous corticosteroids at the time of diagnosis of PAH (Table 4). Thirteen patients (61.9%) had received oral anticoagulants. Six patients (28.6%) in the SLE-PAH group died during follow-up.

As shown in Table 5, there were no significant differences in demographic, clinical, or laboratory variables between NYHA class I/II and NYHA class III/IV SLE-PAH patients. Although MPAP, CI, and PVRI were worse in class III/IV patients than in class I/II patients, these differences were not significant. There were 5 deaths in the NYHA class III and IV group and only one death in the NYHA class I and II group. No association was found between MPAP or CI values on RHC and clinical or laboratory variables (data not shown).

In the univariate analysis, miscarriage, RP, and SD pattern on capillaroscopy were significant risk factors for PAH ($p = 0.05$; $p = 0.06$; $p = 0.003$, respectively). In turn, arthritis was a protective factor against the development of PAH (p = 0.05) (Table 6). In the multivariate analysis, SD pattern on NC was the single variable associated with an increased risk of PAH, with an OR of 6.393 (95% CI: 1.530–26.716; $p = 0.011$).

Table 3 Results of right heart catheterization for patients with PAH

	SLE-PAH $n = 21$
MPAP (mm Hg)	48.9 ± 11.7
CI (L/min/m^2)	2.47 ± 0.7
PCWP (mm Hg)	10.7 ± 2.5
PVRI (WU/m^2)	10.9 ± 8.8

Data are expressed as the mean ± standard deviation. *MPAP* mean pulmonary artery pressure, *CI* cardiac index, *PAH* pulmonary arterial hypertension, *PCWP* pulmonary capillary wedge pressure, *PVRI* pulmonary vascular resistance index, *SLE* systemic lupus erythematosus

Discussion

PAH is a devastating disorder that might lead to right ventricular dysfunction and, consequently, death. Recent studies have suggested that PAH associated with SLE involves heterogeneous conditions with a variable response to treatment. The identification of risk factors might contribute to improved screening and treatment management. To the best of our knowledge, this is the first study to analyze NC among patients with SLE associated with PAH. Thus, in the present study there was a 6.3-fold higher risk of PAH development in patients with the SD pattern on capillaroscopy.

NC is useful for analyses of microvascular abnormalities in the peripheral circulation and for the early diagnosis of SSc [28]. The SD pattern occurs in up to 98% of patients with SSc, and it may be found in 2 to 15% of patients with SLE [28, 31]. In a study of SLE patients, the SD pattern was associated with the presence of RP and anti-RNP antibodies, which were associated with PAH in other studies [31].

NC abnormalities in SSc are associated with more severe visceral involvement and digital ulcers [21, 32]. Studies evaluating NC in patients with scleroderma and PAH found a reduced capillary density among patients

Table 4 Treatment for SLE and PAH

	SLE-PAH $n = 21$	SLE-nPAH $n = 44$	*P*-value
Corticosteroids, n (%)	17 (85)	44(100)	0.009
Antimalarial agents, n (%)	17 (85)	44(100)	0.009
Immunosuppressants, n (%)			
Azathioprine	8 (40)	25 (56.8)	0.212
Mycophenolate	1 (5)	13 (29.5)	0.028
Cyclophosphamide	3 (15)	25 (56.8)	0.002
Methotrexate	11 (55)	19 (43.2)	0.380
PAH treatment			
Sildenafil, n (%)	12 (57.1)	–	
Bosentan, n (%)	10 (47.6)	–	
Cyclophosphamide IV, n (%)	10 (47.6)	–	
Methylprednisolone IV, n (%)	8 (38.1)	–	
Oral anticoagulants, n (%)	13 (65)	–	

nPAH no PAH, *PAH* pulmonary arterial hypertension, *SLE* systemic lupus erythematosus

with PAH compared with those without PH [22, 24]. In a study of 24 patients with SSc, 12 with and 12 without PAH, Riccieri et al., observed greater devascularization and a higher frequency of the active and late NC pattern compared with the early pattern among patients with PAH [23]. In addition, more severe NC abnormalities, such as a higher avascular score and lower capillary density, have been associated with a higher MPAP, suggesting an association between pulmonary arterial disease and the degree of abnormalities on NC [22, 23]. Interestingly, Hofstee et al., observed an inverse correlation between pulmonary arterial pressure and capillary density among patients with PAH, either idiopathic or secondary to SSc [22].

In our study, in addition to the higher frequency of the SD pattern among patients with PAH, we also found a higher degree of devascularization and larger number of dilated capillaries among patients with PAH compared with those without PAH. Although not fully elucidated, the pathogenesis of PAH involves an imbalance between vasodilation and vasoconstrictor mediators, and excessive vasoconstriction and increased PVR have been associated with endothelial and smooth muscle proliferation and pulmonary vascular remodeling [16, 18]. The findings of the present study suggest that the peripheral microangiopathy might have a similar pathogenesis to pulmonary vascular bed microangiopathy. Our findings further suggest that patients with SSc and SLE share similar pathogenic mechanisms involved in the development of PAH.

The multivariate analysis did not reveal an association with variables previously reported as correlating with a higher risk of PAH, such as the presence of RP, serositis, and anti-RNP and anticardiolipin antibodies. This discrepancy might derive from the sample characteristics or the small number of patients with PAH analyzed.

Several studies have described an association of RP and digital vasculitis with PAH [19, 33–36]. In the present study, 81% of the patients with SLE and PAH and 56% of the patients without PAH exhibited RP. By univariate analysis, the presence of RP was associated with a 3.2-fold higher risk of PAH, which suggests that this variable might be relevant for the identification of this subpopulation of patients.

Anti-RNP and antiphospholipid antibodies have also been associated with an elevated risk of PAH among patients with SLE [19, 37–39]. Several autoantibodies might cause endothelial damage, vasoconstriction, and immunocomplex formation, and might be deposited on the pulmonary arterial wall [37]. In a study of Chinese individuals, anti-RNP and anticardiolipin antibodies were independent predictors of PAH among SLE patients, with ORs of 5.3 and 3.7, respectively [19]. A systematic review also of Chinese patients reported a higher frequency of anti-RNP (51.5%) and anticardiolipin (46.6%) antibodies among patients with SLE and PAH [38]. While some studies found a higher prevalence of anti-RNP antibodies among patients with SLE and PAH, other did not find a significant difference between SLE patients with or without PAH [11, 36]. In the present study, 65% of the patients with PAH had positive anti-RNP compared with 43% of the patients without PAH.

Antiphospholipid antibodies are classically associated with antiphospholipid syndrome and a higher risk of arterial or venous thrombosis and recurrent pregnancy loss. Cefle et al. (2011), found a higher frequency of antiphospholipid antibodies among SLE patients diagnosed with PAH on echocardiogram compared with patients without PAH [37]. However, other studies have failed to find such association [11, 33, 36, 40]. In the present

Table 5 Demographic and clinical characteristics of patients with SLE and PAH by NYHA functional classes I/II and III/IV

	NYHA class I/II $n = 9$	NYHA class III/IV $n = 12$	*P*-value
Female sex, n (%)	9 (100)	11 (91.7)	0.375
Age at SLE diagnosis	26.7 ± 10.9	30.3 ± 9.9	0.219
Age at PAH diagnosis	35.8 ± 11.7	35.3 ± 12.3	0.922
SLE length at PAH diagnosis	9.1 ± 7.5	4.9 ± 4.9	0.138
Smoking, n (%)	1 (11)	0 (0)	0.352
Miscarriage, n (%)	3 (33)	3 (25)	0.676
Pregnancy, n (%)	6 (66.7)	8 (66.7)	1.000
Raynaud's phenomenon, n (%)	7 (77.8)	10 (81)	0.748
Livedo reticularis, n (%)	1 (11.1)	0 (0)	0.237
Arterial thrombosis, n (%)	0 (0)	1 (8.3)	0.375
Venous thrombosis, n (%)	4 (44.4)	1 (8.3)	0.055
Anti-SM, n (%)	2 (25)	2 (22.2)	0.893
Anti-RNP, n (%)	4 (50)	7 (77.8)	0.232
Anti-Ro, n (%)	2 (25)	3 (33.3)	0.707
Anti-La, n (%)	0 (0)	2 (22.2)	0.156
Positive anti- aCL IgM, n (%)	1 (12.5)	1 (10)	0.867
Positive anti- aCL IgG, n (%)	1 (12.5)	2 (20)	0.671
Positive anti-dsDNA, n (%)	2 (25)	1 (11.1)	0.453
C2 (mg/dL)	85.2 ± 34.3	88.1 ± 28.6	0.859
CH100 (mg/dL)	83.8 ± 30.2	93.1 ± 31.4	0.579
CRP (mg/dL)	3.43 ± 2.01	19.20 ± 50.20	1.000
SLEDAI	2 ± 4.5	3.0 ± 3.4	0.299
6-min walk test	413 ± 14.8	417.7 ± 92.9	0.934
FVC (%)	84.1 ± 17.5	75.7 ± 13.2	0.143
Dco (%)	52.2 ± 8.3	44.5 ± 23.2	0.548
Death, n (%)	1 (11.1)	5 (41.7)	0.125
Nailfold capillaroscopy			
SD pattern, n (%)	4 (66.7)	5 (50)	0.515
Normal or unspecific	2 (33.3)	5 (50)	
RHC			
MPAP	47.6 ± 7.7	50.0 ± 14.6	0.654
CI	2.61 ± 0.66	2.36 ± 0.75	0.441
PVRI	8.86 ± 3.0	12.62 ± 11.47	0.824
Treatment			
Sildenafil, n (%)	4 (44.4)	8 (67)	0.309
Bosentan, n (%)	5 (55.6)	5 (41.7)	0.528
Cyclophosphamide IV, n (%)	4 (44.4)	6 (50)	0.801
Methylprednisolone IV, n (%)	3 (33.3)	5 (41.7)	0.697
Oral anticoagulants, n (%)	6 (66.7)	7 (63.6)	0.642

Data are expressed as the mean ± standard deviation or n (%). *SLE* systemic lupus erythematosus, *PAH* pulmonary arterial hypertension, *anti-aCL* anticardiolipin, *CI* cardiac index, *CRP* C-reactive protein, *Dco* carbon monoxide diffusing capacity, *FVC* forced vital capacity, *IV* intravenous, *MPAP* mean pulmonary artery pressure, *NYHA* New York Heart Association, *PVRI* pulmonary vascular resistance index, *SLE* systemic lupus erythematosus, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index

Table 6 Variables associated with PAH among SLE patients in the univariate logistic regression analysis

Variables	Odds ratio	95% CI	*P*-value
Sex	0.952	0.081–11.134	0.969
Age at SLE diagnosis	1.019	0.972–1.069	0.437
Pregnancy	1.385	0.466–4.111	0.558
Miscarriage	4.000	0.989–16.179	0.052
Smoking	0.526	0.055–5.035	0.577
Raynaud's phenomenon	3.230	0.933–11.182	0.064
Venous thrombosis	1.652	0.455–5.993	0.445
SLEDAI (total)	0.945	0.802–1.113	0.501
Malar rash	0.812	0.141–4.640	0.809
Photosensitivity	0.313	0.057–1.703	0.179
Arthritis	0.136	0.018–1.003	0.050
Serositis	3.172	0.708–14.213	0.131
Renal involvement	0.881	0.191–4.068	0.871
Neuropsychiatric involvement	0.560	0.105–2.989	0.498
Anti-Sm	1.046	0.278–3.932	0.947
Anti-RNP	2.412	0.756–7.694	0.137
Anti-La	1.040	0.182–5.953	0.965
Anti-Ro	1.250	0. 359–4.348	0.726
Anticardiolipin IgM	1.667	0.254–10.931	0.594
Anticardiolipin IgG	1.029	0.234–4.521	0.970
Anti-DNA	0.414	0.103–1.670	0.215
C2	1.006	0.984–1.029	0.574
CH 100	1.003	0.981–1.026	0.787
CRP	1.005	0.984–1.027	0.634
SD pattern on capillaroscopy	6.796	1.897–24.345	0.003

95% CI 95% confidence interval, *CRP* C-reactive protein, *PAH* pulmonary arterial hypertension, *SD* scleroderma pattern, *SLE* systemic lupus erythematosus

study, we did not observe a significant difference in the proportion of aCL IgM and IgG between the groups. One should note that the measurement of lupus anticoagulants and anti-beta-2 glycoprotein I is not available at our service, and thus the levels of antiphospholipid antibodies might have been underestimated.

In agreement with previous studies, we did not find an association between disease activity as assessed by SLEDAI and the development of PAH [34, 39, 41].

Miscarriage occurred in a significantly higher proportion of patients in the SLE-PAH group, all of which occurred prior to the diagnosis of PAH. It is noteworthy that termination of pregnancy should be considered for patients with PAH due to the high risk of maternal death [42].

NYHA functional class, 6MWT, and hemodynamic parameters have considerable clinical relevance, as they are the main final outcomes in PAH and have strong association with mortality [3]. Upon investigating possible correlations between the severity of PAH and clinical and laboratory markers, we did not find a difference between patients with a higher (NYHA class III/IV) or lower (NYHA class I/II) functional class severity. In addition, we did not identify an association between CI and MPAP in the RHC with the analyzed variables. However, five deaths occurred among the NYHA class III/IV patients versus only one among the NYHA class I/II patients, indicating more severe disease among patients with higher functional class.

The treatment for PAH has undergone substantial changes over the past decades. Pulmonary vasodilators, such as prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, have significantly improved symptoms and reduced the rate of clinical deterioration [3]. In the present study, 57% of the patients had received sildenafil, 47% bosentan, and 23.8% combined treatment; none of the patients had received prostacyclin analogs, which remain scarcely available in our country. Because the immune system and/or inflammatory response abnormalities seem to be involved in the pathogenesis of PAH, especially among patients with SLE, immunosuppressant therapy is suggested for patients with SLE and PAH [42–45]. In our study, 47% of the patients had received cyclophosphamide pulse therapy for PAH.

The present study has some limitations, such as the small number of patients with PAH and prior exposure of some patients in the control group to NC, which might have resulted in selection bias, i.e., the inclusion of a larger number of patients with RP. A further limitation derives from the retrospective design of the study, which was based on a review of medical records, hindering the analysis of relevant aspects such as the response to PAH treatment. In addition, only a portion of the patients with SLE but without PAH (43%) underwent an echocardiogram for PAH screening, and thus, we could not rule out the possible inclusion of some asymptomatic PAH patients in the normal control group. Although we excluded patients with SSc overlap syndrome, we could not rule out the possible inclusion of patients with subclinical SSc in the study.

It is worth noting that this study included only patients with PAH confirmed on RHC, which is considered the gold standard for both the diagnosis and analysis of factors related to a poorer prognosis, such as elevated right atrial pressure and reduced CI [2, 3]. Due to its low prevalence, there is no recommendation for screening patients with SLE for PAH, in contrast to patients with SSc. Nevertheless, Khanna et al. (2013) [45], recently suggested that screening with Doppler echocardiography, pulmonary function tests with Dco, and serum markers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), should be performed for patients with mixed connective tissue disease or SLE with SSc-related manifestations and symptoms suggestive of PAH.

Conclusions

In conclusion, the frequency of the SD pattern on NC was significantly increased among SLE patients with PAH compared with those without PAH. The presence of the SD pattern was associated with a 6.7 times higher risk of PAH. Thus, the present results lead us to consider the relevance of capillaroscopy evaluation for SLE patients, who are also at high risk of developing this serious and potentially fatal complication. We suggest the utilization of NC, a non-invasive method, as a screening method for patients with SLE and further annual PH screening for patients who present the SD pattern, as currently conducted for patients with SSc. Prospective and multicenter studies are needed to better elucidate the role of NC in the determination of the risk of PAH development among patients with SLE, as well as to confirm the present results.

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Availability of data and materials
The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions
JFSD, EVMF, JOA, and CK contributed to the conception and design of the study, and to the acquisition of the data. JFSD and CK contributed to analysis and interpretations of data, and were the major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the local research ethics committee at the Federal University of São Paulo (no. 503,630). All patients gave their informed consent prior to their inclusion in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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