Clinical characteristics, predictors and prognosis of systemic sclerosis with scleroderma renal crisis and pulmonary arterial hypertension

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Abstract

Objective

To characterise the clinical features, predictors, and prognosis of patients with systemic sclerosis (SSc) who had both scleroderma renal crisis (SRC) and pulmonary arterial hypertension (PAH).

Methods

In this retrospective cohort study, we reviewed 234 patients diagnosed with SSc at our institute between January 2013 and April 2024. Clinical characteristics and prognosis were compared among patients with both SRC and PAH, PAH alone, SRC alone, and neither PAH nor SRC. Predictors of the coexistence of PAH and SRC were identified using multivariate logistic regression analysis.

Results

Among the 234 patients with SSc, 17 (7.3%) had both PAH and SRC. PAH preceded SRC in five patients, followed SRC in three, and occurred simultaneously in nine. Compared with patients with SRC alone, those with both SRC and PAH had a higher prevalence of interstitial lung disease, a higher rate of gastrointestinal bleeding (GIB), and lower serum albumin levels. GIB (OR=9.545, 95%CI: 1.679, 54.264; p=0.011) was independently associated with the coexistence of PAH and SRC compared with SRC alone, whereas older age at disease onset (OR=1.200, 95%CI: 1.014, 1.420; p=0.033) and elevated NT-proBNP (OR=1.001, 95%CI: 1.000, 1.001; p=0.030) were independently associated with the coexistence of PAH and SRC compared with PAH alone.

Conclusion

PAH may precede, follow, or coincide with SRC. Patients with both SRC and PAH had a significantly higher risk of GIB. Older age and elevated NT-proBNP were independent factors associated with the coexistence of SRC and PAH.

Key words

systemic sclerosis, scleroderma renal crisis, pulmonary arterial hypertension

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Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder characterised by vasculopathy, inflammation, and fibrosis. Patients with SSc may develop a broad spectrum of vascular complications, including pulmonary arterial hypertension (PAH) and scleroderma renal crisis (SRC). PAH, reported in approximately 12-27% of patients with SSc, is characterised by pulmonary arterial vasoconstriction and cellular proliferation (1, 2). These changes lead to elevated pulmonary arterial pressure, right ventricular overload and ultimately heart failure, making PAH the leading cause of mortality in patients with SSc (2). In contrast, SRC is a relatively rare but life-threatening vascular complication of SSc. Although outcomes have improved following the introduction of angiotensin-converting enzyme inhibitor (ACEi) therapy, SRC remains clinically challenging owing to the rapid progression of kidney injury and subsequent target organ dysfunction (3).

Previous studies have proposed the concept of generalised microvascular damage in SSc (4). Clinical manifestations, such as telangiectasia and digital ulcers, have been identified as predictors of PAH in cohort studies (5-7), and similar vascular pathologies, including intimal proliferation and luminal obstruction, have been observed in both pulmonary and renal vessels of patients with SSc (2). Despite these shared features, the coexistence of PAH and SRC in patients with SSc is rarely observed. PAH more frequently occurs in patients with limited cutaneous SSc (lcSSc) and typically at later stages of disease, whereas SRC is more often observed in diffuse cutaneous SSc (dcSSc) and tends to develop earlier. Differences in the mechanisms of endothelial injury may further contribute to this divergence (8). Gunduz *et al*. reported a case series of 11 patients with SSc who developed both PAH and SRC, demonstrating a high prevalence of serum antibodies to Th/To RNA polymerase III and U3 RNP, along with poor clinical outcomes (9). However, the clinical characteristics, antibody profiles, and prognosis of these patients have not been systematically compared with those of other patients with SSc, particularly those with PAH or SRC alone.

In this study, we aimed to characterise the clinical features and prognosis of patients with SSc who develop both SRC and PAH, and to identify clinical predictors of their coexistence, with the goal of improving understanding and informing the management of these patients.

Method

Patients

We retrospectively reviewed 340 inpatients with SSc treated at our institute between January 2013 and April 2024. All patients fulfilled the 1980 ACR or 2013 ACR/EULAR classification criteria for SSc. Patients with overlapping connective tissue diseases or those diagnosed with malignant tumours prior to the onset of SSc were excluded. A total of 234 patients were included in the final analysis. The study was approved by the institutional review board of our institute (I-24PJ1922).

Data collection

Disease onset was defined as the occurrence of the first non-Raynaud's phenomenon. Follow-up duration was calculated from disease onset to the last follow-up or death.

Clinical data, including general characteristics, clinical manifestations and laboratory parameters, were collected at the initial visit and during regular follow-up every 3–6 months. General characteristics included age, sex, disease duration, smoking history and history of systemic hypertension.

PAH was defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest, pulmonary artery wedge pressure (PAWP) ≤15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units measured by right heart catheterisation (RHC), or an estimated systolic pulmonary artery pressure ≥40 mmHg on echocardiography when RHC was unavailable (10). SRC was diagnosed according to the 2015 classification criteria established by the Scleroderma Clinical Trials Consortium (3, 11, 12). Additional clinical manifestations included: 1) peripheral vasculopathy, comprising Raynaud's phenomenon,

telangiectasia, digital ulcers, and digital gangrene; 2) interstitial lung disease (ILD), diagnosed based on characteristic high-resolution computed tomography findings assessed by experienced radiologists; 3) cardiac involvement, including arrhythmia, myocardial involvement, and pericardial effusion, with myocardial involvement defined by evidence of myocardial injury on cardiac magnetic resonance, and pericardial effusion identified by echocardiography; 4) gastroesophageal reflux disease (GERD), diagnosed based on reflux-related symptoms responsive to empiric acid-suppressive therapy or confirmed by endoscopy or ambulatory reflux monitoring (13, 14); and 5) gastrointestinal bleeding (GIB), defined by haemorrhagic symptoms (hematemesis, haematochezia, or melena) and confirmed by endoscopy or computed tomography angiography (CTA) of the abdomen and pelvis (15).

Laboratory parameters included white blood cell count, haemoglobin, platelet (PLT) count, serum albumin (Alb), N-terminal pro-brain natriuretic peptide (NT-proBNP), neutrophil-to-lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR), ferritin (Fer) and complement C3. Antibody profiles included antinuclear antibodies, anti-ds-DNA, anti-Sm, anti-SSA, anti-SSB, anti-topoisomerase I (Scl-70), anti-RNP, anti-centromere antibodies (ACA) and anti-mitochondrial antibody M2 subtype.

Statistical analysis

Statistical analyses were performed using Python (version 3.11). Categorical variables were presented as counts and percentages and compared using the chi-square test or Fisher's exact test. Continuous variables were expressed as mean ± standard deviation for normally distributed data and as median (25th percentile, 75th percentile) for non-normally distributed data. Group comparisons were conducted using Student's *t*-test or the Mann-Whitney U test, as appropriate. Variables with $p<0.05$ in univariate analysis were further evaluated using least absolute shrinkage and selection operator (LASSO) regression to identify candidate predictors. These variables were subsequently included in a multivariate binary logistic regression model (forward: LR) to determine independent predictors. Survival analysis was performed using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test.

Results

Participants' baseline characteristics

A total of 234 patients with SSc were included in this study. Of these, 188 (80.3%) were female and 46 (19.7%) were male (male-to-female ratio, 1:4.1). The mean age at diagnosis was 48.8±13.2 years. The median follow-up duration was 41.0 months (10.0, 96.0), corresponding to a total of 1168 person-years. Overall, 127 patients (54.3%) were classified as having lcSSc and 107 (45.7%) as having dcSSc. All patients were of Han ethnicity, except for four individuals belonging to ethnic minorities (one Manchu, one Korean and two Mongolian).

Regarding clinical manifestations, Raynaud's phenomenon was the most common peripheral vasculopathy, affecting 197 patients (84.2%). Telangiectasia was observed in 60 patients (25.6%), digital ulcers in 78 (33.3%), and digital gangrene in 30 (12.8%). Musculoskeletal involvement included arthritis in 76 patients (32.5%) and muscle involvement in 20 (8.5%). ILD and pulmonary hypertension were identified in 196 (83.8%) and 78 (33.3%) patients, respectively. SRC occurred in 54 patients (23.1%), including 17 (7.3%) with coexisting PAH and renal crisis. Gastrointestinal involvement included GERD in 107 patients (45.7%), and GIB in 13 (5.6%). Cardiac involvement included arrhythmia in 48 patients (20.5%) and cardiomyopathy in 40 (17.1%).

The autoantibody profile revealed that 209 patients (89.3%) were positive for antinuclear antibodies. Anti-Scl-70 was detected in 67 patients (28.6%), ACA in 30 (12.8%), and anti-RNP in 38 (16.2%).

Characteristics of SSc patients with SRC and PAH

The clinical characteristics, treatment, and outcomes of the 17 patients with SSc who developed both SRC and PAH are summarised in Table I. Among these patients, 15 (88.2%) were female and 2 (11.8%) were male. The mean age at diagnosis was 56.8±12.2 years. The median disease duration at diagnosis was 1.0 year (0.1, 5.0), and the median follow-up duration was 2.3 years (1.3, 6.3). Twelve patients (70.6%) were classified as having dcSSc.

Regarding clinical manifestations, Raynaud's phenomenon was present in 14 patients (82.4%), telangiectasia in 3 (17.6%), and digital ulcers in 6 (35.3%); however, digital gangrene was not observed in any patient. ILD was present in all patients. Cardiac involvement included cardiomyopathy in 3 patients (17.6%), arrhythmia in 4 (23.5%), and pericardial effusion in 9 (52.9%). GERD was observed in 4 patients (23.5%), and 6 (35.3%) experienced GIB during the disease course. PAH was diagnosed by right heart catheterisation in 4 patients and by echocardiography in 13 patients.

Autoantibody testing showed antinuclear antibody positivity in 14 patients (82.4%). Anti-Scl-70 was detected in 5 patients (29.4%), ACA in 2 (11.8%), and anti-U1-RNP in 2 (11.8%).

SRC and PAH were diagnosed simultaneously in 9 patients (52.9%). PAH preceded SRC in 5 patients (29.4%), whereas SRC preceded PAH in 3 (17.6%). Twelve patients (70.6%) had received glucocorticoid therapy with prednisone >15 mg per day to control systemic inflammation prior to the onset of SRC. Among the five patients in whom PAH preceded SRC, 4 (80.0%) had received a medium-to-high dose of glucocorticoids before SRC onset. ACEi therapy was initiated in all patients immediately after SRC diagnosis. Renal function remained stable under medical treatment in 11 patients, whereas 5 required dialysis at SRC onset.

We compared the demographic and clinical characteristics across four groups: patients without PAH or SRC, patients with PAH alone, patients with SRC alone, and patients with both PAH and SRC (Table II). Patients with both PAH and SRC had a significantly higher age at disease onset than those with PAH alone or neither condition. The prevalence of dcSSc was also higher in

Table I. Clinical characteristics, treatment and prognosis of SSc patients with both SRC and PAH.

n.	Sex/Age at diagnosis	Disease type	Disease duration at diagnosis (years)	Duration from SRC to PAH (months)	Serum autoantibody	GC>15mg before developing SRC	Treatment	Outcome
1	F/73	lcSSc	6.0	0	Scl-70, ACA	No	Prednisone 15mg qd, CTX, IVIG ERAs, PDE5i, ACEi	Lowered PASP, stable renal function
2	F/61	lcSSc	2.0	0	-	Yes	Prednisone 50mg→5mg qd, CTX, PDE5i, ACEi	Stable renal function
3	F/66	lcSSc	2.0	-12	-	Yes	Prednisone 50mg→12.5mg qd, CTX, IL-6i, ERAs, PDE5i, ACEi	Renal function partially recovered; Died from GIB in 5 months after SRC
4	F/61	dcSSc	8.0	0	RNP	Yes	MP 40mg→12mg qd, MTX, ERAs, ACEi	Stable PASP and renal function
5	M/50	dcSSc	0.1	-6	Scl-70	No	Prednisone 15mg→5mg qd, CTX, IVIG, ERAs, ACEi Dialysis	Dialysis
6	F/63	dcSSc	4.0	0	ACA	No	MP 12mg qd CTX, ERAs, ACEi	Stable PASP and renal function
7	F/48	dcSSc	0.25	0	-	No	Prednisone 30mg→10mg qd CTX, JAKi, ERAs, ACEi	Dialysis
8	F/67	dcSSc	8.0	0	-	No	MMF, ERAs, PDE5i, ACEi	Lowered PASP, stable renal function
9	F/46	dcSSc	0.1	1	-	Yes	Pred 40mg qd for 10 days MTX→CTX, ACEi	Dialysis Cerebral haemorrhage
10	F/59	dcSSc	0.1	-2	-	Yes	MP 80mg→20mg qd→Pred 15mg qd MMF→CTX, ACEi	Stable renal function
11	F/33	dcSSc	1.0	60	-	Yes	Prednisone 50mg→10mg qd→ MP 16mg qd→2mg qd, MMF ERAs, ACEi	Stable PASP and renal function
12	F/57	dcSSc	0.1	0	Scl-70	Yes	MP 24mg→4mg qd, MTX+TII, ACEi	Died from acute heart failure
13	F/31	lcSSc	15.0	-204	RNP	Yes	Pred 30mg→10mg qd, CTX ERAs, PDE5i, selaxipag, ACEi	Stable PASP and renal function
14	F/67	lcSSc	0.2	0	-	Yes	MP 40mg→8mg q12h, CTX ACEi	Died from acute heart failure
15	F/62	dcSSc	1.7	0	Scl-70	Yes	Prednisone 30mg qd, CTX, ACEi	Dialysis Died during follow-up
16	F/71	dcSSc	0.1	1	Scl-70	Yes	Prednisone 30mg qd, CTX, ACEi	Dialysis Died from acute heart failure
17	M/51	dcSSc	0.7	-1	-	Yes	Prednisone 40mg→10mg qd, CTX, ERAs, ACEi	Improved renal function and separation from dialysis Lowered PASP

SSc: systemic sclerosis; SRC: scleroderma renal crisis; PAH: pulmonary arterial hypertension; GC: glucocorticoid; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; Pred: prednisone; MP: methylprednisolone; CTX: cyclophosphamide; MTX: methotrexate; TII: tripterygium glycosides; MMF: mycophenolate mofetil; IVIG: intravenous immunoglobin; ERAs: endothelin receptor antagonists; PDE5i: phosphodiesterase type 5 inhibitor; ACEi: angiotensin converting enzyme inhibitor; JAKi: Janus kinase inhibitor; PASP: pulmonary artery systolic pressure; GIB: gastrointestinal bleeding.

patients with both PAH and SRC than in those with PAH alone. Arrhythmia occurred more frequently in patients with PAH alone than in those without PAH or SRC. Patients with SRC showed higher rates of pericardial effusion and elevated cardiac troponin I (cTnI) levels compared with the other groups. GERD was more common in patients without SRC, whereas patients with both PAH and SRC were more likely to develop GIB. In terms of antibody profiles, anti-RNP positivity was more frequent in patients with PAH alone. Laboratory findings indicated that patients with SRC had higher levels of NT-proBNP, neutrophil-to-lymphocyte ratio (NLR), ESR, and ferritin

Table II. Clinical characteristics of patients with neither PAH nor SRC, PAH alone, SRC alone and both PAH and SRC.

	Neither PAH nor SRC (n=119)	PAH alone (n=61)	SRC alone (n=37)	PAH and SRC (n=17)	*p*-value
Demographic characteristics					
Gender, female (%)	95/119 (79.8%)	52/61 (85.2%)	26/37 (70.3%)	15/17 (88.2%)	0.262
Age at disease onset, years	47.3 ± 13.8	47.9 ± 12.2	51.4 ± 12.2	56.8 ± 12.2	**0.023**
Disease duration at diagnosis, years	1.0 (0.2,2.8)	2.0 (0.3,4.0)	0.5 (0.1,1.5)	1.0 (0.1, 5.0)	0.193
Smoking history	19/119 (16.0%)	9/61 (14.8%)	6/37 (16.2%)	2/17 (11.8%)	0.971
dcSSc, n (%)	56/119 (47.1%)	18/61 (29.5%)	24/37 (64.9%)	12/17 (70.6%)	**0.001**
Arthritis, n (%)	42/119 (35.3%)	20/61 (32.8%)	8/37 (21.6%)	6/17 (35.3%)	0.478
Muscle involvement, n (%)	15/119 (12.6%)	3/61 (4.9%)	2/37 (5.4%)	0/17 (0.0%)	0.133
Peripheral vasculopathy					
Raynaud's phenomenon, n (%)	98/119 (82.4%)	57/61 (93.4%)	28/37 (75.7%)	14/17 (82.4%)	0.099
Telangiectasias, n (%)	31/119 (26.1%)	23/61 (37.7%)	3/37 (8.1%)	3/17 (17.6%)	**0.011**
Digital ulcer, n (%)	40/119 (33.6%)	24/61 (39.3%)	8/37 (21.6%)	6/17 (35.3%)	0.346
Digital gangrene, n (%)	20/119 (16.8%)	8/61 (13.1%)	2/37 (5.4%)	0/17 (0.0%)	0.111
ILD, n (%)	101/119 (84.9%)	51/61 (83.6%)	27/37 (73.0%)	17/17 (100.0%)	0.087
Cardiac involvement					
Arrhythmia, n (%)	18/119 (15.1%)	21/61 (34.4%)	5/37 (13.5%)	4/17 (23.5%)	**0.014**
Myocardial involvement, n (%)	15/119 (12.6%)	15/61 (24.6%)	7/37 (18.9%)	3/17 (17.6%)	0.241
Pericardial effusion, n (%)	28/119 (23.5%)	8/61 (13.1%)	18/37 (48.6%)	9/17 (52.9%)	**<0.001**
cTnI elevation, n (%)	23/119 (19.3%)	14/61 (23.0%)	20/37 (54.1%)	12/17 (70.6%)	**<0.001**
LVEF, %	68.0 (63.0,71.0)	65.0 (60.0,71.8)	65.0 (61.3, 71.8)	65.0 (58.5, 69.0)	0.587
GERD	57/119 (47.9%)	36/61 (59.0%)	10/37 (27.0%)	4/17 (23.5%)	**0.004**
GIB	2/119 (1.7%)	3/61 (4.9%)	2/37 (5.4%)	6/17 (35.3%)	**<0.001**
Antibodies					
ANA, n (%)	105/119 (88.2%)	58/61 (95.1%)	32/37 (86.5%)	14/17 (82.4%)	0.328
Anti-SSA, n (%)	24/119 (20.2%)	14/61 (23.0%)	9/37 (24.3%)	5/17 (29.4%)	0.822
Anti-SSB, n (%)	1/119 (0.8%)	4/61 (6.6%)	1/37 (2.7%)	0/17 (0.0%)	0.124
Anti Scl-70, n (%)	38/119 (31.9%)	14/61 (23.0%)	10/37 (27.0%)	5/17 (29.4%)	0.648
Anti-centromere, n(%)	21/119 (17.6%)	6/61 (9.8%)	1/37 (2.7%)	2/17 (11.8%)	0.095
Anti RNP, n (%)	11/119 (9.2%)	21/61 (34.4%)	4/37 (10.8%)	2/17 (11.8%)	**<0.001**
Anti-mitochondrial M2, n(%)	9/119 (7.6%)	2/61 (3.3%)	1/37 (2.7%)	0/17 (0.0%)	0.362
Laboratory parameters					
Hb	127.0 (116.0, 138.0)	124.0 (112.5, 139.0)	102.0 (85.5, 116.5)	90.0 (71.0, 112.5)	**<0.001**
WBC	6.87 (5.04, 9.29)	6.66 (5.13, 8.92)	7.20 (5.32, 10.33)	6.3 (4.6, 10.5)	0.782
PLT	224.0 (173.0, 298.0)	188.0 (157.0, 259.0)	148.0 (99.0, 221.5)	153.0 (106.5, 182.5)	**<0.001**
Alb	38.5 (35.0, 42.0)	38.0 (34.5, 41.5)	36.0 (32.5, 40.5)	32.0 (29.5, 34.5)	**<0.001**
NT-proBNP	216.0 (75.3, 785.5)	1732.0 (419.0, 2995.0)	4918.0 (2726.8, 26084.0)	12607.0 (4437.0, 34256.0)	**<0.001**
NLR	3.25 (2.15,4.97)	4.29 (2.70, 7.30)	7.0 (4.3, 10.5)	7.06 (3.79, 13.04)	**<0.001**
ESR	16.0 (10.0,27.0)	17.5 (7.0, 32.3)	25.5 (13.0, 39.8)	29.0 (11.0, 46.0)	**0.017**
Fer	75.0 (20.5,210.8)	58.0 (26.3, 152.8)	480.0 (152.5, 724.0)	246.0 (82.0, 508.0)	**<0.001**
C3	1.00 (0.83, 1.17)	1.02 (0.84, 1.10)	0.84 (0.65, 0.93)	0.79 (0.74, 0.85)	**<0.001**

PAH: pulmonary arterial hypertension; SRC: scleroderma renal crisis; dcSSc: diffuse cutaneous systemic sclerosis; OR: odds ratio; CI: confidence interval; ILD: interstitial lung disease; LVEF: left ventricular ejection fraction; GERD: gastrointestinal reflux disease; GIB: gastrointestinal bleeding; ANA: antinuclear antibodies; Hb: haemoglobin; WBC: white blood cells count; PLT: platelets count; Alb: serum albumin; NT-proBNP: N-terminal pro-brain natriuretic peptide; NLR: neutrophil-to-lymphocyte ratio; ESR: erythrocyte sedimentation rate; Fer: ferritin; C3: complement C3.

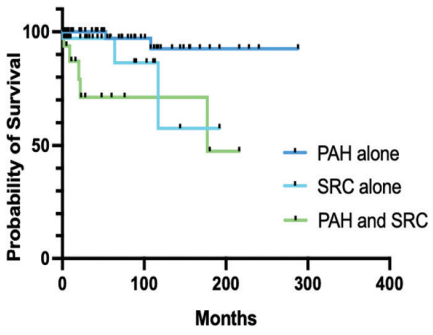

Fig. 1. Survival analysis curves of patients with PAH alone, SRC alone and both PAH and SRC. PAH: pulmonary arterial hypertension; SRC: scleroderma renal crisis.

(Fer), along with lower haemoglobin (HGB), PLT, serum Alb, and complement C3 levels.

Prognosis of the patients was further evaluated (Fig. 1). Among the 17 patients with both SRC and PAH, 5 (29.4%) died during follow-up, including one death owing to GIB and four owing to acute heart failure. One additional patient remained in a coma following cerebral haemorrhage. Patients with SRC alone and those with both SRC and PAH had significantly poorer survival than with patients with PAH alone (p=0.048 and p<0.001, respectively). No significant difference in survival was observed between patients with SRC alone and those with both SRC and PAH (p=0.261).

Factors related to SSc with both SRC and PAH

To identify factors related to systemic sclerosis with both SRC and PAH, we compared the characteristics of patients with SRC and PAH to those only with SRC or only with PAH. Clinical characteristics and laboratory parameters with significant difference were presented in Table III and Table IV, respectively.

Table III. Factors related to the development of both PAH and SRC comparing to patients with PAH alone.

	PAH alone (n=61)	PAH and SRC (n=17)	Univariate *p*-value	Multivariate analysis OR (95%CI)	Multivariate analysis *p*-value
Clinical characteristics					
Age at disease onset, years	47.9 ± 12.2	56.8 ± 12.2	0.005	1.200 (1.014, 1.420)	0.033
dcSSc, n(%)	18/61 (29.5%)	12/17 (70.6%)	0.002		0.140
Pericardial effusion, n(%)	8/61 (13.1%)	9/17 (52.9%)	0.001		
cTnI elevation, n(%)	14/61 (23.0%)	12/17 (70.6%)	<0.001		0.110
GERD	36/61 (59.0%)	4/17 (23.5%)	0.010		0.272
GIB	3/61 (4.9%)	6/17 (35.3%)	0.003		
Laboratory parameters					
Hb	124.0 (112.5, 139.0)	90.0 (71.0, 112.5)	<0.001		0.090
PLT	188.0 (157.0, 259.0)	153.0 (106.5, 182.5)	0.002		0.373
Alb	38.0 (34.5, 41.5)	32.0 (29.5, 34.5)	<0.001		0.565
NT-proBNP	1732.0 (419.0, 2995.0)	12607.0 (4437.0, 34256.0)	<0.001	1.001 (1.000, 1.001)	0.030
C3	1.02 (0.84, 1.10)	0.79 (0.74, 0.85)	<0.001		

PAH: pulmonary arterial hypertension; SRC: scleroderma renal crisis; OR: odds ratio; CI: confidence interval; dcSSc: diffuse cutaneous systemic sclerosis; GERD: gastrointestinal reflux disease; GIB: gastrointestinal bleeding; ANA: antinuclear antibodies; Hb: haemoglobin; PLT: platelets count; Alb: serum albumin; NT-proBNP: N-terminal pro-brain natriuretic peptide; C3: complement C3.

Table IV. Factors related to the development of both PAH and SRC comparing to patients with SRC alone.

	SRC alone (n=37)	PAH and SRC (n=17)	Univariate *p*-value	Multivariate analysis OR (95% CI)	Multivariate analysis *p*-value
Clinical characteristics					
ILD, n (%)	27/37 (73.0%)	17/17 (100.0%)	0.022		0.999
GIB	2/37 (5.4%)	6/17 (35.3%)	0.009	9.545 (1.679, 54.264)	0.011
Laboratory parameters					
Alb	36.0 (32.5, 40.5)	32.0 (29.5, 34.5)	0.010		0.194

PAH: pulmonary arterial hypertension; SRC: scleroderma renal crisis; OR: odds ratio; CI: confidence interval; ILD: interstitial lung disease; GIB: gastrointestinal bleeding; Alb: serum albumin.

When compared to patients with PAH (Table III), the age at disease onset was significantly higher in patients with SRC and PAH (56.8±12.2 *vs*. 47.9±12.2, *p*=0.005). The proportion of patients with dcSSc was significantly higher in those with SRC and PAH (12/17, 70.6% *vs*. 18/61, 29.5%, *p*=0.002). Patients with SRC and PAH also demonstrated higher rate of GIB (6/17, 35.3% *vs*. 3/61, 4.9%, *p*=0.003), pericardial effusion (9/17, 52.9% *vs*. 8/61, 13.1%, *p*=0.001), and elevated cTnI (12/17, 70.6% *vs*. 14/61, 23.0%, *p*<0.001), and lower rate of GERD (4/17, 23.5% *vs*. 36/61, 59.0%, *p*=0.010). The antibody profile was not significantly different between patients with SRC and PAH and those only with PAH. Considering laboratory parameters, SSc patients with SRC and PAH presented with significantly lower HGB levels (90.0 (71.0, 112.5) *vs*. 124.0 (112.5, 139.0), *p*<0.001), lower PLT count (153.0 (106.5, 182.5) *vs*. 188.0 (157.0, 259.0), *p*=0.002), and lower serum Alb level (32.0 (29.5, 34.5) *vs*. 38.0 (34.5, 41.5), *p*<0.001) when compared to patients only with PAH. We also found significantly higher NT-proBNP level (12607.0 (4437.0, 34256.0) *vs*. 1732.0 (419.0, 2995.0), *p*<0.001) and lower C3 levels (0.79 (0.74, 0.85) *vs*. 1.02 (0.84, 1.10)) in SSc patients with SRC and PAH. Machine learning LASSO regression yielded a final selection of eight potential predictive factors (dcSSc, cTnI elevation, haemoglobin, platelet count, serum albumin, NT-proBNP, age at disease onset and GERD). Multivariate logistic regression confirmed that age at disease onset (OR=1.200 (1.014, 1.420), *p*=0.033) and NT-proBNP level (OR=1.001 (1.000, 1.001), *p*=0.030) were independent factors associated with SSc with both SRC and PAH.

When compared to patients with SRC alone (Table IV), the proportion of ILD was significantly higher in patients with SRC and PAH (17/17, 100% *vs*. 27/37, 73%, *p*=0.022). GIB was significantly more prevalent in patients with SRC and PAH (6/17, 35.3% *vs*. 2/37, 5.4%, *p*=0.009). Serum albumin levels were significantly lower in patients with SRC and PAH (32.0 (29.5, 34.5) *vs*. 36.0 (32.5, 40.5), *p*=0.010). Logistic regression analysis showed that GIB was significantly related to SSc with both SRC and PAH.

Discussion

PAH and SRC are severe vascular complications and leading causes of mortality in patients with SSc (16). Although these complications are not mutually exclusive, their coexistence has been rarely reported (9). Previous studies have demonstrated differential expression of serum soluble adhesion molecules, such as E-selectin and sVCAM-1, in patients with SRC and PAH, suggesting distinct mechanisms of endothelial activation underlying these complications (8).

This study presents a case series of 17

patients with SSc who developed both PAH and SRC and, to our knowledge, is the first to identify factors associated with their coexistence. Gunduz *et al*. previously reported 11 patients with SSc who developed both complications between 1979 and 1999 (9). In that series, pulmonary hypertension preceded SRC in 10 patients, with a mean interval of 4.3 years, while both conditions occurred simultaneously in one patient. In contrast, our findings demonstrate that PAH may precede, follow, or coincide with SRC. Notably, five patients developed PAH prior to SRC, which contrasts with the typical pattern in which SRC occurs early and PAH develops later in the disease course. Importantly, 80% of patients in whom PAH preceded SRC had received high-dose glucocorticoid therapy prior to SRC onset. Exposure to glucocorticoids at doses >15 mg/day has been identified as a predictor of SRC, likely owing to vasoconstrictive effects on renal arteries and impaired renal perfusion (17-19). Given that patients with connective tissue disease-associated PAH often receive glucocorticoids to control inflammation, high-dose glucocorticoid exposure might contribute to the development of SRC following PAH.

We observed a higher prevalence of GIB in patients with SSc who had both SRC and PAH, and GIB was identified as an independent factor associated with their coexistence compared with SRC alone. Previous studies have reported an increased risk of GIB in patients with SSc, with hazard ratios ranging from 1.08–3.93 compared with the general population (20, 21), and this risk is further elevated in the presence of organ involvement. Mucosal telangiectasia is the most common cause of GIB in SSc, while other causes include peptic ulcer disease, erosive gastritis, and combined oesophageal and gastric varices (22). The association between PAH or SRC and an increased risk of GIB or mucosal telangiectasia has not been well established; however, cutaneous telangiectasia has been strongly associated with PAH (6). In our cohort, patients with both SRC and PAH exhibited a higher prevalence of telangiectasia than those with SRC alone, although this difference was not statistically significant. These findings suggest that patients with both conditions may have more extensive and severe vascular involvement, including mucosal telangiectasia, contributing to an increased risk of GIB. Compared with patients with PAH alone, older age at disease onset and elevated NT-proBNP levels were independently associated with the coexistence of PAH and SRC. NT-proBNP was regarded as a biomarker of hemodynamic impairment, reflecting pulmonary hypertension and cardiac dysfunction, and is a strong predictor of survival in patients with SSc-associated PAH (23-25). In patients with both SRC and PAH, elevated NT-proBNP levels likely reflect the combined effects of cardiac and renal dysfunction. Although renal impairment contributes to increased NT-proBNP levels, previous studies have demonstrated that NT-proBNP remains an independent predictor of survival in patients with pulmonary hypertension despite renal dysfunction (26), highlighting the importance of monitoring NT-proBNP in this population.

Lower haemoglobin levels were also observed in patients with both SRC and PAH compared with those with PAH alone, consistent with previous reports identifying anaemia as an independent predictor of SRC (17, 18). Anaemia in SSc may result from multiple factors, including systemic inflammation, chronic gastrointestinal blood loss owing to vascular ectasia, and thrombotic microangiopathy (17, 27). The observed elevation in ferritin levels and reduction in complement C3 further support the contribution of inflammation and microangiopathy to anaemia in these patients.

The prognosis of patients with both SRC and PAH in our cohort was more favourable than that reported in earlier studies. In the case series by Gunduz *et al*. (9), 10 of 11 patients died, with most deaths attributed to pulmonary hypertension (n=8). In contrast, five patients in our cohort died during follow-up. This improvement is consistent with evidence of advances in vascular outcomes in SSc over time (28). The improved prognosis of pulmonary hypertension can be attributed to the use of targeted therapies (29). In addition, endothelin receptor antagonists (ERAs) and phosphodiesterase-5 inhibitors (PDE5i) have been associated with delayed onset of SRC in patients with digital ulcers (30). In our cohort, immediate initiation of ACEi following SRC diagnosis resulted in stable renal function in 64.7% of patients. ACE inhibitors remain the cornerstone of SRC management, and their effectiveness in preserving renal function is consistent with previous reports, including those by Gunduz *et al*., in which 3 out of 7 patients who initially required dialysis subsequently recovered renal function and discontinued the treatment (9).

This study has several limitations. First, the retrospective design and extended period of data collection may have introduced selection bias. Second, the rarity of patients with both SRC and PAH resulted in a limited sample size, which may affect the reliability of regression. The number of events per variable (EPV) in the multivariate model, which included two variables, was approximately 8.5, slightly below the conventional threshold of 10 but within an acceptable range for exploratory analyses in the context of rare clinical events. External validation in larger, multicentre cohorts is required to confirm these findings. Third, RHC was not performed in all patients owing to its invasive nature and current guideline recommendations favouring non-invasive screening for PAH, which may have reduced diagnostic sensitivity for PAH (31). Additionally, patients in our study were not routinely tested for anti-Th/To and anti-RNA polymerase III, which have been associated with an increased risk of subsequent PAH (9), thereby limiting evaluation of their associations with clinical manifestations.

Conclusions

This study demonstrates that SRC and PAH, albeit rarely, can coexist in patients with SSc. PAH may precede, follow, or coincide with SRC. The increased risk of gastrointestinal bleeding in these patients warrants close monitoring. Older age at disease onset and elevated NT-proBNP levels were identified as independent factors associated with the coexistence of SRC and PAH.

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