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ORIGINAL RESEARCH

Latent trajectory modelling of pulmonary artery pressure in systemic sclerosis: a retrospective cohort study

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ABSTRACT

Objectives To visualise the trajectories of pulmonary arterial pressure (PAP) in systemic sclerosis (SSc) and identify the clinical phenotypes for each trajectory, by applying latent trajectory modelling for PAP repeatedly estimated by echocardiography.

Methods This was a multicentre, retrospective cohort study conducted at four referral hospitals in Kyoto, Japan. Patients with SSc who were treated at study sites between 2008 and 2021 and who had at least three echocardiographic measurements of systolic PAP (sPAP) were included. A group-based trajectory model was applied to the change in sPAP over time, and patients were classified into distinct subgroups that followed similar trajectories. Pulmonary hypertension (PH)-free survival was compared for each trajectory. Multinomial logistic regression analysis was performed for baseline clinical characteristics associated with trajectory assignment.

Results A total of 236 patients with 1097 sPAP measurements were included. We identified five trajectories: rapid progression (n=9, 3.8%), early elevation (n=30, 12.7%), middle elevation (n=54, 22.9%), late elevation (n=24, 10.2%) and low stable (n=119, 50.4%). The trajectories, in the listed order, showed progressively earlier elevation of sPAP and shorter PH-free survival. In the multinomial logistic regression analysis with the low stable as a reference, cardiac involvement was associated with rapid progression, diffuse cutaneous SSc was associated with early elevation and anti-centromere antibody was associated with middle elevation; older age of onset was associated with all three of these trajectories.

Conclusion The pattern of changes in PAP over time in SSc can be classified into five trajectories with distinctly different clinical characteristics and outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pulmonary hypertension, defined as elevated pulmonary arterial pressure (PAP), is an important organ involvement leading to increased mortality in systemic sclerosis (SSc).

⇒ Prediction of the pattern of PAP elevation and future risk of pulmonary hypertension (PH) in individual patients has not been established.

WHAT THIS STUDY ADDS

⇒ By latent trajectory modelling, we show that changes in PAP over time in patients with SSc could be divided into five distinct trajectories.

⇒ Each trajectory differed in PH-related outcomes and was characterised by baseline clinical characteristics of SSc during the 3 years from onset.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further studies focusing on temporal changes in PAP may lead to more accurate clinical prediction of PH and establishment of risk-stratified treatment strategies.

INTRODUCTION

Systemic sclerosis (SSc) is an immune-mediated rheumatic disease with high mortality characterised by systemic vasculopathy and fibrosis.[1 2] Pulmonary hypertension (PH), defined as elevated pulmonary arterial pressure (PAP), is a life-threatening organ involvement that occurs in approximately 12%–23% of patients with SSc.[3–5] While other organ involvement in SSc often appears within the first 3 years of disease onset, PH tends to develop after prolonged disease[6]; hence, echocardiographic PAP estimation is recommended and accepted as an annual screening.[7–10] Recently, therapeutic agents have been developed to target the triad of SSc pathophysiology: autoimmunity, vasculopathy and fibrosis. The challenge is how to stratify the risk of PH progression to provide individualised treatment.[1]

Currently, it is difficult to identify patients who are potentially developing PH because PAP elevation does not occur until pulmonary vascular damage is advanced.[11] Prediction of PH progression is not well established, and

early intervention based on stratified risk for future PH has not been achieved. Some studies focusing on changes in PAP over time have reported an association with PH development and death.[12 13] However, because of within-individual fluctuations in PAP and variable timing of the elevation, it has not been possible to predict when and how PAP will change in an individual patient.

In this study, we hypothesised that changes in PAP over time in SSc comprise several distinct patterns and that patients with SSc can be classified into subgroups that follow certain trajectories. Latent trajectory modelling is an epidemiological technique for identifying and characterising homogeneous populations based on changes in indicators measured over time, such as disease biomarkers,[14 15] and has been used for changes in pulmonary function and skin score in SSc.[16 17] We applied latent trajectory modelling to systolic PAP (sPAP), which is repeatedly measured by echocardiographic estimation, to visualise the PAP trajectories in SSc and to identify the clinical phenotype of SSc characterising each trajectory.

METHODS

Study design and settings

This was a multicentre retrospective cohort study conducted at four referral hospitals in Kyoto, Japan (University Hospital of Kyoto Prefectural University of Medicine, Japanese Red Cross Kyoto Daiichi Hospital, Japanese Red Cross Kyoto Daini Hospital and Fukuchiyama City Hospital).

Patients

Adult patients (≥18 years) with SSc fulfilling the 2013 classification criteria of the American College of Rheumatology/European Alliance of Associations for Rheumatology[18 19] who visited a study site between April 2008 and March 2021 and who had at least three echocardiographic measurements of sPAP were included. Among these patients, we excluded those (a) who started pulmonary vasodilators (eg, ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat, epoprostenol, iloprost, treprostinil and selexipag) before three echocardiographic measurements of sPAP, (b) with a diagnosis of other rheumatic diseases or chronic heart failure of any cause prior to SSc, and (c) with missing clinical data (pre-assumed to be quite small).

Data collection

The information used in this study was obtained from the patients' medical records, and each variable was classified into the following three categories:

1. Baseline data: the onset date of SSc defined as the date of onset of clinical symptoms other than Raynaud's phenomenon, age at onset, sex, smoking history, coexisting hypertension and the following clinical manifestations during the 3 years from onset: type of specific autoantibodies (eg, anti-centromere antibody, anti-topoisomerase I antibody, anti-RNA polymerase III antibody), disease type (diffuse cutaneous SSc (dcSSc) vs limited cutaneous SSc (lcSSc)), lung fibrosis, cardiac involvement (define as inflammatory/fibrotic lesions of the myocardium and/or pericardium primarily due to SSc, for example, cardiomyopathy and pericarditis) and digital ulcers.
2. Time series data for PAP: sPAP values repeatedly measured by echocardiographic estimation and the duration from the onset to the date of each test. sPAP was calculated by adding the right ventricular to right atrial systolic gradient estimated by the simplified Bernoulli equation using the peak tricuspid regurgitation velocity (TRV) and the right atrial pressure estimated on the basis of the diameter and respiratory variation of the inferior vena cava.[7 8] If patients started pulmonary vasodilators (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, guanylate cyclase stimulators and prostacyclin agonists), subsequent data were excluded from the analysis as these drugs can decrease sPAP.
3. Clinical outcomes relevant to elevated PAP: PH, pre-capillary PH, hospitalisation for heart failure from any cause and death from any cause. The presence of each outcome and the duration from the onset were recorded. PH and pre-capillary PH were defined and classified using the criteria of the sixth World Symposium on Pulmonary Hypertension on the basis of right heart catheterisation performed at the discretion of the physician.[20] Namely, PH was defined as mean PAP (mPAP) >20 mm Hg and pre-capillary PH as mPAP >20 mm Hg and pulmonary artery wedge pressure (PAWP) ≤15 mm Hg, and pre-capillary PH was further classified by adding pulmonary vascular resistance (PVR) >2 or >3 Wood units (WU) to the definition.

The follow-up period for individual patients was from disease onset through death, lost to follow-up or March 2021.

Latent trajectory modelling

To identify patterns of PAP change over time, a group-based trajectory model (GBTM) was fitted to the time series of sPAP data measured by echocardiographic estimation. GBTM is a statistical application of finite mixture modelling, which aims to assign individual patients to distinct subgroups that follow similar trajectories (patterns of change) by modelling between-person differences in within-person change on longitudinal observational data. To select an appropriate model, the analysis was performed with reference to the proposed frameworks.[14 15] First, we sequentially generated models in which the number of trajectories ranged from two to seven, and the shape of the trajectories was represented by polynomial functions ranging from first to third order. The appropriate model was determined using the following adequacy criteria: (a) the average posterior probability of assignments for each trajectory should be >0.7, (b) the odds of correct classification for each trajectory should be >5, (c) the relative entropy should be >0.5 and (d) the minimum number of individuals assigned to each trajectory should exceed 3% of the total population. Of the models that met all of the above criteria, one final

model was identified based on the Bayesian information criterion and clinical interpretability for the number and shape of the trajectories.

To assess the clinical plausibility of the modelling, clinical outcomes were compared for each identified trajectory. The primary outcome was PH-free survival (time until PH or death from any cause), and the secondary outcomes were PH, pre-capillary PH, hospitalisation for heart failure from any cause and death from any cause. For sensitivity analysis, PH redefined as mPAP ≥25 mm Hg instead of mPAP >20 mm Hg and pre-capillary PH with PVR >2 or >3 WU in addition to mPAP >20 mm Hg and PAWP ≤15 mm Hg were also evaluated.

To investigate the clinical phenotype characterising each identified trajectory, we examined the clinical characteristics of SSc during the baseline period of 3 years from disease onset. As candidate factors, 11 variables were prespecified in accordance with previous studies and clinical perspectives, comprising age of onset, sex, smoking history, coexisting hypertension (these four variables are also surrogate markers of left heart disease and lung disease other than SSc), anti-centromere antibody positive, anti-topoisomerase I antibody positive, anti-RNA polymerase III antibody positive, dcSSc, lung fibrosis, cardiac involvement and digital ulcers. These baseline clinical factors during the 3 years from onset were described for each trajectory, and their association with each trajectory was evaluated.

Statistical analysis

Data were summarised using number and percentage (%) for categorical variables and median and IQR for continuous variables. Survival time data (time-to-event data) were described using Kaplan-Meier survival curves or cumulative incidence functions accounting for death as a competing risk.

Baseline clinical characteristics during the 3 years from onset associated with each trajectory were estimated by multinomial logistic regression with the clinical factors (11 variables) as independent variables and trajectory membership as a dependent variable (with the group with the largest number of patients as a reference). As a sensitivity analysis, we also performed ordinal logistic regression with the assumption of proportional odds; that is, the effect of each clinical factor on trajectory membership is constant regarding the order in which PAP elevates earlier. The magnitude of the association was described using point estimates of ORs and 95% CIs.

Stata V.17.0 (Stata Corp, College Station, Texas, USA) was used for fitting the GBTM, and R software V.4.03 (R Foundation for Statistical Computing, Vienna, Austria) was used for all other analyses.

RESULTS

Patient characteristics

Of the 447 patients with SSc, 251 had ≥3 sPAP measurements. We enrolled 236 patients, excluding 15 who met the exclusion criteria (figure 1). The median age of onset in the study population was 61 years (IQR: 49–69); 204 (86%) were female, and the median observation period was 10.7 years (IQR: 6.6–15.6). A total of 1097 echocardiographic estimations of sPAP were performed, with a median of four measurements per patient (IQR: 3–5), median interval of 1.2 years (IQR: 0.9–2.1) and median sPAP of 28 mm Hg (IQR: 23–32).

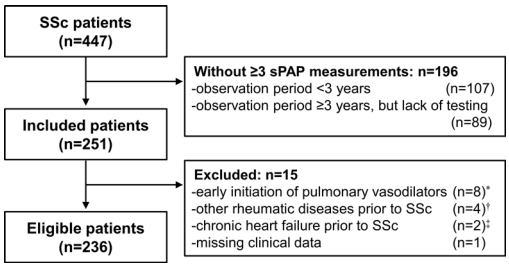

Figure 1 Patient flow diagram. *Four for pulmonary arterial hypertension and four for digital ulcers. †One dermatomyositis, one microscopic polyangiitis, two systemic lupus erythematosus. ‡One valvular heart disease and one atrial fibrillation. sPAP, systolic pulmonary arterial pressure; SSc, systemic sclerosis.

PAP trajectories

We selected a model fitting a quadratic function to the five groups that met all selection criteria and that was clinically interpretable (online supplemental table 1). Five distinct trajectories of PAP elevation were identified: rapid progression (n=9, 3.8%), with a rapid increase in sPAP from early disease onset; early elevation (n=30, 12.7%), with an increase within 5 years of onset; middle elevation (n=54, 22.9%), with an increase after 5 years of onset; late elevation (n=24, 10.2%), with an increase after 10–15 years of onset; and low stable (n=119, 50.4%), with persistently low values (figure 2A).

During the observation period, 47 patients underwent right heart catheterisation, 36 of whom were diagnosed with PH (including 31 with pre-capillary PH); the clinical classification of PH and haemodynamic parameters for patients diagnosed with PH are shown in online supplemental table 2. When assessing clinical outcomes, PH-free survival was shorter for trajectories with earlier elevation in sPAP (figure 2B). Similar to PH-free survival, compared with trajectories with later sPAP elevations, trajectories with earlier sPAP elevation showed approximately shorter times to all secondary outcomes: PH, pre-capillary PH, hospitalisation for heart failure from any cause and death from any cause (figure 2C–F). The sensitivity analysis with different definitions of PH and pre-capillary PH demonstrated consistent results (online supplemental figure 1).

Baseline clinical characteristics associated with each trajectory

Table 1 shows the clinical characteristics of each trajectory during the baseline period of 3 years from disease onset. In the multinomial logistic regression (with low

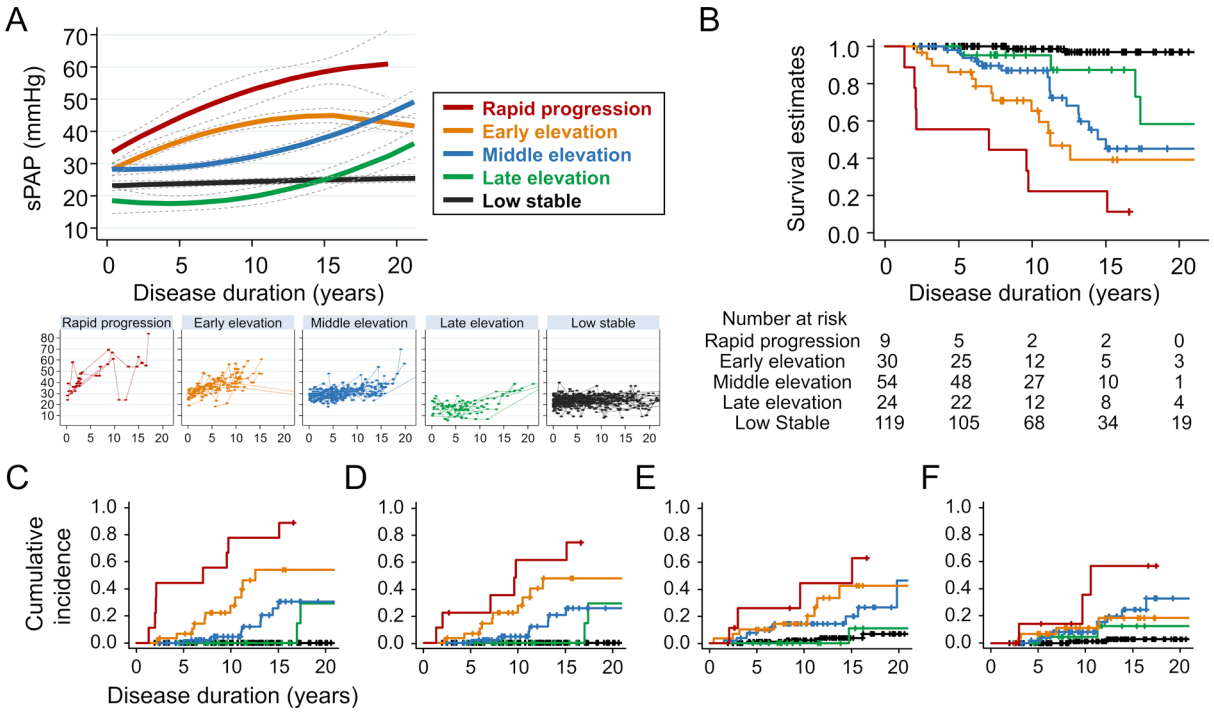

Figure 2 Trajectories of pulmonary arterial pressure and clinical outcomes in patients with systemic sclerosis. (A) Trajectories of sPAP with 95% CIs, identified by group-based trajectory modelling and individual patient fluctuations in each trajectory. (B) Kaplan-Meier survival estimates for PH-free survival in each trajectory. (C–F) Cumulative incidence functions of PH (C), pre-capillary PH (D), hospitalisation for heart failure from any cause (E) and death from any cause (F) in each trajectory. PH, pulmonary hypertension; sPAP, systolic pulmonary arterial pressure.

stable as a reference), cardiac involvement was associated with rapid progression, dcSSc was associated with early elevation and anti-centromere antibody positive was associated with middle elevation trajectories (table 2). Older age of onset was associated with rapid progression, early elevation and middle elevation trajectories. No

Table 1 Baseline clinical characteristics of the 236 patients with SSc

Clinical factors	All (n=236)	PAP trajectories				
		Rapid progression (n=9)	Early elevation (n=30)	Middle elevation (n=54)	Late elevation (n=24)	Low stable (n=119)
Age of onset (years)	61 (49–69)	73 (55–74)	67 (61–71)	65 (58–70)	51 (45–58)	58 (48–67)
Female	204 (86)	8 (89)	27 (90)	42 (78)	22 (92)	105 (88)
Ever smoking	65 (28)	4 (44)	9 (30)	16 (30)	6 (25)	30 (25)
Hypertension	81 (34)	5 (56)	13 (43)	24 (44)	8 (33)	31 (26)
Type of autoantibody*						
Anti-centromere	142 (60)	4 (44)	13 (43)	38 (70)	12 (50)	75 (63)
Anti-topoisomerase I	47 (20)	1 (11)	7 (23)	12 (22)	7 (29)	20 (17)
Anti-RNA polymerase III	13 (5.5)	2 (22)	3 (10)	1 (1.9)	1 (4.2)	6 (5.0)
Diffuse cutaneous SSc	58 (25)	2 (22)	13 (43)	14 (26)	8 (33)	21 (18)
Lung fibrosis	82 (35)	6 (67)	16 (53)	21 (39)	8 (33)	31 (26)
Cardiac involvement	18 (7.6)	5 (56)	3 (10)	5 (9.3)	2 (8.3)	3 (2.5)
Digital ulcers	70 (30)	5 (56)	11 (37)	19 (35)	7 (29)	28 (24)

Patient clinical characteristics overall and for each trajectory during the baseline period of 3 years from disease onset. Age of onset is described as median (IQR), and other categorical variables are described as number (%).
*Of the patients who were negative for all three autoantibodies shown, 15 were ANA positive (10 with the nucleolar pattern) and 19 were ANA negative.
ANA, antinuclear antibody; PAP, pulmonary arterial pressure; SSc, systemic sclerosis.

Table 2 Clinical factors associated with each trajectory

	Rapid progression		Early elevation		Middle elevation		Late elevation	
Clinical factors	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Age of onset (years)	**1.09**	**1.00 to 1.18**	**1.08**	**1.03 to 1.13**	**1.04**	**1.01 to 1.07**	0.98	0.95 to 1.02
Female	5.86	0.23 to 148.2	3.88	0.72 to 21.03	0.48	0.16 to 1.50	2.21	0.39 to 12.36
Ever smoking	1.53	0.20 to 11.49	2.11	0.67 to 6.63	1.07	0.43 to 2.66	1.01	0.32 to 3.20
Hypertension	1.39	0.23 to 8.52	1.66	0.65 to 4.23	1.87	0.90 to 3.89	1.76	0.65 to 4.77
Type of autoantibody								
Anti-centromere	0.92	0.10 to 8.70	0.65	0.17 to 2.43	**4.50**	**1.11 to 18.19**	0.83	0.22 to 3.20
Anti-topoisomerase I	0.54	0.02 to 14.26	0.58	0.13 to 2.51	2.63	0.54 to 12.75	1.50	0.31 to 6.85
Anti-RNA polymerase III	3.84	0.22 to 68.52	1.31	0.19 to 9.25	0.90	0.07 to 11.63	0.90	0.08 to 10.18
Diffuse cutaneous SSc	1.61	0.13 to 20.19	**4.08**	**1.27 to 13.12**	1.92	0.66 to 5.59	1.97	0.60 to 6.48
Lung fibrosis	3.47	0.57 to 21.0	1.90	0.65 to 5.60	1.62	0.69 to 3.84	0.94	0.29 to 3.03
Cardiac involvement	**28.85**	**3.21 to 259.5**	2.83	0.43 to 18.84	3.45	0.68 to 17.65	3.54	0.50 to 25.26
Digital ulcers	2.29	0.39 to 13.43	1.76	0.64 to 4.85	1.85	0.82 to 4.15	0.89	0.30 to 2.63

The ORs and 95% CIs adjusted for all 11 variables in a multinomial logistic regression model with the low stable trajectory as the reference are shown. Results are highlighted in bold when the 95% CI did not exceed 1.0 (the null value).
SSc, systemic sclerosis.

obvious differences in clinical characteristics were found when comparing the late elevation and low stable trajectories.

A sensitivity analysis using ordinal logistic regression showed that older age of onset, dcSSc and cardiac involvement were associated with a shift in membership towards trajectories with earlier sPAP elevation (online supplemental table 3). These results were approximately consistent with those of the multinomial logistic regression.

DISCUSSION

In this study, we performed latent trajectory modelling for changes in PAP over time in patients with SSc and identified five trajectories with different patterns of elevation. Depending on which trajectory the patient belonged to, there were differences not only in PH-related clinical outcomes, but also in baseline clinical characteristics during the first 3 years after disease onset. Specifically, the rapid progression, early elevation, middle elevation and late elevation trajectories, in that order, showed earlier sPAP elevation, more frequent PH progression and poorer survival. About half of the patients belonged to the low stable trajectory, in which there was no elevation of sPAP. Furthermore, of each trajectory, the rapid progression was associated with older age of onset and cardiac involvement, the early elevation was associated with older age of onset and dcSSc, and the middle elevation was associated with older age of onset and anti-centromere antibody positive.

This study identified cardiac involvement, dcSSc and anti-centromere antibody positive as baseline predisposing phenotypes for the trajectories exhibiting PH progression. These results were consistent with those in previous studies showing a higher frequency of PH in a population of patients with SSc characterised by cardiac involvement and dcSSc[21] and anti-centromere antibody positive.[22 23] In particular, the fact that each of these clinical factors was associated with distinct trajectories exhibiting different rates of PH progression may provide novel insights. The pathophysiology of PH in SSc is known to be a complex mechanism that overlaps pulmonary arterial hypertension, PH due to left heart disease, and PH due to lung disease and/or hypoxia. Our findings support the hypothesis that multiple risk factors do not share a common effect on a single entity of PH, but rather contribute to PAP elevation additively through separate pathological mechanisms.[24] As an example, compared with other trajectories, most patients who belonged to the rapid progression trajectory were eventually diagnosed with PH and often had features of PH associated with left heart disease as well as pre-capillary PH, which may be due to the association between cardiac involvement during the first 3 years from onset and rapid progression trajectory. Note that patients with chronic heart failure preceding SSc were excluded from this study, and this association was also independent of the surrogate markers of SSc-unrelated left heart disease such as age of onset, sex, smoking and hypertension.

On the basis of this hypothesis discussed above, it is possible to interpret the seemingly contradictory data that PH is more frequent in dcSSc compared with lcSSc, whereas anti-centromere antibody positive is associated with a higher risk of PH compared with anti-topoisomerase I antibody positive. Patients with dcSSc, in which organ damage tends to progress earlier than in lcSSc, were more likely to follow the early elevation trajectory for PAP, while patients with anti-centromere antibody positive, in which organ damage tends to progress

after long-term disease, were more likely to follow the middle elevation trajectory, suggesting that the rate of PH progression may be diverse, depending on the SSc phenotype.

There is a couple of possible explanations why older age of onset was a characteristic of the trajectories with a higher risk of PH progression. It has been previously reported that older onset predicts PH.[4 22 25] The onset of SSc, defined by the onset of clinical symptoms other than Raynaud's phenomenon, is often difficult to determine precisely, and older patients may be less likely to be aware of clinical symptoms. Hence, the period until PH development and PAP elevation tends to be apparently shorter in patients with older onset (the so-called lead-time bias[26]). Additionally, environmental factors, which theoretically have a greater influence on older-onset SSc than genetic factors, and left ventricular diastolic dysfunction, which is known to increase with ageing,[27] are also implicated in the development of PH.

The PAP trajectories identified in this study indicate that the timing and rate of elevation of PAP as well as the risk of PH may vary depending on the clinical characteristics of SSc in each patient. SSc is a heterogeneous disease, and recent evidence suggests that phenotyping by autoantibody profile and extent of organ involvement is useful in clinical prediction.[5 21 28] Attempts to identify homogeneous subgroups regarding clinical course and therapeutic response will contribute to optimising management by stratifying the risk of disease progression. Although annual PH screening for all patients with SSc is currently recommended and generally accepted,[7–10] it would be worthwhile to adjust the follow-up interval not only based on whether the TRV and PAP measured at each test exceed the set thresholds, but also on their trend over time and the clinical phenotype of SSc.

This study has some inherent limitations. First, due to the retrospective design, the timing, interval and frequency of echocardiographic evaluations in the study population were not standardised. This may have hampered the identification of differences in clinical characteristics between similar trajectories, such as late elevation and low stable, through patient misclassification. Further prospective studies with regular and long-term monitoring of PAP may be beneficial. Second, some information on SSc was not available in this study. As mentioned above, there may be a discrepancy between the 'true' onset date of SSc and the date of onset of clinical symptoms other than Raynaud's phenomenon, depending on the disease subtype of SSc and the age of the patient. In addition, there is a possibility of residual bias in the association between baseline clinical characteristics and PAP trajectories because of the lack of information on comprehensive autoantibody profiles (other than anti-centromere antibody, anti-topoisomerase I antibody and anti-RNA polymerase III antibody), severity of organ involvement (eg, skin score, diastolic myocardial function and pulmonary function) and their changes over time. Further multitrajectory modelling combining these indicators with PAP may better clarify the causal relationship of each organ involvement. Third, patients with mild disease, such as those who require no specific treatment, were more likely to be excluded due to the lack of sPAP measurements (online supplemental table 4). Although these patients are expected to follow a trajectory similar to that of the low stable trajectory, continued PH screening is warranted because PH can occur after long-term follow-up. The number and shape of the identified trajectories may change with different populations, thus reproducibility must be validated using external data.

Regarding future perspectives, to apply the concept of 'several patterns in the natural course of PAP in SSc' visualised in the present study to clinical practice, it is necessary to develop a clinical prediction model of PH based on TRV/PAP changes over time and to verify the effectiveness of therapeutic intervention for the trajectories prone to PH progression. Our results suggest that changes in PAP over time follow non-linear trajectories; therefore, for more accurate prediction of PH, a combination of SSc disease duration and TRV/PAP trends should be considered.

In conclusion, in this study, the temporal changes in PAP in SSc were classified into five distinct trajectories, with differences in the risk of PH progression and baseline clinical characteristics for each trajectory. Focusing on PAP changes over time was considered an important concept for predicting PH and establishing treatment strategies based on risk stratification.

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Patient consent for publication Not required.

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