Article

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Clinical Features and Risk Factors of Rapidly Progressive Systemic Sclerosis in a Single Center in China: Anti-RNA Polymerase III Antibodies as a Predictor

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Objectives: Systemic sclerosis (SSc) have been classified in two clinical subsets (diffuse and limited) based on the extend of skin thickening. In this study, we classified a novel subset of SSc defined rapidly progressive systemic sclerosis (RPSSc), which based on the rate of skin thickening progression and the progressive of interstitial lung disease (ILD). We aimed to evaluate RPSSc clinical characteristics and predictive factors in a Chinese single center.

Method: Overall, 75 patients diagnosed with SSc, classified into RPSSc (n = 14) and non-rapidly progressive SSc (non-RPSSc, n = 61) were retrospectively included in the study. Clinical characteristics, disease severity and autoantibodies were collected. Logistic regression, least absolute shrinkage, and selection operator (LASSO) regression analysis was used to identify RPSSc predictors. Receiver operating characteristic (ROC) analysis and Delong test was conducted to evaluate and compare different indexes.

Results: RPSSc rate was 18.7%. ILD (64.3%), cardiac involvement (42.9%) were the most common organ system involvement of RPSSc, while Raynaud's phenomenon incidence significantly decreased. Disease duration (12 vs 72, months), sex (42.9% vs 11.5%, male %), SSc subset (85.7% vs 27.9%, diffuse cutaneous SSc (dsSSc) %), modified Rodnan total skin score (mRSS) (20.5 vs 6), Raynaud's phenomenon (64.3% vs 98.4%), cardiac involvement (42.9% vs 18%), higher incidence with malignancy (28.6% vs 1.6%) and positive anti-RNA polymerase III antibodies (ARA) (64.3% vs 1.6%) were statistically significant differences among the RPSSc groups and non-RPSSc groups ($p < 0.05$). Univariate analysis showed that positive ARA, male, dsSSc and malignancy were RPSSc risk factors, while long-disease duration, Raynaud's phenomenon was RPSSc protective factors. ARA was the strongest factor associated to RPSSc (OR 108, 95% CI 11.287–1033.327, $p < 0.001$). LASSO logistic regression model identified six factors: Disease duration, dsSSc, malignancy, cardiac involvement, positivity of ARA were RPSSc risk factors, Raynaud's phenomenon was RPSSc protective factors.

Conclusions: RPSSc is an SSc clinical category which should be accounted for early detection of organ involvement and close follow-up of malignancy. ARA might be used as a predictor for RPSSc and organ involvement.

Keywords: rapidly progressive systemic sclerosis; clinical characteristics; predictors; anti-RNA polymerase III antibodies; malignancy

Key Points:
- RPSSc rate in this Chinese single center was 18.7%. ILD and cardiac organs were the most involved organ system in RPSSc, while Raynaud's phenomenon incidence was decreased.
- Male, dsSSc, positive ARA and malignancy were RPSSc risk factors. ARA might be used as a predictor for RPSSc and organ involvement.
- RPSSc is a clinical category that should be accounted for early detection of organ involvement and close follow-up of malignancy.

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by a dysregulation of the immune system, which leads to a progressive skin and internal organs fibrosis generating vasculopathy [1]. An important feature in SSc is the alterations of innate immunity, involvement of macrophages and T and B lymphocytes, and the presence of circulating antinuclear antibodies (ANA), antitopoisomerase I antibodies (ATA or anti-Scl-70), anticentromere antibody (ACA), and anti-RNA polymerase III antibodies (ARA) [2,3]. SSc patients show a particular clinical presentation due to SSc complex pathophysiology and

specific different antibodies. According to the degree of skin and internal organ involvement in the disease and progression rate, various SSc clinical subsets have been defined to evaluate the SSc severity, such as diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) [4]. Both dcSSc and lcSSc are systemic and can affect organ involvement. Some SSc patients show quick progression and early internal organ involvement [5], what reduces the effectiveness of conventional treatment. Usually, these SSc patients show poor prognosis and a high mortality [5–8]. It is important to distinguish patients at risk of progression through by discovering specific predictors and biomarkers.

In this study, SSc was classified into rapidly progressive systemic sclerosis (RPSSc) and non-rapidly progressive SSc (non-RPSSc) based on the rate of skin thickening progression and the progressive of interstitial lung disease (ILD) in order to clarify the disease clinical characteristics, disease-specific autoantibodies and, disease severity in Chinese Han SSc patients. Additionally, factors predicting RPSSc early stage were identified.

Materials and Methods

Patients

Overall, 75 patients with SSc who were admitted between 2017 and 2021 enrolled in this study after informed consent. All SSc patients were Chinese and met the criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) [4]. Patients with active or severe infection, coronary atherosclerotic heart disease and organ transplant were excluded.

Definition

As there is not a consensus to define RPSSc [5–8], the following criteria was used:

- Initial modified Rodnan total skin score (mRSS) >12 in SSc patients with recent onset skin disease (<12 months).
- mRSS increased by >12 points during a 6-month interval.
- Forced Vital Capacity (FVC) or Total Lung Capacity (TLC) declined by >15% during a 6-month interval.

Organ System Involvement

Organ system involvement was defined on the basis of the clinical features observed during SSc course, excluding the possibility of other disorders. Sclerosis was measured using the mRSS. ILD was determined based on evidence of pulmonary fibrosis or ground glass opacities on chest radiograph or high-resolution CT (computed tomography) scan or FVC less than 70% with a forced expiratory volume in one second (FEV1)/FVC ratio lower greater than 80%. Pulmonary arterial hypertension (PAH) was defined as an elevated right ventricular systolic pressure (>40 mmHg) by echocardiography, or subsequently, as an elevated mean pulmonary artery pressure (>25 mmHg) by cardiac catheterization. Cardiac involvement included pericarditis, myocarditis or cardiomyopathy, conduction system abnormalities, confirmed by electrocardiogram (ECG), CT or echocardiogram, and not attributable to pulmonary hypertension or left heart disease, with or without cardiac enzyme abnormalities. Gastrointestinal involvement was defined as objective evidence of esophageal dysmotility on esophagography or manometry, esophageal structure, small bowel hypomotility or dilation on imaging. Scleroderma renal crisis (SRC) was defined as renal involvement with clinical manifestation including new onset hypertension (blood pressure >140/90 mmHg) and/or elevated serum creatinine, with or without evidence of microangiopathic hemolytic anemia.

Clinical and Laboratory Assessments

Laboratory tests data were recorded for analysis including complete blood count, liver and renal function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum Ig levels, serum complement levels, creatine phosphokinase (CK), ANAs (antinuclear antibodies) and urinalysis examination. Sera samples were also analyzed for the presence of autoantibodies. Antinuclear antibodies, ACA and ATA were determined by line immunoassay (LIA) using HEp-2 cell substrates (YHLO, Shenzhen, China, 925912703020). ARA was also determined by LIA (EUROIMMUN, Lubeck, Germany, CD210818LD). Patients' examinations data at baseline and annually were also recorded, including ultrasonography, ECG, highresolution CT scan, pulmonary function tests and esophageal dysmotility or manometry. mRSS and previously validated SSc severity scale were extracted for each visit. All patients underwent nail-fold video-capillaroscopy (NVC) examination (Jiangsu Xuzhou Tong-Ren Medical Electronic Technology Company, model: TR-8000, Xuzhou, China), and "giant capillary loops and/or absence of capillary loops" were defined as characteristic NVC changes of SSc [4].

Statistical Analysis

SPSS Statistics (version 22.0; IBM, Armonk, NY, USA) and R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria) and the "glmnet" package (version 3.6.1, The R Foundation, Vienna, Austria) were used for statistical analyses. All variables are expressed as mean values and standard deviation (SD) or by median values and interquartile ranges (IQR). Parameters were compared by Chisquare or Fisher tests. Student's T or Mann-Whitney tests were used to perform comparison between groups. The Univariate Logistic Regression Analysis was used to identify RPSSc predictors. Least absolute shrinkage and selection operator (LASSO) regression analysis was used to optimize variable selection and for the predicting model. Receiver operating characteristic (ROC) analysis and Delong test were used to evaluate and compare different indexes. p-value < 0.05 was considered for statistical significant difference. Figures were generated by

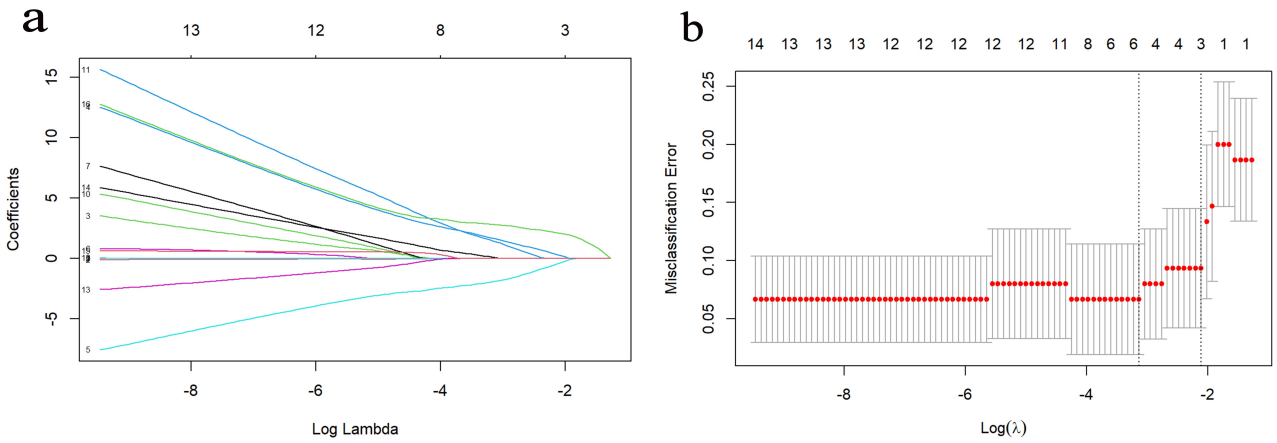

Fig. 1. Variable selection by LASSO binary logistic regression model. (a) A coefficient profile plot was produced against the log(lambda) sequence. Six variables with nonzero coefficients were selected by optimal lambda. (b) By verifying the optimal parameter (lambda) in the LASSO model, the partial likelihood deviance (binomial deviance) curve was plotted versus log(lambda) and dotted vertical lines were drawn based on 1 standard error criteria.

Table 1. Baseline characteristics differences between RPSSc and non-RPSSc patients.

Baseline characteristics	RPSSc (n = 14)	non-RPSSc (n = 61)	Z/χ^2	*p* value
Demographics				
Age at enrollment (years), median (IQR)	54.5 (46.5, 60.25)	52 (44.5, 58.5)	–0.429	0.668
Disease duration (months), median (IQR)	12 (6, 30)	72 (36, 120)	–4.015	<0.001
Sex (male), n (%)	6 (42.9%)	7(11.5%)	7.826	0.005
SSc subsets			13.719	<0.001
dcSSc, n (%)	12 (85.7%)	17 (27.9%)		
lcSSc, n (%)	2 (14.3%)	44 (72.1%)		
Clinical manifestations				
mRSS	20.5 (13.75, 28.25)	6 (4, 14)	–3.905	<0.001
Raynaud's phenomenon, n (%)	9 (64.3%)	60 (98.4%)	13.632	<0.001
Digital ulcers, n (%)	5 (35.7%)	20 (32.8%)	0.044	0.834
Skin telangiectasis, n (%)	2 (14.3%)	18 (29.5%)	0.683	0.409
NVC changes, n (%)	9 (64.3%)	40 (65.6%)	0.008	0.927
Joint involvement, n (%)	4 (28.6%)	17 (27.9%)	<0.001	1
Myositis, n (%)	2 (14.3%)	2 (3.28%)	0.987	0.32
ILD, n (%)	9 (64.3%)	32 (52.5%)	0.643	0.423
PAH, n (%)	2 (14.3%)	16 (26.2%)	0.356	0.551
Cardiac involvement, n (%)	6 (42.9%)	11 (18%)	4.003	0.045
Gastrointestinal involvement, n (%)	5 (35.7%)	12 (19.7%)	1.672	0.196
Renal crisis, n (%)	1 (7.1%)	0 (0%)	-	0.187
Malignancy, n (%)	4 (28.6%)	1 (1.6%)	9.298	0.002
Antibody			33.441	<0.001
Positive of ARA, n (%)	9 (64.3%)	1 (1.6%)		
Elevated ESR or CRP	6 (42.9%)	22 (36.1%)	0.224	0.636

Abbreviations: dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; RPSSc, rapidly progressive systemic sclerosis; Non-RPSSc, nonrapidly progressive systemic sclerosis; mRSS, modified Rodnan total skin score; NVC, nailfold video-capillaroscopy; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; ARA, anti-RNA polymerase III antibodies; ATA, antitopoisomerase I antibodies; ACA, anticentromere antibody; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

GraphPad Prism 9.0 (GraphPad Software Inc., San Diego, CA, USA).

Table 2. Univariate analysis to identify predictors for rapidly progressive SSc.

Variables	Univariate logistic regression analysis			LASSO analysis		
	HR	95% CI	*p*-value	β	*p*-value	LASSO coefficient
Disease duration (months)	0.969	0.949–0.991	0.005	–0.031	0.005	–0.001535617
Male	5.786	1.547–21.641	0.009	1.775	0.009	-
dcSSc	15.529	3.141–76.777	0.001	2.743	0.001	1.652418247
Raynaud's phenomenon	0.03	0.003–0.287	0.002	–3.507	0.002	–1.888499107
Malignancy	24	2.427–237.304	0.007	3.178	0.007	1.428476027
Cardiac involvement	3.409	0.983–11.823	0.053	1.226	0.053	0.087473699
Positive of ARA	108	11.287–1033.327	<0.001	4.682	<0.001	2.821626230

Abbreviations: dcSSc, diffuse cutaneous systemic sclerosis; ARA, anti-RNA polymerase III antibodies.

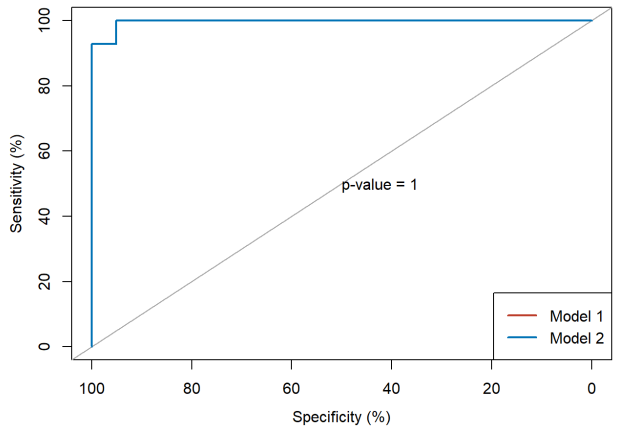

Fig. 2. ROC curve analysis was performed on model 1 and model 2. The model 1 was built using disease duration, dsSSc, Raynaud's phenomenon, malignancy, positivity of ARA as predictors, while model 2 was built using the after mentioned 5 predictors and being male. AUC for both model 1 and model 2 was 0.9964871, *p* value = 0.31331, which was coincide completely.

Results

Demographic Data

All 75 SSc patients (62 women and 13 men; Mean age 54 years; Range 29–77 years) were divided into RPSSc and non-RPSSc groups. 12 dcSSc and 2 lcSSc of 75 SSc patients were developed become RPSSc, with an overall incidence of 18.7%.

Clinical Manifestations

The clinical manifestations of the two groups are summarized in Table 1. ILD (64.3%) with cardiac involvement (42.9%) was the organ system with a highest involvement in RPSSc, while Raynaud's phenomenon incidence (64.3%) significantly decreased.

Differences among the two groups in terms of disease duration, sex, SSc subset, mRSS, Raynaud's phenomenon, cardiac involvement, malignancy and antibody were statistically significant ($p < 0.05$), while in terms of age at enrollment, digital ulcers, skin telangiectasis, NVC changes, joint involvement, and myositis were not statistically significant ($p > 0.05$) (Table 1).

RPSSc Predictive Factors at Baseline

Univariate Logistic Regression analysis showed that male (OR 5.786, 95% 1.547–21.641, $p = 0.009$), diffuse cutaneous SSc (dsSSc) (OR 15.529, 95% CI 3.141–76.777, $p = 0.001$), malignancy (OR 24, 95% CI 2.427–237.304, $p = 0.007$) and positivity of ARA (OR 108, 95% CI 11.287–1033.327, $p < 0.001$) were RPSSc risk factors, and Raynaud's phenomenon (OR 0.03, 95% CI 0.003–0.287, $p = 0.002$), and disease duration (OR 0.969, 95% CI 0.949–0.991, $p = 0.005$) were RPSSc protective factors. LASSO logistic regression identified six factors: Disease duration, dsSSc, malignancy, cardiac involvement, positivity of ARA were RPSSc risk factors, while Raynaud's phenomenon was RPSSc protective factor (Fig. 1 and Table 2).

Then, a predictive model was developed including the predictors after the LASSO Regression Analysis and the Univariate Logistic Regression Analysis, which included including disease duration, dsSSc, Raynaud's phenomenon, malignancy, positivity of ARA. Model 1 was built with these 5 predictors, while model 2 was built by these 5 predictors and being male as sex was found as significant difference between RPSSc and non-RPSSc. Additionally, ROC curve analysis was performed on these models to assess their ability to diagnose RPSSc DeLong's test for the two models was not significant, the area under the ROC curve (AUC) for both models was 0.9964871, *p* value = 0.31331, which was coincide completely. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) was used to compare the specificity of model 1 and model 2. There is no statistical difference between the two models: NRI (Categorical) was 0.0164, (95% CI 0.0155–0.0483), *p* value = 0.31331, while IDI was 0.0033 (95% CI: –0.0061–0.0128), *p* value = 0.49045 (Fig. 2).

Ten SSc Patients with ARA Clinical Characteristics

Since ARA was the most significant risk factor predicting RPSSc, the clinical ARA positive SSc phenotype was further evaluated. Ten SSc clinical characteristics of

Table 3. Ten SSc patients with ARA clinical characteristics data.

No.	Sex	Age	Disease duration	SSc subsets	RPSSc or non-RPSSc	mRSS	Clinical manifestations of onset	Organ involvement clinical characteristics	Malignancy
1	M	70	6	dcSSc	RPSSc	26	rapid progressive of skin sclerosis	cardiac involvement; Gastrointestinal involvement; Finger ulcers	stomach cancer
2	M	51	12	dcSSc	RPSSc	13	Raynaud's phenomenon	ILD; SRC; Cardiac involvement	none
3	M	47	12	dcSSc	RPSSc	24	Raynaud's phenomenon	ILD; Finger ulcers	none
4	F	54	84	lcSSc	non-RPSSc	10	Raynaud's phenomenon	hematologic system involvement (platelets decrease)	none
5	M	60	6	lcSSc	RPSSc	12	puffy fingers; Puffy face	none	none
6	M	58	12	dcSSc	RPSSc	12	rapid progressive of skin sclerosis	cardiac involvement; Gastrointestinal involvement	none
7	F	54	18	dcSSc	RPSSc	20	Raynaud's phenomenon; Rapid progressive of skin sclerosis	PBC; Joint involvement; Trigeminal nerve involvement	breast cancer
8	F	47	120	lcSSc	RPSSc	4	Raynaud's phenomenon, ILD	ILD; Finger ulcers	rectal cancer
9	F	61	6	dcSSc	RPSSc	20	Raynaud's phenomenon; Rapid progressive of skin sclerosis	cardiac involvement	none
10	F	77	24	dcSSc	RPSSc	14	ILD	ILD	none

Abbreviations: M, male; F, female; SSc, systemic sclerosis; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; RPSSc, rapidly progressive systemic sclerosis; Non-RPSSc, non-rapidly progressive systemic sclerosis; mRSS, modified Rodnan total skin score; ILD, interstitial lung disease; SRC, scleroderma renal crisis; PBC, primary biliary cholangitis.

patients with ARA are summarized in Table 3. Patients with ARA had a mean age of 56 years (range 47–77 years), female to male ratio of 1:1, 7 cases were dcSSc (all progressed to RPSSc) and 3 cases were lcSSc. Only one case of lcSSc was non-RPSSc.

Although Raynaud's phenomenon was the initial symptom in the majority of SSc patients, 4 out of 10 patients with ARA did not experienced Raynaud's phenomenon. All of these patients were diagnosed based on antibodies and other clinical manifestations, which included puffy fingers and facial swelling (1 case), severe interstitial lung disease (1 case) and rapidly progressive skin sclerosis (2 cases).

Overall, the median mRSS was 13.5 (range 4–26), 9 out of 10 patients with ARA, had organ involvement, ILD (4/10, 40%) and cardiac involvement (4/10, 40%) were the most commonly affected organs, 3 cases had finger ulcers, 2 cases had gastrointestinal tract involvement, 1 case had hematologic system involvement (thrombocytopenia), 1 case had Trigeminal nerve involvement, 1 case was diagnosed with primary biliary cholangitis (PBC), 1 case developed SRC which was proved by renal biopsy. In addition, 3 out of 9 RPSSc patients developed tumors, respectively for gastric cancer, rectal cancer, and breast cancer (Fig. 3).

Discussion

Recently, research has focused on mechanisms and organ involvement in SSc. Some studies have identified early (eaSSc, disease duration <5 years) or long-standing SSc (lsSSc, disease duration >5 years) depending on disease duration [9]. "Very early diagnosis of systemic sclerosis (VEDOSS)" was identified as a condition characterized by the presence of Raynaud's phenomenon, puffy fingers, diseasespecific autoantibodies, and abnormal nailfold capillaries (requiring at least two, or better, all three items to be present) [10]. Some VEDOSS patients progress to SSc but others not [11,12].

RPSSc is characterized by skin induration rapid progression and target organ damage at early disease stage [8]. 2004, Emi Nishimagi *et al.* [6] suggested that skin thickening rapid progression was an important factor to consider for SSc prognosis. In 2011, Robyn T Domsic *et al.* [5] reported that rapid skin fibrosis could be a predictor of mortality and early internal organ involvement in dsSSc. While 2020 S. Wangkaew *et al.* [13] found that rapid skin fibrosis was associated with high cardiopulmonary complications incidence in patients with early dsSSc. Rapid skin fibrosis and internal organ involvement severity and rate determines the optimal therapeutic interventions for SSc [7]. Therefore, as practicing physicians, it is important to identify RPSSc early in to allow more extensive evaluation

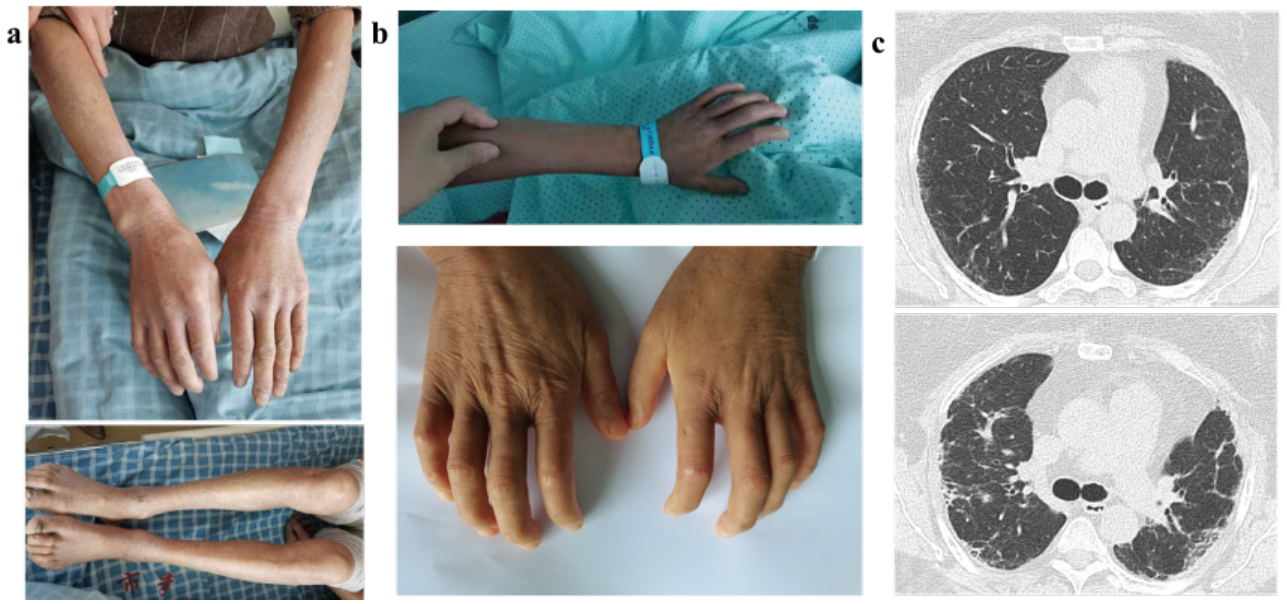

Fig. 3. The clinical features of 3 RPSSc patients who developed tumour. (a) RPSSc patient with stomach cancer, who was dcSSc with rapid skin sclerosis onset progression and had cardiac involvement, gastrointestinal involvement and finger ulcers. (b) RPSSc patient with breast cancer, who was dcSSc with Raynaud's phenomenon and rapid skin sclerosis progression. The case was diagnosed with PBC and had joint involvement and trigeminal nerve involvement. (c) RPSSc patient with rectal cancer, who was lcSSc with Raynaud's phenomenon and ILD. The case was defined as RPSSc due to evidence of pulmonary fibrosis on high-resolution CT scan and a decline in FVC >15% during 6-month interval.

and a close follow-up that can apply treatment in RPSSc early stage. However, little is known about RPSSc in Chinese Han SSc patients. In this study, clinical and serological characteristics were compared between RPSSc and non-RPSSc patients to identify possible RPSSc predictors at early stage.

In our one single-center cohort, RPSSc developed in 18.7% of patients with a median disease duration of 12 months. The clinical characteristics RPSSc patients included in this study was rapid disease development, high proportion of males, lower prevalence of Raynaud's phenomenon at onset of disease, and a higher malignancy incidence. It was worth mentioning that although the organ involvement was similar between the two groups, while disease duration was significantly longer in non-RPSSc patients. Therefore, we might speculate that: If both groups have the same disease duration, wether the RPSSc paitents represent more severe disease accompanied with major organ involvement and diffuse cutaneous progression at early stage? This is worthy of prospective research for us in the future.

Autoantibodies profile are well known as key classification criteria for SSc patients [14]. Patients were stratified into more homogenous subsets with more favorable SSc outcomes in SSc based on their antibodies profile [15]. Autoantibodies and skin subsets are strong predictors of organ involvement in SSc. SSc risk stratification could be performed by use of combined autoantibodies and skin subsets [16]. In this cohort of 75 SSc patients, ARA was positive in 64.3% of RPSSc while 1.6% sera of non-RPSSc patients. The presence of ARA in RPSSc was significant ($p < 0.001$). Logistic Regression and LASSO Regression Analysis showed that ARA, malignancy, dcSSc, male were risk factors for RPSSc, while Raynaud's phenomenon was a protective factor for RPSSc. Meanwhile, it was found that ARA was the strongest correlated factor with RPSSc.

It was previously reported that ARA was the third type of antinuclear autoantibody detected in patients with SSc. RP155 and RP11 are human ARA subunits [4]. Different authors reported that ARA was found in 5–23% of SSc patients according to race differences and geographic factors [17]. However, Chinese Han SSc patients ARA autoantibodies profile has rarely been reported. Only Liu C *et al*. [18,19] have reported that ARA was found in 5.93% of Chinese Han SSc patients and can predict SSc renal crisis between 2019–2020. In this study, ARA was considered highly specific for the diffuse cutaneous subset, more severe skin involvement, and can be an SSc marker with a rapid onset and a rapid skin fibrosis, in line with previous reports [20–23].

In this study, RPSSc was strongly associated with malignancy (stomach cancer, rectal cancer, breast cancer, lung cancer). In recent years, research on SSc patients and malignancy has also attracted more and more attention [24]. Studies have reported that ARA positivity is a risk factor for tumor development in patients with SSc, breast cancer,

melanoma, hematological tumors, and lung cancer are the most common [25]. At the same time, male patients have a significant increased risk of comorbid tumors [26]. Cancer and fibrosis may share the same mechanisms to promote vascular and profibrotic in SSc. Such scenario is further reinforced by fibrogenesis and oncogenesis which share common mechanisms (notably, telomere shortening and epigenetic alterations) [27]. Several studies have found two important periods of incidental tumor at SSc diagnosis (mainly ARA positive, up to 55%, and mainly breast cancer) [28] and 10 years later (mainly lung cancers) [29].

There are some limitations in this study. First, this is a single-center study, so conclusions may not apply to all medical institutions. The sample was small, and thus, a multivariate logistic regression analysis could not be carried out in this study. Meanwhile, objective evaluation methods for gastrointestinal involvement, such as gastroscopy, esophageal manometry, and lung function, are lacking because some patients could not tolerate it. Moreover, the follow-up time of this study was short and had some deficiencies. Increasing the sample size and follow-up time is needed in future studies.

Conclusions

In conclusion, it is important to early identify RPSSc, which allows a more active treatment strategy. Positive of ARA, male, dcSSc subset and malignancy were RPSSc risk factors, and Raynaud's phenomenon and long-disease duration were RPSSc protective factors. It is important to determine positivity of ARA, and malignancy close follow-up to timely start appropriate therapies in SSc patients.

Abbreviations

RPSSc, rapidly progressive systemic sclerosis; Non-RPSSc, non-rapidly progressive systemic sclerosis; SSc, systemic sclerosis; dsSSc, diffuse cutaneous SSc; lcSSc, limited cutaneous SSc; mRSS, modified Rodnan total skin score; ARA, anti-RNA polymerase III antibodies; ANA, antinuclear antibodies; ATA, anti-topoisomerase I antibodies; ACA, anticentromere antibody; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; ILD, interstitial lung disease; FVC, Forced Vital Capacity; TLC, Total Lung Capacity; PAH, pulmonary arterial hypertension; ECG, electrocardiogram; SRC, scleroderma renal crisis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CK, creatine phosphokinase; LIA, line immunoassay; NVC, nail-fold videocapillaroscopy; LASSO, least absolute shrinkage and selection operator; ROC, receiver operating characteristic; SD, standard deviation; IQR, interquartile ranges; AUC, area under the ROC curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement; PBC, primary biliary cholangitis; VEDOSS, very early diagnosis of systemic sclerosis.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

QY—designed the research, analyzed the data and wrote the manuscript; LF, TY, BL—participated in case, data acquisition and wrote the manuscript; JD—designed the study, contributed to disease diagnosis, revising it critically for important intellectual content; JZ—designed the study, wrote the manuscript, and helped optimize the research and proofread the paper. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Ningbo Medical Center Lihuili Hospital, Affiliated to Ningbo University, Zhejiang, China (Approval Number: KY2021PJ149).

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Conflict of Interest

The authors declare no conflict of interest.

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