ORIGINAL ARTICLE

Cross-sectional study on association of autoantibodies and organ involvement in systemic sclerosis patients

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ABSTRACT

Introduction: Systemic sclerosis (SSc) is a connective tissue disease characterised by inflammation, fibrosis, and vascular abnormalities affecting multiple organs, including the skin, lungs, heart and kidneys. Between 75% and 95% of SSc patients have positive SSc-associated autoantibodies. The 2013 European League Against Rheumatism/American College of Rheumatology classification criteria for SSc includes autoantibodies as an important domain, highlighting their importance when clinical manifestations are subtle. However, the association of autoantibodies and specific clinical manifestations vary across different geographical regions and ethnicities, warranting further study across diverse populations. Hence, the objective of this study is to evaluate the association between autoantibodies and organ involvement in SSc patients at a tertiary centre in Malaysia.

Materials and Methods: This cross-sectional study included 48 SSc patients who received follow-up care at a tertiary centre in Malaysia from July 2013 to June 2023 (a ten-year period). Demographic, clinical, laboratory and radiological information were extracted from patient records.

Results: A total of 48 patients were enrolled in our study. Forty-five (93.8%) patients were female and 3 (6.2%) patients were male. Regarding ethnicity, 26 (54.2%) patients were Malay, 17 (35.4%) patients were Chinese and 5 (10.4%) patients were Indian. Mean age at diagnosis was 52.96 years (SD ± 13.99). Thirty-nine (81.2%) patients had limited subtype and 9 (18.8%) patients had diffuse subtype. The most common clinical manifestations were sclerodactyly (97.9%) and Raynaud's phenomenon (79.2%). The most commonly found autoantibodies were anti-Ro-60 (37.5%) and anti-Scl-70 (33.3%) while anti-Jo-1 (2.1%) was the least detected. Antinuclear antibody (ANA) was detected in 87.5% of our cohort. Anti-Scl-70 was significantly associated with interstitial lung disease (ILD) and ILD progression. Anti-Centromere was significantly associated with telangiectasia and gastroesophageal reflux disease (GERD). Meanwhile, anti-La was associated with synovitis and anti-Ribonucleoprotein (RNP) was associated with microstomia. Twenty-nine (60.4%) patients had evidence of ILD and 11 (22.9%) patients had progressive ILD. Additionally, pulmonary hypertension of varying severity was observed in 14 (29.2%) patients.

Conclusion: This study supports the well-established association of anti-Scl-70 with ILD and ILD progression. Other unique associations observed in this study could be due to the distinct ethnic and genetic background in the Malaysian population. To gain a more comprehensive understanding of these unique autoantibody-clinical manifestation patterns in Malaysian SSc patients, larger multicentre studies are recommended.

KEYWORDS:
Autoantibodies, organ involvement, systemic sclerosis

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterised by inflammation, fibrosis, and vascular abnormalities affecting multiple organs, including the skin, lungs, heart and kidneys. The two main subtypes of SSc are limited SSc and diffuse SSc based on the extent of the skin involvement. Between 75% and 95% of SSc patients have positive SSc-associated autoantibodies. The 2013 European League Against Rheumatism/American College of Rheumatology classification criteria for SSc includes autoantibodies as an important domain, highlighting their importance when clinical manifestations are subtle. However, the association of autoantibodies and specific clinical manifestations vary across different geographical regions and ethnicities, warranting further study across diverse populations.[1] Hence, the objective of this study is to evaluate the association between autoantibodies and organ involvement in SSc patients at a tertiary centre in Malaysia.

MATERIALS AND METHODS

This cross-sectional study included 48 SSc patients who received follow-up care at a tertiary centre in Malaysia from July 2013 to June 2023 (a ten-year period). Patients with overlap syndrome were included, while patients with mixed connective tissue disease were excluded. Demographic, clinical, laboratory and radiological information were extracted from patient records. The definitions and measurements of organ involvement are summarised in Table I. The autoantibodies analysed include anti-Ro-52, anti-Ro-60, anti-Jo-1, anti-Smith, anti-Centromere, anti-La, anti-Ribosomal P, anti-Scl-70 and anti-Ribonucleoprotein (RNP). These antibodies were recorded as dichotomous variables based on their positivity and assessed for

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Table I: The definitions of organ involvement

Organ involvement	Types of involvement	Definition	Assessment
Cutaneous involvement	Sclerodactyly	Skin thickening and tightening.	Physical examination
	Microstomia	Mouth opening limited to the patient's three middle fingers.	Physical examination
	Raynaud's phenomenon	A history of excessive cold sensitivity and recurrent events of sharply demarcated pallor and/or cyanosis of the digits.	History or physical examination
	Telangiectasia	Erythematous matted skin lesions of vascular origin, thus they blanch after local pressure.	Physical examination
	Digital ulceration	Active ulcers are defined as denuded areas with defined borders, loss of epidermis and dermis distal to the proximal interphalangeal joint on the volar aspect of a finger.	Physical examination
	Calcinosis	Calcium deposition in any soft tissue.	Physical examination or radiological study
Musculoskeletal involvement	Synovitis	Joint inflammation.	History or physical examination
	Myopathy	Decreased proximal muscle power.	Physical examination
Pulmonary involvement	ILD	NSIP, UIP, organising pneumonia (OP) attributable to SSc.	Physical examination, radiological study and lung function test
	Progressive ILD	Defined as at least two of the following three criteria occurring within the past year with no alternative explanation: 1. Worsening respiratory symptoms. 2. Physiological evidence of disease progression (either of the following): a. Absolute decline in forced vital capacity (FVC) ≥5% predicted b. Absolute decline in diffusing capacity of the lungs for carbon monoxide (DLCO) ≥10% predicted 3. Radiological evidence of disease progression.	History or physical examination, lung function test and radiological study
Cardiac involvement	Pulmonary hypertension	Mean pulmonary arterial pressure ≥ 25mmHg based on right heart catheterisation or pulmonary artery systolic pressure ≥ 30mmHg based on echocardiogram.	Echocardiogram, right heart catheterisation
	Cardiomyopathy	Evidence of myocarditis, cardiac arrhythmia or heart failure attributable to SSc.	History, physical examination, laboratory tests and echocardiogram
	Pericarditis	Pericardial effusion	Echocardiogram
Gastrointestinal involvement	GERD	Symptoms of heart burn or gastritis.	History
	Chronic constipation	Fewer than three bowel movements a week for more than 3 months.	History
	Chronic diarrhoea	Persistent alteration in stool consistency, with loose stools and increased frequency for a duration exceeding four weeks.	History
Renal involvement	Renal crisis	A sudden onset of hypertension (above 140/90 mmHg, a 30 mmHg increase in systolic blood pressure, or a 20 mmHg increase in diastolic blood pressure) and associated disorders, including an increase of more than 50% in serum creatinine or above 120% of normal range, proteinuria, microscopic haematuria, thrombocytopenia, haemolysis or hypertensive encephalopathy.	History, physical examination and laboratory tests

Note: Adapted from Motaghi P, Daneshbodi M, Karimifar M. Correlation between autoantibodies and internal organs involvement in Iranian systemic sclerosis patients. Immunopathol Persa 2022; x(x): e24238.

correlation with clinical findings using Fisher's exact test and two-by-two tables; p-value of ≤ 0.05 was considered significant.

RESULTS

A total of 48 patients were enrolled in our study. Forty-five (93.8%) patients were female and 3 (6.2%) patients were male. Regarding ethnicity, 26 (54.2%) patients were Malay, 17 (35.4%) patients were Chinese and 5 (10.4%) patients were Indian. Mean age at diagnosis was 52.96 years (SD ± 13.99). Thirty-nine (81.2%) patients had limited subtype and 9 (18.8%) patients had diffuse subtype. Eighteen (37.5%) patients in the cohort had overlap syndrome with other rheumatic diseases. The most common clinical manifestations were sclerodactyly (97.9%) and Raynaud's phenomenon (79.2%). The demographic characteristics and clinical manifestations are summarised in Table II.

Forty (83.3%) patients had at least one positive autoantibody and 24 (50%) patients had more than one autoantibody. The most commonly found autoantibodies were anti-Ro-60

Table II: Demographic, clinical, and serologic characteristics (n=48)

Gender, n (%)	
Male	3 (6.2)
Female	45 (93.8)
Age at diagnosis, mean ± SD (years)	52.96 ± 13.99
Ethnic, n (%)	
Malay	26 (54.2)
Chinese	17 (35.4)
Indian	5 (10.4)
Disease subtype, n (%)	
Limited	39 (81.2)
Diffuse	9 (18.8)
Clinical Manifestation/Organ involvement, n (%)	
Sclerodactyly	47 (97.9)
Microstomia	25 (52.1)
Raynaud's phenomenon	38 (79.2)
Telangiectasia	24 (50)
Digital ulceration	10 (20.8)
Calcinosis	4 (8.3)
Synovitis	19 (39.6)
Myopathy	6 (12.5)
ILD	29 (60.4)
Progressive ILD	11 (22.9)
Pulmonary hypertension	14 (29.2)
Cardiomyopathy	1 (2.1)
Pericarditis	2 (4.2)
GERD	19 (39.6)
Chronic constipation	0 (0)
Chronic diarrhoea	2 (4.2)
Renal crisis	0 (0)
Antibody positivity, n (%)	
ANA	42 (87.5)
Anti-Ro-52	14 (29.2)
Anti-Ro-60	18 (37.5)
Anti-Jo-1	1 (2.1)
Anti-Smith	4 (8.3)
Anti-Centromere	10 (20.8)
Anti-La	4 (8.3)
Anti-Ribosomal P	2 (4.2)
Anti-Scl-70	16 (33.3)
Anti-RNP	15 (31.3)

Table III: The correlation and predictive values of autoantibodies for organ involvement

Autoantibodies	Organ involvement	p-value	Odds/Risk ratio
Anti-Ro-52	None	-	-
Anti-Ro-60	None	-	-
Anti-Jo-1	None	-	-
Anti-Smith	None	-	-
Anti-Centromere	Telangiectasia	0.004	13.800
	GERD	0.036	5.506
Anti-La	Synovitis	0.020	2.933
Anti-Ribosomal P	None	-	-
Anti-Scl-70	ILD	0.007	0.027
	ILD progression	7.933	5.444
Anti-RNP	Microstomia	0.047	3.732

(p-value of ≤ 0.05 was considered significant.)

(37.5%) and anti-Scl-70 (33.3%) while anti-Jo-1 (2.1%) was the least detected. Antinuclear antibody (ANA) was detected in 87.5% of our patient cohort. Anti-Scl-70 was significantly associated with interstitial lung disease (ILD) and ILD progression. Anti-Centromere was significantly associated with telangiectasia and gastroesophageal reflux disease (GERD). Meanwhile, anti-La was associated with synovitis and anti-RNP was associated with microstomia. Table III summarised these correlations and predictive values of autoantibodies for organ involvement.

Twenty-nine (60.4%) patients had ILD and 11 (22.9%) patients had progressive ILD. For patients with ILD, 16 (55.2%) patients had non-specific interstitial pneumonia (NSIP) ILD pattern, 8 (27.6%) patients had usual interstitial pneumonia (UIP) ILD pattern and 5 (17.2%) patients had other or non-specific pattern. Out of the 11 patients with progressive ILD, 4 (36.4%) patients received mycophenolate mofetil, 4 (36.4%) patients received cyclophosphamide and 3 (27.2%) patients received azathioprine as first line immunosuppressive therapy. Additionally, pulmonary hypertension of varying severity was observed in 14 (29.2%) patients.

DISCUSSION

According to the 2024 Malaysia national census, the ethnic composition of the population comprises 70.3% Malay and indigenous groups, 22.4% Chinese, 6.5% Indian and 0.8% other races.[2] The ethnic distribution in our cohort, with Malays (54.2%), Chinese (35.4%), and Indians (10.4%), was broadly similar to that of the overall population. The higher prevalence of SSc among the Chinese population could be due to genetic factors, as certain human leucocyte antigens have been closely linked to SSc susceptibility in China.[3]

In our study, limited SSc (81.3%) was the predominant subtype, which was consistent with a study conducted in Malaysia in 2014.[4] This finding was also similar to studies from Japan and India but contrary to studies from Thailand, Singapore and China.[5-9] The two most common clinical presentations were sclerodactyly and Raynaud's phenomenon, which were consistent with the European Scleroderma Trials and Research group (EUSTAR) cohort.[10] A lower proportion of our patients (79.2%) had Raynaud's phenomenon compared to the EUSTAR cohort (96.3%). This could be attributed to Malaysia's warm climate and possible underreporting of symptoms. Sixty percent of our SSc patients had evidence of ILD and 29% had evidence of pulmonary hypertension. These findings were broadly similar to those in the EUSTAR cohort. As expected, NSIP (55.2%) was the major ILD pattern in our cohort.

In the EUSTAR cohort, the most common SSc associated antibodies were anti-Scl-70 (36.8%), followed by anti-Centromere (32.3%).[10] In our cohort, the most commonly found autoantibodies were anti-Ro-60 (37.5%) and anti-Scl-70 (33.3%). Only 18.6% of our patients tested positive for anti-Centromere antibody. These findings are consistent with data from our neighbouring country, Singapore.[5] Anti-Scl-70 is widely recognised for its association with ILD and ILD progression, which was also reflected in our cohort. The significance of associations between anti-Centromere with telangiectasia and GERD, anti-La with synovitis, anti-RNP with microstomia are not well established. Hence, larger multicentre studies are needed to confirm these associations found in our cohort. Anti-RNA polymerase III antibodies are specific markers for SSc and are known to be associated with diffuse skin involvement and severe internal organ complications.[11] However, this marker is not routinely tested in Malaysia due to unavailability in the commercial panels.

LIMITATIONS

There are some limitations in our study. First, the study was based on retrospective data and some data were incomplete. Secondly, the study only involved a single tertiary centre in Malaysia and might not fully reflect the diverse ethnic and genetic background of our population. Thirdly, the detection of organ involvement relied on patient-reported symptoms and the initiative of the attending clinician to actively screen for them. As a result, the true frequency of organ involvement might be underestimated.

CONCLUSION

This study supports the well-established association of anti-Scl-70 with ILD and ILD progression. Other unique associations observed in this study could be due to the distinct ethnic and genetic background in the Malaysian population. To gain a more comprehensive understanding of these unique autoantibody-clinical manifestation patterns in Malaysian SSc patients, larger multicentre studies are recommended.

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ETHICAL APPROVAL

This study involved human participants and was registered via National Medical Research Register Malaysia with a Research ID of NMRR ID-23-02432-GBB.

REFERENCES

1. Motaghi P, Daneshbodi M, Karimifar M. Correlation between autoantibodies and internal organs involvement in Iranian systemic sclerosis patients. Immunopathol Persa 2022; x(x): e24238.
2. Department of Statistics Malaysia. Population Table: Malaysia [Internet]. Putrajaya: OpenDOSM; 2024 Jul 31 [cited 2025 Jun 13]. Available from: https://open.dosm.gov.my/data-catalogue/population_malaysia.
3. Luo Y, Wang Y, Wang Q, Xiao R, Lu Q. Systemic sclerosis: genetics and epigenetics. J Autoimmun 2013; 41: 161-7.
4. Sujau I, Ng CT, Sthaneshwar P, Sockalingam S, Cheah TE, Yahya F, et al. Clinical and autoantibody profile in systemic sclerosis: baseline characteristics from a West Malaysian cohort. Int J Rheum Dis 2015; 18: 459-65.

5. Panicheewa S, Chitrabamrung S, Verasertniyom O, Vanichaphantu M, Kraisit SO, Chiewsilp P, Vatanasuk M. Diffuse systemic sclerosis and related diseases in Thailand. Clin Rheumatol 1991; 10(2): 124-9.
6. Ling ALH, Gee TG, Giap LW, Cheng NS, Santosa A, Chan G, et al. Disease Characteristics of the Singapore Systemic Sclerosis Cohort. Proceedings of Singapore Healthcare 2013; 22(1): 8-14.
7. Wang J, Assassi S, Guo G, Tu W, Wu W, Yang L, et al. Clinical and serological features of systemic sclerosis in a Chinese cohort. Clin Rheumatol 2013; 32(5): 617-21.
8. Gupta R, Thabah MM, Gupta S, Shankar S, Kumar A. Clinical significance of antiphospholipid antibodies in Indian scleroderma patients. Rheumatol Int 2009; 30(2): 277-9.
9. Hashimoto A, Endo H, Kondo H, Hirohata S. Clinical features of 405 Japanese patients with systemic sclerosis. Mod Rheumatol 2012; 22(2): 272-9.
10. Meier FM, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2012; 71(8):1355-60.
11. Lazzaroni MG, Airò P. Anti-RNA polymerase III antibodies in patients with suspected and definite systemic sclerosis: Why and how to screen. J Scleroderma Relat Disord 2018; 3(3): 214-220.