Original Article

International Journal of Integrated Health Sciences (IIJHS)
ISSN Print: 2302-1381; ISSN Online: 2338-4506

Autoantibody Profile and Thorax HRCT Scan in Systemic Sclerosis with Restrictive Lung Disease

Winda Agnestia Maranna Saragih,[1] Rachmat Gunadi Wachjudi,[2] Verina Logito,[3] Anna Tjandrawati,[3] Sumartini Dewi[2]

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
[2]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
[3]Department of Pathology Clinic, Faculty of Medicine, Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Article History

Received: October 07, 2022
Accepted: March 06, 2023
Published: March 30, 2023

DOI: 10.15850/ijihs.v11n1.3023
IJIHS. 2023;11(1):42–49

Correspondence:
Winda Agnestia Maranna Saragih, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran-Dr. Hasan Sadikin General Hospital, Bandung, Indonesia
E-mail: windasaragih2010@gmail.com

Abstract

Objective: To identify auto-antibodies in systemic sclerosis with interstitial lung disease (ILD).

Method: This was a descriptive categorical study on auto-antibody profile in systemic sclerosis patients visiting the Rheumatology Clinic of Dr. Hasan Sadikin General Hospital, West Java, and Bandung during the period of January 2018 to December 2019 who were registered in the West Java Systemic Sclerosis Registry. Auto-antibody identification was performed using the Euroline immunoblot assays.

Results: Thirty six cases were identified during the study period with most of the cases involved women (n=35, 97.2%). The average age of patients participating in this study was 40 years, with an average duration of disease of 18 months. Diffuse cutaneous systemic sclerosis was found in 22 (61.1%) cases and limited cutaneous systemic sclerosis was observed in 14 (38.9%) cases. Specific autoantibodies were positive in 33 (91.6%) cases, with anti-topoisomerase I as the largest group, positive in 22 (52.9.3%) cases. This was followed by anti-Th/To in eight (15.7%) cases; anti-Ro52 in four (7.8%) cases; anti-centromere in three (5.9%) cases; anti-RNA polymerase in three (5.9%) cases; anti-fibrillarin in three (5.9%) cases; anti-Ku in two (3.9%) cases; and anti-PDGF in one (2.0%) case. High-resolution computed tomography of the lung showed 34 (94.4%) cases with ILD and 22 (61.1%) cases with severe lung fibrosis. Usual interstitial pneumonia was seen in 19 (52.8%) cases and non-specific interstitial pneumonia in 15 (41.7%) cases.

Conclusion: Anti-topoisomerase I, anti-Th/To, and anti-Ro52 are the most common autoantibodies observed in systemic sclerosis patients with ILD as the most prevalent feature detected with lung HRCT.

Keywords: Autoantibodies, diffuse cutaneous, lung fibrosis, restrictive lung disease, systemic sclerosis

Introduction

Interstitial lung disease is the leading cause of death in SSc patients.[1-2] Early diagnosis and assessment of the organs involved, especially the lung, will have an impact on morbidity, mortality, and quality of life of patients by providing early treatments.[1-3] But early diagnosis of systemic sclerosis is difficult. Many patients come to the hospital with advanced disease or visceral organ involvement. Early diagnosis of organ involvement in the early stages will have implications for more aggressive treatment. Immunosuppressants

(mycophenolate sodium, cyclophosphamide) given in the early stage will decrease the disease progression as seen with decreased autoantibody titer. Intravenous chemotherapy, such as cyclophosphamide is given in SSc patients with interstitial lung disease. Delays in this therapy will increase morbidity and mortality. Thorax HRCT scan is the gold standard for diagnosis of ILD, especially for early-stage disease.[4,5]. Usual interstitial pneumonia is associated with a worse prognosis due to rapid disease progression. Pulmonary function test with spirometry as a screening test often shows restrictive lung disease, but this result should be viewed cautiously because the extrapulmonary factor may influence the result.[6-7] Autoantibody testing has become the gold standard for the detection of autoimmune disease and is often associated with disease progression.

Early assessment of autoantibody testing will benefit the patients, especially in the early diagnosis SSc with organ involment. In addition, autoantibody testing has become the gold standard for detecting autoimmune disease and may contribute to the diagnosis of SSc and the organs involved, especially the lung.[8,9] Autoantibody titers are often associated with disease progression. Previous study conclude that SSc specific-autoantibody is associated with organ involvement. [9] For example, Anti-topoisomerase I, anti-U11/U12, anti-Ro52, and anti Th/To are associated with lung involvement. Anti-centromere is associated with cardiovascular involvement (PAH). Anti-RNA polymerase is associated with cardiovascular (PAH) and kidney (acute renal crisis). Anti-fibrillation is associated with cardiovascular involvement (PAH) and musculoskeletal injury (myositis). There is an association between autoantibody subtype and clinical manifestation along with organ involvement. Severe manifestation is found in SSc with lung involvement; thus patients will seek treatment earlier. To date, there are no specific clinical markers for lung involvement. Therefore in the future, it is expected that the SSc specific autoantibodies testing may be used as a modality for diagnosis organ involvement. Specially detecting SSc patients with interstitial lung disease in the early stages.[7,8]

Methods

This was a descriptive study with a cross-sectional method. Data were collected from West Java Systemic Sclerosis Registry. Diffuse and limited SSc outpatients visiting the Rheumatology Clinic at Dr. Hasan Sadikin General Hospital, who were treated from January 2018 to December 2019, aged over 18 years old, were included in this study. Systemic sclerosis patients with overlap syndrome with other rheumatic autoimmune diseases and incomplete medical records were excluded from this study. Systemic sclerosis was diagnosed based on ACR/EULAR 2013 criteria.[10] Restrictive lung disease was defined based on ATS criteria.[11] Using spirometry data, all participans meet restrictive lung disease criteria. All patients underwent HRCT thorax examination as gold standard for ILD. Interstitial lung disease was defined based on Wernick's semi-quantitative scoring system category.[12] The scoring describe ILD progressivity by radiological pattern and lung segments involved. Statistical Product and Service Solution (SPSS) version 22 for Windows was used for data analysis. Number and percentage were used for categorical variables. Mean ± standard deviation was used for measurement data following the normal distribution. Median was used for non-normal distribution measurement data. This study had approved by the ethical committee of Dr. Hasan Sadikin General Hospital (reference no: LB.02.01/X.6.5/24/2020). The patient's selection is shown in Fig 1.

Results

There were 4653 outpatients visiting Rheumatology Clinic at Dr. Hasan Sadikin General Hospital, with all rheumatology cases were 1923 patients, Rheumatoid Arthritis is 435 patients, Systemic Lupus Erythematosus is 730 patients, and SSc is 70 patients. There were 36 patients in West Java Systemic Sclerosis Registry from January 2018 to December 2019 who met the criteria for this study. The patient's characteristics are shown in Table 1.

More women were affected by SSc in this study (35, 97.2%). Mean age at diagnosis was 40 ± 12 years. The median disease duration was 18 (4-58) months. Patient with dcSSc was the common subtype in this study (22, 61.6%), followed by lcSSc (14, 38.9%). Raynaud's phenomenon was the most common clinical manifestation found (34, 94.4%) followed by sclerodactyly (30, 83.3%), skin stiffness (23, 63.9%), fingertip scar (21, 58.3%), salt and pepper appearance (20, 55.6%), telangiectasia (18, 50%), puffy fingers (5, 13.9%), and fingertip ulcer (4, 11.1%).

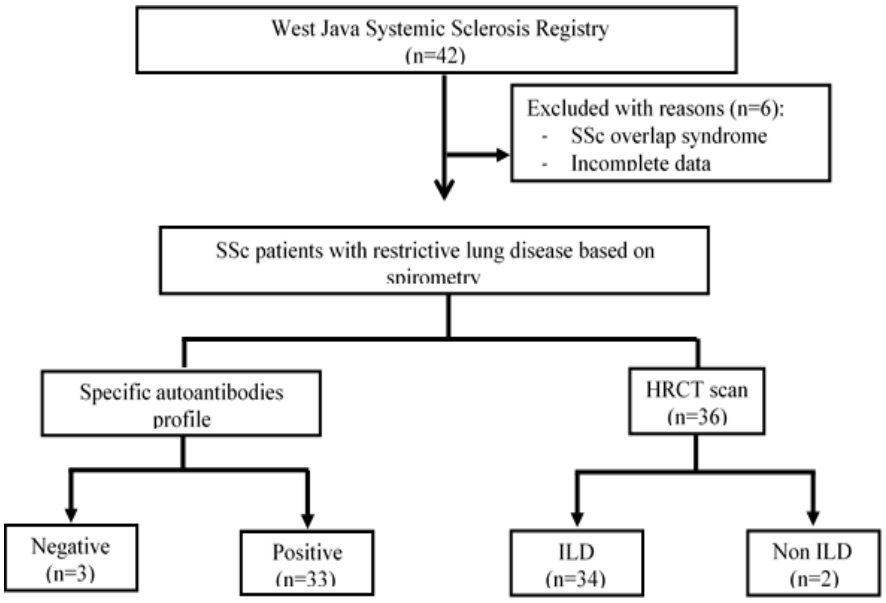

Fig 1. Patient's Selection

Table 1 Patient's Baseline Characteristics

Variables	Number of Participants (n=36)
Age at Diagnosis (years)	40 ± 12
Female n (%)	35 (97.2)
Duration of disease (months) median (min-max)	18 (4 – 58)
Subtype, n (%)	
dcSSc	22 (61.1)
lcSSc	14 (38.9)
mRSS median (min-max)	18 (5-45)
Restrictive Lung Disease, n (%)	
Moderate to Severe	13 (36.1)
Severe	7 (19.5)
Moderate	6 (16.7)
Mild	6 (16.7)
Very Severe	4 (11.0)
Clinical Manifestation, n (%)	
Raynaud's phenomenon	34 (94.4)
Sclerodactyly	30 (83.3)
Skin stiffness	23 (63.9)
Fingertip scar	21 (58.3)
Salt and pepper appearance	20 (55.6)
Telangiectasia	18 (50.0)
Puffy fingers	5 (13.9)
Fingertip ulcer	4 (11.1)
Immunosuppressant therapy	
Methotrexate	32 (88.9)
Cyclophosphamide	4 (11.1)
Mycophenolate sodium	4 (11.1)
Azathioprine	3 (8.3)

dSSc, diffuse systemic sclerosis; HRCT, High Resolution Computed Tomography; lSSc, limited systemic sclerosis; MRSS, modified Rodnan Skin Score; ILD, interstitial lung disease. All participant meet criteria restrictive lung disease. All patients receive immunosuppressant therapy because the SSc severity manifestation

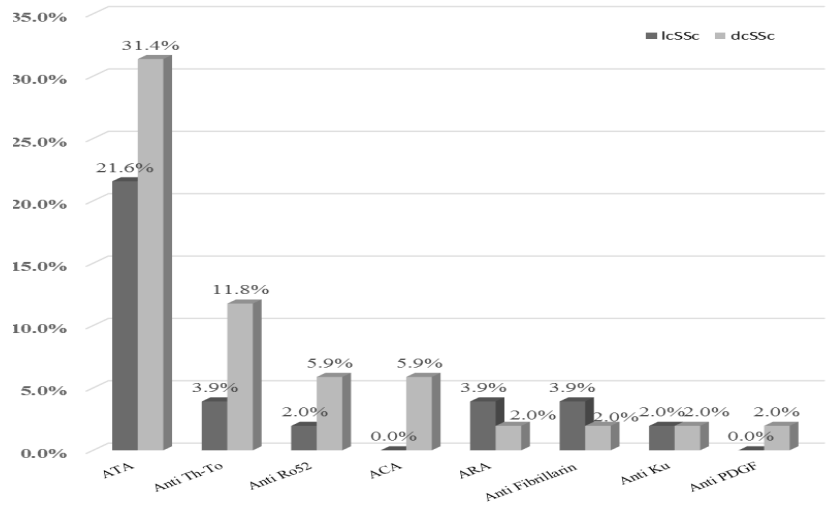

Fig 2. Overview of SSc Specific Autoantibody

Anti-topoisomerase I was predominantly found in interstitial lung disease, both as single and overlap autoantibody, followed by anti-Th/To, and anti-Ro52, as shown in Fig 2. Two types of specific autoantibodies for SSc was positive in half of the patients (50%), followed by one type autoantibody (41.7%), and negative autoantibody (8.3%). Overview of specific autoantibody is shown in Fig 2.

HRCT showed that almost all patients had ILD (34, 94.4%) with lung fibrosis 22 (61.1%) cases among it. Further classification using Wernick's semi-quantitative scoring system category, found that severe ILD was the most common finding (22, 61.1%), followed by moderate cases (6, 16.7%), and mild cases (6, 16.7%).[12,13] Severe ILD was found 41.7% in dcSSc and 19.4% in lcSSc, respectively. HRCT showed usual interstitial pneumonia (UIP) was 52.8% cases, followed by non-specific

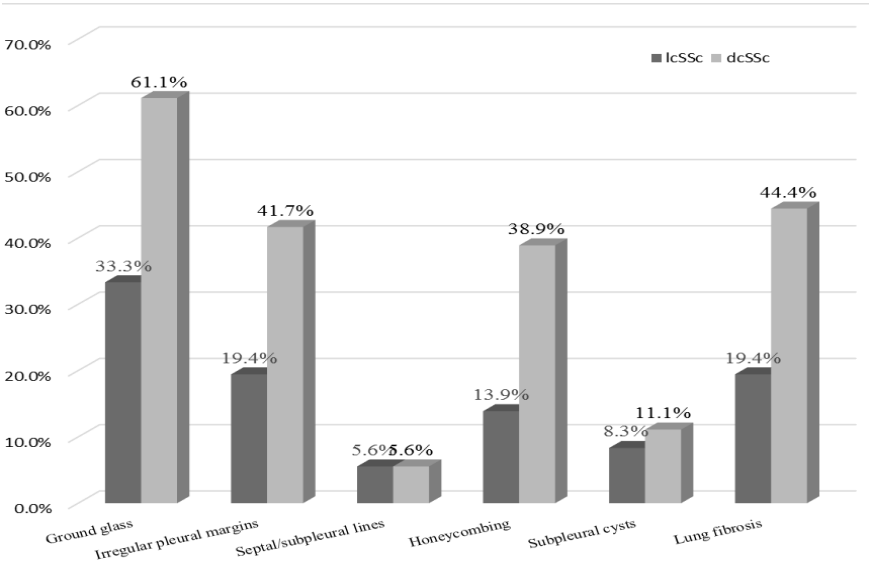

Fig 3. Interstitial Lung Disease Morphology[15]

interstitial pneumonia (NSIP) (41.7%) cases. ILD morphology is shown in **Fig 3**.

Discussion

This study describes specific autoantibodies and thorax HRCT in SSc patients. This result differs from other studies and may suggest there is a difference in characteristics and disease progression of SSc patients in Indonesia. Younger age at diagnosis and shorter duration of illness was found in this study compared to other studies conducted in Singapore, Malaysia, Australia, and Europe.[1,2,7,14] Even though early case finding better in those counties. Interstitial lung disease occurs in an early stage and younger age, is usually severe and have strong relation with higher standardized mortality rate.[1,2,15]

Subtype SSc classification is useful for the prediction of organ involvement and disease prognosis. The dsSSc subtype is at higher risk of death. It is associated with rapid progression and the risk of organ involvement in the early stage of the disease.[16] This study showed dsSSc subtype was more common and consistent with the finding of younger age at diagnosis and shorter duration of illness. Higher prevalence of dcSSc and ATA compared with Caucasians have been reported in Han Chinese, also suggesting that racial differences may contribute.[17] The environment is also a trigger factor for SSc, even though it was not fully understood. Some environmental factors that may trigger SSc, include chemical exposure of vinyl, chemical solvents, epoxy resin dan silica. Infection cytomegalovirus (CMV), parvovirus, smoking and alcohol is also play a role in triggering SSc.[16,18]

Specific autoantibodies testing has become the gold standard for the diagnosis of SSc, in which it is often associated with disease progression. Early assessment of specific autoantibodies will give benefit to the patients, especially SSc with organs involvement. In this study, we found three dominant specific autoantibodies for SSc : anti-topoisomerase I, anti-Th/To, and anti-Ro52. Studies conducted by Ibrahim *et al*. in Malaysia and Ching *et al*. in Thailand reported anti-topoisomerase, anti-Th/To, anti-Ro52, and anti-centromere as major autoantibodies in SSc.[14,19] Anti-Th/To and anti-Ro52 are not included in ACR/EULAR 2013 for the diagnosis criteria of SSc, due to the difference of populations that were studied. Specific autoantibodies differences between Asian and European. Singapore and Malaysia, which are multi-racial countries, showed differences with the population in this study.[2,14] This might be due to the more diversity in human races of the two countries. HLA-DRB1*11 is found in anti-topoisomerase I; HLA-DRB1*01, HLA-DRB1*04 HLA-DRB1*05 are found in anti-centromere and HLA-DRB1*04, HLA-DQB1*03 are found in anti-RNA polymerase of Caucasians-Hispanics.[17,18,20] Not much research on chromosomes has been done before. Further research is needed in Asian populations, especially in Indonesia, to determine the differences between major autoantibody and disease progression between Asian and European.

Specific SSc autoantibodies is associated with organ involvement. There is an association between autoantibody subtype and clinical manifestation along with organ involvement.[21,22] Two types of specific autoantibodies for SSc was positive in half of the participants (50%) followed by one autoantibody (41.7%), and negative autoantibody (8.3%). In several studies using IIF, immunoprecipitation, and immunodiffusion, only a very small proportion of SSc specific autoantibodies were found to have more than one SSc-related antibody.[7,19] Anti-topoisomerase I was the dominant autoantibody found in ILD, both as single and overlap autoantibody, followed by anti-Th/To, and anti-Ro52, where this autoantibody related to SSc-ILD. This fact is consistent with this study finding. Anti-topoisomerase was found in 31.4% of diffuse subtype cases and 21.6% of limited subtype cases. Anti-topoisomerase I is often associated with diffuse subtype and interstitial lung disease occurrence. Other studies, found anti-topoisomerase I as the most common finding in diffuse SSc with interstitial lung disease.[1,8,10,22] Anti-Th/To was found in 15.7% cases and second most dominant autoantibodies. These results were not consistent with the literature, which states that anti-Th/To is lesser compared with other autoantibodies, study in Japan shows only 2-5% of cases and none were found in Greece population .[20,21] In our study from 7 of 8 positive anti-Th/To patients, had interstitial lung disease. This result was similar to the previous study in Malaysia and Thailand, which reported SSc with anti-Th/To positively increases the severity and mortality rate and due to lung involvement.[14,19] There are differences in dominan autoantibody found in Japan and Greece population, compared to our population. Anti-Ro52 was found in 5.9% of diffuse subtype cases and 2% of limited subtype cases. All patients with Anti-Ro52 positive had

interstitial lung disease. This result is similar to a study conducted by Ibrahim *et al*.[14] Anti-centromere was found in 5.9% of a diffuse subtype with overlapping anti-topoisomerase I autoantibody. This group showed severe interstitial lung disease. This finding is not consistent with the literature, which stated that anti-centromere has a good prognosis because it is often found in a limited subtype with rarely visceral organ involvement.[21] This may be associated with the presence of two or more autoantibodies simultaneously, especially high titer anti-topoisomerase I. Anti-RNA polymerase was found in 3.9% of diffuse subtype cases and 2% of a limited subtype with overlapping anti-topoisomerase I autoantibody. The literature states SSc with anti-RNA polymerase rarely develops into severe interstitial lung disease. This is not consistent with the results. Interstitial lung disease in this group can be associated with the presence of two concurrent autoantibodies, especially high titer anti-topoisomerase I. This study found three dominant autoantibodies, which consist of anti-topoisomerase I, anti-Th/To, and anti-Ro52. Studies conducted by Ibrahim *et al*. in Malaysia and Ching *et al*. in Thailand reported anti-topoisomerase, anti-Th/To, anti-Ro52, and anti-centromere as dominant autoantibodies.[14,19] Anti-Th/To and anti-Ro52 are not included in ACR/EULAR 2013 for the diagnosis of systemic sclerosis. This is because ACR/EULAR 2013 is based on the European and American populations, while there is differences in autoantibody dominant between Asian and European populations.[10,17,23, 24]

This study also found three negative cases on specific autoantibodies but with a positive ANA test. Factors that may play a role in autoantibody difference results include autoantibodies test and autoantibodies titer.[9,22] Euroline immunoblot assay can detect 13 autoantibodies, but there are several other autoantibodies related to systemic that are not included in this kit such as anti-endothelial, anti-fibroblast, anti-matrix metalloproteinase, and anti-survivin which cannot be examined in this study. A high titer is associated with disease progression.

HRCT showed that almost all patients had ILD and with UIP pattern. These results differ from the other studies conducted in Europe, which NSIP was the common pattern.[13,25] UIP is associated with worse prognosis due to rapid disease progression, it's presents a craniocaudal gradient of peripheral septal thickening, bronchiectasis, and honeycombing.[26] Further classification by Wernick's semi quantitative scoring system found that severe ILD was the most common finding, consist with the UIP pattern.[12] ILD progression is related to morphology of lung lesion.[13,25] . This study showed that many patients seek healthcare after later stages of the disease with visceral organ involvement such as interstitial lung disease.

Risk factors for interstitial lung disease in SSc include men, older age, African-American, duration of illness, diffuse subtype, presence of ATA, decreased Forced Vital Capacity (FVC), and biomarker.[26,27] The participants in this study were mostly women, aged between 30 – 40 years, duration of illness less than 18 months, diffuse subtype, anti-topoisomerase 1 positive with decreased FVC. There were differences in gender, age, race, and duration of illness in this study.

In West Java, SSc with ILD is commonly found, with diffuse cutaneous subtype as the predominant group. Anti-topoisomerase I, anti-Th/To and anti-Ro52 were the most common autoantibodies. In line with the pathogenesis, Anti- topoisomerase I trigger adhesion and activation of monocytes by binding to DNA–topoisomerase I expressed on fibroblasts.[28] This potentially lead to amplification of the fibro genetic cascade. Anti-Th/To and anti-Ro52 are also associated with higher prevalence of SSc-ILD. HRCT demonstrated majority of SSc with ILD in this population. This study identify similar autoantibodies associate with ILD amongst SSc patients. Some limitations should be noted. There are no data of living environment, profession, chemical exposure and previous disease history from West Java Systemic Sclerosis Registry because the registry is still in progress.

References

1. Proudman SM, Huq M, Stevens W, Wilson ME, Sahhar J, Baron M, et al. What have multicentre registries across the world taught us about the disease features of systemic sclerosis?. J Scleroderma Related Disorders. 2017;2(3):169–82.

2. Santosa A, Tan CS, Teng GG, Fong W, Lim A, Law WG,. Lung and gastrointestinal complications are leading causes of death in SCORE, a multi-ethnic Singapore systemic sclerosis cohort. Scand J Rheumatol. 2016;45(6):499–506.
3. Herrick AL. Systemic sclerosis: clinical features and management. Medicine. 2018;46(2):131–9.
4. Chowaniec M, Skoczyńska M, Sokolik R, Wiland P. Interstitial lung disease in systemic sclerosis: challenges in early diagnosis and management. Reumatologia. 2018;56(4):249–54.
5. Schoenfeld SR, Castelino FV. Evaluation and management approaches for scleroderma lung disease. Ther Adv in Respir Dis. 2017 Aug;11(8):327–40.
6. Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, Denton CP, et al. Systemic sclerosis. Nat Rev Dis Primers. 2015;1:15002.
7. Cappelli S, Bellando RS, Camiciottoli G, De Paulis A, Guiducci S, Matucci-Cerinic M. Interstitial lung disease in systemic sclerosis: where do we stand?. Eur Respir Rev. 2015;24:411–9.
8. Bahmer T, Romagnoli M, Girelli F, Claussen M, Rabe KF. The use of auto-antibody testing in the evaluation of interstitial lung disease (ILD)-A practical approach for the pulmonologist. Respir Med. 2016;113:80–92.
9. Kayser C, Fritzler MJ. Autoantibodies in systemic sclerosis: unanswered questions. Frontiers in Immunology. 2015;6:167.
10. Frank van den H, Dinesh K, Jaap F, Sindhu RJ, Murray B, Alan Tyndall, et al. 2013 Classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11):2737–47.
11. American Society Thoracis. Lung function testing: selecting of reverence value and interpretative strategies. American Rev Res Dis. 1991;144(5):1202–18.
12. Assayag D, Kaduri S, Hudson M, Hirsch A, Baron M. High Resolution Computed Tomography Scoring Systems for Evaluating Interstitial Lung Disease in Systemic Sclerosis Patients. Rheumatology. 2012;1.
13. Bastos AL, Correa RA, Ferreira GA. Tomography patterns of lung disease in systemic sclerosis. Radiol Bras. 2016;49:316–21.
14. 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.
15. Marco AA, Cesar V, Carmen PS, Vicent F, Luis T, Maria VE, et all. Early- versus late-onset systemic sclerosis: differences in clinical presentation and outcome in 1037 Patients. Medicine (Baltimore). 2014;93(2):73–81.
16. Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017;390(2017):1685–99.
17. Jiucun W, Shervin A, Gang G, Wenzhen T, Wenyu W, Li Y, et al. Clinical and serological features of systemic sclerosis in a Chinese cohort. Clin Rheumatol. 2013;32(5):617–21.
18. Domsic RT, Medsger TA. Autoantibodies and their role in scleroderma clinical care. Curr Treat Options in Rheum. 2016;2:239–51.
19. Foocharoen C, Watcharenwong , Netwijitpan S, Mahakkanukrauh A, Suwannaroj S, Nanagara R. Relevance of clinical and autoantibody profiles in systemic sclerosis among Thais. Int J Rheumatic Dis 2017;20:1572–81.
20. Murdaca G, Miriam C, Gulli R, Mandich P, Puppo F. Genetic factors and systemic sclerosis. Autoimmunity Reviews. 2016;15:427–32.
21. Mastaka Kuwana. Circulating anti-neclear antibodies in systemic sclerosis:utility in diagnosis and disease subsetting. J Nippon Med Sch. 2017;84:56–63.
22. Liaskos C, Marou E, Simopoulou T, Barmakoudi M, Efthymiou G, Scheper T, et al. Disease-related autoantibody profile in patients with systemic sclerosis. Autoimmunity. 2017;50:414–21.
23. Le Gouellec N, Duhamel A, Perez T, Hachulla AL, Sobanski V, Faivre JB, et al. Predictors of lung function test severity and outcome in systemic sclerosis-associated interstitial lung disease. PLoS One. 2017;12(8):e0181692.
24. Jung E, Suh CH, Kim HA, Jung JY. Clinical characteristics of systemic sclerosis with interstitial lung disease. Arch Rheumatol 2018;33(3):322–7.
25. Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). Respir Res. 2019;20(1):13.
26. Silver CP, Silver RM. Management of systemic-sclerosis-associated interstitial lung disease (SSc-ILD). Rheum Dis Clin of North Am. 2015;41:439–57.
27. De Martinis M, Ciccarelli F, Sirufo MM, Ginaldi L. An overview of environmental risk factors in systemic sclerosis. Expert Rev Clin Immunol. 2015;12:465–78.
28. Maaike B, Jaap AB, Annette G, Maarten KN, Nina AM, Corrie ME, et al. Association of

Anti-Topoisomerase I Antibodies of the IgM Isotype With Disease Progression in Anti-Topoisomerase I-Positive Systemic Sclerosis. Arthritis Rheumatol. 2020;72(11):1897–1904.