Correlation between Interstitial Lung Disease Morphology Scores Based on High-resolution Computed Tomography Chest and Skin Fibrosis Degree Based on Modified Rodnan's Skin Score on Systemic Sclerosis

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ABSTRAK

Latar belakang: *Sklerosis sistemik (SSc) merupakan penyakit autoimun sistemik yang mengenai jaringan ikat multisistem dan salah satu penyebab terjadinya interstitial lung disease (ILD). Modified Rodnan's Skin Score (MRSS) merupakan pemeriksaan standar baku emas yang bersifat semikuantitatif, non-invasif untuk mengukur fibrosis kulit pada SSc. Kelainan fibrosis paru pada SSc terutama berbentuk ILD merupakan penyebab mortalitas terbanyak dan seringkali terlambat dalam diagnosis. Pemeriksaan baku emas untuk menilai morfologi ILD adalah dengan High Resolution Computed Tomogaphy (HRCT) scan thoraks, namun ketersediaannya masih sangat terbatas. Derajat fibrosis kulit berdasarkan MRSS pada SSc dapat memprediksi adanya ILD pada beberapa penelitian, namun belum banyak diteliti di Indonesia. Tujuan penelitian ini untuk mengetahui hubungan morfologi ILD berdasarkan HRCT scan thoraks dengan derajat fibrosis kulit berdasarkan MRSS pada sklerosis sistemik.* ***Metode:*** *Penelitian ini merupakan penelitian observasional analitik retrospektif dengan desain cross sectional. Subjek penelitian ini adalah pasien sklerosis sistemik yang memiliki data hasil pemeriksaan MRSS dan HRCT scan thoraks sejak Juli 2019 hingga Maret 2020. Analisis statistik yang menggunakan uji korelasi Spearman's.* ***Hasil:*** *Terdapat 42 subjek penelitian, terdiri dari 41 perempuan (97.6%) dan satu laki-laki (2.4%) dengan rerata usia 41.29±12.045 tahun dengan rentang usia dari 19 tahun hingga 60 tahun. Hasil uji korelasi berdasarkan Spearman's terdapat korelasi sedang dengan R= 0,429 yang bermakna (p = 0.005) antara skor morfologi ILD dengan nilai MRSS.* ***Kesimpulan:*** *Terdapat korelasi sedang yang bermakna antara skor morfologi Interstitial Lung Disease berdasarkan HRCT thoraks dengan derajat fibrosis kulit berdasarkan Modified Rodnan's Skin Score pada sklerosis sistemik.*

Kata kunci: *high-resolution computed tomography chest, interstitial lung disease, modified Rodnan's skin score, sklerosis sistemik.*

ABSTRACT

Background: *Systemic sclerosis (SSc) is a systemic autoimmune disease multiorgan/multisystem involvement. Modified Rodnan's Skin Score (MRSS) is a gold standard for measuring skin fibrosis in*

SSc. In SSc, lung fibrosis disorders, especially interstitial lung disease (ILD), are the leading cause of mortality and often late in diagnosis. High-Resolution Computed Tomography (HRCT) Chest scan is a gold standard for evaluating ILD morphology, but its availability is limited. The degree of skin fibrosis based on MRSS in SSc can predict the presence of ILD in several studies but has not been widely studied in Indonesia. This study aimed to determine the relationship of the ILD morphology based on thoracic HRCT scan with the degree of skin fibrosis based on MRSS in SSc. ***Methods****: This study is a retrospective analytic observational study with a cross-sectional design. The subjects of this study are SSc patients who had data of MRSS and HRCT chest scan from July 2019 to March 2020. Statistical analysis uses Spearman's correlation test.* ***Results:*** *There were 42 study subjects, consisting of 41 women (97.6%) and one man (2.4%) with an average age of 39.50 years old (age range of 19 years to 60 years old). Correlation test results based on Spearman's show a moderate correlation between the morphological score of ILD with MRSS with R = 0.429, which is significant (p = 0.005).* ***Conclusion:*** *There is a significant moderate correlation between the morphological scores of ILD based on HRCT chest and the degree of skin fibrosis based on MRSS in SSc.*

Keywords**:** *High-resolution computed tomography chest, interstitial lung disease, modified Rodnan's skin score, systemic sclerosis.*

INTRODUCTION

Systemic sclerosis (SSc) is a systemic autoimmune disease affecting multisystem connective tissue and one of the causes of interstitial lung disease (ILD).[1,2] The number of patients with systemic sclerosis continues to increase and has the potential for increased morbidity and mortality due to visceral organ fibrosis.[3,4] Data on the incidence and prevalence of systemic sclerosis in Indonesia are not yet available. However, the number continues to increase and has the potential to become a severe and life-threatening disease. Systemic sclerosis is the third most common disease in Rheumatology Polyclinic of RSUP Dr. Hasan Sadikin Bandung, after systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In 2019, there were 100 systemic sclerosis patients (7%) of the total patients visiting the rheumatology polyclinic. The survey was conducted in 2015 - 2016 by the rheumatology division, Department of Internal Medicine, Faculty of Medicine, Padjadjaran University (UNPAD) Bandung at Dr. Hasan Sadikin Bandung, and there were 24 (42.1%) patients who had involvement of pulmonary fibrosis.[1,3]

In SSc, lung involvement may include pulmonary fibrosis or a ground- glass opacity image on a high-resolution computed tomography (HRCT) chest scan with a forced vital capacity (FVC) value of less than 80% and a forced expiratory volume/FVC ratio of more than 80%.[5,6] ILD is the leading cause of morbidity and mortality in systemic sclerosis patients up to 40% within ten years after disease onset.[7]

Matsuda *et al.*[5] in 2019 stated that there is an association between MRSS and organ involvement; higher MRSS significantly increased the prevalence of SSc-related ILD. A study by Deepa *et al.*[6] in India in 2016 revealed that Rodnan's score was significantly associated with severe lung involvement. Likewise, a study by Cottrell et al.[7] in 2014 mentioned that the incidence of moderate to severe restrictive lung disease (RLD) was associated with an increase in skin sclerosis scores. These evidences refer that MRSS (Modified Rodnan's skin score) can be used as an alternative marker of lung involvement in systemic sclerosis.

MRSS is a semi-quantitative, non-invasive gold standard examination to measure skin fibrosis in SSc. In SSc, pulmonary fibrosis disorder, especially ILD, is the most common cause of mortality and lattermost diagnosed. Chest X-ray is not specific for ILD. The gold standard examination for assessing ILD morphology is the High-resolution Computed Tomography (HRCT) chest scan, but its availability is still very limited. The degree of skin fibrosis based on MRSS on SSc can predict the presence of ILD shown in

several studies, but it has not been widely studied in Indonesia. Research on the morphological relationship between ILD and MRSS has never been conducted in Indonesia. It is expected that this study would increase the evidence regarding MRSS scoring to predict the presence of ILD; hence the management of complications of systemic sclerosis will be more effective.

METHODS

This research is an observational analytic correlation study with a cross-sectional model, using retrospective data. This study measures the relationship between risk factors and their outcome. The risk factors and outcomes were observed once and at the same time. The subjects of this study were systemic sclerosis patients who met the 2013 ACR/EULAR criteria and visited the Rheumatology Department of Internal Medicine at Dr. Hasan Sadikin Bandung from July 2019 to March 2020.

This study has received ethical approval from the Research Ethics Committee of the Faculty of Medicine, Padjadjaran University, and Dr. Hasan Sadikin Bandung with a letter of ethics number LB.02.01/X.65/73/2020.

Subjects

The inclusion criteria for the subjects of this study were subjects aged 18-60 years old diagnosed with systemic sclerosis, who have completed data on the degree of skin fibrosis based on MRSS and spirometry results of restrictive lung abnormalities. Subjects with restrictive lung disease due to autoimmune diseases other than systemic sclerosis and subject with tuberculosis and malignancy were excluded from our study.

MRSS and ILD Evaluation

The range of MRSS values is 0 - 51. The standard value is achieved by transforming MRSS values into an interval scale with the following formula: Transformation value 100 = (Actual value - lowest actual value)/Value range x 100.

The HRCT chest examinations utilize the Multidetector CT/MDCT 128-Slice (Hitachi SCENARIA SE-128 –slice, Hitachi Healthcare), which produce digital Imaging and Communication in Medicine (DICOM) data.

The ILD morphological score was obtained from the analysis of HRCT imaging based on the Warrick semi-quantitative method. The total score based on the parenchymal lesion pathology and the extent of the lesion ranged from 0 to 30.45.54. Degree of severity include Mild (<8), Moderate (8-15), and Severe (> 15).

Statistical Analysis

Statistical analysis was conducted to assess the correlation between the ILD morphological score based on chest HRCT and the pulmonary fibrosis score based on MRSS on systemic sclerosis patients. Spearmen correlation was used to determine the correlation between numerical and ordinal data. Interpretation of hypothesis test results was based on correlation strength, correlation direction, and p-value: Correlation strength (r) based on Guillford's criterion (1956): 0.0 - <0.2 = very weak; 0.2 - <0.4 = weak; 0.4 - <0.7 = moderate; 0.7 - <0.9 = strong; 0.9 -1.0 = very strong.

RESULTS

The study subjects were 42 patients who met the inclusion and exclusion criteria as described in **Figure 1**.

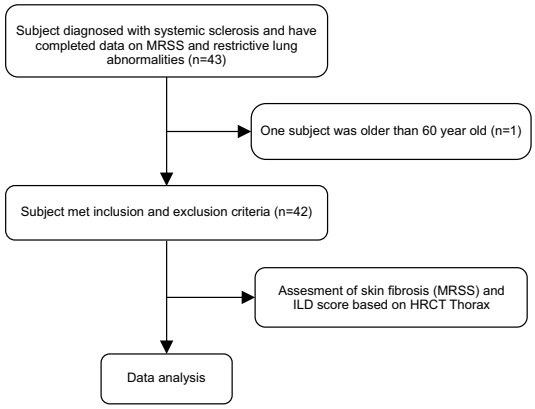

Figure 1. Patient flow chart.

Table 1 shows a total of 42 study subjects consisting of 41 women (97.6%) and one male (2.4%) with an average age of 39.5 years old and age range of 19 to 60 years old. The median duration of disease was three years with the range from 1 to 13 years. Most initial symptoms were presented as skin fibrosis in

Table 1. Subject Characteristic.

Variables	N=42
Sex, n (%)	
Male	1(2.4)
Female	41(97.6)
Age	
Median	39.50
Range (min-max)	19.00-60.00
Duration of disease (years)	
Median	3.00
Range (min-max)	1.00-13.00
Initial symptoms, n (%)	
Skin Fibrosis	38 (90.5)
Raynaud's Phenomenon	4 (9.5)
Chest X-ray, n (%)	
Normal	23 (54.8)
Bronchopneumonia	9 (21.4)
Bronchitis	3 (7.1)
Pneumonia	2 (4.8)
Inactive pulmonary TB	2 (4.8)
Pleura thickening	1 (2.4)
Active pulmonary TB	1 (2.4)
Interstitial lung disease	1 (2.4)
Morphology of ILD, n (%)	
Ground glass opacities	42 (100)
Irregular pleural margin	32 (76.2)
Septal or subpleural lines	40 (95.2)
Honeycombing	23 (54.8)
Subpleural cyst	19 (45.2)

Note: Categorical data are presented with number/ frequency and percentage, while numeric data are presented with mean, median, standard deviation, and range.

38 (90.5%) subjects. Previous chest X-ray results were normal in 23 (55%) subjects, bronchopneumonia in 9 (21.4%) subjects, and bronchitis in 3 (7.1%) subjects, respectively. Only one (2.4%) patient was described as ILD.

After HRCT chest was performed, the ground glass opacities were found in all study subjects, septal or subpleural lines in 40 (95.2%) subjects, irregular pleural margins in 32 (76.2%) subjects, honeycombing in 23 (54.8%) subjects, and subpleural cysts in 19 (45.2%) subjects.

Table 2 shows an overview of the ILD morphological score, ILD, and MRSS morphological categories. The ILD morphological score has a median of 18.00 with a range of 6.00-27.00, consisting of 4 (9.5%) mild subjects, 11 (26.2%) moderate) subjects and 27 (64.3%) severe subjects. MRSS has a mean of 18.93 (SD 8.247).

Table 2. ILD Morphological Score, ILD and MRSS Morphological Categories.

Variables	N=42
ILD Morphological Score	
Median	18.00
Range (min-max)	6.00-27.00
ILD Morphological Category, n (%)	
Mild	4 (9.5)
Moderate	11 (26.2)
Severe	27 (64.3)
MRSS	
Mean (SD)	18.93 (8.247)

Note: Categorical data are presented with number/ frequency and percentage, while numeric data are presented with mean, median, standard deviation, and range.

Table 3. Analysis of the correlation between ILD Morphological Score and MRSS

Variables	Correlation	R	p-value
Correlation between Skor Morphological ILD score and MRSS value	Spearman	0.429	0.005**

Note: p-value significance <0.05. Sign ** indicates statistically significant or significant a. r: correlation coefficient.

Table 3 shows the Spearman's correlation test between the ILD morphological score and MRSS obtaining a p-value of 0.005 (p-value <0.05) and an R-value of 0.429 (Guilford's criteria). R-value ≥ 0.40 (<0.70) indicates a moderate correlation between the ILD morphological score and the MRSS score.

MRSS value towards ILD morphological score shows a positive trend **(Figure 2)**, which is explained by an increase in the MRSS value yet followed by an increase of ILD morphological score.

DISCUSSION

The results of this study show that the female distribution was more than male, i.e. 41 (97.6%) women and one (2.4%) man, with the median age of 39.5 years old. This is consistent with research by Vinent et al, Denton et al. and Budiman et al. stating that systemic sclerosis patients are dominated by women compared to male patients, with the most frequent range in patients at age 25-55 years.[1-3]

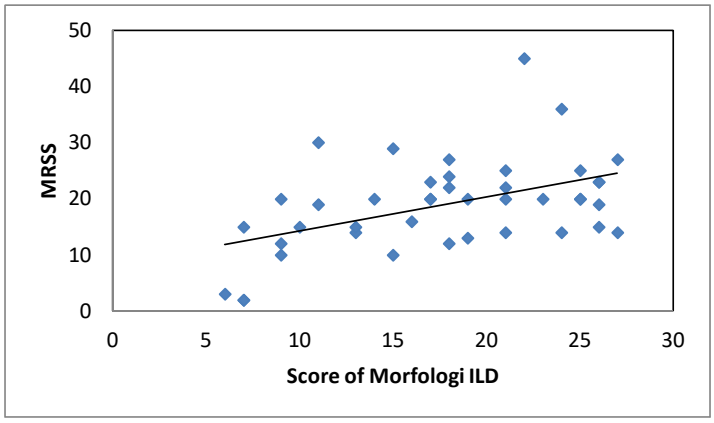

Figure 2. Correlation between ILD Morphological Score and MRSS Value.

Chest x-ray examination obtained normal results in 23 (55%) study subjects, whereas the others (45%) suggested bronchopneumonia disorders, bronchitis features, pneumonia, old pulmonary tuberculosis, pleural thickening, active pulmonary tuberculosis, and ILD. In SSc, patients with early symptoms of pulmonary involvement may have normal chest x-rays, but this does not eliminate the possibility of ILD. The ground-glass image is predominantly found in the basal lung area and can only be assessed in 25-44% of SSc patients.[8,9] This chest x-rays imaging was described previously as bronchopneumonia, bronchitis, pneumonia, and pulmonary tuberculosis.

In this study, all subjects with the mild to severe category had ground-glass opacities morphology because of increased lung attenuation. This is consistent with research by Deepa *et al.* in 2016 in the Italian population, explaining that the initial changes of the ILD process were alveolitis which featured ground-glass opacity, septal/subpleural lines, and irregular pleural margins as a result of the thickening of the interstitial intralobular tissue. The subsequent process is fibrosis which gives a honeycombing and subpleural cyst morphology. Histologically, ILD in SSc includes non-specific interstitial pneumonia (NSIP) with more inflammatory features and less fibrosis, usual interstitial pneumonia (UIP) characterized by fibrosis and scarring, as well as a combination of both.[6,10,11,12] In addition, **Table 4** explains the value of the MRSS with a mean of 18.93 (SD 8.247), where is different from the research by by Matsuda *et al.*[5] with a mean of 9.9 (SD 8.9) and Deepa *et al.*[6] with a mean of 29.9 (SD 7.13). Correlation between ILD morphological score and MRSS value.

Our study revealed that there was a moderately significant correlation between ILD morphological scores based on chest HRCT and the degree of skin fibrosis based on MRSS. Our results are in line with Matsuda *et al.*[5] in 2019 in the Japanese population that stated higher MRSS was associated with the presence of ILD in SSc ($p < 0.05$). Deepa *et al.*[6] in 2016 in the Indian population stated that Rodnan's score was significantly associated with severe lung involvement ($p = 0.031$). Cottrell *et al.*[7] in 2014 showed that in the United States population patients with higher skin fibrosis scores may develop to moderate to severe restrictive pulmonary involvement ($p < 0.001$).

The strong correlation between skin fibrosis and pulmonary fibrosis as ILD in SSc patients may be affected by similarities in the pathophysiology of skin and lung involvement in SSc, namely the presence of inflammatory cell invasion in the early stages and proliferation accompanied by degeneration of collagen fibers in the late stages of the disease.[8]

A similar study by Wu *et al.*[13] in 2018 used a large European Scleroderma Trial and Research (EUSTAR) database, multicenter and prospective study to assess the association of increased skin fibrosis with organ involvement and increased mortality in diffuse SSc patients.

Out of 1021 subjects, 78 subjects had increased skin fibrosis within one year of observation. The study found that the increase in skin fibrosis in one year was associated with decreased lung function (p = 0.004) and a worse survival rate (p = 0.063); hence it can be confirmed that MRSS is an alternative marker for diffuse SSc.[13]

A study by Wangkaew *et al.*[14] in 2016 in the Thai population showed a correlation between changes in HRCT and changes in clinical variables such as FVC, MRSS, erythrocyte sedimentation rate (ESR), and changes & SpO2 in the early phase of SSc patients. On the other hand, a study by Yani *et al.*[15] in 2019 concluded there is no correlation between serum Krebs von den Lungen (KL-6) levels with FVC and MRSS value of subjects with both restrictive lung disease and diffuse type systemic sclerosis. The KL-6 is a serum biomarker that IS produced by alveolar pneumocytes WHENEVER there is a fibrogenesis activity in the lungs. This study used the cohort method involving 31 subjects who underwent HRCT chest examination at the beginning and observation for the next 12 months, then calculated the HRCT score based on ILD morphology. The HRCT score was found to be a useful and sensitive method for assessing disease progression in SSc-related ILDs (r = −0.38, P <0.05).

However, our study did not reflect the initial incidence of ILD in SSc patients. SSc patients who were sent for HRCT scan with suspected ILD were already undergoing modification therapy for Anti Rheumatic Drugs (DMARD)/ conventional immunosuppressants with different doses and duration of therapy. There was no initial data on the chest HRCT examination when the patient was diagnosed with SSc; therefore, the chest HRCT examination during the study did not reflect the changes that occurred. Further cohort research with the completed HRCT dan MRSS baseline data is required in SSc patients for early detection of ILD and evaluating changes over a period of time.

CONCLUSION

There was a moderately significant correlation between the ILD morphological score based on HRCT chest and the degree of skin fibrosis based on modified Rodnan's skin score on systemic sclerosis.

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IH, SS, HS, and SD conceived and designed the study. SS acquired the data. All authors contributed to the writing of the manuscript. This study was funded by Universitas Padjadjaran Internal Grant.

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