Research Article

Modified Rodnan Skin Score and its Association with Extent of Lung Damage in Systemic Sclerosis Patients

Ayesha Mahmood Ali Malik[1], Tafazzul H. Mahmud[2], Aflak Rasheed[3], Abu Bakar Mahmood Malik[4], Adnan Wajih Akhtar[5], Javed Iqbal[6], Usman Hafeez[7], Asma Malik[8], Roma Gulzar[9], Nadeem Afzal[10]

[1-6-7-9-10]Trainee Resident, Department of Rheumatology & Immunology, Shaikh Zayed Medical Complex, Lahore; [2]Dean Division of Medicine, Head Department of Rheumatology & Immunology, Shaikh Zayed Medical Complex, Lahore; [3]Associate Professor, Department of Rheumatology & Immunology, Shaikh Zayed Medical Complex, Lahore; [4]Assistant Professor, King Edward Medical University, Lahore; [5]MD Trainee, Department of Rheumatology & Immunology, Shaikh Zayed Medical Complex, Lahore; [8]Consultant Neurologist, USA;

Abstract

Back Ground: Systemic sclerosis is a progressive, multi-organ autoimmune connective tissue disorder associated with widespread skin and internal organ fibrosis. Skin thickness correlates with organ involvement. Modified Rodnan skin score (MRSS) is a reliable way to measure skin thickness for assessing severity and outcome of the disease.

Objective: To evaluate association of MRSS with severity of lung disease in systemic sclerosis.

Methods: A cross-sectional study was conducted at Department of Rheumatology and Immunology Shaikh Zayed Hospital, Lahore from January 2020 - June 2020. After approval from Institutional Review Board 35 patients fulfilling the inclusion criteria were included through non-probability/convenience sampling. After a detailed history MRSS was measured using standard method. Pulmonary manifestations and internal organ assessment were done performing Force Vital Capacity (FVC), X-ray chest, echocardiography and High-Resolution CT scan chest (HRCT). Data was analyzed in SPSS ver: 25.0. Pearson correlation was calculated for MRSS and FVC. MRSS was cross tabulated with interstitial lung disease (ILD) and pulmonary hypertension. Chi-square test was used for statistical significance at $p < 0.05$.

Results: The mean age was 43.17 years + 11.67. 85.7% were females. 88.6% were married, with no family history of disease and smoking. Mean FVC was 67.428 + 16.077. MRSS range was 4-45 with a mean MRSS score of 17.800 + 11.208. Pearson product moment correlation revealed negative correlation of MRSS with FVC, r = -0.428 P = 0.010. MRSS was cross tabulated with ILD and showed statistically significant result with P = 0.006. Pulmonary hypertension was present in 42.9% of patients. Of these 53.3% had mild, 33.3% and 13.3% had moderate and severe thickening on MRSS respectively. (p = 0.590).

Conclusion: MRSS is a reliable tool for assessing and evaluating severity of lung disease in systemic sclerosis.

Corresponding Author | Dr. Ayesha Mahmood Ali Malik, Trainee Resident, Department of Rheumatology & Immunology, Shaikh Zayed Medical Complex, Lahore **Email:** ayeshamalik81@yahoo.com

Key Words: ILD, FVC, HRCT, MRSS, Systemic Sclerosis.

Introduction

Systemic sclerosis is an autoimmune connective tissue disorder, involving multiple organs with a female preponderance and an age range of thirty to fifty years[1,2]. It is characterized by immunological abnormalities along with progressive fibrosis of skin and internal organs. The disease mechanism involves activated autoimmune cells along with fibroblast hyperplasia leading to enhanced collagen production and decreased collagen breakdown[3,4]. Systemic sclerosis is divided into two subsets, depending on the degree of skin involvement. Patients with diffuse cutaneous systemic sclerosis (dcSSc) have skin involvement proximal and distal to knees and elbows along with severe damage to internal organs like heart and lungs. Limited cutaneous systemic sclerosis (lcSSc) usually involves skin distal to the knees and elbows.[2, 5] Interstitial lung diseases is one of the most common manifestations and a prime cause of mortality in systemic sclerosis patients. Myocardial, GIT, Neurological involvement, Raynaud's phenomenon, malignant hypertension, Musculoskeletal and Renal involvement are also salient features of the disease.[6,7]

The MRSS is a simple and reliable way to measure skin thickness and can be used for measuring the severity and outcome of the disease. Studies document that with increased skin thickness, there is an increased risk of damage to the internal organs which leads to increased mortality. Improvement of MRSS in some cases is related to favorable outcome of the disease[8,9]

This study aims to evaluate association of Modified Rodnan skin score (MRSS) with severity of lung disease among patients of systemic sclerosis.

Methods:

A Cross-sectional study was conducted at Department of Rheumatology and Immunology Shaikh Zayed Hospital, Lahore from January – June 2020. After approval from Institutional Review Board a sample size of 35 was calculated using formulae i.e. $n = (z)\ 2\ p\ (1 - p) / d2$ where $z = 1.96$ at 95% confidence interval, $p = 90\%$[10] and $d = 10\%$ margin of error. Patients fulfilling the inclusion criteria age, 25 – 60 years of either gender with systemic sclerosis were included in the study through Non-probability / convenience sampling. Patients with other connective tissue and collagen vascular disorders were excluded. A detailed history including disease duration, age, gender, marital status, smoking history, family history, and occupation were recorded. MRSS was measured in 17 designated skin areas. These areas included face, bilateral upper arms, forearms and hands, fingers, anterior chest, abdomen, bilateral thighs, leg and feet. Scoring of each individual cutaneous area and grading is usually done as 0 (Uninvolved), 1(Mild thickening: When the examiner can easily make skin folds between 2 fingers; fine wrinkles are acceptable), 2(Moderate thickening: When the examiner feels difficulty in making skin folds and no wrinkles), 3 (Severe thickening: When the examiner in unable to make skin folds between 2 examining fingers). A score range of minimum 1 to maximum 51 was obtained and categorized as Mild thickening (MRSS 1-17), Moderate thickening (MRSS 18-34) and Severe thickening (MRSS 35-51).[9]

Pulmonary manifestations including pulmonary hypertension, interstitial lung disease and dyspnea were also evaluated. Lung and heart assessment were done performing FVC, X-ray chest, High-Resolution CT Scan and echocardiography. Data was analyzed in SPSS ver: 25.0. Quantitative variables like Age, FVC, Disease duration and MRSS was presented as Mean and Standard deviation. Qualitative variables like Socio-demographic details and Clinical variables like pulmonary hypertension and interstitial lung disease were presented as frequency and percentages. Pearson correlation was calculated for MRSS and FVC to assess severity of disease. MRSS was cross tabulated with ILD and pulmonary arterial hypertension. Chi-square test was used for statistical significance at $p < 0.05$.

Results:

35 patients were enrolled in the study. Mean age ranged between 43.17 years $\pm$ 11.67 with a minimum of 25 years and maximum age 60 years. 48.6% were between ages of 40 to 60 years. Male to female ratio was 1:6. 88.6% (n=31) of the subjects were married among females 85.7% (n=30) were housewives with no family history of disease and smoking. (Table no: 1).

Pulmonary arterial hypertension was present in 42.9% of patients with 74.3% having less than 6 years disease duration. 60.0% of patients had dyspnea with 45.7% having reticulo-nodular shadowing on chest X-Rays. 14.3% had no interstitial lung disease.34.3% had Nonspecific interstitial pneumonia (NISP) while 51.4% had usual interstitial pneumonia (USIP). 22.9% had ground glass appearance, 11.4 %

had basilar and sub pleural predominance. 17.1% had honeycomb appearance, 20.0% had reticulo-nodular opacities and 14.3% had traction bronchiectasis on HRCT Scan of the chest. FVC was evaluated for severity of lung disease. Mean FVC was 67.428± 16.077, with a minimum of 39 and maximum of 93. 85.7% of patients had FVC < 70%. MRSS Mean score was 17.800 ± 11.208 with a minimum of 4 and maximum of 45. Mild thickening (MRSS 1 - 17) was present in 62.9 % of patients, moderate thickening (MRSS 18 - 34) in 25.7% of patients whilst 11.4% had severe thickening (MRSS 35 - 51). (Table no: 2).

Table 1: *Socio-demographic profile of patients*

Variables n=35	Frequency	Percent
Age Mean= 43.17 SD= 11.67 Min= 25 Max= 60		
< 40 years	18	51.4
40 – 60 years	17	48.6
Gender		
Male	5	14.3
Female	30	85.7
Marital Status		
Married	31	88.6
Unmarried	4	11.4
Occupation of respondents		
Non- working / House wife	30	85.7
Working	5	14.3
Family History		
No	35	100.0
Smoking History		
No	35	100.0

Table 2: *Clinical profiles of patients*

Variables n=35	Frequency	Percent
Pulmonary Arterial Hypertension		
Yes (≥25 mm Hg)	15	42.9
No (≤25 mm Hg)	20	57.1
Duration of disease Mean= 4.924 SD= 3.189 Min= 1 Max= 12		
< 6 years	26	74.3
6 – 12 years	9	25.7
Dyspnea		
Yes	21	60.0
No	14	40.0
X ray chest		
Normal	19	54.3
Reticulo-Nodular shadowing	16	45.7
Interstitial Lung Disease		
No Interstitial lung disease	5	14.3
Nonspecific interstitial pneumonia (NISP)	12	34.3
Usual interstitial pneumonia (USIP)	18	51.4
FVC Mean= 67.428 SD= 16.077 Min= 39 Max= 93		
≤ 70%	23	65.7
≥ 70 %	12	34.3
MRSS Score Mean= 17.800 SD= 11.208 Min= 4 Max= 45		
Mild thickening (MRSS 1 - 17)	22	62.9
Moderate thickening (MRSS 18 - 34)	9	25.7
Severe thickening (MRSS 35 - 51)	4	11.4

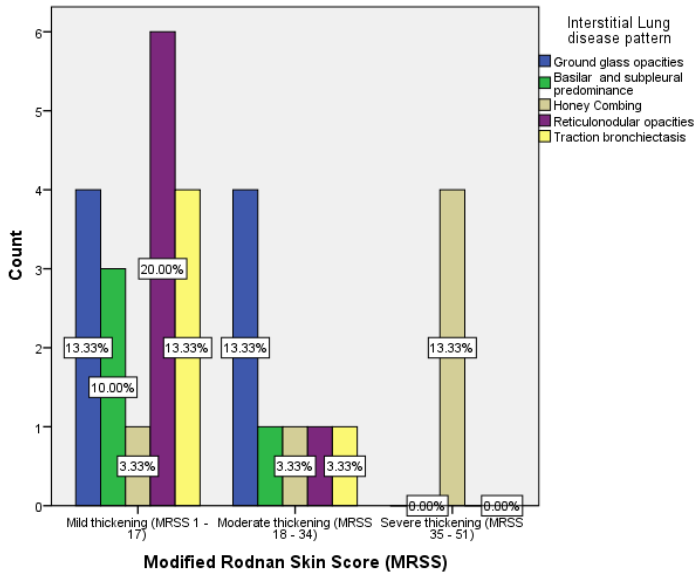

Figure 1: *Interstitial lung disease and pattern*

Pearson product moment correlation calculated for MRSS score and FVC revealed statistically significant results with R= -0.428 P =0.010. (Table no: 3).

Interstitial lung disease and pulmonary arterial hypertension were cross tabulated with MRSS scoring. 50.0% of patients with ground glass opacities had Mild thickening (MRSS 1- 17) and 50.0% had mode-

rate thickening (MRSS 18- 34). 75.0% of patients with Basilar and sub pleural predominance, 85.7% with reticulonodular opacities and 80.0% with traction bronchiectasis had Mild thickening (MRSS 1-17). 66.7% of patients with honeycombing pattern on HRCT had severe thickening (MRSS 35-51). (P = 0.006). 53.3% of patients with pulmonary arterial hypertension had mild thickening (MRSS 1- 17), 33.3% had moderate thickening (MRSS 18- 34) and 13.3% had severe thickening (MRSS 35- 71) P = .590. (Table no 4).

Table 3: *Correlation of MRSS score and FVC.*

Correlations			
		MRSS Score	FVC
MRSS Score	Pearson Correlation	1	-0.428*
	Sig. (2-tailed)		0.010
	N	35	35

***. Correlation is significant at the 0.05 level (2-tailed).**

Table 4: *Interstitial Lung disease pattern and pulmonary arterial hypertension * MRSS Cross tabulation*

Variables		MRSS Scoring			Total	Chi-Square P value
		Mild thickening (MRSS 1 - 17)	Moderate thickening (MRSS 18 - 34)	Severe thickening (MRSS 35 - 51)		
Interstitial Lung disease pattern N=30	Ground glass opacities	4	4	0	8	X^2= 21.614 P=0.006
		50.0%	50.0%	0.0%	100.0%	
	Basilar and sub pleural predominance	3	1	0	4	
		75.0%	25.0%	0.0%	100.0%	
	Honey Combing	1	1	4	6	
		16.7%	16.7%	66.7%	100.0%	
	Reticulonodular opacities	6	1	0	7	
		85.7%	14.3%	0.0%	100.0%	
	Traction bronchiectasis	4	1	0	5	
		80.0%	20.0%	0.0%	100.0%	
Pulmonary Arterial hypertension	Yes (> 25 mm)	8	5	2	15	X^2 = 1.055 P = 0.590
		53.3%	33.3%	13.3%	100.0%	
	No (< 25 mm)	14	4	2	20	
		70.0%	20.0%	10.0%	100.0%	

Discussion:

Systemic sclerosis also known as orphan disease, is an autoimmune disorder manifested by obliterative vasculopathy involving the visceral and peripheral vasculature along with fibroblast dysfunction leading to excessive skin and internal organ fibrosis[1]. Patients with systemic sclerosis are divided into diffuse cutaneous systemic sclerosis (dcSSC) and limited cutaneous systemic sclerosis (lcSSc), depending on the degree of skin involvement. MRSS is used to measure thickness of skin and thus indirectly assess severity of internal organ involvement. Our study successfully correlates the skin thickness with pulmonary involvement as indicated by changes in the HRCT, FVC and echoc-ardiographic findings.

MRSS in patients with diffuse cutaneous systemic sclerosis (dcSSC), with varying duration of disease have been evaluated in various randomized contr-olled trials (RCT).[11] Rapid skin changes occur in diffuse cutaneous systemic sclerosis, which makes it easier to study in short clinical trials. Therefore it has been used widely in many clinical trials.[12, 13] Skin thicknesses is used to assess disease severity in patients with dcSSc. An increased skin thickness, correlates with internal organ involvement and thus increase mortality in these patients.[12] Conversely, an improvement in skin score as assessed by MRSS has beneficial outcomes.[14] The extent and severity of skin involvement can be used to identify high risk patients in order to enroll them into clinical trials.[15]. MRSS has been used as a primary outcome due to its

reliability, validity, feasibility, and responsiveness to change in multicenter clinical trials.[16].

Our study results showed a male to female ratio of 1:5.9. 85.7% were females, with a mean age at diagnosis 43.17±11.67.In our cohort, MRSS score was 17.800 ±11.208 (4 to 45). The Pearson product moment correlation calculated for MRSS score and FVC showed statistically significant results with r = -0.428 p = 0.010.

These results were comparable to results of previous studies.[2,17,19] A study done by Mahmoud et al in 50 Egyptian patients, reported an MRSS score of 17.48 ± 10.44 (4 to 45) with 80% subjects having abnormal pulmonary function tests and interstitial lung disease. The mean FVC was 63.56 ± 22.18%. There was a negative correlation between MRSS and FVC%.[2] Similar results were reported in a cohort of Spanish patients. ILD was detected in 43% of the patients having a mean FVC 85 ±22 with 25% patients having FVC <70.[17] A study by Ooi et al, in 45 Chinese patients reported MRSS score of 21.22 ±9.9, along with a positive correlation with ILD and PFTs.[18] Also results by Bakhuni et al showed higher skin score and its association with ILD, low FVC and cardiac involvement.[19] In a study by Bilbir et al, there was 30% reduction in FVC (0%, 8%, and 31% of patients), and MRSS (31%, 54%, 62%) at years 1, 4 and 7 respectively. During the years 0-4 and 4-7, annual changes in FVC and MRSS were 3.2 vs. 0.42% ($p < 0.040$), and 1.8 vs. 0.2 ($P = 0.002$). The yearly reduction in FVC and DLCO, during 4 years correlated with mortality ($P = 0.022$) .However no difference was reported, regarding doses of CYC < 6 G or > 6 G.[20] Researchers also found in SSc patients showed a significantly lower BP than healthy subjects at fingertips, periungual areas and palm of hands ($p < 0.0001$), but not at the level of face and dorsum of hands.[21,22]

Skin sclerosis is a clinical hallmark of systemic sclerosis (SSc) and provides a means to classify and evaluate patients. In the diffuse cutaneous subset, skin involvement is often widespread and warrants direct therapy. Currently, main stay of treatment is broad spectrum immunosuppressive agents but more targeted specific approaches are now developing along with new diagnostic approaches. Several researches has reviewed the diagnostic criteria and efficacy of current treatment approaches and future developments for managing skin disease in early diffuse cutaneous SSc.[23-25]

Our study highlights the existence and prevalence of systemic sclerosis in a developing country like Pakistan, where it is still an unrecognized entity amongst General practitioners. It underscores the advantage of MRSS in better understanding the severity of lung disease and to individualize patient management with a goal to improve treatment outcomes.

There were a few limitations in our study. Firstly we had a small sample size. Secondly our patients largely belonged to underserved socioeconomic backgrounds, not having ready access to tertiary care facilities for early diagnosis and treatment. Also our study lacked a control group so we were unable to comment on how it would replicate under different demographics. Nevertheless, MRSS scoring serves as a guide to avoid delays in identifying underlying organ involvement and instituting treatment earlier on in the disease to avoid morbidity and mortality associated with involvement of vital organs like heart and the lungs.

Conclusion:

The results of our study conclude that MRSS scoring is a reliable indicator of skin thickness and can be used to evaluate severity of lung disease in systemic sclerosis patients.

Ethical Approval: Given
Conflict of Interest: The authors declare no conflict of interest
Funding Source: None

References:

1. Deepa AS, Rachel RP, Ramchandran P, Devaraj U, Arnold SA, Shobha V, et al. Pulmonary involvement in systemic sclerosis: A clinical profile. Lung India: official organ of Indian Chest Society. 2016;33(2) :144.
2. Mahmoud A, Alhefny A, Abugabal M, Abdelmoteleb S, Alhassanein KF. Characteristics of Progressive Systemic Sclerosis in a Cohort of Egyptian Patients. Arch Med. 2018;10(1):1-7.
3. Varga J, Wigley FM. Scleroderma-Systemic Sclerosis. In: Clinical Immunology, 3rd Ed; Elsevier, 2019.
4. Pattanaik D, Brown M, Postlethwaite BC, Postlethwaite AE. Pathogenesis of systemic sclerosis. Frontiers in immunology. 2015;6(1):272.
5. Derrett-Smith EC, Martyanov V, Chighizola CB, Moinzadeh P, Campochiaro C, Khan K, et al. Limited cutaneous systemic sclerosis skin demonstrates

distinct molecular subsets separated by a cardiovascular development gene expression signature. Arthritis research & therapy. 2017;19(1):156.
6. Giacomelli R, Liakouli V, Berardicurti O, Ruscitti P, Di Benedetto P, Carubbi F, et al. Interstitial lung disease in systemic sclerosis: current and future treatment. Rheumatology international. 2017;37(6):853-863.
7. Denton CP, Khanna D. Systemic sclerosis. The Lancet. 2017;390(10103):1685-1699.
8. Khanna D, Clements PJ, Volkmann ER, Wilhalme H, Tseng CH, Furst DE, et al. Minimal Clinically Imp-ortant Differences for the Modified Rodnan Skin Score: Results from the Scleroderma Lung Studies (SLS-I and SLS-II). Arthritis research & therapy. 2019;21(1):23.
9. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. Journal of scleroderma and related disorders. 2017;2(1):11-18.
10. Schoenfeld SR, Castelino FV. Evaluation and management approaches for scleroderma lung disease. Therapeutic advances in respiratory disease. 2017 ;11(8):327-340.
11. Amjadi S, Maranian P, Furst DE. Course of the modified Rodnan skin thickness score in systemic sclerosis clinical trials: analysis of three large multicenter, double-blind, randomized controlled trials. Arthritis Rheum. 2009;60(8):2490-2498.
12. Clements PJ, Hurwitz EL, Wong WK, Seibold JR, Mayes M, White B, et al. Skin thickness score as a predictor and correlate of outcome in systemic sclerosis: high-dose versus low-dose penicillamine trial. Arthritis Rheum. 2000;43(11):2445-2454.
13. Khanna D, Merkel PA. Outcome measures in systemic sclerosis: an update on instruments and current research. Curr Rheumatol Rep. 2007;9(2):151-157.
14. Steen VD, Medsger TA Jr. Improvement in skin thickening in systemic sclerosis associated with improved survival. Arthritis Rheum. 2001;44(12):2828-2835.
15. White B, Bauer EA, Goldsmith LA, Hochberg MC, Katz LM, Korn JH, et al. Guidelines for clinical trials in systemic sclerosis (scleroderma). I. Disease-modifying interventions. The American College of Rheumatology Committee on Design and Outcomes in Clinical Trials in Systemic Sclerosis. Arthritis Rheum. 1995;38(3):351-360.
16. Clements P, Lachenbruch P, Siebold J, White B, Weiner S, Martin R, et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol. 1995;22(7):1281-1285.
17. Tolosa-Vilella C, Morera-Morales ML, Simeón-Aznar CP. Digital ulcers and cutaneous subsets of systemic sclerosis: Clinical, immunological, nailfold capillaroscopy, and survival differences in the Spanish RESCLE Registry. Semin Arthritis Rheum. 2016;46(2):200-208.
18. Ooi GC, Mok MY, Tsang KW, Wong Y, Khong PL, Fung PC, et al. Interstitial lung disease in systemic sclerosis. Acta Radiol. 2003;44(3):258-264.
19. Bhakuni DS, Vasdev V, Garg MK, Narayanan K, Jain R, Mullick G. Nailfold capillaroscopy by digital microscope in an Indian population with systemic sclerosis. Int J Rheum Dis. 2012;15(1):95-101.
20. Balbir GA, Yigla M, Guralinink L, Hardak E, Solomonov A, Rozin AP, et al. Long-term Follow-Up of Patients With Scleroderma Interstitial Lung Disease Treated With Intravenous Cyclophosphamide Pulse Therapy: A Single-Center Experience Isr Med Assoc J. 2015;17(3):150-156.
21. Narayanan MK, Gautam M. Nailfold capillaroscopy by digital microscope in an Indian population with systemic sclerosis. International journal of rheumatic diseases. 2012;15(2). 95-101.
22. Ruaro B, Sulli A, Pizzorni C, Paolino S, Smith V, Cutolo M. Correlations between skin blood perfusion values and nailfold capillaroscopy scores in systemic sclerosis patients. Microvasc Res. 2016;105 :119-124.
23. Nihtyanova SI, Denton CP. Current approaches to the management of early active diffuse scleroderma skin disease. Rheum Dis Clin North Am. 2008;34 (1):161-179.
24. Frech TM, Shanmugam VK, Shah AA, Assassi S, Gordon JK, Hant FN, et al. Treatment of early diffuse systemic sclerosis skin disease. Clin Exp Rheumatol. 2013;31(2):166-171.
25. Solomon JJ, Olson AL, Fischer A, Bull T, Brown KK, Raghu G. Scleroderma lung disease. Eur Respir Rev. 2013;22(127):6-19.