

## A comparative study of Limited Cutaneous Systemic Sclerosis versus diffuse cutaneous systemic sclerosis

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### Abstract

**Introduction:** Systemic Sclerosis (SSc) is a multi-system connective tissue disorder of unknown aetiology characterised by thickening and stiffening of skin. SSc is clinically classified as limited cutaneous systemic sclerosis (LCSSc) and diffuse cutaneous systemic sclerosis (DCSSc).

**Objective:** To compare the cutaneous and systemic features of LCSSc with those of DCSSc.

**Materials and Methods:** A cross-sectional, descriptive study was conducted over a period of eight years in a tertiary care centre. All the patients of SSc were classified as LCSSc and DCSSc. Cutaneous features, systemic features and laboratory parameters were evaluated and compared between these two groups.

**Results:** 54 cases of SSc were recruited for the study; of which 18 belonged to LCSSc and 36 to DCSSc. Female to male ratio was 5:1 in LCSSc and 11:1 in DCSSc. Mean age were 26.10±10.68 years and 34.72±15.95 years in LCSSc and DCSSc respectively. Statistically significant difference was observed in parameters like mean age, duration of Raynaud's phenomenon, digital pitted scars, microstomia, diffuse hyperpigmentation, salt and pepper pigmentation, dyspnea on exertion, arthralgia, raised ESR and abnormality in spirometry.

**Conclusion:** The duration of Raynaud's phenomenon and digital pitted scars were significantly higher in LCSSc than DCSSc whereas microstomia, diffuse hyperpigmentation, salt and pepper pigmentation, dyspnea on exertion, arthralgia, raised ESR and restrictive ventilatory defect were significantly higher in DCSSc than LCSSc. Pulmonary, renal and cardiac involvement were relatively less in our study population compared to other studies.

**Keywords:** Limited cutaneous systemic sclerosis, diffuse cutaneous systemic sclerosis, Raynaud's phenomenon, microstomia, digital pitted scars, salt and pepper pigmentation.

### Introduction

Systemic Sclerosis (SSc) is a multi-system connective tissue disorder of unknown aetiology characterised by thickening and stiffening of skin and by structural and functional abnormalities of visceral organs including gastrointestinal tract, lung, heart, kidney. It is characterized pathologically by microangiopathy, excess collagen deposition and dysregulation of immune system. Patients with systemic sclerosis are classified as limited cutaneous systemic sclerosis (LCSSc) and diffuse cutaneous systemic sclerosis (DCSSc). Based on extent of skin involvement, LCSSc is defined as skin involvement confined to areas distal to elbows and knees and also face and neck whereas DCSSc as that extending proximal to the elbows and knees, face, neck and trunk. Patients with LCSSc have long duration of Raynaud's phenomenon, esophageal dysmotility or reflux, gastrointestinal problems, pulmonary fibrosis and pulmonary hypertension late in the course of their disease. They are often positive for anticentromere antibody. Patients with DCSSc have short duration of Raynaud's phenomenon preceding onset of cutaneous features, fatigue, arthralgia, gastrointestinal manifestations, pulmonary fibrosis, cardiac involvement and renal crisis. They often have antibodies to Scl-70.<sup>1</sup> SSc mimics many other skin conditions like generalized morphea, scleromyxedema, scleredema of Buschke, primary systemic amyloidosis, chronic graft-versus-host disease, eosinophilic fasciitis etc.<sup>1</sup> The criteria for classification of systemic sclerosis have

been established by the sub-committee for scleroderma criteria of American Rheumatism Association (now called the American College of Rheumatology). The single major criterion is presence of sclerodermatous involvement proximal to the digits, affecting limbs, face, neck, or trunk usually in a bilateral and symmetrical pattern; the minor criteria are sclerodactyly, digital pitted scars or tissue loss of volar pads of fingertips, and bibasilar pulmonary fibrosis. The diagnosis is based on presence of either the major criterion or at least two of minor criteria. These criteria have 97% sensitivity and 98% specificity. The addition of Raynaud's phenomenon and nail fold capillary microscopy and systemic sclerosis selective antibodies as additional minor criteria improve the sensitivity of these criteria.<sup>2</sup>

There is a meagre of study which compares the clinical features of LCSSc with those of DCSSc. Hence, this study was aimed to compare the cutaneous and systemic features of LCSSc with those of DCSSc.

### Materials and Methods

A cross-sectional, descriptive study was conducted over a period of eight years in a tertiary care centre in Eastern part of India. All the patients of SSc giving written consent for the study and fulfilling the criteria laid down by the sub-committee for scleroderma criteria of the American College of Rheumatology were recruited for the study.<sup>2</sup> Based on the extent of skin involvement, patients were classified as LCSSc and DCSSc. Patients with overlap syndrome, mixed

connective tissue disorders and drug induced SSc were excluded from the study. Detailed history taking, clinical examination and routine investigations including chest X-ray, electrocardiography and spirometry were done in all cases. Special investigations like high resolution CT scan, skin biopsy, echocardiography were performed in a subset of patients. The clinical and laboratory parameters of LCSSc and DCSSc were analyzed and compared using Microsoft Office Excel 2007 and SPSS.

## Results

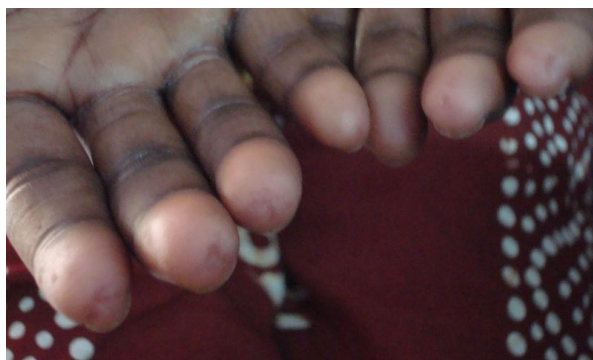
A total of 54 cases of SSc were evaluated; of which 36(66.67%) belonged to DCSSc and 18(33.3%) to LCSSc. The demographic and cutaneous features of LCSSc and DCSSc observed in our study are summarized in Table 1.

Age of patients ranged from 16 years to 44 years in LCSSc patients whereas in DCSSc, age of patients ranged from 12 years to 65 years. Among the patients with LCSSc, 10(55.5%) were housewives, 6(33.3%) were students, 1(5.5%) was farmer, 1(5.5%) was businessman by occupation. In DCSSc group, 28(77.7%) were housewives, 4(11.1%) were students, 3(8.3%) were farmers and 1(2.7%) was industrial worker by occupation.

Statistically significant difference ( $p$  value  $<0.05$ ) between LCSSc and DCSSc was observed in parameters such as mean age, duration of Raynaud's phenomenon, digital pitted scars (Fig. 1), microstomia (Fig. 2), diffuse hyperpigmentation and salt and pepper pigmentation (Fig. 3). No statistically significant difference ( $p$  value  $> 0.05$ ) between these two groups was observed in parameters like fingertip ulcers, sclerodactyly (Fig. 4), digital gangrene, calcinosis cutis, radial furrows around the mouth and pinched nose (Fig. 2).

The systemic features of LCSSc and DCSSc observed in our study are summarized in Table 2. Statistically significant difference ( $p$  value  $<0.05$ ) between the two groups was observed in parameters such as dyspnea on exertion and arthralgia.

The laboratory and radiological findings in LCSSc and DCSSc are summarized in Table 3. Statistically significant difference ( $p$  value  $<0.05$ ) between LCSSc and DCSSc was found in raised erythrocyte sedimentation rate (ESR) and restrictive pattern of ventilatory defect in spirometry.



**Fig. 1:** Digital pitted scars in a case of limited cutaneous systemic sclerosis.



**Fig. 2:** Microstomia and pinched nose in a case of diffuse cutaneous systemic sclerosis.



**Fig. 3:** Salt and pepper pigmentation in a case of diffuse cutaneous systemic sclerosis.



**Fig. 4:** Sclerodactyly in a case of diffuse cutaneous systemic sclerosis.

**Table 1:** Demographic and cutaneous features in Limited versus Diffuse cutaneous SSc

| Variables   | Limited Cutaneous SSc (n=18)                  | Diffuse Cutaneous SSc (n=36)                   | p Value               |
|---|---|--|-----------------------|
| Gender  | Female – 15, Male – 3<br>(F to M ratio - 5:1) | Female – 33, Male – 3<br>(F to M ratio - 11:1) | 0.3883*               |
| Mean Age (years)  | 26±10.68                                      | 34.72±15.95                                    | 0.0414†<br>(t=2.0919) |
| Duration of disease(years)  | 2.51±2.86                                     | 3.55±3.03                                      | 0.2315†<br>(t=1.2108) |
| Raynaud's phenomenon  | 16 (88.8%)                                    | 28 (77.7%)                                     | 0.4663*               |
| Duration of Raynaud's phenomenon (years)                          | 3.58±3.33                                     | 2.07±1.2                                       | 0.0058†<br>(t=2.8767) |
| Raynaud's phenomenon preceding skin lesions                       | 16 (88.8%)                                    | 23 (63.8%)                                     | 0.0625*               |
| Simultaneous occurrence of Raynaud's phenomenon with skin lesions | 0   | 5 (13.8%)                                      | 0.1567*               |
| Finger tip ulcer  | 15 (83.3%)                                    | 21 (58.3%)                                     | 0.0769*               |
| Digital pitted scars  | 14 (77.7%)                                    | 16 (44.4%)                                     | 0.0239*               |
| Sclerodactyly   | 15 (83.3%)                                    | 33 (91.6%)                                     | 0.3883*               |
| Digital gangrene  | 2 (11.1%)                                     | 1 (2.7%)                                       | 0.255*                |
| Calcinosis cutis  | 2 (11.1%)                                     | 2 (5.5%)                                       | 0.5936*               |
| Microstomia   | 13 (72.2%)                                    | 35 (97.2%)                                     | 0.0127*               |
| Radial furrows around the mouth                                   | 3 (16.6%)                                     | 15 (41.6%)                                     | 0.0769*               |
| Pinned nose   | 8 (44.4%)                                     | 25 (69.4%)                                     | 0.087*                |
| Diffuse hyperpigmentation   | 3 (16.6%)                                     | 27 (75%)                                       | 0.0001*               |
| Salt and pepper pigmentation                                      | 6 (33.3%)                                     | 32 (88.8%)                                     | 0.0001*               |

The significance of difference was tested by \*Chi-square test and † Unpaired t-test

**Table 2:** Systemic features in Limited versus Diffuse cutaneous SSc

| Variables               | Limited Cutaneous SSc (n=18) | Diffuse Cutaneous SSc (n=36) | p Value (Chi-square test) |
|-------------------------|------------------------------|------------------------------|---------------------------|
| Gatro-esophageal reflux | 5 (27.7%)                    | 20 (55.5%)                   | 0.0825                    |
| Dysphagia               | 8 (44.4%)                    | 20 (55.5%)                   | 0.5658                    |
| Dyspnea on exertion     | 4 (22.2%)                    | 26 (72.2%)                   | 0.0011                    |
| Cough                   | 0                            | 6 (16.6%)                    | 0.1627                    |
| Arthralgia              | 5 (27.7%)                    | 25 (69.4%)                   | 0.008                     |
| Palpitation             | 0                            | 4 (11.1%)                    | 0.2888                    |

**Table 3:** Laboratory and radiological features in Limited versus Diffuse cutaneous SSc

| Variables                                  | Limited Cutaneous SSc (n=18) | Diffuse Cutaneous SSc (n=36) | p Value (Chi-square test) |
|--|------------------------------|------------------------------|---------------------------|
| Anemia                                     | 14 (77.7%)                   | 35 (97.2%)                   | 0.0375                    |
| Raised erythrocyte sedimentation rate(ESR) | 11 (61.1%)                   | 35 (97.2%)                   | 0.0011                    |
| ANA positivity                             | 15 (83.3%)                   | 31 (86.1%)                   | 1                         |
| Proteinuria                                | 0                            | 4 (11.1%)                    | 0.2888                    |
| Abnormality in X-ray hand                  | 4 (22.2%)                    | 14 (38.8%)                   | 0.3587                    |
| Abnormality in chest X-ray                 | 1 (5.5%)                     | 9 (25%)                      | 0.1379                    |
| Restrictive pattern of ventilatory defect  | 3 (16.6%)                    | 29 (80.5%)                   | 0                         |
| Abnormal ECG                               | 0                            | 3 (8.3%)                     | 0.5428                    |

## Discussion

The mean age of presentation in our study was  $26 \pm 10.68$  years in LCSSc and  $34.72 \pm 15.95$  years in DCSSc and the difference was statistically significant. Ghosh et al. also had similar observation ( $26.5 \pm 10.9$  years in LCSSc and  $31.8 \pm 12.9$  years in DCSSc) but the difference was not statistically significant.<sup>3</sup> We found female preponderance in our study with female to male ratio of 5:1 in LCSSc and 11:1 in DCSSc. Most of the studies in literature also noted female preponderance with female to male ratio varying from 3.9:1 to 8.37:1.<sup>3-7</sup> Occupational history is important in SS as scleroderma like lesions occur in workers exposed to chemicals like Vinyl chloride, Perchloroethylene, Trichloroethylene, Organic solvents, Pesticides, Epoxy resins etc.<sup>1</sup> However, none of our patients had history of exposure to these chemicals.

Mean duration of disease in our study was  $2.51 \pm 2.86$  years in LCSSc and  $3.55 \pm 3.03$  years in DCSSc. Sharma et al. noted a higher duration of disease ( $6.49 \pm 4.34$  years) in their study.<sup>4</sup> The early detection of the disease in our study population is reflected in the difference in systemic features which are directly proportional to the duration of the disease.

We observed Raynaud's phenomenon in 88.8% patients with LCSSc and 77.7% patients with DCSSc. Basel et al. found this in 96.7% patients with LCSSc and 100% patients with DCSSc.<sup>8</sup> We also observed that duration of Raynaud's phenomenon was longer in patients with LCSSc compared to DCSSc and the difference was statistically significant. However, Ghosh et al. observed that duration of Raynaud's was longer in DCSSc patients compared to LCSSc but the difference was not statistically significant.<sup>3</sup> In our study, Raynaud's appeared before skin tightening in 88.8% cases of LCSSc and in 63.8% cases of DCSSc; thus Raynaud's phenomenon is the earliest clinical manifestation which should not be overlooked by the treating physician. This observation is very similar to Ghosh et al. who found Raynaud's phenomenon before skin involvement in 88.2% cases of LCSSc and 79.2% of DCSSc.<sup>3</sup> However, Krishnamurthy et al. noted Raynaud's phenomenon in only 28.2% cases of SS.<sup>5</sup>

Fingertip ulceration was observed in 83.3% patients with LCSSc and 58.3% patients with DCSSc and is a direct reflection of the digital ischemic changes which is more in LCSSc. However, Ghosh et al. found this to be more common in DCSSc compared to LCSSc.<sup>3</sup> In our study, digital pitted scars was observed in 77.7% cases with LCSSc and in 44.4% cases with DCSSc and the difference was statistically significant.

We noted sclerodactyly in 83.3% and 91.6% cases of LCSSc and DCSSc patients respectively. In contrary, Ghosh et al. observed this in 89.5% and 77.8% cases of LCSSc and DCSSc respectively.<sup>3</sup>

Calcinosis cutis is most commonly found in fingers and is more common in female than in males. It may lead to ulceration with discharge of chalky materials. We noticed calcinosis cutis in relatively higher proportion of cases

compared to Ghosh et al. (2.2%) and Al-Adhath et al. (4%).<sup>3,7</sup>

Microstomia was found in 72.2% cases of LCSSc and 97.2% cases of DCSSc and there was statistically significant difference between the two groups. Ghosh et al observed microstomia in 84.2% and 81.5% cases of LCSSc and DCSSc respectively but the difference was not statistically significant.<sup>3</sup>

We observed diffuse hyperpigmentation in 16.6% cases of LCSSc and 75% cases of DCSSc and the difference was statistically significant. Sharma et al. noted diffuse hyperpigmentation in a higher proportion of cases.<sup>4</sup> Salt and pepper pigmentation was found in 33.3% cases of LCSSc and 88.8% cases of DCSSc and this difference was also statistically significant. Sharma et al. found this in 51.2% cases and Dia et al. in 70% cases of SS.<sup>4,6</sup>

Esophagus is the most common part of gastrointestinal tract (GIT) to be involved in SS and gastroesophageal reflux and dysphagia are common gastrointestinal symptoms. Gastroesophageal reflux was found in 27.7% cases of LCSSc and 55.5% cases of DCSSc and the difference was not statistically significant. Basel et al also had similar observation and they found this in 36.1% and 50% cases of LCSSc and DCSSc respectively.<sup>8</sup> Dysphagia was found in 44.4% cases of LCSSc and 55.5% cases of DCSSc in the present study. Basel et al found dysphagia in 65.6% and 78.6% cases of LCSSc and DCSSc respectively.<sup>8</sup> However, Gupta et al. noted dysphagia in a higher proportion cases of LCSSc (82.6%) compared to DCSSc (60.7%).<sup>9</sup>

Pulmonary involvement occurs in about 40% to 90% cases in SS. Pulmonary fibrosis is usually associated with diffuse cutaneous SS and pulmonary hypertension with limited cutaneous SS.<sup>10</sup> Dyspnea on exertion and cough are common pulmonary symptom in SS. In our study, dyspnea on exertion was observed in 22.2% cases of LCSSc and 72.2% cases of DCSSc and there was statically significant difference between these groups. Sharma et al observed this in 51.1% and Arakkal et al. in 64.3% cases of SS.<sup>4,11</sup> Arakkal et al. noted cough in a higher proportion of patients (32%) compared to our findings.<sup>11</sup>

Arthralgia was noted in 27.7% and 69.4% cases of LCSSc and DCSSc respectively and the difference was statistically significant. Basel et al found joint involvement to be more common with LCSSc compared to DCSSc though the difference was not statistically significant.<sup>8</sup> Sharma et al. noted arthralgia in 36.7% and Krishnamurthy et al. in 53.8% cases of SS.<sup>4,5</sup>

11.1% of our DCSSc patients complained of palpitation which is very similar to observation by Aakkal et al. (14.3%).<sup>11</sup>

In our study, 77.7% of LCSSc and 97.2% of DCSSc patients were anemic and this difference was statistically significant. Hemoglobin less than 10gm/dl was found in 42.9% cases by Arakkal et al. whereas Al-Adhath et al. observed anemia in only 31% patients.<sup>7,11</sup>

We noted raised ESR in about 61.1% and 97.2% cases of LCSSc and DCSSc respectively and the difference was

statistically significant. This finding was consistent with the observation by Sharma et al.<sup>4</sup> However, Arakkal et al. found raised ESR in a lower proportion (53.6%) of patients.<sup>11</sup>

In the present study, ANA level was raised in 83.3% cases of LCSSc and 86.1% cases of DCSSc. Ghosh et al. found ANA positive result in 84.2% in LCSSc and 74.1% in DCSSc whereas Pradhan et al. found this in 87.5% in LCSSc and 86.7% in DCSSc.<sup>3,12</sup>

Mild proteinuria is the most common renal manifestation, often early in the disease. In this study, proteinuria was noted in 11.1% cases of DCSSc only. Basel et al. found proteinuria in 3.3% cases of LCSSc and 21.4% cases of DCSSc.<sup>8</sup>

X-ray hand showed changes like acro-osteolysis, contracture, calcinosis, erosive arthropathy etc. We observed abnormality in X-ray hand in only 22.2% cases of LCSSc and 38.8% cases of DCSSc.

In our study, abnormality in chest X-ray was noted in 5.5% cases of LCSSc and 25% cases of DCSSc. This finding was higher in studies by Sharma et al., Arakkal et al. and Teh et al.<sup>6,11,13</sup> Spirometry is very useful investigation in SSc and it shows restrictive changes with a decreased forced vital capacity and total lung capacity. Abnormalities in pulmonary function test may precede symptoms, or changes in chest X-ray. We noted restrictive pattern of ventilatory defect in 16.6% cases of LCSSc and 80.5% cases of DCSSc and the difference was statistically significant. Arakkal et al. found this in 72.7% cases of LCSSc and 88.2% cases of DCSSc.<sup>11</sup> Perera et al. found pulmonary involvement in 18.8% cases with LCSSc and 81.2% cases of DCSSc.<sup>14</sup> HRCT could not be done in all our cases due to infrastructural constrain.

Cardiac involvement in SSc includes myocardial disease, conduction system abnormalities, arrhythmia and pericardial disease. Resting ECG is abnormal in about 50% cases and includes bifid P waves and T wave changes.<sup>15</sup> In our study, 8.33% of DCSSc patients had abnormal ECG which is very less compared to observations by Arakkal et al. (71.4%).<sup>11</sup>

## Conclusion

The duration of Raynaud's phenomenon and digital pitted scars were significantly higher in LCSSc than DCSSc; thus it is imperative that patients with LCSSc can be diagnosed early if the physician is vigilant about these features. Microstomia, diffuse hyperpigmentation, salt and pepper pigmentation, dyspnea on exertion, arthragia, raised ESR and restrictive pattern of ventilator defects were significantly higher in DCSSc than LCSSc. The systemic symptoms makes a DCSSc patient more vulnerable to morbidity and needs frequent follow up. Pulmonary, renal and cardiac involvement were relatively less in our study population compared to other studies which can be because of the fact that the delay in diagnosis was less in our study population than in other studies.

## Limitation

The study is limited by the fact that it is of cross-sectional design and future longitudinal studies are needed to evaluate the prognosis in LCSSc and DCSSc. Due to infrastructural constraints HRCT, anti-centromeric and anti-topoisomerase antibody could not be evaluated.

**Conflict of Interest:** None.

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