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ORIGINAL ARTICLE

Clinical and laboratory differences between early- and late-onset systemic sclerosis: A comparative analytical study.

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ABSTRACT… Objective: To compare the clinical and laboratory changes between early- and late-onset systemic sclerosis. **Study Design:** Comparative Analytical Cross-sectional study. **Setting:** Fauji Foundation Hospital (FFH), Rawalpindi (RWP). **Period:** 1st September, 2025 to February, 2026. **Methods:** A non-probability consecutive sampling was applied to recruit 100 individuals with confirmed 'systemic sclerosis' (SSc). Patients were recruited and categorized as Early Onset SSc (EOSSc) (onset ≤ 40 years) and Late Onset SSc (LOSSc) (onset >50 years). Groups were compared using t-test, chi-square, and fisher's exact test with significance set at p ≤0.05. Results: Mean age was 32.4 ± 5.1 years in EOSSc and 52.7 ± 6.3 years in LOSSc (p < 0.001). EOSSc had more diffuse cutaneous involvement than LOSSc (p < 0.001). EOSSc increased inflammatory markers (p = 0.01; p = 0.002). Anti-Scl-70 was more prevalent in EOSSct (p < 0.001), whereas anti-centromere antibodies were more frequent in LOSSc (p < 0.001). Pulmonary arterial hypertension (p = 0.01), interstitial lung disease (p = 0.04), and renal involvement (p = 0.02) were more frequent in LOSSc. **Conclusion:** There are clinical and serological patterns that are associated with age at the onset of the disease in SSc. Early onset disease is more diffuse in nature, with skin inflammation, but the late onset disease has increased prevalence of vascular and organ complications.

Key words: Age Factors, Inflammation, Pulmonary Arterial Hypertension, Scleroderma, Systemic Complications.

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INTRODUCTION

Scleroderma, or systemic sclerosis (SSc), is a chronic, multisystem, autoimmune disease with an immune dysregulation, generalized microvascular injury, and fibrotic progression of the skin and internal organs.[1] There is a heterogeneity in clinical presentation, progression, and prognosis of SSc. Early identification and stratification are essential for optimal management.[2] The disease predominantly occurs in women with a female-to-male ratio of about 4:1, and normally occurs between the ages of 30 and 50 years, but cases in younger and older ages pose different clinical challenges.[3]

Worldwide, the incidence of SSc is 10 to 20 cases per million population annually and prevalence is 50 to 300 cases per million by geographic location and diagnostic criteria.[4] Although SSc is rare, it has a high morbidity and mortality rate, with 10-year survival rates between 55% and 70% years, and greatly depends on the severity of involvement of internal organs, especially pulmonary, cardiac, and renal complications.[5] SSc may be categorized into early-onset and late-onset forms based on the age at which the disease starts.[6] Onset of the disease is usually characterized by early-onset disease (≤ 40 years) with an aggressive immune profile characterized by a pronounced cutaneous disease and the presence of autoantibodies.[7] Late-onset systemic sclerosis (>50 years) is, in contrast, beginning to be seen as a distinct subcategory, often characterized by more comorbidities, later diagnosis, and more organ involvement, especially that of pulmonary hypertension and interstitial lung disease.[8]

There is growing evidence that the clinical symptoms and laboratory markers of SSc patients are significantly influenced by the age at onset.[6] There have been reports of changes in the frequency of Raynaud phenomenon, skin thickening, digital ulcers, visceral involvement, and autoantibodies such as anti-topoisomerase I and anti-centromere antibodies.[9]

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Nevertheless, the literature is already limited and even contradictory, especially in the regional populations, where genetic, environmental, and access to healthcare factors can modify the manifestation of the disease.

To improve diagnostic precision, risk assessment, and individualized patient therapy, it is critical to comprehend the clinical and laboratory distinctions between early and late onset systemic sclerosis. The consequences of diseases are further complicated in most developing healthcare environments, such as Pakistan, due to delayed diagnosis and inaccessibility of advanced immunological tests. Comparative analytical methodology will assist in determining certain trends related to age at onset, which will allow recognizing high-risk patients sooner and providing specific therapeutic interventions. Furthermore, the research will add to the existing knowledge base by offering regional data, which is rather deficient, but is the most important to support evidence-based clinical practice. The goal of the current study was to examine the laboratory parameters and clinical characteristics of individuals with early-onset and late-onset systemic sclerosis.

METHODS

The study was a comparative analytical cross-sectional study, which was carried out in the Department of Rheumatology, Fauji Foundation Hospital (FFH), Rawalpindi (RWP) during a six-month span from Sep, 2025 to Feb, 2026. Ethical approval was obtained from IRB of Fauji Foundation Hospital, RWP, approval no: 1087/RC/FFH/RWP, Dated: 10 March, 2026.

The sample size was determined using the OpenEpi version 3.01 to compute the sample size for comparing two proportions. This calculation was based on the difference in the prevalence of pulmonary hypertension in a previous study who found pulmonary hypertension was present in 25% of patients with late onset systemic sclerosis and 12% of those with early onset.[10] The minimum 100 patients (50 patients per group) were estimated by using a 1:1 allocation ratio, a 95% confidence level, and an 80% power.

A non-probability consecutive sampling was used. Adults of either gender with a confirmed diagnosis of Systemic Sclerosis according to the 2013 ACR/EULAR criteria for systemic sclerosis (SSc) were included in the study. Those with a disease duration of at least six months were only eligible. In addition, respondents willing to participate in the research and having signed informed consent were recruited. The study excluded patients who had overlap connective tissue diseases such as Systemic lupus erythematosus, Polymyositis, and Rheumatoid arthritis. Moreover, secondary causes of scleroderma, patients with major comorbid conditions that would impact organ performance independent of systemic sclerosis, pregnant females, patients with fibromyalgia and incomplete clinical or laboratory history were also excluded.

Data collection was started after ethical consent was given by the ERC. All participants were informed and gave written consent before enrolling. A structured and pre-designed proforma was used to record all relevant information. The study period was used to enroll patients using non-probability consecutive sampling. All registered patients were separated into two groups according to the age at which the disease started. Patients whose disease onset was at ≤ 40 years were grouped as Early-Onset Systemic Sclerosis (EOSSc), whereas those whose disease onset was >50 years were grouped as Late-Onset Systemic Sclerosis (LOSSc).

Demographics such as age, gender, of onset of the disease, and years of disease duration were captured. Each patient was examined in detail, clinically. Skin involvement was estimated with the modified Rodnan skin score and categorized into limited or diffuse cutaneous subtypes.[11,12] Additional clinical features such as raynaud's phenomenon, digital ulcers, pitting scars, musculoskeletal involvement (including arthritis and myositis), gastrointestinal involvement (including dysphagia, gastroesophageal reflux, and esophageal dilation on HRCT), pulmonary involvement including interstitial lung disease, pulmonary arterial hypertension, and renal involvement including scleroderma renal crisis were evaluated and documented.

Laboratory testing were performed in accordance with standard hospital procedures. Hematological

data were recorded, including platelet count, total leukocyte count, and hemoglobin. C-reactive protein and erythrocyte sedimentation rate were indicators of inflammation. Proteinuria, hematuria, urinary casts, and the urine protein creatinine ratio were assessed. Renal function tests and levels of creatine phosphokinase were also reported. Antinuclear, anti-topoisomerase I (Anti-Scl-70), anti-centromere, and anti-RNA polymerase III antibodies were all included in the immunological profile. To ascertain lung involvement, pulmonary function tests were performed. Imaging data was analyzed to look for signs of esophageal dilatation and interstitial lung disease. To identify pulmonary arterial hypertension, echocardiography was used to evaluate pulmonary artery pressure.

Statistical Package of Social Sciences (SPSS) version 24 was used to enter and analyze the data. Quantitative variables were reported as mean and standard deviation (SD) based on normality of distribution which was checked by Shapiro-Wilk test, their age, age at onset of disease, disease duration, modified Rodnan skin score, laboratory parameters like hemoglobin, total leucocyte count, platelets count, ESR, CRP, CPK, Qualitative variables (gender, cutaneous subtype (diffuse or limited), Raynauds phenomenon, digital ulcers, musculoskeletal involvement (arthritis, myositivity), gastrointestinal involvement (dysphagia, reflux, esophageal dilation), pulmonary involvement (interstitial lung disease), pulmonary arterial hypertension, renal involvement and immunological mark. The independent samples t-test was used to compare Early-Onset Systemic Sclerosis (EOSSc) and Late-Onset Systemic Sclerosis (LOSSc) groups of normal continuous variables. The chi-square test and fisher's exact test was used to analyze associations between categorical variables where the expected frequencies were below five. A p-value < 0.05 was considered statistically significant.

RESULTS

The study included 100 participants with a confirmed diagnosis of Systemic Sclerosis. Half of the patients were classified as Early-Onset Systemic Sclerosis (EOSSc) and the other half patients as Late-Onset Systemic Sclerosis (LOSSc). The mean age of the EOSSc group was 32.4 ± 5.1 years, while the LOSSc group reported a mean age of 52.7 ± 6.3 years. In both groups, females had a higher percent (80% in EOSSc, and 76% in LOSSc) and the average length of disease was similar in both early- and late-onset patients. (Table-I)

Diffuse skin disease was also more common in EOSSc group, and limited cutaneous involvement was more reported in the late-onset cohort. The modified Rodnan skin score showed that EOSSc patients compared with LOSSc patients, had more extensive skin fibrosis. Raynaud's phenomenon was prevalent in both groups, but musculoskeletal manifestations, such as myositis, were more prevalent in early-onset patients. (Table-II)

Both groups had dysphagia and esophageal dilation with no significant difference. Pulmonary complications such as interstitial lung disease were a more common occurrence among LOSSc patients, and so was pulmonary arterial hypertension. Pulmonary function tests supported these findings, showing that patients with LOSSc had considerably lower FVC, indicating more severe pulmonary involvement. (Table-III)

The EOSSc group had higher levels of inflammatory markers than the LOSSc group, according to laboratory analysis. Patients with early onset of the illness also had elevated CPK levels of muscle enzymes. The groups' hematological indices, including platelet counts, hemoglobin, and total leukocyte counts, were comparable. Immunological analysis showed age-specific trends. Anti-Scl-70 antibody positivity was substantially higher in patients with EOSSc, but anti-centromere antibody positivity was higher in individuals with LOSSc. Both groups had high levels of ANA positivity, and there was no discernible difference in anti-RNA polymerase III antibody levels. (Table-IV)

DISCUSSION

This comparative analytic study of early and late onset SSc showed significant differences in terms of cutaneous, clinical, immunological, and internal organ involvement between the two categories of sclerosis.

TABLE-I

Demographics and disease characteristics

Variable	Early-Onset SSc (n=50) n(%)/ Mean ± SD	Late-Onset SSc (n=50) n(%)/ Mean ± SD	P-Value
Age (years)	32.4 ± 5.1	52.7 ± 6.3	<0.001
Gender			
Males	10 (20%)	12 (24%)	0.61
Females	40 (80%)	38 (76%)	
Disease duration (years)	4.2 ± 2.1	3.8 ± 2.0	0.38
Age at disease onset (years)	28.5 ± 6.2	52.7 ± 6.3	<0.001

TABLE-II

Cutaneous and musculoskeletal features

Clinical Feature	Early-Onset SSc (n=50) n(%)/ Mean ± SD	Late-Onset SSc (n=50) n(%)/ Mean ± SD	P-Value
Subtype			
Diffuse cutaneous	32 (64%)	12 (24%)	<0.001
Limited cutaneous	18 (36%)	38 (76%)	
Modified Rodnan Skin Score	18.5 ± 6.2	10.2 ± 4.5	<0.001
Raynaud's phenomenon	45 (90%)	44 (88%)	0.74
Digital ulcers	20 (40%)	12 (24%)	0.09
Arthritis	25 (50%)	18 (36%)	0.18
Myositis	12 (24%)	4 (8%)	0.03

TABLE-III

Organ involvement, pulmonary function, and imaging

Variable	Early-Onset SSc (n=50) n(%)/ Mean ± SD	Late-Onset SSc (n=50) n(%)/ Mean ± SD	P-Value
Dysphagia	28 (56%)	22 (44%)	0.21
Esophageal dilation on HRCT	15 (30%)	12 (24%)	0.51
Interstitial lung disease	18 (36%)	28 (56%)	0.04
Pulmonary arterial hypertension (PAP >25 mmHg)	6 (12%)	18 (36%)	0.01
Renal involvement (scleroderma renal crisis)	2 (4%)	10 (20%)	0.02
FVC	78 ± 12	65 ± 15	0.002

In particular, the early onset disease was linked to increased prevalence of diffuse cutaneous involvement, higher levels of inflammatory markers and increased anti Scl 70 positivity, and the late onset disease was described by predominantly limited cutaneous involvement, increased prevalence of pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), renal involvement, and a higher proportion of anti-centromereantibodies. The results are consistent and comparable to findings of recent national and international research.

Different clinical phenotypes have been shown in a number of studies based on the age at which the disease first manifests. Our finding of increased organ morbidity in late onset disease is supported by a recent longitudinal analysis of late and early onset SSc, which found that patients with late onset had significantly greater rates of PAH, renal impairment, and cardiac involvement than patients with early onset.[6] Equally, a population-based registry study of Italy indicated that elderly onset cases of SSc had less cutaneous involvement but more prevalence of

TABLE-IV

Laboratory and immunological findings

Parameter	Early-Onset SSc (n=50) n(%)/ Mean ± SD	Late-Onset SSc (n=50) n(%)/ Mean ± SD	P-Value
Hemoglobin (g/dL)	12.5 ± 1.2	12.8 ± 1.4	0.33
Total leukocyte count (×10³/µL)	8.5 ± 2.1	7.8 ± 1.9	0.09
Platelets (×10³/µL)	280 ± 65	270 ± 60	0.42
ESR (mm/hr)	38 ± 15	28 ± 12	0.01
CRP (mg/L)	12 ± 6	7 ± 4	0.002
CPK (U/L)	210 ± 85	150 ± 60	0.01
Serum creatinine (mg/dL)	0.86 ± 0.18	1.05 ± 0.25	0.02
Urine protein/creatinine ratio (mg/mg)	0.18 ± 0.09	0.42 ± 0.20	0.001
ANA pattern			0.03
Homogeneous	18 (36%)	14 (28%)	
Speckled	20 (40%)	18 (36%)	
Nucleolar	7 (14%)	10 (20%)	
Other/atypical	5 (10%)	4 (8%)	
Anti-Scl-70 positive	28 (56%)	8 (16%)	<0.001
Anti-centromere antibody positive	6 (12%)	24 (48%)	<0.001
Anti-RNA polymerase III positive	4 (8%)	6 (12%)	0.50

PAH and anti-centromere antibodies, which are also in line with our observations of limited cutaneous type and anti-centromere positivity in late onset cases.[13]

Age-related mechanisms could account for the differences observed in clinical and immunological phenotype between early and late onset systemic sclerosis. Dysregulated innate and adaptive immune responses also occur in older people, and this is linked to changes in autoantibody expression and the development of chronic low-grade inflammation, known as immunosenescence. Furthermore, endothelial dysfunction and higher vascular stiffness are common features of the aging process which can lead to poor repair of microvasculature and greater risk of pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD). In elderly patients, the regenerative ability may be limited, as well as the ability of fibroblasts to regulate tissue repair, making the process of tissue injury and organ fibrosis even worse. Overall, these pathways indicate that age at disease onset may be an independent factor in disease expression in systemic sclerosis via immune and vascular effects.

The increased rate of pulmonary arterial hypertension (PAH) seen in the current study may be due in part to changes in vascular and cardiopulmonary systems with aging, as well as disease-specific factors. With ageing, endothelial dysfunction is progressive, NO bioavailability decreases and the vessels stiffen which can further contribute to pulmonary vascular remodeling in vulnerable subjects. In addition, patients with late onset are more likely to have secondary cardiovascular comorbidities that may worsen PVR and, in turn, lead to the development of PAH. Due to its strong association with microvascular disease, age-related vascular repair dysfunction may also contribute to the increased burden of PAH in older-onset patients, in a synergistic manner.

The disparity in the distribution of skin involvement that we observed in our study, with greater prevalence of diffuse cutaneous SSc in the subjects with early onset and limited cutaneous SSc in the subjects with late onset, resembles the classic phenotypic descriptions in the literature. A major cohort study established that diffuse cutaneous disease and

antiScl-70 antibodies are more prevalent in younger onset SSc and are associated with increased risk of organ fibrosis and inflammation, and limited cutaneous disease is often linked to anti centromere antibody and vascular disease.[14,15] These data support the immunological and clinical stratification seen in our population.

Higher inflammatory factors (ESR and CRP) in the early onset SSc are also corroborated by the findings of the studies that have demonstrated that diffuse cutaneous subsets tend to have stronger immune activation and inflammatory phenotypes, which can be the basis of more aggressive skin and musculoskeletal involvement in younger patients. This has been highlighted in cohort studies that have related the inflammatory cytokine profiles and autoantibody expression to disease severity.[16]

The autoantibody pattern in our investigation namely; the high rate of antiScl-70 in early disease and anti-centromere antibodies in the late disease is consistent with other international cohorts. AntiScl-70 antibodies in a Pakistani cohort (cross sectional), but not anti-centromere antibodies, were associated with diffuse disease, which is in agreement with our immunologic patterns.[17] In addition, a multicentric immunology review repeated that antiScl-70 is associated with ILD and fibrotic complications, with anti-centromere commonly associated with vascular phenomena such as PAH, which confirms our trends.[15]

Anti-Scl-70 positivity was present in a higher percentage of patients with interstitial lung disease (ILD) in systemic sclerosis (SSc), although ILD was more common in the late onset SSc group of patients. The multifactorial nature of PSSc (pulmonary involvement in SSc) may account for this apparent paradox: lung pathology may also reflect the cumulative vascular injury in SSc as well as age-related pulmonary vulnerability in these patients that are also likely to be age-related. For late-onset patients, lung susceptibility due to structural changes can be more important than serological risk patterns and may also predominate in the development of ILD. On the other hand, while anti-Scl-70 was more common in early onset disease, not all Scl-70 seropositive patients had clinically important ILD in early onset disease or at a comparable stage or severity. These results indicate that autoantibody status is a risk stratifier instead of a ruling factor of organ involvement and that age may play a role independently in the pulmonary involvement of systemic sclerosis.

Although PAH is higher in patients who have mild cutaneous disease who often have ant-centromere antibodies, disease-specific analyses of how ILD risk is increased in patients with diffuse disease and anti-Scl 70 positive patients support our finding of more ILD and PAH in LOSSc with regard of pulmonary involvement.[18,19] This subtle association between the autoantibody profile, cutaneous subtype, and pulmonary vascular disease is becoming more apparent in large SSc cohorts.

The association between specific autoantibodies and clinical features was also observed using a Moroccan cohort study, with anti-topoisomerase I significantly associated with ILD and anti-centromere positivity is significantly associated with PAH, which resonates with the patterns of organ distribution in our study.[20] These similarities point to a parallel serological clinical correlation with different populations.

Although renal involvement in SSc may be inconsistent, our late onset group had a higher renal complication rates, which is in line with what has been observed internationally that age and comorbidity has been associated with older patients to extreme organ dysfunction. Likewise, the analysis of the European registry showed elevated cases of organ complications such as renal and cardiac complications in old age SSc.[6] Unlike other historical reports that failed to identify any meaningful differences in fundamental demographic measures, such as gender distribution, between subsets, the majority of modern studies including ours still occur to present a female preponderance in both early and late subsets and underscore the fact that sex is still an epidemiological feature associated with SSc.[21]

Renal involvement was more strongly associated with late onset systemic sclerosis in this study, possibly because of age-related susceptibility and/or injury to the vessels of the kidney associated with

systemic sclerosis. Older patients may be more susceptible to scleroderma renal complications because they have baseline endothelial dysfunction and less renal reserve, as well as comorbid conditions like hypertension. Furthermore, misdiagnosis of systemic sclerosis in the elderly may result in later stages of vascular involvement at the time of diagnosis. It should also be noted that such a percentage may be subject to sampling variation due to the relatively small sample size and should be used with caution. In the present study, therefore, renal involvement in late onset SSc is more likely to be a multifactorial process involving age-related susceptibility of the vessels and SSc-related microangiopathy than due to an age-related increasing incidence.

The results of the present research indicate that age at disease onset has a major impact on clinical presentation, organ distribution, and autoantibody in systemic sclerosis. Patients with early-onset disease can be identified early and detected closely to monitor cases of diffuse skin involvement, musculoskeletal complications, and aggressive inflammatory activity, whereas patients with late-onset disease should undergo close screening of pulmonary arterial hypertension, interstitial lung disease, and renal dysfunction. Individualization of surveillance and therapeutic approaches depending on age-related phenotypes can enhance earlier identification of complications, inform immunosuppressive or supportive treatment, and possibly decrease morbidity in SSc patients.

LIMITATIONS

There are a number of limitations in this study. As a single-center cross-sectional study, the results might not be applicable to all populations. The sample size was quite small, which compromised the possibility to identify less frequent manifestations or uncommon antibody relationships. Also, the variability in the duration of diseases may have affected organ involvement and the researchers did not have a long-term follow-up to determine the progression or survival rates. Lastly, certain tests, including HRCT and echocardiography, required the patient to be available and consent to the test, which could have caused selection bias.

CONCLUSION

The clinical and immunological characteristics of early and late onset systemic sclerosis are different. Early-onset SSc has been associated with a more pronounced immune profile and greater cutaneous involvement, and increased anti-Scl-70 positivity, which is indicative of an aggressive course of the disease. Conversely, late-onset SSc features limited cutaneous features, increased occurrence of pulmonary arterial hypertension, interstitial lung disease, renal issues, and anti-centromere antibody, emphasizing morbidity and organ susceptibility based on age. The results of the study highlight the significance of age-related risk stratification, early detection, and specific monitoring of organ involvement and to better manage patients. The identification of these patterns will help clinicians to tailor therapy and avoid severe complications in patients with systemic sclerosis of various age groups.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Madiha Noor:** Data collection, analysis, writing.
2	**Tehreem Sultana Hamid:** Discussion writing.
3	**Shahida Perveen:** Writing.
4	**Haris Gul:** Literature review, data entry.
5	**Saba Samreen:** Data analysis.
6	**Babur Salim:** Proof reading.