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Original Article

A study of the clinical and epidemiological characteristics of patients with systemic sclerosis at a single center in Baghdad

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Abstract

Background In patients with systemic sclerosis, a chronic autoimmune illness, the immune system becomes dysregulated, blood vessels are damaged, and organs and skin become fibrotic. Biomarkers are essential in clinical practice because they allow for accurate diagnosis, the prediction of disease development, and the assessment of the effectiveness of treatment. The aim of the study is to determine the variety aspects of clinical and epidemiological factors of Iraqis' systemic sclerosis.

Methods A cohort of 39 individuals diagnosed with Systemic Sclerosis (SSc) were involved in the current cross-sectional investigation. The research was carried out from December 15, 2022, to May 30, 2023, utilizing a specifically crafted questionnaire.

Results Overall, 100% of the people who took part had thicker skin. Following this were Raynaud's phenomenon (97.5%), abnormal nail fold capillaries (94.9%), telangiectasia (85.8%), oral puckering, dysphagia, and puffy fingers (79.5%), and finally shortness of breath and sclerodactyly (77%). Additionally, 73.8% of participants had ILD, and 19.0% had pulmonary hypertension. ANA positivity was seen in 90% of the patients. There is a strong association between the presence of anti-Sc1-70 antibodies and DcSSc. In the limited form, only one case (2.56%) tested positive, while 23 cases (58.97%) tested positive. This association was shown to be statistically significant with a p-value < 0.001. Patients with limited cutaneous systemic sclerosis (LcSSc) were much more likely than those with diffuse cutaneous systemic sclerosis (DcSSc) to have anti-centromere antibodies (ACA), with rates of 17.95% for LcSSc and 10.25% for DcSSc (p = 0.037).

Conclusion SSc has a higher frequency among the female population. Typically, the first clinical manifestation is Raynaud's phenomenon, but other symptoms may manifest at any stage of the disease's unpredictable course.

Key words
Systemic sclerosis; Interstitial lung disease; Diffuse systemic sclerosis.

Introduction

Systemic sclerosis, also known as SSc, is an autoimmune disorder with an unidentified cause. The clinical features of this multisystem autoimmune disease include vascular abnormalities, connective tissue sclerosis, skin atrophy, and malfunctions in several internal organs, including the digestive tract, lungs, heart, kidneys, blood vessels, and digestive system.[1]

Skin involvement is a key criterion for sub-classifying SSC patients according to EULAR

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and ACR criteria. Within LcSSc, fibrosis develops in the face and distal to the elbows and knees, while with DcSSc, skin thickening affects the trunk and proximal limbs.[2]

In systemic sclerosis (SSc), autoantibodies serve as valuable indicators of distinct subtypes of the disease according to Senécal *et al*. (2020).[3] Anticentromere antibodies (ACA) represent the most commonly detected antibodies, typically linked to limited skin involvement (lcSSc) and the development of pulmonary arterial hypertension (PAH). On the other hand, Scl-70 antibodies are correlated with widespread skin involvement (dcSSc) and the presence of interstitial lung disease (ILD), as highlighted in the study by Nihtyanova and Denton.[4] It is noteworthy that the mortality rate tends to be notably higher among individuals with dcSSc compared to those with lcSSc, a finding that was initially reported by Carwile LeRoy *et al*. in 1988.[5]

Walker and colleagues made a discovery in 2007 indicating that a small number of Scl-70 patients may exhibit a restricted form of skin involvement, while ACA patients could display a widespread skin involvement. They suggested that the type of antibodies and disease subtype could impact the characteristics of the disease and which organs are affected.[6]

The global trend of scleroderma shows a higher occurrence of systemic sclerosis in European, North American, and South American individuals compared to East Asian patients. Nevertheless, the highest occurrence rate (47 per 100,000) was seen among the indigenous population of Canada as reported by Calderon & Pope. (2021).[7] The combined prevalence is 17.6 cases per 100,000 individuals, and the combined incidence rate is 1.4 cases per 100,000 person-years. Among the research conducted in Asia, the prevalence was consistently observed to be relatively low, indicating the lowest rates compared to other regions, according to Bairkdar *et al*. in 2021.[8]

There is a scarcity of data about the epidemiological aspects of illness in Iraq and other Arab countries. As far as we know, this is the first research undertaken in Iraq, an analysis that explores the clinical and epidemiological characteristics of individuals diagnosed with scleroderma

Methods

The total of 39 convenient samples diagnosed with systemic scleroderma within the cross-sectional study were based on the 2013 criteria set by the American College of Rheumatology and the European League Against Rheumatism. In the Baghdad governorate, rheumatology clinics within the Baghdad Teaching Hospital of Medical City collected data on socio-demographic, clinical, serological, and epidemiological variables. Hepatitis, TB, endocrine disorders, cancer, and other rheumatologic diseases are examples of conditions that need exclusion.

An Excel spreadsheet contained coded responses to a questionnaire. The data was analyzed utilizing IBM SPSS-29 (IBM Statistical Packages for Social Sciences, version 29, Chicago, IL, USA). Analysis involved basic statistical measures such as frequency, percentage, mean, standard deviation, and range calculations.

To assess the significance of mean differences in quantitative data, either Students-t-test, Paired-t-test, or ANOVA tests were employed. For qualitative data, the significance of percentage variances was determined using the Pearson Chi-square test (χ2-test) with Yate's correction or Fisher Exact test when appropriate. A

statistical significance was considered when P values were 0.05 or lower.

Ethical approval All individuals who took part in the research gave their informed consent after receiving ethical clearance from Baghdad Teaching Hospital/ College of Health and Medical Techniques in Baghdad vide notification number Ministry of Health/ Repulic of Iraq #15357 with date 19/4/2023. The research followed all of the guidelines laid out by the 1964 Declaration of Helsinki when it involved human subjects**.**

Results

A total of 39 Iraqi SSc patients were included in the present study; 12 (30.8%) had lcSSc, 27 (69.2%) had dcSSc. 36 (92.3%) were female and 3 (7.7%) were male, with a female-to-male ratio of 12:1. Patients were predominantly middle-aged, with a mean age of 45.84±12.28 years; the mean time of disease onset was 36.23±10.66 years, with disease duration10.02±7.37 years. In the dcSSc group, 24 (61.5%) were female and 3 (7.7%) were male and in the lcSSc group, 12 (30.8%) were females and there no males. Socio-demographical and epidemiological characteristics of patients are summarized in **Table 1**.

Clinical manifestations of the overall study comprised of skin thickening (finger, hand and Forearm 100% and 94.9%, respectively) followed by Raynaud's phenomenon (97.5%), abnormal nail fold capillaries (94.9%), telangiectasia (85.8%), both oral puckering, dysphagia and puffy fingers (79.5%), both shortness of breath and sclerodactyly (77%), digital ulcer 56.5%, weight loss 46.2%, diarrhea 43.6%, Interstitial lung disease (ILD) (79.49%) and pulmonary hypertension (20.51%), as showed in **Table 2**.

Immunological features of SSc patients are presented in **Table 3**. Ninety per cent of patients were ANA positive. Anti-Sc1-70 were significantly associated with dcSSc 23 (58.97%) vs. 1(2.56%), p<0.001. ACA were significantly more common in lcSSc 7 (17.95%) vs. 4 (10.25%), p =0.037.

Table 1 Distribution of Socio-demographic and epidemiological characteristics.

Socio-demographic characteristics	*N (%)*
Age	
Mean (SD)	45.84±12.28
Sex	
Male	3 (7.7%)
Female	36 (92.3%)
Residency	
Urban	31 (79.5%)
Rural	8 (20.5%)
Education level	
Illiterate	19 (48.7%)
Primary	9 (23.1%)
Intermediate	5 (12.8%)
Secondary	4 (10.3%)
College	2 (5.1%)
Occupation	
Employed	1 (2.6%)
Unemployed	38 (97.4%)
Marital status	
Single	7 (17.9%)
Married	29 (74.4%)
Divorced	3 (7.7%)
Epidemiological characteristics	Mean (SD)
Age of first visit	37.48±11.84
Age at diagnosis	40.35±12.16
Age at onset of disease	36.23±10.66
Interval between onset of disease & diagnosis/ years	3.94±5.35
Duration of disease	10.02±7.37

Discussion

The present study is the first study to examine the clinical manifestations, autoantibody profile, and epidemiological characteristics of people with systemic sclerosis (SSc) in Iraq. It is also one of the few published papers from the Middle East, where there is little data on SSc. Scleroderma (SSc) is a rare disease that affects around 19 people per million each year. Its prevalence rate in western countries ranges from 19 to 75 cases per 100,000 people. Systemic

Table 2 Association between clinical and epidemiological characteristics and disease subtype.

Variables		*Systemic subtype*			*test*	*value*	*P value*
		Limited		*Diffuse*			
Age	mean± SD	48.66±10.40		44.59±13.01	t	1.04	0.30 NS
Age of diagnosis	mean± SD	42.66±9.34		39.33±13.25	t	0.89	0.37 NS
Sex	male female	0 (0.0%) 12(30.8%)		3 (7.7%) 24 (61.5%)	Fisher's Exact test	--	0.539 NS
Duration of disease	mean± SD	13.36±9.03		8.66±6.26	t	1.57	0.137 NS
Sign & Symptoms of scleroderma		*Systemic subtype*			*test*	*value*	*P value*
**Skin thickening components*		*N(39)%*	*Limited*	*Diffuse*			
*Fingers	Yes No	100	12 (100%)	27(100%)	--	--	--
*Hand	Yes No	100	12 (100%)	27(100%)	--	--	--
*Forearm	Yes No	94.9	10 (82.3%) 2 (17.7%)	27 (100%) 0 (0.0%)	Fisher's Exact test	--	0.089 NS
*Trunk	Yes No	69.3	0 (0.00%) 12 (100%)	27 (100%) 0 (0.00%)	Fisher's Exact test	--	< 0.01*
Puffy fingers	Yes No	79.5	4 (33.3%) 8 (66.7%)	27(100%) 0(0.00%)	Fisher's Exact test	--	0.002*
Digital ulcer	Yes No	56.5	3 (25%) 9 (75%)	19 (70.4%) 8 (29.6%)	Pearson chi-square	6.95	0.008*
Fingertip pitting scars	Yes No	61.6	4 (33.3%) 8 (66.7%)	20 (74.1%) 7 (25.9%)	Fisher's Exact test	--	0.031*
Telangiectasia	Yes No	85.8	10 (83.3%) 2 (16.7%)	25(92.6%) 2 (7.4%)	Fisher's Exact test	--	0.57 NS
Abnormal nail fold capillaries	Yes No	94.9	11 (91.7%) 1 (8.3%)	26(96.3%) 1 (3.7%)	Fisher's Exact test	--	0.52 NS
Raynaud's phenomenon	Yes No	97.5	12 (100%) 0 (0.00%)	26(26.3%) 1 (3.7%)	Fisher's Exact test	--	1.00 NS
Dry eyes	Yes No	20.6	1 (8.3%) 11(91.7%)	7 (25.9%) 20 (74.1%)	Fisher's Exact test	--	0.39 NS
Dry mouth	Yes No	35.9	3 (25%) 9 (75%)	11 (40.7%) 16 (59.3%)	Fisher's Exact test	--	0.47 NS
Dysphagia	Yes No	79.5	7 (58.3%) 5 (41.7%)	24 (88.9%) 3 (11.1%)	Fisher's Exact test	--	0.079 NS
Shortness of breath	Yes No	77	8 (66.7%) 4 (33.3%)	22 (81.5%) 5 (18.5%)	Fisher's Exact test	--	0.41 NS
Diarrhea	Yes No	43.6	4 (33.3%) 8 (66.7%)	13 (48.1%) 14 (51.9%)	Pearson chi-square	0.740	0.38 NS
Weight loss	Yes No	46.2	5 (41.7%) 7 (58.3%)	13 (48.1%) 14 (51.9%)	Pearson chi-square	0.14	0.70 NS
Sclerodactyly	Yes No	77	6 (50%) 6 (50%)	24 (88.9%) 3 (11.1%)	Fisher's Exact test	--	0.014 *
Oral puckering	Yes No	79.5	7 (58.3%) 5 (41.7%)	24 (88.9%) 3 (11.1%)	Fisher's Exact test	--	0.079 NS
Interstitial lung disease	Yes No	79.49	8 (66.7%) 4 (33.3%)	23(85.2%) 4 (14.8%)	Fisher's Exact test	--	0.22 NS
Pulmonary hypertension	Yes No	20.51	1 (8.3%) 11(91.7%)	7 (25.9%) 20 (74.1%)	Fisher's Exact test	--	0.39NS

NS: Non-significant, *: significant difference.

sclerosis is primarily characterized by Raynaud's phenomenon and skin involvement, although the extent of internal organ involvement varies as an additional component according to Ruaro *et al*. in (2016).[9]

This study had a higher percentage of females, diffuse type of scleroderma disease, and a higher prevalence of ILD and anti-Sc1-70. Among the many interesting aspects of this research, it appears that the female preponderance was high,

with an even larger female-to-male ratio of 12:1. Furthermore, these findings were in line with prior research. Libya Elbraky *et al*. in 2020[10] reviewed the data of the 30 patients out of whic, including 28 (93.3%) females (female: male ratio 14:1); Asif *et al*. (2021) a Pakistanis study showed a higher percentage of females compared to males with a ratio of 16:3, with 84.2% females.[11] Arif *et al*. (2019), an Indian study shows female to male ratio of as high as 10:1.[12] A retrospective research in Qatar that included 42 patients of mixed races discovered that 88.1% of them were female.[13] Li *et al*;[14] Chinese study showed that in a total of 227 patients with SSc that were included (Female:male ratio=4.82:1) female percentage was 82.8%. In Iraq from total of 50 patients with systemic sclerosis involved in the study, the majority of patients were females (96%).[15] Another Iraqi study[16] showed the female percentage as 80.0%. In Milan, Italy from total sample of 34 patients, 94.1% were women.[17] Çevik *et al*. 2023 was a multi-center, cross-sectional study conducted in Turkey at twelve hospitals between January 2018 and January 2019, in 256 SSc patients, 92.2% were females.[18] Brazil Silva *et al*. 2020[19] had a total of 60 patients, most of whom were female (91.7%). Iranian study involved 200 patient and 91.5% of the enrolled patients were female.[20] An Egyptian study El-Safty *et al*.[21] was conducted over 60 patients with systemic sclerosis, and 90% of the cases were female. This gender based differences result from the effects of hormones, especially sex hormones, that affect the immune system.

In contrast to the literature, which indicates a higher percentage of patients suffering from limited subtypes, this research found a higher percentage of patients with diffuse scleroderma. Such as Gorial & Swady, in 2018[16] found (Limited 60.0% vs. Diffuse 40.0%). In Poland Żebryk *et al*;[22] revealed limited 56% vs. diffuse 33%. A Chinese cross sectional study reported limited 65.6% vs. diffuse 34.4%.[14] Current findings are similar to the reported data from various regions such as those reported in Elbraky *et al*;[10] who reported that 80% had dcSSc and 20% had lcSSc in Libyan patients.[10] In UAE overall, limited was in 45.5% vs. diffuse was in 54.5%.[23] In Egypt, limited 28% vs. diffuse 72% was reported by Alian *et al*.[24] Moreover, all of recent Indian cohort patients had cutaneous involvement with limited 41.5% vs. diffuse 58.5% according to Ghosh *et al*.[25]

In the herein study, the duration of scleroderma (Mean±SD) was 10.02±7.37 years, with mean age of disease onset 36.23±10.66 years, delay of first rheumatologically visit was observed with a mean of delay of 3.94±5.35, the mean age of

Table 3 Investigation findings and disease subtype.

Variables		*N (39)* *%*	*Systemic subtype*		*test*	*value*	*P value*
			Limited	*Diffuse*			
ANA	positive negative	89.74	11 (28.20) 0 (0.0)	24(61.53) 0 (0.0)	--	---	----
ACA	positive negative	28.21%	7(17.95) 1(2.56)	4(10.25) 7(17.95)	Fisher's Exact test	--	0.037 *
anti-Sc1-70	positive negative	61.54	1(2.56) 7(17.95)	23(58.97) 1(2.56)	Fisher's Exact test	---	<0.001*
Anti-RNA polymerase III	positive negative	2.56	1(2.56) 9 (23.07)	0(0.00) 21(53.84)	Fisher's Exact test	---	0.323 NS
ESR (mm/h)	mean± SD		39.10±34.21	47.07±29.42	t	-0.697	0.49 NS
Hb (mg/dl)	mean± SD		11.17±1.41	11.46±1.24	t	-0.60	0.55 NS

NS: Non-significant, *: significant difference.

diagnosis was 40.35±12.16 years. This finding is in the line of agreement with the findings of several studies, such as, Elbraky *et al*. a Libyan study,[10] who found, the disease duration (Mean±SD) was 9±4.5 years, mean age at the time of diagnosis was 40.5±21.5 years. Another Egyptian study using 50 patients with SSc showed that the mean disease duration was 5.36±4.86 years. In India, the age of onset of the disease was 35.8 years and mean duration of disease was 8.9±8.1 years.[12] In a cross-sectional and prospective study carried out in Poznan, Poland, the study population consisted of 96 adult patients with SSc and found that disease duration since diagnosis was 6.2±7.9 years.[22]

On the other hand, a longer mean disease duration was reported by Heyne *et al*; in a German cross-sectional analysis study from 2016 to 2018 (12.12±10.27 years).[26] In Algeria, by Tahiat *et al*. (2020), the disease's average duration was 12.0±9.3 years.[27] The discrepancy in findings across these studies could potentially be attributed to ethnic variations among the patient populations under investigation. Furthermore, it might be linked to delays in receiving a diagnosis or consulting a rheumatologist, especially in socioeconomically disadvantaged regions.

Autoantibody screening of current patients showed antinuclear antibody (ANA) (89.74%), anti-topoisomerase antibodies (anti-Sc1-70) (61.54%), anti-centromere (ACA) (28.21%), Anti-RNA polymerase III (2.56%). Other investigations in this study were chest CT and pulmonary function tests (79.49%), ESR mean in limited was 39.10±34.21 and in diffuse was 47.07±29.42. These findings are in line with a bulk of literature, such as, Ng & Low in 2022. An Asian study documented 85.5% antinuclear antibody and 22.7% ACA-positive patients.[28] A total of 150 Algerian SSc patients were included in Tahiat *et al.* study, 92.7% patients were positive for ANA, ATA were present in 50.7% of the patients while ACA was present in 15.3% of the patients. Anti-RNAP III was found at lower frequencies, 6%.[27] While, In the study conducted by Ghosh and colleagues in 2023, it was determined that patients from North India exhibit certain phenotypic variances when compared to individuals of Caucasian descent, showcasing an increased percentage of patients manifesting with interstitial lung disease at a rate of 71.7%, along with a higher prevalence of Scl70 antibodies detected in 61.3% of the patient population.[29]

Although present findings were challenged by other studies, in recent Portuguese multicenter prospective cohort study, where a total 1054 patients with SSc were included, 89.8% of patients were antinuclear antibody positive, 52.5% were Anti-centromere antibody positive and 21% were anti-topoisomerase positive, according to Freitas *et al*.[30]

Additionally, important indicators in confirming the diagnosis and predicting the prognosis of systemic sclerosis include anti-nuclear antibodies (ANA), which are found in about 90% of SSc patients. Mahler *et al;* in 2020 reported that autoantibodies have been linked to significant SSc symptoms, including the categorization criterion autoantibodies (anti-centromere, anti-topoisomerase I and anti-RNA polymerase III).[31]

It is important to note that the current study shows that ACA was less common because the majority of patients had the dcSSc form, which is strongly associated to the limited form. In addition, half of the patients who showed positive for this autoantibody had interstitial lung disease, and current evidence suggests that antiScl-70 is the cause behind diffuse skin fibrosis. Cottin and Brown (2019) and Stochmal *et al.*[32,33] both reached similar conclusions.

While other studies have shown a high correlation between anti-centromere antibodies and lcSSc. Elbraky *et al.* in 2022[10] found that anti-Scl 70 antibodies were strongly related with the dcSSc subtype.

Additionally, compared to SSc cohorts from Algeria (6% of the total) and France (4% of the total), the Moroccan study found a higher percentage of anti-RNAP III (13%), which is comparable to the Brazilian cohort (15.2%), indicating a potential influence of epigenetic factors, as reported by Ouazahrou *et al.;* (2023).[34] While the precise process behind these discoveries remains unknown, it is interesting to note that SSc-related autoantibodies are distributed differently among nations. It is possible that ethnic and regional variables influence the formation of autoantibodies in SSc. In addition, the fact that SSc-related autoantibodies are highly influenced by both race and sex might explain the difference in the results. Furthermore, particular autoantibodies may be produced by a variety of genetic and environmental variables according to Krzyszczak *et al*.[35]

Conclusion

Scleroderma is more common in females in our group, and the diffuse form of the illness is somewhat more common overall. In addition, there is a critical window of opportunity for early detection due to the diagnostic delay between Raynaud phenomenon and systemic illness. Interstitial lung disease occurs at a much higher rate. The incidence of ACA continuing to limited sub type was lower in our patients, whereas the frequency of anti-Scl-70 was greater. Anti-Scl-70 has been associated with ILD and diffuse subtype, as has been shown in other ethnic groups; our investigation verifies these correlations.

Limitations There are some limits that stand out. The study only looked at one center and had a small number of people with a rare disease. However, the sample size is about the same as in a number of other studies.

Recommendation It's possible that other important differences between the factors seen in this study would become clearer if a multicenter study was conducted, where the sample size was larger and the disease duration study was longer.

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Conflict of interest Authors declared no conflict of interest.

Authors' contribution

DAD: Literature search, data collection and analysis, data interpretation, manuscript witting.

IA: Literature search, data interpretation, manuscript editing.

AHA: Study design diagnosis of cases, data collection, manuscript review.

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