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ORIGINAL ARTICLE

# Association of Serum IL 6 with Different Clinical Presentations of Systemic Sclerosis Patients: A Case-Control Study

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## ABSTRACT

Systemic sclerosis "SSc" is an autoimmune multiple system connective tissue disorder characterized by impairment of the microvasculature and fibrosis of skin and internal organs. The study aimed to assess serum interleukin 6 (IL-6) as a potential biomarker of SSc in association with clinical presentation and laboratory investigations in Egyptian SSc patients. Twenty-seven SSc cases diagnosed according to "the 2013 American College of Rheumatology/European League Against Rheumatism" (ACR/EULAR) and controls were enrolled in this study. For all participants, detailed history was undertaken, and clinical examination and laboratory investigations were performed. In addition, serum IL-6 was evaluated using Enzyme−Linked Immunosorbent Assay (ELISA) technique. Serum IL-6 level was significantly higher in cases than controls (14.7±8.9 ng/L VS 6.7±3.5 ng/L respectively) (p-value=0.0001). The receiver operator characteristics (ROC) curve showed the best cutoff value for serum IL-6 in SSc patients to be 8.9 ng/L, with a sensitivity of 92%, specificity 78%, accuracy 85% and CI 95% (0.87-1.0) (AUC=0.94). It was significantly higher among SSc cases with Interstitial Lung Disease (ILD) than those without ILD and among patients with skin fibrosis than those without fibrosis (P-value=0.02 and 0.03) respectively. Significant positive correlations were found for serum IL-6 level with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (r=0.6 and 0.7 respectively). Serum IL-6 level may be used as a noninvasive predictor of organ involvement and disease progress in SSc. Further researches are needed to assess its possible role in treatment of Egyptian SSc patients.

**Keywords:** Systemic Sclerosis; Disseminated pulmonary fibrosis; Interleukin-6; Idiopathic Diffuse Interstitial Pulmonary Fibrosis

## INTRODUCTION

Systemic sclerosis "SSc" is an autoimmune multiple system connective tissue disorder characterized by impairment of the microvasculature and fibrosis of skin and internal organs. Prominent clinical manifestations of SSc include pulmonary arterial hypertension (PAH), pulmonary fibrosis, Interstitial Lung Disease (ILD), pitting scars, and finger thickening [1-3]. The pathogenic mechanism of SSc is not completely understood. However, Immune

dysregulation is well demonstrated in SSc by immune cells secreting autoantibodies and abnormal cytokines, which amplify the disease process [4,5].

The diagnostic criteria for SSc as approved by "American College of Rheumatology/European League Against Rheumatism" (ACR/EULAR), include common symptoms such as skin thickening of the fingers, Raynaud's phenomenon, and ILD as well as SSc-related autoantibodies such as anti-centromere antibodies (ACA), anti-topoisomerase I antibodies (anti-Scl-70), and anti–RNA polymerase III antibodies [6]. Still, SSc diagnosis is a complicated and prolonged process, that's why predictive markers that correlate with SSc pathology are required [7].

IL-6 is a multifunctional cytokine, affecting a wide variety of cells on the interior and exterior of the central nervous system. In experimental autoimmune encephalomyelitis (EAE), IL-6 exacerbates clinical symptoms and spinal cord pathology, by endorsing T helper (Th) 17 cell generation in the peripheral lymphoid organs, which initiate and perpetuate neuroinflammation and demyelination in this model [8]. The mechanisms of promoting fibrosis in SSc by IL-6 are through activation of the transcription factor STAT3 and stimulating Th17cells differentiation, which secrete IL-17 [9]. Additionally, it was shown that IL-6 is responsible for the balance between Th17 and regulatory T cells (Tregs), consequently targeting IL-6 would lead to suppression of inflammatory Th17 cells while at the same time increasing Tregs [10]. Several studies have reported the elevated levels of serum interleukin 6 (IL-6) in SSc and it has been investigated as a potential biomarker of SSc [11,12]. Expression level of IL-6 correlated with disease duration, activity, severity, disability, worse outcome and reduced survival [13-15].

There are clinical trials for anti-IL-6 treatment in SSc with promising results [10, 16, 17]. The present study aims to assess serum IL-6 in association with clinical presentation and laboratory investigations in Egyptian SSc patients.

## METHODS

### Study design and patients

This case control study was conducted at the Immunology Research Laboratory, Microbiology, and Immunology Department in Zagazig University. Twenty-seven SSc patients (above 16 yrs. of age) were randomly recruited from the outpatient clinic and inpatient ward of Rheumatology Department in Zagazig University Hospitals, collected over a period of 12 months from January 2018 to January 2019. The patients were assessed according to the 2013 ACR/EULAR Systemic Sclerosis classification criteria [6]. An equal number of apparently healthy, age and sex-matched, controls were also included in the study with no history of acute or chronic infections, autoimmune, inflammatory diseases, malignancies, anti-inflammatory medication and any surgical interventions within the previous two months. Written informed consent was obtained from all participants. The study followed the principles of the Helsinki Declaration and ethical approval was received from the Institutional Review Board (IRB) of Zagazig University Hospitals. Patients with autoimmune overlap syndromes were excluded.

### Patient assessments

For all patients, detailed history was undertaken, and clinical examination was performed. In addition, routine investigations including complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), kidney function tests, liver function tests, and complete urine analysis were performed. Chest and heart were assessed by plain X-rays, high resolution CT (HRCT) without contrast, pulmonary function tests (PFTs), electrocardiogram (ECG) and echocardiography.

Serological assessment for anti-nuclear antibodies (ANA) was done by indirect immunofluorescence (IIF) assay [Biorad, USA] in accordance with the manufacturer's instructions. Anti-Topoisomerase I (anti-Scl70) antibodies was performed by ELISA [Euroimmun, Germany] according to the manufacturer's instructions.

### Measurement of serum IL-6 level

Serum IL-6 was evaluated using ELISA

[Bioassay Technology Laboratory, China] according to the manufacturer's instructions. Stat Fax 303 Plus reader [Awareness Technology, USA] was used for reading at 450 nm. [Bioassay Technology Laboratory, China] according to the manufacturer's instructions. All samples were done in duplicate; and mean absorbance, was determined at a wavelength of 450 nm for each sample. Calibration curves were used to determine the concentration of "serum IL-6". Concentrations of IL-6 were evaluated as ng/L in serum samples, with a limit of sensitivity1.03 ng/L.

**Statistical Analysis**

All data were analyzed using MedCalc 13 [MedCalc Software bvba, Ostend, Belgium] and SPSS 22.0 [SPSS Inc., Chicago, IL, USA]. The normality was checked by Shapiro-Wilk test (sig) and Q-Q plot. Appropriate tests were used to compare two groups. The diagnostic performance of continuous variable was calculated using receiver operator characteristics (ROC) curve. $P < 0.05$ was statistically significant (S) and $P < 0.001$ was highly statistically significant (HS).

## RESULTS

This study included 27 adult Egyptian SSc patients and 27 age and sex matched healthy controls. The mean age of patients was 40.7±10.9 years (range 17-65) years and that of controls was 34.5 ± 8 years. Five patients (18.5 %) were males and 22 (81.5%) were females (M: F = 1: 4.4) with no statistically significant difference between cases and controls. **(Table 1)**

Regarding clinical characteristics of cases, all patients had Raynaud's phenomena (100.0%) followed by cutaneous lesions (92.6%) then ILD in (85.2%). Arthritis was present in (66.7%) followed by GIT manifestations (51.9%) and cardiac symptoms were the least common recorded in (44.4%). **(Table 2)**

Twenty-four cases (88.9%) were ANA positive and three cases (11.1%) were negative who were males with less vasculopathy and all had lower GIT upsets while only one healthy control (3.7%) was ANA positive (speckled pattern) with statistically significant difference (**p-value=0.0001**). Thirteen cases (48.2%) had speckled ANA pattern while 11 cases (40.7%) had nucleolar one. Regarding Anti-Scl70, there was statistically significant difference between cases and controls (**p-value=0.002**). It was detected in 8 cases (29.6%) while all controls were negative (100.0%) with sensitivity, specificity, PVP, PVN and accuracy of 29.6%, 100.0%, 100.0%, 58.7% and 64.8% respectively **(Table 1)**.

Concerning serum IL-6 level, it was significantly higher in cases than controls (14.7±8.9 ng/L VS 6.7±3.5 ng/L) respectively (**p-value=0.0001**). **(Table 1).**

In **figure** 1, ROC curve for serum IL-6 level shows that at a cut-off point (8.9 ng/L), it has AUC (0.94 with CI. 95% (0.87-1.00)) and its sensitivity, specificity, PVP, PVN and accuracy were (92%, 78%, 80.7%, 90.6% and 85%) respectively (figure 1).

Serum IL-6 was significantly higher among SSc cases with ILD than those without ILD and among cases with skin fibrosis than those without skin fibrosis (15.9±6.1 ng/L VS 13.2±9.7 ng/L and 16.7±7.8 ng/L VS 14.0± 2.9 ng/L) (p-value=0.02 and 0.03) respectively **(Figure 2).** Significant positive correlations were found for serum IL-6 with CRP and ESR (r=0.6 and 0.7 respectively, p-value=<0.001 for both) **(Figure 3)**.

**Table 1.** Demographic and preliminary data of the studied groups

| Variables | SSc cases (No.=27) | Control (No.=27) | P |
|---|---|---|---|
| Age (years) | 40.7±10.9 | 47.7±8.08 | 0.8^ |
| Sex<br>Males<br>Females | <br>5 (18.5%)<br>22 (81.5%) | <br>6 (22.2%)<br>21 (77.8%) | <br>0.5# |
| ANA positivity | 24 (88.9%) | 1 (3.7%) | 0.0001#** |
| ANA pattern<br>Speckled<br>Nucleolar<br>Centromere<br>Absent | <br>13(48.2%)<br>11 (40.7%)<br>0.0 (0.0%)<br>3 (11.1%) | <br>1 (3.7%)<br>0.0 (0.0%)<br>0.0 (0.0%)<br>26 (96.3%) | <br><br>0.0001#** |
| Anti-Scl70 | 8 (29.6%) | 0.0 (0.0%) | 0.002* |
| Serum IL-6 (ng/L) | 14.7±8.9<br>15. 2<br>(5.4-23.6) | 6.7±3.5<br>5.3<br>(2.3-10.7) | <br><br>0.0001^^** |

**Note:** ^independent t-test,#Chi square test, ^^Mann-Whitney test, *statistically significant ($p<0.05$), ** statistically highly significant ($p<0.001$). **Abbreviation:** Systemic sclerosis (SSc)**.**

**Table 2.** Clinical characteristics of the SSc cases

| Variables | SSc cases<br>NO. (%) |
|---|---|
| Arthritis | 18 (66.7%) |
| Raynaud's | 27 (100.0%) |
| Skin fibrosis | 25 (92.6%) |
| Gastrointestinal manifestations | 14 (51.9%) |
| ILD | 23 (85.2%) |
| Cardiac manifestations | 12 (44.4%) |

**Abbreviation:** Systemic sclerosis (SSc)**,** Interstitial Lung Disease (ILD)

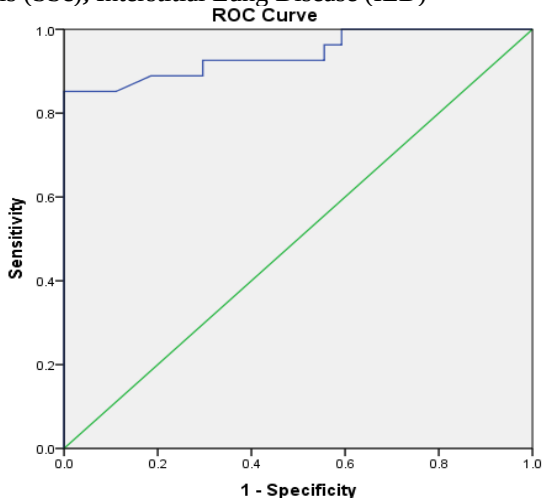


**Figure 1.** ROC curve for the diagnostic ability of serum IL-6 to diagnose Systemic sclerosis (SSc) patients

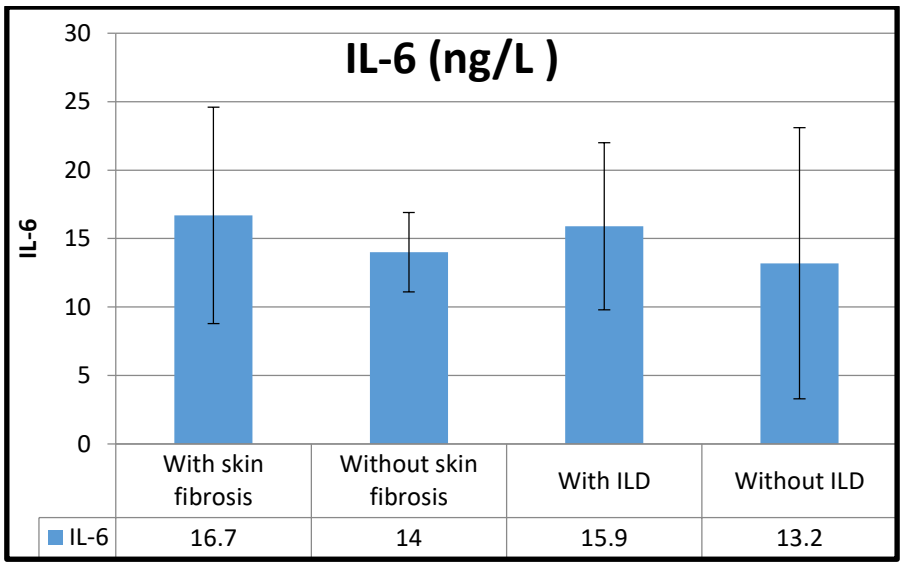


**Figure 2.** Bar chart for the difference in serum IL-6 between Systemic sclerosis (SSc) patients with and without interstitial Lung Disease (ILD) and SSc patients with and without skin fibrosis

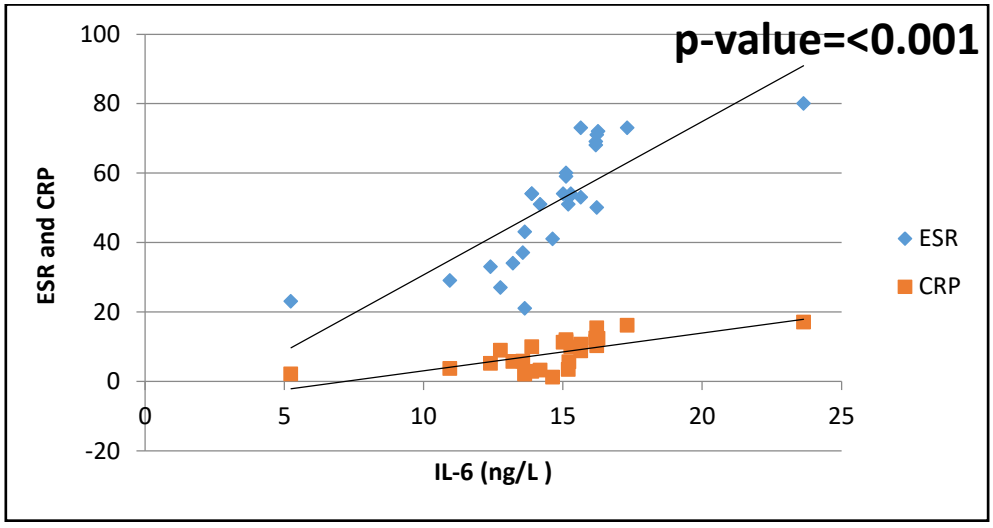


**Figure 3.** Scatter plot with line chart for the correlation between serum IL-6 with ESR and CRP in SSc patients.

## DISCUSSION

SSc is a complicated connective tissue disorder originating from impaired biological cell function, affecting bone marrow cells, lymphocytes, monocytes, endothelial cells, and fibroblasts [18]. The main clinical presentations of patients with SSc are attributed to vasculopathy and tissue fibrosis. SSc patients show various presentations and outcomes [19]. The exact pathogenesis is unclear as multiple factors are responsible for their development and progression of the disease. However, several evidences indicated that SSc shows that production of cytokines is deregulated, but their link with clinical outcomes is still ambiguous [20].

The prerequisite for biomarkers in SSc is great to help delineate patients, distinguish potential subgroups for treatment modalities, and evaluate their response to therapy. Reason for this is that SSc is a multisystem disorder with varying clinical severity and outcome. In

addition, there is no single treatment modality that has been proven to modify the overall disease course [19]. Accordingly, measures that can mirror this variability are of significant potential significance for the assessment and evaluation of patients [7].

At this time, clinical and objective measurements of organ function (such as PFTs, HRCT) are available [21]. However, new serum biomarkers can provide rapid, simple and non-invasive techniques to evaluate disease severity and define the effect of treatment. In addition, such markers might represent pathogenic mediators that could be targeted for therapy. In this study, we evaluated to what extent this is true regarding serum IL-6 as a biomarker in Egyptian SSc patients

In our study, ANA was a good diagnostic test, but its absence couldn't exclude the disease as 11.1% of SSc cases were negative for ANA. Autoantibody production in SSc linked to gene polymorphism in the human leukocyte (HLA) regions and the association of some of the class II alleles with ANA positivity has been reported [22]

As mentioned above, serum Anti-Scl70 level was a good negative test having (100.0%) specificity but a poor diagnostic test with only (29.6 %) sensitivity and high false negative rate (70.3% missed cases).

Regarding serum IL-6, it was significantly higher in cases than controls **(Table 1)**. ROC curve shows that at a cut-off point (8.9 ng/L**)**, it has AUC (0.94(0.87-1.00)) with (92%, 78%, 80.7%, 90.6% and 85%) sensitivity, specificity, PVP, PVN and accuracy respectively **(Figure 1)**. For its association with clinical manifestations, it was significantly higher among SSc cases with ILD and those with skin fibrosis (p-value=0.02, 0.03) respectively **(Figure 2).** In addition, there was a significant positive correlation between serum IL-6 level and CRP and ESR among patients (r=0.6 and 0.7 respectively, p-value=<0.001 for both) **(Figure 3)**.

IL-6 is a pleiotropic cytokine with distinct physiological functions in the direction and control of the immune response and metabolism. It was originally recognized as a B lymphocytes stimulatory factor [23]. Further studies showed that IL-6 is a pro-inflammatory cytokine secreted locally in inflammation and is involved in its pathological features 'swelling, redness and pain'. In addition, IL-6 induces the liver to produce acute-phase reactants including serum amyloid A (SAA), CRP, and fibrinogen [24]. Beside its physiological roles, IL-6 stimulates the proliferation of fibroblasts and the release of fibronectin and procollagen which are involved in pathological process of SSc [25].

Several studies have reported high levels of serum IL-6 in SSc patients [7, 14, 26-29]. These elevated levels may be due to over production of IL-6 locally in damaged sclerotic tissues or due to IL-6 produced by peripheral blood mononuclear cells (PBMC) of SSc patients [30, 31]. Nevertheless, IL-6 isn't high in the serum of all SSc patients, and it has been discovered that there is a distinction in IL-6 level depending on the specific diseased organ. In addition, there was statistically significant correlations between serum levels of IL-6 and the seriousness of skin thickening and progress in ILD [13,28], which are distinguished by tissue fibrosis. Remarkably, deletion of IL-6 gene in SSC murine model diminished autoimmunity and consequent fibrosis. Furthermore, IL-6 deletion adjusted the number and percentage of Th17 cells and increased T-regulatory cells (Tregs) [10]. The role of IL-6 in SSc-related tissue fibrosis gives the rationale for its targeting to treat SSc patients. Anti-IL-6 monoclonal antibodies have been investigated, but they were unsuccessful in the initial clinical trials. Additional path was aiming the receptor of cytokine instead of the cytokine itself, using a humanized anti IL-6Rα "Tocilizumab". The hopeful findings supported the continual progress of tocilizumab in the treatment of SSc, which is being explored in a phase 3 trial [32,33]. Measurement of serum IL-6 in Egyptian SSc patients and its association with different clinical presentation helps to identify potential subgroup of patients that can benefit from this new treatment modality and to assess their response to it.

**Study limitations**

Limitations of the study include relatively small sample size, and that serial IL-6 levels during the course of the disease was not done to assess the variation of IL 6 levels during the disease course.

## CONCLUSION

Serum IL-6 level may be used as a noninvasive predictor of organ involvement and disease progress in SSc. Further researches are needed to assess its possible role in treatment of Egyptian SSc patients.

**Declaration of interest:**

The authors declare no conflict of interest.

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