Correlation between Serum Interleukin-6 Level and Modified Rodnan Skin Score in Systemic Sclerosis Patients

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Abstract

Objective: To determine the correlation between serum levels of IL-6 and MRSS in systemic sclerosis patients.

Methods: This was a crossectional observational study on patients with SSc visiting the Rheumatology Clinic of Dr. Hasan Sadikin General Hospital Bandung, Indonesia from January 2019 to December 2020. Registered SSc patients, with validated MMRS by a rheumatologist, and available biological materials for IL-6 measurement were included. Patients with other autoimmune diseases, acute infection, diabetes mellitus, and obesity were excluded from this study

Results: Of the 51 SSc patients, 42 patients met the inclusion criteria. Women comprised the majority of these patients (95.2%), while patients' mean age was 43±12 years. The mean duration of disease was 20 months, with diffuse SSc (78.6%) as the most frequent type. Bivariate analysis showed that IL-6 was positively correlated with MRSS (100-scale) with r=0.397 and p=0.005.

Conclusion: There is a medium positive correlation between MRSS and interleukin-6 serum among systemic sclerosis patients visiting Dr. Hasan Sadikin General Hospital Bandung, Indonesia.

Keywords: Disease activity interleukin-6, modified rodnan skin score, systemic sclerosis

Introduction

Systemic sclerosis is a chronic systemic autoimmune disease affecting multisystem connective tissue characterized by fibrosis of the skin and visceral organs and microvascular abnormalities. To date, the etiology of SSC is still unknown, and the clinical course of the disease is unpredictable. Extensive and progressive organ fibrosis may occur. Systemic sclerosis has the potential to become a severe and life-threatening connective tissue disease.[1] Systemic sclerosis is a sporadic disease with a worldwide distribution and affects all races.[2] The number of SSc cases in Indonesia is increasing every year. A prior research conducted at Hasan Sadikin General Hospital, Indonesia, in 2014 has shown a significant increase in visits by patients with connective tissue disease from 51.2% to 63.5% of the total annual visits before and after the National Health Insurance policy. Based on these data, SSc ranks the third most common connective tissue disease after Systemic lupus erythematosus (SLE) and Rheumatoid Arthritis (RA).[3]

Systemic sclerosis can cause progressive multiorgan fibrosis with a high mortality rate. Assessment of disease activity is an important aspect of patient management and can be assessed using simple clinical parameters.

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Modified Rodnan Skin Score is the most widely used clinical parameter for assessing skin fibrosis. Modified Rodnan Skin Score has some limitations. The examination is subjective and not sensitive enough to assess small changes since the changes are recognized after three to six months. Therefore, biological markers that can support MMRS are needed to assess disease progress more objectively, quantitatively, sensitively, and quickly, especially assessing fibrosis, which is a significant factor in the clinical course.[1,4,5]

Interleukin-6 is a pro-inflammatory cytokine that plays an essential role in the pathogenesis of SSc. Overproduction of IL-6 activates fibroblast, which results in cell proliferation and migration accompanied by increased cytokine production. Cell differentiation into myofibroblasts can also occur. Fibroblasts can activate the IL-6 gene, which results in increased IL-6 production. This cycle continues to repeat, resulting in a vicious cycle or fibrosis cascade. The process can be permanent and progressive, leading to tissue accumulation and fibrosis.[6] Interleukin-6 has potential as a marker of disease activity. This study aims to determine the correlation between serum levels of IL-6 and MRSS in SSc patients. This research is expected to provide information about the role of IL-6 to measure disease activity and as a more objective and rapid therapeutic target.

Methods

This was an observational study with a cross-sectional method in patients with systemic sclerosis. Data is retrieved based on the systemic sclerosis registry. All patients were treated in the Rheumatology Clinic of Hasan Sadikin General Hospital from January 2019 to December 2020. The diagnosis of SSC was based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2013. Patient data listed on the SSc Registry with MMRS validated by a Rheumatologist and available biologic material in the form of serum for measurement of IL-6 was included. Patients with other autoimmune diseases, acute infection, diabetes mellitus, and obesity were excluded from this study. This study had received approval from the Health Research Ethics Committee of Hasan Sadikin General Hospital, ethical number LB.02.01/X.6.5/44/2021.

Interleukin-6 measurements were done in the Clinical Pathology Laboratory of Hasan Sadikin General Hospital. Materials were stored at a temperature of -80°C. Serum sampling and biological material were storaged immediately after the MMRS examination. Examination of IL-6 using the Human IL-6 ELISA kit (Elabscience®) with the sandwich ELISA method.

Continuous variables with normal distribution were presented as mean and standard deviation (SD). Otherwise, it was reported as median and range. Categorical variables were described as numbers (percentage). Log transformation was conducted for IL-6 serum levels. The MRSS was transformed to a scale of 100. The correlation between IL6 and MMRS was assessed using Pearson's correlation test.

Results

There were 51 SSc patients from January 2019

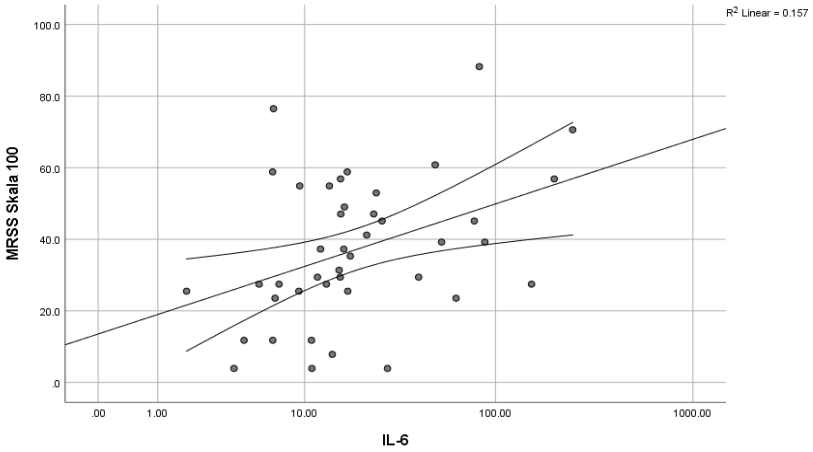

Figure Scatter Plot Diagram Between IL-6 and MRSS
Shown that MMRS and IL-6 have a weak positive correlation

Table 1 Patient's Characteristic

Variables	Number (%)[a] (N=42)
Age (years), mean ± SD	43±12
Gender	
Men	2 (4,8)
Women	40 (95.2)
Ethincity	
Sundanese	39 (92.9)
Others	3 (7.1)
Subtype	
Diffuse SSC	33 (78.6)
Limited SSC	9 (21.4)
Duration of Illness (months), median (range)	30 (4–180)
Treatment History	
Methylprednisolone	36 (85.7)
Methotrexate	33 (78.6)
Mycophenolate mofetil	2 (4.8)
Azathioprine	2 (4.8)
Cyclosporine	1 (2.4)
Nifedipine	11 (26.2)
Diltiazem	18 (42.9)
Cyclophosphamide	7 (16.7)
MRSS, median (range)	19 (2 – 45)
MRSS (100-scale), mean±SD	37±20
IL-6 Serum (pg/ml), median (range)	15.72 (1.79–246.69)

a) otherwise presented; SD: standard deviation; MRSS: modified Rodnan skin score: IL: Interleukin

to December 2020. Nine patients were excluded due to overlap autoimmune syndrome. A total of 42 patients met the inclusion criteria. Most of the patients were women (95.2%), with a mean age of 43±12 years. The mean duration of disease was 20 months, with diffuse SSc (78.6%) as the most frequent type. A total of 36 subjects (85.7%) received methylprednisolone. Other treatments administered included methotrexate (78.6%), diltiazem (42.9%), nifedipine (26.2%), mycophenolate mofetil (4.8%), azathioprine (4.8%), and cyclosporine (2.4%). Seven patients had received chemotherapy with cyclophosphamide. Patient's characteristic is shown in Table 1.

The median of MMRS was 19 (2 – 45) with a mean of 100-scale of 37±20. Serum levels of IL-6 were (15.72 (1.79–246.69) pg/mL. Bivariate analysis showed IL-6 was positively

Table 2 The association between IL-6 and MRSS (100-scale)

Variable	MRSS (100-scale)	
	r	p-value
Interleukin-6 Serum[a] (pg/mL)	0,397	0,005*

a) Log-transformation; MMRS: Modified Rodnan Skin Score

correlated with MRSS (100-scale) with r=0.397 (Figure 1) and p=0.005 (Table 2).

Discussion

This study showed mean age was 43±12 years at the time of MMRS examination and serum collection. SSc mainly occurs in the fourth to fifth decades of life. The results follow other studies conducted by Sato *et al*.[7], which found the mean age of SSc was 47±18. On the other hand, Muangchan *et al*.[8] in Canada found the mean age of 55.39±12.13 years. The mean age differences in specific populations may be influenced by racial differences resulting in differences in autoantibody expression and genetic factors that play a role in the pathophysiology of systemic sclerosis. The incidence of SSc tends to be more common in older people in Caucasians than Asians.[9]
Systemic sclerosis occurs more frequently in women. A previous study conducted by Sato *et al*.[7] and Royce *et al*.[10] (83.2%) found women were more likely affected with proportion 90.62% and 83.2%, respectively. In men, the incidence of SSc is higher in the European than Asian. Women were more likely to develop SSc. Several reasons can cause this, one of which is genetic factors, namely the IRAK1 genes, X-linked genes that influence the pathogenesis of SSc [11]

Most of the patients had diffuse systemic sclerosis (78.6%). These results were similar to Komura *et al*.[12], which found the prevalence of diffuse SSc was 55%, while another study by Muangchan *et al*.[8] in Kanada found limited SSc was more common (62%). The type of SSC difference can be caused by ethnicity and skin color. Patients with darker skin color tend to have more severe manifestations resulting in diffuse skin and lung involvement. Another possible cause is antibodies involved, one of which is the anti-fibrillarin antibody (AFA). AFA is found more frequently in blacks and is associated with diffuse skin and internal organ involvement.[2]

The median duration of illness in this study was 30 months. The treatment follows the recommendations from EULAR and is adjusted based on the patient's clinical manifestations.[13] Corticosteroids were the most commonly given treatment. The use of corticosteroids is based on the fact that an inflammatory component in systemic sclerosis may cause skin and musculoskeletal involvement. Corticosteroids can reduce pain and itching of the skin and reduce musculoskeletal symptoms such as arthralgia and myalgia, which are also caused by inflammation.[14] Based on this, in this study, corticosteroids were still the most widely administered treatment (85.7%). However, there is still controversy in the use of corticosteroids in SSc patients. Although corticosteroids can suppress the musculoskeletal manifestations and pruritus that are very disabling in early disease, patients with early dcSSc are those at high risk of developing scleroderma renal crisis.[14]

Methotrexate is the most commonly used disease modifying anti-rheumatic drugs or DMARD (78.6%). Methotrexate is the first-line treatment for skin involvement and inflammatory arthritis. Calcium channel blockers such as diltiazem and nifedipine were administered to patients with Raynaud's phenomenon accounting for 42.9% and 26.2% of patients, respectively. Calcium channel blockers are the first-line treatment for patients with Raynaud's phenomenon and digital ulcers because of their vasodilator effect.[13]

The median of MRSS in this study was 19 (2 –45). This result is higher compared to a study by Muangchan *et al*.[8] in Canada, which found the mean of MMRS was 10.04±9.54. However, this results are almost identical to those of Komura *et al*.[12] and Sato *et al*.[7] in Japan, with a mean MMRS of 19.7±4.2 and 19.1±8.6, respectively. Asians have higher MRSS scores than Caucasians or Europeans. Patients with darker skin color tend to have more severe manifestations resulting in more diffuse skin involvement.[2]

The median of interleukin-6 was 15.72 pg/mL, with a range of 1.79 – 246.69 pg/mL. These results are consistent with Khan *et al*.[15], which obtained a mean IL-6 of 14.39, a median of 10.1, and a range of 3.23-51.3 pg/mL but higher than a study by Sato *et al*. al.[7] with a mean of 3.5 ± 8.5. The high levels of IL-6 in this study contradict previous studies, which stated that pro-inflammatory levels in Asians were lower than Caucasians and African-Americans. [16] Varied IL-6 levels in systemic sclerosis, which are characterized by high ranges and standard deviations, are not only influenced by racial differences but may also be caused by other diseases that have not been detected, such as under stress conditions that occur in tissue damage, infection, or inflammation and chronic disease.[16,17] The wide range of values of IL-6 can affect the strength of the correlation because the value of r in the correlation test is strongly influenced by outliers.

Analysis showed there was a significant

correlation between MRSS and interleukin-6 serum with r=0.397 and p=0.005. These results are similar to the study of Khan *et al*.[15], which found a positive correlation between IL-6 and MRSS with r=0.514 and p=0.000 at the time of the first visit. After 36 months of follow-up, there was still a positive correlation between IL-6 at the first visit and MRSS with r=0.795 and p <0.001, indicating a very strong correlation. Interleukin-6 may predict disease progression in the next three years. However, the study did not mention the intervention given in three years.[15]

A prior study conducted by Sato *et al*.[7] also found a positive correlation between serum interleukin-6 levels and MRSS with r=0.625 and p <0.0001, which also showed a strong correlation between the two variables. Hax *et al*.[18] also reported a positive correlation between serum Interleukin-6 levels and MRSS, although with a weak relationship with r=0.291 and p=0.041. On the other hand, Hasegawa *et al*.[19] showed no significant correlation between serum interleukin-6 and MRSS. These results may be due to the method used to detect serum chemokines and cytokines that are less sensitive so that serum IL-6 in most patients and controls cannot be detected.

Interleukin-6 is a pro-inflammatory cytokine produced by many immune cells and plays a role in T cell activation. IL-6 also stimulates hematopoietic precursors that cause B cell maturation into antibody-producing cells and cell differentiation. Therefore, IL-6 is elevated in most autoimmune diseases such as systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis.[20] Interleukin-6 can also be elevated in stressful conditions such as tissue damage, infection, inflammation, and chronic diseases such as malignancy, Castleman disease, multiple myeloma, anemia in chronic disease, Crohn's disease, Alzheimer's disease, idiopathic juvenile arthritis, ankylosing spondylitis, diabetes mellitus, and obesity.[17] Given the number of diseases that can increase IL-6, complete exclusion criteria would increase the accuracy of the correlation between IL-6 and MRSS.

The different results between our study and previous studies may be due to the exclusion criteria used. In the study conducted by Khan *et al*.[15], no other diseases were excluded that could increase the IL-6 concentration. In the study of Sato *et al*.[7], which had a strong correlation, only patients who had other rheumatic diseases were excluded and still included patients with Sjogren's syndrome. In the study conducted by Hax *et al*.[18], which had a weak correlation, the exclusion criteria used included: patients who had overlap syndrome, lymphoproliferative disease, cancer, and acute infections such as HIV, Hepatitis B, or hepatitis C but did not mention the exclusion criteria for subjects with other chronic diseases. In our study, subjects with other autoimmune conditions, acute infection, diabetes mellitus, and obesity were excluded. Thus, the fewer exclusion criteria applied, the stronger the correlation. This shown IL-6 increased can be caused by many factors.

Limitation of this study is most patients had received therapy that may affect interleukin-6 and MRSS. Further studies are needed with a larger population and sample with stricter exclusion criteria and in patients who have not received therapy since a larger nunber of samples will overcome the problem of outliers.

Interleukin-6 was significantly correlated with MRSS in patients with systemic sclerosis, reflecting disease activity. IL-6 and MRSS had a medium positive correlation with r=0.397 and p=0.005.

References

1. Christian B, Distler O, Jorg HW, Distler JH. Scleroderma from Pathogenesis to Comprehensive Management. 2nd ed. USA: Springer; 2013. p. 285-8.
2. Reveille JD. Ethnicity and race and systemic sclerosis: how it affects susceptibility, severity, antibody genetics, and clinical manifestations. Curr Rheumatol Rep. 2003;5(2):160–7.
3. Mulasimadhi K, Wachjudi RG, Rahmadi AR. Perubahan pola penyakit pasien di klinik reumatologi RSUP Dr. Hasan Sadikin Sebelum dan sesudah era Jaminan Kesehatan Nasional. Rematologi Klinik Bandung Bandung; 2015.
4. Valentini G, Iudici M, Walker UA, Jaeger VK, Baron M, Carreira P, *et al*. The European Scleroderma Trials and Research group (EUSTAR) task force for the development of revised activity criteria for systemic sclerosis:

derivation and validation of a preliminarily revised EUSTAR activity index. Ann Rheum Dis. 2017;76(1):270–6.
5. Muangchant C, Pope J. IL-6 in scleroderma; potential implications for targeted therapy: A systematic analysis. J Rheumatol. 2012;39(6):1120–4.
6. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nat Med. 2012;18(7):1028–40.
7. Sato S, Hasegawa M, Takehara K. Serum levels of interleukin-6 and interleukin-10 correlate with total skin thickness score in patients with systemic sclerosis. J Dermatol Sci. 2001;27(2):140–6.
8. Muangchan C, Harding S, Khimdas S, Bonner A, Group CSR, Baron M, *et al*. Association of C-reactive protein with high disease activity in systemic sclerosis: results from the Canadian Scleroderma Research Group. Arthritis Care Res (Hoboken). 2012;64(9):1405–14.
9. Alba MA, Velasco C, Simeón CP, Fonollosa V, Trapiella L, Egurbide MV, *et al*. Early- versus late-onset systemic sclerosis: differences in clinical presentation and outcome in 1037 patients. Medicine (Baltimore). 2014;93(2):73–81.
10. Royle JG, Lanyon PC, Grainge MJ, Abhishek A, Pearce FA. The incidence, prevalence, and survival of systemic sclerosis in the UK Clinical Practice Research Datalink. Clin Rheumatol. 2018;37(8):2103–11.
11. Dieude P, Bouaziz M, Guedj M, Riemekasten G, Airo P, Müller M, *et al*. Evidence of the contribution of the X chromosome to systemic sclerosis susceptibility: association with the functional IRAK1 196Phe/532Ser haplotype. Arthritis & Rheumatism. 2011;63(12):3979–87.
12. Komura K, Fujimoto M, Matsushita T, Yanaba K, Kodera M, Kawasuji A, *et al*. Increased serum soluble CD40 levels in patients with systemic sclerosis. J Rheumatol. 2007;34(2):353–8.
13. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, *et al*. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327–39.
14. Herrick AL. Controversies on the Use of Steroids in Systemic Sclerosis. J Scleroderma Related Disorders. 2017;2(2):84–91.
15. Khan K, Xu S, Nihtyanova S, Derrett-Smith E, Abraham D, Denton CP, *et al*. Clinical and pathological significance of interleukin 6 overexpression in systemic sclerosis.Ann Rheum Dis. 2012;71(7):1235–42.
16. Coe CL, Love GD, Karasawa M, Kawakami N, Kitayama S, Markus HR, *et al*. Population differences in proinflammatory biology: Japanese have healthier profiles than Americans. Brain Behav Immun. 2011;25(3):494–502.
17. Tanaka T, Narazaki M. Interleukin-6 inhibition in inflammatory diseases: results achieved and tasks to accomplish. J Scleroderma Related Disorders. 2017;2(2_suppl):S20–8.
18. Hax V, Gasparin AA, Schneider L, Monticielo OA, Soares HMF, Streit MDA, *et al*. Vitamin D and Cytokine Profiles in Patients With Systemic Sclerosis. J Clin Rheumatol. 2020;26(7):289–94.
19. Hasegawa M, Fujimoto M, Matsushita T, Hamaguchi Y, Takehara K, Sato S. Serum chemokine and cytokine levels as indicators of disease activity in patients with systemic sclerosis. Clin Rheumatol. 2011;30(2):231–7.
20. Muangchan C, Pope JE. Interleukin 6 in systemic sclerosis and potential implications for targeted therapy. J Rheumatol. 2012;39(6):1120–4.