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Original Article

Association of C-Reactive Protein and Modified Rodnan Skin Score with Carotid Intima-Media Thickness in Systemic Sclerosis

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Abstract

Background : Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by vasculopathy and progressive fibrosis with an increased risk of cardiovascular disease. The common carotid artery intima-media thickness is an indicator of subclinical atherosclerosis and may reflect inflammatory activity in SSc. Quantitative C-reactive protein (CRP) and the modified Rodnan Skin Score (mRSS) are associated with SSc disease activity, although their relationship with common carotid intima-media thickness remains unclear.
Aims : To evaluate the relationship between quantitative CRP levels and mRSS values with common carotid intima-media thickness in adult patients with SSc.
Methods : A cross-sectional study was conducted on 26 SSc patients at Dr. Kariadi General Hospital, Semarang. Common carotid intima-media thickness was measured using ultrasonography on both sides. Subjects were categorized based on the presence of intima-media thickening according to the ≥75th percentile for age and sex. Quantitative CRP levels were analyzed using the Mann-Whitney test, while differences in mRSS were analyzed using an independent T-test.
Results : Increased common CIMT was observed in 9 patients (34.6%). There was no significant difference in quantitative CRP levels between subjects without and with intima-media thickening (0.40 [0.07–1.10] vs. 0.40 [0.20–0.83] mg/L; P = 0.787). mRSS values also did not differ significantly between the two groups (18.29 ± 9.38 vs. 18.78 ± 12.48; P = 0.912).
Conclusion : There was no significant relationship between quantitative CRP levels or mRSS values and common carotid intima-media thickness in patients with SSc. These findings may be influenced by immunosuppressive therapy and study design.

Keywords : Systemic sclerosis, Skin fibrosis, Common carotid intima-media thickness, C-reactive protein, Modified Rodnan skin score

INTRODUCTION

Systemic sclerosis (SSc), also known as scleroderma, is a chronic autoimmune rheumatic disease characterized by fibrosis of the skin and visceral organs. The autoimmune reaction targets connective tissue throughout the body, involving the skin, vasculature, gastrointestinal system, heart, lungs, and kidneys. This systemic involvement leads to a broad spectrum of clinical presentation, from mild cutaneous manifestations to life-threatening visceral organ dysfunction. The heterogeneity of organ involvement contributes to significant variability in disease course, prognosis, and response to treatment among patients.[1] SSc is a relatively rare condition which prevalence is estimated at 17.6 cases per 100,000 population with an incidence of 1.4 cases per 100,000 per year. Despite the lack of epidemiological data for Indonesia, SSc prevalence in Asia is lower at approximately 6.8 per 100,000 population. Geographic variation in SSc prevalence may imply the influence of genetic background and environmental exposure in SSC pathogenesis.[2] Similar to other autoimmune diseases, SSc occurs more frequently in women up to 3–7 times higher than men.[3,4]

The exact etiology of SSc remains unclear. Genetic susceptibility and environmental exposures contribute to SSc development. Proposed environmental triggers include cytomegalovirus and Epstein Barr virus infections, as well as exposure to silica dust and organic solvents. Occupational exposure and chronic oxidative stress have also been suggested to be involved in the disease initiation.[5,6] The pathogenesis of SSc involves vascular injury, immune dysregulation, and progressive fibrosis. Endothelial activation promotes vasoconstriction, coagulation, and smooth muscle proliferation, leading to chronic inflammation and microvascular damage. Impaired vascular repair results in persistent hypoxia.[7] Abnormal immune activation also plays a significant role as cytokine imbalance promotes profibrotic pathways while activated B cells produce disease specific autoantibodies.[8]

SSc presents with heterogeneous clinical manifestations depending on disease subset and organ involvement. The three major subsets are limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc), and SSc sine scleroderma (ssSSc). Cutaneous involvements include skin thickening, Raynaud phenomenon, and digital ulcers. Internal organ involvement contributes to significant morbidity, including interstitial lung disease, arthritis, and scleroderma renal crisis.[7,8]

Cardiovascular complications are increasingly recognized in SSc.[9] Microvascular dysfunction appears early in the disease course and contributes to macrovascular abnormalities, such as increased large artery stiffness, atherosclerotic plaque formation, and increased carotid intima media thickness (CIMT). Patients with autoimmune diseases show a higher prevalence of carotid arterial thickening than healthy individuals.[10,11] Chronic inflammation accelerates vascular smooth muscle proliferation and extracellular matrix deposition, resulting in arterial wall thickening. These vascular changes may occur in the absence of traditional cardiovascular risk factors, suggesting the role of immune-mediated injury in vasculopathy and atherosclerosis development in SSc.[12–15]

C-reactive protein (CRP) is an acute phase reactant produced in response to systemic inflammation and is widely available. Although traditionally viewed as a passive inflammatory marker, CRP may also contribute to disease progression through complement modulation and immune complex clearance.[16] Reports on CRP levels in SSc vary widely due to heterogeneity in disease phenotype and activity.[17] The modified Rodnan skin score (mRSS) is a semiquantitative clinical tool that assesses skin thickening in SSc. It correlates well with histopathological findings of SSc and is widely used to monitor disease severity and treatment response. Both CRP and mRSS have been proposed as markers to reflect systemic inflammatory state and fibrosis burden. However, their ability to reflect vascular involvement remains uncertain, especially in the context of subclinical atherosclerosis.[18]

Several studies have explored associations between CRP or mRSS and CIMT in SSc with inconsistent findings.[19–23] Evidence remains limited in the Indonesian population, whereas understanding these relationships may improve cardiovascular risk stratification in SSc. Identifying clinical and laboratory markers associated with subclinical vasculopathy and atherosclerosis may facilitate early identification of patients at higher cardiovascular risk, allowing closer monitoring to reduce long-term complications. Therefore, this study aims to analyze the association between quantitative CRP levels and mRSS with CIMT in patients with SSc.

METHODS

This cross-sectional study was conducted at the Rheumatology Outpatient Clinic, Central General Hospital Dr. Kariadi, Semarang, Indonesia in May to August 2025. We recruited adult patients (≥18 years of age) diagnosed with SSc based on the ACR/EULAR 2013 criteria (Table 1). Consecutive sampling was applied to minimize selection bias and represent a real-world outpatient setting. Patients that presented with other autoimmune disease, acute infection, tuberculosis, malignancy, or pregnancy were excluded. Ethical approval was received from the Health Research Ethics Committee of the Faculty of Medicine, Diponegoro University/Central General Hospital Dr. Kariadi Semarang (No. 16416/EC/KEPK-RSDK/2025). The study was conducted in accordance with the Declaration

TABLE 1
ACR/EULAR criteria for the diagnosis of systemic sclerosis

Criteria	Sub-criteria	Score
Skin thickening of the fingers of both hands from proximal to the metacarpophalangeal joints		9
Skin thickening of the fingers (*count the highest score)*	Puffy fingers	2
	Sclerodactyly (distal to MCP but proximal to the PIPs)	4
Finger tip lesions	Digital tip ulcers	2
	Finger tip pitting Scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Lung involvement	Pulmonary arterial hypertension or interstitial lung disease	2
Raynaud's phenomenon		3
Scleroderma-related antibodies	At least one of anticentromere antibody, anti-topoisomerase I antibody, or anti-RNA polymerase III antibody	3

ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; MCP: metacarpophalangeal; PIP: proximal interphalangeal joint; RNA: ribonucleic acid.

of Helsinki and all participants provided written informed consent prior to enrollment.

Data were collected during outpatient visit through interview, physical examination, laboratory examination, and carotid ultrasonography (Figure 1). Baseline characteristics data included age at initial presentation, sex, and cardiovascular comorbidities, such as hypertension, type 2 diabetes mellitus (DM), and hyperlipidemia. Hypertension was diagnosed if systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and/or the patient was currently taking antihypertensive medications.[24] Type 2 DM was diagnosed if fasting plasma glucose ≥126 mg/dL, plasma glucose ≥200 mg/dL two hours after a 75 gram–oral glucose tolerance test, random plasma glucose ≥200 mg/dL in the presence of classic symptoms or hyperglycemic crisis, HbA1c ≥6.5%, or current use of antidiabetic medications.[25] Dyslipidemia was diagnosed if plasma lipid panel had total cholesterol ≥200 mg/dL, LDL cholesterol ≥130 mg/dL, HDL cholesterol <40 mg/dL or >60 mg/dL, and/or triglyceride >150 mg/dL.[26] History of immunosuppressants consumption in the context of SSc treatment was retrieved from the electronic medical record.

Assessment of mRSS was performed on 17 skin areas reported by Clements *et al*.: fingers, dorsum of the hands, forearms, upper arms, face, chest, abdomen, thighs, lower legs, and dorsum of the feet (Table 2). Each area was given a score of 0 to 3 according to the most severe thickening in the corresponding area. A score of 0 indicated normal skin with no signs of thickening, 1 indicated mild thickening, 2 indicated moderate thickening, and 3 indicated severe thickening with inability to pinch the skin. The total mRSS score ranged from 0 to 51 with higher scores indicating more extensive skin involvement. To reduce interobserver variability, all examinations were conducted by an experienced rheumatologist who had undergone standardized training in mRSS assessment.[18,27]

Quantitative CRP was measured from the venous blood using the Quantikine® human CRP enzyme-linked immunoassay (ELISA) kit (R&D Systems, Minneapolis, USA) at an independent out-of-hospital laboratory. CIMT was measured by a cardiovascular specialist using a B-mode ultrasound system (LOGIQ™ S7, GE HealthCare, Wisconsin, USA) and a 12 MHz transducer (GE HealthCare, Wisconsin, USA) during the outpatient visit. Measurements were taken from the lumen intima border to the media adventitia border. The evaluation was conducted on the far wall of the common carotid artery, located 1 cm proximal to the carotid bifurcation. Both the right and left carotid arteries were assessed.[29] Increased CIMT was defined when at least one measurement was equal to or above the 75th percentile

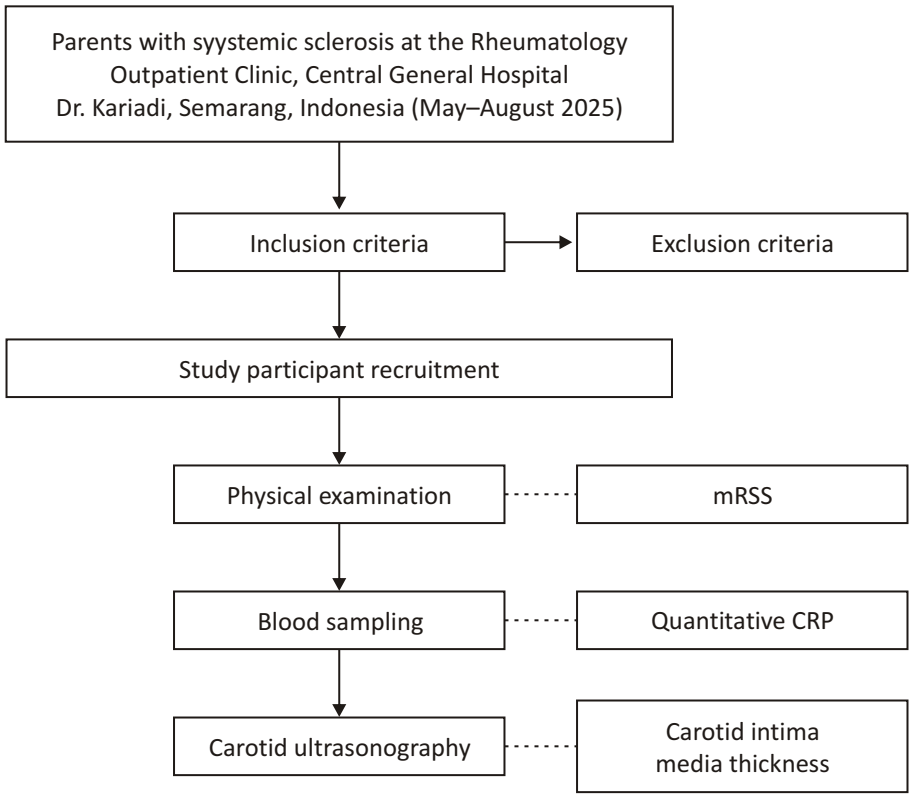

Figure 1. Flow of study participants recruitment.
mRSS: modified Rodnan skin score; CRP: C-reactive protein.

TABLE 2
Modified Rodnan skin score assessment technique based on the skin area.[28]

Skin area	Technique
Fingers	The backs of the fingers between the proximal interphalangeal and metacarpophalangeal joints are evaluated.
Forearms and upper arms	The extensor side is prefered to the flexor side.
Face	The cheeks (below the zygomatic arch and over the mandible) are prefered to the forehead.
Chest	The patient is seated and skin thickening is evaluated from the uppermost to the lowermost margin of the sternum, including the breasts.
Abdomen	The patient is in the supine position and skin thickening is evaluated from the lowermost margin of the sternum to the uppermost margin of the pelvis.
Thighs, lower legs, and dorsum of the feet	The patient is in the supine position with bent knees.

for age and sex based on Asian population reference values (Table 3).[30]

Continuous data were reported as mean ± standard deviation (SD) or median (quatile 1–quartile 3), as appropriate. Data normality was tested using the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages. Comparisons of pre-test and post-test data were performed using the paired T-test or Wilcoxon test according to the data distribution normality. Independent T-test or Mann-Whitney test were used to compare the control groups to the treatment groups. For normally distributed numerical data, one-

TABLE 3
Normal range of carotid intima media thickness based on sex, age, and location in Asian population.[30]

Sex	Age (years)	Left carotid (mm)			Right carotid (mm)		
		P25	P50	P75	P25	P50	P75
Male	<30	0.42	0.44	0.49	0.39	0.43	0.48
	31–40	0.44	0.47	0.57	0.42	0.46	0.50
	41–50	0.50	0.55	0.61	0.46	0.50	0.57
	>50	0.53	0.61	0.70	0.46	0.52	0.62
Female	<30	0.30	0.44	0.46	0.39	0.40	0.43
	31–40	0.44	0.47	0.51	0.42	0.45	0.49
	41–50	0.46	0.51	0.57	0.44	0.48	0.53
	>50	0.52	0.59	0.64	0.50	0.54	0.59

way analysis of variance (ANOVA) were conducted and followed by the post-hoc analysis; otherwise, the Kruskal-Wallis test and Mann-Whitney test were used, consecutively. Statistical significance was defined as *P* value of ≤0.05. A two-tailed analysis approach was used for all statistical analysis. SPSS™ Statistics Version 26 (IBM®, Illinois, USA) software was used to perform all statistical analysis.

RESULTS

During the data collection period, 26 patients met the eligibility criteria and were included in the analysis. A total of 25 participants were women, and more than half were aged 40 years or older with an age range of 20 to 72 years. All participants were in the dcSSC spectrum and receiving at least one type of immunosuppressive agent with mycophenolate mofetil (MMF) being the most frequently prescribed. Eighteen participants (69.2%) had a history of receiving or were currently receiving two or more immunosuppressive drugs, most commonly a combination of MMF and either methylprednisolone or prednisone. The least frequently used agents were hydroxychloroquine and methotrexate. The baseline characteristics of the study subjects are presented in Table 2.

Participants were categorized into two groups based on the presence of intima media thickening. Among nine participants with increased CIMT, only one demonstrated bilateral thickening. The group with CIMT thickening had a higher mean age compared to the group without intima media thickening, although the difference was not statistically significant (P = 0.083). Three participants had a diagnosis of hypertension, and all of them exhibited increased CIMT. The baseline characteristics of participants according to CIMT status are presented in Table 3.

There was no significant difference in quantitative CRP levels and mRSS scores between the groups with and without intima media thickening. The comparison of quantitative CRP levels and mRSS scores based on CIMT status is presented in Table 4.

DISCUSSION

Our study found no significant association between quantitative CRP levels and mRSS with CIMT in patients with SSc. Most participants in this study were women, which is consistent with the higher susceptibility of female sex to autoimmune diseases in general. Women may have up to a five-fold increased risk of developing SSc,[31] possibly due to hormonal factors, abnormal X-chromosome inactivation, and stronger B-cell–mediated immunity.[32] Estrogen has been shown to modulate immune responses by enhancing humoral immunity and promoting autoantibody production, while X-linked gene expression may further amplify this immune dysregulation cascade.[33] These mechanisms may contribute to the sex disparity in SSc prevalence. All participants had dcSSc which is more frequently observed in Asian patients.[34] Genetic differences, particularly affecting HLA alleles, may contribute to this pattern by manipulating antigen presentation and the development of disease specific autoantibodies. In addition, regional differences in environmental exposures and healthcare access may influence the clinical phenotype and timing of diagnosis, thus affecting the observed distribution of disease subsets.[35]

A third of participants of this study showed increased common carotid intima media thickness which was mostly unilateral. The left carotid artery was more frequently affected; this is expected due to its direct origin

TABLE 4
Baseline characteristics of the study population

Characteristics	Total (n = 26)
Age (years)	41.62 ± 13.43
<40	12 (46.2)
≥40	14 (53.8)
Female sex	25 (96.2)
Hypertension	3 (11.5)
Type 2 diabetes mellitus	2 (7.7)
Hyperlipidemia	1 (3.8)
SSc subsets	
lcSSc	0 (0.0)
dcSSc	26 (100.0)
ssSSc	0.46
Immunosuppressants use	
Mycophenolate mofetil	23 (88.5)
Cyclophosphamide	8 (30.8)
Cyclosporine	2 (7.7)
Hydroxychloroquine	1 (3.8)
Methotrexate	1 (3.8)
Methyprednisolone/Prednisone	11 (42.3)
Carotid intima-media thickness (mm)*	
Average	0.46 (0.42–0.54)
Right	0.45 (0.41–0.52)
Left	0.44 (0.41–0.52)

*Median (Q1–Q3)
SSc: systemic sclerosis; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ssSSc: sine scleroderma SSc.

from the aorta. Participants with increased CIMT tended to be older, consistent with increasing age as a risk factor of thickened CIMT.[36] This trend is also observed in Indonesian population.[37] Age-related vascular remodeling involves progressive endothelial dysfunction, increased arterial stiffness, and accumulation of extracellular matrix, all of which contribute to CIMT progression.[38] Sex and age had no significant influence on the CIMT status because this study controlled those confounding factors using sex and age specific reference values.[39] All hypertensive participants demonstrated increased CIMT thickening. This finding was likely related to chronic shear stress on the vascular wall, regardless the presence of any vasculopathy or atherosclerosis.[40]

The finding of unilateral carotid thickening predominance, particularly in the left carotid artery, may also be explained by hemodynamic factors. The left common carotid artery arises directly from the aortic arch that exposes it to higher pulsatile pressure and turbulent flow compared to the right side, which originates from the brachiocephalic trunk. This anatomical difference may predispose the left carotid artery to earlier vascular remodelling, including increased CIMT. Certain vascular geometry and flow may also influence regional susceptibility to endothelial dysfunction.[36]

In this study, quantitative CRP levels and mRSS values did not differ significantly between groups with and without increased CIMT. CRP is an acute phase protein which level fluctuates depending on the

TABLE 5
Baseline characteristics of the study population according to the carotid intima media thickness status

Characteristics	Increased CIMT (n=17)	Normal CIMT (n=9)	*P*
Age (years)	38.29 ± 11.04	47.89 ± 15.88	0.083
<40	10 (58.8)	2 (22.2)	0.110
≥40	7 (41.2)	7 (77.8)	
Sex			1.000
Male*	1 (5.9)	0 (0.0)	
Female*	16 (94.1)	9 (100.0)	
Hypertension*	0 (0.0)	3 (33.3)	**0.032**
Type 2 diabetes mellitus*	0 (0.0)	2 (22.2)	0.111
Hyperlipidemia*	0 (0.0)	1 (11.1)	0.346
SSc subsets			–
lcSSc	0 (0.0)	0 (0.0)	
dcSSc	17 (100.0)	9 (100.0)	
ssSSc	0 (0.0)	0 (0.0)	
Immunosuppressants use*			
Mycophenolic acid	14 (82.4)	9 (100.0)	0.529
Cyclophosphamide	5 (29.4)	3 (33.3)	1.000
Cyclosporine	2 (11.8)	0 (0.0)	0.529
Hydroxychloroquine	1 (5.9)	0 (0.0)	1.000
Methotrexate	1 (5.9)	0 (0.0)	1.000
Methyprednisolone/Prednisone	9 (52.9)	2 (22.2)	0.217

*Fisher's exact test
**Mann-Whitney test
CIMT: carotid intima media thickness; SSc: systemic sclerosis; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; ssSSc: sine scleroderma SSc.

TABLE 6
C-reactive protein level and modified Rodnan skin score based on the carotid intima media thickness status

Characteristics	Total (n=26)	Increased CIMT (n=17)	Normal CIMT (n=9)	*P*
CRP (mg/L)	0.40 (0.16–0.99)	0.40 (0.07–1.10)	0.40 (0.20–0.83)	0.787
mRSS	18.46 ± 10.30	18.29 ± 9.38	18.78 ± 12.48	0.912

*Mann-Whitney test
**Independent-T test
CIMT: carotid intima media thickness; CRP: C-reactive protein; mRSS: modified Rodnan skin score

inflammatory activity. Because this study used a cross-sectional design, the measurements did not necessarily reflect peak inflammatory levels throughout the disease course. SSc has heterogeneous disease progression. Early disease is characterized by active inflammation which may increase CRP levels, while later stages are dominated by fibrosis and stabilization of inflammatory markers. Skin fibrosis usually appears after one to three

years in dcSSc.[41] Therefore, a single time-point measurement adapted in the cross-sectional approach may underestimate the cumulative inflammatory condition experienced by the patient over time. Longitudinal assessment of CRP levels may provide a more accurate representation of chronic inflammation and its relationship with vascular changes.

Inflammatory biomarkers such as ESR, CRP, and leukocyte counts do not always increase in untreated systemic rheumatic diseases. In SSc, inflammation tends to be less pronounced than in other autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus.[42] This relatively low-grade inflammatory profile may explain the weak association between CRP and structural vascular changes, such as CIMT. Although CRP may reflect inflammatory vascular injury, CIMT measurement by ultrasound cannot differentiate whether increased CIMT is due to vasculopathy or atherosclerosis. This limitation is quite significant in SSc where both immune-mediated vasculopathy and classic atherosclerosis plaque development may coexist and contribute to arterial wall thickening. Similarly, mRSS reflects the extent of skin fibrosis rather than direct vascular involvement. Although fibrosis and vasculopathy share common pathogenesis, including cytokine activation and endothelial dysfunction, the temporal progression of these processes may be different. As a result, mRSS may not accurately represent the degree of vascular remodeling occurring alongside with skin thickening.[1,5,43]

No significant elevation in CRP levels and mRSS may also be secondary to the use of immunosuppressive therapy. All participants were already receiving immunosuppressants at the time of blood sampling. Immunosuppressive agents used in SSc commonly reduce inflammatory cell activity or inhibit IL-6 mediated pathways.[44] Methotrexate inhibits AICAR transformylase that increases extracellular adenosine levels and suppresses T cell activation to reduce IL-6 production.[44] Mycophenolic acid inhibits inosine monophosphate dehydrogenase that inhibits lymphocyte proliferation.[45] Cyclophosphamide is an alkylating agent that induces apoptosis in rapidly dividing immune cells. Rituximab targets CD20 that affects the depletion of B lymphocytes.[46] Short-term glucocorticoids also provide potent anti-inflammatory effects by suppressing transcription factors, such as nuclear factor-kappa B (NF-κB) dan activator protein-1, thereby reducing proinflammatory cytokine production. Slightly different from other immunosuppressant agents, tocilizumab exerts its anti-inflammatory effects by blocking IL-6 receptors directly and thus inhibits CRP synthesis in hepatocytes.[47] As a result, CRP levels in patients receiving tocilizumab may not accurately reflect the true inflammatory state, leading to underestimation of its association with vascular changes. When inflammation subsides or improve due to treatment, Skin fibrosis may therefore regress spontaneously in advanced disease stages. This regression involves suppression of fibroblast activity which is driven by proinflammatory signaling. Prolonged immunosuppressive therapy may also alter the natural course of vascular remodeling by reducing endothelial activation and limiting progression of subclinical atherosclerosis.[48] Another possible explanation for the lack of association is the relatively small sample size which limits the statistical power to detect slight correlations between variables. Individual variability in disease duration, treatment response, and comorbid conditions may confound the results of this study. Moreover, the cross-sectional approach used in this study did not allow the identification of causal relationships between inflammation, fibrosis, and vascular changes.

Our study had several limitations. First, the measured quantitative CRP levels and mRSS scores did not necessarily reflect the peak inflammation state throughout the course of the disease due to the cross-sectional approach. Second, clinical data were obtained in patients already taking immunosuppresants, potentially reducing the systemic inflammation by the time of examination. Third, our study did not document the onset of the disease, autoantibodies present in each patient, medication history and its duration of administration. Difference on disease onset and duration of drug administration might cause variability on the inflammatory state. Lastly, carotid ultrasound cannot accurately distinguish whether increased CIMT is mainly contributed from vasculopathy or atherosclerosis. Overall, the widespread use of immunosuppressive therapy in this study population might have already suppressed the skin fibrosis by reducing systemic inflammation, cytokine production, and fibroblast activity. These mechanisms may explain the lack of significant association between CRP, mRSS, and CIMT in this study. Despite these findings, the presence of increased CIMT in a significant proportion of patients presents the importance of cardiovascular risk assessment in SSc, even in the absence of increased inflammatory markers. Further longitudinal prospective study is needed, preferably in patients naive to immunosuppressants, to reflect the true inflammatory state of each individuals. Disease onset, autoantibodies, and the duration of immunosuppressants also need to be documented to observe any difference in the inflammatory markers and CIMT.

CONCLUSION

There was no association between quantitative CRP levels and mRSS scores with CIMT in SSc patients. These findings may be influenced by the use of immunosuppressant agents in the cohort which may not

reflect the peak inflammatory state in SSc patients. The cross-sectional design may limit the ability to identify temporal changes in systemic inflammatory state and vascular remodeling.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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