RHEUMATOLOGY RESEARCH JOURNAL

Vol. 9, No. 1, January 2024,
Webpage: http://rheumres.org
Email: rheumres@gmail.com
ISSN:2476-5856
doi: 10.32592/RR.2024.9.1.38

Original Article **Open Access**

Clinical and capillaroscopy correlation of Pentraxin 3 and mean platelet volume in patients with systemic sclerosis: A case control study

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Systemic sclerosis (SSc) is a systemic connective tissue disease with vasculopathy and tissue fibrosis. Mean platelet volume (MPV) indicates the platelet activation and independent risk factor for arterial diseases. Long pentraxin, or pentraxin-3 (PTX3), is a homologous pattern recognition receptor mainly presented in inflammatory diseases with some inhibitory effects on chronic inflammation. This study aimed to evaluate the relationship between clinical and capillaroscopy manifestations of patients with SSc, MPV, and PTX3 levels compared to the control group. This case-control study was conducted on patients who met the SSc diagnostic criteria. Accordingly, clinical manifestations and capillaroscopy data were recorded. Thus, the MPV and PTX3 levels of the patients and the control group were checked. Then, the relationship between the clinical and capillaroscopy results was evaluated. The mean ± SD of MPV in the control group and patients was 10.11 ± 0.96 fL and 9.65 ± 1.13 fL, respectively (P-value = 0.043). In addition, the PTX3 level was 3.60 ± 8.98 and 1.79 ± 5.77 ng/ml, respectively (P-value = 0.223). The relationship of these factors with the clinical and capillaroscopy results was insignificant (P-value > 0.05). Based on the results, the MPV level was significantly lower in patients with SSc than controls, while the PTX3 level did not differ between the groups. Moreover, there was no relationship between PTX3 and MPV levels with the capillaroscopy and clinical results. However, further studies with larger sample sizes are recommended.

Keywords: Systemic sclerosis; Mean platelet volume; Pentraxin 3; Capillaroscopy

Introduction

Systemic sclerosis (SSc) is a rheumatic disease, which is mainly presented with fibrosis and vasculopathy [1], affecting the skin, blood vessels, muscles, and internal organs [1, 2]. Abnormalities observed in nail fold capillaries can be considered the manifestation of microvascular disease, which can be detected using direct in-vivo microscopy [3, 4]. Platelet volume is a marker of activation and function, measured using mean platelet volume (MPV) [5, 6]. Increased MPV may be reflected either by increased platelet activation or increased numbers of large, hyper aggregable platelets, which is accepted as an independent risk factor for coronary and peripheral artery disease [5, 6]. Furthermore, platelet abnormalities are observed in SSc, which play an essential role in the

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Received: 3 June 2023; **Accepted:** 10 **January** 2024

pathogenesis of vasculopathy [6].

Some studies have evaluated the level of MPV in SSc and its relationship with the severity of the manifestations. Two studies on patients with SSc and a control group have indicated no significant relationship between the MPV levels and clinical signs of disease [7, 8]. However, another study showed that MPV was significantly higher in patients and was related to clinical presentation, especially in patients with cardiac involvement, digital ulcers, and gangrene [9].

The Pentraxin superfamily includes long and short pentraxins; the short pentraxins are comprised of C-reactive protein (CRP) and serum amyloid P component (SAP), whereas pentraxin 3 (PTX3) is considered a long pentraxin [10]. Both long and short pentraxin have essential functions related to innate immunity and autoimmunity [10, 11], which can bind to microorganisms, nuclear remnants of the cells undergoing apoptosis, and extracellular matrix proteins [10]. The complement system can also be activated by binding to C1q [10-12]. As opposed to short pentraxin, long ones inhibit the changes mediated by fibroblast growth factor 2 (FGF2) because of its high affinity to the FGF2 N-terminal domain [10-12]. FGF2 affects the inflammation process in many different ways with various consequences. Despite promoting vessel formation, endothelial cell adhesion molecules expression, fibroblast proliferation, and smooth muscle activation, the transforming growth factor inhibits chronic inflammation [12] and tissue fibrosis by reducing collagen synthesis [10-12]. The PTX3 level can represent vascular involvement and inflammation in the arteries in Takayasu arteritis [12, 13]. In addition, PTX3 increases in giant cell arthritis and leukocytoclastic infiltration sites [14, 15]. Several studies have reported an elevated pentraxin level in autoimmune and inflammatory diseases. Some studies in juvenile systemic sclerosis (JSS), juvenile localized sclerosis (JLS), and SSc have confirmed the relationship between the pentraxin level and skin fibrosis [16, 17], in which pentraxin level was significantly higher in patients' JSS and JLS compared with the control group [16]. However, in another study, the level of PTX3 was significantly higher in adults with SSc compared to the controls, but no relationship was observed between the pentraxin level and fibrosis [18]. Moreover, several studies have found the significant role of elevated PTX3 with prominent vascular manifestations, such as Raynaud's phenomenon and digital ulcerations, in connective tissue disorders and systemic lupus erythematosus (SLE) [18-20].

This study aims to evaluate clinical and capillaroscopy manifestations in selected patients with SSc compared to the control group and find their relationship to the clinical and capillaroscopic data.

Materials and methods

This case-control study was conducted from June 2019 to 2020. This study included patients with a definite diagnosis of SSc who were referred to the rheumatology clinic or the Hafez Rheumatology Ward and met the 2013 ACR/EULAR SSc classification criteria [55, 56]. All patients were aged 16-65 years. Meanwhile, a controlled sex- and age-matched normal group with no history of ischemic heart disease or hypertension was selected from blood donors who were referred to the lab, and their samples were reserved.

The sub-investigators received a checklist with inclusion and exclusion criteria. Cases with overlap syndrome, diabetes mellitus, ischemic heart disease, and hypertension, patients with any clinically significant infection and malignancy, smokers, patients with no available capillaroscopy, or those unwilling to participate in the study were excluded.

The patients and the control groups signed the consent form before being included. The ethics committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1398.479) approved the study. The clinical manifestations of the patients and their organ involvement were recorded during the evaluation, and the patients were divided into two subsets of the disease: diffuse cutaneous systemic sclerosis (dsSSc) and limited cutaneous systemic sclerosis (lcSSc). A rheumatologist performed physical examination and saved the data in a chart. The patients were assessed based on their sex, age, disease duration (since the clinical manifestations of the disease),

and serological (anti-Scl-70, anticentromere, and antinuclear antibody) and clinical (diffuse or limited) subsets according to LeRoy et al.'s study. The skin was scored based on the definition by LeRoy et al. by MRSS scoring (Modified Rodnan Score) [21, 22]. During the last six months, HRCT was used to examine the pulmonary involvement at first screening or after detecting low DLCO < 80% or low FEV1 < 75% in PFT at least. Vascular involvement was assessed by cutaneous ulcerations and pulmonary artery hypertension using echo-cardiography.

A rheumatologist evaluated the capillaroscopy parameters on the same day using a stereomicroscope Euromex ST. 1740, made in Holland in the power of ×250. Distribution, capillary morphology, dimensions based on the largest diameter of the apical side (dilated > 20μm, giant > 50μm), capillary length (normal or elongated: ≥ 300μm), mean capillary density (low density was defined as reducing the normal number of the capillaries below 7 per linear millimeter), avascular area (inter-capillary distance > 500 μm), and microhemorrhages based on the last standardization of nailfold capillaroscopy and International Delphi consensus for reporting the data (2020) were the capillaroscopy parameters [23]. The results were defined as normal, scleroderma pattern, or non-specific abnormalities using the international Delphi consensus for reporting the data [23, 24]. The patients who fulfilled the inclusion criteria were referred to Hafez Hospital's labratory to be checked for MPV and PTX3. The serum level of PTX3 was determined using enzyme-linked immunosorbent assay (ELISA) kits (Bioassay Technology Laboratory, Shanghai, China). Blood samples were taken from patients and controls and centrifuged immediately for 200-300 rounds per minute (RPM) in 20 minutes. Then, the sera were separated and sent for laboratory analysis. MPV level was measured using System KX 21 Hematology Analyzer. ESR and CRP were measured using the Westergren method and nephelometry, respectively. The sample size was calculated by MedCalc software, version 19.0.7, based on the most related articles.

Descriptive statistics were based on mean (SD) and number (%). The correlation among the severity of disease, MPV level, and PTX3 level was estimated using the Pearson correlation. A T-independent test was applied to compare the means of MPV level and PTX3 level in two independent groups. The relationship between categorical variables was measured via the Chi-square test. P-value < 0.05 was considered significant.

Results

A total of 44 patients with a definite diagnosis of SSc and without exclusion criteria were referred and enrolled in the target center during this study. In addition, 44 age- and sex-matched healthy controls who met our inclusion criteria entered the study after signing the informed consent. A flow diagram of the patient's selection and study process is shown in Figure 1.

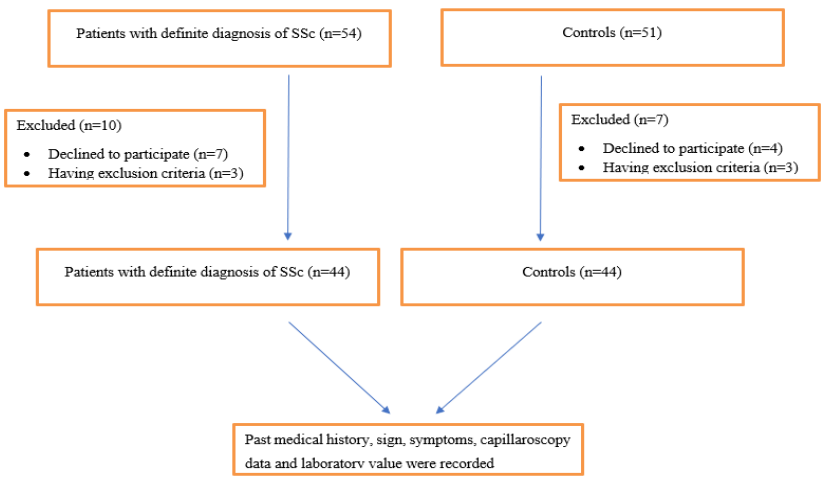

Figure 1. Flow diagram of patients' selection and study process

The patients were aged 16-64, with a mean of 43.06 ± 9.17 years. The mean age of the controls was 42.2 0± 8.77 years. Both groups did not differ significantly regarding age (P-value 0.653). In the case group, 4 (9.1%) of the 44 patients were males and 40 (90.9%) were females. Five males (11.4%) and 39 females (88.6%) were in the control group. There was no significant difference between the studied groups regarding sex (P-value > 0.50).

The MPV level was significantly higher in the controls than in patients (P-value=0.043), but the difference in the pentraxin level between the subgroups was insignificant (P-value = 0.223). Signs and symptoms of the patients with SSc and the laboratory and capillaroscopy results are summarized in Table 1.

Table 1: The frequency and prevalence of clinical manifestations, along with laboratory and capillaroscopy results in patients with SSc

Manifestations	**Total (n = 44)**	**Diffuse (n = 21)**	**Limited (n = 23)**
Disease duration[1], mean (SD)	70.77 (63.32)	66.92 (65.01)	74.28 (66.33)
Digital tip ulcer, N (%)	11 (25)	2 (9.5)	9 (39.1)
Fingertip pitting scar, N (%)	15 (31.4)	2 (9.5)	13 (56.5)
Telangiectasia, N (%)	22 (50)	8 (38)	14 (63.6)
Pulmonary arterial hypertension, N (%)	2 (4.5)	0	2 (8.6)
Gastrointestinal involvement, N (%)	38 (86.4)	18 (85.8)	20 (87)
Pulmonary involvement, N (%)	21 (47.7)	16 (76.1)	5 (21.7)
Myocardial involvement, N (%)	0)		
Renal involvement, N (%)	0		
Raynaud's phenomenon, N (%)	39 (88.6)	17 (80.9)	22(95.6)
FTP[2], N (%)			
Normal	7 (15.9)	4(19)	3(13)
Mild	13 (29.5)	8(38)	5(21.7)
Moderate	2 (4.5)	0	2(8.6)
Severe	3 (6.8)	1 (4.7)	2(8.6)
Total skin score, N (%)			
Normal (0)	0 (0)	0 (0)	0 (0)
Mild (1-14)	21 (47.7)	5 (23.9)	16 (69.5)
Moderate (15-29)	21 (47.7)	14 (66.6)	7 (30.4)
Severe (30-39)	2 (4.5)	2 (9.5)	0 (0)
End stage (>40)	0 (0)	0 (0)	0 (0)
Abnormal nail fold capillary (including nonspecific and scleroderma pattern), N (%)	44 (100)	21 (100)	23 (100)
Abnormal Dimension (Dilated capillary):			
< 33 %	6 (13.6)	2 (9.5)	4 (17.3)
33 – 66 %	4 (9.0)	1 (4.7)	3 (13.0)
66 % < of ectasia of total capillary	34 (77.2)	19 (90.4)	15 (65.2)

Abnormal dimension (giant capillary):			
< 33 %	13 (29.5)	6 (28.5)	7 (30.4)
33 – 66 %	3 (6.8)	1 (4.7)	2 (8.6)
66 % < of total capillary	10 (22.7)	6 (28.5)	4 (17.3)
Distribution, N (%)			
Normal	7 (15.9)	3 (14.2)	4 (17.3)
Abnormal	37 (84.1)	18 (85.7)	19 (82.6)
Morphology			
Normal	22 (50.0)	9 (42.8)	13 (56.5)
Abnormal **:**			
< 33 %	10 (22.7)	5 (23.8)	5 (21.7)
33 – 66 %	0 (0.0)	0 (0.0)	0 (0.0)
66 % <	12 (27.2)	7 (33.3)	5 (21.7)
Mean capillary density:			
Good density (7 - 9 mm)	10 (22.7)	5 (23.8)	5 (21.7)
Reduced density (4 – 6 mm)	26 (59.0)	10 (47.6)	16 (69.5)
Very low density (<4 mm)	8 (18.1)	6 (28.5)	2 (8.6)
Avascular area	9 (20.5)	6 (28.4)	3 (13)
Micro-hemorrhages	20 (45.4)	11 (52.3)	9 (39.1)
Scleroderma pattern	37 (84.0)	18 (85.7)	19 (82.6)
Scleroderma pattern			
Early	7 (15.9)	3 (14.2)	4 (17.3)
active	19 (43.1)	10 (47.6)	9 (39.1)
Late	11 (25.0)	5 (23.8)	6 (26.0)
MPV level, mean ± SD fL	9.65 (1.13)	9.67 (1.03)	9.63 (1.24)
Pentraxin level, mean ± SD ng/ml	1.79 (5.77)	1.64 (4.25)	1.93 (6.82)
ANA Positive (n = 23), N (%)	21 (47.7)	16 (76.1)	5 (21.7)
High CRP[3] (n = 44), N (%)	2 (4.5)	1 (4.7)	1 (4.3)
High ESR[4] (n = 44), N (%)	10 (22.7)	5 (23.8)	5 (21.7)
Anti-centromere antibody positive (n = 13), N (%)	5 (11.4)	4 (19)	1 (4.3)
Anti Scl 70 positive (n = 19), N (%)	16 (36.3)	10 (22.7)	6 (13.6)

SSc, systemic sclerosis; SD, standard deviation; MPV, mean platelet volume; ANA, anti nuclear antibody; ESR, erythrocyte sedimentation rate; CRP, C reactive protein

[1]months since clinical manifestations, [2]finger to palm ratio, [3]High: > 6 , [4]High : > 30

The medications were also recorded. Prednisolone, aspirin, methotrexate (MTX), and mycophenolate mofetil were the most frequent medications used in 29 (65.9%), 21 (47.7%), 11 (25%), and 10 (22.7%) patients, respectively. Cyclophosphamide and Iloprost were prescribed for 9 (20.5%) and 9 (20.5%) patients. Six (13.6%) patients received pentoxyphilin, 4 (9.1%) received rituximab, and 4 (9.1%) received cyclosporine. Colchicine, hydroxychloroquine, and sildenafil were used in only 2 (4.5%) patients. Drug effects on data were not evaluated due to the variation of medications in patients. In addition, the relationship between the MPV and PTX3 levels and disease manifestations was evaluated. The results of the analysis are shown in Table 2.

Table 2: The relationship of MPV and PTX3 level with the disease manifestations and capillaroscopy results

Variables	MPV level		PTX3 level	
	Mean (SD)	P- value	Mean (SD)	P-value
Pulmonary involvement				
Yes	9.47 (0.77)	0.643	0.371 (0.221)	0.922
No	9.69 (1.19)		2.06(6.27)	
GI$^+$ involvement				
Yes	9.37 (0.77)	0.572	1.97 (6.11)	0.151
No	9.69 (1.19)		2.06(5.43)	
Digital tip ulceration				
Yes	9.90 (1.45)	0.349	1.83 (5.55)	0.450
No	9.55(0.981)		1.77 (5.93)	
Capillaroscopy finding: Dimension				
Normal	10.60 (0.80)	0.138	6.90 (11.60)	0.962
Abnormal	9.58 (1.13)		1.41 (5.19)	
Morphology				
Normal	9.86 (1.20)	0.287	0.794 (1.54)	0.415
Abnormal	9.49 (1.08)		2.55 (7.52)	
Distribution				
Normal	9.52(1.20)	0.749	0.328 (0.14)	0.745
Abnormal	9.68 (1.13)		2.07 (6.27)	
Avascular area				
Yes	9.96 (1.35)	0.365	1.02 (2.20)	0.658
No	9.57 (1.08)		1.99 (6.38)	
Micro hemorrhages				
Yes	9.34 (0.835)	0.146	0.652 (1.01)	0.961
No	9.85 (1.26)		2.51 (7.28)	
Scleroderma pattern				
Early or active	9.04 (2.17)	0.083	2.84 (1.24)	0.791
Late	9.57 (1.13)		2.02 (6.19)	

MPV, mean platele level; PTX3, pentraxin 3; GI, gastrointestinal

The relationship between the MPV level and skin score was insignificant (P-value = 0.747). Moreover, the relationship between this factor and the disease duration was insignificant (P-value = 0.585). In addition, the pentraxin level was not significantly related to the skin score and disease

duration was insignificant (P-value = 0.585). In addition, the PTX3 level was not significantly related to the skin score and disease duration (P-value > 0.05). The results showed no significant relationship between the MPV and PTX3 levels and capillaroscopy results (P-value > 0.05). Further, the relationship between the MPV and PTX3 level and the clinical manifestations, including pulmonary involvement, gastro-intestinal (GI) involvement, digital tip ulcer, and disease duration, was insignificant (P-value > 0.05). In the capillaroscopy evaluation, the patients were divided according to the early or active and late scleroderma pattern, and the MPV and PTX3 levels were evaluated (Table 2). The results showed no significant difference regarding the MPV and pentraxin levels between the patients with early or active scleroderma pattern and those with late (P-value > 0.05).

The relationship between the pattern of the disease (diffuse and limited) and MPV/pentraxin level was also evaluated. The two groups had no significant difference in the MPV and PTX3 levels (P-values were 0.915 and 0.505, respectively). The relationship between the ESR and MPV levels was insignificant (P-value = 0.430). There was no significant relationship between the ESR level and PTX3 (P-value = 0.982). The mean ± SD of the MPV level among patients with positive and negative CRP was 9.66 ± 1.15 fL and 9.50 ± 0.707 fL, respectively (P-value = 0.343).

The relationship between the GI problem, MPV, and PTX3 levels was insignificant (P-value > 0.05). MPV/pentraxin level and developing lung fibrosis also showed no relationship (P-value > 0.05). No significant relationship was observed between FTP and MPV/pentraxin level (P-value > 0.05).

Discussion

To the best of our knowledge, the present research is one of the few studies evaluating the relationship between the MPV and PTX3 level and the clinical and capillaroscopic results of patients with SSc. The results indicated that the mean MPV level was lower in patients with SSc than in healthy controls, but no relationship was observed between the clinical characteristics and capillaroscopy results.

These results were inconsistent with those of Yayla et al., which showed no relationship between the scleroderma patients and controls regarding the MPV level [8]. In contrast to these results, Soydinc et al. found that MPV level was significantly higher in patients with SSc [9]. In addition, the MPV level in that study was negatively related to the disease activity scores [9]. However, this study suggested that the MPV level is a predictive marker in the diagnosis of macro- and micro-vascular involvement, and patients with cardiac involvement, digital ulcers, and gangrene had higher levels of MPV than others [9].

The results showed no relationship between the MPV level and capillaroscopy results, skin score, pulmonary and GI involvement, and digital tip ulceration. The relationship between the scleroderma capillaroscopic pattern (late, active, early) and MPV level was evaluated, which was not significant. No article was found about the relationship between capillaroscopy and the MPV level. Further studies with larger sample sizes are recommended to assess the relationship between the activity of SSc and the studied factors. Yazici et al. indicated that MPV was significantly higher in patients with AS and reduced by conventional or anti-TNF therapy [25]. The present study did not assess the effect of treatment on the MPV level, but this factor should be evaluated in further studies to determine the exact impact of MPV and pentraxin in the disease process. Similar to the present research, a recent survey by Yayla et al. on patients with SSc revealed no relationship between the MPV and clinical presentation of the disease [8]. Soydinc et al. evaluated some cardiovascular complications regarding the MPV level in patients with SSc and concluded that the MPV level was significantly higher in patients with cardio-myopathy, digital ulcers, and gangrene [9]. In contrast with these results, the present study showed no significant relationship between the MPV level and clinical manifestations, including pulmonary and GI involvement, digital tip ulcer, and skin score.

In the present study, there was no significant difference in the pentraxin level between patients and controls, but in Shirai et al., the pentraxin level in SSc patients was significantly higher

compared to the controls (P < 0.001) [18].

However, the present study showed an insignificant relationship between the sclero-derma pattern and pentraxin level. Accordingly, Adrovic et al. found that pentraxin level was significantly higher in JSS and JLS (P-value < 0.001) [16]. Moreover, no relationship was found between the vascular changes in capillaroscopy and the pentraxin level, which was consistent with the results of Adrovic et al., revealing no relationship between the pentraxin level and capillaroscopy changes in JSS and JLS [16]. This result does not align with the relationship of the elevated PTX level with prominent vascular manifestations in SSc patients in Shiraei et al. [18].

The present study showed no relationship between the pentraxin level and the skin score. In contrast, Adrovic et al. found that pentraxin level was positively correlated with the modified rod skin score in JSS and JLS (P-value = 0.03) [16]. In addition, Iwata et al. showed correlations between the pentraxin level and various fibrotic aspects, such as pulmonary fibrosis, cardiac disease, and pitting scar/ulcer, in patients with SSc [17]. Further, Shiraei et al. reported the relationship between pentraxin and mRSS, which represented skin thickening in SSc similarly, but there was no relationship between the pentraxin level and lung fibrosis [18].

This study aimed to find the relationship between two factors: one as an available and cheap lab test (MPV) as an indicator for activation of the platelet and risk of arterial disease with the clinic and capillary damage of patients with SSc, but it was lower in patients with SSc. No relationship was found with their presentation. In addition, the PTX3 was checked as an inflammatory marker, and there was no relationship with the manifestation of SSc patients. The small sample size was the major limitation of the present study. Further studies are recommended to determine the exact role of MPV and pentraxin levels on vascular changes.

Conclusion

Based on the results, the MPV level was significantly lower in patients with SSc than in the controls. In contrast, the pentraxin level did not differ significantly among the patients and controls. No relationship was found between pentraxin, MPV level, and capillaroscopy changes. Moreover, there was no relationship between the clinical manifestations and MPV/pentraxin level. However, further studies with larger sample sizes should be performed while considering confounding factors and exact histopathologic pathways.

Acknowledgments

The authors thank Shiraz University of Medical Sciences, Shiraz, Iran, the Center for Development of Clinical Research of Namazee Hospital, and Dr. Nasrin Shokrpour for editorial assistance.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

Funding

This thesis was supported by the Dean of the School of Medicine based on research project number 18225 and sponsored by the Vice Chancellor of Shiraz University of Medical Sciences.

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