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Association of sVCAM1 with interleukin -6 among rheumatoid arthritis patients

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Abstract Symmetric synovitis is a histological characteristic of Rheumatoid Arthritis (RA), a systemic inflammatory connective tissue disease. An accelerated atherosclerosis process is the primary mechanism by which RA increases cardiovascular morbidity and mortality. The subject of the study consisted of two groups, the first group included 40 patients, all over the age of 18, with 35 females and 5 men participating also second group included 40 healthy controls who did not have any autoimmune disorders. The biochemical analyzer konelab prime 30ISE (bioMérieux france, craponne, france) was used to measure C-reactive protein and other parameters. The levels of inflammatory and immunological parameters, such as ESR, RF, CRP, and ACPA, were importantly higher in RA patients (52.37 ± 10.41, 44.28 ± 14.75, 57.00 ± 17.67, and 45.17 ± 12.3), respectively ($p< 0.001$). IL-10 pg/ml, IL-6 pg/ml, TNF-α pg/ml, and sVCAM ng/ml in RA patients (21.70 ± 3.08,54.42 ± 5.36,40.69 ± 7.26 and 7.12 ± 0.81) respectively ($p< 0.001$). The Logistic regression model shows that immunological parameters such as sVCAM correlate directly with IL-10 among RA patients. This result might refer to the fact that the RA condition enhances the production of sVCAM about IL-10. Also, it showed that the sVCAM directly correlates with IL-6 among RA patients. RA patients showed an association of sVCAM-1 directly correlated with IL-6. This result might refer to the fact that the RA condition enhances the production of sVCAM about IL-6.

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Keywords: *Rheumatoid Arthritis; Cardiovascular Morbidity; Inflammatory Parameters; sVCAM; IL-6*

1. INTRODUCTION

It is a chronic inflammatory condition caused by autoimmune responses, leading to local and systemic bone damage, as well as joint deformities and decreased function called rheumatoid arthritis (RA). Anti-inflammatory medications help reduce inflammation, but patients often continue to experience sleep disturbances due to persistent bouts of pain. This suggests that non-inflammatory elements may also re-establish a role in the pathogenesis of pain in RA (1).

an inflaammatory autoiimmune diseasse affecting referring 1% of the global population, with a female-male ratio of 3:1. RA preferably act on the joints, resulting in mutual swelling and deformities, observed by ankyloses (2).

The endothelium plays a crucial role as an endocrine organ responsible for maintaining the body's overall balance, encompassing technical epithelial cells that line the vascular procedure, the heart and lymphatic vessels . Its roles include regulating the contraction of vascular smooth muscles and cardiomyocytes, managing the coagulation and rheological effects of blood, facilitating adhesion, and controlling vascular wall permeability. In normal situations, the endothelium orchestrates communication between blood and tissues through various signaling molecules. Consequently, endothelial dysfunction disrupts this homeostatic tool, leading to the development of pathologies (3).

The research also indicated the involvement of endothelial cells in rheumatoid arthritis (RA) by assessing the number of abnormal endothelial cells, which exhibit visible morphological changes under a microscope. Additionally, there were notice changes in the levels of vascular endothelial adhesion moleecule type 1 (sVCAM-1) and endothelins, suggesting their modulation in the context of RA (4). TNF-α is known to increase the interaction in the middele of circulating leukocytes and endothelial cells (ECs) by upregulating the production of endothelial adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1) (5,6 and 7). IL-6 is also implicated in early RA-related vascular dysfunction, with elevated levels of sVCAM-1 correlating with the advancement of subclinical atherosclerosis. The inflammatory processes initiated by RA onset in individuals susceptible to cardiovascular disease (CVD) may accelerate the progression of atherosclerosis (8, 9, and 10).

2. MATERIAL - METHODS

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For this study, researchers used two sets of criteria: one set derive from the 1987 ACR basis and another set based on the 2010 ACR/EULAR basis; forty sick person (35 females with 5 males) over the age of 18 were involved in the research. The control collection involves of forty healthy persons. Here are the criteria that were used to exclude: a history of biological treatment, being pregnant or nursing, having another autoimmune disease, having an infection either recently or within the past few months, high blood pressure, thyroid disorders, heart disease, diabetes, liver or renal failure, cancer, smoking, and alcohol use. Using the DAS28-erythrocyte sedimentation rate (DAS28-ESR), the RA activity was assessed at baseline. Excluded from the trial were patients who did not show any improvement after receiving the medication. The biochemical analyzer konelab Prime 30ISE (bioMérieux Fraance, Craponne, Fraance) was used to measure immunoglobulin M, rheumatoid factor, and C-reactive protein. A German company called Euroimmun developed an enzyme-linked immunosorbent assay (ELISA) that could identify the anti-CCP antibodies. Furthermore, the Westergren method (Seediplus® S2000, Saarstedt, Geermany) was used to determine ESR, which is typical for women to be between 3 and 12 mm/h. . A quantitative sandwich enzyme-linked immunosorbent check (ELISA) was used to assess the serum levels of IL-10, IL-6, vascular cell adhesion molecule-1 (VCAM-1), and TNF-

3. RESULTS AND DISCUSSION

Table (1) shows the demographic characteristics of sick persons with rheumatoid arthritis and healthy control subjects; 40 rheumatoid arthritis patients and forty healthy control participants were involved in the current study, which shows there is no difference of statistical significance between the average ages of the two groups (p >0.05)

Table (1): *Demographic characteristics of patients with rheumatoid arthritis and healthy control subjects*

Characteristic	Patients *n* = 40	Healthy control *n* = 40	*P*
Sex female	35 (87.5%)	31 (77.5%)	0.239
Age (years)	38.75 ± 7.92	36.47 ± 6.41	0.300
Duration of disease			
< 5 years, *n* (%)	18 (45.0 %)		
5-9 years, *n* (%)	13 (32.5%)		
≥ 10 years, *n* (%)	9 (22.5%)		
Number of painful and swollen joints			
Negative, *n* (%)	6 (15.0%)		
1-5 joints, *n* (%)	11 (27.5%)		
6-9 joints, *n* (%)	15 (37.5%)		
≥ 10 joints, *n* (%)	8 (20.0%)		
Morning stiffness duration			
Negative, *n* (%)	15 (37.5%)		
< 30 min, *n* (%)	11 (27.5%)		
≥ 30 min, *n* (%)	14 (35.0%)		

n: number of cases; SD: standard deviation; †: independent samples t-test; ¥: Chi-square test; NS: not significant at P > 0.05.

table (2) shows the mean level of immunological parameters of rheumatoid arthritis used in the diagnosis of rheumatoid arthritis (ESR mm/hr, CRP mg/dl, RF U/ml, and ACPA EU/ml), which show increased levels of the inflammatory parameters (52.37 ± 10.41, 44.28 ± 14.75, 57.00 ± 17.67, and 45.17 ± 12.3) respectively (p value <0.001). Also, increased levels of (IL-10 pg/ml, IL-6 pg/ml, TNF-α pg/ml, and sVCAM ng/ml) (21.70 ± 3.08, 54.42 ± 5.36, 40.69 ± 7.26, and 7.12 ± 0.81) (p value <0.001).

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Table (2): *Mean levels of inflammatory and immunological parameters in patients with rheumatoid arthritis and healthy control subject*

Characteristic	Patients *n* = 40	Healthy control *n* = 40	*P*
ESR mm/hr	52.37 ± 10.41	9.95 ± 4.18	< 0.001
CRP mg/dl	44.28 ± 14.75	1.69 ± 0.88	< 0.001
RF U/ml	57.00 ± 17.67	5.28 ± 1.61	< 0.001
ACPA EU/ml	45.17 ± 12.3	3.38 ± 1.23	< 0.001
IL-10 pg/ml	21.70 ± 3.08	11.43 ± 2.22	< 0.001
IL-6 pg/ml	54.42 ± 5.36	8.95 ± 3.84	< 0.001
TNF-α pg/ml	40.69 ± 7.26	11.34 ± 1.86	< 0.001
scam ng/ml	7.12 ± 0.81	1.60 ± 0.20	< 0.001

n*: number of cases;* ***SD****: standard deviation; †: independent samples t-test; NS: not significant at P value > 0.05.*

Table (3): *Correlation between immunological and inflammatory parameters.*

Characteristic	IL-10 level		IL-6 level		TNF-α level		scam level	
	R	P	R	P	R	P	R	P
ESR	0.182	0.262	0.085	0.602	0.174	0.283	0.150	0.356
CRP	0.028	0.865	0.146	0.368	0.005	0.977	0.045	0.782
RF	0.135	0.630	0.172	0.288	0.199	0.218	0.153	0.347
ACPA	0.200	0.216	0.141	0.387	0.277	0.166	0.199	0.217

r: correlation coefficient.

Table (3-5): Roc curve of immunological parameters

Characteristic	***IL-10 level***	***IL-6 level***	***TNF-α level***	***sVCAM level***
Cutoff value	> 15.85	> 30.5	> 20.45	> 2.16
P value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Sensitivity %	100.0 %	100.0 %	100.0 %	82.5 %
Specificity %	100.0%	100.0%	100.0%	80.0%
PPV %	100.0 %	100.0 %	100.0 %	80.5 %
NPV %	100.0%	100.0%	100.0%	82.1%
AUC (95% CI)	1.00 (1.00- 1.00)	1.00 (1.00- 1.00)	1.00 (1.00- 1.00)	0.808 (0.71- 0.91)

CI: Confidence interval, AUC: Area under curve.

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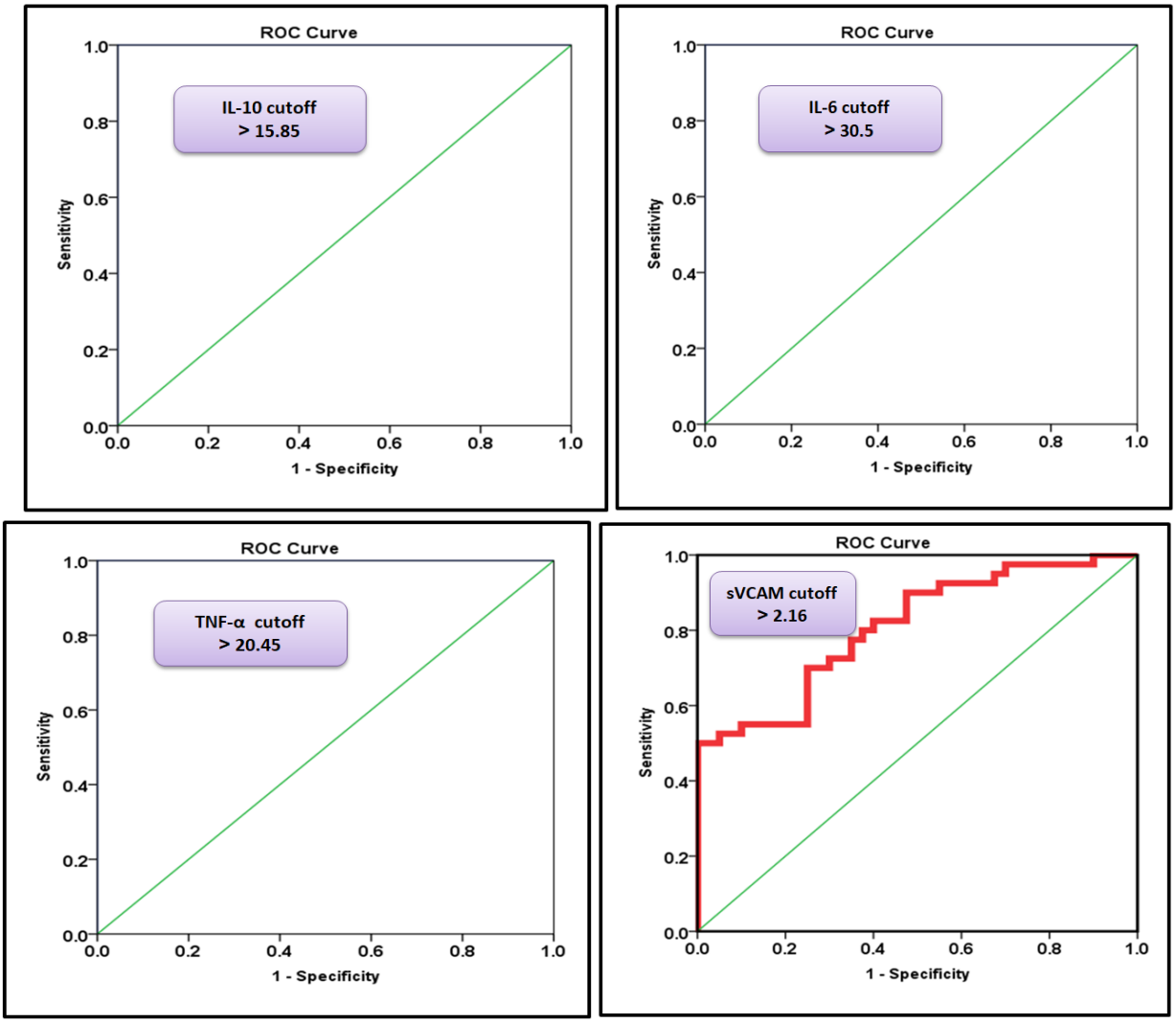

FIGURE (1): *Analyzing receiver operator characteristic (ROC) curves of immunological parameters aims to derive a potential diagnostic cutoff value.*

Logistic regression correlations between different parameters.

The Logistic regression model shows the correlation of immunological parameters such as sVCAM, which have directly correlated with IL-10 among RA patients, as in figure (1); this result might refer to that RA condition enhances the production of sVCAM about IL-10. Also, it shows that the sVCAM directly correlates with IL-6 among RA patients, as in figure (2); this result indicates that RA condition enhances the production of sVCAM about IL-6.

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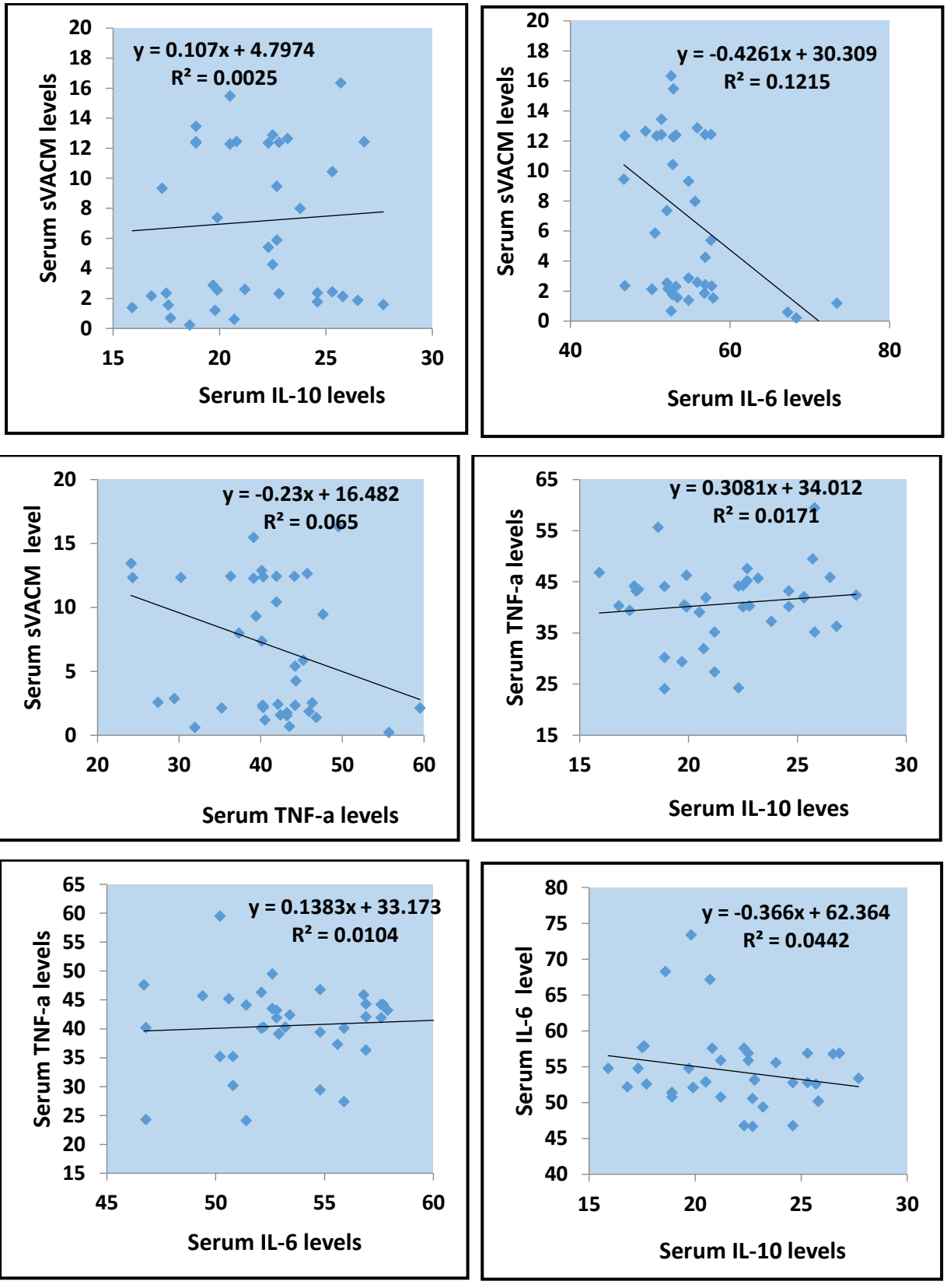

Figure (2): *Logistic regression correlations between different parameters.*

RA now recognized as an autonomous cardiovascular risk factor, elevating the likelihood of atherosclerotic cardiovascular disease (CVD) by approximately 50%, even among individuals with subclinical or initial-stage RA (11,12). Notably, Vascularr Cell Adhesion Molecule-1 (sVCAM-1) exhibits a prognostic significance surpassing that of other biological mediators (13,14). Studies have shown that individuals with rheumatoid arthritis (RA) exhibit notably

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higher levels of VCAM-1 compared to healthy individuals (15,16). Consequently, these molecules could play a key role as mediators in the growing of atherosclerotic lesions among rheumatic patients.

This research reveals that individuals with rheumatoid arthritis (RA) have elevated levels of sVCAM compared to those without autoimmune conditions, and the concentration of sVCAM in peripheral blood correlates with immunological markers such as RF. It's well established that sVCAM-1 plays important role in the growth of atherosclerotic plaques, contributing to their pathogenesis (17). In the study conducted by JF. Varona et al., it was found that sVCAM-1 levels were strongly linked to early atherosclerotic disease among patients categorized as having low to intermediate cardiovascular risk (18). sVCAM-1 is implicated in the progression of atherosclerosis through various mechanisms, although the predominant mechanism remains incompletely understood. One perspective suggests that these soluble adhesion molecules bind to receptors on circulating leukocytes before they interact with the vessel wall, potentially exerting an anti-adhesive effect that could mitigate the immune-inflammatory response (19).

Enhanced concentrations of soluble adhesion molecules for cells (sVCAM-1) indicate endothelial dysfunction that facilitates proinflammatory and prothrombotic conditions(20). scam-1 concentration was elevated in RA IL-6 involve in carrdiovascular disease (CVD) in the general public , but It is role in CVD in RA is unspecified. Trans-signaling is pro-in signaling trans-signaling of IL-6 signaling, whereas classical s-signaling is linked with inflammation resolution. (21)

interleukin-6 (IL-6) is a vital inflammatorry cytokines in the pathogenesiis of rheumatoid arthritis (RA), a disease also linked with endothelial perrturbation and increased serum amount of adhesion moleculess like Vcam-1 (22)

In conclusion, RA patients showed an association of sVCAM-1 directly correlated with IL-6 among RA patients. This result might be referring to the fact that the RA condition enhances the production of sVCAM about IL-6. In RA, endothelial activation (as Svcam-1) correlates with markers of inflammation

Author contributions

Shahad F. Obeid: Collecting data and determine the methodology's

Wasnaa Jomaa Mohammed: check the results

Noor Alhuda Kh Ibrahim: Determine the problem statement and results analysis

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