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Association of soluble triggering receptor expressed on myeloid cells-1 with rheumatoid arthritis in iraqi patients: A case-control study

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ABSTRACT

Rheumatoid arthritis (RA) is a common chronic immune-mediated inflammatory arthritis, impacting 0.5-1% of the global population, and leading to progressive deterioration of the musculoskeletal and joint systems. This study aims to analyze the serum levels of soluble triggering receptors expressed on myeloid cells-1 (sTREM-1) in Iraqi patients with RA and healthy individuals. It also intends to assess the diagnostic significance of these receptors, investigate their association with disease activity and examine their correlation with the sociodemographic and clinical characteristics of the patients. From December 2020 to June 2021, 117 RA patients with a mean age of 50 years participated in the study. The patients were categorized into inactive and active disease groups based on their DAS28 score and CDAI, as determined by a Rheumatologist. The serum levels of a specific triggering receptor expressed on myeloid cells-1 (TREM-1) (Pg/mL) were measured. The results showed that the active RA patients had significantly higher levels of the receptor (270.17±187) compared to both the inactive RA patients (112.81±37.48) and the healthy controls (43.89±29.53) ($P < 0.001$). The sTREM-1 demonstrated a high discriminatory ability (AUC ≥ 0.936) between RA and control groups. Moreover, a direct association was observed between the DAS-28ESR and sTREM-1 levels.

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Introduction

Rheumatoid arthritis (RA), which is the most common form of inflammatory arthritis, impacts approximately 0.5 to 1% of the worldwide population (1). The degradation of joints and musculoskeletal systems is mostly caused by chronic immune-mediated inflammatory diseases, including RA (2,3). TREM-1, a member of the immunoglobulin superfamily, is expressed as a transmembrane receptor on myeloid cells-1 (4). One extracellular V-type immunoglobulin-like domain, a transmembrane domain, and a brief cytoplasmic tail are among the structural features of TREM-1 (5). The transmembrane domain of TREM-1 contains negatively charged residues that interact with the positively charged residues of DNAX Activating Protein of 12 kDa (DAP12). DAP12 is a member of type I transmembrane adaptor proteins and contains an immunoreceptor tyrosine-based activation motif (ITAM) (6). The cell surface receptor known as TREM-1, which is primarily found on monocytes and neutrophils as well as endothelial cells, white blood cells (WBC), smooth muscle cells, and platelets, is crucial for amplifying the immune response in cases of bacterial infection and sterile inflammation (7,8). TREM-1 heightens the inflammatory response in both acute and long-lasting inflammatory conditions. Numerous proinflammatory cytokines, including TNF-a, IL-8, monocyte chemoattractant protein 1, interleukin-1, and others are released as a result (9). TREM-1 is broken down by proteolytic cleavage, and the main fragment, known as sTREM-1, is released into the circulation. This specific subtype of TREM-1 can be discharged into the bloodstream or other bodily fluids after an illness (10). The natural ligand of TREM-1 works as a decoy receptor for the soluble version of TREM-1, which lessens TREM-1 activation (11). As a result, sTREM-1 competes with TREM-1's ligands, which reduces the proinflammatory cascade brought on by this interaction. TREM-1 is more often produced in the synovial tissues of RA patients, and pharmacologically suppressing this protein lessens the severity of the pathological lesions caused by collagen-induced arthritis (12). Only a few research have suggested that the blood level of sTREM-1 may be able to predict the presence of RA. The association between the amount of sTREM-1 in the blood and the subsequent response to therapy hasn't been studied before, and these investigations only included a limited number of people (13–15). TREM-1, a recently identified cell surface receptor connected to DAP-12, is mostly expressed in monocytes and neutrophils. Its function entails boosting the inflammatory reactions caused by TLR-4 (16). Targeting TREM-1 with -TREM-1 therapy may be a viable therapeutic strategy for inflammatory bowel disease, according to the interaction between TREM-1 and DAP12, an adaptor molecule with an immunoreceptor tyrosine-based activation motif (ITAM) (17). As a potential biomarker for targeted therapy as well as the quick and early diagnosis of infectious illnesses, the measurement of sTREM-1 shows promise (18,19). Many peptides have shown positive results in reducing damaging immunolo-

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gical reactions. Additionally, TREM-1 signaling has been shown to be affected by well-known anti-inflammatory drugs such as corticosteroids and antibiotics. As a result, it is worthwhile to examine this receptor as a therapy target because of its therapeutic potential (20). TREM-1's presence on alveolar macrophages suggests that it may have a role in the inflammatory reactions of the lungs to infections. Additionally, the presence of sTREM-1 in the blood has a bearing on a patient's prognosis for lung cancer (21). sTREM-1 holds promising potential as a valuable biomarker for predicting non-viral acute pneumonia (NVAP) in the Department of Pediatrics (22). Enhanced activity of the TREM-1 pathway is observed in individuals experiencing cardiogenic shock, serving as an early indicator of organ damage and offering valuable prognostic insights into the patient's clinical trajectory (23). According to research, sTREM-1 amounts in the blood and TREM-1 expression on immune cells were higher in sepsis patients. These results point to an increased mortality risk (24)

The goal of this research is to assess the sTREM-1 levels in Iraqi RA patients and contrast them with healthy controls. Additionally, the study seeks to assess the relationship between sTREM-1 basal serum levels and disease activity in RA patients and to examine any possible relationships between these levels and the sociodemographic and clinical aspects of the illness.

Materials and Methods

This case-control study was carried out at Baghdad Teaching Hospital / Medical City and Biochemistry Department, College of Medicine, University of Baghdad, Baghdad, Iraq. Patients studied were admitted from December 2020 to March 2022. The current study is part of a larger investigation that included 117 Iraqis who were identified as having RA using the updated 2010 classification criteria for RA established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) (25). Our center serves many governorates' worth of varied populations in Iraq, including those in rural, urban, and inner-city areas. Under the direction of experts, every patient underwent a diagnosis and therapy. Participants ranged in age from 30 to 80 years old. The patients were separated into two groups in accordance with the EULAR outcome criteria, which evaluates the clinical response using the Disease Activity Score 28 (DAS28) (26). Group 1: RA patient with active disease group includes 62 samples, Group 2: RA patients with inactive disease group includes 55 samples and healthy served as a control group who will undergo routine physical examinations with no underlying RA, diabetes mellitus, autoimmune diseases, pregnancy, OA, and other complications includes 58 samples.

Inclusion criteria were as follows: having confirmed RA according to revised 2010 ACR/EULAR RA classification criteria, ages ≥30 years, disease duration >2 years, Remission-to-high Disease Activity Score in 28 joints (DAS28), erythrocyte sedimentation rate (ESR) and Present results recorded of renal function tests, urea and creatinine, and the liver function tests, GOT and GPT were found to be within the normal range. Recent joint surgery within the previous six months, osteoarthritis, lupus, spondyloarthropathies (like ankylosing spondylitis, psoriatic arthritis, or Sjogren's syndrome), gout, scleroderma, infectious arthritis, or polymyalgia rheumatica were all exclusion criteria for the study. Children and teenagers were also not included in the study. Patients having a history of renal, hepatic, cardiac, or infectious diseases as well as those who were pregnant or who had concurrent renal, hepatic, or cardiac disorders were also disqualified. Each patient gave their written informed permission before taking part. The Scientific and Ethical Committee of the College of Medicine at the University of Baghdad and the Rheumatology Medical Department at the Baghdad Teaching Hospital gave their approval to the study procedure (Protocol No. 819, Date: 25/10/2020). The Declaration of Helsinki's guiding principles were followed during the study's execution.

Data collection

Interviews with the patients allowed us to gather details about their demographics, such as age, weight, disease duration, and recent laboratory results like the erythrocyte sedimentation rate (ESR), WBC count, number of swelling and pain in the joints, and patient-reported Visual Analog Scale (VAS) scores. A specifically designed patient information chart was used to systematically collect and record this data for the purpose of this study.

Gathering and preparing samples

Peripheral venous blood samples were collected from both the patients and control subjects by puncturing the forearm vein. Approximately eight to ten milliliters of blood were aspirated from each participant and divided into two separate parts for further analysis. First, 6-8 ml of the sample were transferred into a plain tube, where they were allowed to clot for 30 minutes. After that, the serum was separated by centrifugation at 2500 rpm for 10 minutes, and it was kept at 20°C until the time of the measurements of the targeted biochemical parameters.

The second portion (2.5 ml) was put into a citrate-containing tube and forwarded to the Baghdad Teaching Hospital Laboratory for hematological and ESR tests. According to the manufacturer's recommendations, the given kit (Instruction manual, Jordan, Cat.No. RDEEH3832) was used to assess the serum sTREM-1 concentrations using the enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

The program IBM SPSS for Windows version 26.0 (IBM Corp., Armonk, NY, USA) was used to do the statistical analysis. Data were presented as the mean ± standard deviation (SD). Statistical differences among groups were carried out by one-way analysis of variance (ANOVA). Using an independent sample t-test, the differences among the two groups were examined. Pearson’s correlation was used to evaluate how the different biomarkers were related to each other, Finally, the sensitivity, specificity, area under the curve, cut of value and accuracy utility was explored with Receiver Operating Characteristic (ROC) curve analysis. P-values less than 0.05 were used to evaluate statistical significance.

Results

Demographic and anthropometric data of the study groups are presented in Table 1.

Disease activity score and used medications of RA patients

Table 2 highlights the result of tender joints count (TJC), swelling joints count (SJC), Patient global assessment, Evaluator global assessment DAS28, CDAI, ESR, and WBC C between RA patients indicating a highly significant difference. Among the 117 RA patients, 43 patients were treated with conventional DMARDs (25 inactive RA groups and 18 active RA groups), 41 with biological DMARDs (20 inactive RA and 21 active RA) and with combination DMARDs (11 inactive RA and 23 active RA), this was statistically significant (P=0.077).

Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)

The findings of this investigation showed that there was a substantial link between study groups in the mean blood levels of the sTREM-1 (Table 3 and Figure 1).

Additionally, as shown in Table 4, substantial variations in sTREM-1 concentrations were seen among RA patients.

The diagnostic criteria of the receiver operator curve of sTREM-1 between studied cases

The results presented in Table 5 demonstrate that sTREM-1 exhibited excellent discriminatory ability between individuals with RA and the control group, as evidenced by an Area Under the Curve (AUC) value of ≥0.936. This is further illustrated in Figure 2.

Table 6 shows the validity parameter sTREM-1 of studied cases which show a specificity of 98.3% and sensitivity of 91.5 % and show that serum TREM-1 level at cutoff value 87.5pg/ml

The correlation coefficient between characteristic features, clinical features, and Lab with sTREM-1 of patients with RA

Table 7 and Figures 3-9 display the correlations between various characteristic features, clinical features, and labo-

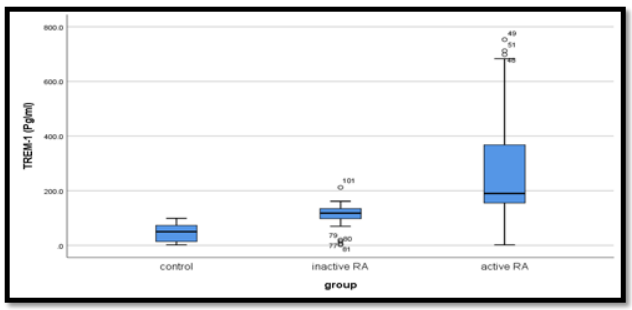

Figure 1. Box plot of sTREM-1 of studied cases.

Table 1. Demographic and anthropometric characteristics of the study groups.

characteristics	control Groups N=58	Inactive RA disease Groups N=55	active RA disease Groups N=62	P value
Age(years)	51.52± 11.31	51.12±11.42	50.20±10.69	0.279
BMI (Kg/m²)	26.55±4.751	27.25±4.831	28.97±4.680	0.017
		Sex, no. (%)		
Female	40 (43.09%)	41 (40.86%)	49 (46.06%)	0.450
male	18 (14.91%)	14 (14.14%)	13 (15.94%)	
female to male ratio	20: 9	82: 28	98: 26	
		Smoking number (%)		
Non-smoker	31 (37.78%)	44 (35.83%)	39 (40.39%)	0.008
Passive smoker	24 (15.58%)	6 (14.77%)	17 (16.65%)	
Smoker	3 (4.64%)	5 (4.40%)	6 (4.96%)	

Table 2. Clinical and laboratory features of RA patients.

parameter	Inactive RA disease Groups N=55	active RA disease Groups N=62	P value
Disease duration (years)	7.51±4.807	8.95±5.871	0.152
Number of tender joints	1±0.816	5.74±3.24	0.000
Number of swollen joints	0.22±0.44	2.57±2.10	0.000
Patient global assessment	1.857±1.864	5.34±1.98	0.000
Evaluator global assessment	3±3.696	4.62±2.36	0.000
CDAI	3.974± 0.462	16.622± 10.116	0.000
DAS-28ESR	2.145± 0.183	4.270±1.166	0.000
	Medications		
Using conventional DMARDs (Methotrexate)	25 (20.41)	18 (22.59	
Using biological DMARDs (etanercept)	20 (19.46)	21 (21.54)	0.077
Using combination DMARDs	11 (16.14)	23 (17.86)	
ESR (mm\hr)	12.27±5.704	32.34±26.983	0.001
WBC 10^9\L	7.32±1.84	8.33±2.04	0.006

Table 3. Comparing study groups' sTREM-1 levels.

Parameter	Control Groups N=58	Inactive RA disease Groups N=55	Active RA disease Groups N=62	P-value
sTREM-1 (Pg\ml)	43.89±29.53	112.81±37.48	270.17±187	0.001

Table 4. Comparison of sTREM-1 of RA patients.

Parameter	Inactive RA disease Groups N=55	active RA disease Groups N=62	P-value
TREM-1 (Pg\ml)	112.81±37.48	270.17±187	0.001

Table 5. ROC curve for sTREM-1 of studied cases.

Variable	AUC	95% CI AUC	P-value
TREM-1(Pg\ml)	0.936	0.896- 0.975	0.001

Table 6. Validity parameters for sTREM-1 of studied cases.

Variable	Cut point	Sensitivity	Specificity	Accuracy	PPV	NPV
TREM-1(Pg\ml)	87.500	91.5 %	98.3%	93.71%	99.07%	85.1%

Where PPV- positive predictive value; NPV- negative predictive value

Table 7. Correlation between characteristic features, clinical features, and Lab with sTREM-1 of patients with RA.

Variables	sTREM-1	
	β	P value
Age(years)	-0.076	0.415
Sex	-0.090	0.386
BMI (kg\m²)	0.148	0.110
Disease duration (years)	0.133	0.154
Number of tender joints	0.225*	0.045
Number of swollen joints	0.224	0.054
Patient Global assessment	0.361**	0.002
Evaluator global assessment	0.457**	0.002
CDAI	0.366**	0.001
DAS-28 ESR	0.430**	0.001
ESR (mm\hr)	0.303**	0.001
WBC 10^9\L	0.233*	0.012

β- correlation coefficient; P<0.05 was considered significant.

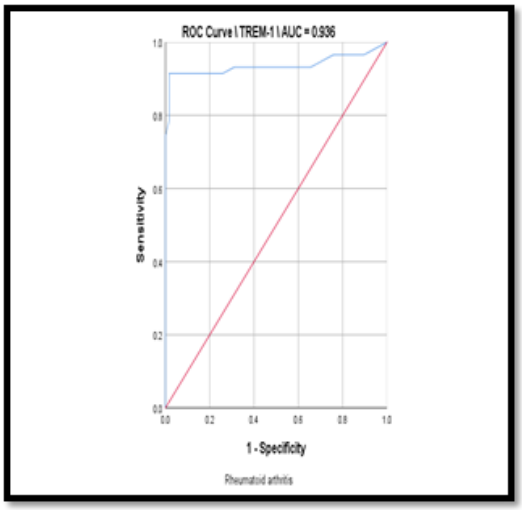

Figure 2. The receiver operator curve (ROC) for sTREM-1 of studied cases shows the cut-off, Sensitivity, Specificity and Area under the curve.

ratory parameters with sTREM-1. In RA patients there was a significant positive correlation between sTREM-1 with the number of tender joints, Patient Global Assessment, Evaluator global assessment, CDAI, DAS-28 ESR, ESR, and WBC.

Discussion

As indicated in Table 1, those with active RA had a mean level of sTREM-1 that was considerably greater ($p < 0.001$) than both inactive RA patients and healthy controls.

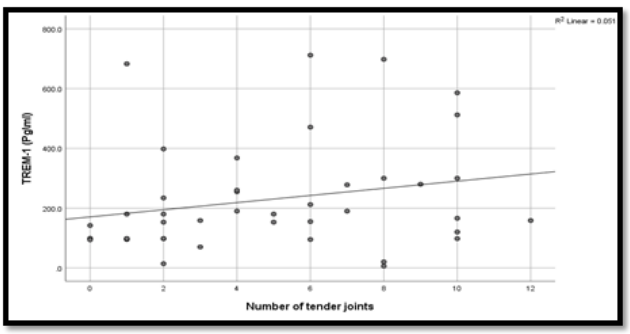

Figure 3. Histogram of the relationship between sTREM-1 with the number of tender joints in RA patients.

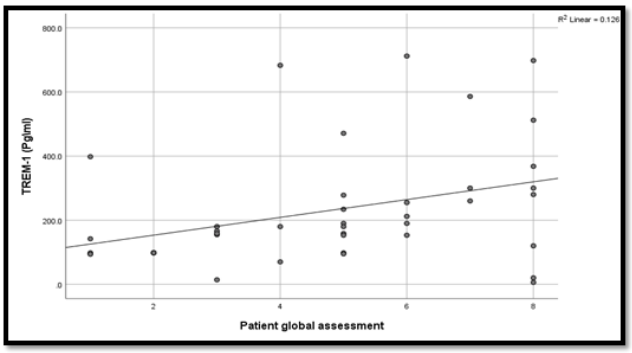

Figure 4. Histogram of the relationship between sTREM-1 with Patient Global assessment in RA patients.

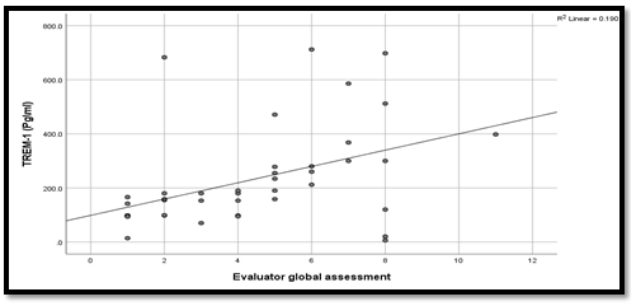

Figure 5. Histogram of the relationship between sTREM-1 with Evaluator global assessment in RA patients.

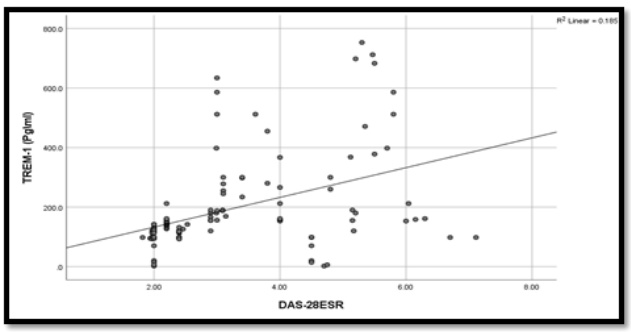

Figure 6. Histogram of the relationship between sTREM-1 with DAS-28 ESR in RA patients.

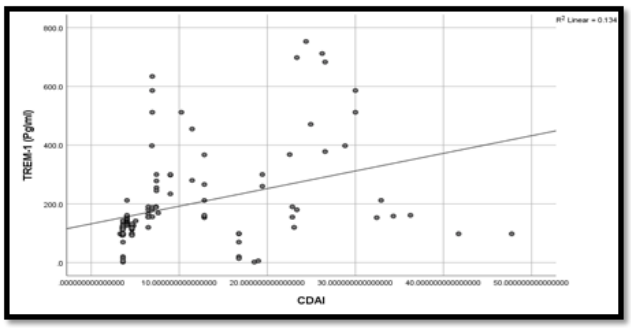

Figure 7. Histogram of the relationship between sTREM-1 with CDAI in RA patients.

These results are consistent with a prior investigation, which showed that TREM-1 had a significant discriminating ability in separating RA patients from controls ((p < 0.0001) AUC of 0.936 (95% CI 0.896- 0.975)). At an optimal cutoff of ≥ 87.500 Pg\ml, the ROC curve yielded a sensitivity of 91.5 %, and a specificity of 98.3%, (Tables 5 and 6) (Figure 2) may be a valuable tool for the diagnosis of RA. The primary segment of TREM-1 is released into the bloodstream as sTREM-1 following proteolytic cleavage. TREM-1 subtype (sTREM-1) can be secreted into the blood or body fluids when an infection is present (10). This soluble form acts as a decoy receptor for the natural TREM-1 ligand and dampens the activation of TREM-1. As a result, the cascade of proinflammatory processes linked to this binding process is diminished because sTREM-1 competes with the ligands of TREM-1 (11). The toll-like receptor-induced inflammatory response is potently stimulated by the TREM-1. It is essential for boosting the immune response when there is inflammation (8,18). The correlation between demographic factors, anthropometric traits, clinical features, and biochemical markers with sTREM-1 in patients with RA was shown in the current study in Table 7 and Figures 3-8. There was a direct significant correlation with the development of arthritis; the number of tender joints, Patient Global Assessment, Evaluator global assessment, CDAI, DAS28 ESR, also the possibility of linking the TREM-1 with non-specific measures of inflammation, such as ESR. The result of the present study found that sTREM-1 is associated significantly with disease activity, both clinically and in the laboratory. Additionally, the present study observed higher levels of sTREM-1 in patients with active disease (DAS28 ESR ≥ 2.6) compared to those with inactive disease (DAS28 ESR < 2.6), as demonstrated in Table 4. This finding implies that sTREM-1 might serve as an indicator of systemic inflammation. Moreover, the results suggest that sTREM-1 can potentially be utilized as a diagnostic tool for identifying RA patients with a worse prognosis (15). Revealed that serum levels of sTREM-1 in patients with RA were significantly increased compared with the control group. A recent study suggests that TREM-1 is an inflammatory protein. TNF-a, IL-8, granulocyte-macrophage colony-stimulating factor, monocyte chemotactic protein 1, and

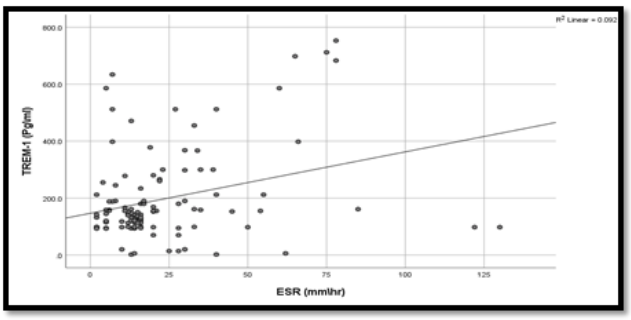

Figure 8. Histogram of the relationship between sTREM-1 with ESR in RA patients.

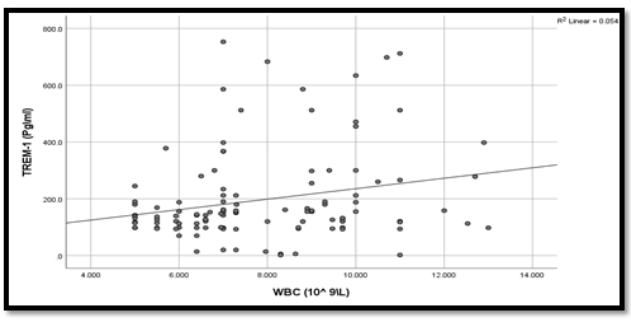

Figure 9. Histogram of the relationship between sTREM-1 with WBC in RA patients.

myeloperoxidase are just a few of the molecules that can be released from activated myeloid cells as a result of TREM-1 engagement alone, which can also cause other molecules to be released that can increase the inflammatory response (9). TREM-1 which has been demonstrated to be related to autoimmune disorders with exaggerated inflammation (e.g., RA, SLE, IBD, etc.) (27). Studies have looked at the usage of molecules that can prevent TREM-1 from acting as possible anti-inflammatory agents. According to recent studies, sTREM-1 acts as a decoy receptor, blocking the interaction of its ligand with membrane-bound TREM-1 and the downstream consequences of TREM-1 activation. These results support the notion that sTREM-1 represents a unique therapeutic target for the treatment of RA (28). Recent studies found that RA patients have higher levels of sTREM-1 than controls. These elevated sTREM-1 levels were shown to have a substantial correlation with a variety of clinical and laboratory markers of disease activity. However, the relationship between sTREM-1 and radiological damage or functional capacity has not been specifically addressed or examined in these research (29). sTREM-1 in RA patients there was significant correlated with WBC (Table 7 and Figure 9) Since there were connections between the levels of sTREM-1 and WBC in the present study, plasmasTREM-1 may be secreted by macrophages, monocytes, or neutrophils in patients with RA.

Acknowledgments
None

Interest conflict
The authors affirm that there are no conflicts of interest to disclose.

Author's contribution
The authors were equally involved in all aspects of the study, including conceptualization, data collection, analysis, manuscript preparation, and revision.

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