

Levels of Plasma-soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) Are Correlated with Disease Activity in Rheumatoid Arthritis

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ABSTRACT. Objective. To determine whether levels of plasma-soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) are elevated in patients with rheumatoid arthritis (RA) and whether levels are correlated with disease activity and other variables.

Methods. Our study included 71 patients with RA and 50 age- and sex-matched healthy controls. Clinical characteristics and laboratory measures, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and 28-joint Disease Activity Score (DAS28) were assessed. Plasma levels of sTREM-1 and tumor necrosis factor- α (TNF- α) were measured by ELISA.

Results. Patients with RA had significantly higher plasma sTREM-1 levels than healthy controls (170.10 ± 84.71 pg/ml vs 97.41 ± 40.64 pg/ml; $p < 0.001$). In patients with RA, plasma sTREM-1 levels were found to be correlated with DAS28, ESR, CRP, white blood cell counts, neutrophil counts, and plasma TNF- α levels ($r = 0.329$, $p = 0.005$; $r = 0.241$, $p = 0.043$; $r = 0.314$, $p < 0.001$; $r = 0.261$, $p = 0.028$; $r = 0.278$, $p = 0.019$; and $r = 0.313$, $p = 0.009$, respectively). Plasma sTREM-1 levels in patients with active disease status (DAS28 > 3.2) were significantly higher than in those with low disease status (DAS28 ≤ 3.2 ; 208.89 ± 100.14 pg/ml vs 150.29 ± 68.70 pg/ml; $p = 0.005$).

Conclusion. Patients with RA had higher plasma sTREM-1 levels than healthy controls, and plasma sTREM-1 levels were correlated with disease activity measures, suggesting that plasma sTREM-1 could play a role in the inflammatory process associated with TNF- α , and that it may be a useful disease activity marker in RA. (J Rheumatol First Release March 15 2012; doi:10.3899/jrheum.111218)

Key Indexing Terms:

TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS-1
RHEUMATOID ARTHRITIS DISEASE ACTIVITY

Rheumatoid arthritis (RA) is an autoimmune inflammatory arthritis characterized by synovial hyperplasia that leads to joint damage. RA is a systemic inflammatory disease, and its clinical manifestations are not limited to arthritis, but also include various systemic problems. Numerous inflammato-

ry cells, such as macrophages, monocytes, T cells, B cells, and neutrophils, are involved in the inflammatory process of RA¹, and various cytokines and chemokines are known to play important roles in the pathogenesis of the disease, although much remains to be determined. Identification of cytokines and chemokines associated with RA may reveal insights on pathogenesis, and they could be used as markers of RA or to monitor treatment response. Further, some of these molecular entities could be useful markers of disease activity.

Triggering receptor expressed on myeloid cells-1 (TREM-1) is a recently described member of the immunoglobulin superfamily, and is expressed on neutrophils, monocytes, and macrophages^{2,3,4}. TREM-1 has been identified as a transmembrane receptor, and the membranous domain of TREM-1 binds to DAP12, an immunoreceptor tyrosine-based activation motif-containing adaptor molecule^{3,5}. TREM-1 serves as a critical amplifier of inflammatory signaling^{2,3,4,5,6}, and is upregulated by various stimuli such as proinflammatory cytokines and microbial Toll-like receptor (TLR) ligands^{3,5,7}. Then it triggers the

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Supported by a Kwandong University College of Medicine, Myongji Hospital Research Grant.

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Accepted for publication December 28, 2011.

secretion of inflammatory mediators such as tumor necrosis factor- α (TNF- α), interleukin 8, granulocyte macrophage colony-stimulating factor, monocyte chemotactic protein 1, and myeloperoxidase^{2,3,4,5,6}. This inflammatory process synergizes with receptors for pathogen-associated molecular patterns, such as the TLR and NOD-like receptors^{2,3,4,8}. TREM-1 expression is elevated in various diseases, including infections and acute and chronic noninfectious inflammatory disorders, such as inflammatory bowel disease and ankylosing spondylitis^{9,10}. More specifically, TREM-1 is upregulated in RA synovium, and its activation induces many proinflammatory cytokines in patients with RA^{11,12}.

In addition to its membrane-bound form, a soluble form of TREM-1 (sTREM-1) has been detected in the blood of patients with sepsis, pneumonia, acute pancreatitis, and peptic ulcer disease^{13,14,15,16}. sTREM-1 is cleaved from membrane-bound TREM-1, and it has been suggested that plasma levels of sTREM-1 could serve as a useful diagnostic biomarker during severe sepsis and pneumonia^{13,14}. It has been reported that plasma sTREM-1 levels are elevated in patients with RA compared to healthy controls¹², and that synovial fluid sTREM-1 levels are greater than those in gouty arthritis, nonseptic/non-RA inflammatory arthritis, and noninflammatory arthritis¹¹. However, it remains unclear whether plasma sTREM-1 levels reflect disease activity in RA. Therefore, our aim was to measure the plasma sTREM-1 level in patients with RA and to evaluate its usefulness as a marker of disease activity in patients with RA compared to other disease activity measures and proinflammatory cytokines.

MATERIALS AND METHODS

Study design and patients. This cross-sectional study included 71 patients with RA and 50 healthy controls. The study was approved by our institutional ethics committee, and we obtained informed consent from all patients and controls. Consecutive patients with RA treated between April 2010 and March 2011 were selected at an outpatient rheumatology clinic at Kwandong University College of Medicine, Myongji Hospital, South Korea. Patients were diagnosed with RA according to the 1987 revised criteria of the American College of Rheumatology (ACR)¹⁷. Sixty-four patients satisfied 2010 revised ACR/European League Against Rheumatism (EULAR) classification criteria¹⁸ for RA. Patients were selected regardless of disease activity status. Exclusion criteria were systemic diseases such as diabetes mellitus, congestive heart failure, pregnancy, an infectious process, impaired renal function (creatinine clearance < 60 ml/min), and elevated hepatic enzyme levels (twice the upper limit of normal), to exclude possible biases from infectious and chronic inflammatory diseases. The study controls were 50 healthy individuals matched with patients for age and sex.

Clinical and laboratory assessments. Age, sex, medication history, body mass index, duration of disease, and extraarticular manifestations of RA were recorded. Clinical and laboratory data were collected when blood samples were obtained. Complete blood counts and routine biochemical analyses including lipid profiles, IgM type of rheumatoid factor, anticitrullinated protein antibody, and antinuclear antibody were undertaken. The following disease activity markers were evaluated: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and 28-joint Disease Activity Score (DAS28)¹⁹. ESR was determined from whole blood using the

Westergren method (Afifax, Padua, Italy), and CRP concentration was assessed in serum by a nephelometric method (Beckman Coulter, Fullerton, CA, USA). Joints were examined in all patients with RA by the same rheumatologist. A DAS28 score > 3.2 was considered to reflect active disease status and DAS28 score \leq 3.2 a low disease status²⁰.

Plasma sTREM-1 and cytokine analysis. Venous blood samples from patients with RA and healthy controls were collected in EDTA tubes and centrifuged at 1000 rpm for 15 min. Plasma samples were stored at -80°C until used. Plasma concentrations of sTREM-1 and TNF- α were measured using sandwich-type ELISA (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's recommendations. Intra- and interassay coefficients of variation (CV) of sTREM-1 were 3.6%–5.2% and 5.8%–7.1%, respectively, and the intra- and interassay CV of TNF- α were 4.6%–5.2% and 5.4%–7.4%. The minimum detectable doses of sTREM-1 and TNF- α were 3.88–30.6 pg/ml and 0.5–5.5 pg/ml, respectively. All assays were performed in duplicate. Standard curves were drawn by plotting optical density versus the log of the concentrations of recombinant sTREM-1 and TNF- α ; the respective coefficients of determination (R^2) were 0.9970 and 0.9943.

Statistical analysis. All measurements are expressed as means \pm SD. Student's *t* test or Mann-Whitney *U* test and the chi-square test were used to compare baseline demographic and clinical data and differences between plasma sTREM-1 levels in the patient and control groups. Correlations between plasma sTREM-1 levels and disease activity measures including ESR, CRP and DAS28 scores, plasma TNF- α levels, white blood cell (WBC) counts, and neutrophil counts were assessed using Pearson's correlation test. Statistical significance was accepted for 2-sided *p* values < 0.05. All analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Plasma sTREM-1 levels in patients with RA. The study cohort comprised 71 patients with RA and 50 healthy controls. There was no significant difference in mean age or sex ratio between the 2 groups [age 55.48 ± 12.89 yrs vs 52.48 ± 4.05 yrs ($p > 0.05$); female ratio 54/71 vs 30/50 ($p > 0.05$), respectively]. Patients with RA had significantly higher CRP levels than controls (1.15 ± 2.32 mg/dl vs 0.16 ± 0.23 mg/dl; $p = 0.001$). The clinical features and laboratory values of patients with RA are summarized in Table 1. In addition, mean plasma sTREM-1 levels in patients with RA were significantly higher than in controls (170.10 ± 84.71 pg/ml vs 97.41 ± 40.64 pg/ml; $p < 0.001$; Figure 1).

Correlations between plasma sTREM-1 and TNF- α levels and disease activity indicators, WBC counts, and neutrophil counts in RA. In patients with RA, plasma sTREM-1 levels were found to be correlated with the following measures: DAS28 score ($r = 0.329$, $p = 0.005$), ESR ($r = 0.241$, $p = 0.043$), CRP ($r = 0.314$, $p < 0.001$), serum WBC count ($r = 0.261$, $p = 0.028$), serum neutrophil count ($r = 0.278$, $p = 0.019$), tender joint count ($r = 0.335$, $p = 0.004$), swollen joint count ($r = 0.324$, $p = 0.006$), and plasma TNF- α level ($r = 0.313$, $p = 0.009$; Figure 2). A positive correlation was found between plasma TNF- α levels and DAS28 scores ($r = 0.341$, $p = 0.004$), ESR ($r = 0.305$, $p = 0.011$), tender joint count ($r = 0.328$, $p = 0.006$), and swollen joint count ($r = 0.318$, $p = 0.008$). However, plasma TNF- α levels showed no correlation with CRP ($r = 0.053$, $p = 0.665$), serum WBC

Table 1. Basic characteristics of patients with RA (n = 71).

| Characteristic | Mean ± SD (range) |
|---|------------------------------|
| Age, years | 55.48 ± 12.89 (26–80) |
| Disease duration, years | 4.4 ± 6.9 (0–30) |
| Body mass index, kg/m ² | 23.5 ± 3.2 (16.4–33.3) |
| DAS28 | 3.1 ± 1.6 (0.6–7.3) |
| ESR, mm/h | 26.8 ± 25.1 (2–113) |
| CRP, mg/dl | 1.15 ± 2.32 (0.01–14.56) |
| White blood cell count, mm ³ | 7,366 ± 4,918 (3,800–17,200) |
| Neutrophil, mm ³ | 2,560 ± 2,287 (1,400–13,300) |
| Total cholesterol, mg/dl | 175.4 ± 29.2 (126–245) |
| HDL cholesterol, mg/dl | 52.6 ± 12.8 (25–92) |
| LDL cholesterol, mg/dl | 107.0 ± 29.0 (42–170) |
| Triglyceride, mg/dl | 128.7 ± 88.1 (35–612) |
| Glucocorticoid, prednisolone, mg/day | 3.94 ± 2.94 (0–10) |
| Female, n (%) | 54 (76.1) |
| Rheumatoid factor positivity, n (%) | 61 (85.9) |
| ACPA positivity, n (%) | 56 (78.9) |
| ANA positivity, n (%) | 12 (17.0) |
| 2010 ACR/EULAR RA criteria, n (%) | 64 (90.1) |
| Methotrexate use, n (%) | 60 (84.5) |
| Sulfasalazine use, n (%) | 19 (26.8) |
| Hydroxychloroquine use, n (%) | 20 (28.2) |
| Leflunomide use, n (%) | 15 (21.1) |
| TNF-α blockade use, n (%) | 4 (5.6) |

DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ACPA: anticitrullinated protein antibody; ANA: antinuclear antibody; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; TNF: tumor necrosis factor.

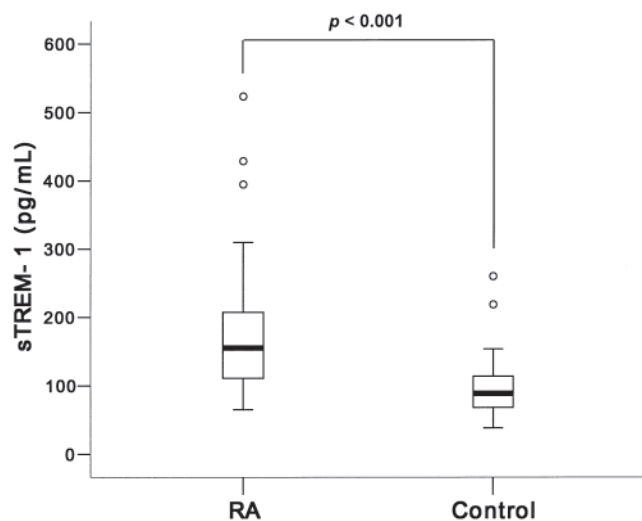


Figure 1. Levels of plasma-soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) were higher in patients with rheumatoid arthritis than in healthy controls.

count ($r = 0.032$, $p = 0.794$), or serum neutrophil count ($r = 0.058$, $p = 0.634$).

Comparison according to disease activity status. Plasma sTREM-1 and TNF-α levels were compared according to

disease activity status. Plasma sTREM-1 levels and TNF-α levels were higher in the patients with active disease status (DAS28 score > 3.2) than in patients with low disease status (DAS28 score ≤ 3.2): 208.89 ± 100.14 pg/ml vs 150.29 ± 68.70 pg/ml ($p = 0.005$); and 2.59 ± 2.81 pg/ml vs 1.35 ± 0.74 pg/ml ($p = 0.045$), respectively (Figure 3). The patients with DAS28 score > 5.1 showed higher plasma sTREM-1 levels than those with DAS28 score ≤ 2.6 (221.16 ± 96.91 pg/ml vs 147.21 ± 55.64 pg/ml; $p = 0.031$). However, mean plasma sTREM-1 levels were not significantly different between the seropositive and seronegative groups.

DISCUSSION

Our study shows that patients with RA have significantly higher plasma sTREM-1 levels than healthy controls. Importantly, plasma sTREM-1 levels were found to be correlated with disease activity indicators such as DAS28, ESR, and CRP, and plasma sTREM-1 levels in patients with active disease status were significantly greater than those in patients with a low disease status. These findings suggest that sTREM-1 contributes to the inflammatory process of RA, and that plasma sTREM-1 levels may be a useful serologic marker of disease activity in RA.

TREM-1 serves as a critical amplifier of inflammatory signaling^{2,3,4,5,6}. When TREM-1 was first cloned, it was considered that TREM-1 is expressed in inflammatory lesions caused by bacteria and fungi, but not in lesions caused by noninfectious inflammatory processes, such as vasculitis or psoriasis^{3,4,5}. Recently, however, expression of elevated TREM-1 has been reported in several noninfectious inflammatory diseases^{9,10,15,16}, including inflammatory arthritis. TREM-1 expression was increased in a mouse model of collagen-induced arthritis (CIA)^{12,21}. Expression of TREM-1 mRNA was found to be elevated in RA synovial tissues compared with normal synovial tissues, and sTREM-1 levels were found to be elevated in synovial fluid and plasma of patients with RA^{11,12}. A soluble form of the TREM-1 molecule has been suggested to arise from the proteolytic cleavage of membrane-bound TREM-1 by matrix metalloproteinases²², and elevated plasma sTREM-1 levels and increased TREM-1 expression have been detected in sepsis, gout, and inflammatory bowel diseases^{8,13,23,24}. In our study, plasma sTREM-1 levels were found to be elevated in patients with RA compared with healthy controls (Figure 1), and to be correlated with disease activity markers (Figures 2A, 2B, 2C). In addition, patients with DAS28 score > 3.2 were found to have higher plasma sTREM-1 levels than patients with DAS28 score ≤ 3.2 (Figure 3A). These findings suggest that plasma sTREM-1 might reflect the degree of systemic inflammation in patients with RA.

TNF-α is one of the most important cytokines, and TLR4 is known to play an important role in RA²⁵. In our study, plasma sTREM-1 levels were found to be correlated with plasma TNF-α levels, and in a previous study, TREM-1 and

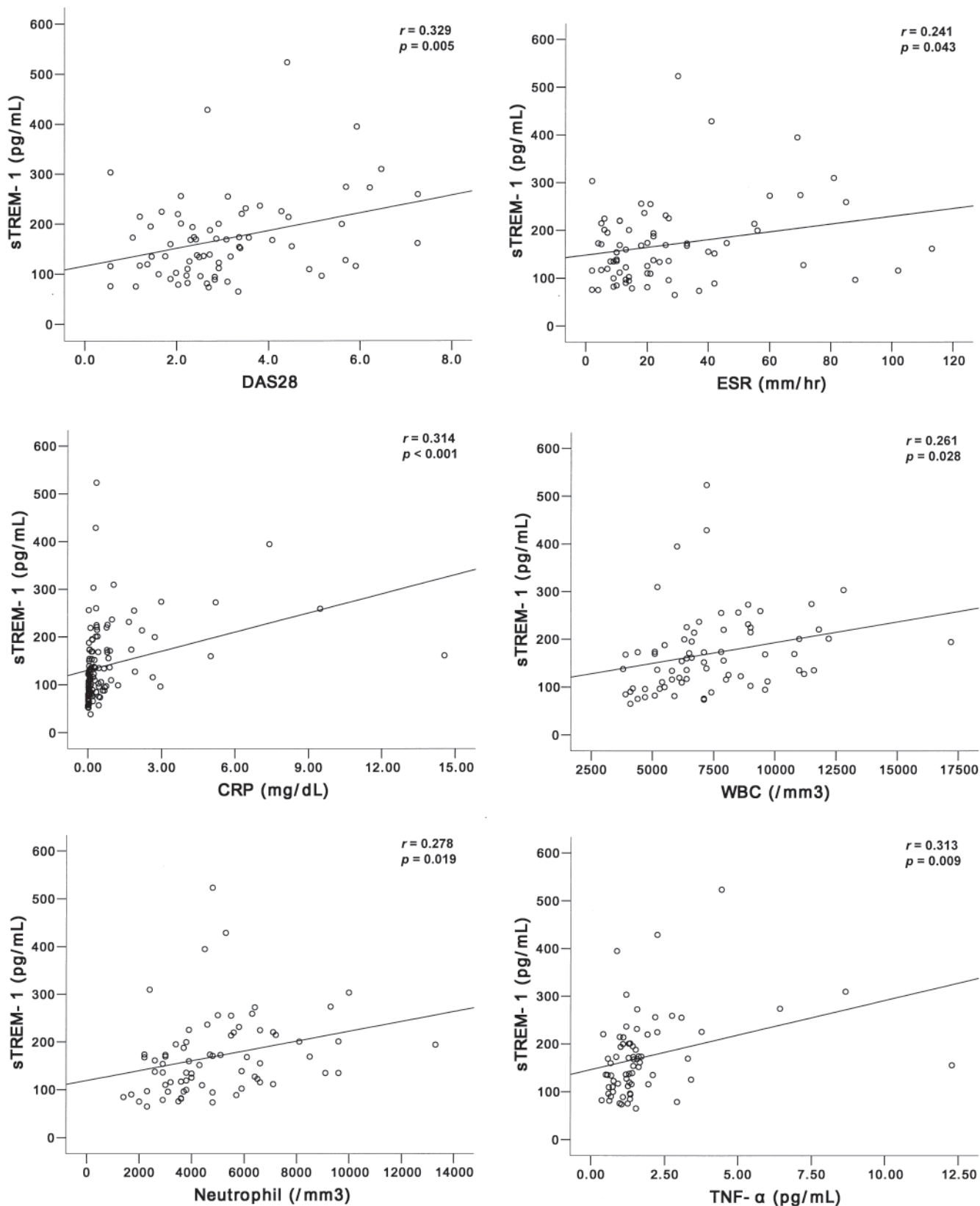


Figure 2. Levels of plasma-soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) were found to be correlated with 28-joint Disease Activity Scores (DAS28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, serum white blood cell (WBC) counts, serum neutrophil counts, and plasma tumor necrosis factor- α (TNF- α) levels in patients with RA.

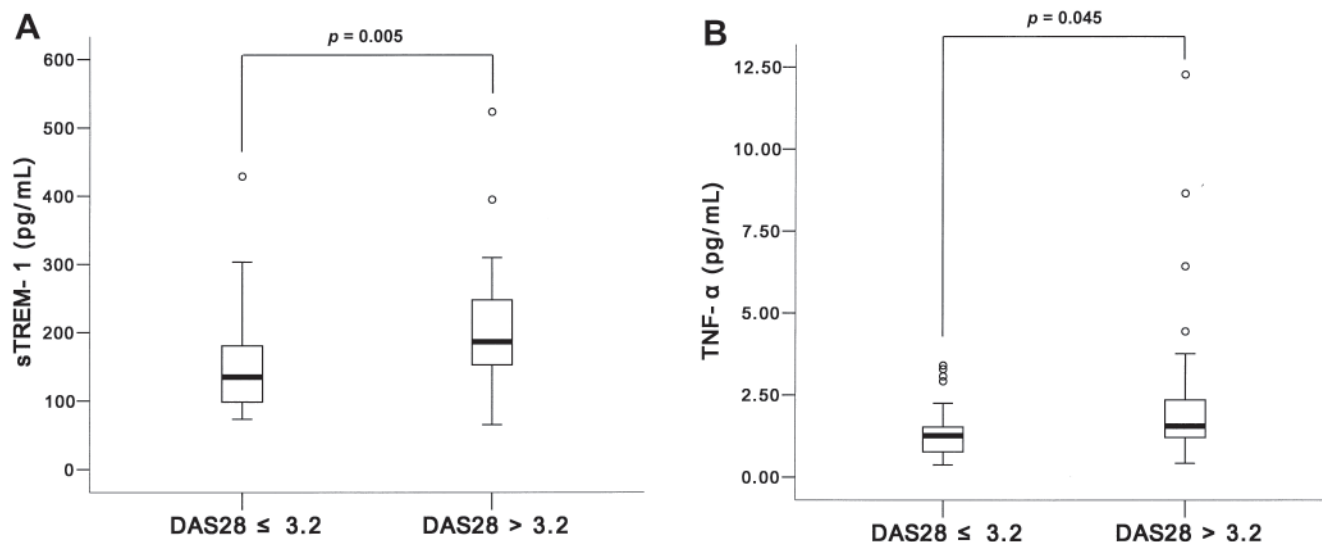


Figure 3. Plasma levels of plasma-soluble triggering receptor expressed on myeloid cells-1 (sTREM-1; A) and tumor necrosis factor- α (TNF- α ; B) were compared with Disease Activity Score (DAS) results, and both were found to be higher in patients with higher disease activity than in patients with lower disease activity. Higher disease activity: DAS28 > 3.2; lower disease activity: DAS28 \leq 3.2.

TNF- α levels were found to be correlated in RA synovial fluid¹¹. TNF- α production has been reported to be triggered by TREM-1, especially in combination with TLR4^{2,26}, and TREM-1 itself can be modestly upregulated by TNF- α ². These findings imply that TREM-1 might participate in the pathogenesis of RA in association with TNF- α . However, it is uncertain which process contributes most to the pathogenesis of RA, that is, whether TREM-1 induces TNF- α expression or TNF- α upregulates TREM-1 expression. There was a report that anti-TNF- α therapy did not appear to influence the expression of sTREM-1 in synovial fluid¹¹, which suggests that the former is more likely. Additional investigations are required to clarify the linkage.

Although the function of sTREM-1 remains unclear, sTREM-1 released from its membrane-bound form is thought to negatively regulate TREM receptor signaling by neutralizing its respective ligands²⁴. sTREM-1 in mice was found to provide protection during sepsis²⁶, and intravenous blockade of TREM-1 was found to significantly suppress the arthritis score in a CIA mouse model²¹. Therefore, it appears sTREM-1 is a candidate molecule for the treatment of RA.

In our study, plasma sTREM-1 levels were found to be significantly correlated with serum WBC and neutrophil counts (Figures 2D, 2E). TREM-1 is expressed on neutrophils, monocytes, and macrophages^{2,3,4}, and therefore plasma sTREM-1 might be released by macrophages/monocytes or neutrophils in patients with RA, which is supported by our finding that plasma TNF- α levels were correlated with DAS28 scores, but not with serum WBC or neutrophil counts, unlike results with sTREM-1. Synovial sTREM-1 levels have been reported to be correlated with synovial WBC counts in RA¹¹, but the possibility that sTREM-1 pro-

duced by synovial membrane in RA is partially released to the systemic circulation cannot be ruled out.

sTREM-1 may be a useful biomarker in several diseases, such as sepsis, pneumonia, and inflammatory bowel diseases. In patients with ventilator-associated pneumonia, levels of sTREM-1 in the bronchoalveolar lavage fluid were found to decrease rapidly in those that responded to antibiotic therapy²⁷. A correlation between plasma sTREM-1 levels and disease activity has been demonstrated in inflammatory bowel diseases²³. Similarly, our study shows that plasma sTREM-1 levels are well correlated with disease activity indicators, including DAS28 score, ESR, CRP, tender joint counts, and swollen joint counts, which suggests that plasma sTREM-1 level could be a potentially useful marker of disease activity in RA.

Our study has several limitations. First, the cohort was not large enough for strong statistical analyses. Second, serial sTREM-1 levels were not measured in individual patients, and thus we cannot comment whether changes of sTREM-1 level reflect prompt changes in disease activity. Third, we were unable to investigate whether plasma sTREM-1 levels predict future relapse. Although patients enrolled in our study met the 1987 revised ACR criteria for RA, more than 90% of patients also satisfied the 2010 ACR/EULAR criteria.

Our study shows that plasma sTREM-1 levels are elevated in patients with RA compared to healthy controls, and that plasma sTREM-1 level is correlated with disease activity measures in RA. These findings suggest that plasma sTREM-1 could play a role in the inflammatory process associated with TNF- α . Plasma sTREM-1 should be viewed as a potentially useful disease activity marker and as a candidate target for therapy in RA.

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