

Serum progranulin level is associated with disease activity following orthopedic surgery in rheumatoid arthritis patients

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Abstract

Background: Few studies have focused on the ability of progranulin to predict postoperative disease activity in rheumatoid arthritis (RA) patients who have undergone surgery. This study evaluated serum progranulin levels in active RA patients and analyzed its relationship with postoperative disease activity.

Methods: One hundred thirty-two patients with active RA and 72 healthy subjects were included in this study. Serum progranulin was measured, and clinical data were collected. The postoperative 1-year Disease Activity Score in 28 joints calculated with C-reactive protein (DAS28-CRP) scores was evaluated as an indicator of disease activity. The predictive value of progranulin in postoperative 1-year disease activity in RA patients was also analyzed.

Results: Serum progranulin was significantly associated with the postoperative 1-year RA disease activity. The mean serum progranulin level in patients with a high disease activity was significantly higher than that of RA patients with low-to-moderate disease activity (54.2 ± 10.6 ng/mL vs. 46.7 ± 8.8 ng/mL). Serum progranulin was also evaluated as an independent predictive factor for postoperative 1-year RA disease activity in multivariate analysis (odds ratio [OR], 2.21; 95% confidence interval [CI], 1.02–8.85).

Conclusions: Serum progranulin levels may be a promising indicator of postoperative disease activity in RA patients who underwent orthopedic surgery.

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Keywords

Rheumatoid arthritis, disease activity, progranulin, orthopedic surgery, postoperative, autoimmune, inflammatory

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune and inflammatory joint disease that presents as chronic synovitis, irreversible cartilage and bone destruction, systemic extra-articular manifestations, and impaired physical function.^{1,2} The RA incidence is estimated to be approximately 0.2% to 0.4% in Chinese people, which could result in severe disability and mortality, and it could cause a poor quality of life and a considerable financial burden for patients.³⁻⁵ Pharmacological treatment has been confirmed to be an effective approach for inhibiting systemic inflammation and progression of joint destruction.^{6,7} However, disease activity cannot be completely managed using anti-rheumatic drugs. Surgical intervention is an optimal option for RA patients with a poor quality of life due to severe joint destruction and impairments, which has been shown to be an effective procedure for improving psychological function, quality of life, and systemic disease activity.^{8,9} However, individual patients have different responses to surgery. Optimal patient stratification and individual treatment planning based on preoperative indicators may be a promising option for RA patients.¹⁰ In current clinical practice, acute phase reactants such as C-reactive protein (CRP) have been used to evaluate disease activity and severity in RA patients.^{11,12} However, more than 50% of RA patients were shown have a normal or low CRP level.¹³ Therefore, a novel serum biomarker that can accurately reflect postoperative disease activity is required.

Progranulin is a glycoprotein that plays an essential role in systemic autoimmune inflammatory diseases.^{14,15} Progranulin mainly originates from inflammatory cells, epithelial cells, and chondrocytes, and it is involved in inflammation and cartilage development and degradation.^{16,17} Progranulin levels were shown to be up-regulated in serum and synovial fluid in RA patients, which was also obviously related to disease activity.¹⁸ Cerezo et al.¹⁸ showed increased progranulin expression at local sites of inflammation and association between progranulin levels, disease activity, and functional impairment in patients with RA. Chen et al.¹⁹ reported that induction of progranulin expression may play a role in RA immune reaction. Additionally, progranulin levels could be a useful biomarker in the RA inflammatory response, but they are unrelated to regulatory B cell (Breg) levels. However, no published study has evaluated the relationship between serum progranulin levels and postoperative disease activity in RA patients. Thus, in this study, we evaluated serum progranulin levels in patients with RA, and analyzed its value as a biomarker of postoperative disease activity in active RA patients who underwent orthopedic surgery.

Materials and methods

Patients

This study was designed as a retrospective cross-sectional analysis of a prospective database that included 132 consecutive RA patients who underwent a single

orthopedic surgery at Tianjin First Central Hospital between 1 June 2016 and 1 June 2018. The study was conducted in accordance with the Declaration of Helsinki and ethics approval was received from the Tianjin First Central Hospital. All participating patients provided written informed consent before enrollment. All patients were diagnosed with active RA in accordance with the American College of Rheumatology (ACR) criteria.²⁰ Patients with a severe comorbidity such as ischemic disorders, severe cardiac or neurological deficits, malignancies, acute and chronic inflammatory and infective disease, chronic lung disease, and immunosuppressive disorders were excluded. Patients who underwent multiple surgeries during enrollment were also excluded from study. All patients received standard appropriate management in accordance with ACR guidelines. Surgical procedures were planned at the surgeons' discretion, and the surgical procedures were classified as replacement surgery or non-replacement surgery including synovectomy, arthrodesis, and arthroplasty without prosthesis. Biological/targeted-synthetic (b/ts) disease-modifying antirheumatic drugs (DMARDs) were recorded. Seventy-two healthy volunteers were enrolled as controls at the corresponding duration.

Clinical evaluation

Demographic and clinical characteristics of all patients were retrospectively collected, including age, sex, duration of RA, medication administration, and laboratory test results such as rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and cyclic citrullinated peptide (CCP). The Disease Activity was evaluated using the Disease Activity Score in 28 joints (DAS28) calculated with C-reactive protein (DAS28-CRP). All patients were followed though regular

outpatient clinic visits for 1 year after surgery. The 1-year disease activity was considered to be the primary outcome. Therefore, all patients were grouped primarily on the basis of the DAS28-CRP score classification criteria.²¹ Low disease activity was considered to be DAS28 ≥ 2.6 to ≤ 3.2 , moderate disease activity was DAS28 > 3.2 to ≤ 5.1 , and high disease activity was DAS28 > 5.1 . Patients with a DAS28-CRP score > 5.1 were defined as the high activity group whereas patients with a DAS28 score of 3.2 to 5.1 were defined as the low to moderate activity group.

Measurement of serum progranulin

Blood samples were obtained from all subjects using venipuncture with aseptic precautions and stored in a sterile tube (BD Vacutainer, Becton, Dickinson and Co., Franklin Lakes, NJ, USA) on the day of admission. After centrifugation at $1006.2 \times g$ for 3 to 5 minutes, the serum samples were decanted and measured immediately using a high-sensitivity commercially available ELISA kit (Adipogen Inc., Seoul, Korea) in accordance with the manufacturer's instructions to analyze the serum progranulin levels.

Statistical analysis

Analyses were conducted using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Results with a two-sided $P < 0.05$ were defined as statistically significant. Categorical variables were presented as a percentage while continuous variables were presented as the mean \pm standard deviation (SD). The χ^2 test or Fisher's exact test was used to compare categorical variables while continuous variables were compared using an independent Student's *t*-test. Receiver operating curves (ROCs) were used to test the optimal cutoff value for progranulin to predict the 1-year disease activity in RA patients.

The odds ratio (OR) was assessed using multivariate logistic regression analysis for variables with significant P values ($P < 0.05$) in the univariate analysis, with postoperative 1-year disease activity categorized as high disease vs. low to moderate disease.

Results

Demographic and clinical characteristics

There were 132 patients with active RA and 72 healthy subjects who were recruited into this study. Among the 132 RA patients, 25 were men and 107 were women, with a mean age of 55.2 ± 11.3 years. The mean disease duration was 5.9 ± 4.8 years from the initial clinical presentation. The mean ESR and CRP were 32.5 ± 17.6 mm/hour and 33.5 ± 25.8 mg/L, respectively. The mean RF-IgM, IgG, and IgA levels were 155.2 ± 95.2 , 136.8 ± 86.2 , and 133.1 ± 89.8 IU/mL, respectively (Table 1). On the basis of the DAS28-CRP score, all 132 patients were grouped as follows: low to moderate disease activity group (49 patients, with $3.2 < \text{DAS28-CRP} < 5.1$) or high disease activity group (83 patients, with $\text{DAS28-CRP} > 5.1$).

Ability of serum progranulin to predict RA disease activity

The mean serum progranulin level in RA patients was significantly higher than that of the healthy controls ($P < 0.01$, Figure 1). The ROC curve analysis showed that a progranulin level of 47.7 ng/mL (area under the curve, $0.73 \text{ ng} \times \text{hour/mL}$; 95% confidence interval [CI]: 0.32–0.98; $P < 0.01$) was considered to be the optimal cutoff level to predict high disease activity in RA patients, with a sensitivity of 72.7% and a specificity of 85.4%, respectively (Figure 2).

Table 1. Demographic and clinical details of the RA patients.

Characteristics	RA patients (n=132)
Male	25 (18.9%)
Age (years)	55.2 ± 11.3
Disease duration (years)	5.9 ± 4.8
ESR (mm/hour)	32.5 ± 17.6
CRP (mg/L)	33.5 ± 25.8
CCP (RU/mL)	341.7 ± 125.4
RF-IgM (IU/mL)	155.2 ± 95.2
RF-IgG (IU/mL)	136.8 ± 86.2
RF-IgA (IU/mL)	133.1 ± 89.8
Progranulin (ng/mL)	48.6 ± 9.6
Swollen joints (n)	2.6 ± 2.1
Tender joints (n)	3.7 ± 3.2
Morning stiffness in minutes	25.6 ± 20.1
Patient assessed global score (0–100)	46.3 ± 30.4
Surgical site, number of patients (Procedure: replacement/non-replacement)	
Elbow	11 (9/2)
Hand/wrist	32 (5/27)
Hip	10 (10/0)
Knee	48 (48/0)
Ankle/foot	31 (1/30)
b/tsDMARD	41 (31.1%)

RA, rheumatoid arthritis; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; Ig, immunoglobulin; b/tsDMARDs biological/targeted-synthetic disease-modifying antirheumatic drugs.

Serum progranulin level associated with 1-year disease activity in RA patients

The results of the univariate analysis showed that patients with high 1-year disease activity had higher mean CRP, ESR, CCP, and RF levels than patients with low to moderate 1-year disease activity (all $P < 0.05$, Table 2). Moreover, the mean serum progranulin level was significantly higher in RA patients with high 1-year disease activity compared with those with low to moderate disease activity (54.2 ± 10.6 ng/mL vs. 46.7 ± 8.8 ng/mL, $P < 0.01$, Table 2).

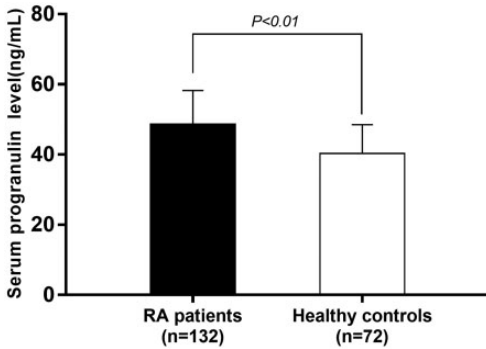


Figure 1. Serum progranulin level in RA patients and healthy controls. The mean serum progranulin level in 132 RA patients was significantly higher than that in 72 age-matched healthy volunteers ($P < 0.01$). RA, rheumatoid arthritis.

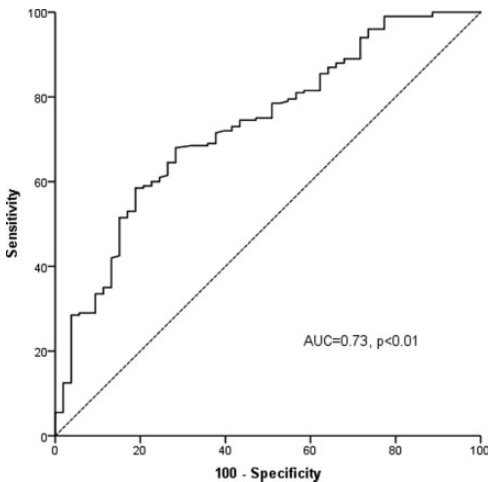


Figure 2. ROC curve results for serum progranulin level predicting postoperative 1-year high RA disease activity. The ROC analysis showed a maximum AUC of 0.73 ng \times hour/mL for the progranulin level.

ROC, receiver-operator characteristic; RA, rheumatoid arthritis; AUC, area under the curve.

A multivariate logistic regression analysis included age, sex, serum CRP, ESR, RF, CCP, and progranulin level to evaluate the independent predictive variables for 1-year disease activity in RA patients. The result

showed that serum progranulin level (OR, 2.21; 95%CI, 1.02–8.85; $P < 0.01$) was an independent predictive factor for postoperative 1-year RA disease activity (Table 3).

Discussion

In the current study, we retrospectively evaluated the serum progranulin level in RA patients and showed that RA patients had a significantly upregulated progranulin level compared with healthy controls. Furthermore, we validated the significant association of serum progranulin level with disease activity in RA patients using univariate and multivariate analyses. Therefore, we concluded that the serum progranulin level can be used to assess the optimal postoperative 1-year disease activity in individual active RA patients who underwent surgery. This can serve as an indicator to evaluate postoperative RA disease activity.

Progranulin has been implicated as an important molecule in inflammatory disease processes including RA.^{22,23} Yamamoto et al.²⁴ reported that significantly upregulated serum and synovial fluid progranulin levels were observed in RA patients compared with healthy subjects. In this study, we also found that patients with active RA had an increased serum progranulin level in RA patients, which was consistent with previously published data. However, the role of progranulin in RA inflammation has not been fully clarified. Progranulin can inhibit tumor necrosis factor (TNF) α -activated intracellular signaling, and thus, prevent TNF α -mediated inflammation.^{15,22} However, the serum progranulin level was shown to be significantly associated with serum the TNF α level, which is also related to disease severity in RA patients.²⁴ Moreover, it is well established that granulins that are converted from progranulin are

Table 2. Univariate analysis of risk factors associated with disease activity in RA patients.

Characteristics	Low-to-moderate activity (3.2 < DAS28 < 5.1, n=49)	High activity (DAS28 > 5.1, n=83)	P
Male (%)	10 (20.4)	15 (18.1)	
Age (years)	53.4 ± 10.2	56.1 ± 12.3	0.20
ESR (mm/hour)	21.2 ± 8.6	78.7 ± 36.5	<0.01
CRP (mg/L)	22.7 ± 6.2	62.3 ± 15.7	<0.01
CCP (RU/mL)	238.7 ± 186.5	591.2 ± 153.2	<0.01
RF-IgM (IU/mL)	114.4 ± 32.2	203.7 ± 131.3	<0.01
RF-IgG (IU/mL)	123.2 ± 84.6	163.8 ± 123.2	<0.01
RF-IgA (IU/mL)	94.6 ± 14.2	160.8 ± 113.1	<0.01
Progranulin (ng/mL)	46.7 ± 8.8	54.2 ± 10.6	<0.01

RA, rheumatoid arthritis; DAS28, Disease Activity Score in 28 joints; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; Ig, immunoglobulin.

Table 3. Multivariate analysis of risk factors associated with disease activity in RA patients.

Characteristics	OR	95%CI	P
CRP	3.42	1.12–8.87	0.03
CCP	1.62	0.98–2.54	0.53
RF-IgA	0.49	0.12–0.98	0.02
Progranulin	2.21	1.02–7.85	0.002
Preoperative use of b/tsDMARDs	0.26	0.03–0.57	0.03

RA, rheumatoid arthritis; OR, odds ratio; 95%CI, 95% confidence interval; CRP, C-reactive protein; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; Ig, immunoglobulin; b/tsDMARDs biological/targeted-synthetic disease-modifying antirheumatic drugs.

proinflammatory, and they have opposite functions compared with those of progranulin.¹⁶ Furthermore, progranulin also participates in the conversion of immunosuppressive regulatory T cells (Tregs) in autoimmune inflammatory conditions.²⁵

Conventional laboratory testing including CRP has been previously evaluated as an important indicator of disease activity in RA patients.²⁶ However, approximately 50% of active RA patients have a normal or low CRP level.²⁷ In addition, serum levels of such acute phase markers may be presented as unchanged in certain patient cohorts and may not serve as a reliable

markers that reflects inflammatory activity.²⁸ Therefore, we evaluated the predictive value of progranulin for postoperative disease activity in RA patients and found that progranulin can serve as a useful biomarker to evaluate postoperative RA disease activity compared with other predictors including CRP, CCP, and RF-IgA. An increased progranulin level may predict a higher postoperative disease activity status in RA patients, so physicians should pay special attention to patients with a high serum progranulin level and start early and appropriate interventions to reduce disease activity.

There were several limitations that may affect the interpretation and application of the conclusions in this study. One limitation is the limited number of subjects. A large-scale, multicenter, prospective study should be performed to obtain more accurate evidence and confirm the results of this study. Furthermore, the serum progranulin level was measured using commercially available ELISA kits, which may have a different sensitivity and specificity compared with other kits. Thus, the results of our study may not be comparable to those of other similar studies. Further validation studies, such as a meta-analysis, may be needed to evaluate the value of progranulin in RA patients.

Conclusion

The serum progranulin level is increased in patients with active RA, which might have additional significance in the evaluation of the postoperative RA disease activity.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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