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BRIEF REPORT

Normal serum matrix metalloproteinase-3 levels can be used to predict clinical remission and normal physical function in patients with rheumatoid arthritis

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Abstract This study aimed to evaluate whether normal serum matrix metalloproteinase-3 (MMP-3) levels can be used to predict clinical remission and normal physical function at a single time point when treating patients with rheumatoid arthritis (RA) in daily practice settings. Subjects were all 1321 RA patients who were treated at our hospital. The accuracy of serum MMP-3 levels was larger than those of C-reactive protein (CRP) levels for predicting clinical remission [Simplified Disease Activity Index (SDAI) ≤ 3.3], normal function [Disability Index of the Health Assessment Questionnaire (HAQ-DI) ≤ 0.5], and both in clinical remission and with normal function (clinical remission + normal function) using receiver operating characteristic curve analysis. Serum MMP-3 levels were significantly correlated with CRP levels [r 0.229 (men), r 0.476 (women)] using Pearson's correlation coefficients. Among patients with normal CRP levels (n = 807), the percentage of patients in clinical remission, with normal function, and with clinical remission + normal function having normal serum MMP-3 levels was significantly higher than those with abnormal serum MMP-3 levels. In addition, among patients with the 28-point count Disease Activity Score-CRP (DAS28-CRP) remission (DAS28-CRP < 2.3), the percentage of patients in clinical remission, with normal function, and with clinical remission + normal function having normal serum MMP-3 levels was significantly higher than those with abnormal serum MMP-3 levels. Our findings suggest that normal serum MMP-3 levels, in combination with CRP levels or disease activity, are useful for predicting clinical remission and normal physical function in patients with RA.

Keywords Clinical remission · Matrix metalloproteinase-3 · MMP-3 · Physical function · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic synovitis that leads to cartilage degradation, subchondral bone erosion, and eventual disability [1]. Serum matrix metalloproteinase-3 (MMP-3), an enzyme produced by synoviocytes that serve as a marker of synovitis, reflecting actual joint destruction in patients with RA, can be used to predict joint destruction in this patient population [2–13], and its levels are correlated with disease activity [14]. In patients with RA treated with tocilizumab, normalization of C-reactive protein (CRP) and serum MMP-3 levels can predict low disease activity and remission [15]. In those who discontinue tocilizumab, normalization of serum MMP-3 levels is associated with long-term low disease activity [16]. In patients with RA treated with adalimumab, high rates of improvement in serum MMP-3 levels at 4 weeks can be used to predict remission at 52 weeks [17]. Although serum MMP-3 is a useful synovitis marker for evaluating disease activity, little is known about how the serum levels of this enzyme affect clinical remission and normal physical function at a single time point when treating patients with RA in daily practice settings. This study aimed to investigate whether normal serum MMP-3

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levels can be used to predict clinical remission and normal physical function in patients with RA.

Methods

Study population and assessed parameters

Subjects were all 1321 RA patients who met the 1987 American College of Rheumatology (ACR) classification criteria for RA or the 2010 ACR/European League Against Rheumatism criteria [18]. All patients included in the study were treated at the Nagoya Medical Center. This study was conducted from January through March 2013, was approved by the ethics committee of our institution, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients in this study. Patient anonymity was maintained during data collection, and security of personal information was strictly controlled.

Among patients with normal CRP levels (n = 807), the following variables were evaluated by serum MMP-3 levels (abnormal and normal levels): age (years), female (%), disease duration (years), Steinbrocker radiographic stage (Stage), Steinbrocker functional class (Class), rheumatoid factor (RF) positivity, body mass index (BMI), estimated glomerular filtration rate (eGFR), methotrexate use, prednisolone use, biologics use, Health Assessment Questionnaire Disability Index (HAQ-DI), the EuroQol five-dimensional descriptive system (EQ-5D), tender joint count assessed on 28 joints (TJC28), swollen joint count assessed on 28 joints (SJC28), the patient's global assessment of disease activity (general-VAS: 0–100 mm), the physician's global assessment of disease activity (physician-VAS: 0–100 mm), CRP, serum MMP-3, the 28-point count Disease Activity Score-CRP (DAS28-CRP), and the Simplified Disease Activity Index (SDAI). Among patients with normal CRP levels and DAS28-CRP remission (DAS28-CRP < 2.3), the following variables were evaluated by serum MMP-3 levels (abnormal and normal): the percentage of patients in clinical remission (SDAI ≤ 3.3), the percentage of patients with normal function (HAQ-DI ≤0.5), and the percentage of patients both in clinical remission and with normal function (hereafter, "clinical remission + normal function"). We determined best cutoff values of CRP and serum MMP-3 levels for predicting clinical remission, normal function, and clinical remission + normal function and examined whether these cutoff values are accurate. We also examined correlations between serum MMP-3 and CRP levels and between serum MMP-3 levels and DAS28-CRP.

DAS28-CRP is known to both significantly underestimate disease activity and overestimate improvement in disease activity compared with DAS28-erythrocyte sedimentation rate (ESR) [19]. The present study used different criteria from those in DAS28-ESR. DAS28-CRP remission was categorized as DAS28-CRP < 2.3, using criteria defined based on a large Japanese cohort study [20]. The threshold of 0.3 mg/dl was used to define normal CRP levels. Values under 0.3 mg/dl were considered normal CRP levels.

Serum MMP-3 levels were determined by latex immunoassay (Panaclear MMP-3 "Latex"; Kyowa Pharma Chemical, Takaoka, Japan). The thresholds of 121.0 (men) and 59.7 ng/ml (women) were used to define normal serum MMP-3 levels. Values under 121.0 (men) and 59.7 ng/ml (women) were considered normal serum MMP-3 levels.

Statistical analysis

Data were analyzed using SPSS for Windows, version 22.0 (SPSS, Inc., Chicago, IL, USA). Demographic and clinical characteristics were reported as descriptive statistics. All results are expressed as mean (SD) or as a percentage. Comparisons of patient background characteristics by serum MMP-3 levels were performed using the chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables. Receiver operating characteristic (ROC) curves were generated to assess factors that predict achievement of clinical remission and normal function, based on area under the ROC curve (AUC) analysis. This analysis was also used to determine cutoff points for achievement of clinical remission and normal function. The best cutoff point was identified as the maximum point of the Youden index. Pearson's correlation coefficients were calculated to explore associations between variables. $P < 0.05$ was considered statistically significant.

Results

Background characteristics

Demographic and clinical characteristics of the study subjects are summarized in Table 1. We evaluated patient background variables and other parameters based on serum MMP-3 levels in patients with normal CRP levels and revealed significant differences with the exception of female sex, disease duration, RF positivity, BMI, and biologics use.

Association of CRP and serum MMP-3 levels with achievement of clinical remission and normal function

For all patients (n = 1321), we evaluated the best cutoff value of CRP and serum MMP-3 levels for predicting clinical remission, normal function, and clinical remission + normal function, as determined by ROC analysis. AUCs of serum MMP-3 levels were larger than those of CRP levels for

Table 1 Subject demographics and clinical characteristics

Variables	All patients (n = 1321)	Normal CRP levels			
		Total (n = 807)	Serum MMP-3 levels		
			Abnormal (n = 332)	Normal (n = 475)	P value
Age (years)	64.1 ± 12.8	62.6 ± 13.6	65.6 ± 14.0	60.5 ± 13.0	< 0.001
Female (%)	82.3	83.8	86.4	81.9	0.084
Disease duration (years)	14.0 ± 11.2	13.0 ± 11.0	13.9 ± 11.6	12.3 ± 10.6	0.050
Stage (I, II/III, IV %)	37.9/62.1	44.8/55.2	40.1/59.9	48.2/51.8	< 0.05
Class (1, 2/3, 4 %)	64.1/35.9	71.4/28.6	61.7/38.3	77.9/22.1	< 0.001
RF positive (%)	78.3	73.1	74.0	72.4	0.640
BMI (kg/m^2)	21.6 ± 3.4	21.5 ± 3.2	21.3 ± 3.3	21.6 ± 3.1	0.152
eGFR (ml/min/1.73 m^2)	71.1 ± 19.8	70.6 ± 19.1	65.8 ± 20.7	74.0 ± 17.0	< 0.001
Methotrexate use (%)	57.2	56.9	51.5	60.6	< 0.05
Prednisolone use (%)	32.3	25.0	47.0	9.7	< 0.001
Biologics use (%)	43.5	48.3	45.5	50.3	0.176
HAQ-DI	0.81 ± 0.85	0.64 ± 0.74	0.82 ± 0.83	0.51 ± 0.64	< 0.001
EQ-5D	0.74 ± 0.20	0.77 ± 0.18	0.73 ± 0.19	0.79 ± 0.17	< 0.001
TJC28	4.5 ± 6.5	4.0 ± 6.0	4.9 ± 6.9	3.3 ± 5.3	< 0.001
SJC28	1.6 ± 3.2	1.1 ± 2.4	1.5 ± 2.7	0.9 ± 2.2	< 0.001
General-VAS (mm)	27.4 ± 23.5	23.1 ± 21.0	29.0 ± 23.0	19.1 ± 18.5	< 0.001
Physician-VAS (mm)	19.7 ± 17.3	15.6 ± 14.5	19.4 ± 16.3	12.9 ± 12.4	< 0.001
CRP (mg/dl)	0.697 ± 1.556	0.190 ± 0.028	0.192 ± 0.032	0.188 ± 0.024	< 0.01
Serum MMP-3 (ng/ml)	123.4 ± 180.1	85.5 ± 81.0	141.9 ± 100.4	46.1 ± 18.6	< 0.001
DAS28-CRP	2.9 ± 1.1	2.51 ± 0.88	2.76 ± 0.93	2.34 ± 0.80	< 0.001
SDAI	10.0 ± 9.2	7.82 ± 7.30	9.85 ± 8.22	6.43 ± 6.22	< 0.001

Values are presented as mean ± standard deviation unless stated otherwise. P values were calculated using the chi-squared test for categorical variables and the Mann-Whitney U test for continuous variables. *Stage* Steinbrocker radiographic stage, *Class* Steinbrocker functional class, *RF* rheumatoid factor, *BMI* body mass index, *HAQ-DI* Health Assessment Questionnaire Disability Index, *EQ-5D* EuroQol five-dimensional descriptive system, *TJC28* tender joint count assessed on 28 joints, *SJC28* swollen joint count assessed on 28 joints, *General-VAS* the patient's global assessment of disease activity, *Physician-VAS* the physician's global assessment of disease activity, *CRP* C-reactive protein, *MMP-3* matrix metalloproteinase-3, *DAS28-CRP* 28-point count Disease Activity Score-CRP (DAS28-CRP), *SDAI* Simplified Disease Activity Index

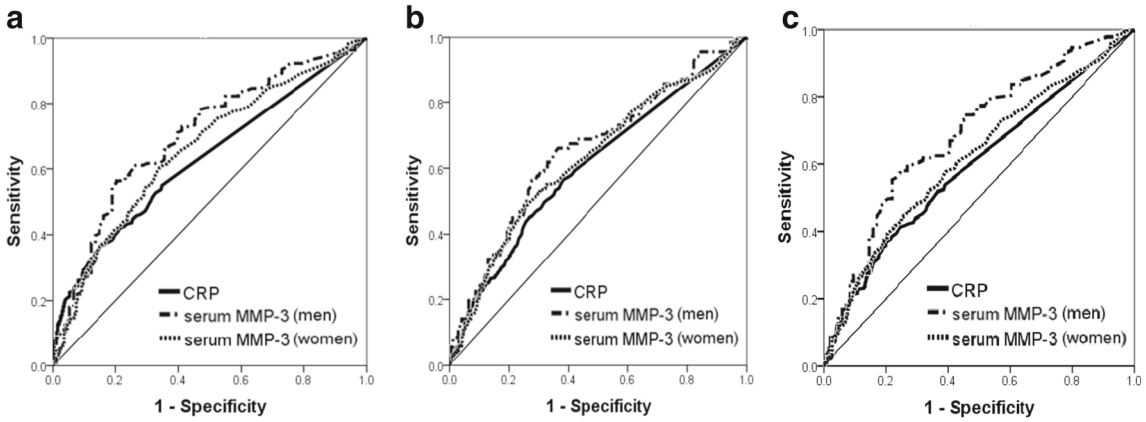
achievement of clinical remission, normal function, and clinical remission + normal function (Fig. 1).

Interrelationships between variables

For all patients (n = 1321), serum MMP-3 levels were significantly correlated with CRP levels [r 0.229 (men), r 0.476 (women)], and serum MMP-3 levels were significantly correlated with DAS28-CRP [r 0.319 (men), r 0.278 (women)]. In all patients with normal CRP levels (n = 807), serum MMP-3 levels were significantly correlated with CRP levels [r 0.228 (men), r 0.469 (women)], and serum MMP-3 levels were significantly correlated with DAS28-CRP [r 0.244 (men), r 0.278 (women)].

Combination of normal CRP levels and normal serum MMP-3 levels predicts clinical remission and normal function

Among patients with normal CRP levels, the percentages of patients in clinical remission having abnormal serum MMP-3 levels and normal serum MMP-3 levels were 15.9 and 39.3%, respectively; the percentages of patients with normal function having abnormal serum MMP-3 levels and normal serum



Outcome measure		Cut-off value	AUC, %	95%CI	Sensitivity, %	Specificity, %
Clinical remission (SDAI≤3.3)	CRP	0.42 mg/dl	62.95	0.60-0.66	36.58	84.64
	serum MMP-3 (men)	113.0 ng/ml	70.35	0.63-0.78	57.32	78.57
	serum MMP-3 (women)	59.5 ng/ml	65.55	0.62-0.69	59.73	66.18
Normal function (HAQ-DI≤0.5)	CRP	0.35 mg/dl	60.67	0.58-0.64	45.21	73.14
	serum MMP-3 (men)	114.5 ng/ml	63.75	0.56-0.72	65.71	62.20
	serum MMP-3 (women)	88.5 ng/ml	61.65	0.58-0.65	48.19	74.56
Clinical remission + Normal function	CRP	0.40 mg/dl	59.43	0.56-0.63	36.58	80.11
	serum MMP-3 (men)	113.0 ng/ml	67.23	0.60-0.75	57.42	74.68
	serum MMP-3 (women)	75.5 ng/ml	61.21	0.58-0.65	46.81	72.22

Fig. 1 Association of CRP and serum MMP-3 levels with achievement of **a** clinical remission, **b** normal function, and **c** clinical remission + normal function in all patients. Receiver operating characteristic (ROC) curves were used to determine the best cutoff value for CRP and serum MMP-3 levels for predicting clinical remission, normal function, and clinical remission + normal function. The table shows the cutoff value, area under the ROC curve (AUC), 95% confidence interval (CI), sensitivity, and specificity for achievement of clinical remission, normal function, and clinical remission + normal function

MMP-3 levels were 48.6 and 67.6%, respectively; and the percentages of patients with clinical remission + normal function having abnormal serum MMP-3 levels and normal serum MMP-3 levels were 13.9 and 34.6%, respectively. Among patients with normal CRP levels, the percentage of patients in clinical remission, with normal function, and with clinical remission + normal function having normal serum MMP-3 levels was significantly higher than those with abnormal serum MMP-3 levels (Fig. 2).

Combination of DAS28-CRP remission and normal serum MMP-3 levels predicts clinical remission and normal function

Among patients with DAS28-CRP remission, the percentages of patients in clinical remission having abnormal serum MMP-3 levels and normal serum MMP-3 levels were 50.3 and 74.2%, respectively; the percentages of patients with normal function having abnormal serum MMP-3 levels and normal serum MMP-3 levels were 69.6 and 82.1%, respectively; and the percentages of patients with clinical remission + normal function having abnormal serum MMP-3 levels and normal serum MMP-3 levels were 38.4 and 64.1%, respectively. Among patients with DAS28-CRP remission, the percentage of patients in clinical remission, with normal function, and with clinical remission + normal function having normal serum MMP-3 levels was significantly higher than those with abnormal serum MMP-3 levels (Fig. 3).

Discussion

Therapies that achieve both DAS28 remission and normalization of serum MMP-3 levels lead to better outcomes than therapies that achieve either of these targets alone in early RA [19]. In this study, we demonstrated that serum MMP-3 levels are comparable if not superior to CRP levels as predictors of clinical remission and normal function, although inflammatory markers such as CRP have thus far been considered the best markers for therapeutic evaluation. Although the accuracy of CRP levels and serum MMP-3 levels used alone was insufficient to predict clinical remission, normal function, and clinical remission + normal function, evaluations that combined normal CRP levels and normal serum MMP-3 levels more accurately predicted clinical

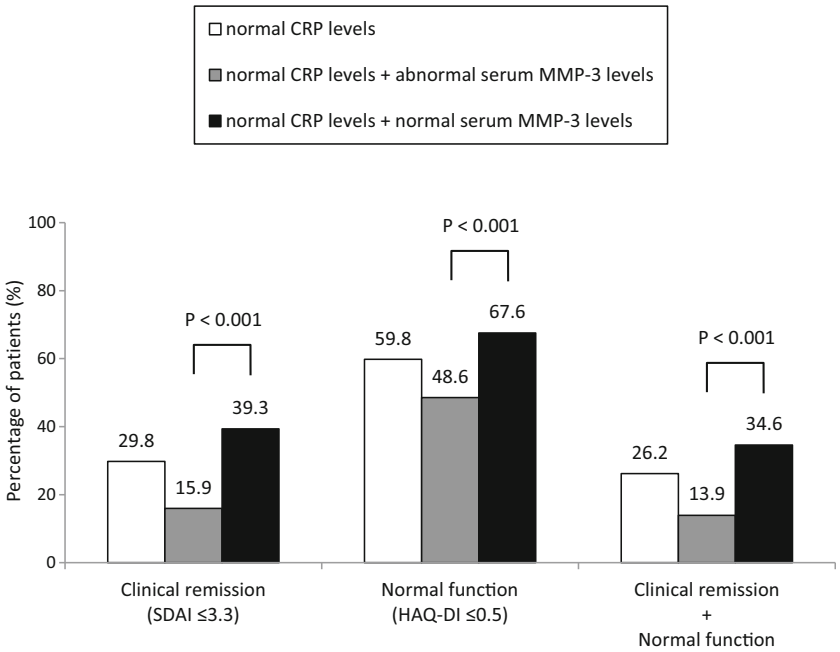


Fig. 2 Combination of normal CRP levels and normal serum MMP-3 levels predicts clinical remission and normal function. SDAI Simplified Disease Activity Index, HAQ-DI Disability Index of the Health Assessment Questionnaire

remission, normal function, and clinical remission + normal function. In addition, evaluations that combined DAS28-CRP remission and normal serum MMP-3 levels predicted clinical remission, normal function, and clinical remission + normal function to an even higher degree. This suggests that, in addition to CRP and DAS28, serum MMP-3 levels could be beneficial when considering treatment strategy for patients with RA. Furthermore, normalized serum MMP-3 levels could also be useful for predicting a reduction in medication dose, long-term sustained remission, and better quality of life, since patients with RA who have normalized serum MMP-3 levels achieve lower disease activity and comprehensive disease remission (defined as the combination of clinical remission and normal function) compared to those with non-normalized serum MMP-3 levels. This is the first study to report that serum MMP-3 levels, when combined with CRP levels or DAS28, can predict remission in patients with RA at a single time point of treatment.

Steroid therapy and renal dysfunction are independently associated with an increase in serum MMP-3 levels in patients with RA [20]. In this study, among patients with normal CRP levels, those with abnormal serum MMP-3 levels had a high rate of prednisolone use and low levels of eGFR. This suggests the need to consider the clinical characteristics of patients when adopting the normalization of serum MMP-3

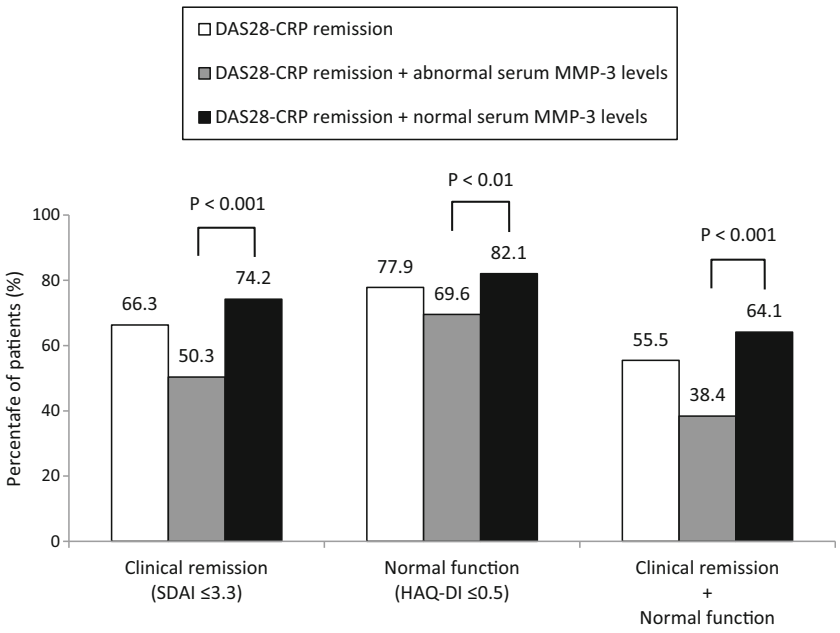


Fig. 3 Combination of DAS28-CRP remission and normal serum MMP-3 levels predicts clinical remission and normal function. SDAI Simplified Disease Activity Index, HAQ-DI Disability Index of the Health Assessment Questionnaire

levels as a treatment strategy for RA. In addition, since those patients were also older and had a longer disease duration, the rate of clinical remission and normal function could have been affected.

Serum MMP-3 levels have been reported to be significantly correlated with CRP levels in patients with RA [r = 0.5, Ribbens et al.; r = 0.478 (women), Hattori et al.] [20, 21]. In this study, a weaker correlation was found between serum MMP-3 and CRP levels in male patients relative to that in female patients, even though no significant difference was observed in the rate of prednisolone use and eGFR levels between male and female patients.

This study has some limitations. First, the results were based on data obtained at a single time point. Therefore, we could not assess the direction of the association, and measurement errors could have influenced the findings. Second, the participants of this study were patients with RA visiting the rheumatology clinic of our hospital. It is possible that this sample population may differ from the patient population as a whole.

In conclusion, normal serum MMP-3 levels, in combination with CRP levels or disease activity, are useful for predicting clinical remission and normal physical function in patients with RA. Our findings suggest that including an assessment of serum MMP-3 levels in the treatment strategy of patients with RA could contribute to the objective and rigorous evaluation that aims to achieve tight control of disease activity.

Compliance with ethical standards This study was approved by the ethics committee of our institute and was conducted from January through March 2013 in accordance with the Declaration of Helsinki. Patient anonymity was maintained during data collection, and security of personal information was strictly controlled. All patients gave their informed consent prior to their inclusion in the study.

Conflict of interest Yosuke Hattori received grants from Pfizer and Janssen Pharma. Daihei Kida received grants from Towa Pharma Corporation and Chugai Pharma Corporation. Atsushi Kaneko received grants from Astellas Pharma.

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