

Modified Disease Activity Score at 3 Months Is a Significant Predictor for Rapid Radiographic Progression at 12 Months Compared With Other Measures in Patients With Rheumatoid Arthritis

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Objective. Progressive rheumatoid arthritis (RA) is responsible for joint damage causing disabilities, but there is no agreement on which disease measures best predict radiographic progression. We aimed to determine which disease activity measures, including the disease activity score, the modified disease activity score in 28 joints with C-reactive protein testing (M-DAS28-CRP), the Clinical Disease Activity Index, and the Health Assessment Questionnaire Disability Index, at baseline and 3 months best predicted rapid radiographic progression (RRP) in patients with early RA.

Methods. Data were used from PREMIER, a 2-year, multicenter, double-blind, active comparator controlled study with methotrexate (MTX)–naïve patients with RA and active disease for less than 3 years. Treatments included adalimumab plus oral MTX, adalimumab, or oral MTX. Only patients in the MTX arm were analyzed in this study. RRP was defined as a change in the modified total Sharp score of less than 3.5 at month 12. The logistic regression analysis assessed the impact of measures at baseline and 3 months on RRP at 12 months. Best cutoff points of the M-DAS28-CRP were also estimated by using area under the receiver operating characteristic curve.

Results. A total of 149 patients were included (female patients: $n = 113$ [75.8%]; positive rheumatoid factor: $n = 127$ [85.2%]; mean [SD] age: 52.9 [13.3] years; mean [SD] disease duration: 0.8 [0.9] year; mean [SD] M-DAS28-CRP: 6.3 [0.9]). After adjusting for potential confounders, only the M-DAS28-CRP at baseline (adjusted odds ratio [AOR] = 3.29; 95% confidence interval [CI]: 1.70–6.36) and 3 months (AOR = 2.56; 95% CI: 1.43–4.56) strongly predicted RRP at 12 months. M-DAS28-CRP of 4.5 and 2.6 at baseline and 3 months, respectively, maximized positive and negative predictive values for prediction of RRP.

Conclusion. The M-DAS28-CRP was a stronger predictor at baseline and 3 months for RRP compared with other disease activity measures. Removing tender joint count and patient global assessment from the DAS28-CRP improves prediction of RRP.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory arthritis (1) that affects up to 1% of the population (2), nega-

tively impacts health-related quality of life (3,4), and is associated with numerous comorbidities (5,6).

Progressive RA is responsible for most disabilities found in this patient population and is usually characterized by radiographic

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SIGNIFICANCE & INNOVATIONS

- There is no agreement on which disease measures best predict radiographic progression in the RA population.
- We identified that compared with other disease activity measures, the modified disease activity score in 28 joints with C-reactive protein testing (M-DAS28-CRP) at 3 months' post initiation of treatment, considered a decision time point, was the strongest predictor for rapid radiographic progression.
- We identified that the optimal cutoff points of the M-DAS28-CRP for predicting rapid radiographic progression were 4.5 and 2.6 at baseline and 3 months, respectively.

damage in affected joints (7). Achieving low disease activity in RA is associated with a reduction in radiographic progression, leading to better patient functional activity (8,9).

In recent years, different measures of disease activity have been developed to score the severity of RA, which consequently allows clinicians to use an appropriate treatment regimen, including biologic agents, for controlling RA disease. However, there is no consistent agreement on which of these disease measures best predicts disease activity and progression (10). Furthermore, each of these disease activity measures has strengths and limitations. For instance, the disease activity score in 28 joints (DAS28), as a validated measure, has been widely used to assess disease activity in RA (11). However, it has different components, including 28 joint counts and laboratory testing of either C-reactive protein (CRP) or the erythrocyte sedimentation rate (ESR), that are not always collected at the time of visits (12). Thus, if other modified measures of disease activity could more accurately predict the disease progression better than the DAS28, both physicians and patients will benefit from this for controlling RA disease. Using randomized clinical trial (RCT) data (The Golimumab Before Employing Methotrexate as the First-Line Option in the Treatment of Rheumatoid Arthritis of Early Onset [GO-BEFORE]) from methotrexate (MTX)-naïve patients, Baker et al (13) identified that four variables, CRP, ESR, swollen joint count in 28 joints (SJC28), and physician global assessment (PhGA), were independently associated with magnetic resonance imaging (MRI)-detected synovitis and bone edema for all time points. They used weighted coefficients of CRP, PhGA, and SJC28 to develop a formula for a novel, modified disease activity score: modified DAS28 with CRP testing (M-DAS28-CRP) = $0.49 \times \text{linear log-transformed CRP} (\ln[\text{CRP}]) + 0.15 \times \text{SJC28} + 0.22 \times \text{PhGA} + 1$ (13).

They also validated superiority of the modified disease activity score, compared with a modified version of the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI), in predicting radiographic progression at 52 weeks in another RCT of patients with RA (GO-FORWARD) (13). However, statistical models and obtained estimates were mostly based on unadjusted models

in which it was assumed that the RCTs were balanced for potential confounders (eg, age, sex, rheumatoid factor [RF], and treatment).

Considering the superiority of the baseline M-DAS28-CRP in predicting radiographic progression in the absence of the tender joint count and patient global assessment (PtGA) (13), we aimed to extend the analysis to evaluate clinical measures, including the M-DAS28-CRP, in early RA 3 months after treatment, which is usually considered a decision time point by most clinicians regarding continuation of therapy.

We compared the ability of composite measures of disease activity (DAS28-CRP, M-DAS28-CRP, and CDAI) and patient-reported outcomes (PROs) (PtGA and Health Assessment Questionnaire Disability Index [HAQ-DI]) at baseline and 3 months to predict rapid radiographic progression (RRP) in RA. To confirm the most predictive component of the M-DAS28-CRP, we also investigated the impact of individual measures (CRP, PhGA, and SJC28) on RRP. Furthermore, we identified the optimal cutoff points of the M-DAS28-CRP for prediction of RRP.

PATIENTS AND METHODS

Study design and population. Data were obtained from the PREMIER study, a 2-year, multicenter, double-blind, active comparator controlled phase III clinical trial. Patients were eligible if they were 18 years of age or older, had disease that fulfilled the American College of Rheumatology (ACR) 1978 revised criteria for classification of RA (14), had active disease, and had a disease duration of less than 3 years. Patients were randomized to one of three treatment groups: adalimumab at 40 mg subcutaneously every other week plus weekly oral MTX (20 mg/wk) (adalimumab plus MTX), adalimumab at 40 mg subcutaneously every other week (adalimumab plus MTX placebo), and weekly oral MTX (MTX plus adalimumab placebo). Details of this clinical trial and patients' eligibility have been published previously (15). For this analysis, only patients enrolled in the MTX arm were included. All patients with available data on disease activity measures and PROs at baseline and follow-up were included in the analysis.

Disease activity measures assessment. A number of measures of disease activity, including the ESR, DAS28-CRP, M-DAS28-CRP, and CDAI, and PROs (PtGA and HAQ-DI) were assessed at baseline and the 3-month follow-up. A change (decrease) in the DAS28-CRP greater than 1.2 from baseline to 3 months was also considered a disease improvement, and its impact was assessed for RRP at 12 months.

Outcome. RRP was defined as a change in the modified total Sharp score greater than 3.5 between baseline and 12 months. This was based on the definition used in the original and previous studies (15,16). Details of radiographic progression definition and evaluation methods have also been explained in the original study (15).

Statistical analysis. Descriptive statistics, specifically the mean and SD for continuous variables and counts and proportions for categorical variables, were produced for all baseline characteristics. Logistic regression analysis was used to assess the impact of disease activity measures at baseline and 3 months to predict RRP at 12 months. The regression models were adjusted for potential confounders, including age, sex, positive RF, previous use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), steroid use, and other disease measures (including DAS28-CRP, CDAI, ESR, PtGA, and HAQ-DI). The presence of multicollinearity between activity measures (as predictors) was checked by estimating the variance inflation factor (VIF) before performing multivariable logistic regression. To have comparable values of disease activities, a log scale of odds ratios (ORs) was used to plot for the impact of measures on RRP. The area under the receiver operating characteristic (ROC) curve (area under the curve [AUC]) for the effect of various disease activity measures and PRO on RRP at 12 months was also calculated.

Research ethics approval for this study was obtained from the Mount Sinai Hospital Research Ethics Board.

Subset analysis. In a subset analysis, we used logistic regression models to assess the impact of three components of the M-DAS28-CRP, including ln(CRP), PhGA, and SJC28, at baseline and 3 months to predict RRP at 12 months. The regression models were adjusted for the same potential confounders.

Using the AUC, we also determined the optimal dose cutoff points of the M-DAS28-CRP at baseline and 3 months that can predict the status of patients in terms of radiograph progression at 12 months. For this purpose, the Youden index (J) (17) was used to obtain the best cutoff points based on positive predictive value (PPV) and negative predictive value (NPV). The Youden index is the maximum potential effectiveness of a diagnostic or predictive test; it maximizes the distance between the chance diagonal line and the point (x, y) on the ROC curve, a point farthest from random. It ranges between 0 and 1. $J = 1$ indicates that there is no false-negative rate or false-positive rate and that the effectiveness of the diagnostic test is perfect. $J = 0$ indicates that the test is not effective and that the predictive or diagnostic test is useless.

RESULTS

Baseline demographics and disease activity measures. A total of 149 patients with RA were included in the analysis (mean [SD] age: 52.9 [13.3] years), with the majority of patients being women ($n = 113$; 75.8%) (Table 1). The mean (SD) duration of RA in the total cohort was 0.8 (0.9) year, with 85.2% ($n = 127$) of patients being RF-positive. In terms of disease activity, the means (SDs) of the DAS28-CRP, CDAI, and M-DAS28-CRP were 6.3 (0.9), 44.7 (12.2), and 5.1 (1.3), respectively. Forty-six (30.9%) and sixty-two (41.6%) patients previously received csDMARDs and steroids, respectively.

Table 1. Baseline characteristics of analysis population

	Total (N = 149)	By RRP Status at 12 mo		<i>P</i>
		No (n = 89)	Yes (n = 60)	
Sex, female, n (%)	113 (75.8)	71 (79.8)	42 (70.0)	0.18
Age, y, mean (SD)	52.9 (13.3)	53.7 (12.6)	51.7 (14.4)	0.38
Positive rheumatoid factor, n (%)	127 (85.2)	70 (78.7)	57 (95.0)	0.01
Prior steroid use, n (%)	62 (41.6)	44 (49.4)	18 (30.0)	0.02
Prior csDMARD use, n (%)	46 (30.9)	29 (32.6)	17 (28.3)	0.58
Disease duration, y, mean (SD)	0.8 (0.9)	0.9 (0.9)	0.7 (0.8)	0.22
ESR, mm/h, mean (SD)	46.6 (23.9)	42.8 (20.5)	52.3 (27.5)	0.03
CRP, mg/dl, mean (SD)	3.9 (4.2)	3.0 (3.2)	5.3 (5.0)	0.002
Patient assessment of pain, mean (SD)	57.7 (24.4)	56.3 (24.8)	59.9 (23.8)	0.38
PtGA, mean (SD)	6.1 (2.6)	6.0 (2.7)	6.1 (2.4)	0.80
PhGA, mean (SD)	6.6 (1.7)	6.3 (1.8)	7.0 (1.6)	0.01
SJC28, mean (SD)	14.7 (5.7)	13.9 (5.7)	15.9 (5.5)	0.03
TJC28, mean (SD)	17.4 (6.5)	17.9 (6.7)	16.6 (6.2)	0.22
DAS28-CRP, mean (SD)	6.3 (0.9)	6.2 (0.9)	6.4 (0.9)	0.17
M-DAS28-CRP, mean (SD)	5.1 (1.3)	4.8 (1.2)	5.5 (1.2)	0.0004
CDAI, mean (SD)	44.7 (12.2)	44.1 (12.6)	45.6 (11.5)	0.47
HAQ-DI, mean (SD)	1.5 (0.7)	1.4 (0.7)	1.5 (0.6)	0.40

Abbreviation: CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP, disease activity score in 28 joints with C-reactive protein testing; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; M-DAS28-CRP, modified disease activity score in 28 joints with C-reactive protein testing; PhGA, physician global assessment; PtGA, patient global assessment; RRP, rapid radiographic progression; SJC28, swollen joint count in 28 joints; TJC28, tender joint count in 28 joints. Significant *P*-values < 0.05 are shown in bold.

Table 2. Unadjusted and adjusted odds ratios for disease activity at baseline and 3 mo and radiographic progression at 12 mo

Disease Measures	RRP at 12 mo, Odds Ratio (95% Confidence Limit), <i>P</i>			
	Baseline		3 mo	
	Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a
DAS28-CRP	1.30 (0.89-1.89), 0.17	0.71 (0.18-2.82), 0.63	1.60 (1.21-2.12), 0.001	1.31 (0.42-4.07), 0.64
CDAI	1.01 (0.98-1.04), 0.47	0.94 (0.87-1.01), 0.08	1.04 (1.01-1.06), 0.004	0.92 (0.85-1.00), 0.05
HAQ-DI	1.24 (0.76-2.03), 0.40	0.82 (0.37-1.80), 0.61	1.70 (1.03-2.77), 0.04	1.09 (0.46-2.59), 0.84
ESR	1.02 (1.00-1.03), 0.02	1.01 (0.99-1.03), 0.42	1.02 (1.00-1.04), 0.03	1.00 (0.97-1.02), 0.70
PtGA	1.02 (0.89-1.16), 0.79	1.07 (0.85-1.36), 0.56	1.18 (1.03-1.35), 0.02	1.10 (0.86-1.41), 0.46
M-DAS28-CRP	1.64 (1.23-2.19), 0.0007	3.29 (1.70-6.36), 0.0004	1.78 (1.37-2.32), <0.0001	2.56 (1.43-4.56), 0.002
DAS change at 3 mo	0.67 (0.50-0.91), 0.01	0.82 (0.49-1.39), 0.46

Abbreviation: CDAI, Clinical Disease Activity Index; DAS, disease activity score; DAS28-CRP, disease activity score in 28 joints with C-reactive protein testing; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; M-DAS28-CRP, modified disease activity score in 28 joints with C-reactive protein testing; PtGA, patient global assessment; RRP, rapid radiographic progression.

^aAdjusted for age, sex, rheumatoid factor positivity, and previous use of steroids and conventional synthetic disease-modifying antirheumatic drugs.

Significant *P*-values < 0.05 are shown in bold.

Disease activity measures and PROs at baseline and RRP at 12 months. An estimated VIF less than 10 indicated that there was no multicollinearity between different variables included in multivariable logistic regression models. Among disease activity measures and PROs at baseline, the M-DAS28-CRP was the strongest predictor for RRP at 12 months (adjusted odds ratio [AOR] = 3.29; 95% confidence interval [CI]: 1.70-6.36). The DAS28-CRP, CDAI, ESR, PtGA, and HAQ-DI showed no significant impact on RRP at 12 months (Table 2).

The AUC of the M-DAS28-CRP at baseline was also greater than that of other measures (AUC = 0.66; 95% CI: 0.57-0.74) (Table 3 and Figure 1). There was a significant difference between the AUC for the M-DAS28-CRP and DAS28-CRP (AUC difference = 0.10; *P* = 0.02) (Table 3). The AUCs for the DAS28-CRP, CDAI, ESR, PtGA, and HAQ-DI were approximately similar and ranged from 0.51 to 0.59.

Disease activity measures and PROs at 3 months and RRP at 12 months. All disease activity measures and PROs (HAQ-DI and PtGA) at 3 months were revealed as significant

predictors for RRP in the univariable logistic regression. However, only the M-DAS28-CRP remained a significant predictor for RRP at 12 months (AOR = 2.56; 95% CI: 1.43-4.56) after applying the multivariable analysis and adjusting for other potential confounders. Of note, the impact of the M-DAS28-CRP at 3 months was smaller than its impact at baseline (Table 2). The AUC for M-DAS28-CRP (AUC = 0.74; 95% CI: 0.66-0.82) at 3 months was also greater than that of other measures (Table 3 and Figure 1). However, there was no significant difference for the AUC between the M-DAS28-CRP and DAS28-CRP (AUC difference = 0.07; *P* = 0.50) (Table 3). All other AUC measures had approximately similar ranges from 0.62 to 0.67 (Figure 1).

Predictive effect of the M-DAS28-CRP components at baseline and 3 months on RRP at 12 months. Table 4 shows the association between M-DAS28-CRP components (ln[CRP], PhGA, and SJC28) at baseline and 3 months and RRP at 12 months. In the multivariable logistic regression analysis, CRP at both baseline (AOR = 2.82; 95% CI: 1.22-6.51) and 3 months (AOR = 4.03; 95% CI: 1.59-10.2) had the strongest

Table 3. AUC for disease activity at baseline and 3 mo and radiographic progression at 12 mo

Disease Measures	AUC for RRP at 12 mo			
	Baseline		3 mo	
	AUC (95% CI)	AUC Difference, <i>P</i>	AUC (95% CI)	AUC Difference, <i>P</i>
DAS28-CRP	0.55 (0.46-0.65)	Reference	0.67 (0.58-0.76)	Reference
CDAI	0.53 (0.44-0.63)	-0.02, 0.33	0.66 (0.57-0.75)	-0.01, 0.72
HAQ-DI	0.52 (0.43-0.61)	-0.03, 0.43	0.62 (0.53-0.71)	-0.05, 0.24
ESR	0.59 (0.50-0.69)	0.04, 0.46	0.64 (0.54-0.73)	-0.03, 0.56
PtGA	0.51 (0.41-0.60)	-0.04, 0.63	0.64 (0.55-0.73)	-0.03, 0.44
M-DAS28-CRP	0.66 (0.57-0.74)	0.10, 0.02	0.74 (0.66-0.82)	0.07, 0.50
DAS change at 3 months	0.65 (0.55-0.74)	-0.02, 0.50

Abbreviation: AUC, area under the curve; CDAI, Clinical Disease Activity Index; DAS, disease activity score; DAS28-CRP, disease activity score in 28 joints with C-reactive protein testing; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; M-DAS28-CRP, modified disease activity score in 28 joints with C-reactive protein testing; PtGA, patient global assessment; RRP, rapid radiographic progression. Significant *P*-values < 0.05 are shown in bold.

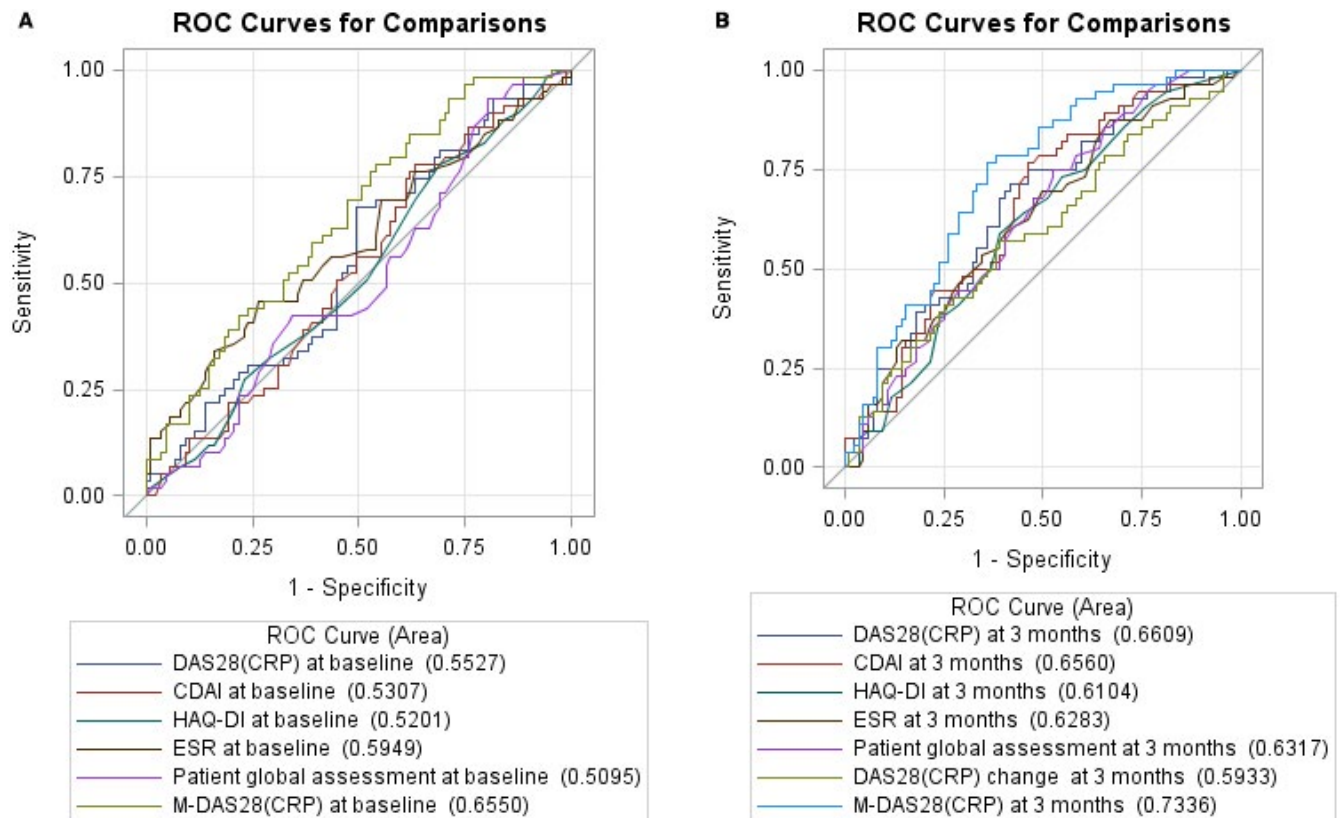


Figure 1. Receiver operating characteristic (ROC) curves for disease activity measures versus rapid progression at 12 months. **A**, Baseline. **B**, 3 months. CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28(CRP), disease activity score in 28 joints with C-reactive protein testing; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; M-DAS28(CRP), modified disease activity score in 28 joints with C-reactive protein testing.

effect on prediction of radiographic progression at 12 months, with a bigger effect at 3 months compared with baseline (Supplementary Figure 1).

Optimal cutoff points for the M-DAS28-CRP at baseline and 3 months predicting RRP at 12 months. The corresponding optimal cutoff point for the M-DAS28-CRP at baseline, determined by the estimated Youden index, was 4.5, with a PPV and NPV of 50.0% and 76%, respectively, in predicting RRP at 1

year. It can be inferred that there is 50% probability that a patient will develop RRP when the M-DAS28-CRP is greater than or equal to 4.5, classifying him or her into the progressor group, and that there is a 76% probability that a patient will not develop RRP when the M-DAS28-CRP is less than 4.5, classifying him or her into the nonprogressor group. The corresponding optimal cutoff point for the M-DAS28-CRP at 3 months was 2.6, with a PPV of 59% and an NPV of 81%. A list of various M-DAS28-CRP cutoff points is provided in Table 5.

Table 4. Unadjusted and adjusted odds ratios for M-DAS28-CRP components at baseline and radiographic progression at 12 mo

M-DAS28-CRP Components	RRP at 12 mo, Odds Ratio (95% Confidence Limit), <i>P</i>			
	Baseline		3 mo	
	Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a
ln(CRP)	3.44 (1.66-7.13), 0.001	2.82 (1.22-6.51), 0.01	4.25 (1.95-9.28), 0.0003	4.03 (1.59-10.2), 0.003
SJC28	1.53 (1.03-2.28), 0.04	1.37 (0.86-2.19), 0.19	2.14 (1.45-3.16), 0.0001	2.09 (1.27-3.45), 0.004
PhGA	3.14 (1.23-8.03), 0.02	1.67 (0.57-4.94), 0.35	2.54 (1.23-5.24), 0.01	0.81 (0.30-21.7), 0.67

Abbreviation: CRP, C-reactive protein; ln(CRP), linear log-transformed C-reactive protein; M-DAS28-CRP: modified disease activity score in 28 joints with C-reactive protein testing; PhGA, physician global assessment; RRP, rapid radiographic progression; SJC28, swollen joint count in 28 joints.

^aAdjusted for age, sex, rheumatoid factor positivity, and previous use of steroids and conventional synthetic disease-modifying antirheumatic drugs.

Significant *P*-values < 0.05 are shown in bold.

Table 5. Clinical cutoff points of the M-DAS28-CRP and relevant sensitivity, specificity, PPV, and NPV

Youden Index	Cutoff Points	Sensitivity	Specificity	PPV	NPV
At baseline					
0.23	4.61	0.75	0.48	0.49	0.74
0.24	4.82	0.70	0.54	0.51	0.73
0.25	4.61	0.77	0.48	0.50	0.75
0.26	4.50	0.78	0.47	0.50	0.76
0.24	4.46	0.78	0.46	0.49	0.76
0.23	4.44	0.78	0.45	0.49	0.75
At 3 mo					
0.37	2.69	0.72	0.65	0.58	0.78
0.38	2.73	0.72	0.66	0.59	0.78
0.39	2.63	0.75	0.64	0.58	0.80
0.41	2.63	0.77	0.64	0.59	0.81
0.40	2.63	0.77	0.63	0.58	0.81
0.39	2.60	0.77	0.62	0.57	0.80

Abbreviation: M-DAS28-CRP, modified disease activity score in 28 joints with C-reactive protein testing; NPV, negative predictive value; PPV, positive predictive value. Optimal values are shown in bold.

DISCUSSION

In this post hoc analysis, we determined the ability of different measures of disease activity (DAS28-CRP, M-DAS28-CRP, and DAS28-CRP change greater than or equal to 1.2) as well as the HAQ-DI and PtGA at both baseline and 3 months to predict RRP at 12 months.

Previous studies have already shown a correlation between conventional disease scores and radiographic progression(18,19). In our current study, we found that the M-DAS28-CRP at baseline and, particularly, at 3 months (as an important clinical decision time point) had a more significant predictive impact on future radiographic progression when compared with other current disease activity measures. One possible explanation for this superiority could be the fact that the M-DAS28-CRP does not include the tender joint count, which can be affected by joint damage and osteoarthritis even more than active synovitis in many cases.

Our finding is supported by a previous study that showed that both conventional and modified scores are correlated with detected synovitis in MRI, with superiority of modified scores compared with conventional scores(13). A recent analysis on data from the AMPLE (abatacept versus adalimumab comparison in biologic-naïve subjects with rheumatoid arthritis with background MTX) clinical trial also showed that compared with the DAS28, CDAI, SDAI, and Routine Assessment of Patient Index Data 3 (RAPID3) at baseline, the M-DAS28-CRP was the strongest predictor of radiographic progression at both 12 and 24 months (20).

We were able to confirm and extend findings of the Baker et al (13) study, which showed that CRP at both baseline and 3 months was an independent and the strongest component of the M-DAS28-CRP for prediction of radiographic progression.

For the first time, we defined optimal cutoff points for the M-DAS28-CRP using radiographic progression as a proxy for

disease activity. These cutoff points, particularly lower values for 3 months compared with baseline, can be used to classify radiographic progression according to their calculated PPV and NPV. However, these cutoff points have moderate accuracy for discrimination of radiographic progression. A lower cutoff point of the modified disease activity score at 3 months was expected because of an improvement in disease severity due to the treatment efficacy of MTX after initiation.

We were not able to assess the cutoff points of the M-DAS28-CRP for different disease activity categories at baseline because we did not have an adequate number of patients in the low or moderate disease groups because of the high disease profile of the patients (Table 1).

Of note, the unadjusted predictive impact of the M-DAS28-CRP at 3 months was slightly larger than that at baseline (OR: 1.78 vs.1.64), which was consistent with the corresponding AUC (0.74 vs.0.66). However, after adjusting for demographic factors and other disease measures, the OR for the M-DAS28-CRP at 3 months was smaller than that at baseline (2.56 vs. 3.29). This implies that characteristics of patients should be taken into account by clinicians in their decision for a treatment strategy. Furthermore, it can suggest that early treatment of patients has a significant protective impact on disease severity and radiographic progression. We assumed that the reason for having a smaller OR for the M-DAS28-CRP at 3 months compared with baseline might be due to entering PtGA in the multivariable model analysis. Therefore, as sensitivity analysis, we excluded PtGA from models. We found that the OR for the M-DAS28-CRP at 3 months still remained smaller (2.67) compared with that at baseline (3.07) (Supplementary Table 1).

The current analysis was a post hoc analysis with a relatively small sample size in the MTX arm of the PREMIER study, which was originally designed for comparison of the efficacy of three treatment groups: adalimumab at 40 mg subcutaneously every other

week plus weekly oral MTX (20 mg/wk) (adalimumab plus MTX), adalimumab at 40 mg subcutaneously every other week (adalimumab plus placebo MTX), and weekly oral MTX (MTX plus placebo adalimumab). An analysis of other treatment arms to assess the predictive impact of disease measures is an advantage to improve generalizability of our findings. However, as a limitation for this study, we did not have access to other treatment arms data.

Lack of data on other important variables, such as smoking and body mass index, could be considered a limitation for this analysis. Study power calculation for the original design might not have been appropriate for this post hoc analysis. Thus, interpretation of results can be affected with this limitation.

In summary, our analysis demonstrated that the M-DAS28-CRP is a stronger predictor of RRP both at baseline and at 3 months compared with other disease activity measures and PROs in patients with early RA initiating MTX. These data showed that removing the tender joint count and PtGA from the DAS28-CRP improved prediction of radiographic progression using clinical measures. Modified version of disease activity scores, such as the M-DAS28, might be beneficial as an alternative measure of disease activity for rheumatologists in the routine care setting for their treat-to-target approach.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Movahedi and Keystone had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Movahedi, Akhavan, Keystone.

Acquisition of data. Weber, Akhavan, Keystone.

Analysis and interpretation of data. Movahedi, Akhavan, Keystone.

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