ORIGINAL ARTICLE

Clinical Prediction Score of 1-Year Sustained Remission to Methotrexate Combination Therapy in Patients with Early Rheumatoid Arthritis

Sujin Lertwises, MD[1], Chatchawan Pirot, MD[2], Todsaporn Sirithiantong, MD[2]

[1] Division of Rheumatology, Department of Medicine, Hatyai Hospital, Songkhla, Thailand; [2] Department of Orthopedics, Hatyai Hospital, Songkhla, Thailand

Objective: To develop a prediction stratification score for the prediction of sustained remission (SR) to methotrexate (MTX) therapy in patients with early rheumatoid arthritis (ERA).

Materials and Methods: Prognostic research with clinical prediction score was conducted. All patients with ERA who experienced moderate to high disease activity at a tertiary hospital were included. Multivariable logistic regression models were used to assess each variable predictor. Logistic coefficients of each predictor were used for generating scores. Predictive performance was internally validated using bootstrapping techniques.

Results: One hundred seventy-five patients, of which 93 had SR, were included. The prediction score had four final predictors, age less than 65 years (0, 2), initial health assessment questionnaires less than 1 (0, 3), baseline disease activity score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR) (0, 1), and DAS28-ESR at three months less than 3.2 (0, 5) were included in the logistic model. The positive predictive value for the high-risk score, which was greater than 3.5, was 87 (95% CI 76.7 to 93.9) results used in the model as a clinical predictor of MTX response. The SR score had a good predictive performance (AUROC 0.85, 95% CI 0.80 to 0.90).

Conclusion: The SR score demonstrated good performance and discrimination for predicting SR to MTX combination therapy in patients with ERA for a safe long term follow up using simplified parameters in a clinical setting.

Keywords: Remission; Rheumatoid arthritis; Clinical predictor; Predictive score

Received 1 July 2024 | Revised 28 September 2024 | Accepted 9 October 2024

J Med Assoc Thai 2024;107(11):873-80

Website: http://www.jmatonline.com

Rheumatoid arthritis (RA) is defined as chronic systemic inflammation of the synovial joints that leads to joint destruction and disability. Sustained remission (SR) has a more stable disease activity, preventing joint destruction, improved functional outcomes, reduced comorbidity risks, and a lower incidence of radiographic progression[1]. Predictors of remission in a systematic review[2] include male gender, higher education level, and lower baseline disease activity. Some SR predictors were male gender, lower baseline disease activity[3], initial use of combination[4], and good EULAR response in the first year[5]. Negatively associated predictors were initial use of oral steroids, baseline pain, obesity, longer duration[4].

Previous multivariate prognostic models have been used to predict the risk of joint destruction[6,7] and remission[8]. The previous prediction scoring systems were to assess insufficient response to MTX therapy by using clinical factors, genetics[9], and erythrocyte folate levels of less than 750 nmol/L[9]. Multi-biomarker disease activity (MBDA)[10] is a reliable prognostic marker of radiographic progression but could not predict response to MTX therapy. Previous models used genetic, metabolic, and serum biomarkers from unconventional laboratory tests and impractical routine examinations as predictors. Previous models had a fair discriminative ability, with an area under the receiver operating characteristic curve (AUROC) of 0.67 to 0.75[8,11,12]. However, no published studies contain data that can be used in the real public health system in Thailand with limited allocation of healthcare resources.

Therefore, the present study aimed to develop a clinical prediction score of SR in patients with ERA

Correspondence to:

Sirithiantong T.
Department of Orthopedics, Hatyai Hospital, Songkhla 90110, Thailand.
Phone: +66-88-7910428
Email: tod.sk123@gmail.com

How to cite this article:

Lertwises S, Pirot C, Sirithiantong T. Clinical Prediction Score of 1-Year Sustained Remission to Methotrexate Combination Therapy in Patients with Early Rheumatoid Arthritis. J Med Assoc Thai 2024;107:873-80.
DOI: 10.35755/jmedassocthai.2024.11.873-880-01337

who had only used conventional synthetic (cs) disease antirheumatic drugs (DMARDs).

Materials and Methods

A prognostic research and clinical score development study was conducted based on a single center; retrospective cohort of patients admitted at a tertiary public health hospital in Southern Thailand. The protocol was approved by the Institutional Ethics Committee (protocol number 37/2564).

Study population

The medical records from the patients who visited the outpatient medical department, Hatyai Hospital between January 2016 and December 2021 were eligible for inclusion if they were older than 18 years old, diagnosed as ERA with a disease duration of less than one year[4], diagnosis based on the 2010 American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) classification criteria[13], moderate to severe disease activity, and DMARD naive. The exclusion criteria were (a) any rheumatic diseases other than secondary Sjogren's syndrome, (b) concurrent malignancy, and (c) insufficiency data for analysis.

To date, no approach has been recommended for sample size calculation in the development of the clinical prediction model. A database was used for score derivation to maximize statistical power and generalizability. The sample size was calculated using the minimum sample size required for developing a multivariable prediction, which suggested the rule-of-thumb of 10 endpoint events per candidate parameter.

Data collection and SR assessment

The clinical baseline characteristics included age, gender, disease duration, body mass index (BMI), comorbidities such as hypertension and diabetes mellitus, smoking history, general health based on a visual analog scale of 100 mm, functional ability health assessment questionnaire (HAQ) score, tender joint count (TJC), and swollen joint count (SJC). Disease activity was evaluated using DAS28-ESR at baseline and via regular follow-up every three months. The initial laboratory tests included ESR, rheumatoid factor (RF), and anticitrullinated protein antibody (ACPA). The treatment strategy was based on the EULAR recommendations[1], starting in combination with MTX and more than one other csDMARDs. The csDMARDs were used starting MTX dose was 7.5 mg/week orally and increasing stepwise 5 mg every 4 to 12 weeks up to 17.5 mg/week due to the average Thai weight less than Europeans and combined with other csDMARDs such as sulfasalazine (SSZ) 1,000 to 2,000 mg/day, hydroxychloroquine (HCQ) 5 mg/kg/day, leflunomide (LEF) 10 to 20 mg/day and concomitant oral glucocorticoid with prednisolone less than 7.5 mg/day, or non-steroidal anti-inflammatory drugs. The rheumatologist selected treatment based on disease activity scores for achieving clinical remission according to the treat-to-target EULAR recommendation for DMARDs in patients with ERA and clinical remission at six months who must continually receive the medication at the same dose for 12 months during remission. All patients were evaluated at baseline visits and regular follow-ups to determine the treatment strategy for clinical remission. SR was defined as a DAS28-ESR remission score of less than 2.6 for at least two consecutive visits at six month or longer[4,14,15]. Data at the endpoint of 12 months were included in the analysis.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD) and as the number of frequencies and percentages for categorical data. Comparisons between categorical variables were performed using the chi-squared (χ^2) tests or Fisher's exact probability tests as appropriate. Variables significant in the univariable logistic regression were subsequently included in the multivariable logistic regression analyses using Stata Statistical Software, version 15.1 (StataCorp LLC, College Station, TX, USA).

Modeling and score development

The predictors were evaluated based on statistical significance, AUROC, or significant clinical-related factors using logistic regression analysis to identify predictors of SR. First, baseline characteristics and treatment modality data were analyzed individually. Then, a multiple logistic regression model with backward selection included significant variables, with a p-value of less than 0.05. The reduced multivariable model was assessed for its predictive performance in terms of discrimination and calibration, using the clinical AUROC to evaluate the model's discriminative ability. Calibration was evaluated using the calibration curve and Hosmer-Lemeshow goodness-of-fit test, where a non-significant χ^2 value indicated a good fit model. The decision curve analysis determined the potential clinical use, calculating the net benefit of using the

model in practice to classify patients across a range of clinically relevant threshold probabilities compared with SR and non-SR to MTX therapy in patients with ERA. The performance of each model was assessed in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

The final predictors were given logistic regression coefficients. After reducing the model, the regression coefficients in log-odds form for the remaining predictors were calculated and used to create a weighted score. The model's lowest coefficient was categorized by dividing each predictor's logistic coefficient and rounding to the nearest non-decimal integer for practicality. The sum score was classified as indicating lower or higher risk. The calculated PPV was used for each score group to show the average prediction for the patients. Calibration and discrimination measures were also conducted using regression with the model's survival rate. A calibration plot comparing the model-predicted risk with the observed risk demonstrated predictive performance. To assess the model's optimism, predictive performance was internally validated using nonparametric ROC regression with 1,000 bootstrapped replicates. A p-value less than 0.05 indicated statistical significance.

The classified scores divided patients into two risk groups, low risk and high risk. For the low-risk group, using lower cutoff points reduced the PPV, while higher cutoff points increased the PPV for the high-risk group. The model's ability to distinguish between the two groups was evaluated using 95% confidence intervals (CIs) to ensure that the specific PPV values did not overlap. The potential clinical usefulness of the model was assessed using a decision curve analysis, which compared the net benefit of applying the model to classify patients across a range of relevant probability thresholds, considering two groups of outcomes, SR or non-SR, in patients with ERA.

Results

Among 230 patients identified, 175 met the inclusion criteria and were enrolled in the present study. Of these patients, 93 had SR, and 82 had non-SR (Table 1). Fifty-five patients were excluded for the coexistence of other connective tissue disease (15), concurrent malignancies (2), and insufficient data for analysis (38). The results of comparisons between the SR and non-SR groups regarding the baseline clinical characteristics and treatment findings can be found in Table 1.

Model development and score

Prognostic factors showing high predictive performance with a significant p of less than 0.05, AUROC greater than 0.59, and clinically meaningful correlation were selected in the univariate logistic regression model ($p<0.05$). The present study model, based on predictors of SR such as age, gender, disease duration, BMI, diabetes mellitus, hypertension, HAQ score, TJC, SJC, RF, and ACPA positivity, baseline DAS28-ESR, and DAS28-ESR at three months, was simultaneously examined using multivariable logistic regression with statistically significant predictors ($p<0.05$). Subsequently, non-contributory and non-significant predictors were gradually eliminated through backward selection. The variables that remained in the final multivariable prediction model were age, baseline DAS28-ESR, initial HAQ, and DAS28-ESR at three months. Multivariable analysis confirmed that each factor was predictive of SR, with scores ranging from 0 to 12.5. Regression coefficients for each level of each clinical predictor were divided by the smallest coefficient of the model and rounded to the nearest 0 or 0.5. The present study transformed the regression coefficients of the model's predictors into simple scores.

The SR sum score was calculated by adding the scores of each variable: Sum score = age [score] + baseline DAS28-ESR [score] + HAQ [score] + DAS28-ESR at three months [score] (Table 2). The model was able to predict SR with good accuracy (AUROC 0.85, 95% CI 0.80 to 0.90), as shown in Figure 1. The model correctly classified with a sensitivity of 64%, specificity of 89%, PPV of 86%, and NPV of 68%.

The calibration plot indicated that the predicted and observed risks of using SR concurrently increased together (C-statistic=0.85, slope=1.0) (Figure 2). The model underwent internal validation using non-parametric ROC with 1,000 bootstrap sampling techniques (bootstrap shrinkage=1.002).

Finally, clinical prediction scores were divided into two risk groups, the low-risk with a score of 3.5 or less and high-risk with a score of more than 3.5 (Table 3). The PPV in the high-risk groups was 87.0 (95% CI 76.7 to 93.9).

The model's performance in terms of clinical usefulness and curve analysis can explain the prediction model's net benefit (SR). A cutoff probability threshold of 0.53, for prevalence point, indicated that the present study predicted model showed a 2.8 times higher net benefit compared to that without the predictive model (Figure 3).

Table 1. Comparison of clinical characteristics of sustained remission vs. non-sustained remission

Clinical parameters	Sustained remission (n=93)	Non-sustained remission (n=82)	p-value	AUROC (95% CI)
Baseline characteristics				
Age (years); mean±SD	51.02±1.22	54.88±1.18	0.025	0.59 (0.32 to 0.49)
Female; n (%)	82 (88.17)	75 (91.46)	0.619	0.51 (0.26 to 1.89)
Disease duration (months); mean±SD	4.48±0.31	5.14±0.34	0.151	0.59 (0.33 to 0.50)
BMI (kg/m^2); mean±SD	24.18±5.9	24.92±6.5	0.436	0.53 (0.38 to 0.55)
Diabetes mellitus; n (%)	10 (10.8)	14 (17.1)	0.227	0.53 (0.38 to 0.49)
Hypertension; n (%)	15 (16.1)	26 (31.7)	0.015	0.57 (0.36 to 0.49)
Smoking; n (%)	6 (6.5)	6 (7.3)	0.824	0.5 (0.46 to 0.53)0
HAQ; mean±SD	1.3±0.07	2.1±0.10	<0.001	0.76 (0.17 to 0.31)
TJC; mean±SD	16.54±0.97	19.13±1.26	0.102	0.56 (0.35 to 0.52)
SJC; mean±SD	14.81±1.1	17.5±1.24	0.099	0.56 (0.35 to 0.52)
Positive RF; n (%)	46 (49.5)	48 (58.5)	0.232	0.54 (0.38 to 0.53)
Positive ACPA; n (%)	25 (26.8)	46 (56.1)	<0.001	0.54 (0.29 to 0.44)
Baseline DAS28-ESR; mean±SD	6.43±0.14	7.1±1.24	<0.001	0.64 (0.27 to 0.44)
DAS28-ESR (>3.2 to 5.1); n (%)	20 (21.5)	6 (7.3)	0.012	0.57 (0.52 to 0.62)
DAS28-ESR (>5.1); n (%)	73 (78.5)	76 (92.7)	0.012	0.57 (0.52 to 0.62)
Treatment modality				
Prednisolone dose <7.5 mg/day use; n (%)	62 (66.4)	61 (74.4)	0.267	0.54 (0.39 to 0.53)
MTX dose (mg/week); mean±SD	13.08±0.33	13.7±0.26	0.143	0.57 (0.35 to 0.50)
SSZ use; n (%)	50 (30.8)	65 (79.3)	0.003	0.63 (0.30 to 0.44)
HCQ use; n (%)	71 (76.3)	59 (72.0)	0.509	0.52 (0.46 to 0.59)
LEF use; n (%)	14 (15.1)	28 (34.2)	0.003	0.59 (0.34 to 0.47)
Treatment regimen				
2 csDMARDs; n (%)	72 (77.4)	69 (84.5)	0.264	0.53 (0.48-0.59)
3 csDMARDs; n (%)	43 (46.2)	56 (68.2)	0.004	0.61 (0.53-0.68)
4 csDMARDs; n (%)	11 (11.8)	17 (20.73)	0.113	0.54 (0.48-0.59)
DAS28-ESR at 3 months; mean±SD	3.92±1.52	5.4±1.4	<0.001	0.78 (0.16 to 0.29)
DAS28-ESR at 6 months; mean±SD	2.71±0.1	4.6±0.16	<0.001	0.88 (0.07 to 0.16)

BMI=body mass index; HAQ=health assessment questionnaire; TJC=total joint count; SJC=swollen joint count; RF=rheumatoid factor; ACPA=anticitrullinated protein antibodies; DAS28-ESR=disease activity 28-erythrocyte sedimentation rate; MTX=methotrexate; SSZ=sulfasalazine; HCQ=hydroxychloroquine; LEF=leflunamide; csDMARDS=conventinal disease modifying antirheumatic drugs; SD=standard deviation; AUROC=area under the receiver operating characteristic curve; CI=confidence interval

Table 2. Predictors for 1-year sustained remission based on multivariate logistic regression analysis

Predictors	OR	95% CI	p-value	Beta coefficient	Adjust beta coefficient@	Score
Age (0 to 1)						
≥65	1.00	Reference	-	-	-	0
<65	5.46	1.22 to 24.25	0.026	1.70	1.95	2
Baseline DAS28-ESR (0 to 1)						
≥5.1	1.00	Reference	-	-	-	0
<5.1	2.39	0.78 to 7.34	0.127	0.87(*)	1	1
HAQ (0 to 3)						
>2	1.00	Reference	-	-	-	0
1 to 2	3.49	1.49 to 8.15	0.004	1.25	1.43	1.5
<1	13.43	4.18 to 43.10	<0.001	2.60	2.98	3
Three months DAS28-ESR (0 to 5)						
≥3.2	1.00	Reference	-	-	-	0
<3.2	95.67	9.02 to 1014.99	<0.001	4.56	5.23	5

DAS28-ESR=disease activity 28-erythrocyte sedimentation rate; HAQ=health assessment questionnaire; OR=odds ratio; CI=confidence interval
@ Adjust beta coefficient=beta coefficient in that Raw/lowest beta coefficient

Table 3. Performance of prediction score at different cutoff value to predict 1-year sustained remission

Score categories	Score	Sustained remission (n=93); n (%)	Non-sustained remission (n=82); n (%)	PPV (%)	95% CI	p-value
Low	≤3.5	33 (31)	73 (69)	31.1	22.5 to 40.9	<0.001
High	>3.5	60 (87)	9 (13)	87.0	76.7 to 93.9	<0.001

PPV=positive predictive value; CI=confidence interval

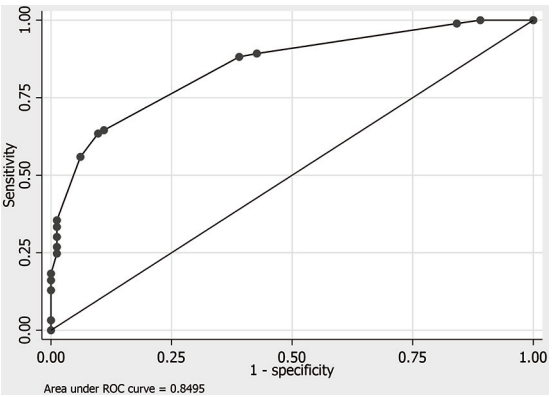

Figure 1. Received operating characteristics curve of the clinical prediction model of sustained remission to MTX therapy after 12 months of treatment in patients with ERA.

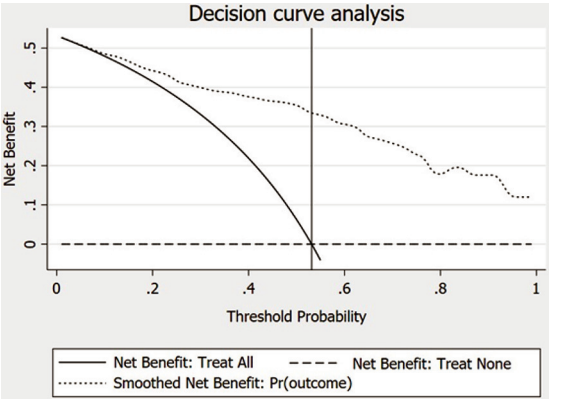

Figure 3. Evaluation of the score performance in terms of clinical usefulness using the decision curve analysis (outcome: sustained remission).

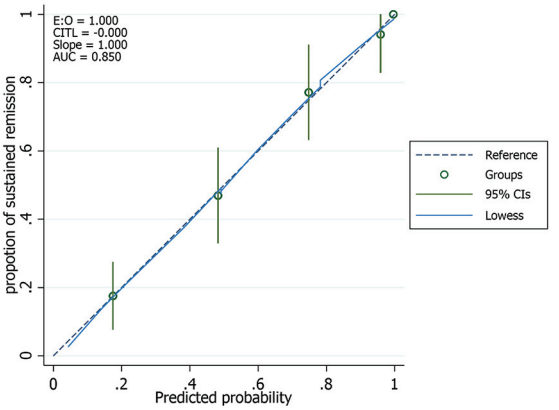

Figure 2. Calibration plot of the score-predicted risk compared with the observed risk of sustained remission to MTX therapy.

Discussion

The present study developed a clinical prediction score for predicting SR. In the cohort, 93 patients (53.1%) had SR, which is in line with the previous reports of 47.1% to 53%[16,17]. The prediction model performed well, achieving an AUROC of 0.85 (95% CI 0.80 to 0.90). It demonstrated strong discrimination and calibration capability, with a C-statistic of 0.85 and a slope of 1.0 (Figure 2). The predictive score only requires specific predictors, such as age, HAQ, baseline DAS28-ESR, and early adjusted DAS28 at three months less than 3.2, and no serology is necessary. Therefore, using parameters from baseline clinical characteristics and tailoring a treatment strategy based on the appropriate therapeutic drugs' efficacy ensures the model's reliability and cost-effectiveness.

In the previous models used to identify the risk for progression of joint damage, which included a larger number of patients with joint damage and RA, the model's performance showed an AUROC of 0.76 to 0.77[6,7,18]. The present model offers benefits such as shorter disease duration and faster adoption of medication compared to previous studies[8]. In the study, it was discovered that younger age, gender, and TJC were linked to achieving remission. The model used had a fair discriminatory performance with an AUROC value of 0.7 and lower sensitivity compared to the current model in use. Furthermore, the study revealed that older age was a significant factor, as it was associated with a lower likelihood of SR due to higher comorbidities and potential adverse effects. This resulted in suboptimal standard dosing of csDMARDs[1]. Gender and TJC were not significantly associated with self-reported outcomes due to the larger proportion of female patients and severe disease. Similar to a previous study conducted in China[19], a DAS28-ESR of less than 3.2 at three months significantly predicted SR and had good discriminatory performance (AUROC 0.78). This

emphasizes the vital role of early effective treatment in reducing ongoing inflammation. Previous studies used earlier biological DMARDS therapy[11,12], erythrocyte folate[9,20,21], and the multi-biomarker disease activity (MBDA) score as a predictor[22]. The testing was limited to routine laboratory examinations, which are not typically available in clinical settings and are restricted to low-income developing countries for biological DMARDs therapy[9,21]. Furthermore, another study found no association between insufficient response to MTX therapy and the baseline adenosine pathway or level of erythrocyte folates[21]. Previous prediction models for inadequate response to MTX therapy had an AUROC range of 0.65 to 0.85[9,11,12,20,23]. It also included a combination of factors, such as genetics, metabolism, HAQ score, DAS28 of more than 5.1[11], current smoking[11], alcohol consumption, and BMI. Alcohol consumption and smoking may not benefit our model due to sociocultural differences and the predominance of the female population. This cohort study had low population-positive RF due to the low sensitivity of RF-positive in the ERA population.

The present study's main strength is that it provides a prediction score that can be used to make informed clinical decisions for patient care. This is achieved by applying the present study model in daily clinical practice, using baseline clinical characteristics as predictors. The focus is on the clinical response to MTX therapy in real clinical settings of developing countries[1,24]. The calibration slope for the predictor was very close to 1. Furthermore, the inclusion criteria included patients with ERA and moderate to high disease activity, which presents a challenge for treatment. In addition, the prediction score for patients with ERA has important implications. The clinical prediction score for SR is an alternative method to predict clinical outcomes in clinical practice and can help figure out the clinical significance for patients with a high-risk score of greater than 3.5, after achieving SR. These patients may have a lower risk of joint flare and a safe, longer follow-up. They can be safely managed and help reduce hospital crowding at busy specialized centers. On the other hand, patients with a low-risk score of 3.5 or less, should be promptly referred to a rheumatologist center and compared to the traditional methods, or the clinical predictors, as this method is more composite and helps in making decisions. These patients have a difficult-to-control disease, which requires specific management strategies such as adding or switching csDMARDs and/or early initiation of biological or targeted DMARDs[1] therapy to help slowing down the advancement of the disease and radiographic joint damage[25]. It is important to consider that treatment success depends on factors like how consistently medication is taken, the presence of fibromyalgia, any other health conditions, and lifestyle habits such as smoking and obesity. Therefore, using risk stratification strategies can be cost-effective and timesaving. This allows healthcare providers to predict treatment success and move towards personalized medicine in ERA.

The current study had limitations. Firstly, it was carried out at a single tertiary-care center, so the clinical prediction score might not be applicable to other healthcare settings. Therefore, a larger prospective external validation study is needed before implementing this system in clinical practice. Secondly, all details were manually assessed by reviewing each patient's medical charts, which could have led to misclassification bias and missing data. Thirdly, the lack of information on switching to or adding csDMARDs may have affected the results of the regression analysis. Additionally, the absence of baseline joint erosion-related variables, which are poor prognostic predictors, may have influenced the outcome. Furthermore, the present study only provided short-term predictions. Therefore, further research is needed to determine the impact of the clinical predictor score on long-term SR after achieving SR.

Conclusion

The prediction model presented in the present study is a new tool developed based on the findings of a real-life study. Its purpose is to assist physicians in providing standard care to patients with ERA who have moderate to high disease activity and a high probability of achieving SR after MTX combination therapy. Using multiple predictors as opposed to a sole one appeared to improve the predictive ability of SR. The value of the score can predict the chance of relapse is low and safe for long-term follow-up in patients with ERA. Further validation of the tool is required before it can be incorporated into routine clinical practice.

What is already known on this topic?

No study has combined predictor factors into a predictor score to predict the likelihood of SR in patients with ERA who have only used csDMARDs.

What does this study add?

The author demonstrates that patients with ERA who receive regular treatment adjustments based on disease activity, such as a change in DAS28-ESR three months after starting MTX therapy and are part of community-based strategies, have an increased chance of achieving SR. In a tertiary public hospital setting in developing country, the clinical prediction score demonstrated good predictive ability for forecasting SR in patients with ERA. However, the scoring system requires validation before it can be applied in a different clinical setting and necessitates sufficient resources for implementation. Further research may be necessary to develop a prediction model for long-term SR, including parameters such as additional information on switching to or adding csDMARDs.

Acknowledgment

The authors would like to acknowledge Dr. Jayanton Patumanond, Dr. Siriporn Juthong, and Dr. Arunchai Chang, who provided expertise and constructive feedback.

Funding disclosure

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors of the study declare no conflicts of interest.

References

1. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685-99.
2. Yu C, Jin S, Wang Y, Jiang N, Wu C, Wang Q, et al. Remission rate and predictors of remission in patients with rheumatoid arthritis under treat-to-target strategy in real-world studies: a systematic review and meta-analysis. Clin Rheumatol 2019;38:727-38.
3. Contreras-Yáñez I, Pascual-Ramos V. Window of opportunity to achieve major outcomes in early rheumatoid arthritis patients: how persistence with therapy matters. Arthritis Res Ther 2015;17:177. doi: 10.1186/s13075-015-0697-z.
4. Kuriya B, Xiong J, Boire G, Haraoui B, Hitchon C, Pope J, et al. Earlier time to remission predicts sustained clinical remission in early rheumatoid arthritis--results from the Canadian Early Arthritis Cohort (CATCH). J Rheumatol 2014;41:2161-6.
5. Darawankul B, Chaiamnuay S, Pakchotanon R, Asavatanabodee P, Narongroeknawin P. The good EULAR response at the first year is strongly predictive of clinical remission in rheumatoid arthritis: results from the TARAC cohort. Clin Rheumatol 2015;34:43-9.
6. de Punder YM, van Riel PL, Fransen J. A simplified baseline prediction model for joint damage progression in rheumatoid arthritis: a step toward personalized medicine. J Rheumatol 2015;42:391-7.
7. Joo YB, Bang SY, Ryu JA, Lee S, Lee HS, Bae SC. Predictors of severe radiographic progression in patients with early rheumatoid arthritis: A Prospective observational cohort study. Int J Rheum Dis 2017;20:1437-46.
8. Ma MH, Ibrahim F, Walker D, Hassell A, Choy EH, Kiely PD, et al. Remission in early rheumatoid arthritis: predicting treatment response. J Rheumatol 2012;39:470-5.
9. de Rotte M, Pluijm SMF, de Jong PHP, Bulatović Ćalasan M, Wulffraat NM, Weel A, et al. Development and validation of a prognostic multivariable model to predict insufficient clinical response to methotrexate in rheumatoid arthritis. PLoS One 2018;13:e0208534.
10. Meznerics FA, Kemény LV, Gunther E, Bakó E, Dembrovszky F, Szabó B, et al. Multibiomarker disease activity score: an objective tool for monitoring rheumatoid arthritis? A systematic review and meta-analysis. Rheumatology (Oxford) 2023;62:2048-59.
11. Teitsma XM, Jacobs JWG, Welsing PMJ, de Jong PHP, Hazes JMW, Weel A, et al. Inadequate response to treat-to-target methotrexate therapy in patients with new-onset rheumatoid arthritis: development and validation of clinical predictors. Ann Rheum Dis 2018;77:1261-7.
12. Eektimmerman F, Allaart CF, Hazes JM, Madhar MB, den Broeder AA, Fransen J, et al. Validation of a clinical pharmacogenetic model to predict methotrexate nonresponse in rheumatoid arthritis patients. Pharmacogenomics 2019;20:85-93.
13. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: A review. JAMA 2018;320:1360-72.
14. Schipper LG, Fransen J, den Broeder AA, Van Riel PL. Time to achieve remission determines time to be in remission. Arthritis Res Ther 2010;12:R97. doi: 10.1186/ar3027.
15. Yilmaz-Oner S, Gazel U, Can M, Atagunduz P, Direskeneli H, Inanc N. Predictors and the optimal duration of sustained remission in rheumatoid arthritis. Clin Rheumatol 2019;38:3033-9.
16. Paulshus Sundlisæter N, Olsen IC, Aga AB, Hammer HB, Uhlig T, van der Heijde D, et al. Predictors of sustained remission in patients with early rheumatoid arthritis treated according to an aggressive treat-to-target protocol. Rheumatology

(Oxford) 2018;57:2022-31.
17. Khabbazi A, Gadakchi L, Moslemi M, Khalaji A, Esalatmanesh K, Ziarati Yazdeli A, et al. Prevalence and predictors of long-term remission in rheumatoid arthritis in real-world practice: a longitudinal study. Clin Rheumatol 2023;42:1537-44.
18. Fautrel B, Granger B, Combe B, Saraux A, Guillemin F, Le Loet X. Matrix to predict rapid radiographic progression of early rheumatoid arthritis patients from the community treated with methotrexate or leflunomide: results from the ESPOIR cohort. Arthritis Res Ther 2012;14:R249. doi: 10.1186/ar4092.
19. Xie W, Li J, Zhang X, Sun X, Zhang Z. Sustained clinical remission of rheumatoid arthritis and its predictive factors in an unselected adult Chinese population from 2009 to 2018. Int J Rheum Dis 2019;22:1670-8.
20. Gosselt HR, Verhoeven MMA, Bulatović-Ćalasan M, Welsing PM, de Rotte M, Hazes JMW, et al. Complex machine-learning algorithms and multivariable logistic regression on par in the prediction of insufficient clinical response to methotrexate in rheumatoid arthritis. J Pers Med 2021;11:44. doi: 10.3390/jpm11010044.
21. Roodenrijs NMT, van der Goes MC, Welsing PMJ, Tekstra J, van Laar JM, Lafeber F, et al. Is prediction of clinical response to methotrexate in individual rheumatoid arthritis patients possible? A systematic literature review. Joint Bone Spine 2020;87:13-23.
22. Hambardzumyan K, Saevarsdottir S, Forslind K, Petersson IF, Wallman JK, Ernestam S, et al. A multi-biomarker disease activity score and the choice of second-line therapy in early rheumatoid arthritis after methotrexate failure. Arthritis Rheumatol 2017;69:953-63.
23. Sergeant JC, Hyrich KL, Anderson J, Kopec-Harding K, Hope HF, Symmons DPM, et al. Prediction of primary non-response to methotrexate therapy using demographic, clinical and psychosocial variables: results from the UK Rheumatoid Arthritis Medication Study (RAMS). Arthritis Res Ther 2018;20:147. doi: 10.1186/s13075-018-1645-5.
24. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3-15.
25. Yamanaka H, Ishiguro N, Takeuchi T, Miyasaka N, Mukai M, Matsubara T, et al. Recovery of clinical but not radiographic outcomes by the delayed addition of adalimumab to methotrexate-treated Japanese patients with early rheumatoid arthritis: 52-week results of the HOPEFUL-1 trial. Rheumatology (Oxford) 2014;53:904-13.