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ORIGINAL ARTICLE

Predictors of persistent high disease activity after methotrexate treatment in rheumatoid arthritis patients

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ABSTRACT

BACKGROUND

Methotrexate (MTX) is the firstline therapy for rheumatoid arthritis (RA). However, 30–40% of RA patients exhibit poor response. Identifying early factors associated with persistent disease activity is critical to guide treatment. This study aimed to identify predictors of persistent high disease activity (DAS28-ESR >3.2) after six months of MTX therapy in RA patients.

METHODS

A retrospective cohort study was conducted involving 204 RA patients who had completed six months of MTX therapy. The primary outcome was DAS28-ESR score at six months. Independent variables included baseline erythrocyte sedimentation rate (ESR), cumulative doses of MTX and low-dose methylprednisolone (LDM), and rheumatoid factor (RF) status. Simple and multiple logistic regression was used to analyze the data.

RESULTS

Significant differences in ESR and cumulative MTX dose were observed between low and high disease activity groups. Multivariate analysis identified four independent predictors of persistent high disease activity (DAS28-ESR >3.2) after six months of MTX therapy: disease duration >11 months (AOR =0.45; 95% CI 0.23–0.89; p=0.025); age at onset >50 years (AOR 0.48; 95% CI 0.24–0.94; p=0.038); cumulative MTX dose >85 mg (AOR 4.75; 95% CI 1.55–14.64; p=0.006); ESR >66 mm/hr (AOR 2.32; 95% CI 1.11–4.89; p=0.026).

CONCLUSION

Greater cumulative methotrexate dose (>85 mg) was the most influential predictor of persistent high disease activity (DAS28-ESR >3.2) after six months of MTX therapy in RA patients. These findings may assist clinicians in identifying patients at risk for poor MTX response and support timely therapeutic adjustments.

Keywords: Persistent disease activity, rheumatoid arthritis, methotrexate, DAS28-ESR, predictors

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by systemic inflammation that can lead to joint destruction, loss of function, and reduced quality of life. The level of disease activity in RA, typically measured by composite indices such as the Disease Activity Score in 28 joints (DAS28), plays a pivotal role in determining long-term prognosis.[1] According to the widely accepted treat-to-target (T2T) strategy, the aim of treatment in RA is to improve patients' health-related quality of life by abrogation of inflammatory burden.[2] Disease-modifying antirheumatic drugs (DMARDs) such as methotrexate are currently recommended as first-line therapy for the treatment of RA.[3,4]

Methotrexate (MTX) is an anti-inflammatory and immunosuppressive agent widely used in the treatment of RA. It acts by reducing cell proliferation, inhibiting folic acid metabolism, and enhancing adenosine release. Methotrexate also modulates the expression of cellular adhesion molecules, cytokine production, humoral responses, and bone metabolism.[1] The 2022 European Alliance of Associations for Rheumatology (EULAR) guidelines recommend MTX as the first-line treatment for RA due to its proven efficacy, safety profile, and affordability.[1, 5] However, approximately 30–40% of patients demonstrate suboptimal response to MTX, necessitating treatment escalation using other conventional or biologic DMARDs.[1]

Reports show that MTX monotherapy achieves an American College of Rheumatology 70% response (ACR70) in only 25% of cases within six months.[6] EULAR recommends treatment modification if no improvement is observed within three months or if therapeutic targets are unmet by six months. Delays in therapeutic adjustment may prolong disease activity, risk irreversible joint damage, and increase the adverse effects of MTX.[5] Thus, identifying early predictors of MTX response is essential to optimize individualized treatment strategies and improve long-term outcomes.[6]

The disease activity score 28 (DAS28), incorporating tender and swollen joint counts, global health (GH) assessment, and inflammatory markers such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), is a widely used index to monitor RA activity.[7] The DAS28 scores are widely used to categorize disease activity in rheumatoid arthritis (RA): remission (<2.6), low (<3.2), moderate (3.2–5.1), and high (>5.1).[8] Numerous studies have explored predictors of MTX treatment response in RA. Risk factors such as female sex, smoking, and positive RF have been identified, but their predictive power remains weak.[5] Several trials, including the OPTIMA and PREMIER studies, found that early disease activity and baseline DAS28 scores are strong predictors of both treatment response and radiographic progression.[9,10] However, these trials were conducted in controlled environments with relatively homogeneous populations, limiting their applicability to real-world clinical practice.

An observational study conducted in routine settings have identified baseline DAS28-ESR as a key predictor of MTX response.[6] The study showed that lower baseline DAS28-ESR was associated with better outcomes. Similarly, a study reported that treatment success with MTX monotherapy was significantly influenced by baseline disease activity.[11] Serological markers, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), have also been linked to treatment outcomes.[6,12] Body mass index (BMI) has emerged as another modifying factor. A study found that higher BMI may negatively affect MTX efficacy, possibly through pharmacokinetic mechanisms.[13] In addition to clinical and biological parameters, psychological factors also appear to be influential, with studies reporting that baseline anxiety and poor coping mechanisms correlate with non-adherence and higher disease activity, suggesting that psychosocial well-being plays a role in MTX treatment response.[12,14]

Recent efforts have also explored machine learning (ML) approaches, such as least absolute shrinkage and selection operator (LASSO) and random forest algorithms. However, studies concluded that ML models did not outperform traditional logistic regression in predicting poor MTX response, highlighting the complexity of modeling treatment outcomes in heterogeneous populations.[6,15]

Our study builds on this literature by using real-world, Electronic Medical Record (EMR)-based data from a tertiary center in Indonesia to develop a pragmatic predictive model for persistent high disease activity (DAS28-ESR >3.2) after six months of MTX monotherapy. Unlike prior studies that depend on advanced biomarker panels or ML algorithms,[6] the Optimal

Protocol for Treatment Initiation with Methotrexate and Adalimumab (OPTIMA), and PREMIER studies in patients with RA, found that in patients with early RA, baseline disease characteristics and early disease activity can predict response to methotrexate treatment and radiographic progression at 6 months.[9] An observational cohort of patients with early RA showed that combining tender joint counts, ESR, and health assessment questionnaire (HAQ) in a simple predictive score prospectively identifies patients with higher risks of persistent disease activity over the next 12 months. More patients with all three risk factors had persistent active disease than those with no risk factors or just one risk factor.[16] Therefore, this study aims to identify simple, clinically relevant predictors of persistent high disease activity in RA patients receiving MTX, using accessible EMR data.

METHODS

Study Design

This was a retrospective cohort study utilizing secondary data from the EMR of the outpatient Rheumatology Clinic at Sardjito General Hospital, collected in June 2024.

Research subjects

A total of 204 RA patient records from the rheumatology outpatient department retrieved from the EMR were included into the study. The inclusion criteria were: patients diagnosed with RA according to the EULAR/ACR 2010 criteria, aged ≥18 years, receiving MTX therapy for the first time for six months, and patients with available data for predictors of persistent high DAS28-ESR scores. Subjects with incomplete data were excluded. Subjects were divided into two groups based on their disease activity: low disease activity (LDA) and high disease activity (HDA). Patients were categorized into the HDA group if their DAS28-ESR score was >3.2 after 24 weeks of MTX therapy, while those with a DAS28-ESR score ≤3.2 were classified in the LDA group.[17]

Data collection

Recorded baseline characteristics included: i) demographics: age at onset of RA, gender; ii) anthropometrics: BMI (kg/m²); iii) laboratory values: baseline ESR, (mm/hr), RF status (positive/negative); iv) treatment data: cumulative dose of MTX (mg) and low-dose methylprednisolone (LDM, mg) over the 6-month period; v) clinical history: duration of disease (months) from symptom onset to MTX initiation.

The independent variables included ESR, cumulative MTX dose, cumulative LDM, and RF. The dependent variable was the persistence of RA disease activity at the end of the sixth month of MTX therapy, as measured by DAS28-ESR. Confounding variables included age at disease onset, disease duration, and gender.

Assessments

Persistent RA disease activity was defined as a DAS28-ESR score >3.2 at the end of the 24th week of MTX therapy. The DAS28-ESR score was calculated using the following formula, as described previously and widely adopted in clinical practice:

$$DAS28\text{-}ESR = 0.56 \times \sqrt{(TCJ28)} + 0.28 \times \sqrt{(SJC28)} + 0.014 \times GH + 0.70 \times \ln(ESR) + 0.96.$$ [18]

Where TJC28 = Tender Joint Count (out of 28 joints); SJC28 = Swollen Joint Count (out of 28 joints); GH = General Health score, based on the patient's self-assessment of overall health using a visual analogue scale (VAS) from 0 to 100; ESR = Erythrocyte Sedimentation Rate (in mm/hr). Data were classified into two groups: DAS28-ESR >3.2 (HDA group); DAS28-ESR ≤3.2 (LDA group). ESR values were recorded as numerical data, measured in millimeters per hour (mm/hr). RF data were obtained from the EMR and classified categorically as positive or negative. The cumulative MTX dose was calculated as the total dose administered from the start to the end of the 24th week of therapy, recorded in milligrams (mg) as numerical data. Similarly, the cumulative LDM dose was calculated as the total amount taken from the start to the end of the 24th week of therapy, recorded in milligrams (mg) as numerical data.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 25.0 (RRID: SCR_019096). The distribution of numerical data was assessed using the Shapiro-Wilk test and visual inspection of histograms and Q-Q plots. Since all continuous variables were found to be non-normally distributed, they were summarized as median and interquartile range (IQR). Categorical variables were presented as

frequencies and percentages. Group comparisons between low and high disease activity (LDA vs. HDA) were performed using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. The relationship between continuous predictors (e.g., baseline ESR, cumulative MTX dose, disease duration) and DAS28-ESR scores was examined using Spearman's rank correlation coefficient (ρ). To determine optimal cut-off values for continuous predictors in predicting persistent high disease activity, ROC curve analysis was employed, and the Youden index was used to define thresholds. Simple and multiple logistic regression were used to determine the predictors of high disease activity (DAS28-ESR >3.2) at 6 months. Predictors with p-values <0.25 in the simple logistic regression were included in a multivariate logistic regression model using backward stepwise elimination to identify independent predictors of high disease activity (DAS28-ESR >3.2) at 6 months. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test.

Ethical clearance

This study was approved by the Universitas Gadjah Mada, Faculty of Medicine, Nursing, and Public Health Ethics Committee for Human Research, in accordance with the Declaration of Helsinki. The ethical clearance was issued by the Medical and Health Research Ethics Committee (MHREC) with reference number KE/1255/08/2024.

RESULTS

A total of 204 RA patients met the inclusion and exclusion criteria. The majority of the sample were female, totaling 183 (90.0%). The median age at first diagnosis was 50.00 years (IQR: 42.00-58.00). Rheumatoid factor was negative in 138 (67.6%) of cases. The median disease duration, BMI, and ESR were 14.00 months (IQR: 6.00-38.50), 22.25 kg/m² (IQR: 18.96-25.74), and 36.00 mm/hour (IQR: 17.00-64.00), respectively. The median cumulative doses of MTX and LDM over six months were 840.08 mg (IQR: 630.00-960.00) and 215.00 mg (IQR: 100.00-300.00), respectively. After six months of MTX treatment, the median DAS28-ESR score was 3.09 (IQR: 2.50-3.25) (Table 1).

Correlation between predictor variables and DAS28-ESR after six months of MTX

A correlation analysis revealed that only ESR at baseline showed a significant positive correlation with DAS28-ESR (r=0.22, p<0.001) (Figure 1).

Table 1. Baseline characteristics of study participants (n=204)

Variables	
Sex (n,%)	
Male	21 (10.3)
Female	183 (89.7)
Age at diagnosis (years)	50.00 (42.00–58.00)
Disease duration (months)	14.00 (6.00–38.50)
BMI at baseline	22.25 (18.96–25.74)
RF at baseline, n (%)	
Positive	66 (32.3)
Negative	138 (67.7)
Cumulative dose of LDM (mg)	840.08 (630.00–960.00)
Cumulative dose of MTX (mg)	215.00 (100.00–300.00)
ESR at baseline	36.00 (17.00–64.00)
DAS28-ESR at month 6	3.09 (2.50–3.25)
DAS28-ESR (2 categories) at month 6 (n,(%)	
Low disease activity (LDA, 1.3–3.2)	51 (25.0)
High disease activity (HDA, 3.21–5.2)	153 (75.0)

Values presented as median (IQR), unless otherwise indicated. RF = rheumatoid factor; LDM = low-dose methylprednisolone; MTX = methotrexate; ESR = erythrocyte sedimentation rate; DAS28-ESR = disease activity score 28 with ESR.

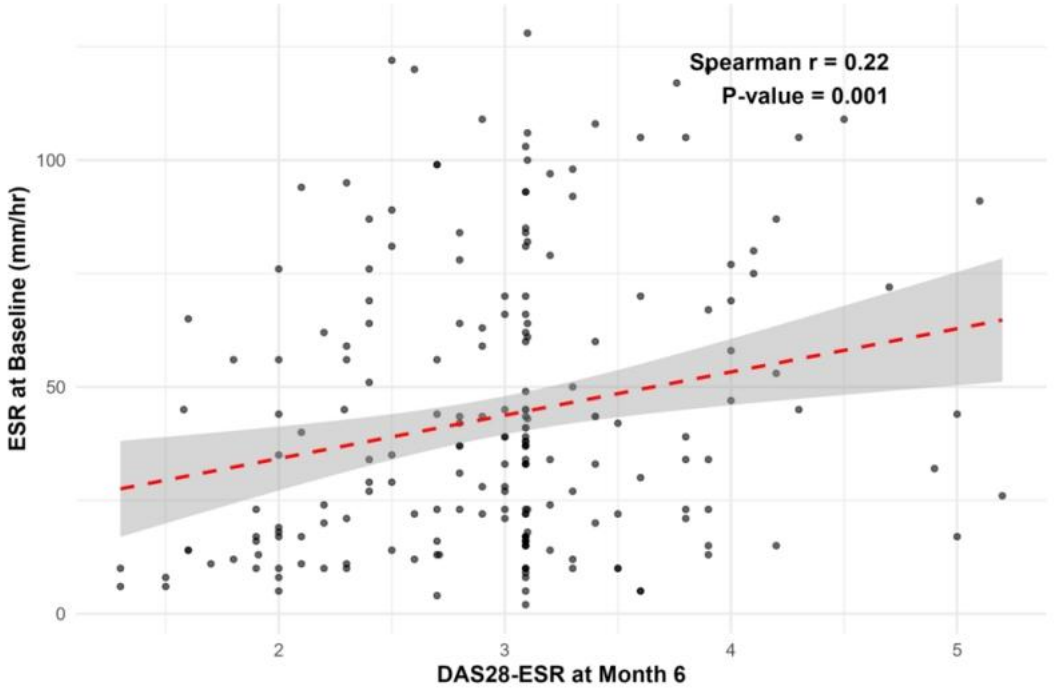

Figure 1. Correlation between ESR at baseline with DAS28-ESR after 6 months of MTX treatment

There was a weak positive correlation between the cumulative dose of MTX and a weak negative correlation between disease duration and DAS28-ESR, but these were not statistically significant (r=0.11, p>0.05). No correlation was found of age, BMI, or cumulative dose of low-dose methylprednisolone with DAS28-ESR after six months of MTX treatment (Table 2).

Median differences of predictor variables according to disease activity groups

Among the study participants, 153 (75.0 %) subjects were classified into the HDA group and 51 (25.0 %) subjects into the LDA group at six months post-MTX treatment. The median ESR in the HDA group was 43.5 mm/hr, while in the LDA group, it was 34.0 mm/hr (Figure 1). A significant median difference in ESR was found between the two groups (p = 0.043). The median cumulative dose of MTX in the HDA group was 250 mg, whereas in the LDA group, it was 200 mg (Table 3). A significant median difference in cumulative MTX dose was observed between the groups (p=0.034) (Table 3). No significant median differences were found for disease duration, age at onset, BMI, or cumulative dose of low-dose methylprednisolone (p>0.05) (Table 3).

Table 2. Correlation between predictor variables and DAS28 after six months

Variables	Coefficient correlation (r)	p-value
ESR at Baseline	0.22	0.001*
Age at Onset	-0.04	0.620
Disease Duration	-0.13	0.073
BMI	-0.05	0.500
Cumulative Dose of LDM	0.00	0.962
Cumulative Dose of MTX	0.11	0.114

Values represent Pearson's or Spearman correlation coefficient (r). *p<0.05 statistically significant

Table 3. Comparison of predictor variables between HDA and LDA groups

Variables	HDA (n = 153)	LDA (n = 51)	p-value²
Sex, n (%)			0.755
Male	15 (9.8)	6 (12.0)	
Female	138 (90.2)	45 (88.0)	
Age at onset (years)	51.00 (42.00–58.00)	47.00 (42.00–58.00)	0.444
Disease duration (months)	15.00 (5.00–39.00)	11.00 (7.00–36.00)	0.925
BMI	22.48 (18.73–25.78)	21.78 (19.47–25.30)	0.632
ESR at baseline (mm/hr)	34.00 (16.00–61.00)	43.49 (22.00–77.00)	0.064
Cumulative dose of LDM (mg)	840.08 (660.00–960.00)	840.08 (600.00–960.00)	0.957
Cumulative dose of MTX (mg)	200.00 (80.00–300.00)	250.00 (120.00–330.00)	0.031*

Values presented as median (IQR), unless otherwise indicated. p-values calculated using Wilcoxon rank-sum test (U-test) for non-normally distributed numeric variables; Chi-squared for categorical variables. *p < 0.05—statistically significant, HDA : high disease activity, LDA : low disease activity LDM : low dose methylprednisolone, MTX : methotrexate, ESR : erythrocyte sedimentation rate.

Predictors of persistent HDA after 6 months of MTX

To identify predictors of persistent HDA, numerical data were converted into categorical data by determining cutoff points for each independent variable using the Youden index. We identified MTX cumulative dose >85 mg and baseline ESR >66 mm/hr as practical, actionable predictors. The bivariate analysis using the simple logistic regression indicated a significant difference in proportions between cumulative MTX dose and ESR at baseline with respect to DAS28-ESR at 6 months post-MTX. Cumulative MTX dose >85 mg was significantly associated with persistent high disease activity (OR=1.26; 95% CI 1.11–1.43; p=0.008), as was ESR >66 mm/hr (OR=1.86; 95% CI 1.14–3.10; p=0.027) (Table 4).

Table 4. Simple logistic regression analysis of predictors for DAS28-ESR

Predictors	OR	95% CI	p value
Sex Female Male	0.98	0.87 – 1.50	0.891
BMI kg/m^2 ≤22.07 >22.07	1.24	0.93 – 1.67	0.260
Disease duration (months) ≤11 >11	1.32	0.95 – 1.85	0.162
Age at onset (years) ≤50 >50	1.35	1.03 – 1.77	0.063
Cumulative dose of LDM (mg) ≤780 >780	1.17	0.79 – 1.73	0.563
Cumulative dose of MTX (mg) ≤85 >85	1.26	1.11 – 1.43	0.008*
ESR at baseline (mm/hr) ≤66 >66	1.86	1.14 – 3.10	0.027*
Rheumatoid factor (RF) Positive Negative	1.21	0.79 – 1.86	0.490

BMI: body mass index, LDM: low dose methylprednisolone, MTX: methotrexate, ESR: erythrocyte sedimentation rate. OR: odds ratio; CI: confidence interval; *Statistically significant at p<0.05

Table 5. Multivariate logistic regression analysis of predictors for persistent high disease activity after 6 months of methotrexate (MTX) therapy

Predictors	AOR	95% CI	p value
Disease duration >11 months	0.45	0.23 – 0.89	0.025*
Age at onset >50 years	0.48	0.24 – 0.94	0.038*
Cumulative MTX dose >85 mg	4.75	1.55 – 14.64	0.006*
ESR at baseline >66 mm/hr	2.32	1.11 – 4.89	0.026*

AOR: adjusted odds ratio; CI: confidence interval; HDA was defined as DAS28-ESR >3.2 at 6 months; *p < 0.05,— statistically significant; Multivariate logistic regression model using predictors with p value <0.25 in the simple logistics regression; ** The AORs are adjusted for all other variables included in the model.

Multivariate analysis

A multivariate analysis was conducted using logistic regression, incorporating all predictor variables that had a significant p < 0.25 in simple logistic regression. These variables included BMI, disease duration, age at onset, cumulative MTX dose, and ESR. A multiple logistic regression analysis was performed using stepwise backward selection, with a 95% CI for the OR and model evaluation using the Hosmer-Lemeshow goodness-of-fit test. Multivariate analysis identified four independent predictors of persistent high disease activity (DAS28-ESR >3.2) after six months of MTX therapy: disease duration >11 months (AOR =0.45; 95% CI 0.23–0.89; p=0.025); age at onset >50 years (AOR 0.48; 95% CI 0.24–0.94; p=0.038); cumulative MTX dose >85 mg (AOR 4.75; 95% CI 1.55–14.64; p=0.006); and ESR >66 mm/hr (AOR 2.32; 95% CI 1.11–4.89; p=0.026) (Table 5).

DISCUSSION

The majority of the subjects were female (90.0%), consistent with established epidemiological data indicating that women are two to three times more likely to develop RA than men due to genetic, hormonal, and immunological factors.[19]The median age at diagnosis in this study was 50 years, also in line with global data showing increased RA incidence among individuals over 40 years of age.[19] Although the median disease duration in this cohort was 14 months, the mean duration was longer at 27.9 months, which is still shorter than the six-year average reported by a study in a different population, highlighting variability across settings.[20]

An interesting finding was the high proportion of RF-negative cases (68.0%), which is contrary to what is commonly reported.[21] This could be explained by the referral pattern to a tertiary center, where many patients are referred based on clinical suspicion rather than serological confirmation. Such patients may present with clinically suspected arthralgia (CSA), a condition with up to 55% likelihood of progressing to RA.[22] Importantly, the diagnosis of RA in this study adhered to the 2010 ACR/EULAR criteria, which include domains beyond RF, such as joint involvement and acute-phase reactants. Therefore, the validity of the diagnosis in these RF-negative patients remains strong.

In our investigation of RA, we observed a negative correlation between BMI and disease duration, as well as positive correlations between disease duration and markers of inflammation such as erythrocyte sedimentation rate (ESR), cumulative methotrexate dose, and corticosteroid use. This finding aligns with existing literature, which identifies the relationship between chronic inflammation and treatment intensity in RA patients. A study reported that clinical characteristics such as lower BMI and shorter disease duration are linked to better treatment outcomes in RA, suggesting that patients with shorter disease duration tend to have lower BMI and less intensive therapeutic regimens.[23]

The literature further supports that prolonged disease duration is associated with increased inflammatory responses, which necessitate higher cumulative doses of medications such as methotrexate and corticosteroids. Cioffi et al.[24] emphasize that longer RA duration can lead to deterioration in cardiac function, highlighting the systemic impacts of chronic inflammation and tying back to treatment intensity. Additionally, inflammatory markers such as IL-6 and TNF-alpha, which have been established as drivers in RA pathology, demonstrate that heightened inflammation correlates with disease duration, emphasizing a progressive disease model where pharmacological interventions become increasingly necessary as the disease advances.[25]

Moreover, several studies have reported that longer disease duration correlates with increased systemic inflammation, reflected in markers such as C-reactive protein (CRP) and ESR. For example, a study indicated that disease duration is pivotal in predicting vascular stiffness, indicating the broader implications of prolonged inflammation on cardiovascular health in patients with RA.[23] Similarly, Pandey et al.[26] noted that components of metabolic syndrome, elevated in RA patients, are significantly associated with increased disease duration and systemic inflammatory markers, thus reinforcing the complex interplay between inflammation, treatment intensity, and overall disease management.

The notion that chronic inflammation leads to escalated treatment regimens is also supported by findings that note higher rates of corticosteroid use in patients with longer RA durations due to increased disease activity and chronic inflammatory responses, which ultimately influence treatment decisions.[27] In light of these findings, it becomes evident that increased disease duration is associated with heightened inflammatory activity, which demands intensified therapeutic strategies to manage disease symptoms and inflammation effectively.

Elevated ESR levels in patients with longer disease duration reflect ongoing systemic inflammation, and ESR continues to serve as a key marker for disease activity and response monitoring.[28] The use of low-dose corticosteroids was positively associated with longer disease duration, suggesting their continued role in long-term disease modulation. Corticosteroids have been shown to reduce ESR significantly, even at low doses, reinforcing their anti-inflammatory effects in RA management.[29]

The BMI was within normal range among most subjects (median 22.6 kg/m²), but its inverse correlation with disease duration supports earlier findings that higher BMI may be associated with delayed diagnosis or less severe early symptoms, which can prolong subclinical disease progression.[30] Obesity is also linked to increased levels of pro-inflammatory cytokines such as TNF-α and IL-6, which may worsen disease activity and attenuate the therapeutic effects of MTX.[31] Furthermore, adipose tissue may serve as a pharmacokinetic reservoir for MTX, reducing its bioavailability and necessitating higher dosages to achieve therapeutic efficacy.[32]

Our findings confirm that a higher cumulative dose of MTX and elevated baseline ESR are significantly associated with persistent high disease activity (DAS28-ESR >3.2) at six months. This observation is consistent with current clinical practices where clinicians escalate MTX dosing in non-responders before considering additional or alternative therapies.[3, 33] However, a systematic review and meta-analysis by Smolen et al.[3] revealed that higher MTX doses do not consistently result in improved clinical outcomes and that efficacy plateaus at moderate doses, especially when MTX is used in combination with glucocorticoids or biologic DMARDs. Moreover, their findings indicate no significant difference in disease activity outcomes between lower and higher starting doses over 3–6 months, highlighting the need for a more individualized dosing strategy.[3]

The CONCERTO study further emphasized that while MTX dose did not significantly affect DAS28-ESR scores, it did influence the proportion of patients achieving LDA or remission. Specifically, patients receiving intermediate MTX doses had higher remission rates compared to those on lower doses, suggesting that appropriate dosing may improve the likelihood of favorable outcomes even if DAS28 scores remain modest.[3] This reinforces the importance of identifying early predictors of MTX response to avoid prolonged ineffective treatment, which not only delays disease control but also increases the risk of cumulative joint damage and medication-related side effects.[34]

In our cohort, 75.0% of patients remained in the HDA category after six months of MTX therapy, although 27% of them had reached remission and 25.0% had low disease activity. Compared to a study in Norway where only 46.0% of patients achieved LDA with MTX alone or in combination, our population showed better outcomes, possibly due to a lower prevalence of smoking and a higher proportion of RF-negative patients, both of which are known to influence therapeutic response.[35]

Of the variables analyzed, only ESR and cumulative MTX dose demonstrated statistically significant correlations and group differences with DAS28-ESR. This supports previous findings that baseline inflammation, as measured by ESR, is a reliable predictor of MTX response, with higher ESR values indicating a higher likelihood of persistent disease activity despite treatment.[3] Our multivariate analysis further identified disease

duration >11 months and age at onset >50 years as independent predictors of poor MTX response. These findings are consistent with earlier studies suggesting that younger patients and those with shorter disease duration typically respond better to MTX due to less irreversible joint damage and a more modifiable immune response.[3]

Taken together, our study highlights the importance of integrating baseline clinical and laboratory parameters—specifically, disease duration >11 months, age at onset >50 years, cumulative MTX dose >85 mg, and baseline ESR >66 mm/hr—as key predictors of persistent high disease activity (DAS28-ESR >3.2) after MTX treatment in RA. By identifying patients with these risk factors early in the course of therapy, clinicians can tailor treatment more effectively, minimize unnecessary medication exposure, and reduce the risk of long-term disability. Future studies should incorporate additional biomarkers, including genetic, epigenetic, and psychosocial variables, which may further refine predictive models and facilitate personalized RA management strategies.[5,6,14]

This study has several limitations. First, although it employed a prospective observational cohort design, data collection was dependent on routine clinical documentation, which may be subject to incomplete entries or variability in measurement practices. Second, the study was conducted in a single tertiary referral center, limiting the generalizability of findings to broader populations, including patients treated in primary or secondary care settings. Third, while we identified statistically significant associations between selected clinical variables and DAS28-ESR scores at six months, causal inferences remain limited due to the non-randomized nature of the study and the presence of potential unmeasured confounders. Future multicenter studies with larger and more diverse patient populations, as well as the inclusion of genetic or serological biomarkers, are recommended to further validate these findings and improve predictive models for methotrexate response in RA management.

CONCLUSION

This study identified four main predictors of persistent high disease activity (DAS28-ESR >3.2) after six months of methotrexate therapy in rheumatoid arthritis patients: disease duration greater than 11 months, age at onset over 50 years, cumulative MTX dose exceeding 85 mg, and baseline ESR above 66 mm/hr. Among these, a cumulative MTX dose >85 mg showed the strongest association with persistent high disease activity, indicating it as the most influential predictor factor.

Conflict of Interest

Competing interests: No relevant disclosures.

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Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work. AP, NK, DNA, DBN : concept and design: AP, NK, DNA, AS, DBN : acquisition, analysis, or interpretation of data: AP, AS, DBN : drafting of the manuscript: AP, NK, DNA, DBN : critical review of the manuscript for important intellectual content:

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on request.

Declaration the Use of AI in Scientific Writing

This manuscript involved the use of generative AI tools (ChatGPT, developed by OpenAI) to support language editing, restructuring of paragraphs, and improvement of academic phrasing. The authors confirm that all content generated using AI was critically reviewed, verified for accuracy, and edited by the authors to ensure intellectual integrity and compliance with academic standards. The final responsibility for the content rests entirely with the authors.

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