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Predictive factors of methotrexate monotherapy success in patients with rheumatoid arthritis in a national referral center: a cohort study

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Abstract

Background Methotrexate (MTX) remains the recommended first-line treatment for rheumatoid arthritis (RA); however, its response varies and is influenced by various factors. This study aimed to identify predictors of MTX monotherapy treatment success in an Indonesian cohort.

Methods This retrospective cohort study included newly diagnosed RA patients receiving MTX monotherapy. Treatment success was defined as achieving remission or low disease activity according to Disease Activity Score-28 with erythrocyte sedimentation rate (DAS28-ESR) after 12 months of MTX therapy. The association between demographic, clinical, and laboratory factors and achieving therapy targets was evaluated using multivariate logistic regression analysis.

Results Among 254 subjects, 59.4% achieved treatment success with MTX monotherapy, with remission attained in 33% and low disease activity in 26.4%. Most subjects were female (95.7%) with a mean age of 48 ± 11 years. Multivariate analysis revealed that lower disease activity (OR 1.97; 95% CI [1.04–3.72]), normal ESR (OR 2.58; 95% CI [1.05–6.34]), normoweight (OR 2.55, 95% CI [1.45–4.49]), and tender joint count ≤ 5 (OR 2.45, 95% CI [1.31–4.58]) were significant predictors of treatment success.

Conclusion The rate of MTX monotherapy success in our study was 59.4%. Lower disease activity, normal ESR, normoweight, and fewer tender joints at baseline were significant predictors of treatment success.

Keywords Rheumatoid arthritis, Methotrexate, Monotherapy, Predictive factor, Remission

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Background

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease which primarily characterized by bilateral, symmetric polyarthritis [1]. While its incidence and prevalence vary across countries, it is estimated to affect approximately 0.5-1% of the global population. Currently, there is no epidemiological data on the national prevalence of RA in Indonesia, but it is estimated to align with global incidence rates. This is supported by a community-based epidemiological study in Malang, which revealed a prevalence of 0.5% in urban areas and 0.6% in rural areas among individuals over 40 years old [2]. Although the prevalence of RA in the population is not notably high, inadequate treatment can result in permanent joint damage, disability, and impaired joint function, imposing substantial economic and social burdens on affected individuals. Moreover, the presence of extra-articular manifestations of RA, such as rheumatoid nodules, interstitial lung disease, or cardiovascular disease, are correlated with increased morbidity and mortality [1, 3].

Disease Modifying Anti-Rheumatic Drugs (DMARDs) constitute a group of medications known for improving function and impeding joint destruction progression in RA. They are classified as conventional, biologic, and the newer targeted-synthetic DMARDs. Methotrexate (MTX) is currently the recommended conventional DMARD in RA management [1]. Widely recognized for its favorable treatment response rates, particularly when combined with glucocorticoids, MTX closely approaches the efficacy of biologics [4, 5]. Moreover, its favorable safety profile, with mostly manageable side effects aided by prophylactic folic acid, and lower cost, render it more financially affordable [6–8]. Consequently, MTX has been recommended as the first-line treatment for RA by various rheumatology organizations, including The European Alliance of Associations for Rheumatology (EULAR), American College of Rheumatology (ACR), Asia Pacific League of Associations for Rheumatology (APLAR), and the Indonesia Rheumatology Association (IRA) [2, 9–11].

MTX treatment outcomes in RA are influenced by various factors. Age [12, 13], sex, disease activity, obesity [13, 14], smoking history [12], genetics [14, 15], swollen and tender joints [16], erosion on radiographs [13], longer disease duration [12, 13], extra-articular manifestations [17], and comorbidities [13] have all been reported to impact MTX treatment outcomes in prior studies. Additionally, laboratory factors such as acute phase reactants (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) [18], serological markers like rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA), interleukin-2 (IL-2), and receptor activator of nuclear factor kappa-B ligand (RANKL) [13, 15] have shown to influence treatment response across various studies. However, these factors remain relatively underexplored in the context of Indonesia. Understanding predictors of treatment success in MTX monotherapy holds promise in guiding RA treatment decisions in routine clinical practice, enabling physicians to identify individuals at risk of non-response and consider alternative treatment strategies early in the disease course.

Methods

Study design and population

This retrospective cohort study involved patients newly diagnosed with RA according to the ACR/EULAR 2010 RA classification criteria, who were DMARD-näive, aged 18 years and older, and receiving MTX monotherapy as their first-line treatment. Patients with contraindications to MTX (active hepatitis B or C, active lung tuberculosis) and those with intolerance or intoxication to MTX were excluded. This study has been approved by the Ethical Committee Board of Faculty of Medicine, Universitas Indonesia and was conducted in compliance with the Helsinki declaration.

Data collection

Data were obtained from medical records of all RA patients diagnosed between January 2019 and September 2023 at Cipto Mangunkusumo National General Hospital using the total sampling method. Demographic data including age, sex, education level, employment status, marital status, body weight, and height were collected. Clinical characteristics including symptom duration, patient global assessment of health, tender joint count (TJC), swollen joint count (SJC), disease activity, baseline glucocorticoid use, and comorbidities were also recorded. Symptom duration refers to the time between symptom onset, as reported by the patient in the medical record, to the initiation of treatment. Tender and swollen joint counts were calculated using the ACR 68/66 full joint count. Symptom duration, TJC, and SJC were then classified based on optimal cut-off values determined using receiver operating characteristic (ROC) curve analysis. Patient global assessment of health was measured using a 0–10 cm Visual Analogue Scale (VAS). The presence of comorbidities was quantified using the Rheumatic Disease Comorbidity Index (RDCI), which comprises 11 types of comorbidities, with a total score ranging from 0 to 9 [19, 20]. Laboratory values, including CRP, ESR, and RF were also obtained.

Methotrexate treatment

As this was a retrospective analysis, the administration of MTX in our patients followed the protocol established at our center. MTX was initiated at a dose of 7.5–10 mg/week and was incrementally increased by 2.5-5 mg/week at each follow-up visit, up to a maximum dose of 25 mg/

week. According to our national insurance policy, stable patients were re-evaluated every 4 weeks at the earliest. As a result, most patients reached their optimal dose after 6 months or more of therapy; therefore, we chose to evaluate treatment response at 12 months.

Definition of treatment success

Disease activity was assessed using the DAS28-ESR. Treatment success was defined as achieving remission or low disease activity (DAS28-ESR≤3.2) after 12 months of MTX therapy, up to a maximum dose of 25 mg/week. Treatment unsuccessful was defined as patients who did not achieve remission or low disease activity after 12 months of maximum tolerated dose of MTX therapy and those who required additional DMARDs or a change of DMARDs at any point during the follow-up period due to an insufficient response to MTX monotherapy after it had been titrated to the maximum tolerated dose. Subjects were excluded if they received other DMARDs alongside MTX as part of their first-line treatment.

Statistical analysis

Descriptive analyses were conducted for demographic and clinical characteristics of the subjects. Categorical data were presented as percentages, while numerical data were presented as means and standard deviations if normally distributed, or as medians and ranges if not. T-tests and Chi-square tests were performed for group comparisons. The association between demographic and clinical factors and achieving therapy targets was evaluated using multivariate logistic regression analysis, with results presented as odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). Variable elimination was conducted with backward multivariate logistic regression analysis, and a p-value of <0.05 was considered statistically significant. A multicollinearity test was conducted among the components of DAS28-ESR to ensure no collinearities existed, allowing these variables to be included in the regression model. Sensitivity analysis was performed through the imputation of missing data for dropout (loss to follow-up) subjects to assess the robustness of our findings. All statistical analyses were conducted using Statistical Package for Social Sciences version 28.0.

Results

Selection process

Figure 1 illustrates the sample selection process. Initially, 383 newly diagnosed RA patients meeting the ACR/EULAR 2010 RA criteria were identified during the study period. Among them, 63 subjects were excluded for not receiving MTX monotherapy as part of their first-line treatment: 17 individuals were on a combination of MTX and other DMARDs, while 46 were prescribed a DMARD other than MTX. Furthermore, 20 subjects were excluded due to contraindications to MTX, including elevated transaminase levels in 5 subjects and intolerance (severe nausea) in 15 subjects. Throughout the study period, 46 subjects were lost to follow-up (dropouts). Consequently, a sensitivity analysis was conducted for this subgroup to assess its impact on the study results.

Characteristics of subjects

A total of 254 patients were included in the analysis. The characteristics of subjects at baseline were detailed in Table 1. The majority of subjects were female (95.7%) and were under 60 years old (89%), with a mean age of 48 years. The mean BMI of the subjects was 23.8 kg/m^2, and obesity was present in 93 subjects (36.6%). Cut-off values for classification of symptom duration, TJC, and SJC were determined using ROC curve analysis, with 152 subjects (59.8%) having a symptom duration from symptoms onset to MTX initiation of more than 6 months. Most subjects had more than 5 tender joints (62.6%) and no swollen joints (75.6%). Regarding comorbidities, as assessed by RDCI, 156 subjects (61.4%) did not have any comorbid conditions.

Initial disease activity assessment revealed that 176 subjects (69.3%) had moderate disease activity. The majority of subjects (61.4%) were using corticosteroids at a dose of more than 7.5 mg of prednisone per day. Elevated ESR levels were found in most subjects (84.6%), while CRP levels were normal in 54.3% of subjects. RF serology was positive in 136 subjects (53.5%).

Outcomes after 12 months of therapy

At the end of 12-month study period, treatment targets (remission or low disease activity) were achieved in 59.4% of subjects (Table 2). The median weekly dose of methotrexate (MTX) at 12 months, as well as the maximum weekly dose during the study, was 15 mg/week (IQR 12.5–20 mg/week).

Comparison of subjects based on MTX treatment outcomes

Table 3 presents the results of bivariate analysis comparing demographic, clinical, and laboratory characteristics between the MTX monotherapy treatment success and unsuccessful groups. Variables with a p-value of <0.25 were included in subsequent multivariate analysis. A multicollinearity test was conducted among ESR, TJCs, SJCs, and disease activity variables, revealing no collinearities between these factors. Therefore, all these variables were included in the model.

Factors affecting MTX treatment response

Multivariate analysis identified four significant predictors of MTX treatment success: lower disease activity

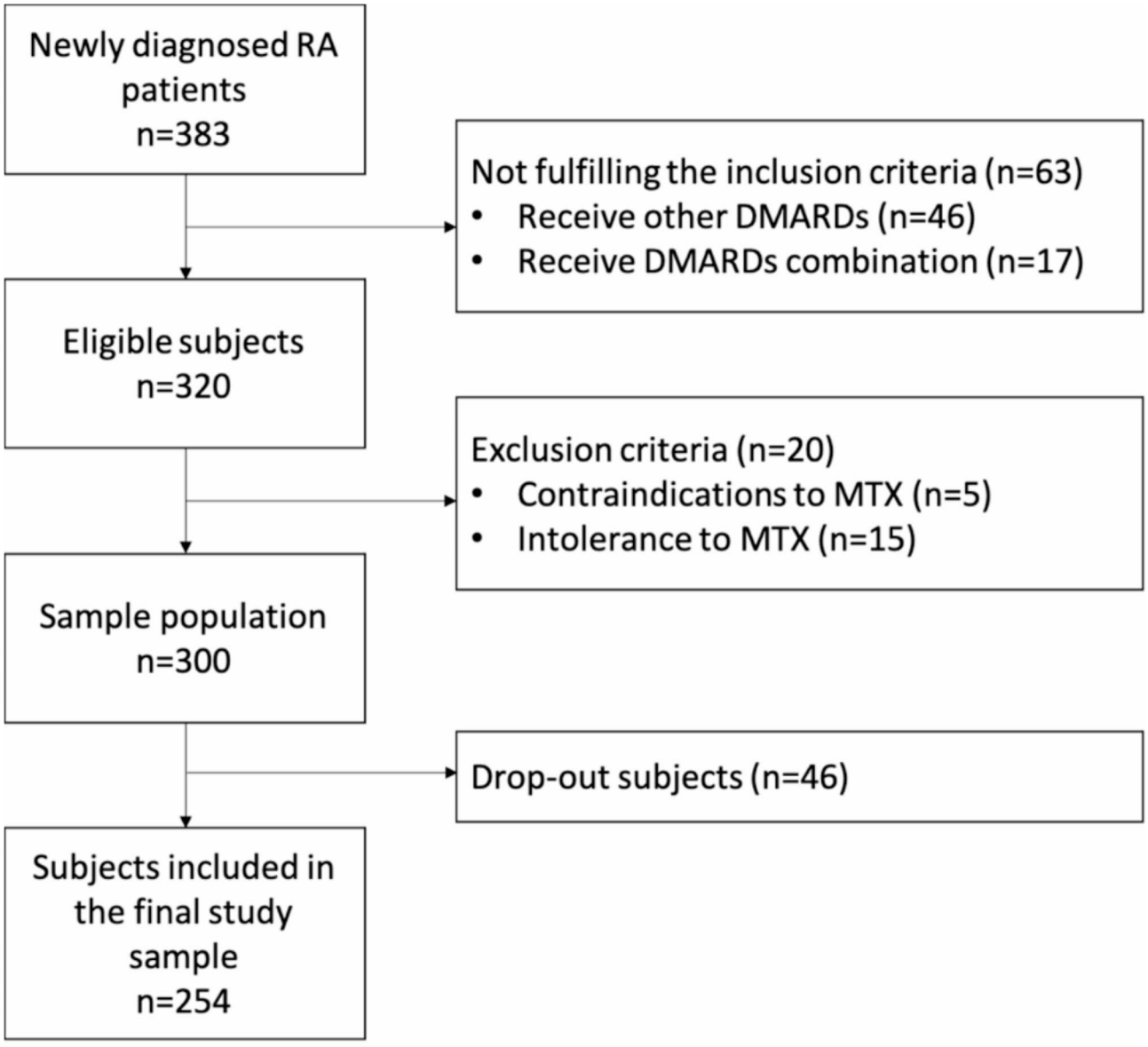

Fig. 1 Study sample selection process

at baseline, normal ESR levels, normoweight status, and TJC≤5, as shown in Table 4.

Discussion

This retrospective study aimed to identify predictors of MTX monotherapy treatment success in RA patients, with outcomes assessed at 12 months. In our centre, it is common practice to uptitrate the MTX dose slowly (by 2.5-5 mg/week) due to the high prevalence of side effects, particularly nausea and vomiting, among Indonesian patients. This is similar to findings from a study among the Japanese population by Kanda et al., which also reported a high prevalence of gastrointestinal side effects even with low-dose oral MTX [21]. We found that 59.4% of subjects achieved treatment success (defined as remission or low disease activity) as assessed by DAS28-ESR, with remission achieved in 33% of subjects. The success rate observed in our study was higher than that reported in a previous study from the same centre, which showed treatment success and remission rates of 41.5% and 13.8%, respectively [22]. Another multicentre study in Indonesia reported treatment response rates of 43.5% and 24.5%, respectively [23]. A study in Thailand demonstrated a proportion of remission and low disease activity of 39.1% [24]. Sun et al., in an Asian-Pacific multicentre study, found a MTX remission rate of 35.5% [17]. These findings indicate that MTX continues to demonstrate an acceptable response rate in achieving treatment targets as the first-line therapy in RA.

Table 1 Baseline characteristics of subjects

Variables	*n* (254)	%
Age (years) mean ± SD	48 ± 11	
• > 60 years	28	11
• ≤ 60 years	226	89
Sex		
• Male	10	4.3
• Female	244	95.7
Education level		
• High school or less	109	43
• Bachelor degree or more	145	57
Marital status		
• Married	189	74.4
• Unmarried	65	25.6
Employment status		
• Actively employed	92	36.2
• Not actively employed	162	63.8
BMI (kg/m^2), mean ± SD	23.8 ± 4.8	
Obesity		
• No	161	63.4
• Yes	93	36.6
Symptom duration (months), median (IQR)	12 (4–24)	
• ≤ 6 months	102	40.2
• > 6 months	152	59.8
Tender joint count (TJC), median (IQR)	8 (4-13.25)	
• ≤ 5	95	37.4
• > 5	159	62.6
Swollen joint count (SJC), median (IQR)	0 (0–0)	
• < 1	192	75.6
• ≥ 1	62	24.4
Comorbidities		
• RDCI 0	156	61.4
• RDCI 1	52	20.5
• RDCI 2	33	13.0
• RDCI ≥ 3	13	5.1
Baseline glucocorticoid use, prednisone equivalent dose (mg/day), median (IQR)	10 (5–10)	
• Prednisone equivalent dose > 7.5 mg/day	156	61.4
• Prednisone equivalent dose ≤ 7.5 mg/day	98	38.6
ESR (mm/hour), median (IQR)	43 (27-68.5)	
• Normal	39	15.4
• Elevated	215	84.6
CRP (mg/L), median (IQR)	4.6 (1.7-13.98)	
• Normal	138	54.3
• Elevated	116	45.7
Rheumatoid factor (RF)		
• Negative	118	46.5
• Positive	136	53.5
Patient's global health (scale 0–10), median (IQR)	3 (3–4)	
Disease activity (DAS28-ESR), median (IQR)	4.47 (3.90–5.29)	
• Moderate	176	69.3
• High	78	30.7

Table 2 Disease activity after 12 months of therapy

Disease activity at 12 months	*N* (254)	%
Remission	84	33
Low disease activity	67	26.4
Moderate	82	32.3
High	21	8.3

Table 3 Comparison between MTX monotherapy treatment success and unsuccessful groups

Variables	Treatment success (*n* = 151)	Treatment unsuccessful (*n* = 103)	*p*-value
Age (years)			
• > 60 years	18	10	0.37
• ≤ 60 years	133	93	
Sex			
• Male	8	2	0.15
• Female	143	101	
Obesity			
• No	107	54	0.00
• Yes	44	49	
Symptom duration (months)			
• ≤ 6 months	56	46	0.14
• > 6 months	95	57	
Tender joint count			
• ≤ 5	69	26	0.00
• > 5	82	77	
Swollen joint count			
• < 1	115	77	0.46
• ≥ 1	36	26	
Comorbidities			
• RDCI 0	89	67	0.64
• RDCI 1	34	18	
• RDCI 2	19	14	
• RDCI ≥ 3	9	4	
Baseline glucocorticoid use, prednisone equivalent dose (mg/day)			
• > 7.5 mg/day	89	67	0.2
• ≤ 7.5 mg/day	62	36	
ESR (mm/hour)			
• Normal	31	8	< 0.00
• Elevated	120	95	
CRP (mg/L)			
• Normal	78	60	0.18
• Elevated	73	43	
Rheumatoid factor			
• Negative	71	47	0.46
• Positive	80	56	
Disease activity			
• Moderate	118	58	< 0.00
• High	33	45	

Additionally, notable differences in subject characteristics were observed compared to previous RA studies. Notably, 95.7% of newly diagnosed RA patients in our cohort were female. This aligns with previous epidemiological studies which indicated that RA primarily affects women with a female-to-male ratio of approximately three to one, often presenting with higher disease activity and disability [25]. The elevated prevalence of RA among women is corroborated by various studies;

Table 4 Multivariate analysis of predictors of MTX treatment success

Predictor	β	OR (95% CI)	*p*-value
Lower disease activity	0.677	1.97 (1.04–3.72)	0.04
Normal ESR	0.946	2.58 (1.05–6.34)	0.04
Normoweight	0.935	2.55 (1.45–4.49)	0.00
TJC ≤ 5	0.895	2.45 (1.31–4.58)	0.00

for instance, Silva-Fernández et al. found that women constituted 61.5% of RA patients in a population-based national survey in Spain [26]. Furthermore, a large epidemiological study across Middle Eastern regions reported an even higher proportion of female patients at 84.9% [27]. Our observation of an overwhelmingly female RA population surpasses the female-to-male ratio reported in most previous studies, potentially attributable to ethnic differences and variances in health-seeking behaviour between genders in Indonesia.

Moreover, we noted that the mean BMI in our cohort was 23.8 kg/m², with 36.6% classified as obese. Obesity has been associated with an increased risk of RA, with a notable proportion of RA patients exhibiting obesity [28]. For instance, a study in the United Kingdom reported a mean BMI of 27.5 kg/m² among RA subjects [16]. This contrasts with studies in the Asia-Pacific region and Indonesia, where mean BMI values of 23.3 kg/m² and 22.5 kg/m², respectively, were reported among RA populations [17, 23]. These discrepancies in RA patient characteristics warrant further exploration, considering potential influences of genetic variations and socioeconomic factors.

Multivariate analysis revealed four significant predictors of MTX treatment success: lower disease activity at baseline (moderate vs. high disease activity) (OR 1.97, $p=0.04$), normal ESR (OR 2.58, $p=0.04$), normal weight (OR 2.55, $p=0.00$), and tender joint count (TJC) ≤ 5 (OR 2.45, $p=0.00$). Sensitivity analysis, including drop-out subjects, yielded similar results, confirming that these four variables were consistent predictors of MTX monotherapy treatment success.

Disease activity was a significant predictor of achieving treatment targets in this study, consistent with the results of a cohort study involving 285 subjects that investigated the effectiveness of MTX. Patients with higher disease activity (DAS28 > 5.1) had a higher risk of MTX treatment failure (OR 3.08, 95% CI 1.26–7.52) [14]. Higher disease activity is considered a poor prognostic factor based on data collected from various randomized controlled trials (RCTs) and cohort studies, in accordance with both EULAR and ACR recommendations [29]. Furthermore, results from OPTIMA and PREMIER studies investigating RA patients on MTX also found that higher disease activity (DAS28 6.4) is a predictor of insufficient response to MTX after 6 months of therapy [30]. Conversely, a study by Sergeant et al. found that lower baseline DAS28 was associated with non-response when assessed by changes in disease activity scores (ACR response criteria or DAS change from baseline). Moreover, higher baseline DAS28 was not significantly predictive of failure to achieve low disease activity or remission [16]. Therefore, employing alternative methods of assessing treatment response, such as ACR or EULAR response criteria, may help to confirm these findings.

The role of ESR in predicting treatment response has also been investigated in previous studies. In a stratified single-blinded trial involving seven secondary and tertiary care clinics, ESR > 40 mm/hour was associated with approximately threefold the risk of MTX non-response compared to subjects with normal ESR values (OR 2.77; 95% CI 1.58–4.85) [14]. Another study conducted in Dublin, which conducted synovial sampling through arthroscopy in RA patients with knee arthralgia, demonstrated a positive correlation between ESR values and the level of inflammation [31]. Higher ESR is also considered a poor prognostic factor when present with other factors, such as moderate disease activity, RF/ACPA positivity, persistent swollen joints, active synovitis, and the presence of bone erosion [29].

Normal BMI was also found to be a predictor of MTX treatment success in our study, consistent with the findings of previous studies. A study investigating predicting factors of insufficient response to MTX among DMARD-naïve RA patients found that obesity was associated with a threefold risk of MTX non-response (OR 3.02; 95% CI 1.31–6.97) [14]. Moreover, in a meta-analysis conducted by Liu et al., obese patients were found to be 43% more likely to fail to achieve remission, and almost all studies included in the review demonstrated that obesity aggravated disease activity, increased the number of tender joints, increased inflammation markers, and increased levels of pain [32]. Another study involving 1,313 RA patients in early and advanced stages of the disease showed that overweight and obese patients required higher doses of MTX, either as monotherapy or in combination with other DMARDs, with an average dose of 20 mg/week, compared to 15 mg/week of MTX in subjects with normal BMI. Aside from the higher dose requirement, overweight or obesity were also associated with a reduced response to therapy in established RA [33]. However, despite the association between obesity, higher inflammation, and increased disease activity, the impact of obesity on radiographic changes has been more contentious. Interestingly, some studies have observed that obesity is associated with lower radiographic joint damage [34]. Further prospective studies are needed to explore the impact of obesity on radiographic progression in RA, which also reflects disease severity, and to elucidate the underlying mechanisms.

The fourth predicting factor of MTX treatment success identified in this study was the number of tender joints. A study by de Rotte et al. reported that patients with TJC>3 had twice the higher risk of having an insufficient response to MTX (OR 2.05; 95% CI 1.08–3.89) [14]. Similarly, results from The Rheumatoid Arthritis Medication Study (RAMS), a large multicentre study involving 38 centres with a total of 1,050 subjects, found that a higher tender joint count was associated with a 6% higher risk of being MTX non-responders [16]. A higher joint count (TJC 21) was also found to be a poor prognostic factor in a 6-month study involving 4 RCTs with 775 RA DMARD-naïve patients [35]. This is further corroborated by the results of the OPTIMA and PREMIER studies, which demonstrated that subjects with a higher tender joint count (TJC 33) tend to have an insufficient response to MTX after 6 months of therapy [30].

In the sensitivity analysis, it was found that there was no difference between the drop out patients and the patients in the research subjects, both in terms of characteristics and in terms of the results of the multivariate analysis.

There are several limitations to this study. This is a retrospective cohort study utilizing data from medical records, thus, there is a limitation in the data available for analysis. For example, ACPA testing was not routinely performed at our center as it is not covered by the national insurance. Additionally, early erosions were not analyzed because not all patients underwent x-ray imaging, primarily due to cost limitations. The variability in symptom duration among our cohort also means that not all patients presented with early-onset RA, making it difficult to distinguish between early and late erosions. Given that this study was conducted in a real-life setting, we were unable to control for symptom duration at the time of presentation. Some data, such as the symptom duration variable, might be subject to recall bias since they were self-reported by patients as recorded in the medical records. While variations in glucocorticoid doses during the follow-up period could influence treatment outcomes, we did not assess the cumulative glucocorticoid dose over the entire follow-up period. Further prospective study is recommended to confirm these findings and obtain more robust results.

Conclusion

The rate of MTX monotherapy success in our study was 59.4%. Lower disease activity, normal ESR, normoweight, and fewer tender joints at baseline were significant predictors of treatment success.

Abbreviations

ACPA	Anti-citrullinated peptide antibody
ACR	American College of Rheumatology
APLAR	Asia Pacific League of Associations for Rheumatology
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
DAS28-ESR	Disease Activity Score-28 with erythrocyte sedimentation rate
DMARD	Disease modifying anti-rheumatic drugs
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
IL	Interleukin
IRA	Indonesia Rheumatology Association
MTX	Methotrexate
OR	Odds ratio
RA	Rheumatoid arthritis
RANKL	Receptor activator of nuclear factor kappa-B ligand
RDCI	Rheumatic Disease Comorbidity Index
RF	Rheumatoid factor
ROC	Receiver operating characteristic
SD	Standard deviation
SJC	Swollen joint count
TJC	Tender joint count

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None.

Author contributions

RH, FF, and FP conceived and designed the study. SAKW, AA, JD, and APA contributed to data acquisition and analysis. RH and FP aided in the interpretation of data. FF took lead in drafting the manuscript. RH, FP, SAKW, AA, JD, and APA substantively revised the manuscript. All authors have read and approved of the final manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to data protection reasons but are available from the corresponding author on reasonable request (only aggregated datasets for temporary use).

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Committee Board of the Faculty of Medicine, Universitas Indonesia, with approval number KET-630/UN2.F1/ETIK/PPM.00.02/2022, and was conducted in accordance with the Declaration of Helsinki. The need for informed consent from the patients was waived by the institutional review board, as the study only utilized data from existing medical records. Permission to access patients' medical records was obtained from Cipto Mangunkusumo National General Hospital, with assurances to maintain the anonymity and confidentiality of personal information.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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