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Achieving and Sustaining Treatment Targets in Rheumatoid Arthritis: A Retrospective Cohort Analysis in Indonesia

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Abstract

Achieving and sustaining low disease activity (LDA) and remission in rheumatoid arthritis (RA) remains challenging. This study examined the rates and predictors of LDA/remission and sustained LDA/remission in an Indonesian RA cohort. A retrospective study of newly diagnosed adult patients attending a rheumatology clinic in 2020-2021 was conducted. Patients were followed for 12 months to evaluate achievement of LDA/remission, defined as DAS28-ESR ≤3.2, and those meeting the target were observed for an additional 12 months to evaluate sustained LDA/remission. Cox regression was used to identify predictors of time to LDA/remission and loss of LDA/remission. Of 166 participants, 91 (54.8%) achieved LDA/remission, with a median time of 10 months. Among these, 39 (41.8%) maintained LDA/remission for 12 months. The median time to loss of LDA/remission was also 10 months. In multivariate analysis, no baseline variables (age, sex, rheumatoid factor (RF) positivity, disease activity, obesity, or disease duration) predicted achieving or sustaining LDA/remission. In this Indonesian cohort, over half of patients reached LDA/remission within 12 months. However, fewer than half sustained it over the following year, highlighting the need for ongoing monitoring and timely treatment adjustments, even after remission is achieved.

Keywords: low disease activity, remission, rheumatoid arthritis, predictor

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that leads to significant disability, limitations in daily physical activity, reduced quality of life, and a substantial socioeconomic burden.[1,2] Consequently, the primary goal of managing RA is to achieve clinical remission, defined as the absence of signs and symptoms of active inflammatory disease, or, alternatively, to achieve low disease activity (LDA), especially in patients with long-standing disease.[1,3] The implementation of treat-to-target (T2T) strategies, as endorsed by international guidelines such as those from the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR), has been shown to improve remission rates.[4–8] Methotrexate (MTX) remains the cornerstone of the first-line disease-modifying antirheumatic drug (DMARD) therapy for RA and is often combined with short-term glucocorticoids. In recent years, biologic DMARDs (bDMARDs) have been increasingly utilized, particularly in patients with poor prognostic factors or in those who have failed to respond adequately to conventional DMARDs (cDMARDs).[5]

By adopting a more aggressive treatment approach and achieving rapid remission, progression of joint damage can be halted, thereby preventing further deformities and disability.[9] Despite these advances, sustained remission remains a significant challenge in clinical practice. Studies have shown that more than half of the patients with RA fail to maintain remission, with sustained remission rates of less than 50% in several studies, depending on the criteria used.[3,10]

This highlights the need for strategies to improve the sustained remission rates. The challenge is even greater in developing countries, including those in Central and Southeast Asia (e.g., Indonesia, India, Thailand, and Pakistan) and Sub-Saharan Africa, where early diagnosis of RA is often and access to newer therapies, such as bDMARDs and targeted synthetic DMARDs

(tsDMARDs), remains limited owing to cost.[2,11] However, few studies have evaluated the remission and sustained remission rates in these regions.

For example, a study from India reported a remission rate of 20% according to the Disease Activity Score 28 with erythrocyte sedimentation rate (DAS28-ESR).[12] A multicenter study in the Asia-Pacific region reported low remission rates in Bangladesh, Vietnam, and Nepal, with DAS28-ESR remission rates of 9.0%, 6.25%, and 17.2%, respectively.[13] These rates are notably lower than those observed in Western cohorts.[14,15] Unfortunately, data from Indonesia remain scarce, and the factors influencing remission in this setting are poorly understood.

Identifying predictors of remission and sustained remission is essential for clinicians to recognize patients at risk of failing to achieve treatment targets or experiencing disease relapse. This would allow for a more aggressive and closely monitored approach to disease management. Several sociodemographic factors, including age, sex, obesity, and smoking history, as well as RA-related characteristics, such as disease activity, inflammatory markers, and the presence of rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), have been associated with remission and its maintenance.[16–20] However, these predictors vary across populations. This study aimed to investigate the rates of LDA/remission and sustained LDA/remission in an Indonesian cohort of patients with RA and identify potential predictors of these outcomes. This study is expected to provide insights that will improve the implementation of the T2T strategy in daily clinical practice.

Method

A retrospective cohort study was conducted at a tertiary referral hospital in Jakarta, including all patients with RA who were newly diagnosed and visited the rheumatology clinic between January 1, 2020, and December 31, 2021. This hospital was selected because it serves as a national referral center with many patients with RA, and includes cases referred from primary and secondary care centers. Newly diagnosed adult patients with RA aged 18 and above who met the 2010 ACR/EULAR classification criteria for RA[21] were included in the study. These criteria include joint involvement, serology (RF or ACPA), symptom duration, and acute-phase reactants (C-reactive protein [CRP] or ESR). Patients with a score of 6 or more and symptoms not better explained by other diseases were classified as having RA.[21] All eligible patients were included regardless of their follow-up status.

Data were extracted from medical records, including demographic information (age, sex, body weight, and height) and clinical characteristics of RA. Permission to access and use patient data for research purposes was granted following the approval of the study by the hospital's Research Ethics Committee. A written request was submitted to the Medical Records Department, which included a copy of the ethical approval letter and a list of patients diagnosed with RA based on clinical coding. Only anonymized data was used in the analysis to ensure patient confidentiality throughout the study.

Age was defined as the patient's age at the time of study and categorized into two groups: ≤60 years and >60 years. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and classified according to the Asia-Pacific BMI classification: obese (BMI ≥25 kg/m^2) and non-obese (BMI <25 kg/m^2).[22] Disease duration was defined as the time elapsed between symptom onset and study inclusion and was categorized as ≤6 months or >6 months. Disease activity was assessed using the DAS28-ESR, which incorporates the number of tender and swollen joints, ESR value, and the patient's global assessment of disease activity on a 100-mm visual analog scale, where 0 represents no disease activity and 100 represents the worst possible disease activity. Based on the DAS28-ESR, disease activity was classified as follows: remission (<2.6), low disease activity (≥2.6 to ≤3.2), moderate disease activity (>3.2 to ≤5.1), and high disease activity (>5.1).[23] Laboratory RF values were also documented; the patients were classified as RF-positive or RF-negative.

Treatment for RA at the study location followed a standardized protocol. The MTXwas the first-line DMARD, starting at 10 mg/week and titrated up to a maximum of 25 mg/week based on treatment response. For patients who were intolerant of MTX, alternative therapies included leflunomide (20 mg/day) and sulfasalazine (3,000 mg/day). If the treatment targets were not achieved with MTX monotherapy, combination therapy with other DMARDs was initiated. The bDMARDs were not used in this study population because they are not covered by the National Health Insurance Program. Glucocorticoids were commonly prescribed, with a maximum prednisolone equivalent dose of 0.5 mg/kg/day, tapered as quickly as clinically possible. Therefore, the medication type and glucocorticoid use were not included as variables in the analysis.

Treatment success was defined as achieving LDA or remission (DAS28-ESR ≤3.2). Patients were followed for

12 months from the time of diagnosis to assess whether they achieved LDA or remission. Patients who achieved the treatment targets within the first 12 months were monitored for an additional 12 months. Sustained LDA or remission was defined as maintaining DAS28-ESR ≤3.2 for 12 consecutive months after the initial achievement. Therefore, the maximum possible follow-up period for each participant was 24 months. The primary outcomes of interest were time to achieve LDA/remission (defined as the time from diagnosis to initial LDA/remission) and time to loss of LDA/remission (defined as the time from initial LDA/remission to loss of LDA/remission). Additionally, the predictors of both LDA/remission and sustained LDA/remission were explored in this study.

Demographic and clinical characteristics were reported as percentages for categorical variables, as means±standard deviations for normally distributed continuous variables, or as medians±interquartile ranges (IQR) for non-normally distributed continuous variables. The Kaplan-Meier method was used to analyze the median time to achieve LDA/remission and the time to loss of LDA/remission. In the initial analysis, patients who did not achieve LDA/remission by the end of the 12-month follow-up period or who were lost to follow-up were excluded. For patients achieving LDA/remission, the loss of LDA/remission at any time in the subsequent 12 months was the event of interest, and patients who remained in LDA/remission or were lost to follow-up were excluded. Log-rank tests were used to assess differences between survival curves for categorical variables. Univariate Cox regression analysis was performed for each predictor variable. Variables with p-values <0.25 in univariate analysis or with established clinical relevance based on prior evidence were included in the multivariate model. Statistical significance was set at a two-tailed p-value of <0.05. All statistical analyses were conducted using the IBM SPSS Statistics for Mac (version 27.0; IBM Corp., Armonk, NY, USA).

Results

A total of 166 patients newly diagnosed with RA met the eligibility criteria within the study period and were included in the analysis. The mean age was 47.60±11.65 years, and the participants were predominantly female (93.4%). Most patients had moderate disease activity at baseline (78.3%). Most patients (79.5%) received methotrexate monotherapy, 9% received other cDMARD monotherapies, and 10.4% received cDMARD combinations. The median disease duration was 6 months (IQR: 3–12 months). The RF-positive and RF-negative patients were equally represented. The baseline characteristics of the patients are summarized in Table 1.

Table 1. Baseline Characteristics of Participants (n = 166)

Variable	n	%
Age (years)		
Mean (SD)	47.60 (11.65)	
Median (IQR)	49 (39-56)	
>60 years	20	12.0
≤60 years	146	88.0
Sex		
Male	11	6.6
Female	155	93.4
BMI (kg/m²), median (IQR)	23.5 (20.8-26.5)	
Non-obese (<25 kg/m^2)	106	63.9
Obese (≥25 kg/m^2)	60	36.1
Disease duration (months), median (IQR)	6 (3-12)	
≤6 months	88	53.0
>6 months	78	47.0
Rheumatoid factor (RF)		
Negative	83	50.0
Positive	83	50.0
Disease activity		
Moderate	130	78.3
High	36	21.7
Types of DMARDs used		
MTX monotherapy	132	79.5
Other cDMARDs monotherapy	15	9.0
Combination of cDMARDs	19	10.4

Notes: BMI = body mass index, cDMARD = conventional DMARD, DMARD = disease-modifying antirheumatic drugs, IQR = interquartile range, MTX = methotrexate, SD = standard deviation, RF = rheumatoid factor.

A total of 91 participants (54.8%) achieved LDA/remission during the follow-up period. The median time to LDA or remission was 10 months (Figure 1). Stratification according to age, sex, BMI category, disease duration, RF status, and disease activity showed that the median time to LDA/remission was longer in older participants (>60 years) (median 12 months vs. 10 months), female (median 11 months vs. 7 months), obese patients (median 12 months vs. 10 months), RF-positive patients (median 12 months vs. 9 months), and those with higher disease activity (median time not reached vs. 9 months). However, none of these differences were statistically significant in the log-rank test (Figure 2).

The multivariate Cox regression analysis showed that none of the assessed baseline variables, age (>60 vs ≤60 years), sex, RF status, disease activity category, BMI category, or disease duration, were significant predictors of achieving LDA/remission within the study period (Table 2). All variables had p-values >0.05, indicating no statistically significant associations. Of the 91 patients who attained LDA/remission, 52 (57.1%) remained in LDA/remission, and 39 (41.8%) remained in LDA/remission at 6 and 12 months.

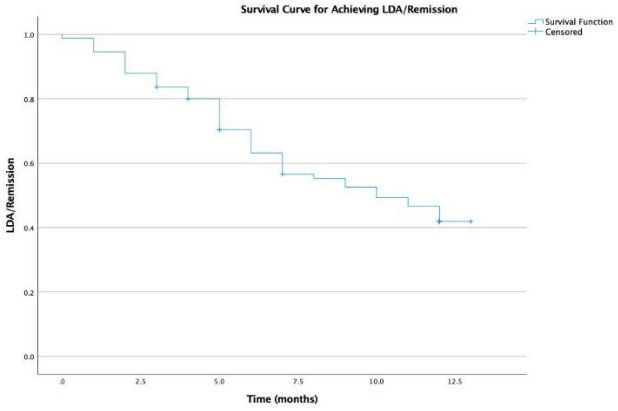

Figure 1. Kaplan-Meier Curve for Achieving Low Disease Activity/Remission
Note: LDA = low disease activity

The median time to LDA/remission loss was 10 months. The loss of LDA/remission was greater in the first 4 months after achieving LDA/remission (Figure 3). On average, the time to loss of LDA/remission was shorter in patients aged ≤60 years (median 4 vs. 10 months), females (median 9 vs. 12 months), obese subjects compared to non-obese subjects (median 5 vs. 10 months), and those with higher disease activity compared with low/moderate disease activity (median 5 vs. 11 months). However, none of these differences were statistically significant in the log-rank test (Figure 4).

In the multivariate Cox regression analysis, none of the assessed baseline variables were statistically significant predictors of LDA/remission loss (all p-values >0.05) (Table 2). However, hazard ratios exhibited certain trends. Patients aged ≤60 years had a higher risk of losing LDA/remission compared with those >60 years (HR = 1.39, 95% CI 0.60–3.23), and obese patients (BMI ≥25 kg/m^2) had a similar risk to non-obese patients (HR = 1.00, 95% CI 0.56–1.80). Male, negative RF status, lower baseline disease activity, and shorter disease duration were associated with a lower hazard of loss of LDA/remission, although these associations were not statistically significant.

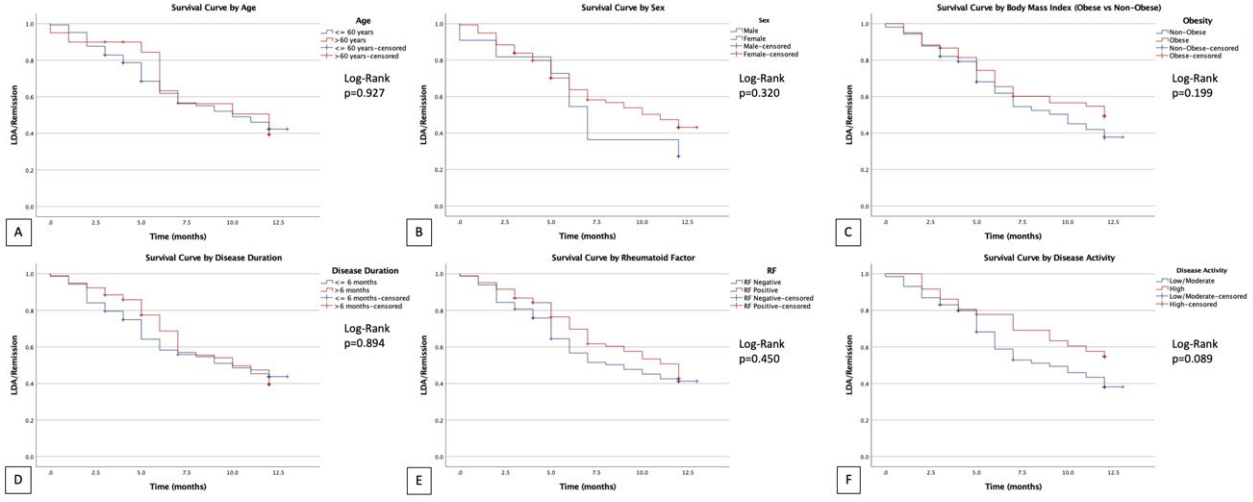

Figure 2. Kaplan–Meier Curves for Time to Low Disease Activity/Remission According to Each Predictor Variable Included in the Study: (A) Age, (B) Sex, (C) BMI category, (D) Disease duration, (E) RF Status, and (F) Disease Activity
Notes: BMI = body mass index, LDA = low disease activity, RF = rheumatoid factor

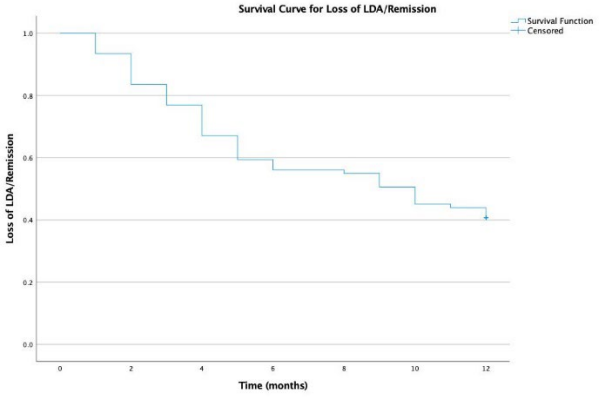

Figure 3. Kaplan-Meier Curve Showing Time to Loss of LDA/Remission

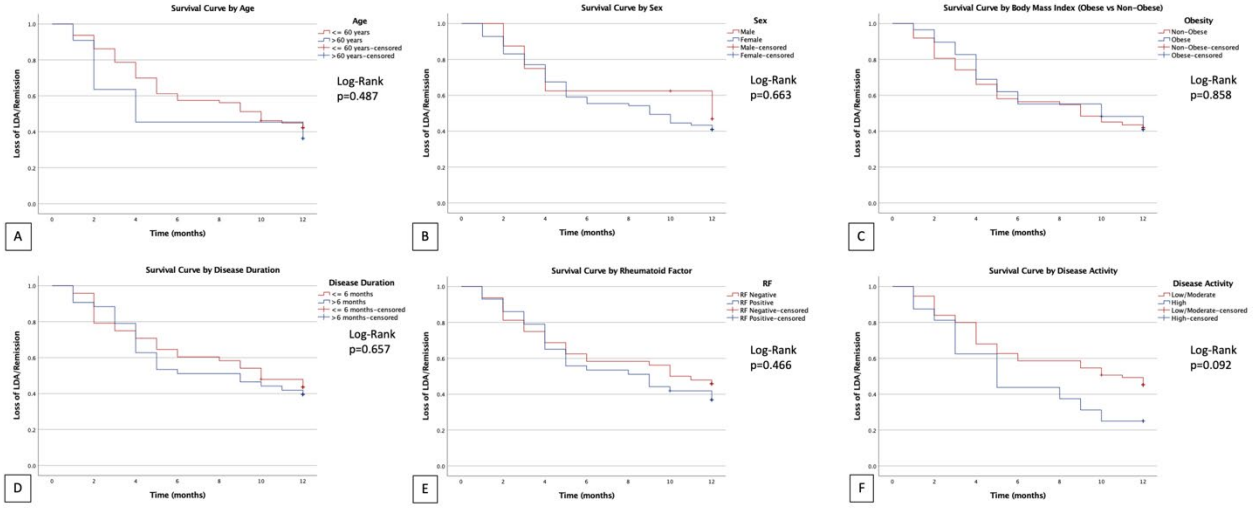

Figure 4. Kaplan–Meier Curves for Time to Loss of LDA/Remission According to Each Predictor Variable Included in the Study: (A) Age, (B) Sex, (C) BMI Category, (D) Disease Duration, (E) RF Status, and (F) Disease Activity

Notes: BMI = body mass index, LDA = low disease activity, RF = rheumatoid factor.

Table 2. Predictors and Loss of Low Disease Activity/Remission

Variables	Predictors of LDA/Remission		Loss of LDA/Remission	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Age				
>60 years	Ref	>0.05	Ref	>0.05
≤ 60 years	0.96 (0.46-1.99)		1.39 (0.60-3.23)	
Sex				
Female	Ref	>0.05	Ref	>0.05
Male	1.53 (0.47-5.03)		0.84 (0.29-2.38)	
RF status				
Positive	Ref	>0.05	Ref	>0.05
Negative	1.04 (0.65-1.68)		0.81 (0.46-1.43)	
Disease activity				
High	Ref	>0.05	Ref	>0.05
Low/Moderate	0.93 (0.54-1.60)		0.53 (0.27-1.05)	
Body Mass Index				
Obese (≥25 kg/m^2)	Ref	>0.05	Ref	>0.05
Non-obese (<25 kg/m^2)	1.02 (0.63-1.65)		1.00 (0.56-1.80)	
Disease duration				
>6 months	Ref	>0.05	Ref	>0.05
≤6 months	1.11 (0.70-1.76)		0.85 (0.49-1.49)	

Notes: LDA = low disease activity, CI = confidence interval, RF = rheumatoid factor

Discussion

A total of 54.8% of patients achieved LDA or remission during follow-up. The rates of LDA and remission reported across studies varied, which may be due to differences in disease activity indices and remission criteria. This study's results were consistent with those of a multicenter study by Thomas *et al.*, in which 57% of patients achieved LDA (DAS28-ESR <3.2) at 1-year follow-up.[24] However, some studies have reported higher LDA/remission rates, possibly owing to the increased use of bDMARDs in recent research compared with the exclusive use of cDMARDs in this study's population. For example, in the United Arab Emirates, LDA and remission rates at 12 months were 72.29% according to the DAS28 (50.9% remission and 21.39% LDA),whereas rates based on the clinical disease activity index (CDAI) and simple disease activity index (SDAI) were both >80%.[18] In another study, 80.1% of the patients achieved clinical remission based on DAS28 at least once, with 54.1% achieving remission within the first year, 23.9% in the second year, and 8.3% in the third year.[25] Similarly, a Finnish study on DMARD-naive patients with RA found DAS28 remission rates of 67% and 71% at 3 and 12 months, respectively. Notably, none of the patients in this study used bDMARDs within the first three months, and only 2.7% used them at 12 months. While this study predominantly involved cDMARDs, it also included a higher proportion of combination therapies, which may have contributed to the higher remission rates.[26]

The median time to LDA or remission in the study population was 10 months, which exceeds the recommended 6-month timeframe outlined in the treat-to-target approach.[27] This longer duration may be attributed to the slower uptitration of methotrexate due to the high incidence of side effects and longer intervals between clinic visits, meaning that the optimal methotrexate dose may not have been reached within six months. At the same time, early and aggressive treatment strategies were increasingly emphasized in RA management in contexts where bDMARDs were not widely accessible, allowing a longer follow-up period for cDMARDs to achieve treatment targets. Nevertheless, if the treatment goals are not met within this extended period, a more aggressive approach should be initiated promptly. This study's results were comparable to those of a Dutch cohort study (1986-2005), which reported a median time to remission of 12 months. The prescription rate of anti-TNF agents was low in that cohort, as bDMARDs were either unavailable or reserved for patients who had failed initial DMARD treatment, as in the study population.[28]

After 12 months of follow-up, 41.8% of patients who had previously achieved remission maintained sustained LDA/remission, with a median time to relapse of 10 months. This result aligned with a Swedish study, which found that 41.9% of patients achieved sustained DAS28 remission. However, remission rates were lower when more stringent criteria, such as the ACR/EULAR Boolean criteria, CDAI, and SDAI, were applied.[29] A Nijmegen cohort study reported that only 36% of the patients who achieved remission maintained remission for a median duration of 19 months.[29] These findings underscore that despite advancements in RA treatment over recent decades, approximately half of patients experience relapse and fail to achieve sustained remission, highlighting the importance of close monitoring of disease activity and timely treatment adjustments even after remission is achieved.

In this study, the relapse rate was higher within the first four months of remission, suggesting that physicians should be careful about the risk of relapse during this early period. Several factors may have contributed to the early relapse. RA is a fluctuating disease with a variable course, and its relapse is influenced not only by clinical RA-related factors but also by external triggers such as psychological stress, infection, and medication changes, which were not further explored in this study.[30,31] Residual subclinical synovitis, detected by imaging studies and potentially missed by DAS28, has also been associated with flares, particularly in the early months of remission (less than one year).[32] Furthermore, nonadherence, which is common in chronic conditions such as RA, and a false sense of well-being without medication in early remission may further increase the risk of relapse.[33,34] Similar findings have been reported in previous studies, showing a higher risk of relapse after the first remission visit, with the risk decreasing once remission is sustained over subsequent visits.[29,30] The likelihood of relapse decreased with increasing remission time.[30]

The associations between demographic and clinical factors and LDA/remission, as well as sustained LDA/remission, were also analyzed in this study. The final multivariate model included age, sex, disease duration, baseline disease activity, BMI category, and RF status, based on clinical relevance and evidence from previous studies.[16,18,20,35] However, no significant predictors of remission or sustained remission have been identified. Previous studies have shown that male and younger patients are positive predictors of remission, whereas obesity, higher baseline DAS, and higher

comorbidity index are negative predictors.[24,28] Factors such as shorter disease duration, earlier time to remission, better functional status, and higher compliance were found to predict sustained remission. In contrast, ACPA positivity was found to be a predictor of relapse.[18,36]

However, these relationships were not observed in this study. This discrepancy could be attributed to several factors. First, the limited sample size might have contributed to the lack of significance of the predictors. Second, the retrospective design limited the inclusion of several variables, such as comorbidities, smoking status, ACPA, functional status, and compliance with the T2T strategy, which have been identified as important predictors in previous studies due to incomplete availability in medical records.[16,18,37] Finally, the predictors identified in Western populations may not be fully applicable to Indonesian patients due to differences in genetics, ethnicity, healthcare system, and treatment availability.[38] However, this study found that patients with moderate disease activity and high disease activity at baseline did not reach the median time to remission by the end of the 12-month follow-up, compared to a median of nine months, suggesting that patients with a high baseline disease activity reach treatment targets much later, potentially increasing the risk of permanent joint deformities. Therefore, a more aggressive treatment approach, including cDMARD combination therapy or biologics, may be necessary in these cases.

Since this study was conducted in a real-world setting, it offers insights into remission patterns, particularly in a developing country where biologics remain largely unaffordable. However, the lack of bDMARD use, as these drugs were not covered by the National Health Insurance program, limits the ability to explore remission and sustained remission rates in accordance with recent treatment recommendations in the Indonesian population. To minimize potential selection bias, all eligible patients were included in the analysis, regardless of their follow-up status, and those lost to follow-up were treated as censored. Nevertheless, residual selection bias could not be excluded if the loss to follow-up was related to outcomes or predictors.

Additionally, as a retrospective cohort study, only variables documented in the medical records could be analyzed as potential predictors of LDA/remission and sustained remission. Information bias was controlled through the application of standardized RA classification criteria and the fact that rheumatologists or trained physicians performed patient assessments in this tertiary hospital. Nevertheless, as an observational study, the quality of measurements recorded in medical records could not be fully controlled, and information bias could not be entirely ruled out. Furthermore, the relatively small sample size might have limited statistical power to detect significant predictors in the final model. Future research involving populations of bDMARD users, prospective studies exploring larger sample sizes, and more potential predictors is recommended to improve RA management and increase sustained remission rates.

Conclusion

The rate of achieving LDA/remission in the Indonesian RA cohort was 54.8%, with a median time to LDA/remission of 10 months. Among those who initially reached the treatment targets, fewer than half maintained LDA/remission over the subsequent 12 months. This highlights the importance of regular disease monitoring and timely treatment adjustments even after remission is achieved.

Abbreviations

RA: rheumatoid arthritis; LDA: low disease activity; T2T: treat-to-target; ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; MTX: methotrexate; DMARD: Disease-Modifying Antirheumatic Drugs; bDMARD: biologic DMARD; cDMARD: conventional DMARD; DAS28-ESR: Disease Activity Score 28 with erythrocyte sedimentation rate; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; BMI: body mass index; IQR: interquartile ranges; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee Board of the Faculty of Medicine, Universitas Indonesia (approval number KET-1660/UN2.F1/ETIK/PPM.00.02/2023) and was conducted in accordance with the Declaration of Helsinki. Because this study used only retrospective medical record data, the Institutional Review Board waived the need for informed consent.

Competing Interest

The authors declare no conflict of interest.

Availability of Data and Materials

The datasets analyzed in this study are not publicly available because of data protection restrictions. However, the aggregated datasets are available from the corresponding author upon reasonable request and are used only temporarily.

Authors' Contribution

FF and RH conceived and designed the study. SAKW, SS, FP, AA, JD, and APA contributed to data acquisition. FF, RH, and SD performed data analysis and interpretation. SAKW, SS, FP, AA, JD, APA, and SD drafted the manuscript. All authors contributed equally to critically revising the manuscript and have read and approved the final version.

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None.

Declaration on the Use of Artificial Intelligence

The authors declare that artificial intelligence (AI) tools were utilized solely for language editing and grammatical refinement to improve the clarity and readability of the manuscript. The specific AI tools used was ChatGPT 4 (chat.openai.com). AI was not involved in content generation, data analysis, interpretation, or any decision-making processes. All scientific content, interpretations, conclusions, and responsibilities related to the manuscript rest solely with the authors.

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