



ORIGINAL ARTICLE

Characteristics and prevalence of clinical remission of rheumatoid arthritis in a nationwide study from Indonesia

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Abstract

Aim: To investigate the clinical characteristics, DMARD treatment pattern, remission rate, and factors associated with disease remission of rheumatoid arthritis (RA) patients in Indonesia.

Method: A multicenter survey was conducted in 2019–2020 involving 16 hospitals in Indonesia. Inclusion criteria were RA patients who fulfilled the 2010 ACR/EULAR classification criteria, were aged ≥ 18 years, and have been treated with 1 DMARD or more for at least 6 months, with exclusion criteria being the co-existence of other autoimmune diseases or pain syndromes. Disease activities and remission rate were defined using DAS28-ESR.

Results: A total of 870 patients were completed for analysis. Remission was achieved in 24.5% of patients, while low disease activity in 18.5%, moderate disease activity in 44.6%, and high disease activity in 12.4%. The distribution of conventional DMARDs from subjects was methotrexate 69.9%, leflunomide 15.9%, sulfasalazine 12.0%, chloroquine/hydroxychloroquine 8.9%, and cyclosporine 4.8%. Patients treated with biologic DMARDs were only 0.3%. The mean methotrexate dose was 11.2 ± 4.0 mg/week, and the mean methotrexate duration was 45.1 ± 36.6 months. The majority of patients received glucocorticoids (65.5%). 71.1% received DMARD monotherapy, while 28.9% had combined DMARDs. According to the multivariate analysis, delayed time to diagnosis and treatment (>6 months), DMARD monotherapy, and glucocorticoid use were negatively associated with disease remission.

Conclusion: The remission rate of Indonesian RA patients is 24.5%, and low disease activity is 18.5%. Methotrexate and leflunomide are the most frequent conventional

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DMARDs used. Delayed diagnosis, delayed treatment, and DMARD monotherapy contributed to the current low remission rate in Indonesia.

KEYWORDS

Indonesia, remission rate, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is the most common systemic inflammatory arthritis characterized by persistent synovitis, systemic inflammation, and autoantibody production.¹ Uncontrolled active rheumatoid arthritis can cause joint damage, disability, decreased quality of life, and cardiovascular and other comorbidities. Onset can occur at any time, but mostly between 30 and 50 years, mainly affecting women, smokers, and those with a family history of the disease.² RA affects 0.5%–1% of adults in developed countries, with 5–50 per 100,000 new cases annually.³

The development of the treatment strategy for managing RA has progressed significantly in recent decades. As per current guidelines, the management of RA is focused on treat-to-target (T2T) to achieve low disease activity (LDA) and remission if possible.⁴ Measuring the disease activity score of 28 joints—erythrocyte sedimentation rate (DAS28-ESR) is a widely accepted method of defining disease activity in RA.⁵ Obtaining disease remission or low disease activity (LDA) remains a challenging task despite the different recommended management strategies suggested for regular practice.

A meta-analysis study found that worldwide remission rates for 82 450 RA patients at 3, 6, 12, and 24 months were 17.2%, 16.3%, 21.5%, and 23.5%, respectively.⁶ Indonesia is the fourth most populous country in the world. A previous epidemiological study conducted in Central Java, Indonesia showed that RA affects about 0.2% of rural and 0.3% of urban populations.⁷ Although Indonesia is a large country, there is currently no data available on the clinical characteristics, treatment patterns, and prevalence of remissions of RA patients. Therefore, this multicenter national study aims to observe the clinical features, prevalence of clinical remission, and factors associated with disease remission of RA patients in a nationwide study.

2 | PATIENTS AND METHODS

2.1 | Study design and subjects

The observational, cross-sectional, multicenter, retrospective study was conducted in 16 centers across Indonesia between January 2019 and December 2020. Subjects of this study were RA patients who were scheduled for routine clinic visits at Rheumatology Clinics in 16 government hospitals in Indonesia. The subjects included in the study were RA patients who met the ACR/EULAR

2010 classification criteria and were 18 years or older.⁸ The exclusion criteria were the co-existence of other rheumatic diseases or pain syndromes, pregnancy, severe infections (such as sepsis), or malignancy. Several laboratory examinations, such as anti-nuclear antibody (ANA) or anti-dsDNA, were also performed to exclude other autoimmune diseases. This study protocol was approved by the Medical Research and Ethics Committee from the Faculty of Medicine Universitas Indonesia (ethics number: KET-183/UN2.F1/ETIK/PPM.00.02/2020), and the study was conducted under the ethics standards of the Declaration of Helsinki. All subjects signed the informed consent form before underwent the study.

2.2 | Data collection

All data were collected during regular clinic visits and from hospital medical records. A standardized form was used to record patient data, including demography, medical history, comorbidities, and recent treatment information, including glucocorticoids and disease-modifying anti-rheumatic drugs (DMARDs). Patients were required to complete the global patient assessment of their general health, pain, and fatigue scores on three separate 100mm visual analog scales (VAS). A rheumatologist performed physical examinations to evaluate the patients' tender joint counts (TJC) and swollen joint counts (SJC). During their visit, patients were also taken for blood samples to measure the erythrocyte sedimentation rate (ESR), anticitrullinated protein antibody (anti-CCP), and rheumatoid factor (RF).

2.3 | Measurement of disease activity

Disease activity was calculated by the disease activity score of 28 joints with ESR values (DAS28-ESR). DAS28-ESR were classified as follows: remission (<2.6), low activity (2.6 to <3.2), moderate activity (3.2 to 5.1), or high activity (>5.1).⁹ In addition, subjects were also classified as remission (DAS28-ESR <2.6) and non-remission (DAS28-ESR ≥2.6) for analysis.

2.4 | Statistical analysis

Descriptive analyses were performed for all variables. Numerical data were presented as mean ± standard deviation (SD) if the data were normally distributed and median (interquartile range [IQR]) if



they were not normally distributed, while categorical data were described as frequency and proportions. Independent t-test or Mann-Whitney test was used to compare two numerical variables, while the chi-squared test was used to compare the frequencies between variables. Binomial regression logistics was used to evaluate the association between variables and disease remission. Multivariate regression logistics was used in the variables that had p -value $\leq .25$ in the univariate analysis. All statistical analyses were computed using SPSS version 25 for Windows.

3 | RESULTS

3.1 | Subjects characteristics

The characteristics of the patients included in this study are shown in Table 1. A total of 1013 patients with RA were recruited from 16 hospitals, and the analysis for 870 patients was completed. The mean age of the subjects was 48.7 years old, with the majority being females (84.9%). The median duration of the disease was 4 (2–7) years from the diagnosis. A majority of patients (60.7%) were diagnosed within 6 months of their first symptoms, with a median time of 2 months (range: 0–11) from onset to diagnosis. Rheumatoid factor (RF) was positive in 247 (28.4%) subjects. On the contrary, anti-citrullinated peptide antibody (ACPA) was positive in 204 (23.4%) patients. However, not all participants performed the ACPA tests because of the limitations of the laboratory in some hospitals.

TABLE 1 Characteristics of the subjects.

Variable	$n = 870$
Age (years)	48.7 ± 12.7
Female (%)	739 (84.9)
Age of onset (years)	46.9 ± 12.8
Disease duration (years)	4 (2–7)
Time from the first onset until diagnosis	
≤6 months, n (%)	528 (60.7)
>6 months, n (%)	342 (39.3)
BMI (kg/m ²)	22.6 (20.1–24.8)
Education	
High school or less, n (%)	433 (49.8)
Bachelor's degree or more, n (%)	437 (50.2)
Employment	
Unemployment, n (%)	481 (55.3)
Employed, n (%)	389 (44.7)
Family history, n (%)	91 (10.5)
Extra-articular manifestations, n (%)	93 (10.7)
Smoking history, n (%)	118 (13.6)
Positive rheumatoid factor, n (%)	247 (28.4)
Positive anti-CCP, n (%)	204 (23.4)

Table 2 shows the treatment patterns of the subjects. Most of the patients in this study received at least one type of conventional synthetic DMARDs (csDMARDs) (71.1%), and the majority got methotrexate (69.9%). Other patients received sulfasalazine (12.0%), cyclosporine (4.8%), leflunomide (15.9%), and hydroxychloroquine (8.9%). The mean dose of methotrexate given to the patients was 11.2 ± 4.0 mg/week, with a dose range of 2.5–25 mg/week. Most patients (65.5%) received glucocorticoid with a mean dose of 5.5 ± 3.1 mg/day of methylprednisolone. Only two patients (0.2%) used the biologic DMARDs (bDMARDs). Most patients received at least one DMARD within 6 months of diagnosis, with a median time of 1 month (range: 0–8 months).

3.2 | Remission characteristics of the subjects

The overall remission rate from all subjects is shown in Table 3. The median DAS28-ESR score from the subjects was 3.49 (2.62–4.46). Based on the DAS28-ESR score, 24.5% of patients had attained remission, 18.5% had low disease activity, 44.6% had moderate disease activity, and 12.4% were still on high disease activity. The comparison of the subjects' characteristics according to disease remission is shown in Table 4. According to the statistical analysis, the number of subjects who had remission was more frequent in patients who had education until high school or less and had at least two types of DMARDs. In addition, the subjects who achieved remission had a significantly higher dose of methotrexate than those who were still not in disease remission. The number of patients who obtained remission was significantly higher in subjects who did not consume glucocorticoids at the moment.

3.3 | Factors affecting the disease non-remission among the subjects

Table 5 shows the univariate and multivariate analysis that estimated the variables associated with disease non-remission among subjects. Univariate logistic regression was performed to verify the association between variables and disease remission. Considering $p \leq .25$ as the cutoff, factors such as age, disease duration, time to diagnosis, education, extra-articular manifestations, time to get DMARDs, number of DMARDs, dose, and duration of methotrexate, and glucocorticoid usage were found to be significant for inclusion in the multivariate logistic regression. According to the multivariate logistic regression model, patients diagnosed later than 6 months were more likely to have non-remission 1.4 times more than those diagnosed earlier. Similarly, subjects who received DMARDs for more than 6 months had increased odds of not having remission (OR 1.2 [1.0–1.8], $p = .034$). Patients who received one DMARD had a higher probability of not having remission 2.0 times than those who got combinations. Patients who consumed glucocorticoid at the moment were associated with disease non-remission 4.7 times compared with the ones who did not consume glucocorticoids.



TABLE 2 Treatment patterns of the subjects.

Variable	n = 870
Time from the diagnosis until got DMARDs, n (%)	
≤6 months	534 (61.4)
>6 months	336 (38.6)
Number of DMARDs, n (%)	
1 type of DMARDs	619 (71.1)
2 or more types of DMARDs	251 (28.9)
Type of DMARDs, n (%)	
Methotrexate	608 (69.9)
Sulfasalazine	104 (12.0)
Cyclosporine	42 (4.8)
Leflunomide	138 (15.9)
Hydroxychloroquine	77 (8.9)
Mean dose of methotrexate (mg/week)	11.2 ± 4.0
Range dose of methotrexate (mg/week)	2.5–25
Mean duration of methotrexate (months)	45.1 ± 36.6
Glucocorticoid use, n (%)	570 (65.5)
Biologic agents use, n (%)	2 (0.2)

TABLE 3 Overall remission rate of RA patients from all centers (n = 870).

	Median (IQR)
Number of TJC	2 (0–8)
Number of SCJ	0 (0–2)
ESR (mm/h)	33.0 (21.0–52.0)
Patient global VAS	3 (1–6)
DAS-28 score	3.49 (2.62–4.46)
Status, n (%)	
Remission	213 (24.5)
Low disease activity	161 (18.5)
Moderate disease activity	388 (44.6)
High disease activity	108 (12.4)

4 | DISCUSSION

This present study demonstrated that only 24.5% of the patients attended a state of remission, and 18.5% had low disease activity in a national survey from 16 different centers across Indonesia. Moderate and severe disease activity was found in 44.6% and 12.4% of patients. Compared with other countries, the number of patients who successfully achieved the treatment target was lower in the present study. Remission rates of RA patients after receiving conventional DMARDs were in Greece (36.5%), Ireland (22.4%), the United States (36.1%), Finland (30.9%), France (29.2%), Sweden (24.4%), England (18.4%), Italy (19.8%), Canada (19.8%), Turkey (14.4%), Germany (18.1%), Argentina (9.2%), and Russia (4.5%).¹⁰ In a multicenter study in the Asia Pacific region, the overall remission

TABLE 4 Comparison of the subject characteristics according to the disease status.

Variables	No remission (n = 657)	Remission (n = 213)	p
Age (years)	49.0 ± 12.7	47.6 ± 13.1	.171
Sex			
Female	561 (85.4)	178 (85.6)	.519
Male	96 (14.6)	35 (16.4)	
Disease duration (years)	4 (2–7)	5 (2–7)	.380
Time from the first onset until diagnosis			
Median (months)	3 (1–8)	2 (0–12)	.237
≤6 months	371 (56.5)	157 (73.7)	<.001
>6 months	286 (43.5)	56 (26.3)	
BMI (kg/m ²)	23.6 ± 21.1	22.7 ± 3.9	.630
Education			
High school or less	308 (46.8)	125 (58.7)	.003
Bachelor's degree or more	349 (53.1)	88 (41.3)	
Unemployment	368 (56.0)	113 (53.1)	.450
Family history present	73 (11.1)	18 (8.5)	.270
Extra-articular manifestations present	77 (11.7)	16 (7.5)	.084
Smoking history present	92 (14.0)	26 (12.2)	.496
Rheumatoid factor positive	200 (51.2)	47 (54.7)	.556
Anti-CCP positive	177 (69.1)	27 (62.8)	.408
Time from the diagnosis until got DMARDs			
Median (months)	1 (0–12)	0 (0–5)	.309
≤6 months	390 (59.4)	144 (67.6)	.032
>6 months	267 (40.6)	69 (32.4)	
Number of DMARDs			
1 type of DMARDs	175 (26.6)	76 (35.7)	.011
2 or more types of DMARDs	482 (73.4)	137 (64.3)	
Mean dose of methotrexate (mg/week)	10.9 ± 3.9	11.7 ± 4.1	.031
Mean duration of methotrexate (months)	46.3 ± 36.3	40.1 ± 37.4	.109
Presently using glucocorticoid	269 (40.9)	31 (14.6)	<.001

rate was 35.5% (DAS28-ESR), which is still higher than our setting.¹¹ Our remission rate was also lower than randomized controlled trials (RCT) employing tight control treatment strategies in patients with early RA, such as CAMERA¹² and TICORA¹³ studies and an RCT in patients with established RA.¹⁴ In these RCTs, the remission rate was achieved in 40%–65% of the patients after at least 1 year of intensive treatment.

One of the contributing factors associated with the disease remission was the time to diagnosis and the initial time of DMARD's introduction. In this study, we demonstrated that subjects who



TABLE 5 Univariate and multivariate analysis estimates of variables associated with non-remission in RA patients.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Age	1.0 (0.9–1.0)	.171	1.0 (0.9–1.0)	.382
Sex (female)	1.1 (0.8–1.8)	.519	–	–
Disease duration	1.0 (1.0–1.1)	.038	1.1 (0.9–1.2)	.094
Time to diagnosis (>6 months)	1.4 (1.0–2.0)	.032	1.4 (1.1–2.3)	.043
BMI	1.0 (0.9–1.0)	.699	–	–
Education (high school or less)	0.6 (0.4–0.8)	.003	1.2 (0.8–1.9)	.081
Employment (unemployment)	1.1 (0.8–1.5)	.450	–	–
Family history (present)	1.4 (0.8–2.3)	.272	–	–
Extra-articular manifestations (present)	1.6 (0.9–2.9)	.087	1.2 (0.6–2.4)	.247
Smoking history (present)	1.2 (0.7–1.9)	.497	–	–
RF positivity (positive)	0.9 (0.5–1.4)	.557	–	–
Anti-CCP positivity (positive)	1.3 (0.7–2.6)	.409	–	–
Time to get DMARDs (>6 months)	2.1 (1.5–3.0)	<.001	1.2 (1.0–1.8)	.034
1 type of DMARD	1.5 (1.1–2.1)	.012	2.0 (1.2–3.2)	.006
Dose of methotrexate	1.1 (1.0–1.1)	.032	1.0 (0.9–1.0)	.108
Duration of methotrexate (months)	0.9 (0.9–1.0)	.110	1.0 (0.9–1.0)	.643
Glucocorticoid (presently used glucocorticoid)	4.1 (2.7–6.1)	<.001	4.7 (2.3–9.7)	<.001

had been delayed for diagnosis and late for receiving DMARDs (>6 months since the first onset) were associated with the non-remission of disease activity. More prolonged initiation of DMARD since the first onset of RA contributed to the failure to achieve the disease remission described in previous studies. Van der Linden et al. demonstrated that administering DMARD <12 weeks was associated with less joint destruction and a higher chance of achieving DMARD-free remission than a longer delay in assessment.¹⁵ American College of Rheumatology (ACR) suggested that initiation of treatment of RA <6 months after the onset of symptoms may be more clinically applicable.⁵ Lack of rheumatologists in Indonesia (only 72 total rheumatologists in Indonesia), unavailability of the DMARDs in some hospitals, limited access to bDMARDs, insurance or cost issues, difference in health-seeking behavior from the patients, or low awareness of RA among general practitioners or internists might be some factors that contributed to the delay of diagnosis and treatment of RA in Indonesia.

Another possibility contributing to the failure to achieve remission was using single csDMARDs in treating RA patients. The combination of DMARD is considered one of the strategies if the treatment target fails to be achieved. Another strategy will be the initiation of biological DMARD or targeted therapy if the target is not achieved.^{16,17} However, the use of biological DMARD in Indonesia was limited because of the cost issues, and it is not available everywhere. The combination of csDMARDs was more feasible in our setting than the biological or targeted therapy DMARD. The most popular initial combination of MTX is hydroxychloroquine plus

sulfasalazine, the so-called triple therapy (TrTh). TrTh treatment was found to be more effective than monotherapy with bDMARDs like TNF α blockers or IL-6 antagonists in some studies.^{18,19} Based on our findings, it is clear that there was a notable lack of combined therapy usage and suboptimal dosing of monotherapy. Besides that, in MTX monotherapy patients, the mean MTX dose used was 11.2 mg per week, which was still low compared with the generally recommended MTX dose of 20–30 mg per week. Further investigation needs to clarify whether these issues are caused by intolerance problems or strategy issues.

The use of glucocorticoids in RA remains controversial today. Glucocorticoid is used as the bridging therapy in combination with csDMARDs in patients with early RA and should be used at the lowest doses and for the shortest time possible (<6 months).²⁰ Several trials demonstrate that early glucocorticoid treatment with the combination of csDMARDs has been proven to be symptomatically and structurally effective.^{21–23} However, prolonged glucocorticoid use will increase the risk of long-term adverse events that increase with cumulative doses.²⁴ In this study, we found that patients presently used glucocorticoids were associated with non-remission in RA patients. However, because this study was done cross-sectionally, we still not conclude that the use of glucocorticoid might decrease the chances of remission in RA patients. In our practice, the addition of glucocorticoid in the use csDMARDs was commonly considered in patients with more severe pain and joint involvements, associated with more severe disease and less remission. This consideration was similar to the previous study that demonstrated an add-on steroid had beneficial



effects in RA.²³ However, according to the previously available guidelines about the management of RA, it was advised to add another csDMARDs or switch to the bDMARDs to achieve disease remission if one csDMARDs failed to attain the target rather than adding the glucocorticoids.^{4,17} This information demonstrated some inconsistencies between guidelines with the clinical practice. However, the lack of data prevented us from drawing any conclusions on the cause or contributing variables behind the inconsistency between the clinical practice and current guidelines. Further investigation is required to ensure that physicians are adhering to clinical guidelines in the future.

Our study demonstrated that subjects with education higher than high school were less likely to be in disease remission. This finding was quite the contrary since education level remained an important factor affecting health literacy and health-seeking behavior. However, previous studies did not find a link between seeking healthcare and sociodemographic characteristics in Indonesia.^{25–27} These studies suggested that other factors might also contribute to the seeking behavior of the patients. However, higher educated subjects in Indonesia might want to seek more than one doctor to cure their disease.²⁸ Different cultures and ethnicities also might contribute to the health-seeking behavior in Indonesia, since this was a multicenter study in the heterogenous populations. People in different regions in Indonesia might have different attitudes toward the musculoskeletal disease. For example, in the previous study in the Malang region of Indonesia, most of the patients with musculoskeletal symptoms would seek traditional healthcare (25.23%) and self-treatment using traditional medications (33.95%).²⁹ On the contrary, in the more urban populations in Indonesia, most of the patients would seek medical treatment from government (33%) or private (44%) clinics.³⁰

Our findings are the first nationwide data in Indonesia showing the remission rate and the factors associated with remission for RA. However, one of the most significant limitations of this study is the cross-sectional design that is still not able to explain the causal-effect relationship in the present data. Since the data are from the tertiary government hospitals in some cities in Indonesia, the generalization of the study findings for the entire RA population in Indonesia may not be accurate. Furthermore, the sample from each city is not equally distributed. Almost all patients were recruited from government hospitals and covered by government insurance, which provides all csDMARDs but none for bDMARDs. In future studies, we need to include patients from private hospitals with more access to biologic treatment. Another limitation of this study was the lack of laboratory examinations from subjects such as ACPA. Not all hospitals in Indonesia were able to perform the ACPA examinations. Therefore, some hospitals relied on the clinical features and RF to classify the RA from the patients.

Physician attitude toward RA in Indonesia also needs to be assessed. The low reported outcome for RA patients might be attributed to the lack of awareness of general practitioners in primary health care. We found that most patients were late for the referral and got DMARDs from rheumatologists (38.6% of patients got DMARDs more than 6 months after the diagnosis). Moreover, some patients also got the diagnosis in more than 6 months from the first

onset. However, further study is still needed to assess the physicians' attitudes toward the clinical guidelines or recommendations of RA. In conclusion, 24.5% of RA patients achieved remission in this study, and 18.5% were in the LDA. MTX and leflunomide are the most frequent csDMARDs used in RA patients and only a few received bDMARDs. Delay in diagnosis, delay in DMARD treatment, and the DMARD monotherapy are significant factors contributing to the failure to achieve remission. Further studies to observe the contributing factor for the delay of diagnosis and treatment for RA and inadequate use of MTX in Indonesia can also be proposed in future to improve the strategy to treat RA patients in Indonesia.

Despite the several limitations of this study, these are the first nationwide RA data in Indonesia and these findings are important and will greatly help to establish the future national RA recommendation for the improvement of care. The interventions for the recommendations should be made according to each level of healthcare systems in Indonesia. The recommendation to prevent the delay of diagnosis and referral should be implemented in the primary healthcare system that increased the awareness of the primary physicians for the diagnosis of RA and early referral to the internist or rheumatologists. The suboptimal dose and lack of combination of csDMARDs should be reevaluated in future guidelines. Therefore, the implementations should be more individualized in the secondary and tertiary hospitals. Finally, the unavailability of bDMARDs in the general hospitals should be a major concern that might contribute to the low disease remission of RA in Indonesia. Thus, this real data might provide a reference to the government and national insurance to cover the bDMARDs in the national insurance in the future.

AUTHOR CONTRIBUTION

Author has proposed the idea and the research project to all of the researchers in this study. Author also actively involved in subjects recruitment, data collection, data analysis, manuscript writing and publication process.

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ACKNOWLEDGMENTS

The authors thank all Indonesian Rheumatology Association (IRA) members for contributing to this study. The authors also thank all the physicians and residents who helped sample the patients in this study. Also thank you very much for Chak Sing Lau from Queen Mary Hospital, University of Hong Kong for comments and suggestions in improving this article.


CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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How to cite this article: Suryana BPP, Hidayat R, Sarmidi S, et al. Characteristics and prevalence of clinical remission of rheumatoid arthritis in a nationwide study from Indonesia. *Int J Rheum Dis*. 2024;27:e15050. doi:[10.1111/1756-185X.15050](https://doi.org/10.1111/1756-185X.15050)