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# Obesity and methotrexate treatment failure in rheumatoid arthritis patients in Cipto Mangunkusumo Hospital, Indonesia

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**ABSTRACT**

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease which mainly manifests in the joints. Methotrexate (MTX) is a widely used pharmacological treatment for RA. To date, no prior research has investigated the effect of obesity on MTX treatment outcomes among RA patients in Indonesia. This research aimed to investigate the effect of obesity on MTX monotherapy failure in RA patients. We conducted a retrospective cohort study using medical records from the Rheumatology Clinic at Cipto Mangunkusumo Hospital from March 2017 to December 2021. Descriptive and estimation analyses were performed to assess the sample characteristics based on each variable and a logistic regression analysis was conducted to evaluate the association between obesity and MTX treatment failure. Out of 72 subjects, the proportion of MTX treatment failure was 57.1% (20/35) among obese patients and 37.8% (14/37) among non-obese patients. Obese subjects exhibited a 2.11-fold increased risk of MTX treatment failure compared to non-obese patients (OR 2.11; 95% CI 0.81-5.45). The number of joints involved was found to emerge as a confounding factor in this study. Our findings suggest that RA patients with obesity potentially have an increased risk of MTX treatment failure compared to non-obese RA patients.



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## 1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory disease primarily characterized by joint pain and swelling which may result in permanent joint damage [1]. Joint swelling typically occurs in the wrist, metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints, often accompanied by morning joint stiffness lasting over 30 minutes to several hours. Joint swelling in RA typically feels soft due to synovitis and effusion, distinguishing it from the hard, bony swelling seen in osteoarthritis [2]. The prevalence of RA varies across countries, but its global prevalence is approximately 0.50% of the total population, occurring 2-3 times more often in women than in men, with a peak incidence around age 60 [3].

Although RA cannot be cured, it needs to be treated immediately to control the disease activity and prevent joint damage, comorbidities, and extra-articular manifestations with drugs called disease-modifying anti-rheumatic drugs (DMARDs). DMARDs are a group of drugs that modify the course of RA disease, improving physical function and inhibiting the progression of joint damage [2], [4]. These drugs are

classified into synthetic agents administered orally and biological agents administered parenterally [5]. The first category of drugs consists of conventional synthetic DMARDs such as methotrexate, sulfasalazine, leflunomide, chloroquine/hydroxychloroquine and targeted synthetic DMARDs such as Janus kinase (JAKs) inhibitors [2]. Methotrexate (MTX) remains the first-line DMARD choice unless there are contraindications or intolerance to the drug [6].

Methotrexate is the first drug of choice in treating RA for many reasons. First, it is success rate is 25-40% when used as a single therapy. When combined with glucocorticoids, the percentage of patients with RA achieving low disease activity or remission is almost equal to that of biologic drugs [7], [8]. Second, side effects such as nausea, hair loss, ulcer, and liver toxicity can be prevented by folic acid prophylaxis (at a dose of 1 mg/day or 10 mg/week) [9]. Third, other classes of DMARDs (conventional, targeted, and biologic) have less efficacy when used as monotherapy than when combined with methotrexate [10]. Fourth, in addition to having good efficacy and good safety profile, economically, the price is also relatively cheaper than other therapeutic modalities [11], [12]. Methotrexate is recommended as a first-choice drug by various international and national organizations such as the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), Asia Pacific League Against Rheumatism (APLAR) and Indonesia Rheumatology Association (IRA) [13]–[16].

Despite rapid advancements in RA management, most RA patients still do not achieve optimal treatment outcomes, leading to persistent joint damage. This issue negatively impacts patients' quality of life and increases mortality due to cardiovascular manifestations [17]. Factors influencing treatment failures are very complex and are partly caused by several non-modifiable factors, such as age and sex, alongside some modifiable factors, such as overweight or obesity [17]–[20]. The prevalence of overweight and obesity worldwide is currently estimated at 39% and 13%, respectively [21], while in RA patients, the overall prevalence of overweight and obesity is even higher, exceeding 60% [18], [22]. Previous studies have shown associations between obesity and poor outcomes of RA, such as high disease activity levels, increased inflammatory markers, and increased occurrence of disability [18]–[20]. Uncontrollable worsening of inflammatory reactions and pain are also typical in obese patients [23]. Additionally, a high body mass index (BMI) compared to normal is associated with failure to achieve therapeutic targets (i.e., low disease activity or remission) [24]–[26].

To date, no reports or studies have examined the influence of obesity on the failure of MTX therapy in RA patients in Indonesia. Based on the reasons mentioned above, the study was conducted to determine whether obesity will influence the outcomes of MTX monotherapy as the first choice of drug for RA patients. The findings of this study are expected to serve as a basis for clinicians to pay greater attention to the management of overweight or obesity as part of comprehensive rheumatoid arthritis therapy.

## 2. METHOD

### 2.1. Study design and population

This retrospective cohort study utilized data extracted from the medical records of patients of the Rheumatology Clinic at RSUPN Cipto Mangunkusumo, a national central general hospital in Indonesia. We conducted data sampling from March 2017-December 2021 consecutively. The inclusion criteria of this study were as follows: patients aged 18 years or older, diagnosed with RA according to ACR/EULAR 2010 criteria, and continuously received MTX monotherapy for at least six months. Meanwhile, the criteria for sample exclusion are RA patients receiving DMARD combination therapy or those with prior MTX therapy, patients with MTX contraindications or intolerance, underweight individuals, and patients with incomplete or missing medical record data.

Data extracted included demographic data such as age, gender, height, and weight, as well as clinical and laboratory data, including early onset of pain, the number of joints involved quantified as tender joint count (TJC) and swollen joint count (SJC), inflammatory markers (C-reactive protein (CRP)) and erythrocyte sedimentation rate (ESR)), serological factors (rheumatoid factor (RF)), and patient global and pain visual assessment scores (VAS). The success or failure of therapy was assessed based on DAS28-ESR criteria over the first six months of treatment, with remission defined as a score of <2.6 and low disease activity as a score of ≤3.2 [14].

Body weight and height measurements upon initial visit were extracted from medical records, typically measured by the attending nurse. BMI was assessed using the National criteria (Ministry of Health of the Republic of Indonesia), classifying patients as obese (BMI >25 kg/m$^2$) or non-obese (BMI 18.5-≤25 kg/m$^2$) [27]. Low-body weight individuals (BMI <18.5 kg/m$^2$) were excluded from the analysis due to low case prevalence and unknown impact on treatment response [28]. The exposure variable was obesity as determined by baseline BMI, compared to patients in the normal BMI category.

The outcome of this study was therapy failure, defined as the non-achievement low disease activity or remission due to the influence of obesity as a predictive factor. Covariates in this study included gender, age, early onset of disease, number of joints involved, CRP, ESR, and rheumatoid factor. The assessment of these variables was carried out by the attending physician and extracted from the medical record. This study has received ethical approval from the Ethical Committee Board Faculty of Medicine, Universitas Indonesia (KET-630/UN2.F1/ETIK/PPM.00.02/2022) and was conducted in accordance with the principles of the Declaration of Helsinki.

### 2.2. Statistical analysis

Descriptive analysis was conducted using Chi-square tests to describe the characteristics of the research subjects based on demographic variables such as gender, age, and other variables such as obesity, early onset of disease, number of joints involved, inflammatory markers (CRP and ESR), and RF, presented as proportion values. Subsequently, to explore the association between obesity and the failure of methotrexate therapy in patients with rheumatoid arthritis, logistic regression analysis was performed. The analysis also aimed to eliminate potential confounders using the backward method. The resulting association was expressed as an odds ratio with a 95% confidence interval. All analyses were conducted using IBM statistical package for the social sciences (SPSS).

## 3. RESULTS AND DISCUSSION

### 3.1. Results

A total of 72 subjects were included in the final analysis. Baseline characteristics of subjects were presented in Table 1. All subjects were female, with 47 individuals (65.3%) aged 45 years or older, and 14 individuals (19.4%) having an initial onset of illness lasting more than six months. Elevated ESR levels were reported in 62 subjects (86.1%), while elevated CRP levels were observed in 39 subjects (54.2%). Positive RF value was found in 40 subjects (55.6%). Involvement of more than 10 joints were observed in 25 subjects (34.7%), and 35 subjects (48.6%) met the criteria for obesity as shwon in Table 1.

Table 1. Characteristics of subjects

| Variable | Frequency | Percentage (%) |
|---|---|---|
| Age | | |
| ≥ 45 years old | 47 | 65.3 |
| < 45 years old | 25 | 34.7 |
| Gender | | |
| Female | 72 | 100 |
| Male | 0 | 0 |
| Duration of illness | | |
| ≥6 months | 14 | 19.4 |
| <6 months | 58 | 80.6 |
| ESR | | |
| Abnormal | 62 | 86.1 |
| Normal | 10 | 13.9 |
| CRP | | |
| Abnormal | 39 | 54.2 |
| Normal | 33 | 45.8 |
| RF | | |
| Abnormal | 40 | 55.6 |
| Normal | 32 | 44.4 |
| Number of affected joints | | |
| >10 | 25 | 34.7 |
| ≤10 | 47 | 65.3 |
| BMI | | |
| Obese | 35 | 48.6 |
| Non-obese | 37 | 51.4 |

Note: BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor

With regards to prognostic factors associated with therapy failure, it was found that obesity posed a greater risk compared to non-obese individuals (OR 1.49; 95% CI 0.92-2.42). Meanwhile, when assessing the influence of age, subjects aged 45 years or older have a higher risk than those under 45 (OR 1.07; 95% CI 0.77-1.5). In terms of inflammatory markers, abnormal CRP and ESR values were associated with an increased risk of therapy failure compared to those with normal inflammation levels, with respective OR values of 1.05 (95% CI 0.87-1.26), and 1.18 (95% CI 0.77-1.8). Furthermore, the involvement of more than

ten joints carried a higher risk compared to those with ten or fewer joints affected (OR 1.4; 95% CI 0.75-2.7). For serological RF values, individuals with RF values above the normal range had a higher risk than those with a normal RF (OR 1.24; 95% CI 0.82-1.87). Notably, contrary to these trends, initial illness duration of six months or more was associated with a lower risk of therapy failure (OR 0.84; 95% CI 0.43-2.17) as shown in Table 2.

Table 2. Overview of prognostic factors for MTX treatment failure

| Variables | Failure (N/%) N=34 | Achieved (N/%) N=38 | OR | p-value |
|---|---|---|---|---|
| Age | | | | |
| ≥45 years old | 23 (48.90) | 24 (51.10) | 1.07 | 0.44 |
| <45 years old | 11 (44) | 14 (56) | (0.77-1.5) | |
| BMI | | | | |
| Obese | 20 (57.1) | 15 (42.9) | 1.49 | 0.08 |
| Non-obese | 14 (37.8) | 23 (62.2) | (0.92-2.42) | |
| Duration of illness | | | | |
| ≥6 months | 6 (42.9) | 8 (57.1) | 0.84 | 0.48 |
| <6 months | 28 (48.3) | 30 (51.7) | (0.32-2.17) | |
| ESR | | | | |
| Abnormal | 30 (48.4) | 32 (51.6) | 1.05 | 0.44 |
| Normal | 4 (40) | 6 (60) | (0.87-1.26) | |
| CRP | | | | |
| Abnormal | 20 (51.3) | 19 (48.7) | 1.18 | 0.3 |
| Normal | 4 (42.4) | 19 (57.6) | (0.77-1.8) | |
| RF | | | | |
| Abnormal | 21 (52.5) | 19 (47.5) | 1.24 | 0.22 |
| Normal | 13 (40.6) | 19 (59.4) | (0.82-1.87) | |
| Number of affected joints | | | | |
| >10 | 14 (56) | 11 (44) | 1.42 | 0.2 |
| ≤10 | 20 (42.60) | 27 (57.40) | (0.75-2.7) | |

Note: BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OR, odds ratio; RF, rheumatoid factor

Based on the initial full model analysis, as presented in Table 3, it was found that the influence of obesity had a factor of 1.93 (95% CI 0.70-5.37) in relation to the failure of MTX therapy compared to patients with normal body weight. The subsequent step involved the construction of a model incorporating independent variables that potentially act as confounders in the relationship between obesity and the failure to achieve therapeutic targets in rheumatoid arthritis patients. The effect assessment was conducted through stepwise elimination of variables, starting with those showing the lowest or no association. The analysis as shown in Table 4 revealed that the number of affected joints emerged as a confounder in the relationship between obesity and the failure to achieve therapeutic targets, with an association value of 2.11 (95% CI 0.81-5.45).

Table 3. Causal model

| Variables | OR | 95% CI | p-value |
|---|---|---|---|
| Obesity | 1.93 | 0.7-5.37 | 0.21 |
| Age | 1.14 | 0.4-3.28 | 0.80 |
| Duration of illness | 0.73 | 0.21-2.54 | 0.62 |
| ESR | 1.01 | 0.22-4.57 | 0.99 |
| CRP | 1.24 | 0.45-3.42 | 0.68 |
| RF | 1.31 | 0.49-3.54 | 0.59 |
| Number of affected joints | 1.64 | 0.60-4.52 | 0.34 |

Note: BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OR, odds ratio; RF, rheumatoid factor

Table 4. The relationship between obesity and not achieving the target of therapy in rheumatoid arthritis patients

| Variables | Treatment failure | | | p-value |
|---|---|---|---|---|
| | B | OR | 95% CI | |
| Obesity | 0.75 | 2.11 | 0.81-5.45 | 0.13 |
| Number of affected joints | 0.47 | 1.61 | 0.59-4.36 | 0.35 |

### 3.2. Discussion

This study was carried out with a retrospective cohort design, which looked at the subjects' weight data recorded at the initiation of methotrexate therapy as the primary variable. Subsequently, the subjects were followed to assess the success of therapy, namely the achievement of remission or low disease activity over a span of six months. This study considered six potential confounding variables: age, gender, onset of pain, number of affected joints, inflammatory markers (CRP and ESR), and RF. The multivariate analysis found that the number of affected joints emerged as a confounder in the relationship between obesity and the failure to achieve MTX therapy targets. However, it is important to acknowledge that other residual confounding factors, which cannot be controlled in a study, may still be present due to limitations in research subjects and limited medical record information.

In this study, the final analysis revealed that subjects with obesity had a 2.11 times higher risk of not achieving therapeutic targets compared to those with normal weight. However, this relationship did not reach statistical significance with a p-value >0.05. The relationship between obesity and an elevated risk of not achieving methotrexate therapeutic targets has been evident in prior studies, such as the retrospective study by Siddiqui *et al.* [29]. This research involved 612 subjects with RA from a hospital in Pakistan who underwent MTX monotherapy for six months. It was observed that subjects with a BMI ≥25 kg/m$^2$ had a lower proportion of achieving therapeutic responses compared to those with a normal BMI (22.4% vs. 54.4%) [29]. Another study involving 1,313 patients, including both early RA patients and those in advanced stages, found that patients with overweight and obesity required higher doses of MTX, either as monotherapy or in combination, with an average dose of 20 mg/week compared to 15 mg/week in patients with a normal BMI. A decline in therapeutic response was also observed in patients with overweight or obesity, especially among advanced RA patients [30].

These findings align with the understanding of the inflammatory process in RA that is associated with the increased production of adipokines from adipose cells, particularly in patients with obesity. The two primary mediators that are categorized as adipokines are leptin and adiponectin, which have opposing effects in most clinical conditions, including metabolic and cardiovascular diseases. Leptin primarily regulates pro-inflammatory factors such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), ultimately stimulating the inflammatory process. Conversely, adiponectin possesses anti-inflammatory effects [31]. RA patients tend to exhibit elevated plasma adipokine levels, notably adiponectin, leptin, and visfatin when compared with healthy controls [32]. Similarly, a meta-analysis examining 813 RA patients and 684 healthy controls across 11 studies showed that the circulating adiponectin levels in RA patients were significantly higher than those in the control group [33]. In RA patients with elevated serum adiponectin levels, it has been evidenced that this particular adipokine contributes to systemic chronic inflammation processes rather than exerting an anti-inflammatory effect [34]. Adiponectin stimulates the production of pro-inflammatory factors such as IL-6, IL-8, and PGE2 in fibroblast-like synoviocytes (FLS), and increases the production of vascular endothelial growth factor (VEGF) and matrix metallopeptidases (MMPs) in FLS, resulting in inflammation and joint damage [33]. Adiponectin also hinders the ability of osteoblasts to mineralize bones, while increasing the resorptive activity of osteoclasts. Furthermore, it stimulates the expression of MMP-9 and tartrate-resistant acid phosphate (TRAP) and increases IL-8 secretion in osteoblasts. However, in RA-induced human bone tissue, adiponectin inhibits osterix expression and induces osteoprotegerin mRNA expression, thereby inhibiting bone formation and aggravating joint damage [31].

The limitation of this study is the limited number of samples. Additionally, the COVID-19 pandemic led to a decrease in the number of hospital visits, further restricting sample size and potentially affecting the robustness of association values. Furthermore, the limited assessment of certain variables in medical records, such as smoking habits and anti-CCP antibody positivity, which could potentially influence MTX therapy outcomes, presents as another study limitation.

## 4. CONCLUSION

In conclusion, this study suggests that obesity may potentially increase the risk of MTX therapy failure in comparison to non-obese RA patients. The outcomes of this study are expected to heighten clinicians' awareness regarding obesity management to reduce risk of MTX treatment failure in RA patients. Further research involving a larger sample size and an exploration of additional potentially confounding variables that may influence the risk of MTX treatment failure are recommended to substantiate these findings.

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