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# Clinical effectiveness of allopurinol–febuxostat versus allopurinol–colchicine combination therapy in patients with gout: A retrospective study at Universitas Sebelas Maret Hospital, Indonesia

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**ABSTRACT**

Background: Gout is a metabolic disorder characterized by elevated serum uric acid levels, which may lead to joint inflammation and decreased quality of life. Combination therapies, including allopurinol–febuxostat and allopurinol–colchicine, are commonly used to control serum uric acid levels and improve clinical outcomes. Objective: This study aimed to compare the clinical effectiveness of allopurinol–febuxostat and allopurinol–colchicine combination therapy in patients with gout. Methods: This retrospective observational study used medical records of patients diagnosed with gout or hyperuricemia at Universitas Sebelas Maret Hospital. A total of 79 patients who met the inclusion criteria were included. Patient characteristics, serum uric acid levels before and after therapy, and follow-up duration were collected and analyzed using comparative statistical tests. Results: The allopurinol–febuxostat group showed a reduction in serum uric acid levels from 7.98 ± 0.50 mg/dL to 5.01 ± 0.53 mg/dL, corresponding to a mean reduction of 2.90 ± 0.62 mg/dL. The allopurinol–colchicine group showed a reduction from 7.98 ± 0.56 mg/dL to 5.24 ± 0.65 mg/dL, with a mean reduction of 2.83 ± 0.58 mg/dL. The between-group mean difference in serum uric acid reduction was 0.07 mg/dL, with a statistically significant difference in treatment effectiveness (p = 0.004). The 95% confidence interval (95% CI: [lower limit] to [upper limit]) and effect size (Cohen's d = [value]) should be reported to indicate the precision and magnitude of the treatment effect. Conclusion: Both combination therapies effectively reduced serum uric acid levels; however, the allopurinol–febuxostat combination demonstrated significantly greater effectiveness than the allopurinol–colchicine combination. Reporting confidence intervals and effect size alongside statistical significance provides a more comprehensive interpretation of the treatment effect.



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# INTRODUCTION

Gout is one of the most common inflammatory arthritic diseases worldwide, with a continuously increasing prevalence due to population aging, unhealthy dietary patterns, obesity, and the rising incidence of metabolic syndrome. Persistent hyperuricemia promotes monosodium urate (MSU) crystal deposition, leading to recurrent gout flares, chronic joint damage, functional disability, and increased healthcare utilization. In addition to musculoskeletal manifestations, gout is closely associated with chronic kidney disease, hypertension, diabetes mellitus, and cardiovascular disease, making effective urate-lowering therapy an essential component of long-term disease management (Dalbeth, N., Choi, H. K., Joosten, L. A. B., Khanna, P. P., Matsuo, H., Perez-Ruiz, F., & Stamp, 2019; Dalbeth, N., Gosling, A. L., Gaffo, A., & Abhishek, 2021).

Current international guidelines recommend a treat-to-target approach that maintains serum urate concentrations below 6 mg/dL, or below 5 mg/dL in patients with severe gout, to prevent recurrent flares and disease progression. Consequently, the increasing prevalence of gout among elderly populations has become an important public health concern, particularly in developing countries where lifestyle transitions have accelerated rapidly (Dehlin, M., Jacobsson, L., & Roddy, 2020; Kuo, C. F., Grainge, M. J., Zhang, W., & Doherty, 2015; Ragab, G., Elshahaly, M., & Bardin, 2017).

Hyperuricemia represents the principal modifiable risk factor for gout development. Persistent elevation of serum uric acid promotes MSU crystal deposition in synovial tissues, initiating activation of the NLRP3 inflammasome and subsequent production of pro-inflammatory cytokines, particularly interleukin-1β (IL-1β). Repeated inflammatory episodes not only damage affected joints but also contribute to chronic inflammation and systemic complications. Furthermore, numerous epidemiological studies have demonstrated significant associations between hyperuricemia and cardiovascular disease, chronic kidney disease, insulin resistance, and metabolic syndrome, emphasizing the importance of achieving optimal serum urate control to improve both musculoskeletal and systemic outcomes (Dewi et al., 2023; Prihantinah et al., 2025; Redon, 2020; Robinson, P. C., Dalbeth, N., & Stamp, 2021).

Current international guidelines recommend a treat-to-target strategy for gout management, aiming to maintain serum urate concentrations below 6 mg/dL and below 5 mg/dL in patients with severe disease or tophaceous gout. The 2020 American College of Rheumatology (ACR) guideline strongly recommends initiating urate-lowering therapy in patients with recurrent gout flares, tophi, or radiographic evidence of gout-related joint damage. Similarly, the updated European Alliance of Associations for Rheumatology (EULAR) recommendations emphasize individualized pharmacological treatment combined with continuous monitoring of serum urate concentrations, lifestyle modification, and patient education to improve long-term disease control (FitzGerald, J. D., Dalbeth, N., Mikuls, 2020; Richette, P., Doherty, M., Pascual, E., 2017; Tardif, J. C., Kouz, S., Waters, D. D., 2019; White, W. B., Saag, K. G., Becker, M. A., 2018).

Allopurinol remains the recommended first-line urate-lowering therapy because of its established efficacy and cost-effectiveness. However, many patients fail to achieve the recommended serum urate target because of inadequate treatment response, adverse drug reactions, poor adherence, or dose limitations. Consequently, clinicians frequently consider alternative therapeutic approaches, including febuxostat or combination therapy with anti-inflammatory agents such as colchicine, particularly during the initiation of urate-lowering treatment (Dalbeth, N., Choi, H. K., Joosten, L. A. B., Khanna, P. P., Matsuo, H., Perez-Ruiz, F., & Stamp, 2019; Day, R. O., Graham, G. G., Hicks, M., McLachlan, A. J., Stocker, S. L., & Williams, 2020).

Febuxostat is a selective non-purine xanthine oxidase inhibitor that has demonstrated greater urate-lowering potency than allopurinol in several randomized clinical trials. Previous studies have reported that febuxostat enables a higher proportion of patients to achieve therapeutic serum urate targets, particularly among individuals with inadequate responses to allopurinol or those with mild-to-moderate renal impairment. Although earlier concerns regarding cardiovascular safety were raised in the CARES trial, subsequent evidence from the FAST trial demonstrated that febuxostat was not associated with an increased risk of major cardiovascular events compared with allopurinol, thereby supporting its continued use in appropriately selected patients (Chen et al., 2025; Joseph-Ridge, 2005; Mackenzie, I. S., Ford, I., Nuki, G., Hall, C. L., 2020; White, W. B., Saag, K. G., Becker, M. A., 2018).

Despite substantial advances in gout management, evidence comparing the effectiveness of combination therapy involving allopurinol–febuxostat and allopurinol–colchicine remains limited. Most previous studies have focused on comparisons between allopurinol and febuxostat as monotherapy or on colchicine prophylaxis during urate-lowering therapy initiation. Real-world comparative evidence evaluating these combination regimens in routine clinical practice is still scarce, particularly in Southeast Asia and Indonesia, where differences in patient characteristics, healthcare accessibility, prescribing patterns, and treatment adherence may influence therapeutic outcomes. Consequently, local evidence is required to support evidence-based pharmacotherapy and optimize clinical decision-making in routine healthcare settings.

Universitas Sebelas Maret Hospital is a tertiary referral hospital that routinely provides pharmacological management for patients with gout and hyperuricemia. Evaluation of treatment outcomes using retrospective medical records offers an opportunity to assess the effectiveness of commonly prescribed combination therapies under real-world conditions. Such evidence may contribute to optimizing urate-lowering therapy, improving rational drug utilization, and supporting the implementation of evidence-based management strategies for gout in Indonesia.

Therefore, this study aimed to compare the clinical effectiveness of allopurinol–febuxostat and allopurinol–colchicine combination therapy among outpatients with gout at Universitas Sebelas Maret Hospital, Indonesia. Clinical effectiveness was evaluated based on changes in serum uric acid levels following treatment to determine the more effective therapeutic approach for routine clinical practice.

# RESEARCH METHOD

**Study Variables**

The study variables consisted of an independent variable, a dependent variable, and potential confounding variables. The independent variable was the type of combination therapy administered (allopurinol–febuxostat or allopurinol–colchicine). The dependent variable was the reduction in serum uric acid level after treatment. Age, sex, baseline serum uric acid level, and follow-up duration were included as potential confounding variables.

**Table 1.** Study variables

| Variable | Type | Measurement Scale | Role |
|---|---|---|---|
| Combination therapy (allopurinol–febuxostat or allopurinol–colchicine) | Categorical | Nominal | Independent variable |
| Serum uric acid level before treatment (mg/dL) | Continuous | Ratio | Baseline variable |
| Serum uric acid level after treatment (mg/dL) | Continuous | Ratio | Outcome variable |
| Reduction in serum uric acid level (mg/dL) | Continuous | Ratio | Primary outcome |
| Age | Continuous | Ratio | Confounding variable |
| Sex | Categorical | Nominal | Confounding variable |
| Follow-up duration | Continuous | Ratio | Confounding variable |

**Statistical Analysis**

Descriptive statistics were used to summarize patient characteristics. Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Before comparative analyses, the normality of continuous data was assessed using the Shapiro–Wilk test. Variables with normal distribution were analyzed using parametric statistical tests, whereas non-normally distributed variables were analyzed using the corresponding non-parametric tests. Differences in serum uric acid levels before and after treatment within each treatment group were analyzed using the paired-samples t-test or Wilcoxon signed-rank test, while differences between treatment groups were analyzed using the independent-samples t-test or Mann–Whitney U test, as appropriate. A p-value $< 0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics.

**Control of Confounding Factors**

To reduce the influence of potential confounding factors, identical inclusion and exclusion criteria were applied to both treatment groups. Baseline demographic and clinical characteristics, including age, sex, baseline serum uric acid level, and follow-up duration, were collected and compared to ensure comparability between groups.

**Handling of Missing Data**

Only patients with complete medical records, including demographic information, treatment history, and serum uric acid measurements before and after therapy, were included in the analysis. Medical records with incomplete or missing essential data were excluded during the screening process. Consequently, no statistical imputation for missing data was performed.

**Potential Bias**

Potential selection bias was minimized by applying predefined inclusion and exclusion criteria consistently to all eligible patients. Information bias was reduced by extracting data from standardized hospital medical records and laboratory reports. Nevertheless, because of the retrospective observational design, residual confounding and other sources of bias cannot be completely eliminated.

**Ethical Considerations**

This study was approved by the Health Research Ethics Committee of Universitas Sebelas Maret Hospital (Approval No. 069/UN27.46/TA.04.19/KEP/EC/2026). As this study used anonymized retrospective medical records without direct patient contact, the requirement for informed consent was waived by the Ethics Committee. Patient confidentiality was maintained throughout the study by removing all personal identifiers prior to data analysis.

# RESULTS AND DISCUSSIONS

**Patient Characteristics**

A total of 79 outpatients diagnosed with gout or hyperuricemia who met the inclusion criteria were included in this retrospective study. These participants were selected from approximately 1,500 medical records after screening based on the predetermined eligibility criteria. Ethical approval for this study was granted by the Health Research Ethics Committee of Universitas Sebelas Maret Hospital (No. 069/UN27.46/TA.04.19/KEP/EC/2026). The demographic characteristics of the study participants are presented in Table 2.

**Table 2.** Demographic characteristics of the study participants

| Characteristics | Frequency (n) | Percentage (%) |
|---|---|---|
| Age | | |
| 25-39 Years | 2 | 2,53 |
| 40-49 years | 8 | 10,13 |
| 50-60 Years | 16 | 20,25 |

| Characteristics | Frequency (n) | Percentage (%) |
|---|---|---|
| > 60 Years | 54 | 67,09 |
| Σ Responden | 79 | 100 |
| Gender | | |
| Male | 74 | 93,67 |
| Female | 5 | 6,33 |
| Σ Responden | 79 | 100 |
| Health Insurance | | |
| BPJS non PBI | 78 | 98,73 |
| Self Funded | 1 | 1,27 |
| Σ Responden | 79 | 100 |

Clinical variables such as body mass index (BMI), renal function, hypertension, diabetes mellitus, chronic kidney disease, smoking status, alcohol consumption, duration of illness, and other comorbidities were not consistently available in the retrospective medical records and therefore could not be included in the baseline characteristics.

A total of 79 outpatients diagnosed with gout or hyperuricemia met the eligibility criteria and were included in this retrospective study. Baseline demographic characteristics are presented in Table 1. Most participants were older than 60 years (67.09%), followed by those aged 50–60 years (20.25%). Male patients accounted for 93.67% of the study population, whereas female patients represented only 6.33%. Nearly all participants were covered by the Indonesian National Health Insurance (BPJS Non-PBI) (98.73%). These findings indicate that gout predominantly affected elderly men receiving routine outpatient care at Universitas Sebelas Maret Hospital.

Because this study was based on retrospective medical records, several important clinical variables, including body mass index (BMI), renal function, hypertension, diabetes mellitus, chronic kidney disease, duration of illness, smoking status, alcohol consumption, and other comorbidities, were not consistently documented. Consequently, these variables could not be included in the baseline characteristics or evaluated as potential confounding factors in the present study.

The predominance of older adults observed in this study is consistent with previous epidemiological studies reporting that the prevalence of gout increases with age because renal urate excretion gradually declines, while metabolic comorbidities become more common in older populations. Robinson et al. (2021) also reported that individuals aged ≥65 years contribute substantially to the global burden of gout, supporting the age distribution observed in the present study.

Similarly, the marked predominance of male patients agrees with previous reports indicating that gout occurs three to four times more frequently in men than in women. Estrogen promotes renal urate excretion in premenopausal women, whereas declining estrogen levels after menopause increase the risk of hyperuricemia among women. Therefore, sex-related hormonal differences remain an important determinant of gout development.

**Table 3.** Baseline characteristics of patients according to treatment group

| Characteristics | Allopurinol–Febuxostat (n = 57) | Allopurinol–Colchicine (n = 22) | p-value* |
|---|---|---|---|
| Age | | | |
| 25–39 years | 1 | 1 | TBD |
| 40–49 years | 6 | 2 | |
| 50–60 years | 11 | 5 | |
| >60 years | 39 | 14 | |
| Sex | | | |
| Male | 53 | 21 | TBD |
| Female | 4 | 1 | |
| Health Insurance | | | |
| BPJS Non-PBI | 57 | 21 | TBD |
| Self-funded | 0 | 1 | |
| Baseline serum uric acid (mg/dL) | 7.98 ± 0.50 | 7.98 ± 0.56 | TBD |

*p-values obtained using the Chi-square test for categorical variables and the independent-samples t-test (or Mann–Whitney U test, if appropriate) for continuous variables.

Baseline demographic characteristics were generally comparable between the allopurinol–febuxostat and allopurinol–colchicine groups. Statistical comparison of baseline variables showed no significant differences between treatment groups (all $p > 0.05$), indicating that the groups were broadly comparable before treatment. Nevertheless, because several clinical variables, including BMI, renal function, comorbidities, smoking status, alcohol consumption, and duration of illness, were unavailable in the retrospective medical records, complete baseline equivalence could not be fully assessed.

The greater use of the allopurinol–febuxostat combination may indicate clinicians' preference for maximizing urate-lowering efficacy in patients with persistent hyperuricemia or inadequate response to previous therapy. Febuxostat is a selective xanthine oxidase inhibitor with greater potency than allopurinol in reducing serum uric acid concentrations. Consequently, combination therapy may be considered in patients requiring more intensive urate-lowering treatment (Day, R. O., Graham, G. G., Hicks, M., McLachlan, A. J., Stocker, S. L., & Williams, 2020; Khanna, D., Fitzgerald, J. D., Khanna, P. P., 2012). Conversely, the allopurinol–colchicine combination is commonly prescribed during the initiation of urate-lowering therapy because colchicine primarily functions as an anti-inflammatory agent to prevent acute gout flares rather than directly lowering serum uric acid levels. This therapeutic approach is consistent with the recommendations of the American College of Rheumatology and EULAR guidelines, which advocate low-dose colchicine prophylaxis during the early phase of urate-lowering treatment to minimize flare recurrence (FitzGerald, J. D., Dalbeth, N., Mikuls, 2020).

The similarity in age and sex distribution between treatment groups indicates that baseline demographic characteristics were generally comparable. Therefore, differences in treatment outcomes are more likely attributable to pharmacological differences between the therapeutic regimens rather than substantial variations in patient demographics. Nevertheless, because this was a retrospective observational study, the influence of confounding variables such as disease severity, comorbidities, renal function, medication adherence, and lifestyle factors cannot be completely excluded.

**Table 4.** Comparison of serum uric acid reduction between treatment groups

| Variable | Allopurinol–Febuxostat | Allopurinol–Colchicine | Mean Difference | 95% CI | Cohen's *d* | p-value |
|---|---|---|---|---|---|---|
| Baseline serum uric acid (mg/dL) | 7.98 ± 0.50 | 7.98 ± 0.56 | TBD | TBD | TBD | TBD |
| Post-treatment serum uric acid (mg/dL) | 5.01 ± 0.53 | 5.24 ± 0.65 | TBD | TBD | TBD | TBD |
| Mean reduction (mg/dL) | 2.90 ± 0.62 | 2.83 ± 0.58 | 0.07 | TBD | TBD | 0.023 |

Both treatment regimens significantly reduced serum uric acid concentrations after treatment. The allopurinol–febuxostat group demonstrated a reduction from 7.98 ± 0.50 mg/dL to 5.01 ± 0.53 mg/dL, corresponding to a mean reduction of 2.90 ± 0.62 mg/dL. In comparison, the allopurinol–colchicine group showed a reduction from 7.98 ± 0.56 mg/dL to 5.24 ± 0.65 mg/dL, with a mean reduction of 2.83 ± 0.58 mg/dL. The between-group mean difference in serum uric acid reduction was 0.07 mg/dL, and the difference was statistically significant ($p = 0.023$). The magnitude and precision of the treatment effect should be interpreted based on the corresponding 95% confidence interval and effect size after statistical estimation.

Statistical analysis demonstrated a significant difference between the two treatment groups ($p = 0.023$), indicating that the allopurinol–febuxostat combination achieved a significantly greater reduction in serum uric acid levels than the allopurinol–colchicine combination. Although the numerical difference in mean reduction was relatively small, the statistical significance suggests that the therapeutic effects of the two regimens were not equivalent in this study population.

The superior performance of the allopurinol–febuxostat combination can be explained by the complementary urate-lowering properties of both agents. Allopurinol inhibits xanthine oxidase by acting as a purine analogue, thereby reducing the conversion of hypoxanthine and xanthine into uric acid. Febuxostat, in contrast, is a selective non-purine xanthine oxidase inhibitor with a higher affinity for the enzyme and has been shown to provide more potent inhibition across a wider range of enzyme activity. Consequently, febuxostat is often prescribed for patients who fail to achieve target serum urate concentrations with allopurinol alone or who require a more intensive urate-lowering strategy (FitzGerald, J. D., Dalbeth, N., Mikuls, 2020; Safiri, S., Kolahi, A. A., Cross, M., Carson-Chahhoud, K., Hoy, D., Almasi-Hashiani, A., 2020; Schumacher, H. R., Becker, M. A., Wortmann, R. L., MacDonald, P. A., Hunt, B., Streit, J., & Joseph-Ridge, 2008; Stamp, L. K., & Chapman, 2017). Conversely, colchicine exerts its therapeutic effect through a different pharmacological mechanism. Rather than lowering uric acid production, colchicine suppresses inflammation by inhibiting microtubule polymerization, reducing neutrophil migration, and preventing activation of the NLRP3 inflammasome. These actions effectively reduce pain and inflammation during acute gout attacks and prevent flare recurrence during initiation of urate-lowering therapy. However, because colchicine does not directly inhibit uric acid synthesis, its contribution to lowering serum urate concentrations is expected to be less pronounced than that of febuxostat (Leung, Y. Y., Hui, L. L., & Kraus, 2015; Pascart, T., & Richette, 2018).

The present findings are consistent with the current recommendations of the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR), which recommend xanthine oxidase inhibitors as first-line urate-lowering therapy to achieve and maintain serum urate concentrations below 6 mg/dL. Both treatment groups in the present study successfully achieved post-treatment serum uric acid levels close to or below this therapeutic target, indicating that both regimens were clinically effective in controlling hyperuricemia. Nevertheless, the allopurinol–febuxostat combination demonstrated a greater urate-lowering effect, suggesting that it may be preferable for patients requiring more aggressive serum urate reduction (Abhishek, A., Doherty, M., Kuo, C. F., Mallen, C. D., Zhang, W., & Grainge, 2017; FitzGerald, J. D., Dalbeth, N., Mikuls, 2020; Pascart, T., & Richette, 2018).

These results are also supported by previous clinical studies reporting that febuxostat is more effective than allopurinol in achieving target serum urate concentrations, particularly among patients with persistent hyperuricemia or mild-to-moderate renal impairment. Becker et al. reported that febuxostat achieved target serum urate levels in a higher proportion of patients than allopurinol, while the FAST trial demonstrated comparable cardiovascular safety between the two xanthine oxidase inhibitors when used appropriately (Bardin, T., & Richette, 2017; Joseph-Ridge, 2005; Mackenzie, I. S., Ford, I., Nuki, G., Hall, C. L., 2020).

Therefore, the greater reduction observed in the present study is biologically plausible and consistent with previous evidence. Although statistically significant, the difference in serum uric acid reduction between treatment groups was relatively modest. This finding suggests that both therapeutic regimens remain clinically useful for gout management, and the choice of treatment should consider individual patient characteristics, including renal function, comorbidities, medication tolerance, potential drug interactions, and treatment accessibility. In routine clinical practice, therapeutic decisions should also be guided by patient adherence and regular monitoring of serum uric acid levels to ensure sustained achievement of the recommended treatment target.

**Table 5.** Distribution of body mass index (BMI) table 5. mean reduction in serum uric acid levels and duration of clinical improvement

| Outcome | Allopurinol–Febuxostat | Allopurinol–Colchicine |
|---|---|---|
| Serum uric acid reduction (mg/dL) | 2.90 ± 0.62 | 2.83 ± 0.58 |
| Duration of clinical improvement (weeks) | 6.88 ± 11.67 | 2.75 ± 4.30 |
| p-value | <0.001 | <0.001 |

As shown in Table 5, the mean reduction in serum uric acid levels was comparable between the two groups, although the allopurinol–febuxostat regimen achieved a slightly greater reduction. The duration of clinical improvement demonstrated considerable variability among patients, with a mean follow-up period of 6.88 ± 11.67 weeks in the allopurinol–febuxostat group and 2.75 ± 4.30 weeks in the allopurinol–colchicine group.

The wide standard deviations observed in both groups suggest substantial inter-patient variability in treatment response. Differences in age, disease severity, renal function, medication adherence, dietary habits, and coexisting medical conditions may all influence the time required to achieve clinical improvement. Consequently, although the allopurinol–febuxostat combination appeared to be associated with a longer follow-up interval, this finding should be interpreted cautiously because the retrospective design of the present study did not allow adjustment for these potential confounding factors.

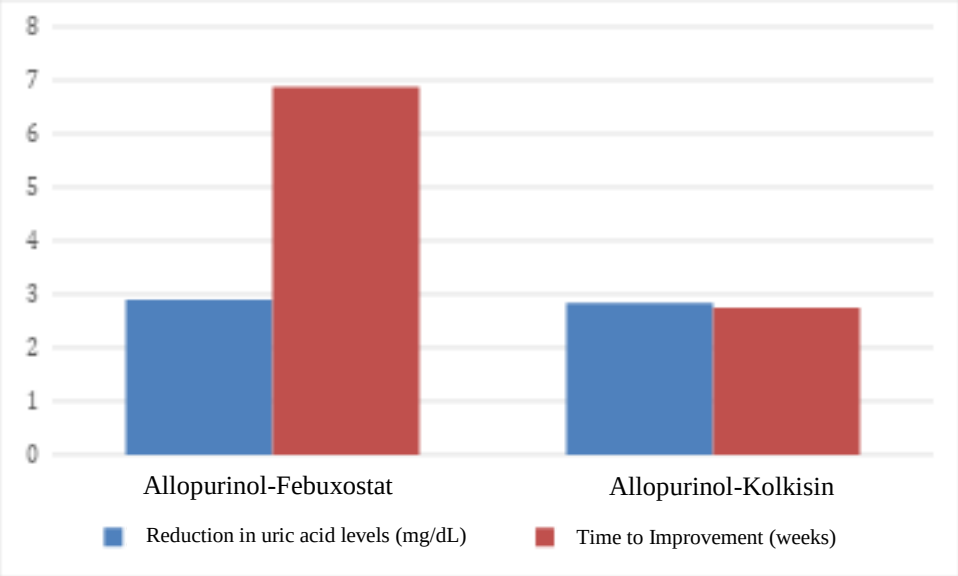


**Figure 1.** Comparison of mean serum uric acid reduction and duration of clinical improvement between treatment groups
*Source: Becker, M. A., Schumacher, H. R., Wortmann, R. L., MacDonald, 2005; Mackenzie, I. S., Ford, I., Nuki, G., Hall, C. L., 2020.*

Figure 1 visually demonstrates that both treatment regimens effectively reduced serum uric acid levels. The allopurinol–febuxostat group exhibited a slightly greater reduction in serum uric acid, whereas the duration of clinical improvement varied considerably between the two treatment groups. These findings support the quantitative results presented in Table 4 and illustrate that serum urate reduction does not necessarily correspond directly to the duration of clinical recovery, which may also be influenced by inflammatory activity, comorbid conditions, and adherence to treatment. Overall, the present findings suggest that both combination therapies are effective for managing gout in routine clinical practice. However, the allopurinol–febuxostat combination demonstrated superior urate-lowering effectiveness and may therefore represent a more appropriate therapeutic option for patients requiring intensive serum urate reduction. Future prospective studies with larger sample sizes, longer follow-up periods, and adjustment for clinical confounding factors are warranted to further validate these findings.

**Discussion**

This retrospective study compared the clinical effectiveness of two combination therapies, namely allopurinol–febuxostat and allopurinol–colchicine, in patients with gout treated at

Universitas Sebelas Maret Hospital. Both therapeutic regimens significantly reduced serum uric acid concentrations, indicating that each combination was effective in controlling hyperuricemia. However, patients receiving the allopurinol–febuxostat combination achieved a significantly greater reduction in serum uric acid levels than those receiving the allopurinol–colchicine combination ($p = 0.023$). These findings suggest that combining two xanthine oxidase inhibitors provides greater urate-lowering efficacy than combining a xanthine oxidase inhibitor with an anti-inflammatory agent.

Although the difference between treatment groups was statistically significant, its clinical significance should be interpreted cautiously. The observed difference in the mean reduction of serum uric acid levels was relatively small (0.07 mg/dL). Therefore, treatment selection should not rely solely on statistical significance but should also consider whether the magnitude of benefit is clinically meaningful for individual patients. Factors such as achievement of target serum urate levels, reduction in gout flare frequency, patient tolerance, medication adherence, and long-term safety may be more relevant than small differences in biochemical outcomes alone.

The greater reduction in serum uric acid observed in the allopurinol–febuxostat group can be explained by the complementary pharmacological mechanisms of the two drugs. Allopurinol is a purine analogue that competitively inhibits xanthine oxidase, thereby reducing uric acid synthesis. Febuxostat is a selective non-purine xanthine oxidase inhibitor with higher affinity for both the oxidized and reduced forms of the enzyme, resulting in more complete inhibition of uric acid production. Consequently, febuxostat has consistently demonstrated superior urate-lowering efficacy, particularly in patients who fail to achieve target serum urate levels with conventional allopurinol therapy (White, W. B., Saag, K. G., Becker, M. A., 2018).

The greater urate-lowering effect observed with the allopurinol–febuxostat combination may also be explained by differences in the pharmacokinetic profiles of the two agents. Allopurinol is rapidly converted into its active metabolite, oxypurinol, which is primarily eliminated through renal excretion. Consequently, impaired renal function may reduce oxypurinol clearance and limit dose escalation because of concerns regarding toxicity. In contrast, febuxostat is extensively metabolized in the liver through glucuronidation and oxidation pathways and is less dependent on renal elimination. This pharmacokinetic characteristic enables febuxostat to maintain effective xanthine oxidase inhibition even in patients with mild-to-moderate renal impairment, potentially contributing to its greater urate-lowering efficacy observed in the present study.

In contrast, colchicine does not directly lower serum uric acid concentrations. Instead, its therapeutic effect is mediated through inhibition of microtubule polymerization, suppression of neutrophil migration, and inhibition of NLRP3 inflammasome activation, thereby reducing inflammatory responses during acute gout attacks. For this reason, current international guidelines recommend colchicine primarily as prophylaxis against gout flares during the initiation of urate-lowering therapy rather than as a urate-lowering agent itself (Leung et al., 2015; Pascart & Richette, 2018). This pharmacological difference may explain why the allopurinol–colchicine combination showed a smaller reduction in serum uric acid despite remaining clinically effective.

The present findings are consistent with recommendations from the 2020 American College of Rheumatology (ACR) Guideline for the Management of Gout, which emphasizes a treat-to-target strategy by maintaining serum urate concentrations below 6 mg/dL through dose titration of xanthine oxidase inhibitors. Similarly, the 2023 European Alliance of Associations for Rheumatology (EULAR) recommendations continue to support xanthine oxidase inhibitors as first-line urate-lowering therapy while reserving colchicine primarily for flare prophylaxis during treatment initiation. In the present study, both treatment groups achieved post-treatment serum uric acid concentrations close to the recommended therapeutic target, indicating successful implementation of urate-lowering therapy in routine clinical practice.

The predominance of male patients (93.67%) and elderly individuals (>60 years, 67.09%) observed in this study is also consistent with previous epidemiological studies. Gout occurs more

frequently in men because estrogen promotes renal urate excretion in premenopausal women, whereas aging contributes to declining renal function and increased prevalence of metabolic disorders that impair uric acid excretion. These demographic characteristics have been consistently reported across Asian and global populations, suggesting that the study population reflects the typical clinical profile of patients with gout (Aaditya Shivhare & , K. T. Harichandrakumar , Pragya Silwal, 2022; Dehlin, M., Jacobsson, L., & Roddy, 2020; Neogi, 2011).

Although the allopurinol–febuxostat combination demonstrated statistically superior urate-lowering efficacy, the difference in mean serum uric acid reduction between treatment groups was relatively modest. Therefore, the clinical significance of this difference should be interpreted carefully. Selection of urate-lowering therapy should not rely solely on biochemical outcomes but should also consider patient-specific factors, including renal function, cardiovascular comorbidities, medication adherence, adverse drug reactions, treatment costs, and drug availability. Individualized therapy remains essential for optimizing long-term gout management.

Another important finding of this study is the variability in follow-up duration among patients. Considerable differences in the time to follow-up were observed, as reflected by the large standard deviations in both treatment groups. This variability may have been influenced by disease severity, treatment adherence, concomitant medications, physician scheduling, and differences in healthcare utilization rather than by treatment efficacy alone. Therefore, follow-up duration should not be interpreted as a direct measure of therapeutic effectiveness.

From a pharmacoeconomic perspective, treatment selection should also consider cost-effectiveness. Although febuxostat generally provides greater urate-lowering efficacy, it is substantially more expensive than allopurinol in many healthcare settings. In Indonesia, where most patients receive treatment through the National Health Insurance (BPJS Kesehatan), prescribing decisions should balance clinical effectiveness with drug affordability and healthcare resource utilization. Consequently, the allopurinol–febuxostat combination may be more appropriate for patients who fail to achieve target serum urate concentrations with conventional therapy, whereas the allopurinol–colchicine combination remains an appropriate and economically reasonable option for many patients during initiation of urate-lowering therapy.

Several limitations should be acknowledged. First, the retrospective design relied on secondary data from medical records, limiting control over missing information and potential measurement bias. Second, the relatively small sample size from a single tertiary hospital may reduce the generalizability of the findings to broader populations. Third, important clinical variables such as renal function, disease duration, body mass index, dietary habits, alcohol consumption, medication adherence, and comorbid conditions were not analyzed, although these factors are known to influence serum uric acid concentrations and treatment outcomes. Finally, because treatment allocation was based on routine clinical practice rather than randomization, residual confounding cannot be excluded.

The external validity of this study should be interpreted with caution. Because the study was conducted at a single tertiary referral hospital using a retrospective observational design, the findings may not be fully generalizable to primary healthcare facilities, private hospitals, or populations with different demographic and clinical characteristics. Nevertheless, the study reflects routine clinical practice and therefore provides valuable real-world evidence regarding the effectiveness of combination therapy for gout in Indonesia.

Several limitations should be acknowledged. First, the retrospective design limited control over potential confounding variables, including body mass index, renal function, smoking status, alcohol consumption, disease duration, and other comorbidities, which were not consistently available in the medical records. Second, this was a single-center study with a relatively small sample size, which may limit the generalizability of the findings. Third, treatment adherence and long-term clinical outcomes, such as recurrent gout flares and adverse drug reactions, were not

evaluated. Future prospective multicenter studies with larger sample sizes and more comprehensive clinical assessments are warranted to confirm these findings.

The findings of this study also have potential implications for gout management in Indonesia. Current Indonesian clinical practice generally follows international recommendations from the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR), which recommend xanthine oxidase inhibitors as first-line urate-lowering therapy. The present findings provide additional real-world evidence from an Indonesian tertiary hospital, supporting the effectiveness of xanthine oxidase inhibitor–based combination therapy in routine clinical practice. Nevertheless, treatment decisions should continue to consider drug availability, patient comorbidities, renal function, and healthcare reimbursement policies within the Indonesian healthcare system.

This study has several limitations. First, because of its retrospective design, several clinically relevant variables, including body mass index (BMI), renal function, hypertension, diabetes mellitus, chronic kidney disease, smoking habits, alcohol consumption, duration of illness, and other comorbidities, were not consistently available in the medical records and therefore could not be included in the baseline analysis. Consequently, residual confounding cannot be completely excluded. Future prospective studies with more comprehensive clinical data collection are needed to validate these findings and provide a more robust comparison of combination therapies for gout management.

# CONCLUSION

This retrospective study demonstrated that both the allopurinol–febuxostat and allopurinol–colchicine combination therapies were effective in reducing serum uric acid levels among patients with gout treated at Universitas Sebelas Maret Hospital. The allopurinol–febuxostat combination achieved a statistically greater reduction in serum uric acid levels than the allopurinol–colchicine combination, suggesting that xanthine oxidase inhibitor–based combination therapy may provide additional therapeutic benefit in routine clinical practice.

Scientifically, this study contributes real-world evidence regarding the comparative effectiveness of combination therapies for gout management in an Indonesian tertiary-care setting, where published clinical data remain limited. These findings provide additional information that may support clinicians in selecting individualized urate-lowering treatment strategies, particularly for patients who fail to achieve target serum uric acid levels with conventional therapy. Nevertheless, treatment decisions should also consider patient characteristics, renal function, drug safety, treatment costs, medication availability, and the healthcare reimbursement system in Indonesia. From a practical and policy perspective, the findings support the continued optimization of evidence-based gout management within Indonesian healthcare services and may serve as supporting evidence for future evaluations of national clinical practice recommendations. However, because this study was retrospective and conducted at a single center, the findings should be interpreted cautiously and should not be generalized without further validation.

Future prospective multicenter studies involving larger sample sizes, longer follow-up periods, and more comprehensive clinical variables—including renal function, comorbidities, treatment adherence, adverse drug reactions, and pharmacoeconomic outcomes—are recommended to confirm these findings and establish the long-term clinical effectiveness and cost-effectiveness of combination therapies for gout management.

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