

Uric acid levels in tuberculosis patients receiving pyrazinamide-ethambutol

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Abstract

Pyrazinamide and ethambutol are essential components of anti-tuberculosis therapy; however, both drugs can affect uric acid metabolism and increase the risk of hyperuricemia. Elevated uric acid levels may potentially cause joint pain and other metabolic disorders that can affect patient adherence to therapy. This study aims to analyze changes in serum uric acid levels before and after the administration of pyrazinamide–ethambutol combination therapy in tuberculosis patients. The study employed a retrospective analytical observational design using secondary data from the medical records of tuberculosis patients undergoing treatment at three type D regional general hospitals in West Jakarta. A sample of 100 patients was selected using a total sampling method. Data analysis was performed using descriptive statistics and a paired-samples t-test. The results showed an increase in the mean serum uric acid levels in both male and female patients after four weeks of therapy. Male patients had higher uric acid levels than females, although the increase was significant in both groups. These findings suggest that pyrazinamide–ethambutol combination therapy leads to an increase in serum uric acid levels during the intensive phase of tuberculosis treatment. Therefore, regular monitoring of uric acid levels is essential for early detection of hyperuricemia and for optimizing patient management in tuberculosis.

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1. Introduction

Tuberculosis remains a major public health challenge, particularly in developing countries. The disease is caused by *Mycobacterium tuberculosis*, which typically affects the lungs but can also involve other organs—such as the lymph nodes, bones, meninges, and skin—under certain conditions (Pitono et al., 2021). Transmission of tuberculosis primarily occurs through inhalation of droplet nuclei expelled by individuals with pulmonary tuberculosis when coughing, sneezing, or speaking (Widada & Wulandari, 2021). Transmission can also occur via the digestive tract or through contact with open wounds contaminated with infectious material (Indrasari & Fathana, 2024). Tuberculosis generally presents with a prolonged productive cough, weight loss, loss of appetite, night sweats, and persistent fatigue, all of which significantly impact the patient's quality of life (Fortuna et al., 2022). Delayed diagnosis and suboptimal treatment can worsen the patient's condition and increase the risk of transmission in the community. Social factors such as poverty, population density, smoking habits, alcohol consumption, and limited access to healthcare services also contribute to the high incidence of tuberculosis (Shinta et al., 2025).

Tuberculosis became one of the leading causes of death from infectious diseases after Coronavirus Disease 2019 (COVID-19), surpassing even human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). The World Health Organization reports that tuberculosis mortality rates have increased following the COVID-19 pandemic, with approximately 1.5 million deaths worldwide, including 214,000 deaths among people living with HIV (Dewi et al., 2024). Indonesia is among the countries with the highest tuberculosis burden in the world. According to the Global Tuberculosis Report, there are an estimated 824,000 tuberculosis cases in Indonesia, placing the country third behind India and China (Nabilla et al., 2024), followed by the Philippines, Pakistan, Nigeria, Bangladesh, and the Democratic Republic of the Congo (Dewi et al., 2024). The latest data also indicate an increase in the number of cases, with approximately 969,000 tuberculosis patients and 144,000 deaths in 2023, including cases of drug-resistant tuberculosis (Indrasari & Fathana, 2024).

Tuberculosis primarily affects the 15–49 age group, resulting in significant social and economic impacts on patients and their families (Wibowo et al., 2023). Patients with pulmonary tuberculosis often experience a significant decline in physical condition, loss of work productivity, and difficulty performing daily activities. On average, tuberculosis patients may lose several months of productive time while undergoing treatment and recovery. The disease increases the risk of transmission to other family members, particularly children, and leads to social isolation and economic strain (Wowiling et al., 2021). These conditions result in tuberculosis and poverty, often forming an interrelated cycle that is difficult to break among vulnerable communities.

The diagnosis of tuberculosis involves a combination of clinical, radiological, and laboratory examinations (Widada & Wulandari, 2021). Laboratory testing plays a crucial role because confirmation of *Mycobacterium tuberculosis* is critical for informing treatment decisions and monitoring therapy. Microscopic examination of sputum using Ziehl–Neelsen (ZN) staining for acid-fast bacilli (AFB) remains widely used because it is relatively simple and affordable. However, this method has low sensitivity and cannot detect drug resistance. Additionally, test results are influenced by the skill of the laboratory personnel conducting the examination. To address these limitations, molecular-based tests such as Xpert MTB/RIF are increasingly being used because they can detect *Mycobacterium tuberculosis* and rifampicin resistance more quickly and accurately (Wibowo et al., 2023).

Global efforts to control tuberculosis have been strengthened through the implementation of the Directly Observed Treatment Short-course (DOTS) strategy recommended by the World Health Organization. The DOTS strategy in Indonesia has been implemented nationwide as part of the tuberculosis control program. Treatment for drug-sensitive tuberculosis generally uses a first-line combination of anti-tuberculosis drugs consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol (Mustaming et al., 2022). During the intensive phase, this drug combination is administered for two months to reduce bacterial load and lower the risk of transmission rapidly. Subsequently, therapy continues with a four-month continuation phase using isoniazid and rifampicin to eradicate dormant bacteria and prevent relapse. This regimen is known as the 2HRZE/4HR protocol.

Patients with a history of prior treatment or relapse may be prescribed a Category 2 regimen with the addition of streptomycin during the intensive phase (Fortuna et al., 2022). Meanwhile, rifampicin-resistant tuberculosis and multidrug-resistant tuberculosis require the use of second-line anti-tuberculosis drugs due to resistance to standard therapy (Adha et al., 2024). Although tuberculosis treatment offers significant benefits in improving cure rates, long-term use of anti-tuberculosis drugs often causes various side effects, including liver, kidney, and pancreatic dysfunction, as well as metabolic disorders. Several studies have reported anemia, nutritional status disorders, and changes in glucose metabolism during anti-tuberculosis drug therapy (Elsa et al., 2025; Susilawati et al., 2023). These side effects can reduce patient adherence to treatment and potentially hinder therapeutic success if not properly monitored.

One of the metabolic complications frequently observed during anti-tuberculosis drug therapy is hyperuricemia, particularly in patients receiving a combination of pyrazinamide and ethambutol. Both drugs are known to interfere with uric acid excretion via renal tubular mechanisms, thereby increasing serum uric acid levels (Sasongko & Hasan, 2020; Shin et al., 2023; Qureshi et al., 2007). Pyrazinamide metabolites can inhibit uric acid secretion in renal tubules, while ethambutol increases urate reabsorption, leading to blood uric acid accumulation. Previous studies have shown a high incidence of hyperuricemia in tuberculosis patients receiving a combination of these two drugs. Sasongko & Hasan (2020) reported a hyperuricemia incidence of 82.3% in patients receiving the pyrazinamide–ethambutol combination, while Taki et al. (2008) found elevated uric acid levels in 84.5% of patients during pyrazinamide therapy. If not

adequately managed, hyperuricemia can progress to arthralgia, gout, monosodium urate crystal deposition, and even renal dysfunction (Azzahra et al., 2023).

Although elevated uric acid levels during anti-tuberculosis drug therapy are quite common, laboratory monitoring of this parameter in clinical practice still receives relatively less attention compared to liver function tests. In fact, biochemical monitoring is crucial for the early detection of metabolic disorders that can affect patients' quality of life and adherence to treatment. Furthermore, data on uric acid levels in tuberculosis patients receiving a pyrazinamide–ethambutol combination at Indonesian healthcare facilities remain limited. Therefore, this study was conducted to analyze uric acid levels in tuberculosis patients receiving pyrazinamide–ethambutol combination therapy after one month of treatment. The study used medical records of patients with drug-resistant tuberculosis undergoing treatment at three Type D regional general hospitals in West Jakarta in 2023. The study results are expected to strengthen the evidence on hyperuricemia associated with anti-tuberculosis drugs and underscore the importance of laboratory monitoring in the management of tuberculosis patients.

2. Method

2.1 Research Design and Participants

This study employed an analytical observational design with a retrospective approach. The data consisted of secondary records from patients with drug-resistant tuberculosis. A retrospective approach was used to evaluate changes in uric acid levels before and after administration of the pyrazinamide–ethambutol combination therapy, based on documented clinical data. The study was conducted at three type D regional general hospitals in West Jakarta, with data collection conducted in 2023. The study population included all patients with drug-resistant tuberculosis who received combination therapy with pyrazinamide and ethambutol and had complete uric acid level test results before treatment and after one month of therapy. The sampling technique used was total sampling, with 100 medical records from the study period included.

2.2 Instruments and Data Collection

The research instrument consisted of an observation sheet used to record patients' demographic data and laboratory test results from their medical records. The independent variable in this study was the administration of the combination therapy of pyrazinamide–ethambutol, while the dependent variable was serum uric acid levels before therapy and after one month of treatment. Uric acid levels are defined as the concentration of uric acid in the blood, recorded in the patient's laboratory test results and expressed in mg/dL. Data collection was conducted after obtaining permission from the relevant institution and the health research ethics committee. Medical records were collected gradually while maintaining patient confidentiality. All data obtained were then coded to exclude any personally identifiable information. Hospital laboratories performed uric acid level tests, which were recorded in medical records, in accordance with the standard operating procedures applicable at each healthcare facility.

2.3 Data Analysis

Data analysis was performed using univariate and bivariate approaches in accordance with the study objectives. Univariate analysis was used to describe uric acid levels before and after therapy, using mean values and standard deviations. Bivariate analysis was performed to assess differences in uric acid levels before and after administration of the pyrazinamide–ethambutol combination therapy. A normality test was conducted to ensure that the assumption of normality was met. Since the data showed a normal distribution, the difference was analyzed using a paired t-test. All statistical analyses were performed using SPSS version 21 with a significance level set at $p < 0.001$.

2.4 Ethical Considerations

This study has received ethical approval from the Health Research Ethics Committee of Muhammadiyah University of Purwokerto, with ethical clearance number KEPK/UMP/60/IV/2023. All research procedures were conducted in accordance with the ethical principles of health research. Patient identities were not disclosed during data collection, analysis, or publication. The researchers ensure that all patient information is kept confidential and used solely for scientific purposes.

3. Results and Discussion

3.1 Results

The study involved 100 tuberculosis patients undergoing combination therapy with pyrazinamide and ethambutol at three Type D regional general hospitals in West Jakarta. The study results present the characteristics of the participants in Table 1 and an overview of changes in uric acid levels before and after 4 weeks of therapy in Table 2.

Table 1. Characteristics of tuberculosis patients by sex and age group

Sex Characteristics	Frequency (n)	Percentage (%)
Male	59	59,0
Female	44	41,0
Age group characteristics (years)		
17-30 (Young Adult)	26	26,0
31-45 (Middle-aged)	31	31,0
46-60 (late adulthood)	32	32,0
>60 (Elderly)	11	11,0
Total	100	100,0

Table 1 displays that the majority of respondents were male, totaling 59 patients (59.0%), while female patients numbered 41 (41.0%). The age distribution indicates that the late-adult age group (46–60 years) was the largest, with 32 respondents (32.0%), followed by the middle-adult group (31–45 years), with 31 respondents (31.0%). Meanwhile, the elderly group (>60 years) was the smallest, comprising 11 patients (11.0%).

Table 2. Mean serum uric acid levels before and after pyrazinamide–ethambutol therapy by sex

Sex	n	Uric acid level at baseline (week 0)	Uric acid level at week 4	p-value
Male	59	5,20 ± 1,019	7,05 ± 1,988	< 0,05
Female	41	4,38 ± 1,078	6,84 ± 2,359	< 0,05

Table 2 explains the increase in mean serum uric acid levels after four weeks of pyrazinamide–ethambutol therapy in both male and female patients. In the male group, the mean uric acid level increased from 5.20 mg/dL to 7.05 mg/dL. While in the female group, the average uric acid level increased from 4.38 mg/dL to 6.84 mg/dL. The paired t-test showed that the increase in uric acid levels before and after therapy in both groups was statistically significant ($p < 0.05$).

3.2 Discussion

This study analyzed changes in uric acid levels in tuberculosis patients receiving combination therapy with pyrazinamide and ethambutol over a 4-week treatment period. The results indicated an increase in serum uric acid levels following treatment in both male and female patients. These findings support the hypothesis that the use of the pyrazinamide–ethambutol combination contributes to the development of hyperuricemia in tuberculosis patients, particularly during the intensive phase of treatment.

Tuberculosis is more common among men than women, consistent with previous studies. A study by Sazkiah et al. (2017) at Sri Pamela Hospital in Tebing Tinggi showed that 73% of tuberculosis patients were male, while only 27% were female. Andayani (2020) also reported that in Ponorogo Regency, the prevalence of pulmonary tuberculosis was higher among men than women. Similar results were demonstrated by Wibowo et al. (2023) at Cisarua Lung Hospital in Bogor, which showed a higher number of male patients despite the proportions being nearly equal. A combination of biological, behavioral, and environmental factors may influence the higher prevalence of tuberculosis cases among men. Women possess estrogen, a hormone known to provide a protective effect on cellular immune responses, which play a crucial role in combating *Mycobacterium tuberculosis* infection (Hong et al., 2025).

Additionally, men are more likely to smoke, consume alcohol, and be exposed to occupational environments that increase the risk of tuberculosis transmission. Higher mobility and social activity among men may also increase the likelihood of contact with sources of tuberculosis transmission in public spaces (Sazkiah et al., 2017). These results indicate an epidemiological pattern consistent with tuberculosis

characteristics across regions. The age distribution of the study shows that the majority of patients were in the 31–60 age group. This age group represents the productive age range, characterized by high levels of social and economic activity. It increases the risk of exposure to *Mycobacterium tuberculosis*, particularly in the workplace and densely populated residential areas (Susilawati et al., 2023). Additionally, the gradual decline in immune function from middle to late adulthood can also affect the body's ability to control latent tuberculosis infection. Comorbid conditions such as diabetes mellitus, chronic fatigue, and smoking habits—which are more commonly found in this age group—also contribute to susceptibility to tuberculosis infection. The number of elderly patients in this study was relatively smaller compared to other age groups. This situation may be influenced by the limited availability of complete medical records for the elderly group and by the low case detection rate in the elderly population. Nevertheless, the elderly remain a vulnerable population requiring special attention in tuberculosis prevention and control efforts. The elderly are characterized by a physiologically occurring decline in immune function, which can increase the risk of disease complications.

The findings also demonstrated an increase in the mean serum uric acid levels after four weeks of combination therapy with pyrazinamide and ethambutol. In men, the average uric acid level rose above the normal range, whereas in women, the average value increased significantly, although it remained slightly lower than in men. It indicates that the effect of anti-tuberculosis therapy on uric acid metabolism is consistent across both genders. These findings are consistent with several previous studies. A study at the Kramatjati Community Health Center among tuberculosis patients undergoing anti-tuberculosis drug therapy reported uric acid levels ranging from 3.5–11.8 mg/dL, with more than half experiencing an increase above normal (Widada & Wulandari, 2021). A study at the Jumpandang Baru and Barabaraya Community Health Centers in Makassar also showed that 60% of tuberculosis patients experienced elevated uric acid levels during anti-tuberculosis therapy (Widada & Wulandari, 2021). Additionally, a study at the Medan City General Hospital found that the majority of patients undergoing anti-tuberculosis drug therapy experienced hyperuricemia, with an average uric acid level of 9.33 mg/dL (Pitono et al., 2021). However, this study measured uric acid levels before and after treatment, unlike the previous study.

An observational cohort study conducted at the Citangkil Community Health Center in Cilegon City also reported a significant increase in uric acid levels following two months of RHZE therapy (Azzahra et al., 2023). These results show a pattern similar to that observed in the present study, although the therapy duration differed. With a larger sample size and data from three regional public hospitals, this study provides additional evidence that the pyrazinamide–ethambutol combination can increase uric acid levels even within the first four weeks of therapy. The increase in uric acid levels in this study can be explained by the pharmacological mechanisms of anti-tuberculosis drugs, particularly pyrazinamide. Pyrazinamide is known as the anti-tuberculosis drug most frequently associated with hyperuricemia because its active metabolite, pyrazinoic acid, can inhibit uric acid excretion in the renal proximal tubules by competing with uric acid for the organic anion transporter (Mustaming et al., 2022). Consequently, uric acid clearance decreases, and serum uric acid levels rise. Several studies indicate that elevated uric acid levels may begin as early as the first two weeks of therapy and persist throughout the intensive phase of treatment (Abdullaey et al., 2017; Putra et al., 2024). These results align with this study's findings, which demonstrated an increase in uric acid levels after 4 weeks of therapy.

In addition to pyrazinamide, ethambutol also contributes to elevated uric acid levels, though its effect is less pronounced (Pitono et al., 2021). Ethambutol is thought to affect renal excretory function, thereby exacerbating uric acid retention when combined with pyrazinamide. Combining these two drugs during the intensive phase of tuberculosis therapy is estimated to produce an additive effect on serum uric acid levels (Azzahra et al., 2023). Genetic variants in the SLC22A12 gene, which encodes a urate transporter, may increase the risk of hyperuricemia associated with pyrazinamide use (Jiangli et al., 2023). These findings suggest that elevated uric acid levels are not only influenced by the drug but may also be influenced by individual genetic factors. The difference in mean uric acid levels between men and women in this study is likely related to physiological factors. Men have higher baseline uric acid levels than women because the hormone estrogen in women helps increase uric acid excretion through the kidneys. Nevertheless, this study shows that both groups experienced an increase in uric acid levels after therapy. It confirms that the metabolic effects of anti-tuberculosis drugs are consistent and not significantly influenced by gender.

The results of this study have important implications for monitoring patients with tuberculosis undergoing pyrazinamide–ethambutol therapy. Elevated uric acid levels can lead to complaints of

arthralgia, joint pain, and even gout attacks, which may affect patient comfort and adherence during long-term treatment. Therefore, monitoring uric acid levels during the intensive phase of therapy should be considered as part of routine laboratory monitoring, particularly in patients with risk factors for metabolic disorders or a history of hyperuricemia. Education regarding a low-purine diet, adequate hydration, and recognition of hyperuricemia symptoms is also important to provide to patients to prevent further complications without disrupting the continuity of tuberculosis therapy. Although this study provides insight into changes in uric acid levels in patients with tuberculosis, several limitations should be noted. The retrospective design using medical record data limits the researchers' ability to control for confounding factors, such as kidney function, dietary patterns, comorbidities, and other medications that may affect uric acid levels. Uric acid levels were measured only at the start of therapy and in the fourth week, so long-term changes and the clinical manifestations of hyperuricemia cannot yet be fully evaluated. This study also did not include a control group with a different treatment regimen, so a causal relationship cannot be fully established. Therefore, prospective studies with longer observation periods and more comprehensive clinical data are still needed to strengthen the findings of this study.

4. Conclusion

The study found that a four-week combination therapy of pyrazinamide and ethambutol led to an increase in serum uric acid levels in both male and female tuberculosis patients. A consistent increase in mean uric acid levels was observed in both gender groups, although higher levels were more prevalent among male patients. Furthermore, the characteristics of the study subjects indicate that tuberculosis is more prevalent among individuals in the productive age group, extending into late adulthood. It highlights the continued high disease burden among age groups with high levels of social and economic activity. The findings reinforce evidence that the use of the pyrazinamide and ethambutol combination during the intensive phase of tuberculosis therapy can affect uric acid metabolism and potentially lead to hyperuricemia as a treatment side effect. The study results underscore the importance of regular monitoring of serum uric acid levels. Laboratory evaluation of tuberculosis patients during the early phase of treatment is crucial to prevent metabolic complications and maintain treatment adherence. Nevertheless, this study has limitations: it used a retrospective design based on medical records and did not account for several confounding factors, such as diet, renal function, comorbidities, and other medications that may affect uric acid levels. Therefore, prospective studies with longer follow-up and a greater number of clinical variables are needed.

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Conflict of Interest

There is no conflict of interest related to this work, according to the authors. This research was conducted with self-funding, and no financial or non-financial support from external institutions or organizations.

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