ASSOCIATION BETWEEN PYRAZINAMIDE-CONTAINING ANTI-TUBERCULOSIS REGIMENS AND THE INCIDENCE OF HEPATOTOXICITY

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ABSTRACT

Background: Tuberculosis (TB), an infectious disease caused by Mycobacterium tuberculosis, remains a major global health burden. According to the WHO, approximately 9.6 million cases were reported in 2014, with 58% occurring in Southeast Asia, including Indonesia. Anti-tuberculosis treatment using Fixed-Dose Combination (FDC) regimens—comprising isoniazid, rifampicin, pyrazinamide, and ethambutol—is associated with several adverse effects, most notably hepatotoxicity.

Objective: To evaluate the impact of pyrazinamide-containing anti-tuberculosis regimens on the incidence of hepatotoxicity in patients with tuberculosis.

Methods: A systematic literature search was conducted across three electronic databases: PubMed, Cochrane Library, and Scopus. Selected studies underwent critical appraisal based on the University of Oxford's Centre for Evidence-Based Medicine (CEBM) guidelines.

Result: Two articles met the eligibility criteria for this report. Both studies compared two patient groups—those receiving the RHZE regimen (with pyrazinamide) and those receiving the RHE regimen (without pyrazinamide)—to monitor the incidence of hepatotoxicity during the first two months of treatment.

Conclusion: The findings suggest that the inclusion of pyrazinamide (PZA) does not significantly increase the incidence of hepatotoxicity in TB patients. A PZA dosage of 20-25 mg/kg/day was found to be within the safety limits for both adults and elderly patients.

Keywords: tuberculosis, drug-induced liver injury, hepatotoxicity, pyrazinamide

ABSTRAK

Latar Belakang: Tuberkulosis (TB), suatu penyakit menular yang disebabkan oleh Mycobacterium tuberculosis, tetap menjadi beban kesehatan global yang besar. Menurut WHO, sekitar 9,6 juta kasus dilaporkan pada tahun 2014, dengan 58% di antaranya terjadi di Asia Tenggara, termasuk Indonesia. Pengobatan antituberkulosis menggunakan rejimen Kombinasi Dosis Tetap (FDC)—yang terdiri dari isoniazid, rifampisin, pirazinamid, dan etambutol—dikaitkan dengan beberapa efek samping, terutama hepatotoksisitas.

Tujuan: Untuk mengevaluasi dampak regimen antituberkulosis yang mengandung pirazinamid terhadap insidensi hepatotoksisitas pada pasien tuberkulosis.

Metode: Pencarian literatur sistematis dilakukan di tiga basis data elektronik: PubMed, Cochrane Library, dan Scopus. Studi yang terpilih menjalani penilaian kritis berdasarkan pedoman Centre for Evidence-Based Medicine (CEBM) Universitas Oxford.

Hasil: Dua artikel memenuhi kriteria kelayakan untuk laporan ini. Kedua studi membandingkan dua kelompok pasien—yang menerima regimen RHZE (dengan pirazinamid) dan yang menerima regimen RHE (tanpa pirazinamid)—untuk memantau insiden hepatotoksisitas selama dua bulan pertama pengobatan.

Kesimpulan: Temuan menunjukkan bahwa penambahan pyrazinamide (PZA) tidak secara signifikan meningkatkan insiden hepatotoksisitas pada pasien TB. Dosis PZA sebesar 20–25 mg/kg/hari ditemukan berada dalam batas keamanan baik untuk pasien dewasa maupun lansia.

Kata kunci: tuberkulosis, kerusakan hati akibat obat, hepatotoksisitas, pirazinamid

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RISK FACTORS FOR PRIMARY LUNG CANCER IN PATIENTS WITH A HISTORY OF TUBERCULOSIS

INTRODUCTION

Case Illustration

A 41-year-old female presented with worsening abdominal pain over the past week prior to admission. The pain was localized in the right upper quadrant, with no radiation, and was unaffected by food intake or defecation cycles. The patient also noted progressive abdominal distension. One month earlier, she was diagnosed with pulmonary tuberculosis and initiated on a first-line intensive phase regimen consisting of Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol (RHZE).

Physical examination and laboratory investigations revealed elevated liver enzymes, with SGOT at 156 U/L and SGPT at 84 U/L, alongside increased bilirubin levels (Total: 2.47 mg/dL, Direct: 1.93 mg/dL, Indirect: 0.54 mg/dL). Based on these findings, the patient was diagnosed with Drug-Induced Liver Injury (DILI) secondary to anti-tuberculosis therapy. Consequently, the intensive phase OAT was discontinued. The patient inquired about which specific medication in her regimen was the likely cause of her liver condition. Therefore, the clinician sought to determine whether the inclusion of pyrazinamide in the anti-tuberculosis regimen significantly increases the incidence of hepatotoxicity in TB patients compared to regimens without pyrazinamide.

Background

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis that can infect the lung parenchyma and other organs, such as bones. Currently, tuberculosis is one of the world's most significant health challenges. According to the WHO report in 2024, In 2024, the global incidence of tuberculosis (TB) reached an estimated 10.7 million cases, with a corresponding incidence rate of 131 per 100,000 population. Most of the people who develop TB disease each year are in 30 high TB burden countries: they accounted for 87% of the global total in 2024, Indonesia at 10%.[1] During the same period, the disease accounted for approximately 1.23 million deaths, reflecting a case fatality rate of 11.5%. Tuberculosis remains a critical global health priority, ranking among the top ten causes of death worldwide and maintaining its position as the leading cause of mortality attributed to a single infectious pathogen.[1] Various studies have shown that nearly 80% of tuberculosis cases can be cured using Fixed-Dose Combination (FDC) regimens. However, FDC drugs have several side effects, one of which is hepatotoxicity. First-line anti-tuberculosis drugs, including isoniazid, rifampicin, pyrazinamide, and ethambutol all possess the potential to induce hepatotoxic effects.[2]

Drug-induced liver injury (DILI) is an adverse drug reaction that can lead to acute hepatitis or even liver failure. TB-associated DILI refers to the impairment of liver function resulting from the use of anti-tuberculosis drugs (OAT). The incidence of OAT-induced hepatotoxicity is estimated to range between 2% and 28%. Research has demonstrated a three-fold increase in liver enzymes, specifically ALT and AST, in the liver function tests of TB patients with DILI. Symptoms may include abdominal pain, nausea, vomiting, and jaundice.[3,4]

Although it has been established that first-line OAT can cause hepatotoxicity with an incidence rate of 2% to 28%, further investigation is required to determine which specific first-line OAT regimen carries a higher potential for inducing liver injury. Therefore, this study will further explore the impact of pyrazinamide-containing OAT regimens on the incidence of hepatotoxicity in TB patients through an evidence-based case report approach.[4,5]

Clinical Question

Does the inclusion of pyrazinamide in anti-tuberculosis drug regimens significantly increase the incidence of hepatotoxicity in patients with tuberculosis?

METHODS

Search Strategy

A comprehensive literature search was conducted on August 27, 2024, across multiple electronic databases, including PubMed, Cochrane Library, and Scopus, along with manual searching to identify relevant evidence. The search utilized

various keywords and Medical Subject Headings (MeSH) related to the PICO framework, such as "Adult", "Tuberculosis", "chemical and drug-induced liver injury", "antitubercular agents", and "pyrazinamide". These terms were applied both as MeSH terms and within the titles or abstracts of the literature. Furthermore, synonyms and related phrases, including "drug-induced liver injury" and "antitubercular drugs", were combined using Boolean operators such as AND and OR to refine the search results. The literature search was limited to articles available in full-text and written in either English or Bahasa Indonesia to ensure a thorough evaluation of the impact of pyrazinamide-containing regimens on TB patients with liver injury.

Table 1. Article Search Strategy

Database	Strategi Pencarian	Temuan
Pubmed	("Adult"[MeSH Terms] OR "Adult"[Title/Abstract]) AND ("Tuberculosis"[MeSH Terms] OR "Tuberculosis"[Title/Abstract]) AND ("chemical and drug induced liver injury"[MeSH Terms] OR "drug induced liver injury"[Title/Abstract]) AND ("antitubercular agents"[MeSH Terms] OR "antitubercular drugs"[Title/Abstract]) AND ("pyrazinamide"[MeSH Terms] OR "pyrazinamide"[Title/Abstract]).	122
Cochrane	#1 MeSH descriptor: [Tuberculosis] #2 MeSH descriptor: [Chemical and Drug Induced Liver Injury] #3 MeSH descriptor: [Antitubercular Agents] #4 MeSH descriptor: [Pyrazinamide] #5 MeSH descriptor: [Adult] #1 AND #2 AND #3 AND #4 AND #5	8
Scopus	adult AND (tuberculosis OR tb) AND ("Drug induced liver injury" OR dili) AND "Antitubercular drugs"AND pyrazinamide	107

Eligibility Criteria

The eligibility criteria for this evidence-based case report were categorized into inclusion and exclusion criteria. The inclusion criteria consisted of:

- Adult patients (aged over 18 years) diagnosed with tuberculosis who received anti-tuberculosis treatment regimens containing pyrazinamide compared with other regimens.
- Measured Outcomes: Incidence of hepatotoxicity, documented through liver function test (LFT) results or other objective diagnostic findings.
- Study Design: Systematic reviews, meta-analyses, randomized controlled trials (RCTs), or cohort studies.
- Conversely, the exclusion criteria included:
- Articles published in languages other than English or Bahasa Indonesia, and studies without accessible full-text or open-access availability.
- Patients with pre-existing conditions that could confound liver function results, including HIV, viral hepatitis, chronic liver disease, or other significant systemic comorbidities.

Critical Appraisal Tool and Level of Evidence

According to the Oxford Centre for Evidence-Based Medicine (CEBM) guidelines, the levels of evidence for the included studies were classified as Level 2, comprising both a randomized controlled trial (RCT) and a prospective cohort study. These designs provide high-quality evidence for evaluating the risk factors and incidence of drug-induced liver injury in the clinical setting.

Article Selection

A literature search was conducted using PubMed, Cochrane, and Scopus databases, yielding 122 articles from PubMed, 8 articles from Cochrane, and 107 articles from Scopus. Following title and abstract screening, articles were excluded according to the predefined exclusion criteria, including studies published in languages other than English or Indonesian, studies without open-access or full-text availability, and studies involving patients with HIV, hepatitis, pre-existing liver disorders, or other chronic diseases. A total of 13 articles remained after the initial screening process. Among these, two duplicate articles were identified and removed, leaving 11 articles for full-text

review. Subsequently, 9 articles were excluded because they did not match the intended intervention and/or outcome criteria. Ultimately, 2 articles met the research question, PICO framework, and eligibility criteria. The flow of studies selection can be seen at Figure 1.

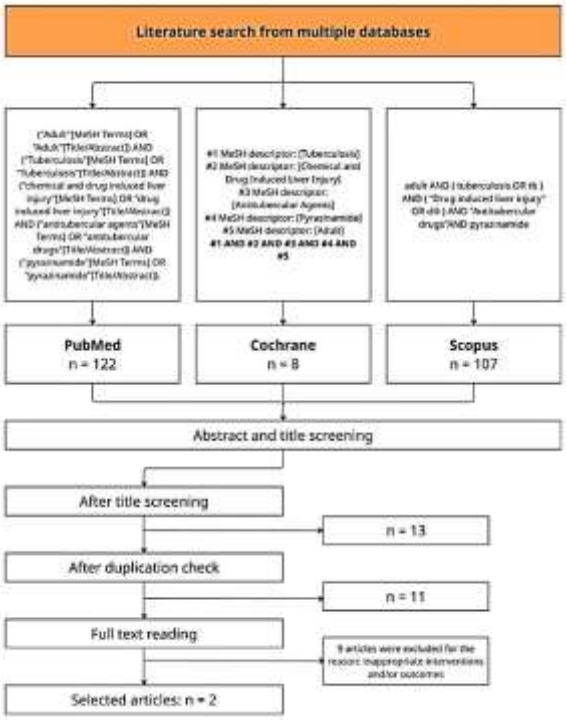

Figure 1. Search Strategy Flow

RESULTS

Study Characteristics

A total of two articles were selected for inclusion in this EBCR, namely the study by Horita N. et al., entitled Currently Used Low-Dose Pyrazinamide Does Not Increase Liver Injury in the First Two Months of Tuberculosis Treatment, and the study by Hagiwara E. et al., entitled Safety of Pyrazinamide-Including Regimen in Late Elderly Patients with Pulmonary Tuberculosis: A Prospective Randomized Open-Label Study. The characteristics of each included study are presented in Table 2.

Table 2. Characteristics of Included Studies

Author (Year)	Study Design	Population	Intervention and Comparison	Outcome
Horita N, et al. (2015)[2]	*Cohort study*	383 adult patients with pulmonary tuberculosis	Intervention: 308 patients receiving the RHZE regimen Comparison: 75 patients receiving the RHE regimen	Drug-induced liver injury (DILI) within the first two months occurred in 24% (18/75) of patients receiving the RHE regimen and 8% (24/308) of patients receiving the RHZE regimen. Across all three analytical models, DILI occurred less frequently among patients treated with the HRZE regimen: model 1, HR 0.30 (95% CI: 0.14–0.68; p = 0.004); model 2, HR 0.37 (95% CI: 0.14–0.96; p = 0.041); and model 3, HR 0.34 (95% CI: 0.12–0.94; p = 0.038).
Hagiwara E, et al. (2019)[3]	Randomized controlled trial (RCT)	89 elderly patients with pulmonary tuberculosis	Intervention: 44 patients receiving the RHZE regimen Comparison: 45 patients receiving the RHE regimen without pyrazinamide	Elevation of AST/ALT levels greater than 2.5 times the upper limit of normal, defined as liver dysfunction, occurred in a total of 18 patients, including 8 of 45 patients (17.8%) in the RHE group and 10 of 44 patients (22.7%) in the RHZE group (p = 0.561).

Critical appraisal

The critical appraisal in this EBCR was conducted using the Centre for Evidence-Based Medicine (CEBM) Oxford Prognosis Worksheet for prognosis-related clinical questions. The CEBM framework assists in critically appraising the validity, importance, and applicability of the literature included in this review.

Validity

In the study conducted by Horita N. et al. (2015), the inclusion criteria consisted of patients with smear-positive tuberculosis who were newly diagnosed with TB. The primary outcome of the study was the incidence of drug-induced liver injury (DILI) during the first two months of treatment; therefore, the study duration was adjusted accordingly and did not evaluate long-term

outcomes. DILI was defined according to the American Thoracic Society guidelines as serum aminotransferase elevation ≥3 times the upper limit of normal accompanied by symptoms, or ≥5 times the upper limit of normal without symptoms. Thus, the study outcome can be considered objective. Baseline patient characteristics were reported; however, the study did not clearly describe adjustments for prognostic factors that could potentially influence patient outcomes. Statistical analyses included the Wilcoxon rank-sum test and Fisher's exact test, followed by univariate and multivariate Cox regression analyses using three different models.

In the study by Hagiwara E. et al. (2019), patients were randomly allocated at the time of hospital admission for tuberculosis, indicating that the administered regimen represented the patients' initial anti-tuberculosis treatment. The primary outcome was discontinuation of anti-tuberculosis treatment due to liver dysfunction; therefore, the study duration depended on the occurrence of hepatic adverse events. However, the duration of follow-up for the enrolled patients was not clearly described. Liver dysfunction was objectively defined as AST/ALT levels exceeding 2.5 times the upper limit of normal. Baseline clinical characteristics of the included patients were also reported, with p-values >0.05 indicating no statistically significant differences between groups. Nevertheless, the study did not explain whether adjustments were made for prognostic factors that could affect patient outcomes. In addition, the study did not clearly describe the use of an independent group "test set." The summary of the validity assessment is presented in Table 3.

Table 3. Validity Assessment According to the CEBM Criteria

Question	Study	Yes/No/ Unclear	Information
Was a defined, representative sample of patients assembled at a common (usually early) point in the course of their disease?	Horita N, et al. (2015)	✓	
	Hagiwara E, et al. (2019)	✓	
Was the follow-up of the study patients sufficiently long and complete?	Horita N, et al. (2015)	UC	
	Hagiwara E, et al. (2019)	UC	
Were outcome criteria either objective or applied in a "blind" fashion?	Horita N, et al. (2015)	✓	Objective
	Hagiwara E, et al. (2019)	✓	Objective
If subgroups with different prognoses are identified, was there adjustment for important prognostic factors?	Horita N, et al. (2015)	UC	
	Hagiwara E, et al. (2019)	UC	
Were there validation in an independent group (test-set) of patients?	Horita N, et al. (2015)	✓	
	Hagiwara E, et al. (2019)	UC	

Notes:* ✓ = yes; ✕ = no; UC = unclear

Importance

In the study conducted by Horita N. et al. (2015), the reported outcome was the occurrence of drug-induced liver injury (DILI) within the first two months of treatment in 24% (18/75) of patients receiving the RHE regimen and 8% (24/308) of patients receiving the RHZE regimen. Across all three analytical models, DILI occurred less frequently among patients treated with the HRZE regimen. In model 1, analyzed using multivariate Cox analysis in the pre-matching cohort, the hazard ratio (HR) was 0.30 (95% CI: 0.14–0.68; p = 0.004). In model 2, analyzed using univariate Cox analysis in the matched cohort, the HR was 0.37 (95% CI: 0.14–0.96; p = 0.041). In model 3, analyzed using multivariate Cox analysis in the matched cohort, the HR was 0.34 (95% CI: 0.12–0.94; p = 0.038). [5]

In the study by Hagiwara E. et al. (2019), the primary outcome was an increase in AST/ALT levels greater than 2.5 times the upper limit of normal, which was defined as liver dysfunction. This outcome occurred in a total of 18 patients, including 8 of 45 patients (17.8%) in the RHE group and 10 of 44 patients (22.7%) in the RHZE group (p = 0.561). The analysis was performed using a 95% confidence interval (CI), a two-sided alpha level of 0.05, and a non-inferiority margin of 0.2. [6]

Applicability

Both studies included in this review involved study populations similar to those in the present clinical scenario, namely adult patients with tuberculosis, and excluded patients with HIV infection or pre-existing liver disease. Therefore, these studies have important clinical relevance and applicability

in supporting the conclusions of this review, as presented in Table 4.

Table 4. Applicability Assessment According to the CEBM Criteria

Question	Study	Yes/No/Unclear
Were the study patients similar to your own?	Horita N, et al. (2015)	✓
	Hagiwara E, et al. (2019)	✓
Will this evidence make a clinically important impact on your conclusion about what to offer or tell your patient?	Horita N, et al. (2015)	✓
	Hagiwara E, et al. (2019)	✓

Notes:* ✓ = yes; × = no; UC = unclear

DISCUSSION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis that primarily affects the lung parenchyma but may also involve other organs, such as the bones. TB remains one of the world's major global health problems. According to the World Health Organization (WHO), approximately 9.6 million TB cases were reported in 2014, with 58% occurring in Southeast Asia, including Indonesia. The recommended anti-tuberculosis treatment regimen consists of a combination of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (ETH). However, these agents are known to have hepatotoxic potential. In liver function testing, the main parameters used to assess the degree of hepatotoxicity are serum glutamic oxaloacetic transaminase (SGOT/AST) and serum glutamic pyruvic transaminase (SGPT/ALT). A previous literature review concluded that pyrazinamide has a higher hepatotoxic potential compared with other first-line anti-tuberculosis drugs, such as isoniazid and rifampicin. [1,6,8]

Drug-induced liver injury (DILI) is an adverse drug reaction that may progress to acute hepatitis and even liver failure. TB-associated DILI refers to liver dysfunction caused by anti-tuberculosis drugs (ATDs). The highest incidence of ATD-induced DILI generally occurs within the first two weeks to two months after treatment initiation. DILI can be identified through liver function tests showing elevated AST and ALT levels, accompanied by clinical manifestations such as abdominal pain, fever, and jaundice. Monitoring hepatotoxicity is essential through periodic liver function evaluation, particularly during the first two months of treatment, because the occurrence of hepatotoxicity during TB therapy may necessitate discontinuation of anti-tuberculosis drugs. Treatment is usually withheld until clinical symptoms resolve and liver function parameters return to normal. [7,9]

Pyrazinamide, as a first-line anti-tuberculosis drug with relatively high hepatotoxic potential, was the primary focus of this study. Other first-line agents, including isoniazid and rifampicin, are also associated with hepatotoxicity, although to a lesser extent than PZA. Therefore, this study included investigations comparing two treatment groups: the RHZE regimen and the RHE regimen without pyrazinamide, in order to evaluate the effect of pyrazinamide on hepatotoxicity incidence among patients with TB. [6]

In the study conducted by Horita N. et al. (2015), DILI occurring within the first two months was reported in 24% (18/75) of patients receiving the RHE regimen and 8% (24/308) of patients receiving the RHZE regimen. Among the 18 patients in the RHE group without pyrazinamide, the mean AST level was 200 ± 169 IU/L, ALT was 140 ± 167 IU/L, and total bilirubin was 2.3 ± 1.5 mg/dL at the time of DILI diagnosis. In the 24 patients receiving the RHZE regimen, the mean AST level was 292 ± 283 IU/L, ALT was 222 ± 226 IU/L, and total bilirubin was 1.7 ± 1.7 mg/dL at the time of DILI diagnosis. In this study, pyrazinamide was administered at a low dose of 20–25 mg/kg/day, and the incidence of hepatotoxicity in the RHZE group was not substantially different from that observed in the RHE group without pyrazinamide. These findings suggest that pyrazinamide-containing regimens may be relatively safe when administered at doses of 20–25 mg/kg/day. [6]

Similarly, the study conducted by Hagiwara E. et al. (2019), which involved elderly patients aged >80 years, reported that elevations of AST/ALT greater than 2.5 times the upper limit of normal, defined as liver dysfunction, occurred in 18 patients overall: 8 of 45 patients (17.8%) in the RHE

group and 10 of 44 patients (22.7%) in the RHZE group. The p-value was 0.561 (>0.05), indicating no statistically significant difference between the groups. In this study, pyrazinamide was administered at a dose of 25 mg/kg/day. Therefore, it may be concluded that pyrazinamide-containing regimens at a dose of 25 mg/kg/day remain within an acceptable safety range regarding hepatotoxicity, even in elderly patients. [7]

CONCLUSION

Based on the two studies included in this review, namely Horita N. et al. (2015) and Hagiwara E. et al. (2019), it can be concluded that pyrazinamide (PZA)-containing regimens did not significantly increase the incidence of hepatotoxicity in patients with tuberculosis. PZA administered at a dose of 20–25 mg/kg/day was considered to remain within a safe range in adult patients, including elderly populations. However, both studies primarily monitored patients during the first two months after initiation of anti-tuberculosis treatment; therefore, the long-term effects of these regimens on hepatotoxicity still require further investigation.

Based on these findings, future studies are recommended to evaluate the long-term effects of anti-tuberculosis treatment on the incidence of hepatotoxicity and to determine whether the risk increases with longer treatment duration. In addition, further investigation regarding the dose of each treatment regimen should be considered to identify which regimen may have the greatest impact on hepatotoxicity incidence among patients with tuberculosis. [6,10]

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