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Analysis of the risk factors of hepatitis on the rate of recovery in pulmonary tuberculosis patients

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Abstract
Tuberculosis (TB) remains a major public health challenge, particularly in developing countries. Although anti-TB drugs are effective, their use is often associated with drug-induced hepatitis (DIH), which can impact treatment outcomes. Understanding the relationship between DIH risk factors and TB cure rates is critical for improving therapeutic success. This study aims to analyze the risk factors associated with DIH and assess their impact on the cure rate of pulmonary TB patients. A retrospective analytical observational study was conducted at Labuang Baji Hospital and Dr. Wahidin Sudirohusodo Hospital between January and March 2025. Data were collected from pulmonary TB patients who developed DIH between June 2023 and June 2024. A total of 90 subjects were included through total sampling. Demographic, clinical, and treatment variables were analyzed using univariate and bivariate methods with SPSS. Ethical approval was obtained prior to the study initiation. Among the 90 subjects, the mean age was 43.92 years, with 63.3% under 50 years old and 64.4% male. Low body mass index (<18.5 kg/m²) was prevalent in 60% of cases. Comorbidities included diabetes mellitus (21.1%), hypertension (21.1%), and HIV (16.7%). Most TB diagnoses were confirmed bacteriologically (78.9%). DIH occurred on average 8 days after treatment initiation, and 91.1% experienced it within 14 days. Extensive lung lesions were present in 37.8% of patients, and 60% were on a three-drug regimen. A cure was achieved in 80% of subjects, while 20% did not recover. Despite the occurrence of DIH, most TB patients recovered. Early identification of risk factors is important to prevent complications and improve outcomes.

Introduction

Tuberculosis (TB) is a significant public health problem in developing countries. Nearly one-third of the world's population is infected with TB, and the disease causes the deaths of nearly 3 million people per year, with the second highest case after HIV/AIDS. TB is an infectious disease caused by *Mycobacterium tuberculosis*. This infection usually affects the lungs, but it can also affect other parts of the body.[1,2]

Effective TB treatment requires a combination of bactericidal and/or bacteriostatic TB drugs. This combination of regimens is the standard therapy that the World Health Organization recommended. Standard therapy consists of two stages: the initial/intensive phase and the advanced stage. The administration of anti-TB drugs (OAT) in the early stages aims to quickly reduce the number of TB germs in the patient's body and minimize the risk of transmission. The initial stage also aims to minimize the influence of a small number of TB germs that may have been resistant to OAT before treatment began. The duration of early-stage treatment in drug-sensitive patients is two months.[3,4]

Treatment continues with an advanced stage. Advanced treatment aims to kill the remaining TB germs that do not die in the early stages, so that they can prevent recurrence. The duration of the advanced stage ranges from 4-6 months.[5,6] In the intensive phase, patients were given a combination of 4 drugs in the form of rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (E) for 2 months, followed by the administration of INH and RIF for 4 months in the advanced phase.[3]

The challenges in the treatment of TB lie in the need for a long duration of treatment, repeated administration of the drug, and the associated toxicity.[7,8] OATs have mild to severe side effects. The side effects that arise not only cause death and pain but also cause the discontinuation of treatment, which has an impact on the failure of healing, and even drug resistance can arise, which ultimately leads to therapy failure. One of the important complications associated with OAT therapy is hepatotoxicity.[9,10]

Drug-induced hepatitis (DIH) is reported to occur in 5-28% of patients undergoing treatment. Research conducted by Perwitasari *et al*. found that the incidence of hepatotoxicity in Indonesia was reported to reach 50%. Most previous studies focused on pulmonary TB patients, while data related to extrapulmonary TB patients are still limited. Three of the first-line drugs used to treat TB (INH, RIF, and PZA) are known to have a risk of DIH, although the hepatotoxicity of RIF is specific and least likely.[11,12]

Measuring the risk of DIH is difficult based on the variability of definitions used, population studies, co-existing risk factors, and combination therapy. However, when used as monotherapy for the treatment of latent TB, the hepatotoxicity rate is estimated to be 0.15-2% with INH and 0.3-2% with RIF.[13,14] The risks associated with PZA individually are unknown because they are not used as monotherapy. However, they are the first-line drugs that most often cause liver damage, and the estimated hepatotoxicity associated ranges from 4.7 to 58% when combined with other agents.[15]

DIH can have serious consequences, such as acute liver failure and death.[16] DIH can also affect the recovery rate of TB patients who are at higher risk of experiencing treatment failure, drug withdrawal, and relapse.[17,18] Research that comprehensively evaluates factors that affect recovery rates, including treatment status (new, relapsed, discontinued) and drug resistance, is still rare in Indonesia.[19] Understanding the factors that affect DIH on the recovery rate of TB patients is important to improve the effectiveness of TB treatment, prevent the occurrence of DIH and its serious complications, and improve the quality of life of TB patients.[20]

This research determined how the risk factors for hepatitis affect drugs and the cure rate in pulmonary TB patients. To determine the risk factors for hepatitis and the impact of drugs on the recovery rate in pulmonary TB patients. There is a relationship between the risk factors for hepatitis due to the drug impact on pulmonary TB patients on the rate of recovery. The results of this study can open new research opportunities on hepatitis affected by anti- TB drugs, such as research on the mechanism of hepatitis due to anti-TB drugs, the development of new drugs for the prevention and treatment of hepatitis affected by anti-TB drugs, and research on non-pharmacological interventions to prevent hepatitis due to anti-TB drugs.

Materials and Methods

This is ab analytical observational study with a retrospective design conducted at Labuang Baji Hospital and Dr. Wahidin Sudirohusodo Hospital from January to March 2025. The target population includes all pulmonary TB patients diagnosed at both hospitals, with an affordable population focusing on patients who developed DIH between June 2023 and June 2024. Total sampling was used, and a minimum of 87 subjects was required based on statistical calculations. Inclusion criteria were pulmonary TB patients experiencing DIH, while exclusion criteria included patients using other hepatotoxic drugs, those with incomplete medical records, and those with chronic hepatitis. Variables identified include risk factors such as age, sex, nutritional status, smoking and alcohol history, comorbidities, and OAT treatment history, with the cure rate of TB as the dependent variable. Data collection involved reviewing medical records for demographic, clinical, and treatment information, then entering and processing the data through editing, coding, tabulating, and cleaning using Excel and SPSS. Data analysis included univariate and bivariate methods, presenting findings through narratives, tables, and graphs. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University, and Dr. Wahidin Sudirohusodo Hospital.

Results

This study has been conducted on 90 subjects who experienced DIH by looking at the occurrence of recovery based on the clinical characteristics of patients with TB.

The study was conducted on 90 subjects who experienced recovery-related DIH based on the clinical characteristics of patients with TB (Table 1). The average age of patients was 43.92 years, with the majority being under 50 years old (57 patients, 63.30%) and the rest being over 50 years old (33 patients, 36.70%). Most were male (58 patients, 64.40%), while fewer were female. The average body mass index (BMI) of patients was 17.69 kg/m², with the majority having a BMI below 18.5 kg/m² (54 patients, 60.00%) compared to a BMI more than equal to 18.5 kg/m² (36 patients, 40.00%). 19 patients (21.10%) had diabetes mellitus (DM), while the majority (71 patients, 78.90%) did not have the disease. Hypertension was found in 19 patients (21.10%), while 71 patients (78.90%) did not have hypertension. A total of 15 patients (16.70%) had HIV, while 75 patients (83.30%) were not infected. Most TB diagnoses were based on bacteriological outcomes (71 patients, 78.90%), while clinical diagnoses included 19 patients (21.10%). The mean time of occurrence of DIH was 8 days, with a time range of between 4 to 26 days after initiating OAT treatment. 34 patients (37.80%) had extensive lesions, while 56 patients (62.20%) had non-extensive lesions. Regarding TB drug doses, most patients took 3 tablets daily (54 patients, 60.00%), while the rest took 4 tablets daily (36 patients, 40.00%). Of the subjects, 80% were cured after treatment, while 18% did not recover.

Table 2 present the patients over 50 had a lower chance of cure than patients under 50, although this association was not statistically significant [odds ratio (OR): 2.00; p=0.19]. Sex showed no significant difference in recovery, with males and females having relatively equal chances (OR: 0.62; p=0.38). BMI also had no significant relationship, although patients with a BMI of less than 18.5 kg/m² tended to be unwell more often than those with higher BMI (OR: 1.43; p=0.52).

DM significantly affects recovery; patients without diabetes have a much greater chance of cure than patients with diabetes (OR: 18.57; p=0.00). Hypertension was also found to have a significant effect, with patients without hypertension having a higher chance of being cured than patients with hypertension (OR: 18.66; p=0.00). The presence of HIV did not show a significant association with recovery, although patients without HIV recovered more often than patients with HIV (OR: 2.39; p=0.16).

TB diagnosis by bacteriological methods is more often associated with cure than clinical methods, although this association is not statistically significant (OR: 2.47; p=0.34). The results showed that although most patients with an incidence time of <14 days were cured, and patients with an incidence time of ≥14 days were also cured, there was no statistically significant difference between the two groups. The extent of the lesion had a significant relationship with healing; patients with non-

extensive lesions had a much higher chance of healing (p=0.00). Doses of four tablets and less than four tablets had no significant effect.

Discussion

Gender, smoking habits, and work history did not show significant values on the influence of KPKBSK incidents compared to the control group. DIH is a serious complication of OAT treatment, with prevalence ranging from 5% to 28%. Risk factors include age over 60, malnutrition, and low BMI. This study involved 90 patients, with most under 50 years old (63.30%) and 36.70% over 50 years old (36.70%). 22 men (64.40%) were more likely to experience DIH, possibly due to hormonal and behavioral factors. Low BMI and low albumin levels were also significant risk factors. Patients with DM and hypertension had a higher chance of recovery. Comorbidities like DM can affect DIH risk, especially in patients with other complications.[21]

The study found that HIV infection in 16.70% of patients did not significantly impact recovery, indicating that optimal management with antiretroviral therapy can improve TB treatment outcomes. TB diagnosis was based mainly on bacteriological outcomes but did not show a significant association with cure. The extent of lesions in patients also had a significant relationship with healing, with non-extensive lesions having a higher recovery rate.The study found that 80% of patients with TB who experienced DIH were cured, with 20% not recovering. Factors like medication adherence, regimen accuracy, and health conditions significantly impacted recovery outcomes. Lower cure rate of 65%, with malnutrition and comorbidities increasing the risk of not recovering.[22]

Elderly age significantly impacts the recovery of TB patients with DIH due to a decrease in hepatocyte regenerative ability, increased oxidative stress, and slower liver drug metabolism. Patients over 55 years of age have a higher risk of hepatotoxicity due to anti-TB drugs. The reduced regenerative capacity of the liver in old age also contributes to longer recovery time. Comorbidity factors like diabetes and hypertension also worsen patients' recovery. Advanced age is linked to an increased risk of treatment failure due to hepatotoxicity.[23]

Gender plays a significant role in the recovery of TB patients with DIH through biological, hormonal, and behavioral mechanisms. Men have a higher risk of severe TB infection and increased mortality due to the immunosuppressive effects of testosterone. In contrast, women have a stable platelet activity level and higher treatment adherence. However, men are more susceptible to hepatotoxicity complications due to smoking and alcohol consumption, which can slow recovery. The relationship between sex and TB recovery is not statistically significant.[24]

Low BMI is linked to poor recovery in TB patients with DIH due to malnutrition and immune response issues. Research shows that patients with a BMI <18.5 kg/m² are more susceptible to hepatotoxicity complications due to impaired liver metabolism. Malnutrition also lowers serum albumin levels, inhibiting liver regeneration and worsening liver damage. Low BMI also increases the risk of unsuccessful treatment outcomes, especially in patients with HIV or diabetes. However, the relationship between BMI and TB recovery with DIH is not statistically significant. DM significantly impacts the recovery of TB patients with DIH through immunological and metabolic disorders. Chronic hyperglycemia in DM weakens the body's ability to control infection, increases the circulation of pro-inflammatory cytokines, and increases the risk of TB drug resistance. Uncontrolled hyperglycemia also increases the risk of TB drug resistance and exacerbates OAT-induced hepatotoxicity, decreasing treatment effectiveness. DM is associated with poor treatment outcomes, increased mortality rates, and longer sputum conversion times in TB patients.[25]

Hypertension significantly impacts the recovery of TB patients with DIH through systemic mechanisms involving chronic inflammation. This inflammation triggers the activation of the renin-angiotensin-aldosterone system, increasing the risk of liver tissue damage and hepatotoxicity. Hypertension often coincides with dyslipidemia and insulin resistance, worsening liver metabolic dysfunction, and hepatocyte regeneration. Chronic hypertension increases the risk of mortality from TB and treatment failure due to poor glucose control. Comprehensive hypertension management is crucial for improving TB patient recovery.[26]

HIV affects the recovery of TB patients with DIH through immune disorders, reducing the number and function of CD4+ T cells, increasing the risk of latent TB reactivation, and increasing the risk of hepatotoxicity due to the interaction between OAT drugs and antiretrovirals. HIV-TB patients often have low CD^{4+} levels, slowing the immune response and prolonging recovery time. While the relationship between HIV and TB treatment outcomes is not statistically significant, optimal management with antiretroviral therapy can improve treatment outcomes.[26]

Bacteriological diagnosis of TB, such as GeneXpert or sputum culture, allows for direct identification of Mycobacterium TB and drug resistance, reducing the risk of hepatotoxicity or DIH due to inappropriate OAT therapy. This method helps prevent the administration of empirical drugs that increase the risk of DIH, especially in patients with fragile liver conditions. Clinical diagnosis, on the other hand, often relies on symptoms and imaging, which can increase exposure to hepatotoxic drugs. Despite the lack of statistical significance, bacteriological methods can significantly reduce the incidence of DIH. Extensive lesions in TB can increase infection and inflammation, leading to hepatotoxicity in treatment. These lesions can trigger pro-inflammatory cytokines, worsen liver damage, and inhibit hepatocyte regeneration. Large lesions are often accompanied by pulmonary cavities, increasing the risk of discharge and DIH. Longer recovery times and drug resistance are associated with extensive lesions. The lesion area significantly impacts recovery in TB patients with DIH, as seen in South Africa and Japan.[27]

The study found that patients with hepatotoxicity (DIH) within 14 days of starting OAT therapy had a lower chance of recovery compared to those who experienced DIH after 14 days. Early onset of DIH may indicate a more serious reaction to OAT, affecting recovery. Delayed DIH may be associated with better treatment outcomes, as patients with tolerance develop over the first two weeks of therapy. The study emphasizes the importance of early monitoring in the first two weeks of OAT therapy to identify and manage DIH risks. By focusing on DIH timing, medical personnel can better plan interventions to increase recovery chances. The study found that the OAT regimen used in treating TB patients with DIH did not significantly impact recovery rates. However, patients receiving a standard regimen, a combination of INH, RIF, pyrazine, and E, had a higher recovery rate. Patients using more complex regimens had better outcomes, indicating the need for an individualized approach in therapy management. This research provides valuable insights for clinical practice and future treatment guidelines.[28]

Limitations

In this study, several limitations need to be considered. The retrospective observational design may limit the ability to draw firm conclusions about the cause-and-effect relationship between risk factors and cure rates. This can result in difficulty controlling confounding variables that may affect the study results. In addition, the limited sample size, i.e., 90 subjects, can reduce the statistical power of the analysis and limit the generalization of results to a broader population. Another limitation is the observation time. The patient observation duration was insufficient to capture all the long-term effects of treatment and hepatotoxicity. Some side effects or complications may appear after a specific period, so the results obtained do not reflect the patient's condition. In addition, psychosocial factors, such as social support and mental state, are not considered in depth. However, these factors can significantly affect a patient's recovery and quality of life. Researchers may recommend future research to use more comprehensive designs, such as holistic data collection and larger sample sizes, to improve the validity and reliability of results.

Conclusions

Risk factors for the occurrence of DIH in pulmonary TB patients in the study were age over 50 years, comorbidities of DM and hypertension, low BMI, and extensive lesions. The recovery rate of pulmonary TB patients who experience DIH reaches 80%. Risk factors for DIH, such as hypertension, DM, and extensive lesions, have a significant impact on the recovery rate of pulmonary TB patients.

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Table 1. Clinical demographic data of subjects with drug-induced hepatotoxicity.

Variable	Red (min-max)	N%
Age	43.92 (18-78) years old	
≥50 years old		33 (36.70)
<50 years old		57 (63.30)
Gender		
Man	-	58 (64.4)
Woman		32 (35.6)
IMT	17.69 (13.20-21.70)	
<18.5 kg/m^2		54 (60.00)
≥18.5 kg/m^2		36 (40.00)
Diabetes mellitus		
Exist	-	19 (21.1)
None		71 (78.9)
Hypertension		
Exist	-	19 (21.1)
None		71 (78.9)
HIV		
Exist	-	15 (16.7)
None		75 (83.3)
Diagnosis TB		
Bacteriologist	-	71 (78.9)
Clinical		19 (21.1)
Time of occurrence of DIH	7.92 (4-26) days	
<14 days		82 (91.1%)
≥14 days		8 (8.9%)
Lesion area		
Broad	-	34 (37.8)
Not spacious		56 (62.2)
Number of drug regimens		
4 regimens	-	36 (40.0)
3 regimens		54 (60.0)
Status		
Recover	-	72 (80.0)
Not cured		18 (20.0)

BMI, body mass index; TB, tuberculosis; DIH, drug-induced hepatitis.

Table 2. **Clinical demographics as a cure factor for tuberculosis with drug-induced hepatitis.**

Variable	Outcome		OR 95% CI	p-value
	Recover	Not cured		
Age,				
≤50 years old	48 (66.70)	9 (50.00)	2.00 (0.70-5.69)	0.19a
>50 years old	24 (33.30)	9 (50.00)		
Gender, n (%)				
Man	48 (82.8)	10 (17.2%)	0.62 (0.22-1.78)	0.38
Woman	24 (75.0)	8 (25.0%)		
BMI				
<18.5 kg/m^2	42 (58.30)	12 (66.70)	1.43 (0.48-4.23)	0.52a
≥18.5 kg/m^2	30 (41.70)	6 (33.30)		
Diabetes mellitus, n (%)				
Exist	7 (9.70)	12 (66.70)	18.57 (5.31-64.97)	0.00a*
None	65 (90.30)	6 (33.30)		
Hypertension, n (%)				
None	65 (91.5)	6 (8.5)	18.66 (5.29-64.39)	0.00*
Exist	7 (36.8)	12 (63.2)		
HIV, n (%)				
None	62 (82.7)	13 (17.3)	2.39 (0.85-1.80)	0.16
Exist	10 (66.7)	5 (33.3)		
Diagnosis TB, n (%)				
Clinical	17 (89.5)	2 (10.5)	2.47 (0.52-11.85)	0.34a
Bacteriologist	55 (77.5)	16 (22.5)		
Lesion area, n (%)				
Not spacious	56 (100)	0 (0)	0.47 (0.33-0.67)	0.00*
Broad	16 (47.1)	18 (52.9)		
DIH occurrence time, n (%)				
<14 Days	64 (78.0)	18 (22.0)	(0.69-0.88)	0.138
≥14 Days	8 (100)	0		
Medication regimen, n (%)				
3 Regimen	41 (75.9)	13 (24.1)	0.51 (0.16-1.58)	0.24a
4 Regimen	31 (86.1)	5 (13.9)		

BMI, body mass index; TB, tuberculosis; DIH, drug-induced hepatitis; OR, odds ratio; CI, confidence index.