Jurnal Ilmiah Ibnu Sina,11(1), Maret 2026, 240-249
p-ISSN: 2502-647X; e-ISSN: 2503-1902

ANALYSIS OF RISK FACTORS AND TREATMENT PHASES ON THE SEVERITY OF HEPATOTOXICITY DUE TO ANTI-TUBERCULOSIS DRUGS

Nazhipah Isnani[1*], Samsul Hadi[1], Dita Ayulia Dwi Sandi[1], Satrio Wibowo Rahmatullah[1], Wirawan Adikusuma[2], Reni Yustiati Saksono[3], Erna Kusumawardhani[4,5], Shafa Alifia Nurjihan[1], Najma Auralia[1], Khelda Maulida[1], Feri Setiawan[1]

[1]Pharmacy Study Program, Faculty of Mathematics and Natural Sciences,Lambung Mangkurat University, Banjarbaru, South Kalimantan, Indonesia
[2]National Research and Innovation Agency, Cibinong, West Java, Indonesia
[3]Pharmacy Installation, Ulin Regional Hospital, Banjarmasin, South Kalimantan, Indonesia
[4]Department of Pulmonology and Respiratory Medicine, Ulin Regional Hospital, Banjarmasin, Indonesia
[5]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine and Health Sciences, Lambung Mangkurat University, Banjarmasin, Indonesia

Email[1*]: nazhipah@ulm.ac.id

Article received: 2026-01-05; Accepted: 2026-03-12
DOI: https://doi.org/10.36387/jiis.2911

ABSTRACT

Hepatotoxicity caused by anti-tuberculosis drugs (OAT) is one of the adverse effects of tuberculosis therapy and may lead to liver dysfunction. This study aimed to analyze the relationship between age, gender, and treatment phase with the severity of OAT induced hepatotoxicity, as well as to assess factors influencing the increase in hepatotoxicity grade. This research employed a retrospective cross-sectional design and was conducted at Ulin Regional Hospital Banjarmasin using a ***total sampling*** *method involving 45 tuberculosis patients. Secondary data were obtained from medical records of TB patients in 2024–2025. The results showed that 62.2% of patients were under 60 years old and 37.8% were over 60 years old. Male patients accounted for 75.6%, while females accounted for 24.4%. The distribution of hepatotoxicity grades was 40% normal, 28.9% grade 1, 20% grade 2, and 11.1% grade 3. Based on the treatment phase, 91.1% of patients were in the intensive phase and 8.9% were in the continuation phase. The Chi square test revealed no significant association between age, gender, or treatment phase and the severity of hepatotoxicity.*

Keywords: *Lung disease, Anti-tuberculosis drugs, Liver function impairment, Side effects, Risk factors*

INTRODUCTION

Tuberculosis (TB) is a long lasting infectious disease that remains a major global health challenge (Adhanty & Syarif, 2023), with Indonesia being the second largest contributor to TB cases worldwide (Delianandа & Azizah, 2022). Indonesia ranks as the second largest contributor to global tuberculosis cases (Delianandа & Azizah, 2022), reflecting the substantial burden of this infectious disease in the country (Mahartati & Syarif, 2024). The DOTS strategy and better primary healthcare services have helped control TB, but drug resistance, side effect of treatment, and patients not following their treatments plans are still big problems (Adhanty & Syarif, 2023; Bawonte et al., 2021). The incidence of DR-TB in South Kalimantan in 2023 was 0.95%, with the highest incidence reported in Banjarmasin City, at 37.36% (Sandi et al., 2025).

Isoniazid, rifampicin, pyrazinamide, and ethambutol are the first-line drugs for tuberculosis (Rifai et al., 2015) . They work very well, but they can also cause side effects (Wiyati et al., 2014). Hepatotoxicity is one of the side effects that happens most often (Wardhana et al., 2018). According to Dasuki et al. (2020), OAT hepatotoxicity is when the drug causes liver enzymes (ALT/AST) to rise above normal levels. This side effect can make the liver work less well, cause the therapy to stop, or change the OAT regimen, which can affect how well the treatment works (Dasuki et al., 2020).

The incidence of anti-tuberculosis drug-induced hepatotoxicity varies considerably across different studies and populations. Indonesian hospital-based studies show significant variation in reported rates, ranging from 5.4% at Dr. Saiful Anwar Hospital Malang (Rifai et al., 2015). Recent studies also show that hepatotoxicity predominantly occurs during the initial phase of treatment Dini (Permata Sari & Andriani, 2024). The some article reports that these variations in incidence are influenced by genetic polymorphisms, treatment regimens, patient demographics, and monitoring protocols (Wahyudi & Soedarsono, 2015). Several risk factors have been consistently associated with increased hepatotoxicity, including advanced age, nutritional status, and baseline liver enzyme levels (Dasuki et al., 2020). However, research results show some inconsistency. While Dasuki et al., (2020) found significant associations between advanced age (OR=8.815) and poor nutritional status (OR=6.478) with hepatotoxicity, and Wardhana et al., (2018)

identified age as a significant risk factor (adjusted OR=1.056), other demographic factors showed variable associations across different study populations, demonstrating the complexity of hepatotoxicity risk assessment in diverse clinical settings.

Several studies in Indonesia have investigated the hepatotoxicity of OAT, but they are generally limited to describing elevated liver enzymes without examining the association with specific risk factors. This study aims to analyze the relationship between age, gender, and treatment phase and the severity of hepatotoxicity due to OAT, as well as to assess factors influencing the degree of hepatotoxicity.

RESEARCH METHODOLOGY

This research has obtained ethical approval from the Ethics Committee for Health Research at Ulin Banjarmasin Regional General Hospital with permit number 112/VIII-Reg Riset/RSUDU/2023. The research design used was a cross-sectional retrospective study, utilizing secondary data from the medical records of tuberculosis (TB) patients undergoing Anti-Tuberculosis Drug (ATD) therapy. Data collection will be conducted from January–December 2024 and January–July 2025.

The study population consisted of all TB patients receiving OAT therapy at Ulin Banjarmasin Regional General Hospital during that period. The sampling technique used total sampling, so all patients who met the inclusion criteria were included in the sample, resulting in 45 patients. The inclusion criteria were: (1) patients diagnosed with TB and receiving OAT; (2) receiving oral hepatotoxic medication according to the standard regimen; and (3) having complete data related to liver function parameters (AST and ALT). Patients with incomplete medical record data or pre-existing liver disease were excluded from the analysis.

Data analysis was performed using SPSS version 29. The relationship between the variables of age, gender, and treatment phase and the severity of hepatotoxicity was analyzed using the Chi-Square test. Additionally, logistic regression analysis was performed to assess the variables influencing the increase in the degree of hepatotoxicity. All statistical graphs were created using R Studio.

RESULT AND DISCUSSION

1. Characteristics of TB Patients

In this study, the majority of tuberculosis patient were male (75.6%), while women only accounted for 24.4% of the total sample. This pattern is consistent with other Indonesian studies such as Wardhana et al., (2018) which reported that 64.5% of Tb patients emphasizing the prevalence of tuberculosis among males. This gender distribution is influenced not only of biological factors, but also by behavioral and environmental factors (Delianandа et al., 2022).

Several studies explain that men are more frequently exposed to risk factors, particularly smoking habits, which significantly increases TB susceptibility (Mahartati & Syarif, 2024). Additionally, men tend to have lower treatment adherence rates compared to women (Adhanty & Syarif, 2023).

By age group, the majority of patients were under 60 years old (64,4%), while 35.6% were over 60 years old. This pattern aligns with the epidemiological characteristics of TB, which predominantly affect the productive age group, Mahartati & Syarif, (2024); Wardhana et al., (2018) reporting a mean age of TB .patients at 38.37 ± 16.74 years. Within this age range, high social activity and mobility, along with environmental factors such as housing density, increase the likelihood of TB exposure (Delianandа & Azizah, 2022).

The majority of patients in this study were in the initial phase of treatment (91.1%), with only a small proportion in the continuation phase (8.9%). This finding is consistent with evidence that most cases of hepatotoxicity occur during the initial phase of TB treatment (Safira et al., 2018), which reported that 67% of hepatotoxicity cases emerged during the initial phase of anti-TB therapy. During this phase, treatment involves the HRZE combination (isoniazid, rifampin, pyrazinamide, ethambutol) (Rifai et al., 2015). Isoniazid and pyrazinamide are two drugs with high hepatotoxic potential (Dasuki et al., 2020), with isoniazid metabolism involving NAT2, CYP2E1, and GST enzymes playing important roles in hepatotoxicity development (Wahyudi & Soedarsono, 2015). And Rifai et al., (2015) reported an incidence of anti-TB drug-induced hepatitis of 5.4% with an average duration of hepatitis therapy of 18 days, while Clarasanti et al., (2016) found that 26% of TB patients experienced elevated transaminase enzymes after anti-TB treatment.

Table 1. Characteristics of TB Patients

Characteristics	TB (N=45)
Gender	
Female	11 (24,4%)
Male	34 (75,6%)
Age	
<60 year	29 (64,4%)
>60 year	16 (35,6%)
Phase of treatment	
Initial Phase	41 (91,1%)
Advanced Phase	4 (8,9%)

2. Hepatotoxicity Events

In this study, hepatotoxicity was identified in 60% of patients undergoing anti-tuberculosis drug (OAT) therapy. The severity distribution showed that most cases fell into Grade 1 (28.9%) and Grade 2 (20%), while Grade 3 occurred in 11.1% of patients. Meanwhile, 40% of patients maintained normal liver function throughout treatment. These findings demonstrate a higher incidence compared with a study conducted at Dr. Saiful Anwar General Hospital, which reported a hepatotoxicity rate of 5.4% (Rifai et al., 2015). Similarly, Clarasanti et al., (2016) documented elevated transaminase levels in 26% of patients at Prof. R.D. Kandou General Hospital. The relatively high proportion observed in the present study is likely attributable to the rigorous laboratory monitoring implemented from the initiation of therapy. Routine liver function testing facilitates early detection of enzyme elevations, allowing even mild hepatotoxicity to be identified and recorded systematically.

Hepatotoxicity in this study predominantly emerged during the intensive phase of treatment. Numerous investigations have shown that the intensive phase is the period most frequently associated with liver dysfunction, as patients receive a full combination regimen containing isoniazid, rifampicin, and pyrazinamide—agents known for their considerable hepatotoxic potential, with pyrazinamide noted as the strongest contributor. A meta-analysis by (Wang et al., 2022) demonstrated that liver enzyme abnormalities occur more commonly during the early phase of therapy than during the continuation phase. These findings align with those of Zhao et al., (2020), who reported that hepatotoxicity tends to develop within the initial months of intensive treatment, underscoring the prominent role of early-phase drug composition in the onset of drug-induced liver injury (DILI).

In this study, the classification of hepatotoxicity severity followed the 2019 guidelines of the European Association for the Study of the Liver (EASL), which outline specific threshold values for ALT, AST, and serum bilirubin as criteria for determining DILI severity (Andrade et al., 2019), as presented in Table 2.

Table 2. Hepatotoxicity Events

	(N=45)	
Normal	18 (40%)	
Grade 1	13	(28,9%)
Grade 2	9	(20%)
Grade 3	5 (11,1%)	
Hepatotoxicity	27 (60%)	
No Hepatotoxicity	18 40%)	

3. Relationship between Risk Factors and Hepatotoxic Events

Chi-square analysis in this study showed no significant relationship between gender, age, or treatment phase and the occurrence of hepatotoxicity (all p-values > 0.05). Nevertheless, the data distribution pattern still provides important clinical insights. Regarding the gender variable, hepatotoxicity was more frequently found in males (22 cases) compared to females (5 cases), but this did not reach statistical significance (p = 0.304). This insignificance is consistent with Wardhana et al., (2018), who found that gender was not significantly associated with the risk of hepatotoxicity, although 64.5% of the TB patients in that study were male. Dasuki et al., (2020) also did not find a significant relationship between gender and increased transaminases, indicating that the results of studies on the influence of gender on hepatotoxicity vary greatly between populations and tend to be influenced by comorbid and pharmacogenetic factors. For the age variable, the >60 years group appeared to have a higher risk tendency (OR 2.08), but this relationship was also not significant (p = 0.351). This result differs from Dasuki et al., (2020), which showed older age as an important risk factor with an OR of 8.815, and Wardhana et al., 2018, which identified age as a significant risk factor (adjusted OR = 1.056). This difference was likely influenced by the relatively small sample size of the study. The treatment phase also did not show a significant relationship with hepatotoxicity (p = 0.286). Although most cases were found during the intensive phase (26 out of 27 cases), statistically, this has not yet been confirmed as a causal relationship. This lack of significance can arise from an uneven distribution of samples between the

intensive and advanced phases. According to research by Shafira et al., 2018, 67% of hepatotoxicity cases occur in the early phase of OAT therapy. This aligns with research conducted by Sari et al., 2024, which examined the relationship between early-phase OAT use and increased liver enzymes, confirming that elevated ALT/AST levels are indeed most common in the early stages of treatment (Wang et al., 2022). Other research also mentions that the incidence of hepatotoxicity varies greatly between populations, depending on patient characteristics, comorbidity patterns, alcohol consumption habits, hepatitis status, and even the frequency of laboratory monitoring. Wahyudi & Soedarsono, (2015) explain that individual variations in the metabolism of anti-tuberculosis drugs, particularly genetic polymorphisms in the NAT2, CYP2E1, and GSTM1 enzymes, can lead to differences in susceptibility to hepatotoxicity among individuals (Zhao et al., 2020). Overall, the chi-square results in this study indicate that no demographic risk factors were statistically proven to be associated with hepatotoxicity. The study findings are presented in Table 3 and Figure 1.

Table 3. Chi Square Analysis of the Relationship between Risk Factors and Hepatotoxic Events

Characteristic Patients	Hepatotoxicity	No Hepatotoxicity	Significant	Odds Ratio (OR)	CI 95%
Gender			0,304	0,455	0,114-1,806
Female	5	6			
Male	22	5			
Age			0,351	2,080	0,578-7,486
<60 year	15	13			
>60 year	12	5			
Phase of treatment			0,286	0,192	0.018-2,018
Initial Phase	26	15			
Advanced Phase	1	3			

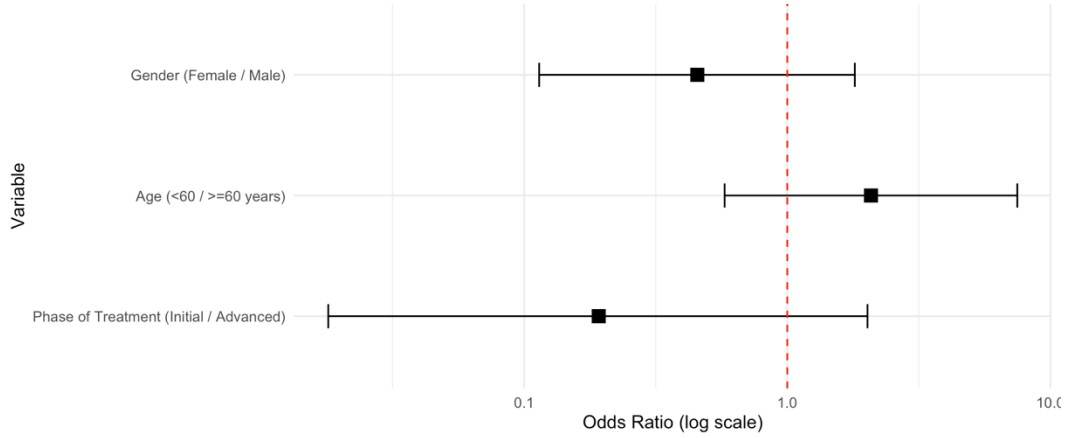

Figure 1. Odds Ratios of Hepatotoxicity by Risk Factor

CONCLUSION

Based on the research findings, the incidence of hepatotoxicity in tuberculosis patients at Ulin Banjarmasin Regional General Hospital is considered quite high, but the majority of cases found are only mild (Grades 1 and 2). Statistical analysis shows no significant relationship between age, gender, or treatment phase and the severity of hepatotoxicity.

ACKNOWLEDGEMENTS

The author expresses gratitude to the Research and Community Service Institute (LPPM) of Lambung Mangkurat University for the financial support provided for this research (Nu. 1856/UN8.2/PG/2025). Gratitude is also extended to RSUD Ulin Banjarmasin for research permits and facilitating access to the necessary medical records.

BIBLIOGRAPHY

Adhanty, S., & Syarif, S. (2023). Kepatuhan Pengobatan pada Pasien Tuberkulosis dan Faktor-Faktor yang Mempengaruhinya: Tinjauan Sistematis. *Jurnal Epidemiologi Kesehatan Indonesia*, *7*(1). https://doi.org/10.7454/epidkes.v7i1.6571

Andrade, R. J., Aithal, G. P., Björnsson, E. S., Kaplowitz, N., Kullak-Ublick, G. A., Larrey, D., & Karlsen, T. H. (2019). EASL Clinical Practice Guidelines: Drug-induced liver injury. *Journal of Hepatology*, *70*(6), 1222–1261. https://doi.org/10.1016/j.jhep.2019.02.014

Bawonte, T. G., Mambo, C. D., & Masengi, A. S. R. (2021). Faktor-Faktor yang mempengaruhi Tuberculosis Multidrug Resistance (MDR-TB).

EBiomedik, *9*(1), 117–125. https://doi.org/10.35790/ebm.9.1.2021.31949

Clarasanti, I., Wongkar, M., & Waleleng, B. J. (2016). Gambaran enzim transaminase pada pasien tuberkulosis paru yang diterapi dengan obat-obat anti tuberkulosis di RSUP Prof. Dr. R.D. Kandou Manado. *Jurnal E-Clinic (ECl)*, *4*(1), 1–6.

Dasuki, A., Muti, A. F., & Yusmaini, H. (2020). Faktor Resiko Kejadian Peningkatan Kadar Transminase pada Penggunaan Obat Antituberkulosis Pasien Tuberkulosis Paru di RST Wijayakusuma Purwakerto. *Jurnal Farmasi Indonesia*, *12*.

Wahyudi, A. D., & Soedarsono. (2015). Farmakogenomik Hepatotoksisitas Obat Anti Tuberkulosis. *Respirasi*, *1*, 103–108.

Mahartati, N. M. N., & Syarif, S. (2024). Risk Factors of Treatment Failure among Pulmonary Tuberculosis Patients: Systematic Review. *Media Publikasi Promosi Kesehatan Indonesia*, *7*(4), 899–906. https://doi.org/10.56338/mppki.v7i4.5157

Permata Sari, D., & Andriani, V. (2024). Kajian Hubungan Penggunaan Obat Antituberkulosis Fase Awal Terhadap Kadar Sgot-Sgpt Pada Pasien Tbc Paru Di Rsud Pasar Rebo Jakarta. *Jurnal Kesehatan Tambusai*, *5*(4), 10783–10792.

Rifai, A., Herlianto, B., Mustika, S., Pratomo, B., & Supriono. (2015). Insiden dan Gambaran Klinis Hepatitis Akibat Obat Anti Tuberkulosis di Rumah Sakit Umum Daerah Dr. Saiful Anwar Malang. *Jurnal Kedokteran Brawijaya*, *28*(3), 238–241.

Safira, Z., Sudarwati, S., & Alam, A. (2018). Profil Pasien Tuberkulosis Anak dengan Anti-tuberculosis Drug Induced Hepatotoxicity di Rumah Sakit Umum Pusat Dr. Hasan Sadikin Bandung. *Sari Pediatri*, *19*(5), 290–294.

Deliananda, S. S., & Azizah, R. (2022). Faktor Resiko Kejadian Tuberkulosis Paru di Indonesia Tahun 2014-2021 : Literature Review. *Media Publikasi Promosi Kesehatan Indonesia*, *5*(9), 1054–1062. https://doi.org/10.31934/mppki.v2i3

Sandi, D. A. D., Nurrahma, I. M., & Isnani, N. (2025). Karakteristik Pasien TB Resisten Obat di Kalimantan Selatan: Studi Korelasi terhadap Kesiapan Implementasi Regimen BPaL/M. *Borneo Journal of Pharmascientech*,

09, 247–258. https://doi.org/10.59053/bjp.v9i2.738

Wang, N., Chen, X., Hao, Z., Guo, J., Wang, X., Zhu, X., Yi, H., Wang, Q., & Tang, S. (2022). Incidence and Temporal Trend of Antituberculosis Drug-Induced Liver Injury: A Systematic Review and Meta-Analysis. *Journal of Tropical Medicine*, *2022*. https://doi.org/10.1155/2022/8266878

Wardhana, M. F., Milanda, T., & Sumiwi, S. A. (2018). Assessment of Risk Factors of Hepatotoxicity among Tuberculosis Patients. *Pharmacology and Clinical Pharmacy Research*, *3*(1). https://doi.org/10.15416/pcpr.v3i1.16450

Wiyati, T., Irawati, D., & Budiyono, I. I. (2014). Studi Efek Samping Obat Dan Penanganannya Pada Pasien Tb Paru Di Puskesmas Melong Asih, Cimahi. *JSTFI Indonesian Journal of Pharmaceutical Science and Technology*, *III*(1).

Zhao, H., Wang, Y., Zhang, T., Wang, Q., & Xie, W. (2020). Drug-induced liver injury from anti-tuberculosis treatment: A retrospective cohort study. *Medical Science Monitor*, *26*. https://doi.org/10.12659/MSM.920350