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Assessment of Risk Factors of Hepatotoxicity among Tuberculosis Patients

Muhammad F. Wardhana[1], Tiana Milanda[2], Sri A. Sumiwi[2]

[1]Dr. H. Abdul Moeloek General Hospital, Bandar Lampung, Lampung, Indonesia
[2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Jatinangor, West Java, Indonesia

Abstract

Tuberculosis is a devastating disease caused by *Mycobacterium tuberculosis*. If left untreated or not properly treated, it could lead to progressive tissue damage and even death. Short-term chemotherapy containing isoniazid, rifampicin. and pyrazinamide were proven to be very effective in the treatment of TB. However, the concern regarding its potential hepatotoxicity might hinder the completion of treatment. Information regarding risk factor of hepatotoxicity among Indonesian tuberculosis patients were limited. This study aimed to investigate risk factors of hepatotoxicity among Indonesian tuberculosis patients. This was a case-control study with retrospective approach conducted at one of the public hospital in Lampung, Indonesia. We included 320 tuberculosis patients who were classified as case (64 patients who were diagnosed with hepatotoxicity during hospitalization) and control (256 patients). Results of multivariate logistic regression analysis showed that age was significant risk factor of hepatotoxicity (adjusted odds ratio (OR) 1.056, 95% CI 1.0121, 1.091), while longer duration of hospitalization had a 1.4 lower odds of hepatotoxicity compared to control (adjusted OR 0.757, 95% CI 0.682, 0.839) ($p<0.005$). The results indicated that older patients were more likely to have hepatotoxicity, while patients with shorter duration of hospitalization tend to have higher risk of hepatotoxicity. In conclusion, age was the risk factor associated with hepatotoxicity among tuberculosis patients.

Keywords: tuberculosis, hepatotoxicity, age, hospitalization

Introduction

Tuberculosis remains a major global public health problem, causing approximately 10 million deaths annually. It is caused by *Mycobacterium tuberculosis*. If left untreated or not properly treated, it could lead to progressive tissue damage and even death.[1,2]

Short-term chemotherapy containing isoniazid (INH), rifampicin (RMP) and pyrazinamid (PZA) were shown to be very effective in the treatment of TB. However, previous study showed that about 15% of the patients could not complete the treatment

Corresponding author: Muhammad F. Wardhana. Dr. H. Abdul Moeloek General Hospital, Bandar Lampung, Lampung, Indonesia. Email: fitrawardhana23@gmail.com
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due to adverse effect associated with tuberculosis drugs. Hepatotoxicity is one of the most common adverse effect causing discontinuation of treatment with INH, RMP, and PZA.[3]

The time interval between initial anti-tuberculosis treatment and the onset of symptoms of hepatotoxicity varies between 3-135 days. In most cases, hepatitis occurs within three months from the beginning of anti-tuberculosis treatment.[4] The pathogenesis of drug-induced hepatotoxicity is still not completely clear. Hypersensitivity is a possible cause of RMP inducing hepatitis, occurring as part of systemic allergic reaction due to unconjugated hyperbilirubinemia which is the result of competition with bilirubin for absorption in plasma hepatocyte membranes. RMP induced hepatotoxicity is more prevalent than that of INH.[5,6]

Indonesia is one of the country with highest tuberculosis burden, worldwide. Information regarding risk factor of hepatotoxicity among Indonesian tuberculosis patients were limited. This study aimed to investigate risk factors of hepatotoxicity among Indonesian tuberculosis patients.

Methods

Research subject and data retrieval

This was a case-control study with retrospective approach conducted at one of the public hospital in Lampung, Indonesia. This study was approved by Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran. This study extracted the data from patient medical records. In this study, the case was a group of tuberculosis patients who experienced hepatotoxicity during hospitalization. The controls

Table 1. Characteristics of participants

Characteristics	Group	
	Hepatotoxicity (%) (n=64)	Non-hepatotoxocity (%) (n=256)
Sex		
Male	41(64)	144 (56.25)
Female	23 (36)	112 (43.75)
Age	36.8 (±11.6)	32.5 (±8.7)
Duration of TB (month)	3.59	2.83
Hospitalization (days)	8.3 (±3.8)	11.3 (±3.7)
Treatment of TB		
Intensive (2 months)	15 (23.4)	83 (84.7%)
Advanced (4 months)	49 (76.6)	173 (77.9%)
Concurrent disease		
Yes	6 (9.3%)	27 (10.5%)
No	58 (90.7%)	229 (89.5%)
Concomitant medication		
Yes	4 (6.25%)	20 (7.8%)
No	60 (93.75%)	236 (92.2%)
Alcohol		
Yes	6 (9.3%)	29 (11.3%)
No	58 (90.7%)	227 (88.7%)

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were patients who did not experience hepatotoxicity. Criteria for the case were subjects who received first-line anti-tuberculosis treatment for at least two months until the onset of symptoms of hepatotoxicity occurred.

Subjects were recruited by purposive sampling method, a non-probability sampling method based on the judgment of the clinical investigators. The inclusion criteria in this study were tuberculosis patients admitted to one public hospital in Lampung, Indonesia during January 2014 to December 2015, aged 18-60 years, had complete medical data, and had normal baseline liver function, *i.e.,* aspartate aminotransferase (AST) <48 u/l, alanine aminotransferase (ALT) <55 u/l, serum bilirubin <1.5 mg/dl.

The exclusion criteria in this study were tuberculosis patients who received other drugs known to be metabolized by the liver (by cytochrome P450 3A4 or P-glycoprotein), experienced multidrug resistant tuberculosis (MDR-TB), were diagnosed with hepatitis A, B, C or E or carrier for HBV & HCV, HIV-positive patients, had chronic liver disease, consumed another hepatotoxic drugs, such as methotrexate, phenytoin, and valproate, experienced malabsorption or drug abuse, were pregnant and lactating women, and had incomplete medical data.

Measurement of variables

The independent variables measured in this study were the clinical characteristics that were estimated to induce hepatotoxicity, *i.e.,* age, sex, concurrent disease, alcohol consumption, duration of tuberculosis treatment, concomitant medication, and duration of hospitalization. The dependent

Table 2. Risk factors of hepatotoxicity

Variables	Hepatotoxicity		P-value
	Case	Control	
Sex			
Male	41 (22.2%)	144 (77.8%)	0.258
Female	23 (17.0%)	112 (83.0%)	
Concomitant disease			
Yes	58 (20.2%)	229 (79.8%)	0.783
No	6 (18.2%)	27 (81.8%)	
Alcohol consumption			
No	58 (20.4%)	227 (79.6%)	0.654
Yes	6 (17.1%)	29 (82.9%)	
Concomitant drugs			
No	60 (20.3%)	236 (79.7%)	0.796
Yes	4 (16.7%)	20 (83.3%)	
Duration of treatment			
≤ 2 months	15 (15.3%)	83 (84.7%)	0.163
> 2 months	49 (22.1%)	173 (77.9%)	
Age (years)	36.8 (±11.6)	32.5 (±8.7)	0.007
Hospitalization (days)	8.3 (±3.8)	11.3 (±3.7)	< 0.001

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variables measured in this study were the results of liver function tests, including AST, ALT, and bilirubin levels. Concurrent diseases included hypertension, coronary arterial disease, congestive heart failure, dyslipidemia, infection, chronic kidney disease, cancer and cirrhosis.

Statistical analysis

Numerical data was presented as mean ± SD (standard deviation) and analyzed by t-test or Mann-Whitney test. Categorical data was presented as percentage (%) of frequency and analyzed by Chi-square test or Fisher's exact test. P<0.05 defined statistical significance. Multivariate analysis was performed to determine the the association between various characteristics and liver function.

Results and Discussion

We included 320 tuberculosis patients who were classified as case (64 patients diagnosed with hepatotoxicity during hospitalization) and control (256 patients). The subjects were in the either intensive or advanced tuberculosis treatment phase. About half (57.8%) of the subjects were male. The mean age of the subjects was 36.8 years. The mean duration of TB treatment was 3.21 months, while the mean of length of hospitalization was 9.8 days.

Bivariate analysis results can be found in Table 2. Bivariate analysis showed that there was no association between the presence of comorbidities, the use of concomitant medications, and alcohol consumption on the risk of hepatotoxicity. Age and the length of hospitalization influenced the risk of hepatotoxicity.

The same findings were observed in multivariate logistic regression analysis showing that that age was significant risk factor of hepatotoxicity (adjusted odds ratio (OR) 1.056, 95% CI 1.0121, 1.091), while longer duration of hospitalization had a 1.4 lower odds of hepatotoxicity compared to the control (adjusted OR 0.757, 95% CI 0.682, 0.839) (p<0.005). The results indicated that older patients were more likely to have hepatotoxicity, while patients with shorter duration of hospitalization tend to have higher risk of hepatotoxicity. The results can be found in the table 3.

Hepatotoxicity may occur at appropriate doses at any time during treatment. It could

Table 3. Multivariate analysis of hepatotoxicity risk factors

Factors	b	SE(b)	P-Value	OR	95.0% CI	
Sex	0.354	0.317	0.265	1.425	0.765	- 2.654
Age	0.054	0.017	0.001	1.056	1.021	- 1.091
Concurrent disease	0.245	0.608	0.688	1.277	0.388	- 4.207
Alcohol consumption	0.302	0.515	0.557	1.353	0.493	- 3.711
Hospitalization	-0.279	0.053	0.000	0.757	0.682	- 0.839
Concomitant medication	0.843	0.669	0.208	2.323	0.626	- 8.615
TB treatment duration	-0.299	0.355	0.400	0.742	0.370	- 1.487
Constant	-1.981	1.279	0.121	0.138		

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cause the interruption of the therapy. The exact mechanism of RMP induced hepatotoxicity is not well established but it was estimated that its metabolites are toxic to the liver. Idiosyncratic reaction was associated with the use of INH. Combination of INH and RMP increases the risk of hepatotoxicity.

Our finding is comparable with previous study showing that age is the risk factors of hepatotoxicity. The elderly might be vulnerable to this ADR because liver function could decrease with age.[8] This vulnerable group requires careful clinical monitoring of liver function over the period of tuberculosis treatment.

In contrast with previous finding,[9] we observed that alcohol consumption was not significantly associated with drug-induced hepatotoxicity. However, the OR was more than 1 (adjusted OR 1.353 95% CI 0.493-3.711), which indicate positive association between alcohol consumption and hepatotoxicity. Relatively limited sample size in this study might prevent the findings from being extrapolated, which could result in different final result with other studies.[10]

Conclusion

In conclusion, age was the risk factor associated with hepatotoxicity among tuberculosis patients.

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Conflict of Interest

None declared

References

1. Sulis G, Roggi A, Matteelli A, *et al*. Tuberculosis: epidemiology and control. *Mediterranean Journal of Hematology and Infectious Diseases*. 2014;6(1):2014.070.
2. Zaman K. Tuberculosis: a global health problem. *Journal of Health, Population, and Nutrition*. 2010;28(2):111-113.
3. Ramappa V, Aithal GP. Hepatotoxicity related to anti-tuberculosis drugs: mechanisms and management. *Journal of Clinical and Experimental Hepatology*. 2013;3(1):37-49.
4. Babalık A, Arda H, Bakırcı N, *et al*. Management of and risk factors related to hepatotoxicity during tuberculosis treatment. *Tuberkulosis Toraks*. 2012;60(2):136-144
5. Abbara A, Chitty S, Roe JK, *et al.* Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. *BMC Infectious Diseases*. 2017;17:231.
6. Bliven EE, Podewils LJ. The role of chronic hepatitis in isoniazid hepatotoxicity during treatment for latent tuberculosis infection. *International Journal of Tuberculosis Lung Diseases.* 2009;13:1054-1060.
7. Bouazzi OE, Hammi S, Bourkadi JE, *et al.* First line anti-tuberculosis induced hepatotoxicity: incidence and risk factors. *The Pan African Medical Journal.* 2016;25:167.
8. Abbasi MA, Ahmed N, Suleman A, *et al.* Common risk factors for the development of anti tuberculosis treatment induced hepatotoxicity. *Journal of Ayub Medical College Abbottabad.* 2014;26:384–388.
9. Abera W, Cheneke W, Abebe G. Incidence of antituberculosis drug induced hepatotoxicity and associated risk factors among tuberculosis patients in Dawro Zone, South Ethiopia: a cohort study.

International Journal of Mycobacteriol. ogy. 2016;5:14-20.

10. Faber J, Fonseca LM. How sample size influences research outcomes. *Dental Press Journal of Orthodontics*. 2014;19(4):27-29.