

# Associations between the Adverse Drug Reactions and the Tuberculosis Treatment Dropout Rates at the Cempaka Putih Islamic Hospital in Jakarta, Indonesia

Indrianti Asril, Vivian Soetikno, Purwastyastuti Ascobat

Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

## Abstract

**Objective:** Tuberculosis (TB) treatment is associated with various adverse drug reactions (ADRs). The aim of this study was to determine the associations between ADRs and the rate of TB treatment dropout among the patients at Cempaka Putih Islamic Hospital in Jakarta, Indonesia. **Materials and Methods:** A cross-sectional study was conducted based on the medical records of the TB patients treated at Lung Polyclinic of Cempaka Putih Islamic Hospital between January 2016 and December 2017. **Results:** Of 178 study participants, 80 had a history of ADR while the other 98 did not. There were statistically significant relationships between the rate of TB treatment dropout and the characteristics of patient, including the age ( $P = 0.022$ , prevalence ratio [PR] = 0.599, 95% confidence interval [CI] = 0.408–0.870) and ADR type ( $P = 0.001$ , PR = 5.333, 95% CI = 1.402–20.285). Furthermore, there were significant relationships between ADRs and comorbid disease ( $P = 0.000$ , PR = 1.871, 95% CI = 1.370–2.555). However, ADR treatment status based on the given guidelines does not have a statistically significant relationship with the rate of TB treatment dropout ( $P = 0.172$ , PR = 2.028, 95% CI = 0.582–7.071). **Conclusion:** The results of this study showed that age and ADR type significantly increased the prevalence of the rate of TB treatment dropout among our patient cohorts.

**Keywords:** Adverse drug reaction, anti-tuberculosis drugs, patient dropouts, tuberculosis

## INTRODUCTION

Tuberculosis (TB) is the ninth leading cause of death worldwide, and it is the leading cause of death from a single infectious agent, ranking above the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome.<sup>[1-3]</sup> In 2016, the rate of TB incidence in Indonesia was approximately 39/100,000 people, with a death rate of 42/100,000 people.<sup>[1]</sup> Anti-TB drugs have been associated with adverse drug reactions (ADRs), which are classified as either minor or major.<sup>[2,3]</sup> These ADRs can cause patients to stop using drugs, which can lead to drug resistance and therapeutic failure.<sup>[4]</sup> Minor ADRs are more common than severe ADRs,<sup>[5]</sup> and several studies have confirmed that there is a significant relationship between ADRs and TB treatment dropouts.<sup>[3,4,6-9]</sup> Hence, in this study, we assessed the associations between ADRs and the rate of TB treatment dropout among our patients cohorts.

## MATERIALS AND METHODS

The medical records of the TB patients admitted to Lung Polyclinic of the Cempaka Putih Islamic Hospital in Jakarta, Indonesia, between January 2016 and December 2017 were retrospectively analyzed using a cross-sectional study design. A total of 178 newly diagnosed lung TB patients were enrolled in the study after applying the inclusion and exclusion criteria. The study participants consisted of 70 patients who completed their TB treatments and 108 patients who dropped out of their treatments. The inclusion criteria were as follows: patients being treated with first-line anti-TB drugs who had readable medical records. The exclusion criteria were as follows: patients

**Address for correspondence:** Dr. Vivian Soetikno,  
Salemba Raya No. 6, Jakarta 10430, Indonesia.  
E-mail: vivian\_09st@yahoo.com

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**Table 1: Characteristics of the patients included in this study**

Variable	Treatment results	
	Completed treatment (n=70)	Dropped out (n=108)
Gender, n (%)		
Male	42 (60.0)	53 (49.1)
Female	28 (40.0)	55 (50.9)
Age, n (%)		
Productive (aged 15-64)	55 (78.6)	98 (64.1)
Nonproductive	15 (21.4)	10 (40.0)
Education, n (%)		
Primary school	5 (7.1)	7 (6.5)
Junior high school	6 (8.6)	12 (11.1)
Senior high school	29 (41.4)	52 (48.1)
Bachelor's degree	16 (22.6)	25 (23.1)
Unknown	12 (17.1)	12 (11.1)
Comorbid disease, n (%)		
Diabetes mellitus	18 (25.7)	14 (13.0)
Hypertension	1 (1.4)	6 (5.6)
Human immunodeficiency virus	4 (5.7)	7 (6.5)
Cardiovascular disease	2 (2.6)	4 (3.7)
Other	1 (1.4)	2 (1.9)
None	39 (55.7)	75 (69.4)
Work status, n (%)		
Unemployed	33 (47.1)	42 (38.9)
Government employee	6 (8.6)	13 (12.0)
Private employee	26 (37.1)	53 (49.1)
Nutritional status (body mass index), n (%)		
Underweight ( $\leq 18.4$ kg/m <sup>2</sup> )	31 (44.3)	54 (50.0)
Normal weight (18.5-25.0 kg/m <sup>2</sup> )	26 (37.1)	47 (43.5)
Overweight ( $>25.1$ kg/m <sup>2</sup> )	8 (11.4)	7 (6.5)

with extrapulmonary TB, TB patients that were not evaluated, pediatric patients, and patients with failed treatments.

All the statistical analyses were performed using IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA). The values were expressed using the prevalence ratio (PR) and 95% confidence interval (CI).  $P < 0.05$  was considered to be statistically significant, and the Chi-square and Fisher's exact tests were used to analyze the data. The study was reviewed and approved by the Institutional Ethics Committee of the Faculty of Medicine at the University of Indonesia.

## RESULTS

About 50.9% of female and 49.1% of male patients dropped out of treatment. The other demographics of patients who dropped out included, productive age individuals (aged 15–64) (64.1%), high school graduates (48.1%), privately employed individuals (49.1%), and underweight individuals (based on the body mass index) (50.0%) [Table 1]. Major ADRs was the most common reason for the patients to drop out of treatment [Table 2].

A statistically significant difference between comorbid diseases and ADRs ( $P = 0.000$ , PR = 1.871, 95% CI = 1.370–2.555)

**Table 2: Adverse drug reactions of the study participants**

Variable	Treatment results		Total, n (%)
	Completed treatment	Dropped out	
Minor ADR, n (%)			
Nausea	23 (53.5)	20 (46.5)	43 (100.0)
Vomiting	8 (50.0)	8 (50.0)	16 (100.0)
Decreased appetite	11 (45.8)	13 (54.2)	24 (100.0)
Stomachache	8 (57.1)	6 (42.9)	14 (100.0)
Joint pain	3 (75.0)	1 (25.0)	4 (100.0)
Neuropathy	0 (0.0)	0 (0.0)	0 (0.0)
Reddish urine	0 (0.0)	0 (0.0)	0 (0.0)
Major ADR, n (%)			
Liver dysfunction	1 (7.7)	12 (92.3)	13 (100.0)
Skin rash	1 (14.3)	6 (85.7)	7 (100.0)
Hearing disorder	0 (0.0)	1 (100.0)	1 (100.0)
Visual impairment	0 (0.0)	0 (0.0)	0 (0.0)

ADR: Adverse drug reactions

was observed [Table 3]. There were statistically significant differences between the patient's age and the treatment outcome ( $P = 0.022$ , PR = 0.599, 95% CI = 0.408–0.879) [Table 4]. A statistically significant difference between the types of

**Table 3: Correlations between the patient characteristics and the adverse disease reactions**

Variable	ADR		PR	95% CI	P
	ADR+, n (%)	ADR-, n (%)			
Gender, n (%)					
Male (n=95)	40 (42.1)	55 (57.9)	0.874	0.632-1.209	0.415
Female (n=83)	40 (48.2)	43 (51.8)			
Age, n (%)					
Productive (n=153)	67 (43.8)	86 (56.2)	0.842	0.555-1.278	0.444
Nonproductive (n=25)	13 (52.0)	12 (48.0)			
Education, n (%)					
Primary school (n=12)	9 (75.0)	3 (25.0)	2.250	1.171-4.324	0.184
Junior high school (n=20)	8 (40.0)	12 (60.0)	1.200	0.560-2.617	
Senior high school (n=81)	38 (46.9)	43 (53.1)	1.407	0.764-2.594	
Bachelor's degree (n=41)	17 (41.5)	24 (58.5)	1.244	0.635-2.437	
Unknown (n=24)	8 (33.3)	16 (66.7)			
Comorbid disease, n (%)					
Yes (n=62)	40 (64.5)	22 (35.5)	1.871	1.370-2.555	0.000
No (n=116)	40 (34.5)	76 (65.5)			
Work status, n (%)					
Unemployed (n=101)	41 (40.6)	60 (59.4)	0.801	0.580-1.107	0.182
Employed (n=77)	39 (50.6)	38 (49.4)			
Nutritional status (BMI), n (%)					
Underweight ( $\leq 18.4$ kg/m <sup>2</sup> ) (n=88)	38 (43.2)	50 (56.8)	1.295	0.609-2.756	0.470
Normal weight (18.5-25.0 kg/m <sup>2</sup> ) (n=75)	37 (49.3)	38 (50.7)			
Overweight ( $> 25.1$ kg/m <sup>2</sup> ) (n=15)	5 (33.3)	10 (66.7)	1.480	0.698-3.138	

PR: Prevalence ratio, CI: Confidence interval, BMI: Body mass index

**Table 4: Correlations between the patient characteristics and the treatment results**

Variable	Treatment results		PR	95% CI	P
	Completed treatment, n (%)	Dropped out, n (%)			
Gender, n (%)					
Male (n=95)	42 (44.2)	53 (55.8)	1.311	0.899-1.910	0.153
Female (n=83)	28 (33.7)	55 (66.3)			
Age, n (%)					
Productive (n=153)	55 (35.9)	98 (64.1)	0.599	0.408-0.879	0.022
Nonproductive (n=25)	15 (60.0)	10 (40.0)			
Education, n (%)					
Primary school (n=12)	5 (41.7)	7 (58.3)	0.833	0.382-1.810	0.809
Junior high school (n=20)	8 (40.0)	12 (60.0)	0.800	0.410-1.563	
Senior high school (n=81)	29 (35.8)	52 (64.2)	0.716	0.436-1.175	
Bachelor's degree (n=41)	16 (39.0)	25 (61.0)	0.780	0.449-1.358	
Unknown (n=24)	12 (50.0)	12 (50.0)			
Comorbid disease, n (%)					
Yes (n=62)	29 (46.8)	33 (53.2)	1.323	0.921-1.901	0.137
No (n=116)	41 (35.3)	75 (64.7)			
Work status, n (%)					
Unemployed (n=101)	35 (34.7)	66 (65.3)	0.762	0.530-1.096	0.144
Employed (n=77)	35 (45.5)	42 (54.5)			
Nutritional status (BMI), n (%)					
Underweight ( $\leq 18.4$ kg/m <sup>2</sup> ) (n=88)	34 (38.6)	54 (61.4)	0.724	0.421-1.245	0.503
Normal weight (18.5-25.0 kg/m <sup>2</sup> ) (n=75)	28 (37.3)	47 (62.7)	0.700	0.401-1.222	
Overweight ( $> 25.1$ kg/m <sup>2</sup> ) (n=15)	8 (53.3)	7 (46.7)			

PR: Prevalence ratio, CI: Confidence interval, BMI: Body mass index

ADR and the results of the treatment ( $P = 0.001$ ,  $PR = 5.333$ ,  $95\% \text{ CI} = 1.402-20.285$ ) was also observed [Table 5].

More patients with major ADRs who dropped out of treatment than patients with minor ADRs.

There was no statistically significant difference between the status of ADR therapy and the results of the treatment ( $P = 0.073$ , PR = 0.403, 95% CI = 0.307–0.528) [Table 6]. Statistically significant differences were not observed between the status of ADR therapy according to the guidelines and the treatment outcome ( $P = 0.172$ , PR = 2.028, 95% CI = 0.582–7.071) [Table 7].

## DISCUSSION

In this study, among 178 patients, there were more male patients (53.4%) than female patients (46.6%), which was consistent with WHO Global TB Report.<sup>[1]</sup> In worldwide, comparison rates between male and female TB patients are 1.9:1.<sup>[10]</sup> This is because smoking, which is one of the high-risk factors for TB is more common in men than women. Cigarette smoke has immunosuppressive effects on the airway's immune system,<sup>[1,10-12]</sup> making patient in productive age more susceptible to TB infections.<sup>[12-16]</sup> Diabetes mellitus (DM) was also the most common comorbidities in this study. Diabetes increases the risk of TB by three folds (relative risk 3.11; 95% CI 2.27–4.26),<sup>[17]</sup> and currently, there are more TB patients with comorbid DM than HIV.

The most common ADRs were nausea, vomiting, and decreased appetite. The World health organization reported in 2008 that dyspepsia is one of the complaints which caused 23% of patients stop treatment in the intensive phase.<sup>[3]</sup>

Nausea, vomiting, decreased appetite, and abdominal pain can occur as a result of the drugs and their metabolites that work as chemical mutagens which stimulate vagus nerve afferent and release of 5-HT which then stimulates the vomiting center at the brain stem.<sup>[18]</sup> These symptoms can be overcome by using anti-TB drugs 2 h after eating or while sleeping and by taking ranitidine, metoclopramide, or omeprazole.<sup>[18-20]</sup> A significant relationship between drop out of treatment and age of patients was observed, which is consistent with similar previous study.<sup>[21]</sup> Among 178 patients, there were 80 patients who had a history of ADRs, and the type of ADRs also influenced the patient to drop out. More patients with major ADRs dropped out of treatment than patients with minor ADRs. However, the status of ADR therapy did not influence the results of the treatment because dropout was influenced by the lack of knowledge of patients about TB, lack of supervision on taking medicines, and the patients perception of being healed.<sup>[17,21,22]</sup> We conclude that TB patients with major ADRs are at a higher risk of dropping out of treatment (90%).

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**Table 5: Correlations between the adverse disease reaction types and the treatment results**

Variable	Treatment result		PR	95% CI	P
	Completed treatment (n=34)	Dropped out (n=46)			
ADR type, n (%)					
Minor	32 (53.3)	28 (46.7)	5.333	1.402-20.285	0.001
Major	2 (10.0)	18 (90.0)			

CI: Confidence interval, PR: Prevalence ratio, ADR: Adverse disease reaction

**Table 6: Correlations between the adverse disease reaction therapy status and the treatment results**

Variable	Treatment result		PR	95% CI	P
	Completed treatment (n=34)	Dropped out (n=46)			
ADR therapy					
Yes	31 (40.3)	46 (59.7)	0.403	0.307-0.528	0.073*
No	3 (100.0)	0 (0.0)			

\*Fisher's exact test. PR: Prevalence ratio, CI: Confidence interval, ADR: Adverse disease reaction

**Table 7: Correlations between the adverse drug reaction therapy status according to the guidelines and the treatment results**

Variable	Treatment result		PR	95% CI	P
	Completed treatment (n=34)	Dropped out (n=46)			
ADR therapy according to guidelines					
Yes	32 (45.1)	39 (54.9)	2.028	0.582-7.071	0.172*
No	2 (22.2)	7 (77.8)			

\*Fisher's exact test. PR: Prevalence ratio, CI: Confidence interval, ADR: Adverse disease reaction

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### Conflicts of interest

There are no conflicts of interest.

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