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Adverse events among pulmonary drug-resistant tuberculosis patients in Banten, Indonesia

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ABSTRACT: Drug-resistant Tuberculosis (DR-TB) treatment requires an extended duration, making adverse events (AEs) a common concern. This study aimed to assess the frequency of AEs, time to events, and their association with treatment outcomes among DR- pulmonary TB patients. A retrospective cohort study was conducted on patients aged >18 years at one of public hospitals at Tangerang, Banten, Indonesia, from March 2021 to May 2023. Bivariate analysis was used to analyze the association between AEs and treatment outcomes. Among 53 patients included in the study, all experienced at least one AEs. Number of AEs mean ± SD; 9.724±4.86. Mild AEs were reported in 100% of patients, while 75.5% experienced moderate AEs, and 81.1% experienced severe AEs. The most common AEs included nausea (90.6%), anemia (73.6%), vomiting (62.3%), decreased appetite (60.4%), and joint pain (60.4%). The AEs were frequently reported during intensive phase (4-6 months). AEs have association with treatment outcome (P<0.05). The frequency of AE among DR-TB patients was high. Early detection and effective management of AEs are essential to improving treatment outcomes for DR-TB patients.

KEYWORDS: Adverse events; drug-resistant tuberculosis; treatment outcome.

INTRODUCTION

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis*, remains a significant global health challenge, mainly in Indonesia. According to the Global TB Report 2023, Indonesia ranks as the country with the second-highest number of TB cases worldwide, following India. In addition, Indonesia is listed among the 10 countries with the highest burdens of drug-resistant TB (DR-TB) [1]. Drug-resistant tuberculosis (DR-TB) can develop from inadequate treatment of TB patients or transmission from individuals already infected with DR-TB. Various factors contribute to the development of resistance to anti-tuberculosis drugs, such as previous TB treatment, patient age, family support, education level, distance to healthcare facilities, adherence to medication, treatment monitoring, coexisting health conditions, and the occurrence of side effects [2].

The treatment for drug-resistant tuberculosis (DR-TB), including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), is both challenging and time-consuming, often requiring 18 to 24 months of therapy. Patients are typically prescribed a larger number of second-line drugs, which are more toxic and significantly increase the risk of adverse events (AEs). In recent years, the World Health Organization (WHO) has introduced newer treatment regimens, such as BPaL (Bedaquiline, Pretomanid, and Linezolid) and BPaLM (with the addition of Moxifloxacin), which reduce the treatment duration to six months [3]. However, while these regimens offer for shorter treatment periods, their safety profiles and the potential for AEs remain areas of concern that require further investigation.

The prevalence of adverse events (AEs) among patients with drug-resistant tuberculosis (DR-TB) is notably high. Studies have shown that 90.7% of DR-TB patients in China [4] and 87.7% in Africa [5] experienced AEs during treatment. The frequency and types of AEs reported vary across studies, reflecting the complexity of managing these cases. While some studies highlight gastrointestinal disturbances as the most common AEs [6], others report hepatotoxicity [5]and depression [7] as frequently encountered side effects. These variations underscore the need for a deeper understanding of AEs in DR-TB treatment.

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Additionally, the relationship between AEs and treatment outcomes remains inconsistent. Some studies suggest a significant association between AEs, especially for lost t0 follow up [8], while others find no such correlation [7]. Given these discrepancies, further research is essential better to understand the impact of AEs on DR-TB management. This study aims to investigate the frequency of AEs, time to event, and their association with treatment outcomes in one of public hospitals in Tangerang, Banten.

▪ MATERIALS AND METHODS

Design and setting

This research was conducted using a retrospective cohort study at one of the public hospitals in Tangerang, Banten, Indonesia. The entry cohort includes patients who began anti-tuberculosis treatment for the first time and were followed until treatment outcomes were documented and any adverse events occurred The data source used was medical records and a Tuberculosis Information System application known as SITB. among pulmonary DR-TB patients from March 2021 to May 2023.

Population and sample

The population in this study consisted of all patients diagnosed with pulmonary DR-TB during the study period at one of hospitals in Tangerang, Banten. The inclusion criteria were pulmonary DR-TB patients aged over 18 years who had completed their treatment outcomes. Patients who transferred to other healthcare facilities did not initiate treatment, and pregnancy was excluded from this study.

Data collection procedure

We used a research form to collect the data from medical record and SITB. These data included sociodemographic data (sex, age, BMI, education level, working status, marital status, and distance from residence to hospital) and clinical data (duration of treatment, number of AEs, the severity of AEs, history of TB treatment, type of resistance, DM status, HIV status, comorbidities, adherence to hospital visit), and laboratory results. At each monthly visit, patients are closely monitored and evaluated for any AEs induced by anti-TB drugs by physicians and nurses based on patient complaints, abnormal laboratory data, or suspected AEs by physicians with reference to national and international (WHO) guidelines.

Operational definition

Adverse effects are systematically categorized based on the physiological systems or organs affected, in accordance with the classifications used in the Tuberculosis Information System application (SITB), such as Gastrointestinal, psychiatric, dermatologist, musculoskeletal, cardiovascular, otic, hepatotoxicity, nephrotoxicity, ocular, nervous system, hematology, hypothyroid, electrolyte.

We grouped AEs based on their severity into mild, moderate, and severe, as explained in Table 1 [9], [10].

Table 1. Severity of AEs.

Severity of AEs	Definition
Mild	Mild reactions are minor reactions but can interfere with patient compliance in taking medication, such as digestive disturbances (such as nausea, constipation, diarrhea), headaches, fatigue, vague muscle aches, malaise (a general feeling of illness or discomfort), and changes in sleep patterns.
Moderate	Moderate reactions are reactions that are very disturbing, troublesome, or intolerable, such as rashes (especially if they are extensive and persistent), visual disturbances (especially in people who wear corrective lenses), muscle tremors, difficulty with urination (a common effect of many medications in older men), any perceptible change in mood or mental function, and certain changes in blood components, such as a temporary, reversible decrease in the white blood cell count or in blood levels of some substances, such as glucose.
Severe	Severe reactions include those that may be life threatening (such as liver failure, abnormal heart rhythms, certain types of allergic reactions), those that result in persistent or significant disability or hospitalization, and those that cause birth defects.

According to the WHO's definitions and Reporting Framework Tuberculosis 2013 revision, treatment outcomes were categorized as successful or unsuccessful [11]. Successful treatment was defined as patients being declared cured by a physician after completing the prescribed treatment duration. Unsuccessful

treatment included patients who were declared treatment failures, those who were LTFU, and those who died. A failure was characterized as a regimen that had to be stopped and changed permanently due to ineffectiveness or adverse effects. LTFU was defined as patients who received treatment for at least four weeks, and the treatment was discontinued for more than eight consecutive weeks. Dead patients were those who died for any reason during the DR-TB treatment period [12].

Data analysis

Sociodemographic and clinical characteristics, the timing of adverse events (AEs), and treatment regimens were analyzed using descriptive statistics. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as means and standard deviations for data with normal distribution. Median and interquartile ranges (IQR) are used for data that is not normally distributed. We performed the Kolmogorov-Smirnov Test to identify the data distribution. A bivariate analysis using Chi-square or Fisher test was performed to examine the relationship between the severity and number of AEs and treatment outcomes. An Independent t-test was conducted to analyze continuous data on AEs and their association with treatment outcomes. Data analysis was conducted using SPSS (Statistical Package for the Social Sciences) software, with statistical significance defined as $P < 0.05$.

Ethical approval

This research was approved by the Ethics Committee number Un.01/F.10/KP.01.1/KE.SP/04.08.039/2023 from Syarif Hidayatullah State Islamic University in Jakarta.

▪ RESULTS AND DISCUSSION

Study participants

A total of 53 patients were included in this study, meeting the inclusion criteria of being DR-TB patients with final treatment outcomes at one of the public hospitals in Tangerang, Banten, Indonesia, from March 2021 to May 2023. Based on treatment outcomes, 13 patients (24.53%) achieved successful outcomes, while 40 patients (75.47%) experienced unsuccessful treatment, consisting of 9 treatment failures, 13 lost to follow-up cases, and 18 deaths.

Characteristic of patients

Table 2 provides an overview of the sociodemographic and clinical characteristics of the DR-TB patients included in the study. Most patients were male (56.6%), with a mean±SD of age 42.23±12.49. Regarding body mass index (BMI), 52.8% had abnormal BMI values (<18.5 or >25.0). Most patients had a low education level (86.8%) and were currently employed (58.5%). Additionally, a significant proportion of patients were married (71.7%). The median distance to the hospital was 9.35 km (IQR 6.88-13.43), and the median duration of treatment was 4 months (IQR 2.0-11.0). In terms of clinical characteristics, nearly half of the patients (47.2%) had no prior TB treatment history. The type of resistance was primarily rifampicin-resistant (60.4%), and 71.7% had long-term treatment. Additionally, common comorbidities included diabetes mellitus (39.6%) and HIV (3.8%). Adherence to treatment was 100% for only 22.6% of patients, highlighting challenges in maintaining consistent follow-up.

Table 3 provides an overview of the treatment regimens used during the intensive phase for DR-TB patients. The most used regimen was a combination of Bedaquiline (Bdq), Clofazimine (Cfz), Cycloserine (Cs), Levofloxacin (Lfx), and Linezolid (Lzd), accounting for 62.26% of patients. Other regimens with additional drugs such as Ethionamide (Eto), Isoniazid (H), and Pyrazinamide (Z) were less frequently used. Regarding individual anti-TB drugs, Clofazimine was used in all cases (100%), followed closely by Bedaquiline (98.11%) and Levofloxacin (96.23%).

Table 4 presents the types and frequencies of AEs experienced by pulmonary DR-TB patients. The most common AEs were gastrointestinal, accounting for 25.2% of all reported reactions, including nausea, mild vomiting, decreased appetite, and abdominal pain. Electrolyte disturbances (13.5%) were the second most frequent, with hypokalemia and hyponatremia being predominant. Musculoskeletal AEs (11.7%), such as joint pain and numbness/tingling, were also notable. Hematological effects, including anemia and thrombocytopenia, accounted for 8.0% of cases. Less frequent AEs included nervous system issues (5.9%),

dermatological reactions (5.5%), cardiovascular effects (4.3%), and psychiatric disturbances (2.9%). Rare AEs, such as nephrotoxicity, hepatotoxicity, otic effects (e.g., decreased hearing), ocular issues, and hypothyroidism, were also observed but occurred in fewer than 2% of patients.

Table 2. Sociodemographic and clinical characteristics of DR-TB patients (Total=53).

Characteristics		N (%)
Male sex		30 (56.6)
Age, years, mean±SD		42.23±12.49
Age (years)	<42	27 (50.9)
	>42	26 (49.1)
BMI (kg/m^2)	Normal (18.5-25.0)	25 (47.2)
	Not normal (<18.5 and >25.0)	28 (52.8)
Education level	High	7 (13.2)
	Low	46 (86.8)
Working status	Currently employed	31 (58.5)
	Otherwise	22 (41.5)
Marital status	Married	38 (71.7)
	Otherwise	15 (28.3)
Distance to Hospital (km), median (IQR)		9.35(6.88-13.43)
History of TB Treatment	New case	25 (47.2)
	Recurring cases	28 (52.8)
Type of resistance	MDR	21 (39.6)
	RR	32 (60.4)
Type of treatment duration	Short-term	15 (28.3)
	Longt-term	38 (71.7)
Actual duration in month, median (IQR)		4.0 (2.0-11.0)
DM, yes		21 (39.6)
Number	HIV, yes	2 (3.8)
	Other comorbidities, yes	24 (45.3)
Adherence to visit	100%	12 (22.6)
	<100%	41 (77.4)
Number of adverse events (AEs) occurred in one patient, Mean (SD)		9.72(4.86)
Severity of AEs	Mild	53 (100)
	Moderate	40 (75.5)
	Severe	43 (81.1)

Note: AEs, Adverse events; BMI, Body mass index; DM, diabetes mellitus; HIV, human immunodeficiency virus; MDR, multidrug-resistant; RR, rifampicin resistant.

Table 3. Overview of the treatment regimen among DR-TB patients (Total = 53).

Characteristics	N (%)
Type of treatment regimen in the intensive phase (year started), all oral regimens	
Bdq Cfz Cs Lfx Lzd	33 (62.26)
Bdq Cfz E Eto H Lfx Z	14 (26.42)
Bdq Cfz Cs E Lfx Lzd	2.0 (3.77)
Bdq Cfz Cs E Lfx	2.0 (3.77)
Bdq Cfz Cs E Lzd	1.0 (1.89)
Cfz Cs Eto Lzd	1.0 (1.89)
Anti-TB drug used	
Clofazimine	53 (100)
Bedaquiline	52 (98.11)
Levofloxacine	51 (96.23)
Cycloserine	39 (73.58)
Linezolid	37 (69.81)
Ethambutol	21 (39.62)
Etionamid	15 (28.30)
Isoniazid	14 (26.42)
Pirazinamide	14 (26.42)

Note: Bdq, bedaquiline; Cfz, clofazimine; Cs, cycloserine; E, ethambutol; Eto, Ethionamide; H, isoniazid; Lfx, levofloxacin; Z, pyrazinamide.

Table 4. Frequency of adverse events among pulmonary DR-TB adult patients at one of Hospitals in Tangerang, Banten from March 2021 to May 2023 (Total AEs=511).

AEs category	N(%)	Type of AEs
Gastrointestinal	129 (25.2)	Nausea (48), mild vomiting (33), decreased appetite (32), moderate to severe vomiting (8), abdominal pain (5), diarrhea (2), and flatulence (1)
Electrolyte	69 (13.5)	Hypokalemia (20), hyponatremia (19), hypocalcemia (15), hypernatremia (8), hypomagnesemia (6), and hyperkalemia (1)
Musculoskeletal	60 (11.7)	Joint pain (32), numbness/tingling (17), joint swelling (6), and ankle pain (5)
Hematology	41 (8.0)	Anemia (36), and thrombocytopenia (5)
Nervous system	30 (5.9)	Headache (21), vertigo (8), and seizures (1)
Dermatologist	28 (5.5)	Skin discoloration (25), rash (2), and allergic skin reaction (1)
Cardiovascular	22 (4.3)	QT prolongation (9), chest pain (9), and faster heart palpitations (4)
Psychiatric	15 (2.9)	Sleep disturbances (6), behavioral changes (5), depression/stress (3), and hallucinations (1)
Nephrotoxicity	10 (2.0)	Nephrotoxicity (10)
Hepatotoxicity	9 (1.8)	Hepatotoxicity (9)
Otic	4 (0.8)	Impaired hearing function (4)
Ocular	2 (0.4)	Blurred vision (2)
Hypothyroidism	1 (0.2)	Hypothyroidism (1)

Table 5 illustrates the number of patients and the time to adverse events (AEs) for the top 10 most frequent AEs among pulmonary DR-TB patients at a public hospital in Tangerang, Banten, Indonesia, between March 2021 and May 2023. Most patients reported AEs during the intensive phase of treatment (4–6 months), as indicated by the gray-shaded columns in the table. After 6 months, the number of patients experiencing AEs decreased. In addition, nausea was the most common AE, affecting 90.6% of patients, with symptoms primarily occurring during the initial phase and, in some cases, persisting for up to 21 months. Anemia, the second most common AE (73.6%), also occurred most frequently during the intensive phase of treatment. Mild vomiting was predominantly reported during the first 4 months of treatment.

Table 5. Number of patients and the time of adverse events among pulmonary DR-TB patients at one of the public hospitals in Tangerang, Banten, Indonesia (March 2021- May 2023).

Most frequently occurring Aes	n	%	Duration of AEs (month)																				
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Nausea	48	90.6	40	35	20	10	10	7	5	2	1	2	3	1									
Anemia	36	73.6	18	23	19	17	18	16	11	9	10	9	8	7	6	5	5	6	6	5	5	1	
Mild vomiting	33	62.3	20	19	8	4			1			1											
Loss of appetite	32	60.4	17	17	13	11	9	8	3	2	1												
Joint Pain	32	60.4	9	12	18	16	17	14	11	14	10	11	11	10	8	9	8	8	8	7	6	3	2
Changes in skin colour	25	47.2	6	10	18	16	17	14	12	13	12	11	11	7	7	8	8	8	8	7	4	1	
Headache/Dizziness	21	39.6	10	5	5	1		2															
Hypokalemia	20	37.7	11	9	5	8	7	3	3	1	1	1	1	1	1	1	1	1	1	1	1	1	
Hyponatremia	19	35.8	5	8	5	7	5	3	3	2	2	1		1		1	2		1	1			
Numbness/ tingling feeling	17	32.1	4	9	7	3	6	4	5	6	5	4	5	3	3	3	3	2	2	2	2		

Table 6 highlights the association between the number and severity of adverse events (AEs) and treatment outcomes in pulmonary DR-TB patients. We have three kinds of AEs, such as the number of AEs as a continuous variable, and we categorized AEs based on the cutoff point using the mean and the severity of AEs. Patients with successful treatment experienced significantly more AEs (Mean = 13.23, SD = 4.00) than those with unsuccessful outcomes (Mean = 8.58, SD = 4.00; P=0.002). AEs occurring at a higher frequency (≥10)

were associated with better treatment success (20.75%) compared to fewer AEs (<10; P=0.008). Additionally, the severity of AEs showed a significant relationship with outcomes (P=0.043).

Table 6. The association between a number of adverse events and the severity of adverse events with treatment outcomes among pulmonary DR-TB adult patients at one of the hospitals in Tangerang, Banten, Indonesia.

	Successful treatment	Unsuccessful treatment	Mean difference/ Odd ratio (95% CI)	P value
Number of adverse events (AEs) occurred in one patient, Mean (SD)	13.23 (4.00)	8.58 (4.00)	4.67 (1.795-7.517)	0.002*
Adverse events			7.44 (1.45-38.05)	0.008**
<10 AEs	2 (3.77)	23 (43.40)		
≥10 AEs	11(20.75)	17 (32.08)		
Severity of AEs			1.43 (1.177-1.745)	0.043***
Not severe	0	10 (18.87%)		
Severe	13 (24.5%)	30 (56.60%)		

*T test; **Chi-Square test, ***Fisher test

▪ DISCUSSION

In this study, we analyzed the frequency of adverse events (AEs), time to event, and their association with treatment outcomes among pulmonary DR-TB patients at one of the public hospitals in Tangerang, Banten, Indonesia. The findings revealed that all patients experienced at least one mild AE, while about 81% reported severe AEs. Patients experienced 9.72 ± 4.86 (mean ± SD) AEs during treatment, presented in Table 2. Similar findings were reported in Nigeria, where 99% of patients experienced AEs during treatment [13] and India [14]. However, the AE frequency observed in this study was higher than in other countries, such as Vietnam (71.3%) [15], Pakistan [6, 16], and China (90.7%) [4]. Variations in AE frequency may be attributed to factors such as differences in drug regimens [17] and treatment duration [18], age, especially for the elderly [17], and patient comorbidities that have the potential to have drug interaction [7],[19]. In this study, the most commonly used drugs were clofazimine, bedaquiline, and levofloxacin, which may also influence the occurrence of AEs. Additionally, most patients in this study were treated with longer regimens. The longer the treatment duration, the higher the potential for AEs. The WHO has recommended shorter treatment durations in its new guidelines [20].

The most common adverse events (AEs) among DR-TB patients vary across studies. In this study (Table 4), we identified gastrointestinal issues (primarily nausea and vomiting), electrolyte disturbances (hypokalaemia and hyponatremia), and musculoskeletal complaints (joint pain) as the most frequent AEs. Similarly, a study conducted in Pakistan reported comparable findings [6], [21]. However, other studies have identified different types of commonly reported AEs, such as arthralgia [22] and depression [7]. Gastrointestinal disturbances are the most common ADR, but patients typically require symptomatic treatment due to their mild to moderate severity, which helps avoid discontinuing the tuberculosis treatment [23].

This study also examined the timing of the top ten most frequently reported AEs, including nausea, anemia, mild vomiting, loss of appetite, skin discoloration, headache, joint pain, hyponatremia, hypokalemia and numbness. Most AEs occurred during the initial intensive phase of treatment (4-6 months), with their frequency decreasing in the continuation phase. This pattern was consistent with findings from studies in Pakistan, which also identified gastrointestinal and electrolyte disturbances as the most commonly observed AEs [6], [17]. Severe AEs were also predominantly observed during the intensive phase of treatment [24]. This can be attributed to the higher number of drugs prescribed during this phase, increasing the risk of adverse effects. These findings emphasize the importance of educating patients that AEs are often temporary. It will tend to decrease after the first six months of treatment. For instance, nausea was most commonly reported during the first three months, anemia within the first six months, vomiting during the initial two months, and loss of appetite within the first four months. Most of these symptoms diminish or even disappear entirely after six months. Patients experiencing such adverse effects should also receive counseling from pharmacists, as practiced in Pakistan, to support adherence and effective management [17].

The relationship between AEs and treatment outcomes remains a subject of debate. Some studies have reported a significant association [4],[25], while others have not [7]. In our study highlights an important finding regarding the relationship between AEs and treatment success. Patients who experienced a higher number of AEs were more likely to achieve successful treatment outcomes. As shown in Table 6, the average number of AEs was greater among patients who completed treatment successfully than those who did not. Similarly, a study by Lecai Ji et al. in China found that patients with three or more AEs demonstrated better treatment outcomes [25]. Other studies in Indonesia found that the cure rate was higher among patients with AEs than those without AEs. Categorizing patients based on the number of AEs revealed that those with more than 10 AEs during treatment had higher cure rates. This could be because these patients adhered to treatment for longer, leading to more AEs being reported. Effective management of AEs likely played a crucial role in enabling these patients to complete their treatment [7]. Conversely, patients who discontinued treatment prematurely reported fewer AEs, as their treatment duration was shorter. These findings highlight the importance of proactive AE management to reduce treatment discontinuation rates and improve overall outcomes. The study was conducted in only one public hospital in Tangerang, Banten, Indonesia. Thus, the findings may not be generalizable to other healthcare settings or regions with different treatment practices, drug regimens, or patient populations.

▪ CONCLUSION

In the current study, AEs were reported in all patients, with most occurring during the intensive phase of treatment, typically within the first 4-6 months. Interestingly, patients who experienced more AEs were more likely to achieve successful treatment outcomes after completing the full course of therapy. Effective management of AEs is essential during DR-TB treatment.

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