MEDFARM: Jurnal Farmasi dan Kesehatan, Vol. 14, No. 1, 2025, Page 172-185
e-ISSN : 2715-9957
p-ISSN: 2354-8487

Impact of Side Effects on Adherence in Drug-Resistance Tuberculosis Treatment at RSD dr. Soebandi Jember

Neny Poerwahyuningrum[1], Fifteen Aprilla Fajrin[2,4], Angga Mardro Rahardjo[5], Irma Prasetyowati[6], Khoiriyatul Muhlishoh Arwi[7], Afifah Machlaurin[2,3*)]

[1)] Magister Pharmacy, Faculty of Pharmacy, Universitas Jember
[2)]Departement of Clinical and Community Pharmacy, Faculty of Pharmacy, Universitas Jember
[3)] Drug Utilization Research Group, Faculty of Pharmacy, Universitas Jember
[4)] Preclinical Pharmacology Research Group, Faculty of Pharmacy, Universitas Jember
[5)] Medical Faculty, Universitas Jember
[6)] Public Health Faculty, Universitas Jember
[7)] Department of MDR-TB center, Public Hospital (RSD) dr. Soebandi, Jember

e-mail:[2,3*)]a.machlaurin.farmasi@unej.ac.id

ABSTRACT

Tuberculosis (TB) is the leading cause of death from infectious disease worldwide. Patient adherence to treatment is crucial for therapy which side effects of tuberculosis treatment are a significant factor affecting compliance. This study aims to analyze the impact of side effects from anti-tuberculosis drugs on the medication adherence of Drug Resistant Tuberculosis patients (DR-TB) at RSD dr. Soebandi in Jember. This study was a retrospective cohort observational that included 245 DR-TB patients register at the dr. Soebandi Hospital from January 2021-December 2023. The electronic medical records, web-based tuberculosis information systems (SITB), and data filling sheets was used. The Proportion of Days Covered (PDC) method was used to evaluate the medication adherence. Data analysis was conducted in SPSS 27.0. Ten patients were excluded due to HIV comorbidities, resulting a final sample of 235 patients. The findings revealed that 53.6% of patients were non-adherence. The three most common types of side effects were gastrointestinal (43.4%), musculoskeletal (29.8%) and skin-related side effects (16.6%). The multivariate logistic regression showed that adherence was significantly reduced by the presence of side effects (aOR: 0,153; 95%CI 0,052-0,448), the number of side effects >2 types (aOR: 0,290; 95%CI 0,101-0,837), and the musculoskeletal-related side effects (aOR: 0,441; 95%CI 0,201-0,972).

Keywords: DR-TB, side effects, adherence, PDC method

Introduction

Mycobacterium tuberculosis is the bacterium that causes tuberculosis (TB), an infectious disease of the lungs (WHO, 2022). According to WHO (World Health Organization) data, TB is the second most common cause of death worldwide and ranks 13th overall morbidity (WHO, 2023). After ischemic heart disease, TB was the third leading cause of death in Indonesia in 2023. In 2021, the province in Indonesia with the second-highest number of TB cases was East Java (Ministry of Health of the Republic of Indonesia, 2022). In Jember, a total 3,170 cases were discovered in 2021,

represented 57% of all cases, made Jember as the second-highest number of TB cases in East Java (Jember Regency Health Office, 2023).

Drug-Resistant Tuberculosis (DR-TB) is a type of TB that is resistant to at least two drugs, isoniazid and rifampicin, which requires several second-line drugs and relatively long treatment. DR-TB is a crucial problem of TB control and health in general in many countries (Ministry of Health of the Republic of Indonesia, 2022). The estimated DR-TB in Indonesia in 2023 is 13% of TB patients who have been treated and estimated 2.4% of all new TB patients (WHO, 2023). In 2022, the burden of DR-TB increased by 3% compared to the previous year (WHO, 2022). The success rate of DR-TB treatment in 2023 was 73% (old DR-TB patients) and 55% (new DR-TB patients), reflected an increase success rate from the previous year of 70% and 53% (WHO, 2023). The high rate of DR-TB treatment failure resulted increasing transmitted disease, which causing the high economic burden related to TB (WHO, 2021).

One of the reasons for low recovery rates for TB patients is non-adherence (Ministry of Health of the Republic of Indonesia, 2022). The frequency of side effects that lead patients to skip doses of their medicine is one of the reasons why patients do not comply with TB treatment (Asriwati et al., 2021). According to a study in Jayapura, there is a strong correlation between side effects and medication adherence; more severe the side effects lead to more medication non-adherence, and vice versa (Ruben, 2023). In order to avoid and control side effects that may arise during DR-TB treatment and improve treatment effectiveness, a literature review research found that it is critical to comprehend the risk variables linked to pharmacological side effects in DR-TB (Handari & Ronoatmodjo, 2024). Drug regimen for DR-TB treatmen tcan cause a range of side effects, from mild (gastrointestinal disorders: nausea or vomiting, diarrhea, and hepatotoxicity) to severe (brain toxicity, nerve toxicity, nephrotoxicity, skin toxicity, and cardiotoxicity)(Prasad et al., 2021). According to research conducted in Indonesia, the most frequent adverse effects among patients with DR-TB were gastrointestinal illnesses (86.9%), followed by peripheral neuropathy (44.0%) and arthralgia (45.2%), with hypothyroidism (2.4%) being the least prevalent (Wibowo, 2023).

Research in Ghana reported that non-adherence to treatment can cause treatment failure in TB patients, which can slow down the healing process and increase the risk of complications or death (Panford et al., 2022). This is also reinforced in a literature review study stating that the factors that have a dominant influence on the side effects of outpatients with DR-TB treatment are consistency in taking medication and treatment history (Anggraini, 2022). Assessment of patient medication adherence is very important, both in research and clinical practice (Babar, 2021). Therefore, an intervention that focuses on the factors that cause non-adherence is needed in order to improve patients adherence comprehensively (Adusi-Poku, 2021). The assessment of patient medication adherence can be evaluated using the proportion of days converted (PDC) method (Anghel et al., 2019). The PDC method has the advantages of its simple calculation, more objective, and not only providing an average picture, but can also be used for various chronic conditions (Dalli et al., 2022). Other advantages are time and cost efficiency and reducing

researcher bias (Anghel et al., 2019). From our knowledge, research using the PDC method to measure medication adherence and side effects determinant in DR-TB patients is still rare. Therefore, this study aims to analyze the impact of side effects from anti-tuberculosis drugs on the medication adherence of DR-TB at RSD dr. Soebandi in Jember.

Method

Types and Research Design

This study is a retrospective cohort study to analyze factors that influence compliance, especially side effects, on TB treatment adherence. Sociodemographic factors such as age, gender, and clinical factors such as patient category, type of treatment, comorbidity, side effects, number of side effects and types of side effects, were analyzed to see which variable have the most significant impact on DR-TB treatment adherence.

Place and Time of Research

This study was conducted in the outpatient unit of TB clinic at RSD dr. Soebandi Jember which is a referral hospital for DR-TB patients from Situbondo, Bondowoso, Banyuwangi and Lumajang, thus, was expected to represent the more widely population. Data on DR-TB patients were obtained from the official government website for TB patients, Tuberculosis Information System (SITB-Sistem Informasi TB) and Electronic Medical Records (E-RM) at RSD dr. Soebandi Jember. The data were collected for the period time from January 2021-December 2023.

Population and Sample

This study used total sampling technique due to the relatively small number of patients. This study used 245 outpatients of DR-TB polyclinic at RSD dr. Soebandi Jember. Inclusion criteria in this study were: adult patients (≥17 years) with a diagnosis of DR-TB and receiving either short-treatment or standard long treatment therapy; patients who have completed treatment; patients with complete SITB records. While the exclusion criteria were: pregnant and lactating patients; patients with immunosuppressants/HIV comorbidity; patients whose treatment has not been completed.

Research Instrumen

The data collection checklist was used in this study to record the subjective and objective data such as symptoms, gender, age, patient category, type of therapy, comorbidities, side effects, types of side effects of DR-TB treatment, adherence data from electronic medical record and web-based tuberculosis system in Indonesia (Sistem Informasi Tuberculosis, SITB).

Research Variables

In this study, there are two variables studied. First, the independent variable which included the sociodemographic profile (age, gender), clinical profile

(patient category, treatment regimen, comorbidities), and side effect profile (presence of side effects, number of side effects and type of side effects). Second, the dependent variable was the adherence DR-TB tratment patients measured by PDC method. PDC was calculated by adding up the total days covered by a treatment divided by the total number of days of study participation multiplied by one hundred percent. The PDC value was range from 0% to 100%. Patients are considered compliant if the PDC proportion value is ≥ 80% and patients are considered non-compliant if the PDC proportion value is <80% (Loucks et al., 2022).

Data Analysis

The data analysis used in this study are univariate analysis and multivariate logistic regression. Univariate analysis was used to obtain a description of the characteristics of respondents presented in frequency and percentage of baseline characteristic such as gender, age, patient category, type of therapy, comorbidities, type of side effects, number of side effects. Before multivariate analysis was conducted, a bivariate analysis was carried out using Chi-square test to analyze the individual relationship between gender, age, patient category, type of therapy, comorbidities, side effects, type of side effects, to the adherence of taking medication for patients with DR-TB.

The variable with p-value <0,25 will be included in the multivariate logistic regression to assess the direction and the strength of the impact from baseline characteristics on adherence presented in aOR (adjusted odds ratio) and 95% confidence interval.

Research Ethics

Through letter No.2746/UN25.8/KEPK/DL/2024, the Health Research Ethics Committee (KEPK) of the University of Jember's Faculty of Dentistry granted ethical approval for this work.

Result

In this study, the total number of DR-TB patients registered at RSD dr. Soebandi Jember for the period 2021-2023 was 245 patients. Of the 245 patients, 10 HIV-positive patients were excluded from this study, because HIV patients have masive immune responses, which can affect the effectiveness of TB treatment and compliance. So that 235 patients met the inclusion criteria in this study (Figure 1). The majority of patients in this study were aged 46-55 years (57 patients, 24.3%) and male (122 patients, 51.9%). The majority of DR-TB patients in this study had Rifampicin Resistance (RR) type of resistance (176 patients, 74.9%) and underwent Long Term Regiment (LTR) type of treatment (143 patients, 60.8%), with comorbidity Diabetes Mellitus (DM) (54 patients, 22.9%) (Table 1).

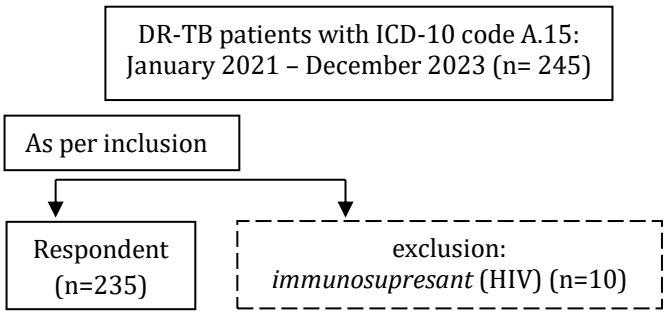

Figure 1. Respondent Selection Scheme Based on Total Sampling Technique

The side effect profile in this study showed that 57.0% (134 patients) experienced side effects from OAT consumption with the number of side effects less than or equal to two side effect symptoms as many as 82.0% (192 patients). Also, the three most common types of side effects reported by DR-TB patients were gastrointestinal side effects as many as 44.0% (103 patients), musculoskeletal side effects 29.4% (69 patients), and skin side effects 16.6% (39 patients). The majority of patients showed compliance with taking medication as many as 46.4% (108 patients) and those who did not comply with taking medication as many as 53.6% (127 patients) based on the PDC categorization (Table 1).

Based on the results of the bivariate analysis, age, patient category, type of treatment, side effects that appeared during treatment, number of side effects reported by patients, types of gastrointestinal side effects, musculoskeletal side effects and skin side effects were include to the multivariate analysis. However, comorbidities, renal and liver side effects, and gender were not significant for further testing (Table 2). The presence of side effects, the number of side effects >2 and musculoskeletal side effects were the three factors that significantly reduced compliance, according to the multivariate test results (Table 2).

Discussion

The findings of this study indicate that more than half of DR-TB patients have low compliance in DR-TB treatment (53.6%). The results were similar with the study in South Korea which showed a compliance rate of 56.5% in DR-TB (Bea et al., 2021). When compared to the developed countries, the level of compliance in Indonesia is relatively lower, such as a study in Italy which reported a higher level of compliance at 89.2% (Gualano & Mencarini, 2019). However, the results of this study was higher when compared to a study in Uganda, at 26% (Batte et al., 2021). These variation in adherence were mainly caused by the variations in basic characteristics of patients and the duration of the compliance observation was studied (Ajema et al., 2020).

According to the findings of multivariate logistic regression analysis, DR-TB adherence was significantly reduced by the presenc of adverse effects (aOR; 0,153; 95% CI 0.052-0.448). One of the causes of treatment failure is the existence of a drug's adverse effects (Tirore & Ersido, 2024). The risk factors for not taking medicine were

the adverse effects, which increased non-compliance (Asriwati et al., 2021). When side effects manifest, the patient's physical suffering will make them less inclined to stick with their medication (Tirore & Ersido, 2024). Side effects become a serious health issue with DR-TB treatment (Handari & Ronoatmodjo, 2024). 57% of the participants in this research reported experiencing adverse symptoms while using OAT. This study is comparable to those conducted in China and Uganda, which revealed that 56.9% and 69.23% of DR-TB patients, respectively, had adverse effects (Ategyeka & Muhoozi, 2023; Shi et al., 2024). However, studies conducted in Southern Ethiopia found that OAT use had fewer adverse effects, at 18.9%(Tirore & Ersido, 2024). This discrepancy can arise from the fact that different countries have different rates and kinds of adverse effects that patients encounter.

Tabel 1. Sociodemographic and Clinical Characteristics and Compliance of DR-TB Patients

Characteristics	Total (n=235)	Percentation (%)
Age (years)		
17-25	24	10,2
26-35	50	21,3
36-45	42	17,9
46-55	57	24,3
56-65	50	21,3
> 65	12	5,00
Gender		
male	122	51,9
female	113	48,1
Patient category		
RR	176	74,9
MDR	53	22,5
Pre-XDR	6	2,60
Types of Treatment		
STR	92	39,2
LTR/individualized treatment	143	60,8
Comorbidity		
DM	54	22,9
No DM	181	77,1
Side effects		
Appear	134	57,0
No side effect	101	43,0
Number of side effects		
>2	43	18,0
≤2	192	82,0
Type of side effects		
Gastrointestinal	103	44,0
Musculoskelatal	69	29,4
Skin	39	16,6
Liver	3	1,30
Kidney	1	0,40
Compliance based on PDC		
Adhere	108	46,0
Not adhere	127	54,0

*) RR = Rifampicin Resistance; MDR = Multi-Drug Resisten; Pre-XDR = Pre-Extensive Drug Resistance; STR = Short Term Regimen ; LTR = Long Term Regimen; DM = Diabetes Mellitus; PDC = Proportion of Days Covered.

In the bivariate logistic regression analysis, the variable adverse effects showed a statistically significant positive association with the adherence (OR = 7.052; 95% CI: 3.880–12.815; p < 0.001). This indicates that, when analyzed independently, the presence of adverse effects was associated with a more than sevenfold increase in the odds of the outcome. However, in the multivariate logistic regression model, the adjusted odds ratio (aOR) for adverse effects was significantly less than 1 (aOR = 0.153; 95% CI: 0.052–0.448; p < 0.001), indicating a strong negative association after controlling for other variables. This discrepancy between the cOR and aOR suggests the presence of confounding variables that affect both the occurrence of adverse effects and the adherence. When these confounders are not controlled (in the bivariate analysis), the relationship appears to be positive. However, after adjustment, the true direction of the association emerges as negative. Several variables included in the multivariate model, such as the number of adverse effects, organ system affected (e.g., gastrointestinal, musculoskeletal, skin), patient age, and type of treatment, may have contributed to this shift in direction. These factors may moderate or mediate the relationship between adverse effects and adherence. Additionally, this pattern may reflect a form of Simpson's paradox, where the direction of the association between two variables reverses after accounting for a third variable. Moreover, it is also possible that patients who experienced adverse effects received more intensive monitoring or intervention, which might have influenced the adherence positively in the unadjusted analysis. However, the adjusted analysis reveals the potentially harmful effect of adverse events on treatment outcomes when confounding factors are considered. Therefore, interpretation of regression outputs must consider both crude and adjusted estimates. Relying solely on bivariate associations may lead to misleading conclusions, particularly in the presence of complex inter-variable relationships.

The number of side effects that have been experienced by patients also significantly lower the adherence in DR-TB patients (aOR; 0.290; 95% CI 0.101-0.837). This study is in line with a study in China which concluded that most DR-TB patients reported one or two side effects (Shi et al., 2024). A study in Southern Ethiopia showed that patients who experienced more than two side effects tended to have lower adherence levels (Tirore & Ersido, 2024). This is because patients with more side effects may receive more attention and support from medical personnel, including dose adjustments or changes in regimens that can improve medication adherence (Potty et al., 2023). Many studies have shown that most DR-TB patients experience side effects which commonly happen in the gastrointestinal (Sazali & Rahim, 2022). Some gastrointestinal side effects include complaints of vomiting, nausea and abdominal pain. OATs suspected of causing gastrointestinal side effects are Levofloxacin (Lfx), Protionamide (Pto) and P-Aminosalicylic Acid (PAS)(Ministry of Health of the Republic of Indonesia, 2022). Gastrointestinal side effects are very subjective. These side effects often require changes in the treatment regimen and the addition of treatment to overcome the side effects symptoms.

Although the most common side effects in this study were gastrointestinal, the type of side effects that significantly affected compliance were musculoskeletal

side effects (aOR: 0,441; 95% CI (0,201-0,972)). Study in Vietnam also showed significant musculoskeletal side effects in DR-TB patients (aOR: 6.36; 95% CI 4.30-9.42). The most frequently reported musculoskeletal side effects were arthritis, muscle pain, arthralgia, and neuralgia. The occurrence of musculoskeletal side effects was mainly caused by bedaquiline, fluoroquinolone, streptomycin, ethambutol, and pyrazinamide, which can cause arthralgia, joint pain, and hyperuricemia (Lan & Ahmad, 2020). Pyrazinamide is one of the causes of arthralgia that is often reported in patients with DR-TB. However, musculoskeletal side effects will resolve in most patients without permanent discontinuation of pyrazinamide (Khan & Amjad, 2022).

The presence of side effects is one of the reasons for treatment failure (Tirore & Ersido, 2024). A literature review study revealed that the factors influencing the occurrence of side effects in DR-TB was patients' perceptions of side effects, social and psychological support, patients' motivation and expectations, non-medical factors (such as distance to health facilities, treatment costs, and accessibility of health services), and previous experience with treatment (Handari & Ronoatmodjo, 2024). The future research was recommended to quantitatively assess the patient preferences, in terms of its experience of side effects, among various options of DR-TB treatment which refer to individualized therapy (Zegeye & Dessie, 2019).

The results of this study are similar to the study by Tukayo et al. (2020) which explained that there was a relationship between side effects and patient compliance in taking medication ($p = 0.012 < 0.05$). The presence of side effects is one of the reasons why treatment fails (Tukayo et al., 2020). This is in line with Meldawaty's study (2023) which explained that the presence of side effects increases the risk of patients taking medication irregularly to the point of stopping taking medication. However, to reduce this, health-care professional must provide counseling to patients regarding the side effects of drugs so that they do not need to worry if they experience side effects during treatment (S Meldawaty et al., 2023). The results of this study prove that the frequency of side effects of more than two reduces compliance. DR-TB patients who reported side effects of treatment were encouraged to continue taking their medications by pharmacists. Factors reported to contribute to poor adherence were feeling well after taking multiple doses and frequent side effects during the intensive phase of treatment (Nezenega & Lewis, 2020)

Non-adherence is one of the causes of low TB patient recovery rates (Ministry of Health of the Republic of Indonesia, 2022). One of the main causes of patients' noncompliance with TB treatment is the prevalence of side effects that cause them to miss medication doses (Asriwati et al., 2021). Side effects and medication adherence are strongly correlated, according to a Jayapura study; more severe side effects result in medication non-compliance, and vice versa (Ruben, 2023). Understanding the risk factors associated with pharmacological side effects in DR-TB patients is crucial for preventing and managing side effects that may occur during therapy and enhancing treatment efficacy, according to a literature review study (Handari & Ronoatmodjo, 2024). According to Indian research, OAT use in DR-TB patients can result in a variety of adverse effects, ranging from minor ones (gastrointestinal disorders: nausea or vomiting, diarrhea, and hepatotoxicity) to serious ones (brain toxicity, nerve toxicity, nephrotoxicity, skin toxicity, and

cardiotoxicity) (Prasad et al., 2021). Research from Indonesia showed that among patients with DR-TB, gastrointestinal disorders were the most common side effect (86.9%), followed by peripheral neuropathy (44.0%) and arthralgia (45.2%), with hypothyroidism (2.4%) being the least common (Wibowo, 2023).

Knowledge about TB, especially DR-TB, is an important factor in the prevention and control of TB disease. Patients who have better knowledge about TB tend to have a better understanding of the importance of adherence to treatment (Mokodompit et al., 2019). In the case of DR-TB, patients must undergo longer treatment and with drugs that have quite a few side effects. Good knowledge of the risks and consequences of non-compliance can help patients stay motivated to complete treatment. In addition, an understanding of how drug resistance can arise also plays a role in increasing patient awareness of the importance of completing treatment as recommended (Wisesa et al., 2020). This is in line with research in Kendari City, Indonesia, which concluded that risk factors for DR-TB besides drug side effects are knowledge and history of previous treatment (Ode et al., 2024).

There are many limitations on this study. First, the method of adherence reporting in medical records is carried out by social volunteers under the supervision of primary healthcare personnel, which may not accurately reflect patients' true adherence to the reporting bias. Social workers often speak with patients one-on-one, but occasionally they rely on community or family reports, which may also be biased or ignorant of the patient's situation. Additionally, social volunteers may have different perspectives on adherence and side effects, which raises the possibility of subjectivity. Second, the strength of the analytic results will be impacted by the relatively small number of patients that match the inclusion criteria. Thus, it was recommended to include large number of respondents. Third, side effects are obtained from subjective patient self-reported data. This study concludes that the presence of side effects, especially musculoskeletal, significantly reduces compliance.

Table 2. Results of Logistic Regression Analysis of Side Effects and Compliance of DR-TB Patients at RSD dr. Soebandi Jember, 2021-2023 (n=235)

Characteristics	Total (n-235)	Percent (%)	Compliance based on PDC		*p-value (bi-variate)*	*cOR (95%CI)*	*p-value (multi-variate)*	aOR (95%CI)
			adhere (n=108)	non-adhere (n=127)				
Age								
< 55year	173	73,6	84 (48,5%)	89 (51,5%)	0,182*	0,669 (0,370-1,209)	0,481	0,780 (0,391-1,556)
≥ 55year	62	26,4	24 (38,7%)	38 (61,3%)				Ref
Gender								
Male	122	51,9	53 (43,4%)	69 (56,6%)	0,422	0,810 (0,484-1,354)		
Female	113	48,1	55 (48,7%)	58 (51,3%)				
Patient Category								
RR	176	74,9	85 (48,3%)	91 (51,7%)	0,214*	1,462 (0,802-2,666)	0,690	0,869 (0,436-1,732)
MDR/Pre-XDR	59	25,1	23 (39,0%)	36 (61,0%)				Ref
Types of Treatment								
LTR/individualize	143	60,8	72 (50,5%)	71 (49,5%)	0,092*	1,577 (0,927-2,685)	0,920	0,968 (0,514-1,823)
STR	92	39,2	36 (39,1%)	56 (60,9%)				Ref
Comorbidity								
DM	54	22,9	28 (51,8%)	26 (48,2%)	0,322	1,360 (0,732-2,500)		
No DM	181	77,1	80 (44,2%)	101 (55,8%)				
Side Effects								
Yes	134	57,0	87 (64,9%)	47 (35,1%)	< 0,001*	7,052 (3,880-12,815)	**< 0,001**	0,153 (0,052-0,448)
No side effects	101	43,0	21 (20,8%)	80 (79,2%)				Ref
Number of side effects								
>2	43	18,0	34 (79,0%)	9 (21,0%)	< 0,001*	6,024 (2,734-13,275)	**0,022**	0,290 (0,101-0,837)
≤2	192	82,0	74 (38,5%)	118 (61,5%)				Ref

Type of side effects								
Gastrointestinal								
Yes	103	44,0	63 (61,2%)	40 (38,8%)	< 0,001*	3,045 (1,783-5,201)	0,161	1,955 (0,765-4,994)
No	132	56,0	45 (34,1%)	87 (65,9%)				Ref
Musculoskeletal								
Yes	69	29,4	53 (76,8%)	16 (23,2%)	< 0,001*	6,685 (1,783-5,201)	**0,042**	0,441 (0,201-0,972)
No	166	70,6	55 (33,1%)	111 (66,9%)				Ref
Skin								
Yes	39	16,6	25 (64,1%)	14 (35,9%)	0,013*	2,431 (1,192-4,960)	0,176	1,987 (0,736-5,367)
No	196	83,4	83 (42,3%)	113 (57,7%)				Ref
Liver								
Yes	3	1,30	2 (66,6%)	1 (33,4%)	0,469	2,377 (0,213-26,584)		
No	232	98,7	106 (45,7%)	126 (54,3%)				
Kidney								
Yes	1	0,40	0 (0,00%)	1 (100%)	0,355	0,000 (0,000-0)		
No	234	99,6	108 46,2%)	126 (53,8%)				

*) p-value ≤ 0.25 were included in the multivariate analysis; RR = Rifampicin Resistance; MDR = Multi-Drug Resistance; Pre-XDR = Pre-Extensive Drug Resistance; STR = Short Term Regimen; LTR = Long Term Regimen; DM = Diabetes Mellitus;PDC= Proportion of Days Covered; bold numbers indicate significance.

Conclusions

The side effects of DR-TB treatment significantly affect the compliance of taking medication. Factors that significantly lower the adherence were the presence of side effects, patients who have side effects more than 2 types, and musculoskeletal related side effect.

The results of this study indicate the importance of proper drug monitoring and education of drug side effects by the pharmacists. It is rec ommended to actively provide support and information to improve treatment compliance to the patient's family or care giver. In the field of health promotion, providing a systematic counseling and training to patients, families, and social worker with various interactive methods might improve knowledge and treatment compliance.

Authors' Contributions

The research idea and conceptualization were carried out by NP and AM. Data collection was performed by NP under the supervision of KMA. Data processing and analysis were conducted by NP and validated by AM and FAP. The initial manuscript draft was prepared by NP with supervision from AM and FAP. Final manuscript revisions were completed by AMR, IP, AM, and FAP.

Conflict of Interest

All authors declare that they have no conflicts of interest related to this research.

Reference

Ajema, D., Shibru, T., Endalew, T., & Gebeyehu, S. (2020). Level of and associated factors for non-adherence to anti-tuberculosis treatment among tuberculosis patients in Gamo Gofa zone, southern Ethiopia: cross-sectional study. *BMC Public Health*, *20*(1), 1–9. https://doi.org/10.1186/s12889-020-09827-7

alsagaff, H., & M. (2008). Alsagaff, H., & Mukty. (2008). Dasar-dasar ilmu penyakit paru. Jakarta : Airlangga University Press. *Airlangga University Press*, *3*(1), 145–150.

Anghel, L. A., Farcas, A. M., & Oprean, R. N. (2019). An overview of the common methods used to measure treatment adherence. *Medicine and Pharmacy Reports*, *92*(2), 117–122. https://doi.org/10.15386/mpr-1201

Asriwati, Yeti, E., Niakurniawati, & Usman, A. N. (2021). Risk factors analysis of non-compliance of Tuberculosis (TB) patients taking medicine in Puskesmas Polonia, Medan, 2021. *Gaceta Sanitaria*, *35*, S227–S230. https://doi.org/10.1016/j.gaceta.2021.10.027

Ategyeka, & Muhoozi. (2023). Prevalence and factors associated with reported adverse-events among patients on multi-drug-resistant tuberculosis treatment in two referral hospitals in Uganda. *BMC Infectious Diseases*, *23*(149).

Batte, C., Namusobya, M. S., Kirabo, R., Mukisa, J., Adakun, S., & Katamba, A. (2021).

Prevalence and factors associated with non-adherence to multi-drug resistant tuberculosis (MDR-TB) treatment at Mulago National Referral Hospital, Kampala, Uganda. *African Health Sciences*, *21*(1), 238–247. https://doi.org/10.4314/ahs.v21i1.31

Dalli, L. L., Kilkenny, M. F., Arnet, I., Sanfilippo, F. M., Cummings, D. M., Kapral, M. K., Kim, J., Cameron, J., Yap, K. Y., Greenland, M., & Cadilhac, D. A. (2022). Towards better reporting of the proportion of days covered method in cardiovascular medication adherence: A scoping review and new tool TEN-SPIDERS. *British Journal of Clinical Pharmacology*, *88*(10), 4427–4442. https://doi.org/10.1111/bcp.15391

Handari, R. D., & Ronoatmodjo, S. (2024). Prevalensi dan Faktor Risiko Kejadian Efek Samping Obat pada Pasien TB-MDR: Literature Review. *Media Publikasi Promosi Kesehatan Indonesia (MPPKI)*, *7*(3), 506–517. https://doi.org/10.56338/mppki.v7i3.4700

Kementrian Kesehatan RI. (2022). *Petunjuk Teknis Penatalaksanaan Tuberkulosis 2022*. Kementerian Kesehatan RI.

Khan, & Amjad. (2022). Assessment of Adverse Drug Events, Their Risk Factors, and Management Among Patients Treated for Multidrug-Resistant TB: A Prospective Cohort Study From Pakistan. *Sec. Drugs Outcomes Research and Policies*, *13*(2022).

Lan, & Ahmad. (2020). Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Meta-Analysis*, *8*(4), 383–394.

Loucks, J., Zuckerman, A. D., Berni, A., Saulles, A., Thomas, G., & Alonzo, A. (2022). Proportion of days covered as a measure of medication adherence. *American Journal of Health-System Pharmacy*, *79*(6), 492–496. https://doi.org/10.1093/ajhp/zxab392

Mokodompit, A. R., Laya, A. A., & Wahyuni, S. (2019). Hubungan Pengetahuan Dengan Sikap PMO Tentang Pencegahan Kekambuhan Pada Pasien TB Paru di Kecamatan Girian Kota Bitung. *Jurnal Kesehatan*, *3*(1). https://ejournal.unimman.ac.id/index.php/jka/article/view/56/

Nezenega, & Lewis. (2020). Factors Influencing Patient Adherence to Tuberculosis Treatment in Ethiopia: A Literature Review. *Int. J. Environ. Res. Public Health*, *17*(15).

Ode, W., Aisyah, N., Sabilu, Y., Ode, L., & Azim, L. (2024). *FAKTOR RISIKO MULTIDRUG RESISTANT TUBERCULOSIS (MDR- TB) DI KOTA KENDARI TAHUN 2024*. *4*(6), 917–928.

Potty, R. S., Kumarasamy, K., Munjattu, J. F., Reddy, R. C., Adepu, R., Singarajipura, A., Lakkappa, M. H., Swamickan, R., Shah, A., Panibatla, V., & Washington, R. (2023). Tuberculosis treatment outcomes and patient support groups, southern India. *Bulletin of the World Health Organization*, *101*(1), 28-35A. https://doi.org/10.2471/BLT.22.288237

Prasad, R., Singh, A., & Gupta, N. (2021). Adverse Drug Reactions with First-Line and Second-Line Drugs in Treatment of Tuberculosis. *Annals of the National Academy of*

Medical Sciences (India), *57*, 16–35. https://doi.org/10.1055/s-0040-1722535

Ruben. (2023). Korelasi Efek Sampipng OAT dengan Kepatuhan Pengobatan Pasien TB Paru. ,. *Journal of Pharmaceutical and Health Research*, *4*(04). https://doi.org/DOI 10.47065/Jharma.V4i3.3670.

S, M., Utami, R. S., & Wulandari, Y. (2023). Faktor-Faktor yang berhubungan dengan Obat Anti Tuberkulosis (OAT) dalam Kepatuhan Minum OAT Pada Pasien Tuberkulosis Paru di Wilayah Kerja UPTD Puskesmas Kabupaten Bintan. *NURSING UPDATE : Jurnal Ilmiah Ilmu Keperawatan P-ISSN : 2085-5931 e-ISSN : 2623-2871*, *14*(1), 199–211. https://doi.org/10.36089/nu.v14i1.1063

Sazali, & Rahim. (2022). Improving Tuberculosis Medication Adherence: The Potential of Integrating Digital Technology and Health Belief Model. *Tuberc Respir Dis (Seoul).*, *23*(86), 82–93.

Tirore, & Ersido. (2024). Non-adherence to anti-tuberculosis treatment and associated factors among TB patients in public health facilities of Hossana town, Southern Ethiopia, 2022. *Sec. Family Medicine and Primary Care*, *11*(2024).

WHO. (2021). *Global Tuberculosis Report 2021*.

WHO. (2022). *Global Tuberculosis Report 2022*.

WHO. (2023). *Global Tuberculosis Report 2023*.

Wibowo. (2023). Gambaran Efek Samping OAT lini Kedua TB-MDR Rawat Jalan di Poliklinik TB-MDR RSU Kota Tangerang Selatan Tahun 2020-2022. *(Skripsi Sarjana), UIN Syarif Hidayatullah Jakarta).*

Wisesa, W., Pebriyani, U., Sudiadnyani, N. P., & Lestari, M. P. (2020). Hubungan Tingkat Pengetahuan tentang Penyakit Tuberkulosis dengan Kesembuhan Penderita Tuberkulosis Paru di Puskesmas Panjang Tahun 2021. *Medula*, *11*(4), 383–390.