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Comparative Safety and Effectiveness of BPaLM/BPaL, Short-Term, and Long-Term Regimens for Drug-Resistant Tuberculosis: A Multicenter Retrospective Cohort Study

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ABSTRACT: Drug-resistant tuberculosis (DR-TB) remains a major global health challenge. Although shorter all-oral regimens have been increasingly adopted, comparative real-world evidence regarding the safety and effectiveness of BPaLM/BPaL, short-term regimen (STR), and long-term regimen (LTR) remains limited. A multicenter retrospective cohort study was conducted among adults with DR-TB treated at three tertiary referral hospitals in South Sulawesi, Indonesia, between January 2021 and December 2025. Treatment effectiveness, adverse drug reactions (ADRs), and severe ADRs were compared across BPaLM/BPaL, STR, and LTR. Multivariable logistic regression identified independent factors associated with treatment effectiveness and severe ADRs. 639 patients were included: 122 received BPaLM/BPaL, 211 STR, and 306 LTR. ADRs occurred in 67.6% and differed across regimens ($p<0.001$). BPaLM/BPaL had highest ADR frequency (77.0%), while LTR had highest severe ADR proportion (22.4%). Gastrointestinal disorders were frequent (57.6%). Among 561 patients, success was 68.3%, highest with BPaLM/BPaL (87.3%), then LTR (63.9%) and STR (61.6%) ($p<0.001$). STR, LTR, older age, and comorbidities independently predicted lower effectiveness, whereas ADR predicted higher success. LTR increased severe ADR risk (adjusted OR 2.45; 95% CI 1.17–5.13). BPaLM/BPaL demonstrated the highest treatment effectiveness, whereas LTR was associated with the greatest risk of severe adverse events. Individualized regimen selection and proactive safety monitoring are essential to optimize outcomes in patients with DR-TB.

1. INTRODUCTION

Drug-resistant tuberculosis (DR-TB) continues to pose a significant global public health issue due to its high rates of illness and death, lengthy treatment periods, and intricate therapeutic management [1]. According to the World Health Organization (WHO), around 410,000 people worldwide developed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) in 2023, with treatment success rates still falling short of the End TB Strategy target [2]. Indonesia ranks among the countries with the

highest burden of DR-TB, with an estimated 22,000 cases each year, many of which remain undiagnosed or untreated [3]. These observations underscore the pressing need to enhance treatment strategies that not only improve clinical outcomes but also reduce treatment-related toxicity [4].

Over the last ten years, the approach to managing DR-TB has significantly transformed with the advent of all-oral regimens and new anti-tuberculosis drugs [5]. While long-term regimens (LTR) are effective, they often involve extended treatment periods and a high rate of adverse drug reactions, which can hinder adherence to treatment [6]. As a result, the WHO advocates for shorter regimens, such as the 9-month short-term regimen (STR) and the 6-month BPaLM/BPaL regimen (comprising bedaquiline, pretomanid, linezolid, with or without moxifloxacin), for patients with DR-TB who meet the criteria [7]. Randomized clinical trials like Nix-TB, ZeNix, and TB-PRACTECAL have shown that BPaLM/BPaL leads to higher treatment success rates and shorter durations compared to traditional regimens, forming the foundation for current global guidelines [8–10]. However, adverse events, notably hematologic toxicity, peripheral neuropathy, and QT interval prolongation, continue to be significant factors influencing treatment adjustments and negative outcomes [11].

While the body of evidence for newer treatment regimens is expanding, there is still a scarcity of real-world comparative data on the safety and efficacy of BPaLM/BPaL, STR, and LTR, especially in high-prevalence areas like Indonesia [12]. Past research in Indonesia has shown varied results concerning treatment outcomes and side effects across different regimens, indicating that factors such as demographic profiles, drug resistance, treatment availability, and clinical practices might significantly impact the effectiveness and safety of these therapies [13,14]. Consequently, this study sought to evaluate the safety and effectiveness of BPaLM/BPaL, STR, and LTR in patients with drug-resistant tuberculosis at referral hospitals. The results are anticipated to offer real-world insights that could aid in evidence-based regimen selection and enhance the clinical management of DR-TB patients.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

In this retrospective cohort study, data were gathered from three tertiary referral hospitals in South Sulawesi, Indonesia, specializing in drug-resistant tuberculosis (DR-TB): Dr. Wahidin Sudirohusodo Hospital, Tadjuddin Chalid Hospital, and Labuang Baji Hospital. The study involved a retrospective review of medical records for patients who received treatment from January 2021 to December 2025. The data collection process took place between April and June 2026, utilizing standardized case report forms.

2.2 Study Population

Adult patients diagnosed with pulmonary DR-TB and treated with one of the three WHO-endorsed therapeutic regimens were considered eligible participants. These regimens included the 6-month BPaLM/BPaL regimen, the 9-month short-term regimen (STR), or the personalized long-term regimen (LTR). The diagnosis of DR-TB was confirmed through the detection of rifampicin resistance using Xpert MTB/RIF (GeneXpert) and/or verified by drug susceptibility testing (DST) or line probe assay (LPA) in line with national tuberculosis guidelines. Inclusion criteria required that comprehensive data on demographic details, treatment regimen, adverse drug reactions, and treatment outcomes be accessible in both medical records and the national tuberculosis information system (SITB). Patients were excluded if they were transferred to another healthcare facility before treatment outcomes could be assessed or if they discontinued treatment during the initial phase for non-medical reasons.

2.3 Sample Size and Sampling Technique

During the study period, all patients who met the inclusion criteria were enrolled through a total sampling method. The sample size was determined using a formula designed to compare two independent proportions, focusing on the primary outcome of treatment success between the BPaLM/BPaL regimen and other regimens. With an assumption of treatment success rates at 85% and 67%, a two-sided significance level of 5%, and a statistical power of 80%, the minimum sample size needed was calculated to be 88 participants for each group. To account for any incomplete records, the target sample size was adjusted to approximately 90–100 patients per treatment group.

2.4 Data Collection

Data for the study were gathered from both electronic and paper medical records, DR-TB program logs, laboratory databases, and the SITB through a standardized data extraction form. The variables collected encompassed demographic details such as age, gender, occupation, and nutritional status; clinical details including prior TB treatments, comorbid conditions, and DR-TB classification; microbiological results like Xpert MTB/RIF, DST, LPA, and drug-resistance profiles; as well as treatment regimen, treatment duration, changes in regimen, adverse drug reactions, and final treatment outcomes.

2.5 Outcome Measures

The main objectives of this research were to assess the effectiveness and safety of the treatment. The evaluation of treatment effectiveness followed the definitions set by the World Health Organization and the Indonesian National Tuberculosis Program. Outcomes were categorized as cured, treatment completed, treatment failed, lost to follow-up, or died. For analysis, treatment effectiveness was divided into successful treatment (cured or treatment completed) and unsuccessful treatment (treatment failure, lost to follow-up, or death).

The safety of the treatment was determined by examining the occurrence, type, severity, onset, and consequences of adverse drug reactions (ADRs). Adverse events were classified into categories such as gastrointestinal, hematological, neurological, cardiovascular, electrolyte, hepatic, ototoxic, ophthalmologic, dermatologic, and musculoskeletal disorders. The severity of these events was graded using the Common Terminology Criteria for Adverse Events (CTCAE) and categorized as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 (life-threatening).

2.6 Statistical Analysis

IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) was utilized for conducting statistical analyses. The normality of continuous variables was evaluated using the Shapiro–Wilk test, with results expressed as mean ± standard deviation (SD) for data following a normal distribution, or as median with interquartile range (IQR) for data not normally distributed. Categorical variables are shown as frequencies and percentages. To compare baseline characteristics across treatment groups, one-way analysis of variance (ANOVA) or the Kruskal–Wallis test was applied for continuous variables, depending on suitability, while Pearson's chi-square test or Fisher's exact test was used for categorical variables.

The relationship between treatment regimen and outcomes such as treatment effectiveness, adverse drug reactions, and severe adverse events was initially explored through bivariate analyses. Variables with a p-value less than 0.25 in these analyses, or those deemed clinically significant, were then included in multivariable binary logistic regression models to determine independent predictors of treatment effectiveness and severe adverse drug reactions. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were provided, and a two-sided p-value of less than 0.05 was deemed statistically significant.

3. RESULTS AND DISCUSSION

3.1 Baseline Characteristics of the Study Participants

Among 639 patients with drug-resistant tuberculosis (DR-TB) included in the final analysis, 122 (19.1%) received BPaLM/BPaL, 211 (33.0%) the short-term regimen (STR), and 306 (47.9%) the long-term regimen (LTR). The study was conducted at three tertiary referral hospitals in South Sulawesi, Indonesia: Labuang Baji Hospital (49.3%), Dr. Tadjuddin Chalid Hospital (41.0%), and Dr. Wahidin Sudirohusodo Hospital (9.7%). Median age was 41 years (IQR, 30–53), mean age 41.8 ± 15.0 years; age distribution was comparable across regimens ($P = 0.730$). 369 (57.7%) were male, with similar sex and employment distributions across groups.

More than half of patients were underweight (57.1%); 35.1% had normal weight, 4.5% were overweight, and 3.3% were obese, with no differences across regimens ($P = 0.359$). Diabetes mellitus was the most common comorbidity (15.0%) and was more prevalent in the LTR group ($P = 0.015$), while HIV infection and hypertension were similar among regimens ($P = 0.681$ and $P = 0.254$). Overall, 196 patients (30.7%) had comorbidity, highest in the LTR group ($P = 0.025$). Tuberculosis treatment history differed by regimen ($P < 0.001$): 39.9% were new cases, 31.3% relapse, 20.0% treatment failure, and 7.5% lost to follow-up. LTR was common in treatment-failure cases, whereas new cases were mainly managed with BPaLM/BPaL and STR. Drug-resistance classification differed across regimens ($P < 0.001$): RR-TB predominated in STR group, MDR-TB and pre-XDR-TB in BPaLM/BPaL and LTR, and all XDR-TB cases received LTR.

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Table 1. Baseline Characteristics of Study Participants According to Treatment Regimen

Characteristic	Overall (n = 639)	BPaLM/BPaL (n = 122)	STR (n = 211)	LTR (n = 306)	*P* value
Study center					<0.001
Dr. Tadjuddin Chalid Hospital	262 (41.0)	62 (50.8)	67 (31.8)	133 (43.5)	
Labuang Baji Hospital	315 (49.3)	45 (36.9)	134 (63.5)	136 (44.4)	
Dr. Wahidin Sudirohusodo Hospital	62 (9.7)	15 (12.3)	10 (4.7)	37 (12.1)	
Age, years					0.730
Median (IQR)	41 (30–53)	38 (30–52)	42 (29–53)	41 (31–52)	
Mean ± SD	41.8 ± 15.0	41.0 ± 15.4	42.1 ± 15.8	41.9 ± 14.3	
Male sex	369 (57.7)	64 (52.5)	132 (62.6)	173 (56.5)	0.167
Employment status					0.204
Employed	269 (42.1)	42 (34.4)	84 (39.8)	143 (46.7)	
Unemployed/Housewife	305 (47.7)	67 (54.9)	101 (47.9)	137 (44.8)	
Student	32 (5.0)	8 (6.6)	13 (6.2)	11 (3.6)	
Others	33 (5.2)	5 (4.1)	13 (6.2)	15 (4.9)	
Nutritional status (BMI)					0.359
Underweight	365 (57.1)	60 (49.2)	117 (55.5)	188 (61.4)	
Normal weight	224 (35.1)	49 (40.2)	78 (37.0)	97 (31.7)	
Overweight	29 (4.5)	8 (6.6)	10 (4.7)	11 (3.6)	
Obesity	21 (3.3)	5 (4.1)	6 (2.8)	10 (3.3)	
Comorbidities					
Diabetes mellitus	96 (15.0)	14 (11.5)	23 (10.9)	59 (19.3)	0.015
HIV infection	32 (5.0)	8 (6.6)	10 (4.7)	14 (4.6)	0.681
Hypertension	87 (13.6)	19 (15.6)	22 (10.4)	46 (15.0)	0.254
≥1 comorbidity	196 (30.7)	35 (28.7)	52 (24.6)	109 (35.6)	0.025
Previous TB treatment history					<0.001
New case	255 (39.9)	61 (50.0)	105 (49.8)	89 (29.1)	
Relapse	200 (31.3)	40 (32.8)	70 (33.2)	90 (29.4)	
Treatment after failure	128 (20.0)	14 (11.5)	20 (9.5)	94 (30.7)	
Treatment after loss to follow-up	48 (7.5)	7 (5.7)	10 (4.7)	31 (10.1)	
Drug-resistant TB classification					<0.001
RR-TB	408 (63.8)	62 (50.8)	175 (82.9)	171 (55.8)	

MDR-TB	173 (27.1)	51 (41.8)	36 (17.1)	86 (28.1)	
Pre-XDR-TB	37 (5.9)	9 (7.4)	0 (0.0)	28 (9.2)	
XDR-TB	21 (3.2)	0 (0.0)	0 (0.0)	21 (6.9)	

Data are presented as n (%) unless otherwise indicated. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]). P values were calculated using Pearson's chi-square test, Fisher–Freeman–Halton exact test, or Kruskal–Wallis test, as appropriate.

3.2 Safety outcomes according to treatment regimen

Table 2 summarizes safety across regimens. Overall adverse drug reactions occurred in 67.6% of patients and differed significantly, highest in the BPaLM/BPaL group (77.0%), followed by LTR (71.6%) and STR (56.4%) ($p<0.001$). Most were grade 1–2, but grade 3–4 reactions were more frequent in LTR (22.4%) than in BPaLM/BPaL (10.6%) and STR (5.8%) ($p<0.001$). Most occurred during the first two months, with no significant difference in onset time ($p=0.484$). Table 3 shows ADR types by regimen. Gastrointestinal disorders were most common (57.6%), followed by neurological (23.8%), dermatologic (23.6%), and musculoskeletal disorders (23.6%); cardiac (8.6%), hematologic (7.7%), hepatic (5.3%), electrolyte abnormalities (4.5%), visual (4.4%), and hearing disorders (1.3%) were less common. BPaLM/BPaL had the highest proportions of gastrointestinal (66.4%), neurological (41.8%), electrolyte abnormalities (12.3%), and hepatic disorders (9.0%) (all $p<0.05$; $p=0.013$). LTR had higher rates of hematologic (11.8%), cardiac (11.4%), visual (8.2%), dermatologic (32.7%), and musculoskeletal disorders (29.1%) compared with the other regimens. Hearing disorders were uncommon and did not differ significantly ($p=0.292$).

Table 2. Safety profile according to treatment regimen

Variable	BPaLM/BPaL (n=122)	STR (n=211)	LTR (n=306)	p-value
A. Overall adverse drug reactions, n (%)				
Any adverse drug reaction	94 (77.0)	119 (56.4)	219 (71.6)	<0.001†
No adverse drug reaction	28 (23.0)	92 (43.6)	87 (28.4)	
***B. Severity of adverse drug reactions, n (%)** **				
Grade 1	65 (69.1)	79 (66.4)	121 (55.3)	<0.001‡
Grade 2	19 (20.2)	33 (27.7)	49 (22.4)	
Grade 3	10 (10.6)	6 (5.0)	47 (21.5)	
Grade 4	0 (0.0)	1 (0.8)	2 (0.9)	
***C. Time to first adverse drug reaction, n (%)** **				
Month 1	62 (66.7)	62 (55.4)	125 (62.5)	0.484†
Month 2	22 (23.7)	29 (25.9)	33 (16.5)	
Month 3	5 (5.4)	7 (6.2)	13 (6.5)	
Month 4	4 (4.3)	8 (7.1)	10 (5.0)	
Month 5	—	3 (2.7)	3 (1.5)	
Month 6	—	—	5 (2.5)	
Month 7	—	1 (0.9)	1 (0.5)	
Month 8	—	1 (0.9)	3 (1.5)	

Month 9	—	—	3 (1.5)	
Month 10	—	1 (0.9)	2 (1.0)	
Month 12	—	—	1 (0.5)	
Month 15	—	—	1 (0.5)	

Percentages for severity and onset were calculated among patients who experienced adverse drug reactions only. † Chi-square test. ‡ Fisher–Freeman–Halton exact test.

Table 3. Types of adverse drug reactions according to drug-resistant tuberculosis treatment regimen

Type of adverse drug reaction	BPaLM/BPaL (n=122)	STR (n=211)	LTR (n=306)	Overall (n=639)	p-value
Gastrointestinal disorders	81 (66.4%)	104 (49.3%)	183 (59.8%)	368 (57.6%)	0.005†
Hematologic disorders	11 (9.0%)	2 (0.9%)	36 (11.8%)	49 (7.7%)	<0.001†
Neurological disorders	51 (41.8%)	25 (11.8%)	76 (24.8%)	152 (23.8%)	<0.001†
Cardiac disorders	9 (7.4%)	11 (5.2%)	35 (11.4%)	55 (8.6%)	0.040†
Electrolyte abnormalities	15 (12.3%)	3 (1.4%)	11 (3.6%)	29 (4.5%)	<0.001†
Hepatic disorders	11 (9.0%)	4 (1.9%)	19 (6.2%)	34 (5.3%)	0.013†
Hearing disorders	0 (0.0%)	2 (0.9%)	6 (2.0%)	8 (1.3%)	0.292‡
Visual disorders	2 (1.6%)	1 (0.5%)	25 (8.2%)	28 (4.4%)	<0.001†
Dermatologic disorders	12 (9.8%)	39 (18.5%)	100 (32.7%)	151 (23.6%)	<0.001†
Musculoskeletal disorders	23 (18.9%)	39 (18.5%)	89 (29.1%)	151 (23.6%)	0.008†

† Pearson's chi-square test. ‡ Fisher–Freeman–Halton exact test.

3.3 Treatment Outcomes and Overall Treatment Effectiveness

Table 4 summarizes final outcomes and treatment effectiveness by regimen. Outcomes differed across the three regimens ($p < 0.001$). Overall, 314 patients (49.1%) were cured, 69 (10.8%) completed treatment, 85 (13.3%) died, 63 (9.9%) were lost to follow-up, 30 (4.7%) had treatment failure, and 78 (12.2%) were reclassified because of a change in diagnosis. BPaLM/BPaL had the most favorable outcomes, with the highest cure (63.9%) and treatment completion (20.5%) and the lowest death (4.1%), loss to follow-up (3.3%), and treatment failure (4.9%). STR had the lowest cure rate (32.2%) and highest change in diagnosis (34.6%), while LTR had an intermediate cure (54.9%) but highest mortality (20.9%).

After excluding patients whose diagnoses changed, the effectiveness of treatment was assessed in 561 individuals. In total, 383 patients (68.3%) experienced successful treatment outcomes, either being cured or completing treatment, while 178 patients (31.7%) faced unsuccessful outcomes, such as treatment failure, loss to follow-up, or death. There was a significant variation in treatment effectiveness across different regimens ($p < 0.001$). The BPaLM/BPaL regimen demonstrated the highest effectiveness at 87.3%, followed by LTR at 63.9% and STR at 61.6%. On the other hand, the BPaLM/BPaL group had the lowest rate of ineffective outcomes at 12.7%, compared to 38.4% in the STR group and 36.1% in the LTR group. These results suggest a significant association between the treatment regimen and both the distribution of final treatment outcomes and overall effectiveness.

Table 4. Treatment Outcomes and Overall Treatment Effectiveness According to Treatment Regimen

Outcome	BPaLM/BPaL (n = 122)	STR (n = 211)	LTR (n = 306)	Total (n = 639)	P-value
Final treatment outcomes					<0.001†
Cured	78 (63.9)	68 (32.2)	168 (54.9)	314 (49.1)	
Treatment completed	25 (20.5)	17 (8.1)	27 (8.8)	69 (10.8)	

Treatment failure	6 (4.9)	9 (4.3)	15 (4.9)	30 (4.7)	
Failure due to change in diagnosis	4 (3.3)	73 (34.6)	1 (0.3)	78 (12.2)	
Lost to follow-up	4 (3.3)	28 (13.3)	31 (10.1)	63 (9.9)	
Death	5 (4.1)	16 (7.6)	64 (20.9)	85 (13.3)	
Overall treatment effectiveness‡					<0.001†
Effective (cured + treatment completed)	103/118 (87.3)	85/138 (61.6)	195/305 (63.9)	383/561 (68.3)	
Ineffective (treatment failure + lost to follow-up + death)	15/118 (12.7)	53/138 (38.4)	110/305 (36.1)	178/561 (31.7)	

Values are presented as n (%). † Pearson's chi-square test. ‡ Patients with *failure due to change in diagnosis* (n = 78) were excluded from the treatment effectiveness analysis.

3.4 Multivariable Analysis of Factors Associated with Treatment Effectiveness and Severe Adverse Events

Table 5 displays the results of multivariable logistic regression analyses concerning factors linked to treatment effectiveness (Panel A) and severe adverse events (Panel B). In Panel A, the treatment regimen was found to be independently linked to treatment effectiveness. Patients on the STR regimen (adjusted OR [aOR] 0.27, 95% CI 0.14–0.53; p<0.001) and those on LTR (aOR 0.30, 95% CI 0.16–0.55; p<0.001) had notably lower chances of achieving effective treatment outcomes compared to those on the BPaLM/BPaL regimen. Additionally, as age increased, treatment effectiveness decreased (aOR 0.98 per year, 95% CI 0.97–0.99; p=0.005). The presence of at least one comorbidity also independently reduced the probability of treatment success (aOR 0.57, 95% CI 0.37–0.88; p=0.012). On the other hand, patients who encountered any adverse event had greater odds of treatment effectiveness (aOR 2.70, 95% CI 1.77–4.12; p<0.001). Factors such as sex, being underweight, previous tuberculosis treatment, and severe adverse events did not show an independent association with treatment effectiveness.

Table 5. Multivariable analysis of factors associated with treatment effectiveness and severe adverse events

Variable	Panel A. Treatment effectiveness			Panel B. Severe adverse events		
	Adjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Treatment regimen						
BPaLM/BPaL	Reference	–	–	Reference	–	–
STR vs BPaLM/BPaL	0.27	0.14–0.53	<0.001*	0.39	0.14–1.05	0.063
LTR vs BPaLM/BPaL	0.30	0.16–0.55	<0.001*	2.45	1.17–5.13	0.018*
Age (per 1-year increase)	0.98	0.97–0.99	0.005*	1.02	1.00–1.04	0.057
Male sex (vs female)	1.08	0.73–1.61	0.695	1.05	0.61–1.82	0.850
Underweight (vs other nutritional status)	0.68	0.46–1.02	0.063	0.61	0.36–1.05	0.073
≥1 comorbidity (vs none)	0.57	0.37–0.88	0.012*	—	—	—
Diabetes mellitus (vs no)	—	—	—	0.47	0.21–1.07	0.074
HIV infection (vs no)	—	—	—	1.48	0.47–4.69	0.504
Previous TB treatment (vs new case)	0.69	0.45–1.04	0.077	0.97	0.55–1.70	0.915
Any adverse event (vs none)	2.70	1.77–4.12	<0.001*	—	—	—
Severe adverse event (vs none)	1.35	0.69–2.66	0.381	—	—	—

Abbreviations: OR, odds ratio; CI, confidence interval; STR, short-term regimen; LTR, long-term regimen; BPaLM/BPaL, bedaquiline–pretomanid–linezolid–moxifloxacin/bedaquiline–pretomanid–linezolid; HIV, human immunodeficiency virus.

Panel B revealed that only the treatment regimen was independently associated with severe adverse events. The LTR regimen was linked to a significantly higher risk of severe adverse events compared to BPaLM/BPaL (aOR 2.45, 95% CI 1.17–5.13; p=0.018), while STR exhibited a non-significant tendency towards reduced odds (aOR 0.39, 95% CI 0.14–1.05; p=0.063). Factors such as age, sex, underweight status, diabetes mellitus, HIV infection, and previous tuberculosis treatment did not show significant associations with severe adverse events after multivariable adjustment.

3.5 Discussion

The present study demonstrated that treatment effectiveness differed significantly across drug-resistant tuberculosis (DR-TB) regimens, with the BPaLM/BPaL regimen achieving the highest treatment success compared with the STR and LTR. These findings are consistent with Conradie et al. (2020), who reported high treatment success among patients receiving BPaL for highly drug-resistant tuberculosis, highlighting the potent bactericidal activity of bedaquiline, pretomanid, and linezolid [1]. Similarly, Gualano et al. (2025) and Khan et al. (2024) observed favorable programmatic outcomes following implementation of BPaLM/BPaL in routine clinical practice [2,3].

The superior effectiveness of BPaLM/BPaL is biologically plausible. The regimen combines multiple drugs targeting different bacterial pathways, including ATP synthase inhibition by bedaquiline, protein synthesis inhibition by linezolid, inhibition of DNA gyrase by moxifloxacin, and nitric oxide-mediated killing by pretomanid. In addition, the shorter treatment duration likely improves adherence and reduces cumulative treatment fatigue, thereby decreasing the risk of loss to follow-up.

Conversely, the lower effectiveness observed in the LTR group should not be interpreted solely as inferior regimen performance. Patients receiving LTR in this cohort presented with more complex baseline characteristics, including higher proportions of previous TB treatment, multiple comorbidities, and more extensive drug resistance. This phenomenon reflects confounding by indication, whereby patients with more severe disease are preferentially assigned to longer individualized regimens. Similar observations were reported by Abidi et al. (2020) and Wahid et al. (2022), who demonstrated that baseline disease severity substantially influences treatment outcomes independent of regimen type [4,5].

Interestingly, STR showed lower treatment effectiveness than reported in several previous cohorts. This finding contrasts with Korotych et al. (2024) and the systematic review by Mahardani et al. (2022), which demonstrated favorable outcomes with standardized nine-month regimens [6,7]. The discrepancy may be explained by differences in patient selection, baseline resistance profiles, implementation period, and the relatively high proportion of patients with revised diagnoses in the present study, which reflects real-world programmatic conditions rather than highly selected clinical trial populations.

Collectively, these findings support the growing evidence that BPaLM/BPaL should be considered the preferred regimen for eligible patients with DR-TB. Nevertheless, individualized long-term regimens remain indispensable for patients with extensive resistance, drug intolerance, or contraindications to newer regimens. Therefore, treatment selection should continue to be individualized based on drug susceptibility testing, clinical characteristics, and patient-specific risk factors rather than regimen duration alone.

ADRs were frequent in cohort and differed across regimens. Patients receiving BPaLM/BPaL had the highest ADR incidence, whereas severe ADRs were more common with LTR. These findings align with Gualano et al. (2025) and Conradie et al. (2020), who reported that although BPaL-based regimens improve outcomes, safety monitoring remains essential because of linezolid-associated toxicity [1,2]. Gastrointestinal and neurological adverse events predominated in the BPaLM/BPaL group, consistent with pharmacological profiles of pretomanid and linezolid. Jaspard et al. (2020) showed that prolonged linezolid exposure is associated with peripheral neuropathy and myelosuppression through mitochondrial dysfunction, whereas pretomanid commonly causes gastrointestinal intolerance [8]. Cardiac adverse events were more frequent with LTR, consistent with Khan et al. (2024) describing QT-prolongation with exposure to QT-prolonging agents [3]. Most ADRs were mild to moderate and occurred in the first two months, emphasizing pharmacovigilance.

Multivariable analysis confirmed treatment regimen as an independent predictor of effectiveness after adjustment for demographic characteristics. Compared with BPaLM/BPaL, STR and LTR were associated with lower odds of successful treatment, supporting findings from Nasution et al. (2026) and Tahitoe et al. (2025) [9,10]. Older age and comorbidities were

associated with poorer outcomes, consistent with studies showing immune response, reduced reserve, and greater treatment complexity in older patients and those with chronic diseases. ADRs were associated with higher treatment success. This should not be interpreted as a protective effect but reflects survivorship (time-at-risk) bias, as patients on longer treatment have more opportunities to experience ADRs and complete therapy successfully.

This study presents several limitations that must be taken into account when interpreting the results. Firstly, the retrospective observational nature of the study, which relies on medical records, prevents the establishment of causal links and is contingent on the accuracy and completeness of routinely gathered clinical data. This reliance may have led to the underreporting of adverse events, their onset, and any changes in treatment. Secondly, treatment regimens were chosen based on clinical indications, drug-resistance profiles, comorbidities, and programmatic factors rather than through random allocation. This selection process introduces the potential for confounding by indication, especially among patients on long-term regimens. Thirdly, since patients were treated with multidrug combination therapy, it was not possible to definitively attribute individual adverse events to a specific drug. Fourthly, the observed link between adverse events and treatment effectiveness might have been affected by time-at-risk (survivorship) bias, as patients who remained on treatment longer had more chances to experience adverse events and achieve successful outcomes. Lastly, several potentially significant determinants of treatment outcomes, such as medication adherence, socioeconomic status, disease severity, microbiological response, and pharmacokinetic or pharmacogenomic factors, were not available for analysis. Consequently, prospective studies with standardized monitoring of adverse events and more thorough adjustment for potential confounders are needed to confirm these findings.

4. CONCLUSION

This research reveals notable differences in the safety and efficacy of DR-TB treatments among BPaLM/BPaL, STR, and LTR. Despite the treatment groups having generally similar demographic profiles, they varied in terms of clinical complexity and drug-resistance patterns. BPaLM/BPaL demonstrated the highest effectiveness in treatment, while LTR was linked to the highest likelihood of severe adverse events. Factors such as treatment regimen, age, comorbidities, and adverse event occurrence were independently linked to treatment effectiveness, with LTR specifically increasing the risk of severe adverse events. These results underscore the necessity of tailoring regimen choices to individual patient characteristics and resistance profiles, along with active safety monitoring, to enhance treatment outcomes for DR-TB patients.

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AUTHOR CONTRIBUTIONS

MAH: Conceptualization, methodology, data collection, formal analysis, manuscript drafting, and manuscript revision.
NL: Study supervision, conceptualization, methodology, manuscript review, and critical revision.
SN: Data interpretation, manuscript review, and critical revision.
ID: Methodological supervision, manuscript review, and critical revision.
MI: Data interpretation, manuscript review, and critical revision.
HAP: Statistical analysis, manuscript review, and critical revision.

All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS STATEMENT

The Health Research Ethics Committee of the Faculty of Medicine at Hasanuddin University granted approval for the study protocol (Approval No. 534/UN4.6.4.5.31/PP36/2026). Access to medical records was authorized by Dr. Wahidin Sudirohusodo Hospital (Research Permit No. DP.04.03/D.XVIII.2/8878/2026) and the involved institutions. Since the study

was retrospective and utilized anonymized secondary data, the ethics committee waived the need for informed consent. To ensure patient confidentiality, all personal identifiers were removed prior to data analysis.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available because they contain confidential patient information. De-identified data may be made available from the corresponding author upon reasonable request and with permission from the participating institutions and ethics committee.

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