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RESEARCH ARTICLE

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Frequency, management and impact of adverse events on treatment outcomes in patients with multidrug resistant tuberculosis in Balochistan, Pakistan

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ABSTRACT

Background: Early detection, monitoring, and managing adverse events (AEs) are crucial in optimising treatment for multidrug-resistant tuberculosis (MDR-TB) patients.

Objectives: To investigate the incidence, factors, management, and impact of AEs on treatment outcomes in MDR-TB patients.

Methods: This study reviewed the medical records of 275 MDR-TB patients at Fatimah Jinnah Institute of Chest Diseases in Quetta, Pakistan. Patient information was collected using a designed data collection form. Mann–Whitney *U* and Kruskal–Wallis tests examined the difference in AEs occurrences based on patients' characteristics. Multiple binary logistic regression identified factors associated with unsuccessful outcomes, with statistical significance set at a p-value < 0.05.

Results: Almost all patients (99.6%) experienced at-least one AE (median = 4/patient, interquartile range:3-6). The most common were GI disturbance (95.3%), arthralgia (80.4%), body pain and headache (61.8%), ototoxicity (61.4%), psychiatric disturbance (44%), hypokalaemia (40.4%), dermatological reactions (26.2%) and hypothyroidism (21.5%). AEs led to treatment modification in 7.3% patients. Educated patients, those with a history of TB treatment, previous use and resistance to any second-line drug had significantly higher number of AEs. A total of 64.0% were declared cured, 3.6% completed treatment, 19.6% died and 12.7.9% were lost to follow-up. Patients' age of 41-60(OR = 9.225) and >60 years(OR = 23.481), baseline body weight of 31–60 kg(OR = 0.180), urban residence(OR = 0.296), and experiencing ototoxicity

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(OR = 0.258) and hypothyroidism (OR = 0.136) were significantly associated with unsuccessful treatment outcomes.
Conclusion: AEs were highly prevalent but did not negatively impact treatment outcomes. Patients at higher risk of developing AEs and unsuccessful outcomes should receive special attention for its early management.

KEYWORDS Adverse events; hypokalaemia; hypothyroidism; MDR-TB; Pakistan; ototoxicity

Introduction

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis* (MTB). Despite the availability of effective diagnosis and treatment regimens, in 2022, approximately 10.6 million (range = 9.9-11.4 million) individuals worldwide developed TB and 1.3 million people died of it (WHO, 2023). Over the past two decades, highly effective anti-TB treatments and public health interventions have prevented an estimated 63 million TB deaths, resulting in a 27% reduction in TB-attributed mortality (WHO, 2020). However, despite these achievements, the occurrence and increasing prevalence of multidrug-resistant TB (MDR-TB) defined as 'TB caused by MTB strain concurrently resistant to both rifampicin (R) and isoniazid (H), the two most effective and well tolerated first line anti-TB drugs' undermining these achievements (Ahmad et al., 2015). In 2022, the projected percentage of individuals diagnosed with TB who had MDR-TB stood at 3.3% for new cases and 17% for individuals with prior treatment (WHO, 2023). In order to improve the efficacy, safety, and affordability of treatment regimens for MDR-TB, the World Health Organization (WHO) has continuously revised its guidelines for managing this condition since 2000. The WHO's latest guidelines published in 2022, classify anti-TB drugs into three groups: Group A (levofloxacin (Lfx)/moxifloxacin (Mfx), bedaquline (Bdq), linezolid (Lzd)), Group B (clofazimine (Cfz), cycloserine (Cs)/terizidone (Tzd)), and Group C (ethambutol (E), delamanid (Dlm), pyrazinamide (Z), meropenem/imepenem-cilastatin, amikacin (Am) /streptomycin (S), ethionamide (Eto)/prothionamide (Pto), para-aminosalicylic acid (PAS)). According to these guidelines, MDR-TB patients without documented resistance to fluoroquinolones (FQ), no prior exposure to second-line drugs (SLD) for more than one month, and without extensive pulmonary or severe extra-pulmonary disease, are recommended to undergo treatment with an all-oral shorter treatment regimen (STR). This regimen entails 4–6 months of treatment with Bdq + Lfx/Mfx + Eto + Cfz + Z + E + high dose isoniazid, followed by an additional 5 months with Lfx/Mfx + Cfz + Z + E. Those MDR-TB patients who are not eligible for treatment with the all-oral STR should undergo treatment with an all-oral longer treatment regimen (LTR) for a minimum duration of 18–20 months. Treatment with

all-oral LTR should commence with four likely effective drugs against MDR-TB. A likely effective drug is defined as one that either demonstrates confirmed susceptibility or, if susceptibility results are unavailable, has not been taken by the patient for more than one month. Ideally, the all-oral LTR should comprise all three agents from Group A and one from Group B. If only one or two agents from Group A are utilised, both agents from Group B should be included. In cases where it is not feasible to construct a regimen likely to be effective from Group A and B agents, agents from Group C should be incorporated (WHO, 2022).

As MDR-TB patients are concurrently resistant to both rifampicin (R) and isoniazid (H), the two most effective and well tolerated first line anti-TB drugs (Ahmad, Ahuja, et al., 2018; Javaid, Shaheen, et al., 2017), therefore, these patients need to take a combination of less effective and potentially more harmful second line anti-TB drugs for longer periods of time (N Ahmad et al., 2015; Lan et al., 2020). This can result in higher rates of treatment failure and adverse events (AEs) in these patients (Ahmad, Javaid, et al., 2015; Ahmad, Ahuja, et al., 2018; Lan et al., 2020). The AEs experienced during MDR-TB treatment can range from mild discomfort (such as gastrointestinal problems) to permanent disability (such as hearing and vision loss) and life threatening events (such as liver, kidney and heart damage) (Ategyeka et al., 2023; Bloss et al., 2010; Buajordet et al., 2001; Furin et al., 2001; Lan et al., 2020; Sagwa et al., 2014; Sonya Shin et al., 2004; SS Shin et al., 2007; Wrohan et al., 2021; Zhang et al., 2017). The management of AEs among MDR-TB patients is difficult for doctors, especially when there are few or no alternative drugs available that are equally effective and safe (Ahmad, Javaid, Sulaiman, et al., 2018; Lan et al., 2020; Merid et al., 2019; Törün et al., 2005). Reducing or stopping the suspected drug, or replacing it with a less effective drug, could compromise the treatment regimen and lead to therapy failure. On the other hand, continuing the treatment with the suspected drug could lead to AEs that affect the patients' quality of life, cause permanent damage or endanger their lives (Ahmad, Javaid, et al., 2018; Lan et al., 2020; Sturdy et al., 2011). This situation is more challenging in resource limited settings where specialist services for managing AEs are often lacking (Ahmad, Javaid, et al., 2018; Lan et al., 2020). Previous quantitative and qualitative research has shown that the occurrence of AEs during MDR-TB treatment is a risk factor for patients' lost to follow up (LTFU) (Burtscher et al., 2016; Sanchez-Padilla et al., 2014; Xing et al., 2021).

Unfortunately, Pakistan is currently ranked as 5th highest burden country in the world for MDR-TB, with an estimated occurrence of 4.5% in new TB patients and 18% in patients who have previously undergone TB treatment (Abudl Wahid et al., 2021). The programmatic management of DR-TB (PMDT) was initiated in Pakistan in 2010, and currently, there are 33 PMDT centres in the country (Abubakar et al., 2021). At these centres, MDR-TB

patients receive care according to uniform protocols recommended by the World Health Organization (WHO) and adopted by the National TB Control Program (NTP) (Abubakar, Ahmad, Atif, Khan, & Ghafoor, 2022; Javaid et al., 2018; Khan et al., 2019; Naz et al., 2021). While there is significant information available from Pakistan regarding the treatment outcomes and predictors of unsuccessful outcomes among MDR-TB patients (Abubakar et al., 2021; N Ahmad et al., 2015; Atif et al., 2017; Javaid et al., 2018; Javaid, Shaheen, et al., 2017; Khan et al., 2019; Naz et al., 2021; Abdul Wahid et al., 2022), there is scarcity of detailed information regarding the occurrence and management of AEs during MDR-TB treatment as well as their impact on treatment outcomes (Atif et al., 2022; Massud et al., 2022) from Pakistan in general and Balochistan in particular, which is the largest province in Pakistan in terms of area. Since early detection, monitoring, and appropriate management of AEs are crucial for optimising MDR-TB treatment, therefore, the current study was conducted with the objectives to evaluate the pattern, frequency, management, and risk factors associated with AEs and as well as their impact on treatment outcomes among MDR-TB patients.

Methods

Study design, settings and subjects

This study involved a retrospective review of medical records of MDR-TB patients irrespective of age, gender and comorbidity status, who underwent treatment at the PMDT unit of Fatimah Jinnah Institute of Chest Diseases (FJICD) in Quetta, Pakistan, between January 2014 and December 2019. During the study period, the chosen study site represented the only PMDT unit in Balochistan. Those patients who suffered from DR-TB other than MDR-TB i.e. mono-DR-TB, poly DR-TB and extensively DR-TB, and MDR-TB patients who received treatment for less than one month and who were transferred out to other PMDT units for treatment were excluded from the study.

Patients' diagnosis and treatment protocols

The diagnostic and treatment protocols of MDR-TB patients at the study site were consistent with those reported in the studies conducted at the same study site and other PMDT units (Ahmad et al., 2015; Atif et al., 2017; Javaid, Hasan, et al., 2017; Javaid, Shaheen, et al., 2017; Khan et al., 2019). In summary, two diagnostic samples of all presumed MDR-TB patients presented to the FJICH were initially examined for infection with RR-TB using sputum smear microscopy and rapid drug susceptibility testing (DST) through Gene-Xpert. Patients with a positive finding of rifampicin resistant-TB were subjected to further laboratory evaluation and enrolled for treatment with an

Table 1. Doses of drugs used for the treatment of RR/MDR-TB patients.

Drugs name	Doses
Amikacin/kanamycin/capreomycin	15–20 mg/kg (up to 1000 mg) six days/week
Levofloxacin	15–20 mg/kg daily (up to 1500 mg)
Ethionamide	15–20 mg/kg daily (up to 1000 mg)
Cycloserine	10–15 mg/kg daily (up to 1000 mg)
Para-amino salicylic acid	150 mg/kg (up to 12 gm)
Pyrazinamide	30–40 mg/kg daily (up to 2500 mg)
Ethambutol	25 mg/kg daily (up to 2000mg)

Notes: mg, milligram; kg, kilogram.

empirical regimen recommended by NTP guidelines (N Ahmad et al., 2015; Atif et al., 2017; Javaid, Hasan, et al., 2017; Javaid, Shaheen, et al., 2017; Khan et al., 2019). Their diagnostic samples were sent to Indus Hospital Karachi Laboratory for conventional DST. Upon receiving DST results, patients were shifted to individualised treatment regimen. MDR-TB patients without resistance to any SLD were treated with amikacin (Am)/kanamycin (Km)/capreomycin (Cm) + Lfx + Eto + Cs + Z + vitamin-B_6, while patients with resistance to any SLD had PAS added to the aforementioned regimen. Patients were given the maximum recommended doses per body weight (Table 1) and treated for a minimum of 18 months after achieving sputum culture conversion (SCC) defined as 'two successive negative sputum cultures taken at a one month interval following a baseline positive culture' (Abubakar, Ahmad, Atif, Ahmad, et al., 2022). Injectable SLD (Am/Km/Cm) was administered for at-least eight months, and a minimum of six months post SCC. After the initial admission for few days to observe tolerance, all patients received ambulatory treatment, and their adherence to the treatment was monitored and reported by trained treatment supporters during monthly visits to the centre.

During the baseline visit, in addition to chest x-ray, the laboratory workup included tests for full blood count (FBC), renal and liver function, thyroid function, random blood glucose, serum electrolytes, uric acid, and screening for Human Immunodeficiency Virus (HIV) and viral hepatitis. Audiometry and visual tests were performed in some patients based on physician's judgment, if and when required. Chest x-ray, FBC, liver and renal function tests, and serum electrolytes were performed monthly during the use of injectable SLD and periodically thereafter. Thyroid function test and uric acid levels were typically checked every six months or as ordered by the physician. As per recommendations of NTP guidelines, on each monthly visit, patient self-reported, physician's observed or objectively confirmed AEs along with their management and outcomes were reported in AEs reporting form.

Data collection

A purpose designed data collection form based on extensive literature review, and input from clinicians, pharmacist and a psychologist at the

Table 2. Definitions of adverse events.

Adverse events	Definition
Gastrointestinal disturbance	Anyone of the following conditions reported by patient and documented by physician: anorexia, nausea, vomiting, abdominal pain, constipation, diarrhoea, dyspepsia, gastritis, peptic ulcer, etc.
General body pain and headache	As reported by patient and documented by physician
Psychiatric disturbance	Anxiety, depression or psychosis as diagnosed and documented by psychologist/physician
Arthralgia	Pain or swelling in joints as reported by patient, and diagnosed or documented by physician with or without arthritis or elevated uric acid level >9 mg/dl*
Dermatological reaction	Any skin manifestation characterised by itching, erythematous rash, skin discolouration or photosensitivity noted by physician
Ototoxicity	Tinnitus and vertigo reported by patient and documented by physician or hearing loss confirmed through audiometry or physical examination
Hypokalaemia	At least one serum potassium value <3.5 mEq/L
Nephrotoxicity	At least one serum creatinine value >1.3 mg/dl for male and >1.1 mg/dl for female
Hypothyroidism	At least one TSH value >5 µU/ml
Hepatotoxicity	i. At least one elevated level of ALT or bilirubin >3 times of the ULN** with symptoms ii. At least one elevated level of ALT or serum bilirubin >5 times of the ULN with or without symptoms
Peripheral neuropathy	Fatigue, pain, stinging, numbness of extremities and burning feet as documented by doctor or diagnosed by nerve conduction studies
Burning or difficulty on micturition	As reported by patient and documented by physician
Vision impairment	As reported by patient and documented by physician
Mouth ulcer	As reported by patient and documented by physician
Menorrhagia	As reported by patient and documented by physician

Notes: ALT, alanine transaminase; mg/dl, milligram per decilitre; mEq/L, milli-equivalent per litre; TSH, thyroid stimulating hormone; ULN, upper limit normal.
**Normal ALT level = 0-41 units per litre; normal bilirubin level <1 milligram/decilitre.

study site was used to collect sociodemographic, microbiological and clinical data of patients from their baseline visit until the reporting of their treatment outcomes. The treatment outcomes of the patients were determined according to the criteria outlined in guidelines proposed by WHO and NTP (WHO, 2016). The outcomes of cured and treatment completed were collectively grouped as successful, whereas death, treatment failure and LTFU as unsuccessful outcomes (N Ahmad et al., 2015; Atif et al., 2017; Javaid, Hasan, et al., 2017; Javaid, Shaheen, et al., 2017; Khan et al., 2019). AEs along with their management and outcomes were noted from the AEs reporting form. The criteria given in Table 2 were used to define AEs.

Statistical analysis

Data were analysed by SPSS version 23. To examine the differences in the number of AEs based on sociodemographic and clinical characteristics, Mann–Whitney *U* test and Kruskal–Wallis test were employed, as appropriate.

To identify factors associated with unsuccessful treatment outcomes, multiple binary logistic regression analysis (MBLRA) was conducted. Only those variables with a *p*-value <0.2 in the univariate analysis were included in MBLRA after checking for correlation. In case where independent variables exhibited high correlation, (Tolerance value <0.1 and/or Variance inflation factor = 10), one of them was excluded from the final model. A *p*-value <0.05 was deemed statistically significant.

Results

Patients' baseline characteristics and drug resistance pattern

A total of 275 patients met the established eligibility criteria and were included in the final analysis. The mean age of study participants was 38.0 ± 17.4 years. Majority of them were females (65.5%), 21–40 years old (51.6%), had body weight of 31-60 kg (83.6%), rural residents (64.7%), uneducated (89.1%), non-smokers (83.3%), had a documented history of TB treatment (85.3%) and no comorbidity (86.9%). Moreover, a notable proportion of patients also had a history of treatment with an SLD (33.5%) (Table 3). Moreover, patients were resistant to a median of 4 drugs (range: 2-8). Almost half of the patients (49.5%) had resistance to any SLD. Among SLDs, resistance was highest for fluoroquinolone (47.3%) followed by Eto (6.9%) (Table 3).

Frequency, management and factors associated with adverse events

Almost all patients (99.6%) experienced at least one AE with a median of four different events per patient (interquartile range (IQR): 3–6 AEs). Seven patients (2.5%) experienced one, 23 (8.4%) two, 47 (17.1%) three, 60 (21.8%) four, 53 (19.3%) five, 39 (14.2%) six, 27 (9.8%) seven, 13 (4.7%) eight and five (1.8%) nine different AEs. Table 4 displays the frequency, management and outcome of each type of AE. The most common AE was GI disturbance (95.3%), followed by arthralgia (80.4%), general body pain and headache (61.8%), ototoxicity (61.4%), psychiatric disturbance (44%), hypokalaemia (40.4%), dermatological reactions (26.2%) and hypothyroidism (21.5%). Patients' counselling and symptomatic treatment by ancillary drugs were the most common management of AEs. Due to AEs, TB treatment regimen was modified in only 20 (7.3%) patients in whom SLI, Cs and Z were permanently stopped in 12, three and one patient each, respectively. Whereas, PAS was temporarily discontinued in three, and the frequency of administration of SLI was reduced in one patient. The results of Mann–Whitney *U* and Kruskal–Wallis tests revealed that educated patients (*p*-value = 0.049), those with a history of TB

Table 3. Patients' sociodemographic and clinical characteristics.

Variable	No. (%)
Sex	
Female	180 (65.5)
Male	95 (34.5)
Age (years)	
≤20	36 (13.1)
21–40	142 (51.6)
41–60	65 (23.6)
>60	32 (11.7)
Baseline body weight (kilogram)	
≤30	14 (5.1)
31–60	230 (83.6)
>60	31 (11.3)
Residence	
Rural	178 (64.7)
Urban	97 (35.3)
Marital status	
Unmarried	49 (17.8)
Married	226 (82.2)
Education	
Uneducated	245 (89.1)
Educated	30 (10.9)
Smoking status	
Non-smokers	229 (83.3)
Active + ex-smokers	46 (16.7)
Presence of comorbidity	
No	239 (86.9)
Yes	36 (13.1)
Type of comorbidity	
Diabetes mellitus	30
Hepatitis C	3
HIV positive	2
Hypertension	3
Others	6
History of TB treatment	
No	40 (14.5)
Yes	235 (85.5)
Previous use of SLD	
No	183 (66.5)
Yes	92 (33.5)
Resistance to ethambutol	144 (52.5)
Resistance to pyrazinamide	179 (65.1)
Resistance to streptomycin	115 (41.8)
Resistance to all five FLD	73 (26.5)
Resistance to any SLD	136 (49.5)
Resistance to fluoroquinolone	130 (47.3)
Resistance to SLI	3 (1.1)
Resistance to ethionamide	19 (6.9)

Notes: FLD, first-line anti-TB drugs; HIV, Human Immunodeficiency Virus; SLD, second-line anti-TB drugs; SLI, second-line injectable anti-TB drugs.

treatment (p-value = 0.004), previous treatment with an SLD (p-value = 0.003), and resistance to any SLD (p-value = 0.001) had significantly higher number of AEs (Table 5).

Table 4. Types, frequency, management and outcomes of adverse events.

Adverse event	Patients experienced No. (%)	Management	Outcome			
			Resolved	Partially resolved	Not resolved	Not documented
GIT disturbances	**262 (95.3)**	All patients were counselled, reassured and asked to take Eto and PAS in divided doses after light meal.	175	65	22	–
Dyspepsia	237	Prokinetics, PPIs and ancillary drugs = 220				
Anorexia and nausea	139	Temporary discontinuation of PAS = 3				
Vomiting	106					
Constipation	18					
Diarrhoea	16					
Arthralgia	**221 (80.4)**	All patients were counselled and reassured Analgesic and anti-inflammatory drugs prescribed = 193 patients	172	21	27	1
Psychiatric disturbance	**121 (44.0)**	All patients were counselled and reassured.	82	6	29	4
Anxiety	20	Antidepressants prescribed = 88 patients				
Depression	50	Cs permanently discontinued = 3 patients.				
Psychosis	51					
Ototoxicity	**169 (61.4)**	All patients were counselled and reassured.	39	20	97	13
Tinnitus	53 (19.2)	Betahistine prescribed = 42 patients				
Hearing loss	116 (42.2)	SLI dose reduced = 1 patient SLI permanently discontinued = 11 patients Referred to ENT specialist = 27 patients				
Dermatological reactions	**72 (26.2)**	All patients were counselled and reassured. Antihistamines and topical hydrocortisone cream prescribed = 38 patients Patient referred to dermatologist = 1 patient Pyrazinamide permanently discontinued = 1 patient	46	–	21	5
Headache and general body pain	**171 (61.8)**	All patients were counselled and reassured. Analgesics prescribed = 133	125	15	30	11
Hepatotoxicity	**1 (0.3)**	No management	–	–	1	–
Hypothyroidism	**59 (21.5)**	All patients were counselled and reassured. Levothyroxine prescribed = 15 patients Referred to endocrinologist = 4 patients	26	–	30	3
Nephrotoxicity	**35 (12.7)**	All patients were counselled and reassured.	15	–	20	–

(*Continued*)

Table 4. Continued.

Adverse event	Patients experienced No. (%)	Management	Outcome			
			Resolved	Partially resolved	Not resolved	Not documented
Neuropathy	**30 (10.9)**	All patients were counselled, reassured and dose of pyridoxine was increased to 200 mg/day. Pregablin/gabapentin and NSAIDS prescribed = 14 patients.	14	–	14	2
Burning or difficulty on micturition	**10 (3.6)**	All patients were counselled and reassured. Urinary alkalizer prescribed = 5 patients Referred to urologist = 1 patient	7	–	2	1
Mouth ulcer	**2 (0.7)**	All Patients were counselled and reassured. Nystatin was prescribed to one patient.	1	–	1	
Vision impairment	**3 (1.1)**	All three patients were counselled, reassured and referred to ophthalmologist.	1	–		2
Hypokalaemia	**111 (40.4)**	All patients were counselled, reassured and asked to take potassium rich food and supplements. SLI permanently discontinued = 1 patient	69	–	40	2
Menorrhagia	**2 (0.7)**	All patients were counselled and reassured.	–	–	2	–

Notes: Cs, cycloserine; ENT, ear, nose, throat; Eto, ethionamide; GIT, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; PAS, para-amino salicylic acid; PPIs, proton pump inhibitors, SLI, second-line injectable anti-TB drugs.

Table 5. Factors associated with the number of adverse events.

Variable	N	Mean rank	*p*-value
Sex			0.272
Female	180	153.76	
Male	95	130.65	
Age (years)			0.612
≤20	36	152.46	
21–40	142	138.76	
41–60	65	132.88	
>60	32	128.43	
Baseline body weight (kilogram)			0.353
≤30	14	106.12	
31–60	230	139.72	
>60	31	140.45	
Residence			0.536
Rural	178	135.88	
Urban	97	142.01	
Marital status			0.832
Unmarried	49	139.98	
Married	226	137.61	
Education			0.049
Uneducated	245	134.39	
Educated	30	169.211	
Smoking status			0.903
Non-smokers	229	137.67	
Active + ex-smokers	46	139.90	
Presence of comorbidity			0.176
No	239	120.80	
Yes	36	140.59	
History of TB treatment			0.004
No	40	102.46	
Yes	245	150.37	
History of SLD use			0.003
No	183	128.10	
Yes	92	157.33	
Resistance to any SLD			
No	136	130.24	
Yes	139	224.29	0.001

Notes: MDR-TB, multidrug resistant tuberculosis; RR-TB, rifampicin resistant tuberculosis; SLD, second-line anti-TB drugs.

Treatment outcomes and factors associated with unsuccessful outcomes

Of 275 patients included in the final analysis, 186 (67.6%) achieved successful treatment outcomes. Among those with successful outcomes, 176 (64.0%) patients were declared cured and 10 (3.6%) treatment completed. The median duration of treatment among patients with successful treatment outcomes was 23.0 months (IQR: 20.0-30.0 months). Of the remaining 89 (32.4%) patients with unsuccessful outcomes, 54 (19.6%) died and 35 (12.7%) were LTFU. Of 54 patients who died, 40 died during the first four months of treatment. The median time to death was 2.50 months (IQR: 2.00–5.50 months). Of 35 patients who were LTFU, 18 did during the first four months of treatment.

Table 6. Factors associated with unsuccessful outcomes.

Variable	Unsuccessful outcome No. (%)	Univariate analysis		Multivariate analysis	
		OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Sex					
Female	52 (28.9)	Referent		Referent	
Male	37 (38.9)	1.570 (0.930–2.650)	0.091	1.410 (0.600–3.310)	0.431
Age (years)					
≤20	4 (11.1)	Referent		Referent	
21–40	33 (23.2)	2.422 (0.789–7.7349)	0.118	5.217 (0.435–27.004)	0.126
41–60	31 (47.7)	7.249 (2.315–22.984)	0.001	9.225 (2.109–65.741)	0.036
>60	21 (65.6)	15.235 (4.290–54.377)	0.002	23.481 (3.350–150.376)	0.004
Baseline body weight (kilogram)					
≤ 30	9 (46.2)	Referent		Referent	
31–60	65 (20.4)	0.219 (0.071–0.678)	0.008	0.180 (0.032–0.790)	0.036
>60	15 (35.7)	0.521 (0.142–1.912)	0.326	0.395 (0.056–2.676)	0.291
Residence					
Rural	69 (38.8)	Referent		Referent	
Urban	20 (20.6)	0.410 (0.230–0.731)	0.002	0.296 (0.140–0.712)	0.009
Marital status					
Unmarried	12 (24.5)	Referent		Referent	
Married	77 (34.1)	1.593 (0.786–3.231)	0.196	0.208 (0.056–1.218)	0.170
Education					
Uneducated	84 (34.3)	Referent		Referent	
Educated	5 (16.7)	0.383 (0.142–1.038)	0.059	0.240 (0.110–1.489)	0.127
Smoking status					
Non-smokers	71 (39.1)	Referent			
Active + ex-smokers	19 (41.3)	1.431 (0.743–2.754)	0.284		
Presence of comorbidity					
No	73 (30.5)	Referent		Referent	
Yes	16 (44.4)	1.819 (0.892–3.710)	0.100	1.603 (0.498–4.671)	0.432
History of TB treatment					
No	19 (47.5)	Referent		Referent	
Yes	70 (29.8)	0.469 (0.237–0.926)	0.029	0.439 (0.156–1.138)	0.088
History of SLD use					
No	62 (33.9)	Referent			
Yes	27 (29.3)	0.811 (0.471–1.396)	0.449		
Resistance to pyrazinamide					
No	28 (29.2)	Referent			
Yes	61 (34.1)	1.255 (0.733–2.150)	0.407		
Resistance to ethambutol					
No	40 (30.5)	Referent			
Yes	49 (34.0)	1.173 (0.707–1.948)	0.536		

(*Continued*)

Table 6. Continued.

Variable	Unsuccessful outcome No. (%)	Univariate analysis OR (95%CI)	*p*-value	Multivariate analysis OR (95%CI)	*p*-value
Resistance to streptomycin					
No	54 (33.8)	Referent			
Yes	35(30.4)	0.859 (0.51–1.437)	0.562		
Resistance to any SLD					
No	37 (27.2)	Referent			
Yes	52 (37.4)	1.599 (0.960–2.665)	0.071	1.439 (0.630–3.018)	0.234
GI disturbance					
No	7 (53.8)	Referent		Referent	
Yes	82 (31.3)	0.541 (0.176–1.660)	0.100	2.158 (0.543–13.645)	0.468
Arthralgia					
No	22 (40.7)	Referent		Referent	
Yes	67 (30.3)	0.633 (0.342–1.169)	0.144	1.572 (0.664.4.392)	0.398
Psychiatric disturbance					
No	67 (43.5)	Referent		Referent	
Yes	22 (18.2)	0.289 (0.165–0.506)	<0.001	0.639 (0.254–1.740)	0.365
Ototoxicity					
No	60 (67.4)	Referent		Referent	
Yes	29 (17.2)	0.159 (0.091–0.276)	<0.001	0.258 (0.098–0.676)	0.011
General body pain and headache					
No	43 (41.3)	Referent		Referent	
Yes	46 (26.9)	0.522 (0.312–0.875)	0.014	0.642 (0.270–1.621)	0.301
Dermatological reactions					
No	70 (34.5)	Referent		Referent	
Yes	19 (26.4)	0.681 (0.0.374–1.239)	0.209	0.707 (0.257–1.944)	0.502
Hypothyroidism					
No	85 (39.4)	Referent		Referent	
Yes	4 (6.8)	0.112 (0.039–0.321)	<0.001	0.136 (0.098–0.567)	0.010
Nephrotoxicity					
No	79 (32.9)	Referent			
Yes	10 (28.6)	0.815 (0.373–1.780)	0.608		
Hypokalaemia					
No	66 (40.2)	Referent		Referent	
Yes	23 (20.7)	0.388 (0.223–0.676)	0.001	0.612 (0.267–1.598)	0.256
Neuropathy					
No	83 (33.9)	Referent		Referent	
Yes	6 (20.0)	0.488 (0.192–1.240)	0.132	0.270 (0.112–1.479)	0.201
Number of different adverse events					
< = 3	53 (68.8)	Referent		Referent	
4–6	26 (21.8)	0.127 (0.066–0.242)	<0.001	0.308 (0.092–1.189)	0.099

(*Continued*)

Table 6. Continued.

Variable	Unsuccessful outcome No. (%)	Univariate analysis OR (95%CI)	Univariate analysis *p*-value	Multivariate analysis OR (95%CI)	Multivariate analysis *p*-value
>6	10 (12.7)	0.066 (0.029–0.149)	<0.001	1.445 (0.134–16.060)	0.620
TB treatment regimen modification					
No	85 (33.3)	Referent			
Yes	4 (20.0)	0.500 (0.162–1.542)	0.228		

Notes: CI, confidence interval; OR, odds ratio; SLD, second-line anti-TB drugs; TB, tuberculosis.

The median time to LTFU was 4 months (IQR: 3.00-9.50 months). In multivariate analysis, patient's age of 41–60 (OR = 9.225, *p*-value = 0.036) and >60 years (OR = 23.481, *p*-value = 0.004), baseline body weight of 31-60 kg (OR = 0.180, *p*-value = 0.036), urban residence (OR = 0.296, *p*-value = 0.009), ototoxicity (OR = 0.258, *p*-value = 0.011) and hypothyroidism (OR = 0.136, *p*-value = 0.010) had statistical significant association with unsuccessful treatment outcomes. This model fit was based on non-significant Hosmer Lemeshow test (*p*-value = 0.618) and overall percentage of 85.7% from classification (Table 6).

Discussion

The aim of this study was to explore the various aspects of adverse events (AEs) experienced by MDR-TB patients and its impact on treatment outcomes at a PMDT unit in Pakistan, a country with a high burden of MDR-TB (WHO, 2023). Our findings revealed that almost all (99.6%) patients encountered at least one AE, with an average of four different events per patient. The frequency of AEs observed in our study was comparable with the rate reported by a study conducted in India (100%) (Jakasania et al., 2020), but was higher than the rates reported by studies conducted at other PMDT units in Pakistan (range: 63.7–72.3%) (Ahmad, Ahuja, et al., 2018; Atif et al., 2022), China (90.7%) (Zhang et al., 2017), KwaZul-Natal (80.6%) (Brust et al., 2013), Namibia (89%) (Sagwa et al., 2014), Latvia (79%) (Bloss et al., 2010) and Viet Nam (71.3%) (Ngoc et al., 2021). Variability in the frequency of AEs among published studies can be attributed to several factors. These factors include: (i) characteristics of the treatment regimen, such as the specific drugs used and the duration of treatment; (ii) patient-related factors, such as age, ethnicity, nutritional status, concurrent medical conditions and medications, overall health, adherence to medication, and their perceptions of the disease and treatment regimen; (iii) health system-related factors, such as the quality of care provided and the healthcare professionals' ability to assess,

detect, and document AEs and (iv) difference in the criteria used by different studies to define AEs (Atif et al., 2022; Lan et al., 2020; Ngoc et al., 2021; Zhang et al., 2017). Variability in the frequency of AEs among published studies underscore the immediate requirement for enhanced reporting of AEs. The WHO guidelines for pharmacovigilance could provide a foundation for the development of a more comprehensive adverse event reporting system (Lan et al., 2020).

In our study, we found that GI disturbance (95.3%), arthralgia (80.4%), and general body pain and headache (61.8%) were the most common AEs. This was consistent with findings from other studies (Ravichandran et al., 2022; Zhang et al., 2017), but with higher rates. This could be due to subjective diagnoses of these events. Despite the high prevalence of these AEs, only GI disturbance led to a temporary discontinuation of PAS in three patients. Ototoxicity was more prevalent (61.4%) (tinnitus = 19.2% and hearing loss = 42.2%) in our study compared to the reported range in other studies conducted in Pakistan (8.9-24%) (Ahmad, Javaid, et al., 2018; Atif et al., 2022; Massud et al., 2022), elsewhere (5.9-41.8%) (Bloss et al., 2010; Ngoc et al., 2021; SS Shin et al., 2007; Törün et al., 2005; Zhang et al., 2017) and by a systematic review (28.3%) (Wrohan et al., 2021). Nevertheless, despite its high incidence, ototoxicity resulted in modification of the TB treatment regimen in only 12 patients. Specifically, SLI was permanently discontinued in 11 patients, and the dose interval was increased in one patient. The high incidence of hearing loss in the current cohort may be attributed to the complacency of doctors at the study site (Ahmad, Javaid, et al., 2018). Previous research has shown that MDR-TB patients who subsequently developed symptomatic hearing loss, exhibited significant changes in audiograms for a period of two months (Sturdy et al., 2011). Since symptomatic hearing loss develops gradually, with high-frequency loss occurring initially (Seddon et al., 2012; Sturdy et al., 2011), therefore, conducting regular audiometric screenings and paying attention to auditory symptoms, even mild hearing loss complaints, may facilitate timely intervention and reduce the incidence of hearing loss in RR/MDR-TB patients.

In our study, 44% patients exhibited psychiatric symptoms. This falls within the range of psychiatric symptoms prevalence reported in studies conducted in Pakistan (29.3-59.4%) (Ahmad, Javaid, et al., 2018; Atif et al., 2022; Massud et al., 2022), but it is higher than the rates reported in studies conducted in Estonia, Latvia, Peru, the Philippines, and the Russian Federation (9.5%) (Nathanson et al., 2004), China (12.9%) (Zhang et al., 2017), and Russia (20.5%) (SS Shin et al., 2007). In addition to toxic effects of SLD, particularly *Cs,* on the central nervous system (Lan et al., 2020), factors such as fatigue and adverse outcomes of the previous episodes of TB treatment (85.3% patients in the current cohort were previously been treated for TB) (Nafees Ahmad et al., 2016), along with patients' poor socioeconomic conditions

and the severe nature of the disease itself may have contributed to the relatively higher incidence of psychiatric manifestations in the current cohort (Ahmad, Javaid, et al., 2018).

The incidence of hypothyroidism in this cohort (21.5%) was higher than that reported by studies conducted in Pakistan (1.5%) (Massud et al., 2022), Turkey (1.1%) (Törün et al., 2005) and Peru (10%) (Furin et al., 2001). However, a comparable (19.1%) and relatively higher incidence (36%) of hypothyroidism among MDR-TB patients has been respectively reported from China (Zhang et al., 2017) and South Africa (Brust et al., 2013). The frequent monitoring of TSH levels in non-symptomatic patients in this cohort could be one of the possible reasons for the disparity in the occurrence rate of hypothyroidism. Furthermore, as 49.5% patients in this cohort were resistance to any SLD, they received both Eto and PAS, which could be another reason for the high rate of hypothyroidism in this study (Andries et al., 2013; Merid et al., 2019). However, despite its high incidence in this study, increased TSH level did not result in modification of TB treatment in any of these patients and were managed by the prescription of thyroxine and referral to an endocrinologist.

In the current study, the frequency of dermatological reactions (26.2%) was within the range reported by studies conducted in Pakistan and elsewhere (12.9-43.3%) (Furin et al., 2001; Kushemererwa et al., 2023; Massud et al., 2022; Zhang et al., 2017). Moreover, in our study, a high proportion of patients developed hypokalaemia (40.4%), which was above the range of hypokalaemia experienced by MDR-TB patients (2.7-31%) (Ahmad, Javaid, et al., 2018; Furin et al., 2001; Kushemererwa et al., 2023; Massud et al., 2022; Sonya Shin et al., 2004; Zhang et al., 2017) in various studies conducted elsewhere, but lower than that reported by a study conducted in Ethiopia (54%) (Merid et al., 2019). Disease chronicity, previous episodes of TB treatment with streptomycin (Cat-II) and SLIs containing regimen which cause electrolytes wastage, poor nutritional status, low body weight, and an aggressive treatment regimen with prolonged use of SLIs could be some of the possible reasons for the high incidence of hypokalaemia in the current cohort of patients (Sonya Shin et al., 2004). Despite high incidence of hypokalaemia, it resulted in permanent discontinuation of the suspected culprit agent (Am) in only one patient. In the present study, the incidence rate of nephrotoxicity (12.7%) and neuropathic pain (10.9%) fell within from other studies conducted elsewhere, which were 2.7-21% for nephrotoxicity (Ahmad, Javaid, et al., 2018; Isaakidis et al., 2012; Merid et al., 2019) and 9.14-16.7% for neuropathic pain (Furin et al., 2001; Merid et al., 2019; SS Shin et al., 2003). The observed incidence of hepatotoxicity (0.4%) in the present study aligned with the findings of studies conducted in Ethiopia (2.96%) (Merid et al., 2019) and Vietnam (3.1%) (Hoa et al., 2015).

We observed that the total number of AEs was significantly higher in educated patients, as well as those with a history of TB treatment, previous treatment with SLD, and resistance to any SLD. In our study, the majority of the commonly reported AEs, such as GI disturbances, arthralgia, headache and general body pain, were based on patients self-reporting. Therefore, higher incidence of AEs in educated patients could be attributed to their relatively higher level of health literacy, awareness regarding potential side effects of medications, and their inclination to recognise and report AEs (Gupta et al., 2020). The current finding of significantly higher incidence of AEs among MDR-TB patients with a history of TB treatment and previous treatment with SLD could be due to the cumulative toxicity of anti-TB drugs (Bannwarth, 2007; Selimoglu, 2007). These drugs may have the adverse effects that can persists or worsen with subsequent treatments, increasing the odds of experiencing AEs in these specific patients groups. In the present study, patients who demonstrated resistance to any SLD, also exhibited significantly higher number of AEs than their counterparts. As per the guidelines recommendation, patients with resistance to any SLD were prescribed the addition of PAS to their treatment regimen. Given that PAS, both alone and when combined with Eto, is widely acknowledged to induce GI disturbances and hypothyroidism (Ategyeka et al., 2023; Bloss et al., 2010; Buajordet et al., 2001; Furin et al., 2001; Lan et al., 2020; Sagwa et al., 2014; Sonya Shin et al., 2004; SS Shin et al., 2007; Wrohan et al., 2021; Zhang et al., 2017), this could potentially account for the observed increase in AEs among patients resistant to any SLD.

In the present study, despite a high prevalence of AEs, the rate of modifying the TB treatment regimen (7.3%) was lower than that reported in studies conducted at another PMDT unit in Pakistan (11%) (N Ahmad et al., 2015), Turkey (55.1%) (Törün et al., 2005), Namibia (29%) (Sagwa et al., 2014), Latvia (84%) (Bloss et al., 2010), Russia (28.7%) (SS Shin et al., 2007) and China (50.1%) (Zhang et al., 2017). The relatively lower rate of regimen modification due to AEs in the current cohort could be due to doctors' complacency towards AEs, the aggressive management of patients, and a high degree of drug resistance that limited the options for replacing the suspected culprit agents with equally effective SLDs. Additionally, since all study participants received the complete treatment as ambulatory patients, their limited interaction with the doctors at the PMDT unit could be another possible reason for lower rate of TB treatment modification in the present study.

In our present cohort, the treatment success rate was found to be 67.6%, which fell within the range reported by studies conducted at other PMDT units in Pakistan (40.5-75.2%) (N Ahmad et al., 2015; Atif et al., 2020; Atif et al., 2017; Javaid et al., 2018; Javaid, Shaheen, et al., 2017; Khan et al., 2019; Abdul Wahid et al., 2022). Notably, the incidence of unsuccessful treatment outcomes was significantly higher in patients aged >40 years, those

with a baseline body weight ≤30 kg and who were residents of rural areas. These factors, older age, baseline low body weight and rural residence have been previously identified as predictors of unsuccessful treatment outcomes in MDR-TB patients, as reported by studies conducted elsewhere (N Ahmad et al., 2015; Javaid, Shaheen, et al., 2017; Khan et al., 2019; Abudl Wahid et al., 2021). In the present cohort, 39.3% (35/89) of the unsuccessful outcomes were attributed to LTFU. Given that by area, the province of Balochistan represents 43.6% of Pakistan and has only one PMDT unit located in the capital city of Quetta, the relatively limited physical accessibility to the centre for rural residents could be a possible explanation for the greater incidence of unsuccessful treatment outcomes among rural residents (Javaid, Shaheen, et al., 2017). We found a positive association between successful treatment outcomes, ototoxicity and hypothyroidism. Although this association seems counterintuitive at first glance, however, there are few potential justifications that could have resulted in this finding. Considering the median duration of treatment among patients with successful treatment outcomes was 23 months, whereas it was only 4 months for those with unsuccessful treatment outcomes, the longer exposure of patients in the former group to the potential culprits (SLIs and Eto) could have contributed to the higher incidence of these AEs in them. Furthermore, the occurrence of these AEs in patients who achieved successful treatment outcomes might be a result of higher adherence to the treatment regimen compared to their counterparts.

The present study has noteworthy limitations. Firstly, it was conducted at a single PMDT unit, which may limit the generalisability of our results to other settings. Secondly, this study relied on a retrospective record review, which prevented us from assessing important information such as patients' body mass index, chest x-ray findings, and their perceptions regarding the disease, treatment regimen and reasons for LTFU. Furthermore, we were unable to conduct a causality assessment of AEs. It is important to note that at the time of study, the treatment guidelines recommended SLI containing regimens (both longer and shorter) for the treatment of MDR-TB patients. However, these regimens have recently been replaced with all oral regimens which do not include SLIs (WHO, 2020).

In conclusion, AEs were highly prevalent in this cohort, but they did not have negative impact on treatment outcomes or necessitate frequent modification of the treatment regimen. The majority AEs were successfully managed by psychological and pharmacological supportive therapy, without compromising the clinical effectiveness of the TB treatment regimen. However, in the present study, the relatively high prevalence of AEs such as GI disturbance, arthralgia, ototoxicity, hypokalaemia, and hypothyroidism, which are presumed to be caused respectively by PAS, Z, SLIs, and Eto, supports the recent guidelines' de-prioritisation of these agents and reclassifying them as group C agents. The revised guidelines

now advocate for their utilisation in treating MDR-TB solely in cases where constructing a regimen with anti-TB drugs classified as group A (including Lfx/Mfx, Bdq, Lzd) and B (Cfz, Cs/Tzd) agents – proven to offer enhanced effectiveness and tolerability – is not feasible (WHO, 2022). Moreover, as in the current cohort, due to cumulative toxicity of the drugs used for prolonged periods, the history of TB treatment and previous use of SLD were associated with high incidence of AEs. Therefore, treating all eligible MDR-TB patient with shorter treatment regimens could alleviate the burden of AEs in MDR-TB patients. By closely monitoring patients, offering enhanced clinical management and special attention to those who are greater risk of developing AEs and experiencing unsuccessful outcomes, we can further optimise the RR/MDR-TB therapy. Furthermore, establishing more PMDT units in the province could increase the patients' accessibility, decrease LTFU rate and improve the rate of successful treatment outcomes.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Ethical approval and consent to participate

Ethical approval to conduct this study was obtained from the Ethics and Research Committee of Faculty of Pharmacy and Health Sciences, University of Balochistan, Quetta. Additionally, permission to conduct this study was taken from the relevant authorities at FJICD Quetta. As it was a retrospective review of patients' medical records, it was not possible to trace all the included patients for taking consent, therefore, the Ethics and Research Committee of Faculty of Pharmacy and Health Sciences, University of Balochistan, Quetta, granted the consent waiver. All the patients' information was anonymised before data analysis.

Data and materials availability statement

All data gathered or analysed during this study are included in the article. The raw data on which conclusions of this manuscript is based is available upon request. Please contact Nafees Ahmad at nafeesuob@gmail.com.

Authors' contributions

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