Saudi Pharmaceutical Journal 30 (2022) 462–469

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Drug resistance patterns, treatment outcomes and factors affecting unfavourable treatment outcomes among extensively drug resistant tuberculosis patients in Pakistan; a multicentre record review

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ARTICLE INFO

Article history:
Received 24 April 2021
Accepted 20 January 2022
Available online 5 February 2022

Keywords:
XDR-TB
Drug resistance
Resistance
Tuberculosis
PMDT
NTP

ABSTRACT

Background: Extensively drug resistant tuberculosis (XDR-TB) is considered as a major threat to global health. This study aimed to analyse the treatment outcomes and identify the factors significantly associated with unfavourable treatment outcomes among XDR-TB patients.
Methods: We conducted a retrospective observational study at 10 Programmatic Management Units of the National Tuberculosis Control Program of Pakistan. The Electronic Nominal Recording Reporting System records were used to collect data of all eligible XDR-TB patients registered at the study sites between March 2012 and August 2018. Treatment outcomes were analysed as per the standard criteria. Factors associated with unfavourable treatment outcomes were analysed by using multivariate binary logistic regression analysis.
Results: Out of the total 184 patients, 59 (32.1%) completed their treatment successfully. Whereby, 83 patients (45.1%) died, 24 (13%) had treatment failure, and 11 (6%) were lost to follow-up. Treatment outcomes were not evaluated in 7 (3.8%) patients. Factors significantly associated with unfavourable treatment outcomes included; conventional therapy with bedaquiline, unfavourable interim treatment outcomes and occurrence of adverse drug events (negative association).
Conclusion: Treatment success rate in the study cohort was sub-optimal (i.e., <75%). The poor success rate and high mortality are concerning, and requires immediate attention of the program managers and clinicians.

1. Introduction

The effects of Drug-resistant TB (DR-TB) is devastating on mankind with substantially higher morbidity and mortality (World Health Organization, 2020b). Multidrug-resistant TB (MDR-TB) is one form of DR-TB, in which *Mycobacterium tuberculosis* (MTB) strains are resistant to two first line anti-TB drugs (FLDs) (i.e., rifampicin and isoniazid) (World Health Organization, 2020b). Extensively drug resistant TB (XDR-TB) is a more severe form of DR-TB in which MTB strains are resistant to second-line anti-TB drugs (SLDs). In 2020, the World Health Organization (WHO) Global Task Force revised the definitions of pre- XDR-TB and XDR-TB. According to new definitions, pre-XDR-TB is DR-TB in which MTB strains are resistant to rifampicin and isoniazid plus at least one of the fluoroquinolones (i.e., levofloxacin and moxifloxacin) (Shibabaw et al., 2020). XDR-TB, on the other hand, refers to DR-TB in which MTB strains are resistant to rifampicin and isoniazid

Abbreviations: **ADE**, Adverse drug event; **AOR**, Adjusted odd ratio; **BMI**, Body mass index; **CI**, Confidence interval; **DR-Congo**, Democratic Republic of the Congo; **DR-TB**, Drug-sensitive TB; **DST**, Drug susceptibility testing; **ENRS**, Electronic Nominal Recording Reporting System; **FLDS**, First line anti-TB drugs; **LPA**, Line probe assay; **MDR-TB**, Multidrug-resistant TB; **MTB**, *Mycobacterium tuberculosis*; **NRL**, National Reference Laboratory; **NTP**, National Tuberculosis Control Program; **PMDT**, Programmatic management units of DR-TB; **SD**, Standard deviation; **SLDS**, Second-line anti-TB drugs; **TB**, Tuberculosis; **WHO**, World Health Organization; **XDR-TB**, Extensively drug resistant tuberculosis.

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2022.01.015
1319-0164/

plus at least one of the fluoroquinolones (i.e., levofloxacin and moxifloxacin) and either bedaquiline or linezolid (or both) (World Health Organization, 2021).

XDR-TB is globally recognized as an emerging threat to public health owing to higher risk of unfavourable treatment outcomes and spread of resistance (Shibabaw et al., 2020; World Health Organization, 2020b). In 2018, an estimated half a million (range, 417, 000 – 556, 000) new cases of rifampicin resistance TB (RR-TB) were recorded worldwide, out of which 78% were MDR-TB cases. Among these 78% cases, 6.2% of the patients were estimated to have XDR-TB (World Health Organization, 2019); 88% of these cases were from European and South-East Asian region.

Pakistan is ranked fourth among countries with high burden of DR-TB (World Health Organization, 2019.). In the country, 562,000 TB patients (all types) were reported in 2018, out of which 28,000 had MDR-TB (4.2% new cases, 16% previously treated cases) (National Tuberculosis Control Program, 2019). Unfortunately, very scarce systematic data is available on the epidemiology of XDR-TB in Pakistan. However, in 2019, one Pakistani study on MDR-TB patients reported an estimated 32% and 3.4% cases of pre-XDR-TB and XDR-TB, respectively, in the study cohort (ul Manan, Naqvi, Mushtaq, & Shafqat, 2019). In the country, more than 30 programmatic management units of DR-TB (PMDT) are providing free-of-cost diagnostic and treatment facilities to all DR-TB patients (Atif, Ahmad, Ahmad, Malik, & Sarwar, 2020b).

Due to the contagious and resistance prone nature of MTB, successful treatment outcomes are always desirable to overcome burden of the disease and to devise patient-centred interventions tailored to local needs (Atif, Ahmad, et al., 2020b). In this context, the WHO suggests evaluating the performance of a country's National Tuberculosis Control Program (NTP) by analysing treatment outcomes among TB patients at various levels of healthcare (World Health Organization, 2014). However, to date, there are only a very few studies regarding treatment outcomes among XDR-TB patients, globally, including Pakistan (Abubakar et al., 2021; Prajapati, Mishra, Desai, Solanki, & Naik, 2017). Therefore, the aim of this large multicentre study was to evaluate treatment outcomes and identify the significant factors associated with unfavourable treatment outcomes among culture confirmed pre-XDR and XDR-TB patients in Punjab, Pakistan. It is hoped that this assembled evidence would urge policy makers to up-scale health-setting measures and restructure programmatic efforts in Pakistan to avert the anticipated repercussions of XDR-TB.

2. Methods

2.1. Study design and population

This was a retrospective observational study (Atif, Ahmad, et al., 2020b) which followed the standardized WHO methodology to achieve the study objectives. We included all pre-XDR and XDR-TB patients who were registered for treatment at the study sites between March 2012 and August 2018, regardless of their age, gender, medical history, comorbidity status, or TB treatment history. The DR-TB patients other than pre- XDR and XDR-TB were excluded from the study. Similarly, extra pulmonary XDR-TB patients were also excluded from the study (Atif, Ahmad, et al., 2020b). Due to the retrospective nature of the study, the cases were defined in accordance with the old definitions of pre-XDR-TB and XDR-TB. According to these definitions, pre-XDR-TB was defined as DR-TB in which MTB strains were resistant to rifampicin and isoniazid plus either to one of the fluoroquinolones or second-line injectable agents (amikacin, kanamycin or capreomycin) but not against both drugs simultaneously (Shibabaw et al., 2020). XDR-TB was defined as DR-TB in which MTB strains were resistant to rifampicin and isoniazid plus at least one of the fluoroquinolones and one of the three second-line injectables (amikacin, kanamycin or capreomycin).

2.2. Study settings

This study was conducted at the 10 PMDT sites of the NTP of Pakistan. These PMDT sites were located in Bahawalpur, Faisalabad, Sargodha, Sialkot, Lahore, Multan, Rahim Yar Khan, Rawalpindi and Murree. The DR-TB clinics at these PMDT sites have their own medical staff consisting of physicians, pharmacists, psychologists, case managers, program assistants, treatment coordinators, social supporters and laboratory attendants. A well-equipped laboratory was established at each of the DR-TB centre for all TB-related diagnosis. Patient samples for diagnosis were sent to the National Reference Laboratory (NRL) in Islamabad for culture, drug susceptibility testing (DST), and line probe assay (LPA). LPA and DST test reports were received within 3–7 days and 1–3 months, respectively. XDR-TB patients were also referred to the radiology and pathology department of their respective hospitals for routine examination.

2.3. Diagnosis, treatment and management of XDR-TB patients at the study site

All XDR-TB patients were diagnosed and treated according to the NTP guidelines (National Tuberculosis Control Program, 2019). Initially, the presumptive cases of TB were screened at the outpatient department of hospitals. The patients who had rifampicin resistance (as diagnosed by Xpert MTB/RIF®test) were referred to the PMDT sites for the treatment of DR-TB, and were further evaluated for drug resistance against FLDs and SLDs by LPA and DST. For this, sputum samples of the patients were sent to NRL Islamabad within 72 h.

Approximate treatment duration of XDR-TB was 20–24 months, including 18 months after culture conversion (National Tuberculosis Control Program, 2019). Patients found to be smear positive and resistant to rifampicin (Xpert MTB/RIF® test report accessible within 1–2 days) were put on appropriate treatment protocol in accordance with the national guidelines (National Tuberculosis Control Program, 2019). Most of the patients were given the standardized conventional therapy (without bedaquiline), consisting of at least five active SLDs such as injectables, fluoroquinolones, linezolid, cycloserine, ethionaminde/proethionamide, clofazimine, pyrazinamide and imipenem/cilastatin. While in some patients, same conventional therapy was given with bedaquiline. Once the DST results were available; the patients were treated with an individualised drug regimen, which included at least five active SLDs. Any adverse drug event (ADE) or clinical deterioration in the disease was treated accordingly, and those who required admission in the hospital were admitted and managed accordingly. A psychologist at each of the PMDT sites provided psychological support to the patients. All patients were treated as outpatients and were asked to have follow-up visit once in a month for treatment compliance, detection of ADEs and clinical response to the treatment regimen. The patient samples were collected every month; positive sputum cultures were sent for DST after every 2 months to Provincial Reference Laboratory (PRL).

2.4. Data sources

The data were extracted in August 2020. Electronic Nominal Recording Reporting System (ENRS) were used to obtain socio-demographic, microbiological, clinical and treatment-related information. The socio-demographic data included; age, gender, occupation, behaviour status (smoking), area of residence

and work status. The clinical data included; body mass index (BMI), presence of comorbidity, history of FLD use, history of SLD use, registration group, duration of sickness prior to diagnosis of DR-TB (in months), and history of hospitalization. The treatment-related data included; treatment strategy (conventional therapy with or without bedaquiline), delamanid use, interim treatment outcomes and final treatment outcomes.

2.5. Treatment outcomes among XDR-TB patients

The treatment outcomes were reported on the basis of the WHO guidelines for the programmatic management of drug-resistant tuberculosis (for details, please refer to Supplementary File 1) (World Health Organization, 2014).

Cured and treatment complete were classified as favourable treatment outcomes, whereas, unfavourable treatment outcomes included died, treatment failure and patients who were lost to follow-up (Khan et al., 2019).

2.6. Statistical analysis

Data analysis was performed by using Statistical Package for Social Sciences statistics for windows version 21.0 (IBM, Armonk, NY, USA). All categorical variables were presented as numbers and proportions (%). Continuous variables were presented as means and standard deviations (SDs). Simple logistic regression analysis was used to analyze the association between a dependent variable (i.e. unfavorable treatment outcome) and patient characteristics. Only statistically significant variables with $p < 0.2$ in the simple logistic analysis were entered in the multivariate binary logistic regression to find the independent factors associated with unfavorable treatment outcomes (Ahmad et al., 2015). Adjusted odd ratio (AOR), p-value and confidence interval (CI) were reported for each variable.

Ethics approval and consent to participate

The ethical approval was obtained from the Pharmacy Research Ethics Committee at the Islamia University Bahawalpur (Ref # 108–2020/PREC, Dated: 13 August 2020). None of the ethics and consent guidelines and regulations were violated in this study. Informed consent for study participation was not required as ENRS were used to obtain the data.

3. Results

3.1. Description of the patients

At the time of data collection, a total of 234 pre-XDR and XDR-TB patients were enrolled at the study site. Out of these, 50 patients were excluded either because they were extra pulmonary XDR-TB cases or did not complete the minimum duration of treatment. Remaining 184 patients (173 XDR-TB and 11 pre-XDR-TB) had their final treatment outcomes (i.e., completed at least 24 months of treatment) available at the time of data collection), and therefore were included in the study (Fig. 1).

3.2. Sociodemographic characteristics of the patients

Out of the total 184 patients, the majority (n = 163; 88.6%) were within the age group of 15 to 54 years. The mean age of the patients was 32.4 (SD = 14) years (Table 1).

3.3. Clinical characteristics of the patients

Out of the total 184 patients, 70 (38%) were previously treated for TB, while 60 (32.6%) patients received treatment after failure. Only 14 (7.6%) patients were enrolled as new cases. 68 (37%) patients had a history of SLD use. Occurrence of adverse drug events were reported in 110 (59.8%) patients (Table 2).

3.4. Drug resistance pattern of the patients

In the study cohort, a total of 64 (34.8%) patients were resistant to four FLDs and 38 (20.1%) were resistant to three FLDs, while resistance to all five FLDs were reported in 40 (21.7%) patients. With regard to SLDs, 44 (23.9%) patients were resistant to two drugs, whereas 67 (36.4%) patients were resistant to four SLDs (Table 3).

3.5. Treatment regimen of the patients

Conventional therapy (without bedaquiline) was used in 163 (88.6%) patients, while the rest of the patients (n = 21, 11.4%) were given conventional therapy with bedaquiline. The use of delamanid was observed in only five (2.7%) patients.

3.6. Final treatment outcomes among the study participants

Among 184 XDR-TB cases, 58 (31.5%) were cured and only one patient (0.5%) completed the treatment (treatment success rate = 32.1%). Out of the remaining 125 (67.9%) XDR-TB patients, 118 (64.1%) had unfavourable treatment outcomes. Of them, 83 (45.1%) died, 24 (13%) had treatment failure and 11 (6%) lost to follow-up. In seven (3.8%) patients, treatment outcomes were not evaluated due to assorted reasons (i.e., transfer out or other unknown reasons) (Table 4). For detailed description of final treatment outcomes with regard to patient characteristics, please see Supplementary File 2. Treatment outcomes with regard to each of the included PMDT is presented in Supplementary File 3.

3.7. Factors associated with unfavourable treatment outcomes

In multivariate binary logistic regression analysis, conventional therapy including bedaquiline (AOR = 4.7; $p = 0.028$), unfavourable interim treatment outcomes (AOR = 18.5; $p < 0.0005$) and occurrence of ADEs (inverse relationship) (AOR 0.2; $p = 0.013$) were identified as significant factors associated with unfavourable treatment outcomes (Table 5).

4. Discussion

Recently, the Global Tuberculosis Report 2021 revealed that high TB burden nations, including Pakistan, have not succeeded in stemming the tide of XDR-TB. Given the status quo, it seems imperative to report treatment outcomes and associated factors to analyse country level performance of TB control programs. This study covered 10 PMDT sites from Pakistan's NTP to reflect the current situation surrounding final treatment outcomes and factors influencing unfavourable treatment outcomes among XDR-TB patients in Pakistan. The study found an overall treatment success (favourable outcomes) rate of 32.1%, thereby indicating that Pakistan is lagging far behind the TB treatment success targets set by the WHO in the End TB strategy (World Health Organization, 2011). Besides, the study revealed that unfavourable treatment outcomes across the seven-year study period (2012–2018) were linked to the use of bedaquiline, unfavourable interim treatment outcomes and adverse drug events (negative association). This baseline information pointed towards more cautious use of bedaquiline and provision of individualized patient care to halt the increasing prevalence of XDR-TB in Pakistan.

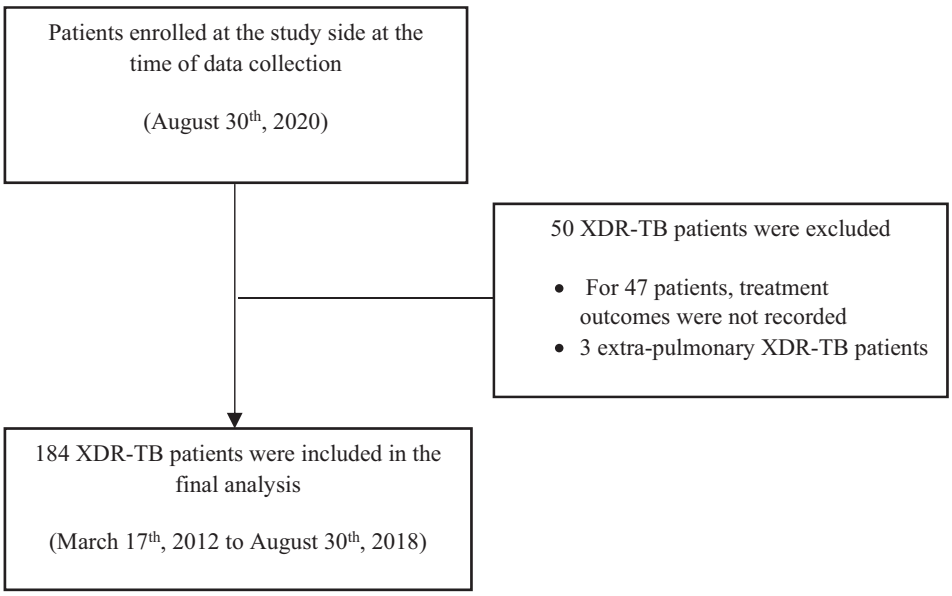

Fig. 1. Inclusion and exclusion criteria of the study. **XDR-TB = Extensively Drug Resistant Tuberculosis.**

Table 1
Sociodemographic characteristics of the patients (n = 184).

Characteristics	Patients, n (%)	Characteristics	Patients, n (%)
Age (years), mean ± SD (32.4 ± 14)		**Work status**	
5–14	5 (2.7)	Employed	25 (13.6)
15–24	63 (34.2)	Self-employed	36 (19.6)
25–34	42 (22.8)	Unemployed	11 (19.6)
35–44	37 (20.1)	Student	40 (21.7)
45–54	21 (11.4)	Retired	3 (1.6)
55–64	12 (6.5)	Others	69 (37.5)
>65	4 (2.2)	**Behaviour status**	
Gender		Smoking	18 (9.8)
Male	93 (50.5)	Alcohol	1 (0.5)
Female	91 (49.5)	Naswar	2 (1.1)
Residence		Missing	163 (88.6)
Urban	95 (51.6)		
Rural	89 (48.4)		

Missing = data not available.

Table 2
Clinical characteristics of the patients (n = 184).

Characteristics	Patients, n (%)	Characteristics	Patients, n (%)
Registration group		**Previous TB centre**	
New	14 (7.6)	Private	55 (29.9)
Previously treated	70 (38.0)	PMDT sites	104 (56.5)
Treatment after failure	60 (32.6)	Missing	25 (13.6)
Treatment after loss to follow up	7 (3.8)	**Previous FLD treatment history**	
Relapse	9 (4.9)	HREZ	90 (48.9)
Unknown previous history	14 (7.6)	HREZS	58 (31.5)
Patients transfer in	10 (5.4)	Unknown	10 (5.4)
BMI at the start of treatment, mean ± SD (23.1 ± 7.7)		Missing	26 (14.1)
Underweight	17 (9.2)	**History of SLD use**	
Normal weight	21 (11.4)	Yes	68 (37.0)
Overweight	11 (6.0)	No	115 (62.5)
Obese	8 (4.3)	Missing	1 (0.5)
Missing	127 (69.0)	**Hospitalization of the patient**	
Comorbidities		Yes	64 (34.8)
Diabetes	16 (8.7)	No	120 (65.2)
Depression	2 (1.1)	**Adverse drug events**	
Liver disease	6 (3.3)	Yes	110 (59.8)
Renal disease	1 (0.5)	No	74 (40.2)
COPD	2 (1.1)		
Hypertension	1 (0.5)		
Not recorded or system missing	156 (84.8)		
Interim treatment outcomes			
Negative SP and CL	67 (36.4)		
Positive SP and CL	36 (19.6)		
Not done – dead	48 (26.1)		
Not done – defaulted	7 (3.8)		
Not done – loss to follow up	4 (2.2)		
Transfer out	1 (0.5)		
Unknown	21 (11.4)		

BMI = body mass index, COPD = chronic obstructive pulmonary disease, PMDT = programmatic management unit of DR-TB, H = isoniazid, R = rifampicin, E = ethambutol, Z = pyrazinamide, S = streptomycin, SLD = second line drugs, SP = sputum, CL = culture, Missing = data not available.

With regard to socio demographic characteristics, this study found that the XDR-TB was most prevalent in the economically productive age group (i.e., 15–54 years). The probable reason for the high number of XDR-TB patients in this category might be due to frequent outdoor contacts of young adults and higher case notification as a result of better awareness. This finding coincided with the findings of studies from India, Democratic Republic of the Congo (DR Congo) and Nigeria (Daniel, Osman, Oladimeji, & Dairo, 2013; Ishibashi, 1998; Kashongwe et al., 2020; Prajapati et al., 2017).

In this study, the prevalence of previously treated XDR-TB cases (38%) was lower than the proportion observed in other low income countries, for example, Ethiopia (90%) and Bangladesh (63.6%) (Shibabaw et al., 2020; Tasnim, Tarafder, Alam, Sattar, & Kamal, 2018). China, on the other hand, listed only 10.5% of such cases (He, Tao, Liu, Zhang, & Li, 2017). The variation in the findings might be due to differences in the national TB control efforts, especially

Table 3
Pattern of drug resistance in patients (n = 184).

Variables	Patients, n (%)	Variables	Patients, n (%)
Resistance to FLDs		**Resistance to SLDs**	
Name of drugs		**Name of drugs**	
Resistance to HR	16 (8.7)	FQ	10 (5.4)
Resistance to HRS	11 (6.0)	Km + FQ	44 (23.9)
Resistance to HRE	7 (3.8)	Km + Am + Cm + FQ	67 (36.4)
Resistance to HRZ	20 (10.9)	Km + Am + Cm + FQ + Eto	10 (5.4)
Resistance to HRES	28 (15.2)	S + Km + Am + Cm + FQ	1 (0.5)
Resistance to HREZ	32 (17.4)	Km + Am + FQ	14 (7.6)
Resistance to HREZS	40 (21.7)	Km + Am + Cm	4 (2.2)
Resistance to HRZS	4 (2.2)	Missing	34 (18.5)
Missing	26 (14.1)	**Number of drugs**	
Number of drugs		1	10 (5.4)
2	16 (8.7)	2	44 (23.9)
3	38 (20.7)	3	18 (9.8)
4	64 (34.8)	4	67 (36.4)
5	40 (21.7)	5	11 (6)

FLDs = first-line drugs, H = isoniazid, R = rifampicin, E = ethambutol, Z = pyrazinamide, S = streptomycin, SLDs = second-line drugs, FQ = fluoroquinolones, Km = kanamycin, Am = amikacin, Cm = kanamycin, Eto = ethionamide.

Table 4
Final treatment outcomes among the study participants (n = 184).

Treatment outcomes	Patients, n (%)	n (%)
Favorable		59 (32.1)
Cured	58 (31.5)	
Treatment completed	1 (0.5)	
Unfavorable		118 (64.1)
Died	83 (45.1)	
Treatment failure	24 (13)	
Loss to follow up	11 (6)	
Not evaluated	7 (3.8)	7 (3.8)

Not evaluated = Transferred out or other unknown reasons.

contact tracing and early treatment of XDR-TB household contacts. However, less number of previously treated XDR-TB cases reported in our study indicated more prudent TB control efforts in Pakistan as compared to other low income counties (Laghari et al., 2019). The percentage of new cases of XDR-TB reported in our study was 14%, which was consistent with the findings of an Ethiopian investigation (10%) (Shibabaw et al., 2020). In contrast, a significantly less number of new cases were reported in China (1.5%) and Iran (0.7%). The relatively higher number of new XDR-TB cases in Pakistan is likely to be linked to primary transmission of the disease, and somewhat vigilant case identification and contact tracing mechanism in Pakistan (Shah et al., 2017).

A high rate of FLDs and SLDs resistance set forth in the study cohort was in accordance with the findings of Indian, Ethiopian and Pakistani studies (Abdella, Abdissa, Kebede, & Abebe, 2015; Dalal et al., 2015; Khan et al., 2019; Rao, Baig, Hussain, Ahmed, & Rao, 2015). Antibiotic resistance has become a major public health challenge in Pakistan, which is attributed to irrational prescribing, dispensing, sale and use of antibiotics, as evidenced by a plethora of Pakistani studies (Asghar et al., 2020; Atif, Asghar, et al., 2019a; Atif & Malik, 2020; Atif, Malik, et al., 2020; Atif, Malik, Mushtaq, & Asghar, 2019b; Malik, Atif, Riaz, Asghar, & Ahmad, 2020; Tasnim et al., 2018). Specifically, the facility of DST culture, DST and LPA is not available at PMDT sites of Pakistan. The samples are sent to NRL Islamabad and the DST results are usually available after 2–3 months. This leads to delays in identification of drug resistance pattern, continuation of standard empiric therapy for unnecessarily longer period and resultant aggravation of the drug resistance.

A wide gap between the treatment success rate (32.1%) identified in this study and the target success rate (≥75%) set by the WHO in the End TB strategy was discouraging, because all PMDT sites in Pakistan provide free-of-cost treatment and individualized care to XDR-TB patients. Parallel to the findings of our study, studies from China reported 30% success rate among XDR-TB patients (Alene et al., 2017; Liu et al., 2011). However, the findings did not match to an Indian study which reported lower treatment success rate (25.9%) (Prajapati et al., 2017). In contrast to this, higher success rate was observed in DR Congo (53.2%) and Brazil (54.5%) (Gallo et al., 2018; Kashongwe et al., 2020). The heterogeneity in the treatment success rates among countries could be because of variability in the degree of care provided at the healthcare settings and certain patient-related factors such as; age, comorbidity, drug resistance pattern, level of sickness, and patients' knowledge, attitude and practices towards TB. The major reasons behind the low treatment success rate in our study was high death rate, followed by more treatment failure cases. The unfavourable treatment outcome among XDR-TB patients jeopardises national TB control efforts, as these groups of patients might spread drug resistant forms of TB to others (Alene et al., 2017).

According to the findings of this study, a total of 45% patients died due to XDR-TB which is alarmingly high (World Health Organization, 2020a). This high rate was consistent with the mortality rate recorded in studies from DR Congo (46.8%) and South Africa (42%)(Kashongwe et al., 2020; O'Donnell et al., 2013). However, China (8.3%) reported a relatively less mortality rate (He et al., 2017). Contrary to this, slightly higher mortality rate was reported in India (51.8%) (Prajapati et al., 2017). The high incidence of mortality among XDR-TB patients might be linked to a combination of factors, including late diagnosis or therapy initiation, concomitant disease, prior incidence of TB, poor therapy or drug resistance and harmful personal habits (i.e., smoking and alcohol intake) (Atif, Ahmad, et al., 2020b). We further analysed our data to identify the factors affecting death among the study patients and found that mortality rate was associated with TB type (pre-XDR-TB more likely), being underweight, patients with unfavourable interim treatment outcomes and patients having ADEs (negative association) (a thorough discussion on the factors associated with death among XDR-TB patients is not within the scope of this paper; however, the data is provided in Supplementary File 3).

In the present investigation, 11 patients (6%) were lost to follow-up during treatment. The same proportion of loss to follow-up among XDR-TB patients was reported in a study from Latvia (6%) (Leimane et al., 2010). Whereby, higher loss to follow-up cases were recorded in China (27–40%) (Alene et al., 2017; He et al., 2017). Comparatively, low loss to follow-up rate set forth in this study is likely to be linked to the provision of patient-centred care, psychological counselling, guaranteed provision of free medicines, and monetary support for the patients and care givers (Atif, Ahmad, Ahmad, Malik, & Sarwar, 2020a; Atif et al., 2018). However, our attempt to expose the status of these 11 loss to follow-up patients revealed that three of them died and one patient denied to take the treatment. Other possible reasons for loss to follow-up might be longer duration of treatment, improvement in the symptoms, poor medication-related knowledge of TB patients, unpleasant attitude of medical staff towards patients and lack of family support (Tupasi et al., 2016).

According to our findings, patients who experienced ADEs during XDR-TB treatment were 3.3 times less likely to have unfavourable treatment outcomes. This could be because patients with ADEs frequently received more individualized consideration and enhanced care (Atif, Ahmad, et al., 2020b). Therefore, their adverse

Table 5
Factors associated with unfavorable treatment outcomes; multivariate binary logistic regression analysis.

Variables	Univariate analysis		Multivariate analysis	
	p-value	OR (95% CI)	p-value	AOR (95% CI)
History of SLD use				
No		Referent		Referent
Yes	0.037	2.083 (1.044 to 4.157)	0.721	1.194 (0.451 to 3.159)
New registration group				
No		Referent		Referent
Yes	0.001	0.114 (0.030 to 0.426)	0.375	0.486 (0.098 to 2.395)
Unsuccessful interim treatment outcome				
No		Referent		Referent
Yes	< 0.0005	20.848 (8.568 to 50.729	< 0.0005	18.568 (6.746 to 51.095)
Adverse drug events				
No		Referent		Referent
Yes	< 0.000	0.273 (0.134 to 0.558	0.013	0.299 (0.116 to 0.771)
Km + Am + FQ resistance				
No		Referent		Referent
Yes	0.176	0.468 (0.156 to 1.405)	0.153	0.326 (0.70 to 1.514)
HRS resistance				
No		Referent		Referent
Yes	0.142	4.789 (0.592 to 38.734)	0.943	0.918 (0.086 to 9.826)
HREZS resistance				
No		Referent		Referent
Yes	0.164	0.598 (0.290 to 1.234)	0.231	0.515 (0.174 to 1.524)
Diabetes				
No		Referent		Referent
Yes	0.145	0.464 (0.165 to 1.305)	0.157	0.327 (0.069 to 1.540)
Smoking				
No		Referent		Referent
Yes	0.065	4.150 (0.916 to 18.797)	0.749	1.360 (0.207 to 8.929)
Km + Am + Cm + FQ				
No		Referent		Referent
Yes	0.123	0.603 (0.317 to 1.147)	0.540	0.744 (0.289 to 1.916)
Conventional therapy with bedaquiline				
No		Referent		Referent
Yes	0.188	2.157 (0.687 to 6.769	0.028	4.734 (1.182 to 18.962)

p-value<0.05 in bold. Unsuccessful interim treatment outcomes = dead + defaulted + loss to follow up + positive sputum and culture, SLD, second-line drug, H = isoniazid, R = rifampicin, E = ethambutol, Z = pyrazinamide, S = streptomycin, km = kanamycin, Am = amikacin, FQ = fluoroquinolones, Cm = capreomycin, *model summary (Hosmer and Lemeshow test [4.144], p = 0.841); Nagelkerke R square (0.536); model summary = χ^2 (86.311), df (11), p < 0.0005.

events subsided and they were more likely to have favourable treatment outcomes, as evidenced by various similar studies conducted in Pakistan, Italy and Russia (Atif, Ahmad, et al., 2020b; De Socio et al., 2019; Shin et al., 2007).

Continuous assessment of TB treatment outcomes is crucial to tailor the therapeutic needs of the patients to achieve treatment success. However, owing to prolonged duration of XDR-TB treatment, the WHO introduced interim benchmarks to track treatment progress and forecast final outcomes (World Health Organization, 2014). In this study, the patients with unfavourable interim treatment outcomes had 18.6 times higher chances of having unfavourable final treatment outcomes as compared to those who had favourable interim results. This finding not only affirmed the WHO's forewarning but it also encourages clinicians to use interim benchmarks to tailor treatment regimen of the patients according to their needs.

This study also found that XDR-TB patients prescribed with bedaquiline had 4.7 times higher chances of unfavourable treatment outcomes as compared to those who were on conventional therapy without bedaquiline. Contrary to this, the use of bedaquiline has been associated with favourable treatment outcomes in many randomized controlled trials (Ahmad et al., 2018; Wang, Wu, & He, 2021). Similarly, BPal regimen, - in which bedaquiline is used in combination with other highly effective drugs, including novel pretomanid, - has been approved recently in view of its promising treatment success rates (Conradie et al, 2020). This disparity in our findings might be due to influence of various socio-demographic and clinical parameters in the real-world scenario, patient condition, poor patient monitoring for bedaquiline associated toxicities, and ineffective patient counselling related to dosage regimen and adverse events (Ahuja SD, Ashkin D, Avendano M, & the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB, 2012; National Center for HIV/AIDS).

5. Limitations

This study is among the few studies from Pakistan that was undertaken using the standardised methodology and filled the gap concerning treatment outcomes among XDR-TB patients and factors affecting unfavourable treatment outcomes. However, it has few limitations. First, this study was conducted in only 10 PMDT sites and did not represent the data of entire population in Pakistan. Second, due to the retrospective nature of the study, some crucial life events, haematological and socioeconomic parameters (for example, education level) of the patients that might have direct or indirect impact on unfavourable treatment outcomes were not reported and analysed. In addition, proportion of missing data on various important parameters, for example, comorbidities, BMI and behaviour status, was high. Therefore, future prospective follow-up multi-site studies are highly recommended to capture the impact of important missing variables on the final treatment outcomes.

6. Conclusion

Considering poor treatment success rate (32.1%) and high mortality (45.1%) among XDR-TB patients in this multi-site study, Pakistan does not appear to be on track to achieve TB elimination targets set by the WHO in the End TB Strategy. The study also found that patients taking conventional therapy with bedaquiline, and those with unfavourable interim outcomes had higher chances of unfavourable treatment outcomes. Whereas, the patients who experienced ADEs were more likely to achieve better treatment outcomes.

7. Impact of findings on practice

1. The low treatment success rate in this study is a wakeup call for the NTP managers. Patients with unfavorable interim treatment outcomes should be given individualized care to improve the final treatment outcomes. In addition, all the socioeconomic and clinical parameters should be carefully assessed and recorded to uncover factors affecting unfavourable outcomes and aid better selection of appropriate patient-centred interventions.
2. Use of bedaquiline should be reserved for only those patients who have failed to respond to other SLDs. Furthermore, efficacy of bedaquiline among DR-TB patients should be evaluated in randomized control trials.
3. The mortality rate among XDR-TB patients can be reduced by providing enhanced care to patients, especially to those who are underweight and have unfavorable interim treatment outcomes. The facility of DST should be available at all PMDT sites to ensure early diagnosis and treatment of patients.

8. Ethics approval and consent to participate

The ethical approval was obtained from the Pharmacy Research Ethics Committee at the Islamia University Bahawalpur (Ref # 108–2020/PREC, Dated: 13 August 2020). None of the ethics and consent guidelines and regulations were violated in this study. Informed consent for study participation was not required as Electronic Nominal Recording Reporting System (ENRS) records were used to collect the data.

9. Consent for publication

Not applicable.

10. Availability of data and materials

The raw data associated with this article will be provided upon receiving reasonable request. Please contact the corresponding author.

Funding

None.

CRediT authorship contribution statement

Muhammad Atif: Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing – review & editing. **Saba Mukhtar:** Conceptualization, Formal analysis, Project administration, Methodology, Writing – original draft. **Sajjad Sarwar:** Conceptualization, Formal analysis, Methodology, Project administration, Writing – original draft. **Mehwish Naseem:** Conceptualization, Formal analysis, Methodology, Project administration, Writing – original draft. **Iram Malik:** Formal analysis, Methodology, Project administration, Writing – original draft. **Azam Mushtaq:** Formal analysis, Methodology, Project administration, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2022.01.015.

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