Effectiveness of Shorter Treatment Regimen in Multidrug-Resistant Tuberculosis Patients in Pakistan: A Multicenter Retrospective Record Review

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Abstract.   In Pakistan, the treatment of multidrug-resistant tuberculosis (MDR-TB) with a shorter treatment regimen (STR), that is, 4–6 months of amikacin, moxifloxacin (Mfx), ethionamide, clofazimine (Cfz), pyrazinamide (Z), ethambutol (E), and high-dose isoniazid, followed by 5 months of Mfx, Cfz, Z, and E, was initiated in 2018. However, there is a lack of information about its effectiveness in Pakistani healthcare settings. Therefore, this retrospective record review of MDR-TB patients treated with STR at eight treatment sites in Pakistan aimed to fill this gap. Data were analyzed using SPSS 23. Multivariate binary logistic regression (MVBLR) analysis was conducted to find factors associated with death and treatment failure, and lost to follow-up (LTFU). A P-value < 0.05 was considered statistically significant. Of 912 MDR-TB patients enrolled at the study sites, only 313 (34.3%) eligible patients were treated with STR and included in the current study. Of them, a total of 250 (79.9%) were cured, 12 (3.8%) completed treated, 31 (9.9%) died, 16 (5.1%) were LTFU, and four (1.3%) were declared as treatment failures. The overall treatment success rate was 83.7%. In MVBLR analysis, patients' age of 41–60 (odds ratio [OR] = 4.9, P-value = 0.020) and > 60 years (OR = 3.6, P-value = 0.035), being underweight (OR = 2.7, P-value = 0.042), and previous TB treatment (OR = 0.4, P-value = 0.042) had statistically significant association with death and treatment failure, whereas patients' age of > 60 years (OR = 5.4, P-value = 0.040) and previous TB treatment (OR = 0.2, P-value = 0.008) had statistically significant association with LTFU. The treatment success rate of STR was encouraging. However, to further improve the treatment outcomes, special attention should be paid to the patients with identified risk factors.

INTRODUCTION

The emergence and spread of multidrug-resistant tuberculosis (MDR-TB) caused by a strain of *Mycobacterium tuberculosis* (MTB) concurrently resistant to both rifampicin (R) and isoniazid (H) pose a significant threat to the successful control of TB.[1,2] In 2018, an approximately 0.5 million people (range, 417,000–556,000) developed R-resistant TB worldwide, of which 78% had MDR-TB.[2] As MDR-TB patients are concurrently resistant to the two most effective, well-tolerated, and cheap first-line anti-TB drugs (FLDs), the WHO initially recommended to treat all MDR-TB patients for a minimum of 20 months with a longer treatment regimen (LTR) that mainly comprised comparatively less effective, more toxic, and expensive second-line anti-TB drugs (SLDs).[3–5] However, the treatment of MDR-TB patients with LTR had the major problems of comparatively lower treatment success (56%), higher incidence of adverse events, high treatment cost, and the acquisition of additional drug resistance during treatment.[1,2,6,7] To overcome the aforementioned problems associated with LTR, in 2016, the WHO recommended a new, shorter, and cheaper regimen known as shorter treatment regimen (STR) for treating MDR-TB under specific conditions. Shorter treatment regimen comprised 4–6 months of amikacin (Am), moxifloxacin (Mfx), ethionamide (Eto), clofazimine (Cfz), pyrazinamide (Z), ethambutol (E), and high-dose H followed by 5 months of Mfx, Cfz, Z, and E.[3] The treatment of eligible MDR-TB patients with STR under operational conditions has produced comparatively better treatment outcomes under elsewhere. The reported treatment success rate of MDR-TB patients treated with STR ranged from 68.7% to 89.2%.[8–14]

Unfortunately, Pakistan is a DR-TB high burden country. With an estimated incidence of 28,000 MDR-TB patients with 4.2% (95% CI = 3.2–5.3) in new and 16% (95% CI = 15–17) in previously treated TB patients, Pakistan currently ranks fourth globally with and first in the east Mediterranean region of the WHO.[2] Pakistan adopted the programmatic management of drug-resistant TB (PMDT) in the year 2010,[15] and currently, there are 32 functional PMDT units across the country. Since the inception of PMDT in the country, MDR-TB patients were treated with the WHO-recommended and National TB Control Program (NTP) adopted LTR. In Pakistan, the reported treatment success rate among MDR-TB patients treated with LTR ranged from 40.5% to 76.9%.[7,15–18] However, after the proven benefits of STR in terms of treatment success rate, shorter treatment duration, and low cost, NTP published a protocol and started the treatment of eligible MDR-TB patients with STR at selective PMDT sites.[19] Evaluating the treatment outcomes of a cohort of patients is an established, widely used, and effective method for analyzing the effectiveness of a treatment regimen under operational conditions.[15,16] However, to the best of our knowledge, information about effectiveness of STR among MDR-TB patients treated is lacking from Pakistan. Therefore, the current study is conducted to evaluate the treatment outcomes and factors associated with unsuccessful outcomes among MDR-TB patients treated with STR. This study will assess the effectiveness of STR in Pakistani MDR-TB patients and help the clinicians to recognize those patients who are at high risk of unsuccessful treatment outcomes before or early in the course of MDR-TB treatment.

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MATERIALS AND METHODS

Study population, settings, and design. This is a retrospective record review of eligible MDR-TB patients treated with STR at the following eight PMDT units: 1) Lady Reading Hospital, Peshawar; 2) Saidu Teaching Hospital, Swat; 3) Medical Teaching Institute, Mardan; 4) Rawalpindi Leprosy Hospital, Rawalpindi; 5) District Head Quarter Hospital, Faisalabad; 6) Nishter Hospital, Multan; 7) Sheikh Zaid Hospital, Rahimyar Khan; and 8) Jinnah Hospital, Lahore. All newly diagnosed, culture-confirmed, pulmonary MDR-TB patients who received STR at the aforementioned sites between January 1, 2018 and July 31, 2019 were included in the study.

Diagnosis and treatment of MDR-TB patients. At all the study sites, in line with the guideline recommendations,[19] presumed pulmonary MDR-TB patients who had no documented history of using SLDs for ≥ 1 month were initially screened for MTB, and R and H resistance with two sputum samples by direct sputum smear microscopy using Ziehl–Neelsen stain, Xpert MTB/R (Cepheid, Sunnyvale, CA), and line probe assay (LPA), respectively. After positive results of sputum smear microscopy, Xpert MTB/R, and LPA, patients were assessed for treatment eligibility with STR, and their sputum samples were sent to reference laboratories for drug susceptibility testing (DST) against anti-TB drugs through conventional culture and DST. The protocols of conducting culture and DST at these reference laboratories have been reported elsewhere.[15,20,21] In summary, DST at the reference laboratories was carried out by using the Agar proportion method on enriched Middlebrook 7H10 medium (BBL; Beckton Dickinson, Sparks, MD) at the following concentrations: H (0.2 μg/mL), R (1 μg/mL), E (5 μg/mL), streptomycin (2 μg/mL), kanamycin (5 μg/mL), Am (4 μg/mL), capreomycin (4 μg/mL), ofloxacin (2 μg/mL), levofloxacin (1 μg/mL), and Eto (5 μg/mL). In compliance with the manufacturer's instructions, DST for Z was conducted at 100 μg/mL by using BACTEC Mycobacterial Growth Indicator Tube (BBL; Beckton Dickinson, Sparks, MD). Meanwhile, MDR-TB patients fulfilling the eligibility criteria of no documented history of treatment with any SLD for ≥ 1 month, no confirmed resistance or suspected ineffectiveness to any SLD in STR, and no intolerance or risk of toxicity to any medicine included in STR were enrolled on STR. In addition to patients who were not fulfilling the aforementioned criteria, those patients were also not enrolled on STR who belonged to anyone of the following categories: clinically severe patients like those suffering from disseminated and extrapulmonary TB such as tubercular meningitis, clinically diagnosed MDR-TB patients, patients with advanced pulmonary diseases (bilateral lung cavitation or lung lesions in more than three zones), coinfected with HIV, had alanine transaminase/aspartate transaminase > 5 times upper normal limit (UNL), creatinine > 2 times of UNL or creatinine clearance < 50 mL/minute, the corrected QT interval > 500 ms, or who were pregnant. The STR regimen comprised 4–6 months with Am-Mfx-Eto-Cfz-Z high-dose H and E, followed by 5 months treatment with Mfx-Cfz-Z-E. The intensive phase of treatment in which the regimen contained an injectable SLD lasted for 4 months. However, if there was no sputum culture conversion (SCC) defined as "two consecutive negative sputum cultures taken at least 30 days apart following a positive culture"[18] by month 4 of treatment, the intensive phase was extended to up to 6 months. The continuation phase lasted for fixed 5 months post-injectable SLD stoppage. However, on positive phenotypic DST finding of resistance to fluoroquinolones (FQs) and/or injectable SLDs, patients were switched from STR to LTR. From the baseline visit, all patients were treated as outpatients. Patients' adherence with treatment regimen was monitored by trained treatment supporters, assessed by the doctors at monthly visits and ensured by a home DOTS linkage facilitator by paying home visits, linking the patients, PMDT units, the district TB officers, and the nearest healthcare facilities. In addition to free of cost treatment, monthly food rations and treatment allowances were given to all patients and their treatment supporters.

Data collection. All PMDT units in the country share the MDR-TB patients' data through electronic nominal recording and reporting system (ENRS) with NTP on monthly basis. A purpose-designed data collection form based on the information present in NTP guidelines and previous published articles was used to extract the patients' sociodemographic, microbiological, and clinical data from the ENRS shared with NTP. Treatment outcomes of patients were categorized in line with WHO guidelines[3] (Supplementary File 1). The outcomes of death, treatment failure, and lost to follow-up (LTFU) were grouped together as unsuccessful treatment outcomes, whereas cured and treatment completed were grouped together as successful treatment outcomes.

Statistical analysis. Data were analyzed using SPSS version 23 (IBM Corp., Armonk, NY). Univariate analysis was conducted to find associations between independent variables and the outcomes of death and treatment failure, and LTFU. All independent variables tested in the univariate analysis were based on previously published articles and their biologically plausible association with death and treatment failure, and LTFU in MDR-TB patients. To obtain the final model of factors associated with death and treatment failure, and LTFU, all independent variables with a P-value < 0.2 were assessed for collinearity and entered in multivariate binary logistic regression (MVBLR) analysis. Independent variables with high correlation (variance inflation factor 10 and/or tolerance value < 0.1) were not entered in multivariate analysis. Discrimination power of final models for evaluating death and treatment failure, and LTFU was examined by using receiver operating characteristic curve (ROC) analysis. Statistical significance was taken at a P-value of < 0.05.

Ethical approval. The study was approved by the Research and Ethics Committee of the Faculty of Pharmacy and Health Sciences, the University of Balochistan Quetta, and permission to conduct the study was granted by NTP via letter Ref No: DSA 2901/2020. Being a retrospective record review, it was not possible to trace all the study participants for taking written or oral consent, so the aforementioned institutions approved consent waiver. All the study participants' information was anonymized before conducting analysis.

RESULTS

Patients' characteristics. During the study period (January 1, 2018 to July 31, 2019), a total of 912 pulmonary MDR-TB patients were enrolled for treatment at the eight PMDT sites. Among them, 313 (34.3%) eligible MDR-TB patients were treated with STR and included in the current study. Of the remaining patients who were not treated with STR, 434

(47.6%) had resistance to an SLD (mostly a FQ) included in STR, 72 had advanced pulmonary disease (7.9%), 53 (5.8%) had a documented history of previous use of SLDs, 21 (2.3) were close contacts of DR-TB patients with confirmed resistance to SLDs, 11 (1.2%) were receiving drugs with potential to cause toxicity on coadministration with Mfx, seven patients (0.7%) were pregnant, and one was HIV positive (Figure 1). The baseline sociodemographic, microbiological, and clinical characteristics of the study participants are given in Table 1. The study participants were 33.7 ± 16.5 years old. The majority of them were females (50.2%), had a history of TB treatment (70%), were nonsmokers (94.2%), and did not suffer from any comorbidity (81.8%). The study participants were resistant to a median of 2 (range 2–5) drugs. A total of 69.1% patients were resistant to two, 20.1% to three, 8.6% to four, and 2.2% to all five FLDs, respectively. No amplification of drug resistance was observed during the course of treatment.

Sputum culture conversion. A total of 272/313 (86.9%) patients achieved SCC. Of the 41 patients who did not achieve SCC, 22 died and 16 were LTFU before SCC, whereas the remaining three patients had no information about sputum culture results. The median time to SCC was 1 month (interquartile range 1–2 months), and 221 (70.6%) patients

were culture negative by the end of second month of treatment. In the current study, a total of 270 patients received STR for ≥ 4 months. Among these 270 patients, 133 (49.2%) received injectable SLDs for > 4 months (extended intensive phase). In the univariate analysis, no independent factor had statistically significant association with extended intensive phase.

Treatment outcomes. Of 313 patients, 250 (79.9%) were declared cured, 12 (3.8%) treatment completed, 31 (9.9%) died, 16 (5.1%) LTFU, and four (1.3%) patients as treatment failures. The overall treatment success rate was 83.7%. Of the 31 patients who died, 16 (51.6%) died in the first 3 months of treatment, and the remaining survived for a median of 6 months (range 4–11 months). Of 31 patients who died, completed mortality review form was available for 19 patients. Among these 19 deceased patients, respiratory failure and cardiopulmonary arrest were, respectively, documented as the immediate cause of death in 10 and nine patients.

The results of MVBLR analysis revealed that patients' age of 41–60 (odds ratio [OR] = 4.9, P-value = 0.020) and > 60 years (OR = 3.6, P-value = 0.035), being underweight (OR = 2.7, P-value = 0.042), and the history of previous TB treatment (OR = 0.4, P-value = 0.042) had statistically significant association
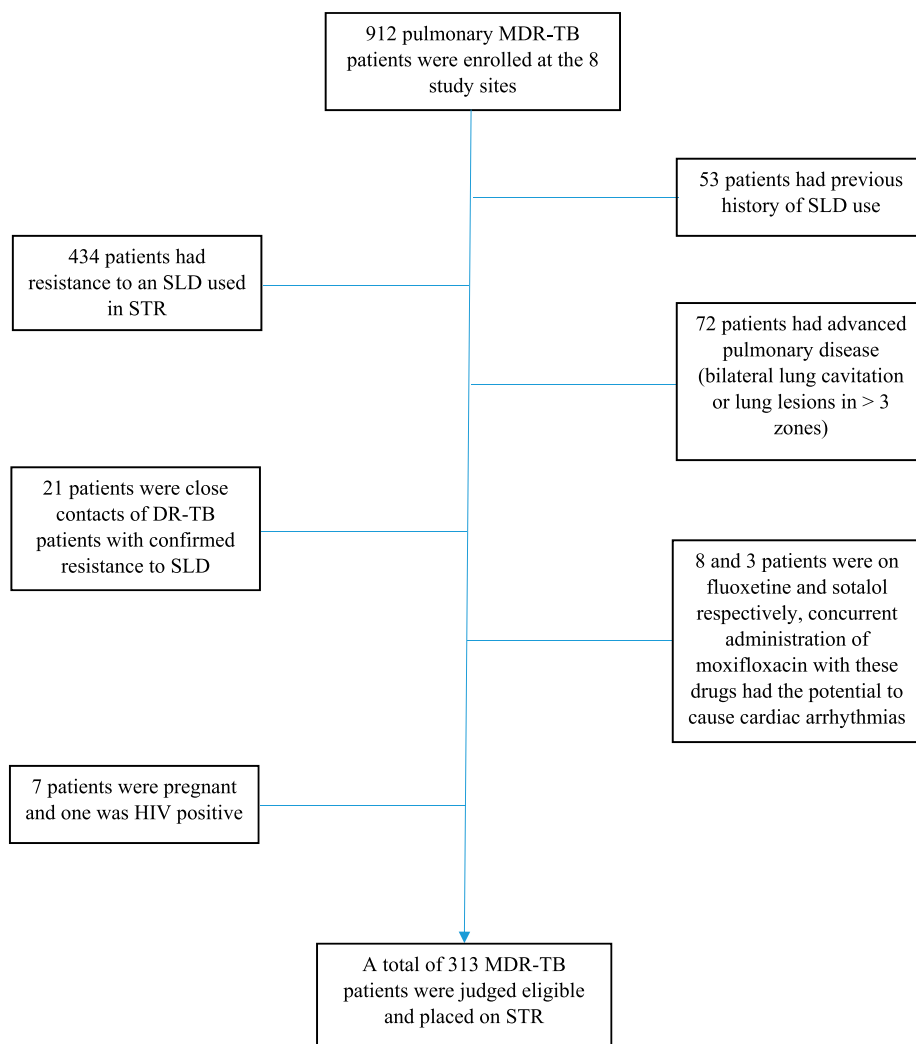

FIGURE 1. Consort diagram of patients' inclusion and exclusion in the study. This figure appears in color at www.ajtmh.org.

TABLE 1
Patients' baseline sociodemographic and clinical characteristics

Variable	No. (%)
PMDT unit	
Lady Reading Hospital, Peshawar	60 (19.2)
Saidu Teaching Hospital, Swat	12 (3.8)
Medical Teaching Institute, Mardan	17 (5.4)
Rawalpindi Leprosy Hospital, Rawalpindi	32 (10.2)
District Head Quarter Hospital, Faisalabad	77 (24.6)
Nishter Hospital, Multan	51 (16.3)
Sheikh Zaid Hospital, Rahimyar Khan	39 (12.5)
Jinnah Hospital, Lahore	25 (8.0)
Gender	
Female	157 (50.2)
Male	156 (49.8)
Age-group (years)	
≤ 20	77 (24.6)
21–40	142 (45.4)
41–60	67 (21.4)
> 60	27 (8.6)
Body mass index (kg/m^2)	
Normal (18.5–22.9)	90 (28.8)
Underweight (< 18.5)	142 (45.4)
Overweight (23–27.5)	43 (13.7)
Obese (> 27.5)	38 (12.1)
Smoking	
No	295 (94.2)
Yes	18 (5.8)
Comorbidity	
No	256 (81.8)
Yes	57 (18.2)
Type of comorbidity	
Chronic liver diseases	4 (1.3)
Chronic obstructive pulmonary disease	2 (0.6)
Depression	5 (1.6)
Diabetes mellitus	37 (11.8)
Hepatitis C	5 (1.6)
Hypertension	2 (0.6)
Others	6 (1.9)
Previous TB treatment	
No	94 (30.0)
Yes	219 (70.0)
Previous TB treatment regimen	
New	94 (30.0)
Cat-I	178 (56.9)
Cat-II	19 (6.1)
Others	22 (7.0)
Previous TB treatment centre	
No history of TB treatment	94 (30.0)
Public	86 (27.5)
Private	109 (34.8)
Public–private mix	12 (3.8)
Unknown	12 (3.8)
Baseline sputum smear grading	
Negative	31 (9.9)
Scanty (1–9 AFB/100 HPF)	42 (13.4)
+1 (10–99 AFB/100 HPF)	134 (42.8)
+2 (1–9 AFB/HPF)	77 (24.6)
+3 (> 9 AFB/HPF)	29 (9.3)
Lung lesions at baseline chest X-ray	
No lesions	15 (4.8)
One zone	113 (36.1)
2–3 zones	175 (55.9)
Not available	10 (3.2)
Resistance pattern	
Resistance to ethambutol	43 (13.7)
Resistance to pyrazinamide	70 (22.4)
Resistance to streptomycin	27 (8.6)
Resistance to two drugs	216 (69.1)
Resistance to three drugs	63 (20.1)
Resistance to four drugs	27 (8.6)
Resistance to all five first line drugs	7 (2.2)
Number of resistant drugs	2 (2–5)*

AFB = acid-fast bacilli; HPF = high power field; PMDT = programmatic management of drug-resistant tuberculosis; TB = tuberculosis.
* Median (range).

with death and treatment failure (Table 2), whereas patients' age of > 60 years (OR = 5.4, P-value = 0.040) and the history of previous TB treatment (OR = 0.2, P-value = 0.008) had statistically significant association with LTFU (Table 3). Receiver operating characteristic curve analysis by the nonparametric method revealed a fair discrimination power of the final model predicting factors associated with death and treatment failure (area under curve [AUC] = 0.754, 95% CI: 0.679–0.830, P-value < 0.001) (Figure 2) and good discrimination power of the final model predicting factors associated LTFU (AUC = 0.860, 95% CI: 0.783–0.937, P-value < 0.001) (Figure 3).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the treatment outcomes and factors associated with unsuccessful outcomes among MDR-TB patients treated with STR in Pakistani healthcare settings. We found that an overwhelming majority of MDR-TB patients (65.7%) enrolled for treatment at the study sites were not eligible for treatment with STR. This finding is in line with the previous reports from Pakistan,[21] Brazil,[22] Southeast Asia,[23] Europe,[24] and Mexico.[25] In compliance with the findings of the aforementioned studies,[21–25] the major reason for patients' ineligibility to be treated with STR at the current study sites was resistance to an SLD (47.6%). In the current study, a significant proportion of patients (30%) had no documented history of previous TB treatment. This was well above the previously reported estimated incidence of new MDR-TB patients (4.2%, 95% CI = 3.2–5.3%) in the country.[2] However, it was in compliance with the recent reports which state that new patients make up more than half of DR-TB incidence[26–28] and advocate for better infection control measures to interrupt the transmission. As a minimum, soon after the diagnosis of an index case, all household contacts should be identified and screened for active TB disease, and rapid DST should be performed for all coincident cases.[29]

The treatment success rate of STR observed in the current study (83.7%) complemented those reported by an individual patient data meta-analysis (83%),[11] and studies conducted in nine African countries (82%),[13] Bangladesh (85%),[8] and Cameroon (89%).[12] But it was superior to the global treatment success rate (56%) of MDR-TB patients treated with LTR.[2] Similarly, it was also better than the range of treatment success rate (40.5–76.9%) reported among MDR-TB patients treated with LTR in Pakistani settings.[7,15–18] The proportion deaths (9.9%) in the current study was in compliance with the mortality range (5.6–7.8%) reported among MDR-TB patients treated with STR elsewhere,[10–13] but was well below the mortality range (18.7–25.1%) observed among MDR-TB patients treated with LTR in Pakistani settings.[7,15–18] Furthermore, the LTFU rate (5.1%) in the current cohort was in the range reported among MDR-TB patients treated with STR (4.8–7.7%) elsewhere[10–13] and LTR (1.1–18.3%) in Pakistani settings.[7,15–17] However, while comparing the current treatment success rate with various cohorts of MDR-TB patients treated with LTR in Pakistani settings,[7,15–18] we observed a stark difference in the pattern of drug resistance between the two sets of patients. The current study participants were resistant to a median of two drugs, and no single patient had resistance to any SLD. On the contrary, the previously reported MDR-TB patients treated with LTR in Pakistani settings

TABLE 2
Factors associated with death and treatment failure

Variable	Death and treatment failure, no. (%)		Univariate analysis OR (95% CI)	P-value	Multivariate analysis OR (95% CI)	P-value*
	No	Yes				
Gender				0.605	–	–
Female	138 (87.9)	19 (12.1)	Referent			
Male	140 (89.7)	16 (10.3)	0.830 (0.410–1.681)			
Age-group (years)						
≤ 20	73 (93.6)	5 (6.4)	Referent		Referent	
21–40	125 (88.0)	17 (12.0)	1.986 (0.703–5.607)	0.195	2.688 (0.904–7.872)	0.075
41–60	52 (86.6)	9 (13.4)	2.266 (0.720–7.128)	0.162	4.923 (1.279–18.943)	**0.020**
> 60	28 (84.6)	4 (15.4)	2.655 (0.656–10.749)	0.171	3.614 (1.183–17.020)	**0.035**
Body mass index						
Normal (18.5–22.9)	71 (91.0)	7 (9.0)	Referent		Referent	–
Underweight (< 18.5)	118 (84.3)	22 (15.7)	1.891 (0.769–4.651)	0.165	2.741 (1.038–7.239)	**0.042**
Overweight (23–27.5)	38 (92.7)	3 (7.3)	0.801 (0.196–3.276)	0.757	0.980 (0.227–4.230)	0.979
Obese (> 27.5)	34 (91.9)	3 (8.1)	0.895 (0.218–3.676)	0.878	1.242 (0.285–5.407)	0.772
Not available	17 (100)	–	Non-computable	–	Non-computable	–
Smoking				0.029		0.180
No	265 (89.8)	30 (10.2)	Referent		Referent	
Yes	13 (72.2)	5 (27.8)	3.397 (1.133–10.189)		2.330 (0.676–8.025)	
Comorbidity				0.771	–	–
No	228 (89.1)	28 (10.9)	Referent			
Yes	50 (87.7)	7 (12.3)	1.140 (0.471–2.757)			
Previous TB treatment				0.083		**0.028**
No	79 (84.0)	15 (16.0)	Referent		Referent	
Yes	199 (90.9)	20 (9.1)	0.529 (0.258–1.086)		0.417 (0.191–0.911)	
Baseline sputum smear grading					–	–
Negative	29 (93.5)	2 (6.5)	Referent			
Scanty (1–9 AFB/100 HPF)	35 (83.3)	7 (16.7)	2.900 (0.559–15.051)	0.205		
+1 (10–99 AFB/100 HPF)	124 (92.5)	10 (7.5)	1.169 (0.243–5.627)	0.845		
+2 (1–9 AFB/HPF)	65 (84.4)	12 (15.6)	2.677 (0.563–12.734)	0.216		
+3 (> 9 AFB/HPF)	25 (86.2)	4 (13.8)	2.320 (0.391–13.753)	0.354		
Lung lesions at baseline chest X-ray						
No lesions	13 (86.7)	2 (13.3)	Referent			
One zone	103 (91.2)	10 (8.8)	0.631 (0.124–3.202)	0.579		
2–3 Zones	153 (87.4)	22 (12.6)	0.935 (0.198–4.423)	0.932		
Information not available	9 (90.9)	1 (10.0)	0.722 (0.057–9.217)	0.802		
Number of resistant drugs				0.111		**0.024**
2	196 (90.7)	20 (9.3)	Referent		Referent	
> 2	82 (84.5)	15 (15.5)	1.793 (0.875–3.673)		2.518 (1.130–5.611)	
Resistance to ethambutol				0.536	–	–
No	241 (89.3)	29 (10.7)	Referent			
Yes	37 (86.0)	6 (14.0)	1.348 (0.524–3.466)			
Resistance to Z				0.352	–	–
No	218 (89.7)	25 (10.3)	Referent			
Yes	60 (85.7)	10 (14.3)	1.453 (0.662–3.193)			
Resistance to streptomycin				0.533	–	–
No	255 (89.2)	31 (10.8)	Referent			
Yes	23 (85.2)	4 (14.8)	1.431 (0.464–4.408)			

AFB = acid-fast bacilli; HPF = high power field; OR = odds ratio; TB = tuberculosis. Model fit was based on the nonsignificant Hosmer–Lemeshow test (P-value = 0.917) and overall percentage = 88.2% from the classification table.
* Bold P-values indicate statistically significant.

were resistant to a median of 4–5 drugs, with SLD resistance ranging from 28.5% to 55.7%.[7,15–18] Moreover, among SLDs, resistance was highest for FQs (29.1–55.7%),[7,15–18] which was reported as a risk factor for unsuccessful treatment outcomes in these studies.[7,15,17,18] Furthermore, as mentioned earlier, only those MDR-TB patients were treated with STR who had no documented history of treatment with any SLD for ≥ 1 month, no confirmed resistance or suspected ineffectiveness to any SLD and no intolerance or risk of toxicity to any medicine in the STR, had no advanced pulmonary disease and clinically severe TB, and who were not coinfected with HIV. This made the current cohort a comparatively healthier group of patients than those who are treated with LTR, and hence attained the expected better outcomes. A comparative analysis of the effectiveness of STR and LTR between MDR-TB patients matched for the aforementioned

factors is suggested to know about the relatively better treatment success rate of STR in Pakistani settings.

In the current study, the multivariate analysis revealed that patients who were > 40 years old, underweight, had no history of previous TB treatment, and resistant to more than two drugs were at significantly greater risk of death and treatment failure. Furthermore, patients who were > 60 years old and had no history of previous TB treatment were at significantly greater risk of LTFU. In the studies conducted elsewhere, the univariate analysis showed a statistically significant positive association between older age and unsuccessful treatment outcomes in MDR-TB patients treated with STR, but this significance was not retained in multivariate analysis.[10,12] However, in compliance with our finding, older age has been reported a risk factor for unsuccessful outcomes among MDR-TB patients treated with LTR in studies conducted in

TABLE 3
Factors associated with lost to follow-up

	Lost to follow-up, no. (%)		Univariate analysis OR (95% CI)	P-value	Multivariate analysis OR (95% CI)	P-value*
Variable	No	Yes				
Gender				0.600	–	–
Female	150 (95.5)	7 (4.5)	Referent			
Male	47 (94.2)	9 (5.8)	1.312 (0.476–3.615)			
Age-group (years)						
≤ 20	75 (96.2)	3 (3.8)	Referent	–	Referent	–
21–40	141 (99.3)	1 (0.7)	0.177 (0.018–1.734)	0.137	0.193 (0.019–1.920)	0.160
41–60	60 (89.6)	7 (10.4)	2.917 (0.723–11.762)	0.132	3.969 (0.851–18.520)	0.079
> 60	21 (80.8)	5 (19.2)	5.952 (1.314–26.970)	0.021	5.373 (1.082–26.677)	**0.040**
Body mass index					–	–
Normal (18.5–22.9)	73 (93.6)	5 (6.4)	Referent	–		
Underweight (< 18.5)	135 (96.4)	5 (3.6)	0.541 (0.152–1.929)	–		
Overweight (23–27.5)	39 (95.1)	2 (4.9)	0.749 (0.139–4.039)	0.343		
Obese (> 27.5)	33 (89.2)	4 (10.8)	1.770 (0.446–7.017)	0.736		
Not available	17 (100)	–	Non-computable	0.417		
Smoking				0.930	–	–
No	280 (94.9)	15 (5.1)	Referent			
Yes	17 (94.4)	1 (5.6)	1.098 (0.137–8.812)			
Comorbidity				0.011		0.155
No	247 (96.5)	9 (3.5)	Referent		Referent	
Yes	50 (87.7)	7 (12.3)	3.842 (1.367–10.799)		2.289 (0.732–7.160)	
Previous TB treatment				0.025		**0.008**
No	85 (90.4)	9 (9.6)	Referent		Referent	
Yes	212 (96.8)	7 (3.2)	0.312 (0.113–0.864)		0.203 (0.063–0.657)	
Baseline sputum smear grading					–	–
Negative	28 (90.3)	3 (9.7)	Referent	–		
Scanty (1–9 AFB/100 HPF)	39 (92.9)	3 (7.1)	0.718 (0.135–3.823)	0.698		
+1 (10–99 AFB/100 HPF)	128 (95.5)	6 (4.5)	0.438 (0.103–1.856)	0.262		
+2 (1–9 AFB/HPF)	74 (96.1)	3 (3.9)	0.378 (0.072–1.897)	0.251		
+3 (> 9 AFB/HPF)	28 (96.6)	1 (3.4)	0.333 (0.033–3.402)	0.354		
Number of resistant drugs				0.286	–	–
2	203 (94.0)	13 (6.0)	Referent			
> 2	94 (96.9)	3 (3.1)	0.498 (0.139–1.791)			
Resistance to Z				0.722	–	–
No	230 (94.7)	13 (5.3)	Referent			
Yes	67 (95.7)	3 (7.3)	0.792 (0.219–2.862)			

AFB = acid-fast bacilli; HPF = high power field; OR = odds ratio; TB = tuberculosis; Z = pyrazinamide. Model fit was based on the nonsignificant Hosmer–Lemeshow test (P-value = 0.519) and overall percentage = 94.9% from the classification table.
* Bold P-values indicate statistically significant.

Pakistan[15–18] and elsewhere.[30,31] The significantly higher rates of death and treatment failure, and LTFU in elderly MDR-TB patients could be due to the combination of multiple risk factors such as physical deterioration, concurrent comorbidities and complex medication schedule, compromised immunity, and difficulty in monthly visits to the PMDT units.[17,32] The current finding of lower body mass index (< 18.5 kg/m^2) as a risk factor for death and treatment failure in MDR-TB patients is in line with the previous studies.[7,15,16,31] The poor bioavailability of oral anti-TB drugs due to poor gastrointestinal absorption and possible insufficient dosing in malnourished underweight patients could have led to subtherapeutic serum concentration of anti-TB drugs and consequently a high rate of death and treatment failure in these patients.[7,15,16,31] Our finding of additional drug resistance as a risk factor for death and treatment failure is in compliance with previous reports where additional resistance to FLDs and SLDs was associated with unsuccessful outcomes in MDR-TB patients.[7,15,33] In the current study, patients with a previous history of TB treatment were significantly less likely to develop the outcomes of death and treatment failure, and LTFU. The studies conducted elsewhere have found no significant association between the previous TB treatment and treatment outcomes among MDR-TB patients treated with STR.[10–13] However, opposite to our finding, the history of TB treatment had a statistically
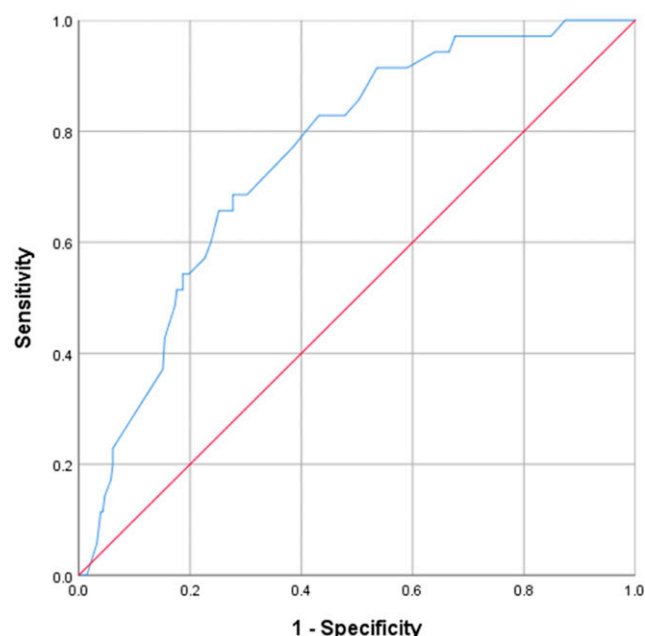

FIGURE 2. Receiver operating characteristic curve of discriminatory power of final model predicting death and treatment failure. This figure appears in color at www.ajtmh.org.
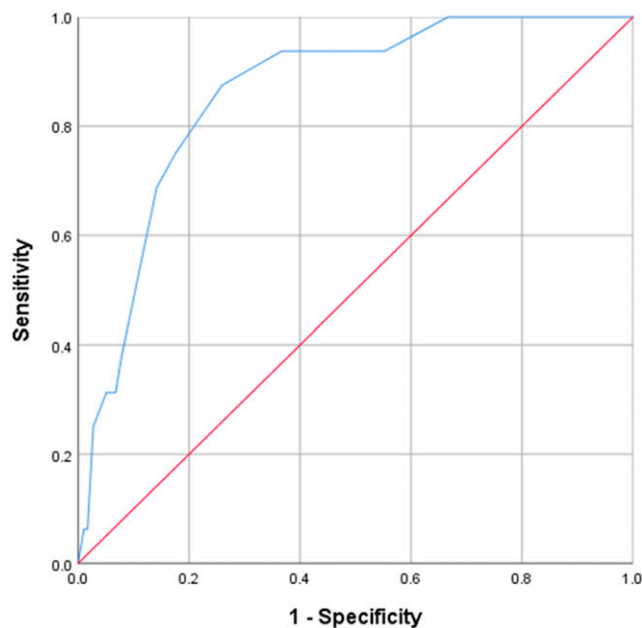
significant positive association with unsuccessful treatment outcomes among MDR-TB patients treated with LTR.[34,35] The high rates of drug resistance in the previously treated TB patients in these studies[34,35] could be a possible reason for unsuccessful treatment outcomes. Furthermore, for the presence of a significantly negative association between the history of previous TB treatment and LTFU, we speculate that the lack of awareness about the total treatment duration and the serious nature of MDR-TB, relief of symptoms after initiating STR, first time experience, and fragility toward the adverse effects of the drugs included in STR could be some of the possible reasons for the significantly high rate of LTFU among the new MDR-TB patients in the current cohort. On the other hand, experiencing the beneficial effects of an effective regimen after their past experiences of long and complicated pathways of care before being diagnosed with MDR-TB and awareness that this is their last treatment resort might have made the patients with the history of TB treatment more adherent and less prone to LTFU.

CONCLUSION

The high treatment success rate of standardized STR among eligible MDR-TB patients at multiple Pakistani PMDT units is encouraging. However, the ineligibility of overwhelming majority of MDR-TB patients (65.7%) to be treated with STR limits its applicability in Pakistani healthcare settings. Providing special attention and enhanced clinical management to MDR-TB patients who are > 40 years old, underweight, had additional resistance to anti-TB drugs, and no history of previous TB treatment may further improve the treatment outcomes. Therapeutic drug monitoring in underweight MDR-TB patients may help in the dose adjustment and manipulation anti-TB therapy in these patients. Although the current study is the first one which reported the

effectiveness of STR among a large number of MDR-TB patients treated at eight different PMDT units in Pakistan, its observational design and retrospective data collection are its major limitations. Whereas no modification in the treatment regimen of a single study participant can be taken as a proxy marker for the nonoccurrence of clinically significant adverse events and tolerability of STR in the current cohort, the lack of information about the nature, frequency, and management of adverse events and relapse is another major limitation of the current study.

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