Treatment Outcomes of Extensively Drug-Resistant Tuberculosis in Pakistan: A Countrywide Retrospective Record Review

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Background: The current study is conducted with the aim to fill the gap of information regarding treatment outcomes and variables associated with unsuccessful outcome among XDR-TB patients from Pakistan.

Methods: A total of 404 culture confirmed XDR-TB patients who received treatment between 1st May 2010 and June 30, 2017 at 27 treatment centers all over Pakistan were retrospectively followed until their treatment outcomes were reported. A p-value < 0.05 reflected a statistical significant association.

Results: The patients had a mean age 32.9 ± 14.1 years. The overall treatment success rate was 40.6% (95% confidence interval [CI]:35.80–45.60%). A total of 155 (38.4%) patients were declared cured, 9 (2.2%) completed treatment, 149 (36.9%) died, 60 (14.9%) failed treatment and 31 (7.7%) were lost to follow up (LTFU). The results of the multivariate binary logistic regression analysis revealed that the patients’ age of >60 years (OR equals 4.69, 95%CI: 1.57–15.57) and receiving high dose isoniazid (OR equals 2.36, 95%CI: 1.14–4.85) had statistically significant positive association with death, whereas baseline body weight >40 kg (OR = 0.43, 95%CI: 0.25–0.73) and sputum culture conversion in the initial two months of treatment (OR = 0.33, 95%CI: 0.19–0.58) had statistically significant negative association with death. Moreover, male gender had statistically significant positive association (OR = 1.92, 95%CI: 1.04–3.54) with LTFU.

Conclusion: The treatment success rate (40.6%) of XDR-TB patients in Pakistan was poor. Providing special attention and enhanced clinical management to patients with identified risk factors for death and LTFU in the current cohort may improve the treatment outcomes.

Keywords: death, high-dose isoniazid, sputum culture conversion, treatment outcomes, XDR-TB
INTRODUCTION

Extensively drug-resistant tuberculosis (XDR-TB) is defined as “TB caused by a strain of Mycobacterium tuberculosis (MTB) concurrently resistant to isoniazid, rifampicin, a fluoroquinolone (FQ) and a second-line injectable anti-TB drug (SLI) i.e., amikacin/kanamycin/capreomycin” (World Health Organization, 2014). It was first reported in 2005, and to date, 123 countries have notified at least one patient suffering from XDR-TB (World Health Organization, 2020). In 2019, a total of 12,350 XDR-TB patients were notified worldwide, and on average 6.2% multidrug resistant TB (MDR-TB) patients have XDR-TB (World Health Organization, 2020). The concurrent resistance to the four most effective first and second anti-TB drugs i.e., rifampicin, isoniazid, an SLI and a FQ, leaves XDR-TB patients to be treated for prolonged periods with a large number of less effective and more toxic drugs, consequently resulting in higher morbidity and mortality. Globally, the treatment success rates for drug susceptible TB, MDR-TB and XDR-TB are 85% (2017 cohort), 56% (2017 cohort) and 39% (2016 cohort), respectively (World Health Organization, 2018; World Health Organization, 2020). The previously reported treatment success rate of various individual cohorts of XDR-TB patients (n = 12–195) ranges from 4 to 65% (Abbate et al., 2012; Alene et al., 2017; He et al., 2017; Prajapati et al., 2017; Gallo et al., 2018; Yuengling et al., 2018; Frank et al., 2019; Makhmudova et al., 2019; Te Riele et al., 2019).

Unfortunately, with an estimated incidence of 28,000 MDR-TB patients, Pakistan is a DR-TB 5th high burden country in the world (World Health Organization, 2020). Pakistan initiated the programmatic management of drug resistant TB (PMDT) in 2010 (Ahmad et al., 2015), and at present there are 33 functional PMDT units all over the country. Since the inception of PMDT in 2010 and until June 30, 2019, a total of 560 XDR-TB patients have been enrolled on treatment at 30 PMDT units throughout country. Under operational conditions, evaluating a cohort of patients for treatment outcomes is a conventional, widely employed and effective method for examining the effectiveness of a program and treatment regimen (Kurbatova et al., 2012). The reported treatment success rate of a number of cohorts of MDR-TB patients treated at various PMDT units in Pakistan ranges from 40.5 to 76.9% (Ahmad et al., 2015; Javaid et al., 2017; Javaid et al., 2018; Khan et al., 2019). However, there was a complete lack of information about treatment outcomes and factors associated unsuccessful treatment outcomes among XDR-TB patients from Pakistan. Therefore, the current research was conducted to assess the treatment outcomes and factors associated with unsuccessful outcomes among XDR-TB patients in Pakistan.

MATERIALS AND METHODS

Study Design, Settings and Population

The current study was a retrospective record review of all culture confirmed XDR-TB patients who received treatment between 1st May 2010 and June 30, 2017 at 27 PMDT units across the country (Supplementary Table S1).

Diagnosis and Treatment of XDR-TB Patients

In compliance with National TB Control Program (NTP) guidelines, all presumed DR-TB patients sent to the PMDT units were evaluated for the presence of MTB, resistance to rifampicin and isoniazid by examining two sputum samples via direct sputum smear microscopy, Xpert MTB/Rif (Cepheid, Sunnyvale, CA, United States) and line probe assay, respectively. After the diagnosis of rifampicin-resistance TB through these tests, patients were enrolled on empirical MDR-TB treatment regimen and their diagnostic samples were sent to national or provincial reference laboratories for drug susceptibility testing (DST) against first-line anti-TB drugs (FLD) and second-line anti-TB drugs (SLD). At these reference laboratories, Agar proportion method on enriched Middlebrook 7H10 medium (BBL; Beckton Dickinson, Sparks, MD, United States) at the following concentrations was used for conducting DST of FLD and SLD: isoniazid (0.2 μg/mL), rifampicin (1 μg/mL), ethambutol (5 μg/mL), streptomycin (2 μg/mL), amikacin, (4 μg/mL), kanamycin (5 μg/mL), capreomycin (4 μg/mL), ofloxacin (2 μg/mL), levofloxacin (1 μg/mL) and ethionamide (5 μg/mL). Complying with manufacturer’s instructions, DST for pyrazinamide was conducted by using BACTEC Mycobacterial Growth Indicator Tube (MGIT, BD, Sparks, MD, United States) at a concentration of 100 μg/mL (Javaid et al., 2018). When the DST results became available, XDR-TB patients were switched to an individualized treatment regimen devised on the basis of DST results and guidelines recommendations (National TB Control Program, 2014; World Health Organization, 2014). They were treated with an individualized longer treatment regimen mainly comprised of an SLI, preferably the one to which the strain is sensitive, a high generation FQ (levofloxacin/moxifloxacin), all available likely effective Group-4 SLD (etionamide, cycloserine and para-amino salicylic acid), ethambutol if the strain was sensitive, pyrazinamide and two or more of the Group-5 drugs (bedaquiline, delamanid, linezolid, clofazimine, amoxicillin/clavulanate, imipenem/ cilastatin + clavulanate, meropenem + clavulanate, high-dose isoniazid, clarithromycin, thioacetazone). The total duration of treatment was a minimum of 20 months with at least 18 months after sputum culture conversion (SCC) defined as “two consecutive negative cultures taken at the gap of at least 30 days following an initial positive culture” (National TB Control Program, 2014; World Health Organization, 2014). SLIs were used for a minimum of 8–12 months. All the included XDR-TB patients were treated as outpatients throughout the treatment. Their adherence with the treatment regimen was monitored by trained treatment supporters, evaluated by the doctors on monthly visits and ensured by a home DOTS (directly observed treatment, short-course) linkage facilitator by visiting their homes, and connecting the patients, nearby healthcare facilities, the district TB officers and the PMDT units. All the patients received free of cost treatment. Moreover, monthly food rations and transportation charges were given to all patients and their treatment supporters.
Data Collection
Every month, the data of DR-TB patients treated at PMDT centers is shared with NTP through an electronic nominal recording and reporting system (ENRS). ENRS is the electronic version of the main four registers in the TB recording reporting system, i.e., basic management unit TB register, second-line TB treatment register, laboratory register for smear microscopy and Xpert MTB/Rif and laboratory register for culture, Xpert MTB/RIF and DST. In ENRS, data are entered on nominal bases at PMDT units using Excel and processed to produce routine reports to the NTP and to calculate indicators. We used a purpose developed data collection form (appendix A) to extract the sociodemographic, microbiological and clinical data of XDR-TB patients from the ENRS shared with NTP.

WHO guidelines were used to categorize patients’ end treatment outcomes (Supplementary Table S2) (World Health Organization, 2014). The treatment outcomes of death, treatment failure and lost to follow-up (LTFU) were grouped together as unsuccessful outcomes, whereas, cure and treatment completed were grouped together as successful outcomes (World Health Organization, 2014).

Statistical Analysis
Statistical Package for Social Science (version 23, IBM Corp., Armonk, N.Y., United States) was used for analyzing data. Univariate analysis was used to assess association between patients’ sociodemographic, microbiological and clinical variables and unsuccessful treatment outcomes i.e., death, LTFU and treatment failure. The entry of the independent variables in univariate analysis was based on the previously published studies, their possible relationship with the treatment outcomes and recommendations from the clinical team and supervisors of the current study. In order to find final factors associated with death, LTFU and treatment failure, multivariate binary logistic regression (MVBLR) analysis was conducted. Independent variables with a p-value <0.2 in univariate analysis were carried forward to MVBLR analysis. Independent variables with a high correlation (tolerance value <0.1 and/or variance inflation factor 10) were not included in MVBLR analysis. Statistical significance was taken at a p-value of <0.05.

Ethical Approval
Ethical approval was taken from Research and Ethics Committee of the Faculty of Pharmacy and Health Sciences, University of Balochistan Quetta and NTP Islamabad (Ref: DRF04/12/19).

RESULTS
Between 01-05-2010 and 30-06-2017, a total of 457 XDR-TB patients received treatment at 27 PMDT units in Pakistan.
and treatment outcomes are given in sociodemographic, clinical and microbiological characteristics. The results of cross-tabulation between patients’ (404 patients and they were included in the current study complete drug resistance pattern information was available for 60. Available.

### Treatment Outcomes and Factors Associated With Unsuccessful Outcomes

In the current study, a total of 40.6% (95% confidence interval [CI]:35.80–45.60%) were treated successfully. Out of 404 patients included in the final analysis, 155 (38.4%) were declared cured, 9 (2.2%) completed treatment, 149 (36.9%) died, 60 (14.9%) treatment failures and 31 (7.7%) as LTFU. The median time to death was 5 months (range 1–30 months). Out of 149 patients who died, 120 died during the first 12 months of treatment. Out of 31 LTFU patients, 29 were LTFU prior to completing the intensive phase of treatment and 24 were culture positive at the time of LTFU.

Upon MVBLR analysis, The results of the multivariate binary logistic regression analysis revealed that the patients’ age of >60 years (OR = 4.69, 95%CI:1.57–15.57, p-value = 0.006) and receiving high dose isoniazid (OR = 2.36, 95%CI:1.14–4.85, p-value = 0.019) had statistically significant positive association with death, whereas baseline body weight >40 kg (kg) (OR = 0.43, 95%CI:0.25–0.73, p-value = 0.002) and sputum culture conversion in the initial two months of

### TABLE 2 | Drug resistance pattern of study participants.

| Variable | No. (%) |
|----------|---------|
| No resistant drugs at baseline visit | |
| Four drugs | 15 (3.7) |
| Five drugs | 40 (9.9) |
| Six drugs | 55 (13.6) |
| Seven drugs | 96 (23.8) |
| Eight drugs | 99 (24.5) |
| Nine drugs | 83 (20.5) |
| Ten drugs | 15 (3.7) |
| Eleven drugs | 1 (0.2) |
| Resistance pattern to FLDs | |
| Isoniazid + rifampicin | 33 (8.2) |
| Isoniazid + rifampicin + ethambutol | 17 (4.2) |
| Isoniazid + rifampicin + pyrazinamide | 36 (8.4) |
| Isoniazid + rifampicin + streptomycin | 19 (4.7) |
| Isoniazid + rifampicin + ethambutol + pyrazinamide | 70 (17.3) |
| Isoniazid + rifampicin + ethambutol + streptomycin | 46 (11.4) |
| Isoniazid + rifampicin + pyrazinamide + streptomycin | 15 (3.7) |
| All five FLD | 166 (41.1) |
| Resistance to SLDs | |
| Resistance to SLI + fluoroquinolone | 355 (87.9) |
| Resistance to SLI + fluoroquinolone + ethionamide | 49 (12.1) |
| Resistance to amikacin | 306 (75.7) |
| Resistance to kanamycin | 305 (75.5) |
| Resistance to capreomycin | 253 (62.6) |
| Concurrent resistance to all three SLIs | 182 (45.5) |

FLD, first-line anti-TB drugs; SLD, second-line anti-TB drugs; SLI, second-line injectables.

### TABLE 1 | Patients’ socio-demographic, clinical and microbiological characteristics and treatment outcomes.

| Variable | No. (%) | Treatment outcomes | p-value |
|----------|---------|--------------------|---------|
| Gender | | Successful | Unsuccessful | |
| Female | 182 (45.0) | 77 (42.3) | 105 (67.7) | |
| Male | 222 (55.0) | 87 (39.2) | 135 (60.8) | |
| Age (years) | | | 0.045 |
| ≤20 | 87 (21.5) | 45 (51.7) | 42 (48.3) | |
| 21–40 | 207 (51.2) | 81 (39.1) | 126 (60.9) | |
| 41–60 | 91 (22.5) | 34 (37.4) | 57 (62.6) | |
| >60 | 19 (4.7) | 4 (21.1) | 15 (78.9) | |
| Baseline body weight (Kg) | | | 0.012 |
| <40 | 140 (34.7) | 45 (32.1) | 95 (67.9) | |
| ≥40 | 260 (65.3) | 119 (45.1) | 145 (54.9) | |
| Smoking | | | 0.058 |
| No | 381 (94.3) | 159 (41.7) | 222 (58.3) | |
| Yes | 23 (5.7) | 5 (21.7) | 18 (78.3) | |
| Comorbidity | | | 0.281 |
| No | 342 (84.7) | 135 (39.5) | 207 (60.5) | |
| Yes | 62 (15.3) | 29 (46.8) | 33 (53.2) | |
| Type of comorbidities | | | |
| Diabetes mellitus | 30 | | |
| Psychiatric disorders | 9 | | |
| Liver diseases | 9 | | |
| HIV | 1 | | |
| Others | 13 | | |
| History of TB treatment | | | 0.006 |
| No | 26 (6.4) | 15 (57.7) | 11 (42.3) | |
| Yes | 378 (93.6) | 149 (39.4) | 229 (60.6) | |
| History of SLD use | | | 0.516 |
| No | 251 (62.1) | 105 (48.1) | 146 (51.9) | |
| Yes | 153 (37.9) | 59 (38.6) | 94 (61.4) | |
| History of MDR-TB treatment | | | 0.346 |
| No | 260 (64.4) | 110 (42.3) | 150 (57.7) | |
| Yes | 144 (35.6) | 54 (37.5) | 90 (62.5) | |
| Site of TB | | | 0.019 |
| Pulmonary | 397 (98.3) | 159 (40.1) | 238 (59.5) | |
| Extra-pulmonary | 7 (1.7) | 5 (71.4) | 2 (28.6) | |
| Baseline smear grading | | | 0.145 |
| Negative | 73 (18.1) | 36 (49.3) | 37 (50.7) | |
| Scanty, a +1 b | 122 (30.2) | 54 (44.3) | 68 (55.7) | |
| +2 a,c, +3 a | 199 (49.4) | 70 (35.2) | 129 (64.8) | |
| Information not available | 10 (2.3) | 4 (40.0) | 6 (60.0) | |

FLD, first-line anti-TB drugs; Kg, kilogram; MDR-TB, multidrug resistant TB; SLD, second-line anti-TB drugs; SLI, second-line injectables.

(Supplementary Table S1). Out of these 457 patients, the complete drug resistance pattern information was available for 404 patients and they were included in the current study (Figure 1). The mean age of patients was 32.9 ± 14.1 years. The results of cross-tabulation between patients’ sociodemographic, clinical and microbiological characteristics and treatment outcomes are given in Table 1. Patients were resistant to a median of 7 drugs (interquartile range [IQR] = 6–8).

A total of 182 (45.5%) patients were concurrently resistant to all the three SLIs and 166 (41.1%) to all the five FLDs (Table 2). Out of 397 pulmonary XDR-TB patients, SCC was achieved by 244 patients (61.5%). Median time to SCC was 3 months (IQR = 2–5 months). Among 244 patients who achieved SCC, 110 (45%) were culture converted by second month of treatment, 170 (69.7%) by 4th and 206 (84.4%) by 6th month of treatment.
Receiving high dose isoniazid

| Variable                           | Died n (%) | Univariate analysis OR (95%CI) | p-value | Multivariate analysis OR (95%CI) | p-value |
|------------------------------------|------------|--------------------------------|---------|---------------------------------|---------|
| Gender                             |            |                                |         |                                 |         |
| Female                             | 78 (42.9)  | Referent                       |         | Referent                        |         |
| Male                               | 71 (32)    | 0.62 (0.41–0.94)               | 0.025   |                                 | 0.510   |
| Age (years)                        |            |                                |         |                                 |         |
| ≥20                                | 29 (33.3)  | Referent                       |         | Referent                        |         |
| 21–40                              | 75 (36.2)  | 1.13 (0.67–1.92)               | 0.635   | 1.35 (0.75–2.41)               | 0.311   |
| 41–60                              | 32 (35.2)  | 1.08 (0.58–2.01)               | 0.797   | 1.68 (0.82–3.42)               | 0.149   |
| >60                                | 13 (88.4)  | 4.33 (1.49–12.57)              | 0.007   | 4.96 (1.57–15.57)              | 0.006   |
| Baseline body weight (kg)          |            |                                |         |                                 |         |
| <40                                | 67 (47.9)  | Referent                       |         |                                 |         |
| ≥40                                | 82 (31.1)  | 0.49 (0.32–0.74)               | 0.001   | 0.43 (0.25–0.73)               | 0.002   |
| Resistance to all five FLD         |            |                                |         |                                 |         |
| No                                 | 97 (40.8)  | Referent                       |         |                                 |         |
| Yes                                | 52 (31.3)  | 0.66 (0.43–1.00)               | 0.054   | 0.68 (0.42–1.11)               | 0.128   |
| Baseline sputum smear grading      |            |                                |         |                                 |         |
| Negative                           | 22 (30.1)  | Referent                       |         |                                 |         |
| Scanty+1                           | 41 (33.6)  | 1.17 (0.62–2.19)               | 0.616   | 0.81 (0.40–1.62)               | 0.544   |
| +2 + 3                            | 84 (42.2)  | 1.69 (0.95–3.00)               | 0.072   | 1.43 (0.75–2.73)               | 0.277   |
| Not available                      | 2 (20)     | 0.58 (0.11–2.95)               | 0.511   | 0.47 (0.09–2.51)               | 0.382   |
| SCC at two months of treatment     |            |                                |         |                                 |         |
| No                                 | 127 (43.5) | Referent                       |         |                                 |         |
| Yes                                | 22 (19.6)  | 0.31 (0.18–0.53)               | <0.001  | 0.33 (0.19–0.58)               | <0.001  |
| Receiving clofazimine              |            |                                |         |                                 |         |
| No                                 | 62 (33.2)  | Referent                       |         |                                 |         |
| Yes                                | 87 (40.1)  | 1.34 (0.89–2.02)               | 0.150   | 1.35 (0.83–2.20)               | 0.222   |
| Receiving high dose isoniazid      |            |                                |         |                                 |         |
| No                                 | 129 (35.5) | Referent                       |         |                                 |         |
| Yes                                | 20 (48.8)  | 1.72 (0.90–3.30)               | 0.099   | 2.36 (1.14–4.85)               | 0.019   |

Note: Only those variables are presented in the table which had a p-value < 0.2 entered in multivariate analysis. This model fit was based on non-significant Hosmer-Lemeshow (p-value = 0.268) and overall percentage 65.6% from classification table.

CI, confidence interval; kg, kilogram; OR, odds ratio; SCC, sputum culture conversion; scanty = 1–9 AFB/100 HPF; **+1 = 9 AFB/100 HPF; ***+2 = 1–9 AFB/HPF; ****+3 > 9 AFB/HPF.

DISCUSSION

To the best of our knowledge, this is the first study which evaluated the treatment outcomes and factors associated with unsuccessful outcomes among XDR-TB patients enrolled for treatment at 27 PMDT units all over Pakistan. As the previously published individual cohorts from different countries have included a relatively small number of XDR-TB patients ranging from 12 to 195 (Kwon et al., 2008; Kliiman & Altraja, 2009; Pietersen et al., 2015; Yuengling et al., 2018; Makhmudova et al., 2019; Yunusbaeva et al., 2019), the large sample size of 404 XDR-TB patients from all over the country is the major strength of this study. In the present cohort, the treatment success rate (40.6%) was comparable with the global treatment success rate (39%) among XDR-TB patients (2016 cohort) (World Health Organization, 2018). However, it was better than the rates reported from Tajikistan (5.6%) (Makhmudova et al., 2019), Russia (12%) (Yunusbaeva et al., 2019), South Africa (4 and 31.4%) (Yuengling et al., 2018; Te Riele et al., 2019), China (14.6 and 30%) (Alene et al., 2017; He et al., 2017), India (25.9%) (Prajapati et al., 2017) and Georgia (33%) (Frank et al., 2019), and lower than the ones reported from Brazil (48.4%) (Gallo et al., 2018) and Argentina (65%) (Abbate et al., 2012).

In the current study, a total of 149 (36.9%) patients died. The mortality rate in our cohort was comparatively higher than the frequency of deaths observed among XDR-TB patients in Georgia (15.09%) (Frank et al., 2019), Estonia (17.54%) (Kliiman & Altraja, 2009) and Russia (23.61%) (Yunusbaeva et al., 2019), and lower than that observed in India (51.8%) (Prajapati et al., 2017) and South Africa (43 and 53%) (Pietersen et al., 2015; Yuengling et al., 2018). The relatively low mortality rate in the aforementioned studies could be due to the hiding of death by high LTUF rate ranging from 14.81 to 37.7% in these studies (Kliiman and Altraja, 2009; Frank et al., 2019; Yunusbaeva et al., 2019) as compared to 7.7% in our cohort. In the multivariate analysis, elderly patients (>60 years old) were significantly more likely to die. The combination of various risk factors like general physical deterioration, multiple comorbidities, complex
medication schedule and poor immunity make the elderly DR-TB patients more prone to death. Similar positive association between older age and unsuccessful treatment outcomes among XDR-TB (Frank et al., 2019) and MDR-TB patients have been reported by studies conducted in Pakistan (Ahmad et al., 2015; Khan et al., 2019) and elsewhere (Kurbatova et al., 2012).

In the present study, there was a statistically significant negative association between death and the patients’ baseline body weight of $\geq 40$ kg. This implies that XDR-TB patients with a baseline body weight of $< 40$ kg were significantly more likely to die than those with a baseline body weight of $\geq 40$ kg. Similar to our finding, the patients’ low body weight/body mass index at baseline visit has been reported as a risk factor for poor treatment outcomes among XDR-TB (Kwon et al., 2008; Jacobson et al., 2010; Tang et al., 2013) and MDR-TB patients (Ahmad et al., 2015; Javaid et al., 2018) have been reported elsewhere. Therefore, like in the case of MDR-TB, predicting validity of time to SCC and factors associated with it among XDR-TB patients can help doctors in identifying patients at high risk of poor outcomes early in the course of XDR-TB treatment.

Those patients of the current cohort who were taking high dose isoniazid were 2.3 times more likely to die than their counterparts. However, the previously published studies among XDR-TB patients have not reported any such finding. Following the assumption that high dose isoniazid may be effective in MTB strains with low-level isoniazid resistance due to mutations in the inhA promoter at positions 8, 15 or 16 (Domínguez et al., 2016), WHO guidelines proposed the high-dose isoniazid in the treatment of XDR-TB patients (World Health Organization, 2016). However, there is a general consensus that high-dose isoniazid treatment cannot overcome the high-level isoniazid resistance caused by mutation in the katG gene at position 315 (Domínguez et al., 2016; Chesov et al., 2017). A study from Republic of Moldova which evaluated the molecular drug-resistance in 2638 MTB strains found that mutation in the katG gene at position 315 was present in 88.1% of the tested strains (Chesov et al., 2017). As the use of high dose isoniazid may be associated with higher incidence of hepatitis, peripheral neuropathy and other unforeseen adverse effects (World Health Organization, 2016), therefore, the indiscriminate use of high dose isoniazid in DR-TB in the absence of comprehensive molecular drug resistance testing should be discouraged (Chesov et al., 2017). Nevertheless, the current finding of positive association between the use of high dose isoniazid and death among XDR-TB patients should be

### TABLE 4 | Factors associated with lost to follow-up.

| Variable                                      | LTFU n (%) | Univariate analysis | Multivariate analysis |
|-----------------------------------------------|------------|---------------------|-----------------------|
| Gender                                        | 9 (4.9)    | Referent            | Referent              |
| Female                                        | 22 (9.9)   | 2.11 (0.84–4.71)    | 1.92 (1.04–3.54)      |
| Male                                          |            |                     |                       |
| Age (years)                                   | 2 (0.9)    | 2.61 (0.6–5.5)      | 1.98 (0.57–5.6)       |
| ≥20                                           | 4 (1.8)    | 2.61 (0.6–5.5)      | 1.98 (0.57–5.6)       |
| 21–40                                         | 20 (9.7)   | 2.61 (0.6–5.5)      | 1.98 (0.57–5.6)       |
| 41–60                                         | 5 (5.5)    | 1.20 (0.31–4.67)    | 1.98 (0.42–4.83)      |
| >60                                           | 2 (0.9)    | 2.61 (0.6–5.5)      | 1.98 (0.57–5.6)       |
| Baseline sputum smear grading                 |            |                     |                       |
| Negative                                      | 4 (5.5)    | Referent            | Referent              |
| Scanty$^a$, $+^b$                             | 11 (9)     | 1.70 (0.52–5.58)    | 1.00 (0.41–2.42)      |
| $+^2$, $+^3$                                  | 14 (7)     | 1.30 (0.41–4.10)    | 1.24 (0.56–2.71)      |
| NA                                            | 2 (20)     | 4.31 (0.67–27.38)   | 1.30 (0.23–7.29)      |
| SCC at two months of treatment                 |            |                     |                       |
| No                                            | 29 (9.9)   | 0.16 (0.03–0.70)    | 1.24 (0.63–2.33)      |
| Yes                                           | 2 (1.8)    |                     |                       |

Note: Only those variables are presented in the table which in univariate analysis had a p-value $< 0.2$ were entered in multivariate analysis. This model fit was based on non-significant Hosmer-Lemeshow (p-value = 0.701) and overall percentage of 85.1% from classification table. CI, confidence interval; kg, kilogram; LTFU, lost to follow up; OR, odds ratio; SCC, sputum culture conversion.

$^a$Scanty = 1–9 AFB (Acid fast bacilli)/100 HPF (High power field);

$^b$≥ 1 = 10–99 AFB/100 HPF;

$^c$+ 2 = 1–9 AFB/HPF;

$^d$+ 3 > 9 AFB/HPF.
interpreted with the major limitation that only 41 (10.1%) patients of the current cohort received high dose isoniazid. Furthermore, these patients who received high dose isoniazid might also have more severe form of TB. Therefore, a study with large number of XDR-TB patients receiving high dose isoniazid is suggested to confirm the current finding.

In the current study, the LTFU rate (7.7%) is in line with studies from China (5.9%) (Tang et al., 2013), South Africa (7.0%) (Pietersen et al., 2015) and India (9.8%) (Prajapati et al., 2017), but lower than the rates reported by studies conducted in Georgia (37.7%) (Frank et al., 2019), South Africa (16.2%) (Yunusbaeva et al., 2019) and Estonia (14.8%) (Kliiman and Altraja, 2009). In the present study, 24/31 patients were LTFU prior to SCC. As those patients who are sputum culture positive are highly infective and potential source of XDR-TB transmission, LTFU prior to SCC is a serious threat to the public health. In

### Table 5: Factors associated with treatment failure.

| Variable                        | Failed n (%) | Univariate analysis | p-value | Multivariate analysis | p-value |
|---------------------------------|--------------|---------------------|---------|-----------------------|---------|
| Gender                          |              |                     |         |                       |         |
| Female                          | 18 (9.9)     | Referent            | 0.012   | 1.73 (0.85–3.52)       | 0.126   |
| Male                            | 42 (16.9)    | 2.12 (1.17–3.84)    |         |                       |         |
| Age (years)                     |              |                     |         |                       |         |
| <20                             | 9 (10.3)     | Referent            | 0.293   | 1.43 (0.62–3.28)       | 0.395   |
| 21–40                           | 31 (15)      | 1.52 (0.69–3.35)    |         |                       |         |
| 41–60                           | 20 (22)      | 2.44 (1.04–5.711)   |         |                       |         |
| >60                             | 0 (0)        | Non-computable      |         |                       |         |
| Baseline body weight (kg)       |              |                     |         |                       |         |
| <40                             | 14 (10)      | Referent            | 0.049   | 1.27 (0.80–2.71)       | 0.520   |
| ≥40                             | 46 (17.4)    | 1.89 (1.00–3.59)    |         |                       |         |
| Smoking                         |              |                     |         |                       |         |
| No                              | 54 (14.2)    | Referent            | 0.127   | 1.22 (0.39–3.77)       | 0.729   |
| Yes                             | 6 (26.1)     | 2.13 (0.80–5.66)    |         |                       |         |
| Resistance to pyrazinamide      |              |                     |         |                       |         |
| No                              | 12 (10.4)    | Referent            | 0.119   | 1.67 (0.73–3.82)       | 0.223   |
| Yes                             | 48 (16.6)    | 1.71 (0.87–3.35)    |         |                       |         |
| Resistance to ethionamide       |              |                     |         |                       |         |
| No                              | 56 (15.8)    | Referent            | 0.169   | 0.40 (0.12–1.24)       | 0.115   |
| Yes                             | 4 (8.2)      | 0.47 (0.16–1.37)    |         |                       |         |
| Receiving clarithromycin        |              |                     |         |                       |         |
| No                              | 19 (11)      | Referent            | 0.066   | 1.89 (0.96–3.68)       | 0.062   |
| Yes                             | 41 (17.7)    | 1.72 (0.96–3.10)    |         |                       |         |
| Receiving bedaquiline           |              |                     |         |                       |         |
| No                              | 57 (15.7)    | Referent            | 0.164   | 0.56 (0.14–2.25)       | 0.418   |
| Yes                             | 3 (7.3)      | 0.42 (0.12–1.42)    |         |                       |         |
| Receiving clofazimine           |              |                     |         |                       |         |
| No                              | 34 (18.2)    | Referent            | 0.082   | 1.01 (0.46–2.23)       | 0.970   |
| Yes                             | 26 (12)      | 0.61 (0.35–1.06)    |         |                       |         |
| Receiving linezolid             |              |                     |         |                       |         |
| No                              | 24 (19.7)    | Referent            | 0.076   | 0.67 (0.33–1.38)       | 0.283   |
| Yes                             | 36 (12.8)    | 0.59 (0.33–1.05)    |         |                       |         |
| Receiving moxifloxacin          |              |                     |         |                       |         |
| No                              | 26 (19.3)    | Referent            | 0.080   | 0.69 (0.32–1.45)       | 0.327   |
| Yes                             | 34 (12.6)    | 0.60 (0.34–1.06)    |         |                       |         |
| Number of resistant drugs       |              |                     |         |                       |         |
| 4–6                             | 10 (9.1)     | Referent            |         |                       |         |
| 7–8                             | 36 (18.5)    | 2.26 (1.07–4.76)    | 0.031   | 1.82 (0.77–4.32)       | 0.172   |
| >8                              | 14 (14.1)    | 1.64 (0.69–3.89)    | 0.256   | 1.37 (0.47–3.93)       | 0.558   |

Note: Only those variables are presented in the table which in univariate analysis had a p-value <0.2 were entered in multivariate analysis. This model fit was based on non-significant Hosmer lemeshows (p-value = 0.471) and overall percentage of 84.9% from classification table.

CI, confidence interval; kg, kilogram; OR, odds ratio.

In conclusion, the rate of successful treatment outcomes (40.6%) in the current cohort was comparable to the global treatment success rate (39%)
among XDR-TB patients, but far lower than the target (75%) set by the WHO. The variables which emerged as risk factors for death and LTFU in the current cohort i.e., patients’ age of >60 years, receiving high dose isoniazid, baseline body weight of <40 kg, failure to achieve SCC in the initial two months of treatment and male gender are easily recognizable before diagnosis or in the very beginning of XDR-TB treatment. Giving special attention and enhanced clinical management, nutritional supplementation, strategies to ensure treatment completion by and decentralizing the treatment in patients at high risk of death and LTFU may improve the treatment outcomes. Therapeutic drug monitoring in those XDR-TB patients who had baseline body weight <40 kg may help in the dose adjustment and manipulation anti-TB therapy in these patients. By evaluating the treatment outcomes of 404 XDR-TB patients from 27 PMDT units all over the country and following the WHO standard methodology, the current study can be considered as a representative of the entire XDR-TB population from Pakistan. However, the observational design, retrospective nature of data collection, convenient sampling method and inability to objectively assess the patients’ adherence with therapeutic regimen are the major limitations associated with this study. This study also lacks information about the radiological findings, body mass index, and incidence and management of adverse events in the current cohort which have previously been reported as factors associated with treatment outcomes in DR-TB patients. Furthermore, life events of patients that can influence an unsuccessful treatment outcome (i.e., lost to follow-up, death or treatment failure) were not recorded and analyzed.

DATA AVAILABILITY STATEMENT
All data gathered or analyzed during this study are included in the article/Supplementary Material.

AUTHOR CONTRIBUTIONS
NA, AHK, MA, AG, SK and AK conceptualized and designed the study. MA, AL collected the data. MA, NA, IA and FS analyzed the data. NA and MA wrote the manuscript. All authors critically reviewed the manuscript. NA also supervised the study.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.640555/full#supplementary-material.

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