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Determinants of treatment outcome in children with multidrug-resistant tuberculosis: a tertiary care hospital experience

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Abstract

This study aimed to analyze the significant factors associated with unsuccessful treatment outcomes among multidrug-resistant tuberculosis in children under 18.

This observational study was conducted at the Bahawal Victoria Hospital, Bahawalpur, Pakistan, at the Programmatic Management Unit of the National Tuberculosis Control Program of Pakistan. The data were collected retrospectively using the Electronic Nominal Recording Reporting System records for all the eligible drug-resistant tuberculosis patients registered at the study sites between June 2014 and September 2022. Multivariate binary logistic regression analysis was used to analyze the factors significantly associated with unsuccessful treatment outcomes.

This study included 88 children. Of the 88 patients, 64 (72.8%) completed their treatment successfully. A total of 13 patients (14.8%) died, 2 (2.3%) had treatment failure, and 9 (10.2%) were lost to follow-up. Factors significantly associated with unsuccessful treatment outcomes included a history of use of second-line drugs and those with favorable interim treatment outcomes (negative association).

The overall treatment success rate among the children was 72.8%, which can be further improved by reducing loss to follow-up and rational use of second-line drugs in treating drug-sensitive tuberculosis. This can be done by devising a careful, targeted treatment regimen and patient education.

Key words: multidrug-resistant tuberculosis, children, chronic diseases.

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Introduction

The World Health Organization (WHO) has recognized the disproportionate impact of TB on children and adolescents. Multidrug-resistant tuberculosis (MDR-TB) in children is a significant global health concern. Many initiatives have been implemented on both national and global scales to mitigate the health consequences associated with tuberculosis (TB) [1]. Nevertheless, it continues to cause the deaths of millions of people annually. By inducing approximately 1.6 million fatalities in the year 2017, TB stands as the eminent lethal infectious disease, surpassing the mortality associated with HIV [2].

In the realm of global health challenges, the emergence and spread of MDR-TB present a formidable obstacle, demanding focused attention and comprehensive strategies for effective management. There were 500,000 fresh instances of MDR-TB and 250,000 fatalities from MDR-TB worldwide in 2018 [3]. The situation is further compounded when considering the vulnerability of a specific demographic, those below the age of 18. Children made up 11% of all TB patients in 2021 [4]. They accounted for 14% of all TB-related deaths [4]. Children and teenagers are particularly vulnerable to drug-resistant TB (DR-TB), which is a severe public health issue. Household contacts of adults with DR-TB are most at risk [5]. Research has indicated that the percentage of MDR-TB in children with TB is comparable to that of adults [6].

In Pakistan, where the burden of TB remains significant [7], understanding the treatment outcomes and the intricate web of factors influencing these outcomes among MDR-TB patients in this age group becomes imperative. Pakistan comprises four provinces and is the sixth most populous nation globally [8]. Regrettably, in the context of MDR-TB prevalence, Pakistan presently holds the fourth position on the global scale [9]. In 2017, the projected incidence of MDR-TB cases in Pakistan amounted to 27,000, with a prevalence of 4.2% [95% confidence interval (CI)=3.2-5.3%] among newly infected individuals and 16% (95% CI=15-17%) among those previously treated for TB [4]. In January 2024, Pakistan introduced a national strategic plan (2024-2026) to enhance TB control efforts. The plan aims to increase the annual identification of TB cases from

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424,559 in 2022 to at least 528,600 by 2026. For MDR-TB, the target is to escalate treatment cases from 3,684 in 2022 to 7,960 per year by 2026, maintaining a treatment success rate above 80% from 2024 onwards [10]. Similar to various manifestations of TB, DR-TB affects individuals across all age strata, encompassing children (≤14 years) [11]. Current estimates point out that on an annual basis, approximately 25,000-32,000 children suffer from MDR-TB, constituting 3% of the total pediatric TB drug cases [12]. The diagnostic challenges inherent in pediatric cases, stemming from the limited ability of children to expectorate sputum, the paucibacillary nature of the disease, difficulties in procuring specimens for culture and drug susceptibility testing (DST), and the presence of nonspecific symptoms, collectively render the diagnosis of childhood TB, including DR-TB, a formidable undertaking. Pediatric MDR-TB diagnosis is challenging due to the paucibacillary nature of the disease and difficulty in obtaining sputum samples. Traditional diagnostic tools often fail, requiring reliance on gastric lavage, induced sputum**,** or molecular tests (GeneXpert MTB/RIF)**,** which are not always accessible in resource-limited settings. Children face limited access to pediatric-friendly drug formulations, making accurate dosing difficult. Adverse drug reactions (ADRs) (*e.g.*, hepatotoxicity, neuropathy, depression) further impact adherence, and the lengthy treatment duration (9-24 months) increases the risk of loss to follow-up, especially in low-resource settings. Consequently, pediatric TB, inclusive of its drug-resistant variants, has historically endured neglect and has not been accorded priority status within the National Tuberculosis Control Program (NTP) worldwide [13].

The study on MDR-TB treatment outcomes in children aligns with WHO's 2022 MDR-TB guidelines**.** The study indicates that children were treated with shorter (STR) and longer (LTR) regimens**,** which aligns with WHO's recommendation for shorter all-oral regimens (9-12 months) where possible. The study considers interim treatment outcomes (negative sputum/culture conversion) as a significant predictor of success, which aligns with WHO's guidelines [14].

Previously, very few studies have been published for individual cohorts of childhood MDR-TB patients. They have reported variable rates of successful treatment outcomes (62-92%) [15-17].

This article delves into the nuanced landscape of MDR-TB treatment outcomes, dissecting the unique challenges faced by children in Pakistan's healthcare system. We aim to shed light on the complex interplay of medical, socioeconomic, and healthcare system-related factors that either facilitate or hinder the unsuccessful treatment of MDR-TB in this vulnerable population.

By unraveling the multifaceted dimensions of treatment outcomes, this research will contribute to the global discourse on MDR-TB management in children. It provides valuable insights that can inform targeted interventions and policies specific to pediatric MDR-TB patients in Pakistan. The knowledge gleaned from this study will hold the potential to drive evidence-based strategies, optimize the efficacy of interventions, and foster a brighter, healthier future for the children of this persistent global health challenge.

Materials and Methods

Study setting

This study was conducted at one of the Programmatic Management Units of the National Tuberculosis (PMDT) sites working under the NTP of Pakistan, established at the Chest Disease Unit (CDU) of the Bahawal Victoria Hospital (BVH). As a tertiary care hospital, the hospital is located in Bahawalpur, in the Southern Punjab, Pakistan. The hospital has a bed capacity of over 1599 [18]. The CDU site provides free-of-cost treatment for all DR-TB patients under the supervision of doctors, pharmacists, program assistants, psychologists, treatment coordinators, and other medical staff. A fully equipped laboratory is present at the DR-TB site of Bahawalpur for TB diagnosis purposes, such as GeneXpert, Xpert-MTB/RIF, and sputum smear microscopy. Specimen samples for line probe assay (LPA) and DST were sent to the National Reference Laboratory (NRL) in Islamabad, Pakistan. Also, DR-TB patients were sent to BVH's radiology and pathology departments for standard examinations.

Study design and population

This was a retrospective study of MDR-TB patients aged below 18 registered at the PMDT site of the BVH from June 2014 to September 2022. All patients with pulmonary MDR-TB for whom final treatment outcomes were available, irrespective of their gender, previous medical history, comorbidities, and previous TB treatment history, were included in this study. All patients with pre-extensively DR-TB (XDR-TB) and XDR-TB and those who were still under treatment at the time of data collection were excluded from the study.

Diagnosis and treatment protocol

Diagnosis and treatment of all MDR-TB patients were done according to WHO guidelines [19]. Initially, all children presenting in the outpatient department of the chest ward of BVH with symptoms of cough, fever, weight loss for more than 2 weeks, or worked up for TB were screened. Children's home respiratory specimens (including sputum, gastric lavage, bronchoalveolar lavage, and biopsy) were retrieved and sent for GeneXpert Rifampicin resistance on Xpert MTB/Rif assay. Those with rifampicin resistance were enrolled at the PMDT site for the treatment of MDR-TB. Further laboratory tests, including LPA and DST, were done to evaluate drug resistance against first-line drugs (FLDs) and second-line drugs (SLDs). Sputum samples from the patients were submitted to NRL Islamabad for this purpose. The children were categorized into STR and LTR based on LPA results and further modified according to DST if needed. Children who were enrolled before 2016 received conventional treatment. Psychological support and education of the caretaker and the patient were conducted regularly every month at each PMDT site to improve treatment adherence, early identification of ADRs, and follow-up.

Children and their caretakers were followed every month. Regular follow-up visits were scheduled to monitor treatment progress, assess response to therapy, manage side effects, and provide ongoing support. At follow-up, the respiratory specimen was resent for DST, and the chest X-ray was repeated.

Data sources and collection

All the data were collected using Electronic Nominal Recording Reporting System (ENRS) records in March 2023. Data validation steps such as cross-checking with hospital records and verifying them were done to reduce errors, such as standardization of data entry and monitoring for inconsistencies. The ENRS records provided all the sociodemographic characteristics, clinical characteristics, treatment regimen, Adverse drug events, drug resistance patterns, and treatment outcome-related data of all the MDR-TB patients. Regular sputum smear and culture tests were performed to track

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treatment progress, ensuring objective data collection on interim and final treatment outcomes. Monthly follow-ups, counselling sessions, and treatment adherence support help maintain comprehensive and up-to-date patient records.

Reporting of treatment outcomes

Treatment outcomes were reported according to the treatment categories suggested by WHO guidelines for the programmatic management of MDR-TB [20]. Cured and treatment-completed outcomes together were categorized as successful treatment outcomes. Whereas patients who died lost to follow-up, or had treatment failure were classified as having unsuccessful treatment outcomes [21].

Data management and analysis

Data were analyzed using Statistical Package for Social Sciences Statistics (SPSS) for Windows version 21.0 (IBM, Armonk, NY, USA). Descriptive statistical analysis was performed. All categorical data were reported using frequencies and proportions (%). Continuous variables were analyzed as means and standard deviations (SDs). A simple logistic regression analysis evaluated the association between patient characteristics and unsuccessful treatment outcomes (dependent variable). After simple logistic regression analysis, those statistically significant variables (*i.e.*, $p<0.2$) were then analyzed using multiple logistic regression analysis with a p-value of 0.05 to identify the final factors associated with unsuccessful outcomes [22]. For each variable, the adjusted odds ratio (AOR), p-value, and CI were reported.

Study approval and ethical considerations

Ethical approval was obtained from the research and ethics committee of QAMC/BVH under reference no. QAMC/BVH-00921.

Results

Sociodemographic characteristics of the patients

The sociodemographic data of the patients have been added to Table 1. The mean age of the patients was 15.8 years, with an SD of 2.1 years, indicating a relatively narrow age range within the study group. Regarding gender distribution, females constituted 71.6% of the patients compared to males at 28.4%. Regarding residence, the data showed a balanced representation, with 48.9% residing in urban areas and 51.1% in rural settings.

Clinical characteristics of the patients

The clinical characteristics are explained in Table 2. Among the total 88 patients, 43(48.9%) were previously treated for TB, whereas 20 (22.7%) had primary MDR-TB. In 53 (60.2%) patients, sputum and culture became negative at interim treatment outcomes. Most patients received HREZ (48.9%) as FLD treatment. Among all 88 patients, 54 (61.4%) were underweight.

The treatment regimen of the patients

Table 3 discusses the results related to the treatment regimen. Among the 88 patients, most received LTR, accounting for 51.1% of the cohort, followed by STR (short-term regimen) at 19.3%. Conventional therapy, likely referring to standard TB treatment protocols, was administered to 29.5% of the patients.

Table 1. Sociodemographic characteristics of the patients (n=88).

Characteristics	Patients, n (%)
Age (years), mean±SD	15.8±2.1
Gender	
Male	25 (28.4)
Female	63 (71.6)
Residence	
Urban	43 (48.9)
Rural	45 (51.1)

SD, standard deviation.

Table 2. Clinical characteristics of the patients (n=88).

Characteristics	Patients, n (%)
Registration group	
Primary MDR-TB	20 (22.7)
Previously treated	43 (48.9)
Treatment after failure	16 (18.2)
Relapse	8 (9.1)
Unknown previous history	1 (1.1)
Interim treatment outcomes	
Negative SP and CL	53 (60.2)
Positive SP and CL	1 (1.1)
Not done – dead	11 (12.5)
Not done – defaulted	6 (6.8)
Unknown	17 (19.3)
Site of the disease	
Pulmonary TB	88
Result of HIV Test	
Positive	1 (1.1)
Negative	86 (97.7)
Not done	1 (1.1)
BMI at the start of treatment, mean±SD (16±2.8)	
Underweight	54 (61.4)
Normal weight	8 (9.1)
Overweight	1 (1.1)
Missing	25 (28.4)
Previous FLD treatment history	
HREZ	52 (59.1)
HREZS	12 (13.6)
No FLD	20 (22.7
Missing	4(4.5)
History of SLD use	
Yes	4 (4.5)
No	84 (95.5)
Hospitalization of the patient	
Yes	0 (0)
No	88 (100)
Adverse drug events	
Yes	52 (59.1)
No	36 (40.9)
Comorbidities	
Yes	4 (4.5)
No	84 (95.5)
Behavior status	
Smoking	1 (1.1)
Drug addicts	2 (2.3)
No addiction	85 (96.6)

MDR-TB, multidrug-resistant tuberculosis; SP, sputum; CL, culture; TB, tuberculosis; BMI, body mass index; SD, standard deviation; FLD, first-line drugs; H, isoniazid; R, rifampicin; E, ethambutol; Z, pyrazinamide; S, streptomycin; SLD, second-line drugs. Missing = data not available.

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Adverse drug events among DR-TB patients during the treatment

Adverse drug events are explained in Table 4. The most commonly reported adverse events were related to the digestive system, with nausea and vomiting affecting 13.6% of patients, followed by anorexia (4.5%), gastritis (4.5%), and gastroesophageal reflux disease (GERD) (7.9%). In the nervous system category, depression was notable, affecting 18.2% of patients, while other neurological symptoms, such as headache, sleep disturbance, and visual disturbances, were reported at lower frequencies. However, arthralgia was noted in 20.5% of the patients.

Table 3. Treatment regimen of the patients (n=88).

Variables	Patients, n (%)
LTR	45 (51.1)
STR	17 (19.3)
Conventional therapy	26 (29.5)

LTR, long-term regimen; STR, short-term regimen.

Table 4. Adverse drug events among drug-resistant tuberculosis patients during the treatment (n=88).

Adverse drug events	Patients, n (%)
Digestive system	
Nausea and vomiting	12 (13.6)
Diarrhea	1 (1.1)
Abdominal pain	1 (1.1)
Anorexia	4 (4.5)
Gastritis	4 (4.5)
Hepatitis	1 (1.1)
Gastroesophageal reflux disease	7 (7.9)
Nervous system	
Dizziness vertigo	1 (1.1)
Depression	16 (18.2)
Headache	3 (3.4)
Sleep disturbance	2 (2.3)
Psychosis	1 (1.1)
Peripheral neuropathy	1 (1.1)
Visual disturbance	2 (2.3)
Auditory system	
Hearing disturbance	4 (4.5)
Tinnitus	1 (1.1)
Integumentary system	
Rash pruritus	4 (4.5)
Others	
Arthralgia	18 (20.5)

Table 5. Final treatment outcomes among the study participants (n=88).

Treatment outcomes	Patients, n (%)	n (%)
Successful		
Cured	62 (70.5)	64 (72.8)
Treatment completed	2 (2.3)	
Unsuccessful		
Died	13 (14.8)	
Treatment failure	2 (2.3)	24 (27.2)
Loss to follow up	9 (10.1)	

Final treatment outcomes among the study participants

Most patients, accounting for 72.8% of the cohort, achieved successful treatment outcomes. Among these successful cases, 70.5% of patients were cured, indicating a favourable resolution of their TB infection. These treatment outcomes are explained in Table 5.

An additional 2.3% of patients completed their treatment successfully, contributing to the overall successful treatment group. However, there were also instances of unsuccessful treatment outcomes, representing 27.2% of patients. Within this subgroup, 14.8% of patients unfortunately succumbed to the disease, highlighting the severity and potential fatality of MDR-TB. Furthermore, 2.3% of patients experienced treatment failure, indicating challenges in managing TB effectively. Moreover, 10.2% of patients were lost to follow-up during treatment, which resulted in unsuccessful treatment outcomes.

Predictors of unsuccessful treatment outcomes

In multivariate binary logistic regression analysis adjusting for potential confounders, the successful interim treatment outcome (negative sputum smear and culture) has an inverse relationship with the unsuccessful treatment outcome (p=0.000, AOR=0.025, 95% CI: 0.005-1.29) while previous history of SLD use (p=0.054, AOR=0.044, 95% CI: 0.002-0.055) remained significantly associated with unsuccessful treatment outcomes. This finding in Table 6 suggests that patients with a history of SLD use and negative interim treatment outcomes (indicating persistent TB infection) were significantly more likely to experience treatment failure or other adverse outcomes.

Discussion

The study investigated various aspects related to MDR-TB in children, encompassing socio-demographic, clinical, and treatment regimens, adverse events, and treatment outcomes. In the final treatment outcome for MDR-TB, 72.8% of the patients had successful treatment outcomes, whereas 27.2% had unsuccessful treatment outcomes. This aligns with previously reported treatment success rates ranging from 82% to 92% for childhood MDR-TB patients in other studies by Molla *et al.* in patients treated at treatment centers in Ethiopia's Amhara and Oromia regions [23]. However, successful treatment outcomes are less than reported in another study conducted in Mumbai, India, which found that 62% of a younger cohort of children under 15 had successful outcomes [17]. Variations in treatment success rates for MDR-TB across different studies can be attributed to several factors. Patient characteristics such as baseline weight and weight gain during treatment significantly influence outcomes; individuals with higher baseline weights or those who gain weight during therapy often experience better success rates [24]. Conversely, co-infection with HIV has been associated with poorer treatment outcomes, highlighting the complexity added by concurrent infections. Additionally, resistance to second-line drugs and the presence of XDR-TB are significant predictors of unsuccessful treatment outcomes [25]. The mortality rate of 14.8% is notably high, underscoring the severity of MDR-TB in this demographic and the pressing need for improved management strategies. Comparatively, global studies have reported varying mortality rates, reflecting differences in healthcare infrastructure, accessibility, and the quality of TB management programs across regions [26,27].

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Our research sheds light on the ignored but vulnerable subpopulation of children aged 11 to 18 who have MDR-TB [28]. Our study's socio-demographic analysis revealed a mean age of 15.8 years, with females representing the majority (71.6%). This is consistent with the study published by Brode *et al*., which reported higher incidences of TB among female adolescents [29]. The nearly equal urban-rural split (48.9% urban and 51.1% rural) in the UK and USA indicates a widespread distribution of MDR-TB across different living environments. This contrasts with certain studies that highlight a higher prevalence of TB in urban areas due to denser populations and increased transmission rates [30,31].

The clinical characteristics of the patients showed that 22.7% had primary MDR-TB, which is consistent with global data indicating significant proportions of primary MDR-TB cases among children [32]. The lack of hospitalizations among the cohort is notable and may reflect the outpatient management protocols at the study site. Only one patient tested positive for HIV, indicating a low co-infection rate, which aligns with findings from regions with lower HIV prevalence. ADRs were common, with depression (18.2%) and arthralgia (20.5%) being particularly noteworthy. These rates are comparable to those reported in other studies conducted in Indonesia [33,34], emphasizing the need for effective management of ADRs to improve treatment adherence and outcomes [35]. Additionally, 61.4% of the patients were underweight, a known risk factor for poor TB outcomes, which enhances the importance of nutritional support in TB treatment programs.

The multivariate regression analysis highlighted two significant predictors of unsuccessful treatment outcomes: previous use of SLDs and interim treatment outcomes. Patients with a history of SLD use were significantly more likely to experience unsuccessful treatment outcomes (p=0.054, AOR=0.044, 95% CI: 0.002-0.055). This suggests that previous exposure to SLDs may lead to increased resistance or more severe disease, complicating subsequent treatment efforts [36,37]. The use of second-line anti-TB drugs in treating MDR-TB has been associated with less favorable outcomes, primarily due to factors such as drug toxicity, patient non-adherence, and the development of further drug resistance. Second-line TB medications are often linked to significant adverse effects. For instance, aminoglycosides like streptomycin, kanamycin, and amikacin can cause ototoxicity, leading to permanent hearing loss [38]. The prolonged treatment duration for MDR-TB, coupled with the severe side effects of second-line drugs, often leads to poor patient adherence. Non-compliance can result in suboptimal drug exposure, reducing treatment efficacy and increasing the risk of developing additional drug resistance [37].

The interim treatment outcome at 6 months, specifically negative sputum smear and culture, was strongly associated with successful outcomes (p=0.000, AOR=0.025, 95% CI: 0.005-1.29). This finding shows the importance of early and effective treatment response as a critical determinant of final treatment success. Monitoring interim outcomes could thus serve as a valuable tool in guiding and adjusting treatment strategies for pediatric MDR-TB patients [17,39]. Comparing these results with existing literature, our findings align with studies emphasizing the challenges posed by drug-resistant TB, the importance of comprehensive care strategies, and the impact of interim treatment responses on overall treatment outcomes [40,41]. However, further research is warranted to explore additional factors influencing treatment success and to develop targeted interventions for improving TB management globally.

In conclusion, this study provides important insights into the treatment outcomes and associated factors for pediatric MDR-TB patients in Pakistan. The high rates of adverse outcomes despite significant treatment efforts highlight the need for enhanced treatment protocols and support systems, particularly focusing on nutritional support, ADR management, and the careful monitoring of interim treatment responses. These findings can inform targeted interventions and policy formulations aimed at improving the management and prognosis of childhood MDR-TB both in Pakistan and globally. This is the first study to be done in the Punjab setting of Pakistan; however, there are certain limitations due to its retrospective nature. Further multicenter collaborations and studies are required; research should be done to observe the factors associated with unsuccessful treatment outcomes in pediatric MDR-TB patients.

Table 6. Factors associated with unsuccessful treatment outcomes, multivariate binary logistic regression analysis.

	Univariate analysis		Multivariate analysis	
Variables	**p**	**OR (95% CI)**	**p**	**AOR (95% CI)**
Male				
No		Referent		Referent
Yes	0.143	0.410 (0.124-1.351)	0.281	0.281 (0.051-1.540)
Previous TB, FLD treatment (HREZ)				
No		Referent		Referent
Yes	0.068	2.647 (0.930-7.536)	0.462	2.097 (0.291-15.104)
History of SLD use				
No		Referent		Referent
Yes	0.063	0.111 (0.11-1.127)	0.054	0.044 (0.002-0.055)
Registration group (primary MDR-TB)				
No		Referent		Referent
Yes	0.171	0.395 (0.104-1.495)	0.322	0.325 (0.035-3.007)
Interim treatment outcome (negative sputum and culture)				
No		Referent		Referent
Yes	0.001	0.040 (0.010-0.154)	0.000	0.025 (0.005-0.0.29)

OR, odds ratio; CI, confidence interval; AOR, adjusted OR; TB, tuberculosis; FLD, first-line drug; H, isoniazid; R, rifampicin; E, ethambutol; Z, pyrazinamide; S, streptomycin; SLD, second-line drug; MDR-TB, multidrug-resistant tuberculosis; model summary [Hosmer and Lemeshow test (3.246), p=0.777]; Nagelkerke R square (0.590); model summary=$\chi 2$ (45.987), df (6), p<0.0005.

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Conclusions

The overall treatment success rate among the children was 72.8%, which can be improved by reducing loss to follow-up and unnecessary use of SLDs in the treatment of drug-sensitive TB. Implementing community-based interventions and leveraging mobile health technologies could significantly enhance patient retention and minimize loss to follow-up, ensuring better adherence and treatment outcomes. Based on these findings, we suggest prioritizing enhanced care for children with MDR-TB who face a higher risk of mortality and treatment interruption in Pakistan. The female participants are in the majority, and there is an irrational use of SLD, which should be avoided. Increased educational efforts should be involved, especially for children's caretakers with limited access to education. Furthermore, Pakistani authorities must ensure continuous and comprehensive drug supply coverage for all MDR-TB patients throughout their treatment duration. Offering counseling services to caregivers will help them manage stress, anxiety, and other emotional burdens associated with caring for TB patients. Emotional support can strengthen caregivers' resilience, enabling them to provide consistent and compassionate care. Further research, particularly prospective studies with larger cohorts**,** is essential to validate these findings and uncover additional factors that influence treatment outcomes, ensuring more robust and generalizable conclusions. Additionally, establishing more treatment centers in rural areas and implementing programs to improve treatment adherence, including patient counselling, is strongly advised.

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