Factors affecting the treatment outcome of injection based shorter MDR-TB regimen at a referral centre in India

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Abstract

Rifampicin-resistant/multidrug-resistant tuberculosis (RR/MDR-TB) is a significant burden on global tuberculosis (TB) prevention and eradication efforts. MDR-TB can be treated, but it is expensive, takes a long time (typically two years) and contains potentially toxic drugs. Under certain conditions, the WHO recommends standard regimens lasting 9 to 11 months rather than individual regimens lasting at least 18-20 months. The current study sought to identify factors associated with treatment outcomes in RR/MDR-TB patients receiving an injection-based regimen for 9-11 months. This ambispective (prospective and retrospective) observational study was conducted at a tertiary tuberculosis institute in New Delhi, India. Between February 2021 and March 2022, patients with RR/MDR-pulmonary TB who received an injection-based shorter regimen were enrolled. Factors related to treatment outcomes were investigated and compared in patients who had a successful outcome *versus* those who did not. A total of 55 patients were enrolled, with 50.91% being successful (cured/treatment completed) and 49.09% failing (including failure, lost to follow up, death, and regimen change). The following factors were significantly associated with the unsuccessful outcome, according to univariate analysis: BMI (<18.5 kg/m^2), anaemia, previous anti-TB treatment, bilateral chest X-ray involvement, and far advanced disease on chest X-ray. BMI (<18.5 kg/m^2), anaemia, and far advanced disease on chest X-ray were all significantly associated with mortality. Anaemia was associated with an unsuccessful outcome (p=0.049) and mortality (p=0.048) in the multiple logistic regression analysis. Early treatment initiation, improved nutrition and anaemia, and regular monitoring can all improve RR/MDR-TB patients' outcomes and prognoses.

Introduction

Globally, tuberculosis (TB) remains the 13th leading cause of death, and it ranks second among the leading infectious causes of death following COVID-19 ranking above human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in 2020 [1]. Even though TB is preventable and curable, it is the leading cause of death worldwide with 1.5 million people dying each year. Around 10.0 million people were affected by TB with 1.2 million deaths according to World Health Organization (WHO) 2021 [1]; however, the estimated number of new TB cases was 1.9 million in India [1]. According to WHO in 2020, rifampicin sensitivity testing was done in 71% of the patients confirmed bacteriologically with TB. Testing has increased comparatively from 2019 (61%) and 2018 (50%). In 2020 among

patients in whom rifampicin testing was done, 0.132 million were rifampicin resistant/multidrug-resistant [1].

MDR-TB treatment regimens are typically longer, more toxic, and more expensive, discouraging many patients from finishing the treatment as intended. Countries with high TB burden should prioritize identifying the factors which can influence the duration and outcome of treatment [2]. Globally, the success rate of RR/MDR-TB treatment is around 57%. This makes it necessary to frame a regimen that requires less time but is equally effective. As a result of observational studies conducted in Asian and African countries, WHO recommended shorter MDR treatment regimens with the advantage of shorter duration (9-11 months) providing relapse-free cure to >85% of selected MDR-TB patients [3]. Through the reduced costs of the shorter regimen, more resources can be allocated to cover the care of the patients, which is expected to favour equity [3].

Injection containing shorter RR/MDR-TB regimen was rolled out in India in the year 2018. However, studies are sparse regarding the efficacy, outcome and factors affecting the outcome of the patients on shorter MDR regimens. This study aimed to study the factors affecting the treatment outcome of TB patients initiated on injection containing shorter RR/MDR-TB regimen.

Methods and Patients

Study setting

This study was conducted between February 2021 and March 2022 at National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi, India (a referral institute for TB management) after obtaining Ethical Approval from Institutional Research and Ethical Committee (Office letter no. NITRD/RC/ 2021/2661 and NITRD/PGEC/2021/5392).

Study design and population

This was an ambispective (combined prospective and retrospective) observational study. Patients with rifampicin resistance (RR) and MDR pulmonary TB who have attended or attending drug-resistant tuberculosis (DRTB) centres associated with NITRD for treatment under National Tuberculosis Elimination Program (NTEP) and who had completed a shorter MDR regimen in the last year or already under shorter MDR regimen / or yet to be on shorter MDR TB regimen in next one year were included. Pregnancy, critically ill patient, any extrapulmonary disease in people living with HIV (PLHIV), intolerance to any drugs in shorter MDR TB regimen or risk of toxicity from medicine in the shorter regimen (*e.g.*, drug-drug interactions), disseminated disease, meningeal or central nervous system TB were excluded. Drug susceptibility testing (DST) showing fluoroquinolone (FQ) or second-line injectable (SLI) resistance or the presence of InhA mutation (for Eto) or resistance to pyrazinamide (Z) were excluded. Also, if the DST (FQ, SLI, Inh A mutation and Z) was not available and there was a history of intake of these second-line drugs for more than 1 month were also excluded. All participants were explained in detail about the study and informed written consent was taken from each participant. Data and records were also analysed for the retrospective group. Patients were treated with injections containing shorter MDR-TB regimen. Cured was considered as successful outcome, while lost to follow-up (LTFU), death and regimen change were considered as unsuccessful outcome.

Shorter MDR-TB regimen

Following the intensive phase of 4 to 6 months of amikacin, moxifloxacin (high dose), ethionamide, isoniazid (high dose), clofazimine, pyrazinamide, and ethambutol, patients underwent a continuation phase of 5 months of moxifloxacin (high dose), clofazimine, pyrazinamide, and ethambutol. Intensive phase could be extended to 5-6 months in case of delayed conversion [4].

Study sample size

The study enrolled all the patients with rifampicin resistance, and MDR-pulmonary TB with age ≥ 18 years meeting the inclusion criteria attending centres associated with NITRD. According to Shorter MDR Bangladesh regimen [5], prevalence of favourable outcome is 82%, hence P=0.82.

Hence sample size:

$$N = \frac{(Z_{\alpha/2})^2 \times P \times (1-P)}{E^2} = \frac{(1.96)^2 \times 0.82 \times (1-0.82)}{(0.05)^2} = 227$$

$Z_{\alpha/2}$=Z statistic at 95% confidence interval=1.96
P=Prevalence
E=Precision assumed to be 0.05

Government of India planned to change the injection based shorter MDR-TB regimen to all oral shorter regimen in 2021. Hence, Study was limited for a duration of one year and according to hospital records, 65 patients were put on shorter MDR TB regimen in 2020. Hence, we applied Cochran's formula to the sample obtained above:

$$n=[n_0/(1+((n_0-1)/N)], \text{ where } n_0=65, N=227$$
$$=50.72\approx51$$

Here n_0 is Cochran's recommended sample size, N is the population size, and n is the new, adjusted sample size.

After applying the formula, the resulting sample size obtained was 51 and it was rounded up to 55.

Data collection

All enrolled patients underwent a comprehensive clinical examination and a detailed medical history. All the findings were entered in a clinical data-collection sheet that included: Demographics and anthropometrics, socio-economic status as per Kuppuswamy scale [6], smoking history, history of previous anti-TB treatment, contact history of TB, diabetes mellitus (DM). Blood samples were sent for hemogram, blood glucose, liver function tests, urea, creatinine, serum electrolytes, direct sputum smear for acid fast bacilli, audiometry and other tests as deemed necessary. All patient's chest radiographic findings were classified into minimal, moderately advanced, and far advanced using the National Tuberculosis Association criteria [7]. Data were also collected from DR-TB centre of the institute for patients who had started TB treatment with shorter MDR regimen in May 2020.

Data entry and statistical analysis

The collected data were transformed into variables, coded, and entered in Microsoft Excel. The data were analysed and statistically evaluated using Statistical Package for Social Studies (SPSS) IBM manufacturer, Chicago, USA, Windows version 23.0. Quantitative

data were expressed in mean ±SD (Standard deviation), and median with 25th and 75th percentiles (interquartile range) while qualitative data were expressed in number and percentage. The data normality was checked by using Kolmogorov-Smirnov test. Quantitative variables were analysed using Kruskal Wallis and ANOVA. Qualitative variables were analysed using Fisher's exact test when at least one cell had an expected value of less than 5. A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population:

A total of 55 patients were enrolled during the defined study period and were treated with injection-based standard shorter MDR-TB protocol. The median (IQR: 20-41) age of the enrolled patients was 26 years and most patients were aged ≤45 years (76.36%). Among the enrolled patients, (30, 54.5%) were females. Among 55 patients, 28 (50.91%) patients had successful outcome (cured) and 27 (49.09%) patients had unsuccessful outcome. Unsuccessful outcome included: lost to follow-up (14, 25.45%) expired (7, 12.73%), and regimen change (6, 10.90%). The reasons for regimen change included drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) in 1 patient and FQ resistance in 5 patients. Seven patients (12.73%) died. Comparisons were done between factors associated with successful and unsuccessful outcome, and between death and alive patients.

Univariate analysis

From the univariate analysis, the factors significantly associated with unsuccessful outcomes were: BMI (<18.5 kg/m^2) (p=0.001), anaemia (haemoglobin <12 g/dl) (p=<0.0001), multiple courses of anti-tubercular treatment (ATT) in the past (p=0.008), bilateral chest X-ray involvement (p=0.0003), far advanced severity on chest X-ray (comparing non far advanced with far advanced) (p=0.0003). Factors that were not significantly associated with the treatment outcome were age, gender, socio-economic class, hypoproteinaemia, interruptions in treatment, history of 2nd line ATT, contact history of TB, occupation, sputum smear grading, diabetes, and presence of single or multiple cavities on chest x-ray. Low BMI (<18.5 kg/m^2; p=0.002), anaemia (p=0.034), and far advanced disease on chest X-ray (p=0.03) were significantly associated with mortality.

The baseline characteristics of the enrolled patients and the univariate analysis are shown in Table 1. Factors associated with mortality are shown in Table 2.

Multivariate analysis

Multiple logistic regression analysis was carried out on the factors that came out to be statistically significant in the univariate

Table 1. Baseline patient characteristics for outcome and univariate analysis.

Factors	Successful outcome (n=28)	Unsuccessful outcome (n=27)	Total (n=55)	p-value
Age (years)				
<45 years	23 (54.76%)	19 (45.24%)	42 (100%)	0.304
≥45 years	5 (38.46%)	8 (61.54%)	13 (100%)	
Gender				
Female	15 (50%)	15 (50%)	30 (100%)	0.883
Male	13 (52%)	12 (48%)	25 (100%)	
Occupation				
Unemployed	20 (52.63%)	18 (47.37%)	38 (100%)	0.702
Employed	8 (47.06%)	9 (52.94%)	17 (100%)	
Social class				
Lower	23 (50%)	23 (50%)	46 (100%)	1
Upper	5 (55.56%)	4 (44.44%)	9 (100%)	
BMI (kg/m^2)				
Underweight (<18.5 kg/m^2)	6 (25%)	18 (75%)	24 (100%)	*0.001**
Normal weight (≥18.5 kg/m^2)	22 (70.97%)	9 (29.03%)	31 (100%)	
History of smoking				
No	22 (53.66%)	19 (46.34%)	41 (100%)	0.485
Yes	6 (42.86%)	8 (57.14%)	14 (100%)	
History of ATT				
No	8 (36.36%)	14 (63.64%)	22 (100%)	0.078
Yes	20 (60.61%)	13 (12.12%)	33 (100%)	
Number of ATT courses in the past				
Single	19 (73.08%)	7 (26.92%)	26(100%)	0.008*
Multiple times	1 (14.29%)	6 (85.71%)	7(100%)	
Past history of 2nd line ATT intake				
No	20 (62.50%)	12 (37.5%)	32 (100%)	0.394
Yes	0 (0%)	1 (100%)	1 (100%)	
TB contact history				
No	20 (51.28%)	19 (48.72%)	39(100%)	0.931
Yes	8 (50%)	8 (50%)	16(100%)	

To be continued on next page

analysis for unsuccessful outcome and for mortality. Only anaemia was independently and significantly associated with unsuccessful outcome [OR: 25.73 (1.18-751.73), p=0.049] and mortality [OR:29.43(1.25-864.86), p=0.048]. Multiple logistic regression analysis of the variables associated with unsuccessful outcome and mortality are shown in Table 3.

Discussion

In this observational study, various factors affecting treatment outcome were assessed among RR/MDR-pulmonary TB patients treated with injection-based shorter MDR-TB regimen in India.

The study observed that low BMI, bilateral disease on chest X-ray, far advanced disease on chest X-ray, anaemia, and previous history of multiple courses of ATT were found to be significantly associated with poor outcomes. Few studies have already reinforced the association between malnutrition and TB. Low BMI indicates malnutrition which leads to decreased immunoglobulins and macrophage activation [8,9]. In general, low BMI patients are more prone to develop tuberculosis; TB-related mortality and chances of recurrent infections are also high in such patients. Therefore, nutrition plays a crucial role in breaking the cycle of malnutrition and tuberculosis. Piubello *et al.* [10] and Soeroto *et al.* [11] had similar findings in their study of MDR patients who received shorter regimen and found low BMI as a predictor for poor outcome. In addition, Singla *et al.* [12] and Aung *e. al*. [5] found that TB patients with a lower BMI were at a higher risk of mortality. The Indian Government has framed a national policy to provide financial aid to all patients for tackling the problem of malnutrition in TB. Money (cash) incentives are provided every month by transferring the money to their accounts till the completion of treatment as an initiative to improve their nutritional status [12].

There is evidence that mycobacterial infection can lead to

Table 1. Continued from previous page.

Factors	Successful outcome (n=28)	Unsuccessful outcome (n=27)	Total (n=55)	p-value
Diabetes mellitus				
No	24 (50%)	24 (50%)	48(100%)	1
Yes	4 (57.14%)	3 (42.86%)	7 (100%)	
Anaemia				
No	20 (90.91%)	2 (9.09%)	22 (100%)	*<0.0001**
Yes	8 (24.24%)	25 (75.76%)	33 (100%)	
Total body protein				
<6g/dl	5 (38.46%)	8 (61.54%)	13 (100%)	0.304
>6g/dl	23 (54.76%)	19 (45.24%)	42 (100%)	
Chest X- ray laterality				
Unilateral	18 (81.82%)	4 (18.18%)	22 (100%)	*0.0003**
Bilateral	10 (30.30%)	23 (69.70%)	33 (100%)	
Cavity				
No	16 (64%)	9 (36%)	25 (100%)	0.076
Yes	12 (40%)	18 (60%)	30 (100%)	
If yes, for cavity				
Single	10 (47.62%)	11 (52.38%)	21 (100%)	0.249
Multiple	2 (22.22%)	7 (77.78%)	9 (100%)	
CXR Severity				
Minimal	6 (85.71%)	1 (14.29%)	7 (100%)	*0.0004**
Moderately advanced	18 (66.67%)	9 (33.33%)	27 (100%)	
Far advanced	4 (19.05%)	17 (80.95%)	21 (100%)	
Far advanced *vs* non far advanced				
Non far advanced	24 (70.59%)	10 (29.41%)	34 (100%)	*0.0003**
Far advanced	4 (19.05%)	17 (80.95%)	21 (100%)	
Sputum smear status				
Scanty positive	0 (0%)	1 (100%)	1 (100%)	0.255
1+	18 (60%)	12 (40%)	30 (100%)	
2+	7 (50%)	7 (50%)	14 (100%)	
3+	3 (30%)	7 (70%)	10 (100%)	
Sputum conversion at end of 3rd month				
Negative	27 (64.29%)	15 (35.71%)	42 (100%)	0.284
Positive	1 (25%)	3 (75%)	4 (100%)	
Sputum conversion at end of 4th month				
Negative	27 (90%)	3 (10%)	30 (100%)	*0.012**
Positive	1 (25%)	3 (75%)	4 (100%)	
History of treatment interruption				
No	28 (52.83%)	25 (47.17%)	53 (100%)	0.236

BMI, body mass index, underweight: <18.5 kg/m^2 and normal weight: ≥18.5 kg/m^2; anaemia (Hb <13g/dl for males and 12 g/dl for females); DM, diabetes mellitus; TB, tuberculosis; CXR, chest X-ray; ATT, anti-tubercular therapy; *p<0.05.

inflammatory anaemia by inducing production of cytokines such as IL-1, IL-10, interferons-γ and TNF-α which cause macrophages to sequester iron and suppress erythropoietin levels [13]. There are many metabolic processes that require iron as a key factor, including immune system modulation [14]. In India, anaemia is very common and more prevalent among lower socio-economic class patients [15]. TB and anaemia both together are commonly found in lower socio-economic class people and are known to coexist in these groups of patients. Our study suggests that anaemia is an independent risk factor for both mortality and unsuccessful outcome. Soeroto *et al*. [11] observed in MDR-TB patients with anaemia who received shorter regimen had a lower chance of successful outcomes. Singla *et al*. [12] found that factors significantly associated with mortality were anaemia and other studies have also shown that anaemia is associated with poor prognosis and increased risk of mortality in TB patients [16,17]. Johnson *et al.* [18] in their study observed that anaemia was also a comorbidity in higher frequency among patients with unsuccessful outcome.

It is known that drug penetration is poor in patients with structural lung disease and bilateral cavities, which is associated with prolonged culture conversion and failure of treatment [19,20]. Our study found that bilateral disease, far advanced disease on chest x-ray were associated with poorer outcome. Aung *et al.* [5], Gadallah *et al*. [21] and Piubello *et al*. [10] found that bilateral extensive disease was also associated with an unsuccessful outcome. Studies done by Singla *et al.* [12] and Whan *et al*. [22] also supported that far advanced disease was associated with increased mortality among TB patients. Thus, patients with bilateral disease and far advanced disease on chest radiographs need to be prioritized for early initiation of an appropriate treatment regimen.

There was an 8.1 times higher risk of RR/MDR-TB in patients treated for TB previously [23]. This may be due to previously treated patients having a higher proportion of smear-positive cases or extensive cavitation on chest radiographs as compared to new patients [24], Increased duration of exposure to ATT in the past also increases the risk of the development of mutation. Our study also found that multiple courses (≥2) in the previous history of ATT were significantly associated with unsuccessful outcome. Soeroto *et al*. [11] and Wahid *et al*. [25] in their study found that the history of previous TB treatment decreases the likelihood of successful outcome and is associated with treatment failure in MDR TB patients who received shorter regimen. Therefore, careful assessment and history of prior ATT should be noted. The likelihood of a successful outcome was higher in patients with RR/MDR-TB on shorter regimen with a normal BMI, unilateral disease on CXR, mild to moderately advanced disease on CXR, and a single ATT course.

Table 2. Significant factors associated with mortality among the study population (Multiple logistic regression analysis).

Factors	Death (n=7)	Alive (n=48)	Total (n=55)	p-value
BMI (kg/m²)				
Underweight	7 (29.17%)	17 (70.83%)	24 (100%)	0.002*
Normal weight	0	31 (100%)	31 (100%)	
Anemia				
No	0	24 (100%)	24 (100%)	0.034*
Yes	7 (22.6%)	24 (77.4%)	31 (100%)	
Severity of CXR involvement				
Minimal	0	7 (100%)	7 (100%)	0.03*
Moderately advanced	1 (3.70%)	26 (96.30%)	27 (100%)	
Far advanced	6 (28.57%)	15 (71.43%)	21 (100%)	
Far advanced *vs* non far advanced				
Non far advanced	1 (2.94%)	33 (97.06%)	34 (100%)	0.01*
Far advanced	6 (28.57%)	15 (71.43%)	21 (100%)	

BMI, body mass index, underweight: <18.5 kg/m² and normal weight: ≥18.5 kg/m²; anaemia (Hb <13g/dl for males and 12 g/dl for females); CXR, chest X-ray; *p<0.05.

Table 3. Factors and their association with unsuccessful outcome and mortality (multiple logistic regression analysis).

Variable	Odds ratio (OR, 95% CI)		p-value	
	Unsuccessful outcome	Mortality	Unsuccessful outcome	Mortality
Body mass index (kg/m²)				
Normal weight	1	1		
Underweight	0.42 (0.033-5.425)	8.19 (0.626-107.228)	0.510	0.109
Anaemia				
No	1	1		
Yes	25.73 (1.183-751.734)	29.43 (1.252-864.861)	0.049*	0.048*
Chest X- ray laterality				
Unilateral	1	1		
Bilateral	1.36 (0.030-62.935)	2.78 (0.127-60.988)	0.874	0.515
Severity of CXR involvement				
Non far advanced	1	1		
Far advanced	3.66 (0.068-197.869)	3.90 (0.127-119.829)	0.523	0.435

BMI, body mass index, underweight: <18.5 kg/m² and normal weight: ≥18.5 kg/m²; anaemia (Hb <13g/dl for males and 12 g/dl for females); CXR, chest X-ray; *p<0.05.

It is well understood that either treatment interruptions or lost of follow-up is one of the major risk factors for the development of additional drug resistance and is also associated with poor treatment outcome which may be due to drug resistance [26]. Lost to follow-up was high (25%) in our study, which might be explained by the fact that this study was conducted in a cosmopolitan city where migration is common.

Head-on comparison of various high-risk factors with treatment outcome in conventional *versus* shorter regimens for RR/MDR-TB patients may help further to clarify the strengths and limitations of shorter MDR-TB regimen. By knowing the factors associated with treatment outcome on shorter regimen, it is possible to triage the patients early to higher centres for further evaluation and early initiation of appropriate treatment. Additionally, necessary measures need to be taken to address such adverse factors. This may help in improving the outcome and prognosis of MDR-TB patients on shorter regimen, and also help to reduce the catastrophic costs associated with TB by improving the outcome in DR-TB cases.

Our study has some limitations: Sample size was small in our study. So, large-scale studies are needed to understand how various factors affect the treatment outcomes among RR/MDR-TB patients on shorter MDR regimen. Time constraints prevented us from following up with the patients after 12 months of completion of treatment, so we did not assess long-term follow-up. Since this was a single-centre, observational study conducted at only one institution, it cannot be applied to the entire country.

In the current study, univariate analysis showed that RR/MDR-TB patients with far advanced disease, bilateral chest X-ray involvement, low BMI, previous history of multiple courses of ATT and anaemia were associated with poor outcome and low BMI (<18.5 kg/m^2), anaemia, and far advanced disease on chest X-ray were associated with higher mortality. Anaemia was the only independent risk factor associated with poor outcome and mortality. Early screening for malnutrition, anaemia and chest X-ray severity, appropriate nutritional intervention and regular monitoring may improve outcome in DR-TB cases.

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