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Original Research Article

Predictors of Treatment Outcomes of Multi-Drug-Resistant Tuberculosis: A Retrospective Hospital-Based Study in a Tertiary Care Teaching Hospital of South Odisha

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Abstract

Objective: To assess the predictors of treatment outcomes of multidrug-resistant tuberculosis cases treated according to the Revised National Tuberculosis Control Programme.

Materials and Methods: A retrospective study was carried out in the Department of Pulmonary Medicine of MKCG MCH. All patients enrolled for multidrug-resistant tuberculosis management between January 2019 to December 2019 were included in the study. Demographic details, symptoms, and sputum examination findings were collected from the multidrug-resistant tuberculosis register. Besides, resistance patterns, adverse drug reactions, medication adherence and final treatment outcomes were noted in a predesigned case record form. Data were analyzed using suitable statistical tests.

Result: Out of 95 patients, males outnumbered females. Most of the cases belonged to rural areas (89%). The mean age of study participants was 39.1 years. The most common resistance pattern (60%) was to Isoniazid and Rifampicin (HR). Among all, 52% were completely cured. 23% were defaulters, and 3% of them had treatment failure. Death was recorded in 21% of cases. The most common Adverse Drug Reaction (ADR) associated with the medications was joint pain. Alcohol and smoking habits, concomitant medications for other co-existing diseases, poor medication adherence, and occurrence of ADRs were the independent negative predictors (P value<0.05) of successful outcomes. Sputum conversion within 3 months positively predicted successful treatment outcomes (P value<0.01). Age, gender, geographical area, and pattern of anti-tubercular drug resistance did not influence the treatment outcomes.

Conclusion: Our study observations revealed that the treatment outcomes of MDR TB as per PMDT guidelines were low. It seems there is a need for conducting more programs among DOTS care providers regarding the awareness of risk factors of poor outcomes and patient health education.

Background:

Drug-resistant tuberculosis (DRTB) is a form of tuberculosis (TB) that is resistant to any of the first-line antituberculosis drugs. There are different types of DRTB, such as monoresistant tuberculosis and multidrug-resistant tuberculosis (MDRTB). The former is a form of tuberculosis, which is resistant to any single drug of the first-line anti-tuberculosis medications. At the same time, MDR TB is resistant to essential first-line antituberculosis(ATT) drugs, rifampicin and isoniazid. Polyresistant tuberculosis is resistant to more than one first-line drug other than both rifampicin and isoniazid. Extensively Resistant Tuberculosis (XDRTB) includes MDRTB and additional resistance to any of the fluoroquinolones and any of the injectable second-line medications. [1]

Despite an increased DRTB awareness and roll-out of molecular tests such as XpertMTB for diagnosis of DRTB, which has enabled early treatment initiation, DRTB and especially MDRTB both of which are diseases of public health concern, warrant further exploration and studies in safety. This affects the global efforts to control TB. [2]

Worldwide, there were an estimated 4,50,000 incident cases of MDR/RR-TB in 2021, up 3.1% from 4,37,000 in 2020. An estimated 191,000 deaths occurred due to MDR/RR-TB in 2021. [3] Among all tuberculosis cases worldwide, 3.7% of newly diagnosed cases and 20% of previously treated cases have DRTB. [4] The global treatment success rate for MDR-TB was found to be 58% in 2019. [1]

As per WHO Global TB Report 2022, India's estimated multidrug-resistant TB (MDR-TB) incidence in 2021 was 1.1 per 100,000 population, which is lower than the global average of 2.9 per 100,000 population. [3]

The standard treatment for MDR-TB is a 24-month regimen, essentially comprising second-line drugs, which are less effective, costly and associated with a high number of adverse events. [5] Not surprisingly, treatment outcomes in MDR-TB are significantly worse than for standard first-line therapy.

According to the final MDRTB, treatment outcome is the most crucial direct measurement of the effectiveness of the MDRTB control program. There are six MDRTB treatment outcomes "cured" (which is restricted to pulmonary TB cases only), "completed," "died," "failed," "lost to follow up," and "MDRTB cases on MDRTB treatment regimen with no outcome assigned (transferred, still on treatment, or unknown)." Successful treatment includes being cured and completing treatment, while unsuccessful treatment includes dying, treatment failure, and loss of follow-up. [6]

Treatment of MDR-TB is complicated, takes a long duration, is associated with several adverse events, and is very expensive [7]. MDRTB treatment is also associated with unsuccessful outcomes compared to non-MDRTB treatment. [8] In the quest to address some of these challenges, WHO has introduced a short treatment regimen for treating MDRTB patients. [8]

Predictors of treatment outcomes are factors that influence the possibility of achieving a successful or unsuccessful outcome for MDR-TB patients. Identifying the predictors of treatment outcomes can not only help in improving MDR-TB patients' management but also optimized use of available resources. [1]

Several studies have investigated the predictors of treatment outcomes among MDR-TB patients in different settings and populations. However, the results could be more consistent or vary depending on the context, diagnostic methods, treatment regimens, and definitions of outcomes. The common predictors that have been reported in the literature are:

- **Demographic factors**: Age, sex, marital status, education level, occupation, income, and social support significantly affect the treatment outcomes of MDR-TB patients. For example, some studies show that male patients, older patients, and married patients have lower odds of treatment success than their counterparts.
- **Clinical factors**: Co-morbidities, such as HIV infection, diabetes, chronic kidney disease, hepatitis, and malnutrition, may worsen the prognosis of MDR-TB patients and increase the risk of adverse events. Additionally, previous TB treatment history, lung damage extent, cavities, and body mass index (BMI) may influence treatment outcomes. For instance, some studies have shown that HIV-positive patients, patients with extensive drug resistance, patients with cavities, and patients with low BMI have lower odds of treatment success than their healthier counterparts. [9,10]

Very few studies have focused on these predicting factors for the outcome of MDR-TB treatment in the state of Odisha, and the country. So, in this study, we reviewed your experience with the MDDR-TB registered for dots-plus over 48 months at your hospital, with a special focus on the factors influencing the outcome of MDDR-TB.

Aims and Objectives: -

1) To describe the demographic profiles of study participants.
2) To observe the drug resistance pattern.
3) Adverse drug reactions, if any.
4) To assess the predictors of treatment outcomes of MDR-TB cases.

Materials and Methods: -

This retrospective hospital-based observational study was carried out in the Department of Pulmonary Medicine in collaboration with the Department of Pharmacology, MKCG Medical College and Hospital, Berhampur Odisha, between September 2022 to October 2022. Data from 95 study participants were collected from the treatment records of the Department of Pulmonary Medicine.

Inclusion Criteria: -

All patients enrolled for MDR-TB management between January 2019 to December 2019 were included.

Study Tools:

Guideline for programmatic management for MDR-TB 2021.

Study Procedure:

Prior to the study, approval from the Institutional Ethics Committee and permission from the Head of the Department of Pulmonary Medicine of MKCG Medical College and Hospital were obtained. Data of subjects enrolled for MDR-TB management between January 2019 to December 2019 were obtained from hospital records. Demographic details, sputum examination findings, resistance patterns, adverse drug reactions, medication adherence, and final treatment outcomes were noted in a predesigned case record form(CRF) from the MDR-TB registry. Study participants who were cured after 48 months of therapy were included in the successful treatment group; the rest included all final treatment outcomes in the unsuccessful treatment group. Poor medication adherence was defined using ≥7 missed doses during IP and CP, estimated by pill counting method from the patient card and

Nikshay software developed by Central TB Division, Ministry of Health & Family Welfare, Government of India, in collaboration with the National Information Centre.

Statistical Analysis: -

The data was compiled using Microsoft Excel, standard spreadsheet software. Data were analysed using Fisher's exact test, Chi-square test, and Odds ratio with the statistical software GraphPad Prism 5.0 software. $P < 0.05$ was considered statistically significant.

Results:

Table 1: Patient profile (n=95)

Characteristics		Frequency (%)	Mean
Age	<45	61(64%)	39.17
	>45	34(36%)	
Gender	Male	74(78%)	
	Female	21(22%)	
Residency status	Rural	85(89%)	
	Urban	10(11%)	

The above table shows that the mean age of study participants was 39.17 years. Most participants were from age group less than 45 (64%). Significantly more number of participants were males and from rural areas.

Table 2: Pattern of drug resistance of the mdr-tb patients

Drug resistance	Number of patients	Percentage
HR	57	60%
R	34	35.8%
HRO	2	2.10%
HRES	1	1.05%
HRK	1	1.05%

(HR-Isoniazid and Rifampicin, R-Rifampcin, HRO- Isoniazid, Rifampicin and Ofloxacin, HRES-Isoniazid, Rifampicin, Ethambutol and Streptomycin, HRK-Isoniazid, Rifampicin and Kanamycin)

Table No-2 shows that isoniazid and rifampicin resistance was most common (60%), followed by only rifampicin resistance (35.8%). The least common resistance was shown in Isoniazid, rifampicin, ethambutol and streptomycin(1.05%) and Isoniazid, rifampicin and kanamycin(1.05%).

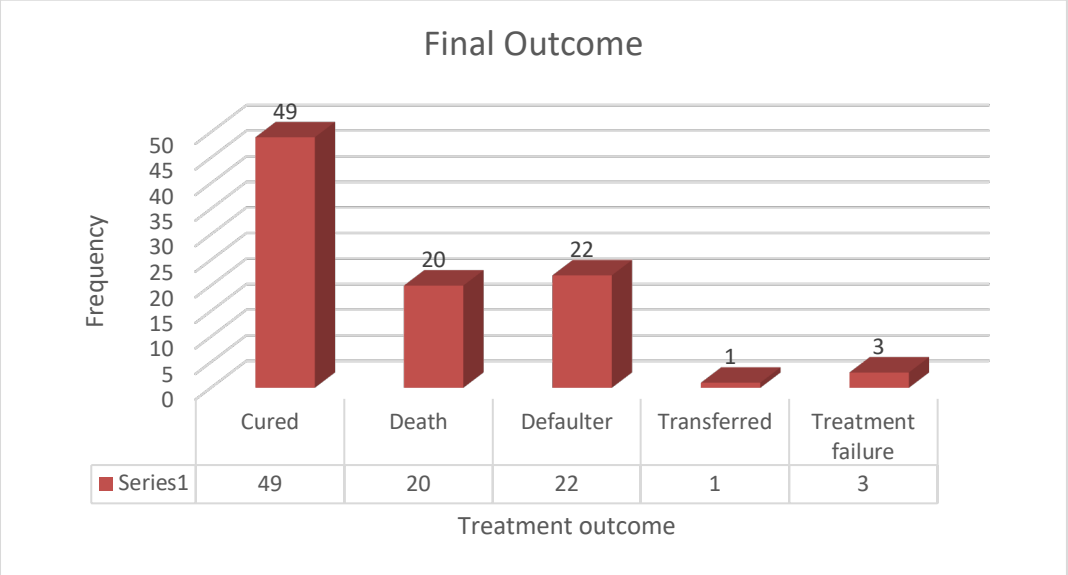

Figure 1: Final treatment outcomes: -

The above Figure-1 shows that 49 (61%) study participants were cured. Death was reported in 20 study participants in spite of adhering to treatment. The rest of the study participants, with a frequency of 22, 3 and 1, were defaulters, treatment failure, transferred to other places, thus unable to trace and treatment failure.

Table 3: Details of adverse drug reactions observed among mdr-tb patients treated with standardized regime (N=37)

Adverse Drug Reaction	Number	Percentage
Joint Pain	8	22%
Nausea and Vomiting	7	19%
Peripheral Neuritis	6	16%
Hepatitis	4	11%
Hearing disturbance	3	8%
AKI	3	8%
Psychiatric disturbances	2	5%
Vertigo	2	5%
Diminished vision	1	3%
Hypersensitive reaction	1	3%

Among 95 study participants treated for MDR TB with the standardised regimen for 48 months, 37 adverse drug reactions were reported. As per Table No. 3, the highest number of adverse drug reactions reported in the study was joint pain (22%), followed by nausea and vomiting (19%) and peripheral neuritis (16%). The least commonly reported adverse drug reactions were diminished vision and hypersensitivity reactions.

Tab 4: Factors associated with treatment outcome in MDR-TB patients treated with standardised regimen (n=95)

Characteristics		Successful n=49(52%)	Not successful n=46(48%)	P value	Odds Ratio	95% confidence interval
Gender	Male	37	37	0.56	1.9	0.82 -4.50
	Female	12	9			
Age (Years)	<45	35	26	0.13	1.33	0.5-3.54
	>45	14	20			
Residence	Rural	45	40	0.44	1.69	0.44-6.41
	Urban	4	6			
ADR	With	9	28	<0.0001	0.144	0.05-0.37
	Without	40	18			
Concomitant diseases	Yes	8	24	0.0004	0.18	0.07-0.46
	No	41	22			
Personal habit	Abuse	9	30	<0.0001	0.12	0.04-0.30
	No abuse	40	16			
Culture conversion within 3months	Yes	41	14	0.009	6.833	1.55-30.10
	No	3	7			
Drug resistance pattern	≥2	17	17	0.833	0.91	0.39-2.09
	<2	32	29			
Medication adherence	Non-adherence	11	30	<0.0001	0.154	0.06-0.38
	Adherence	38	16			

The above Table No-4 shows that alcohol and smoking habits, concomitant medications for other co-existing diseases, poor medication adherence, and occurrence of ADRs were the independent negative predictors (P< 0.05) of successful outcomes. Sputum conversion within 3 months positively predicted successful treatment outcomes (P< 0.01). Age, gender, geographical area and pattern of anti-tubercular drug resistance did not influence the treatment outcomes.

Discussion:

A retrospective record-based observational study was conducted in MKCG Medical College and Hospital, Berhampur, and a tertiary care teaching hospital. The study aimed to observe the demographic profile, pattern of antitubercular drug resistance, adverse drug reaction that occurred owing to drug therapies and the predictors of treatment outcomes of multidrug-resistant tuberculosis cases.

The results of the study show that the treatment success rate of MDR-TB patients treated with standardized regimens was 52%, which is lower than the global average of 58% [9,10]. The main factors which influenced the treatment outcome were alcohol and smoking habits, concomitant diseases, medication adherence, adverse drug reactions, and culture conversion within 3 months. These findings are consistent with a few previous studies that have

identified similar predictors of treatment outcomes in MDR-TB patients [1,11,12].

The high proportion of patients with alcohol and smoking habits (41%) in this study fairly reflects the social and cultural norms of the study population. Consequently, alcohol and smoking impair the immune system, increase the risk of drug toxicity, and reduce the efficacy of anti-TB drugs [13]. Therefore, it is imperative to provide counseling and support for MDR-TB patients in quitting or reducing alcohol and smoking consumption. Personalized and structured counseling in tandem with reinforcement of ATT drug adherence coupled with advice pertaining to adequate dietary practices needs to be enforced to curb negative outcomes.

The presence of concomitant diseases, such as diabetes, HIV, and chronic kidney disease, significantly affect the treatment outcome of MDR-TB patients. These diseases can increase the risk of drug interactions, adverse events, and mortality. Therefore, it is recommended to screen and manage the co-morbidities of MDR-TB patients. Providing appropriate treatment regimens and rigorous monitoring, can also augment achieving therapeutic end outcomes.

Medication adherence is a critical factor for achieving successful treatment outcomes in MDR-TB patients. However, adherence can be challenging due to the long duration, complex regimen, and adverse effects of MDR-TB treatment. In this study, 43% of the patients were non-adherent to their treatment, which may have contributed to the poor treatment outcome. Therefore, it is necessary to implement strategies to improve adherence, such as patient education, counseling, social support, and directly observed therapy.

Adverse drug reactions (ADRs) are common and severe complications of MDR-TB treatment. They can affect the quality of life, adherence, and treatment outcomes of MDR-TB patients. In this study, 39% of the patients experienced ADRs, which were mainly joint pain, nausea and vomiting, peripheral neuritis, and hepatitis. These ADRs are similar to those reported in other studies. Therefore, it is essential to monitor and manage the ADRs of MDR-TB patients and provide appropriate treatment modifications and supportive care.

Sputum culture conversion within 3 months was this study's only positive predictor of treatment outcome. This finding agrees with other studies that have shown that early culture conversion is associated with higher treatment success and lower mortality in MDR-TB patients. Therefore, it is essential to ensure timely diagnosis and initiation of effective treatment for MDR-TB patients and to monitor their culture conversion.

Conclusion:

Alcohol and smoking habits, concomitant medications for other co-existing diseases, poor medication adherence, and occurrence of ADRs were the independent negative predictors ($P< 0.05$) of successful outcomes. Sputum conversion within 3 months positively predicted successful treatment outcomes ($P< 0.01$). Age, gender, geographical area, and pattern of anti-tubercular drug resistance did not influence the treatment outcomes. This study and its observations revealed that the treatment outcomes of MDR TB as per PMDT guidelines were low. It is inferred that there is a need for conducting more programmes among DOTS care providers regarding the awareness of risk factors of poor outcomes and patient health education.

Limitation:

The limitations of this study include the retrospective design, the small sample size, and the lack of data on some potential confounders, such as nutritional status, socio-economic status, and drug susceptibility testing results. Therefore, the results of this study have reduced generalizability to other populations at large. Further prospective and more extensive studies are required to confirm and expand as well as improve upon the findings of this study.

Recommendations:

Based on our study results, some recommendations are:

1. The treatment regimen should be individualized according to the drug susceptibility testing results and the patient's clinical condition to improve the cure rate and reduce the death rate.
2. To reduce the defaulter rate, the treatment should be supervised by trained health workers and supported by community-based interventions such as health education, counselling, and social support.
3. To improve medication adherence, the patients ought to be informed and explained about the benefits and risks of the treatment, the possible ADRs and their management, and the importance of regular follow-up visits.
4. It is imperative to design, and structure follow up visits and implement systematic mechanisms which improve upon the experience of the patients which can significantly improve all quarters of drug regimen adherence, provide mental health support and enhance reporting of ADRs.
5. The propagation of further discourse on MDR TB plays a vital role in overall public health as well as medication adherence. Community level Sensitization about TB in general, grassroot-level dissemination to non-TB subjects and care givers about the advantage, ADRs and benefits is imperative for successful therapeutic outcomes.

6. To prevent and manage ADRs, the patients should be monitored for the signs and symptoms of ADRs, the doses of the drugs should be adjusted according to the patient's weight and renal function, and appropriate symptomatic and preventive measures should be provided.
7. Investigations like LFT, RFT, CBC and Diabetes as well as serological investigations of HIV prior to commencement of treatment for MDRTB and regular three months-six months follow up on LFT, RFT and CBC can significantly help in minimization of ADRs and enhance early detection.
8. To enhance the sputum conversion, the patients should be encouraged to produce good quality sputum samples at regular intervals, and the laboratory services should be strengthened to ensure timely and accurate diagnosis and monitoring of the treatment response.

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