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Original research article

Predictors of Unfavorable Treatment Outcome in Patients with Multidrug-Resistant Tuberculosis: A Prospective Study

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Abstract

Background: World health organization suggest that final multidrug resistant tuberculosis treatment outcome is the most important direct measurement of the effectiveness of the multidrug resistant tuberculosis treatment control Programme, thus WHO conditionally guideline recommended standardised shorter9-12 month regimens for multidrug resistant TB treatment. Thus, for better understanding of the risk factor for unfavorable outcomes this study has conducted.

Material and Methods : A Prospective study including patients with sputum CBNAAT diagnosed as DR TB, who has undergone treatment with shorter MDR TB regimen as in patient & out patient in the District Nodal TB centre, department of Pulmonary Medicine, Government Medical College, Siddipet, during the period of one and half year. After getting ethical approval from, institutional committee.

Results : In the study we have enrolled 100 patients, out of 52% were males and 48% were females, mean age of all the patients were 41.86 ± 16.56 years also mean body mass index of the patient was 19.23 ± 6.45. Out of all 23% of the patients unfavorable outcomes were observed in that, 10 patients died for 9 patients treatment regimen changed, we lost follow up for 3 patients and for only one patient treatment was failed.

Conclusion : We can conclude from above results and observation that, though the success rate of our study was nearer to WHO global rate to stop TB. To achive this strategies for early diagnosis and management of MDR-TB should improve treatment outcomes to reduce death and stop further transmission.

Keywords: MDRTB, CBNAAT, Tuberculosis

Introduction

Tuberculosis (TB) is a disease caused by bacteria that are spread from person to person through the air. TB usually affects the lungs, but it can also affect other parts of the body, such as the brain, the kidneys, or the spine. In most cases, TB is treatable and curable; however, people with TB can die if they do not get proper treatment. The bacteria that cause TB can develop resistance to the antimicrobial drugs used to cure the disease.

Multidrug-resistant TB (MDR TB) is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs. These drugs are used to treat all persons with TB disease. MDR TB has become a major obstacle to successful TB control worldwide, especially in developing Countries like India and others [1].

Drug resistance in TB is a human-created phenomenon caused by inaccurate prescribing practices by physicians and patient noncompliance, and it may also be a consequence of primary infection, thus demanding more intensive interventions. MDR-TB treatment is more expensive, longer, less effective and causes more adverse effects compared to drug susceptible TB treatment [2].

The standard treatment for MDR-TB is a 24-month regimen largely comprising second-line drugs that are less effective, more costly and associated with a high number of adverse events. [3] Not surprisingly, treatment outcomes in MDR-TB are significantly worse than for standard first-line therapy.

Global incidence of MDR-TB is 3.4% in new cases and 18% in previously treated cases. Globally, 78% of the rifampicin-resistant TB (RR-TB) cases were multidrug-resistant. Indian government survey from 2014 to 2016 estimated the incidence of MDR-TB as 2.84% in new cases and 11.6% among previously treated patients [4] and worldwide in 2018, the treatment success rate of MDT TB patients was 59%.

Although a few studies in India have reported on treatment outcomes, there is insufficient knowledge about the sociodemographic and clinical factors associated with unfavourable treatment outcomes. A better understanding of these risk factors is necessary to design effective interventions that might help reduce morbidity and mortality and thereby improve treatment success.

Materials and Methodology :
A Prospective study including patients with sputum CBNAAT diagnosed as DR TB, who has undergone treatment with shorter MDR TB regimen as in patient & out patient in the District Nodal TB centre, department of Pulmonary Medicine, Government Medical College, Siddipet, during the period of one and half year.

INCLUSION CRITERIA:
- Patients with Rifampicin resistant pulmonary Tuberculosis
- Patients with MDR tuberculosis

EXCLUSION CRITERIA:

❖ **DST BASED CRITERIA**:
- If DST result for FQ or SLI is resistant or
- Presence of InhA mutation (for Eto) or
- Resistance to Z (when ever available)
- History of use for >1 month/ intolerance to Mfx(h), Km, Eto or Cfz

❖

❖ **Non DST based criteria**
- Pregnancy
- Any extra pulmonary disease in PLHIV
- Disseminated, meningeal or CNS TB

Intolerance to any drug in the shorter MDR TB

Methodology

Follow-up with:

- Smear microscopy: Monthly from 3rd month onwards till end of IP, Monthly in extended IP only if previous month Sputum positive.
- **Sputum culture**: End of IP, end of extended IP and end of Rx.
- **DST:** FL & SL LPA and LC DST (Mfx 1.0, Lzd, Cfz* & Z*) if smear /culture positive at end of IP, end of extended IP and end of Rx.

Statistical Analysis : Collected data were entered in Microsoft Excel 2019 for further analysis, Qualitative data were presented with frequency and proportion and that of Quantitative data were presented with mean and standard deviation. Multivariate analysis was done to know the unfavorable outcome. Analysis was done in statistical Package for social sciences (SPSS) version 25. P-Value <0.05 were considered as statistical significant.

Observation and Results :

In the study we have enrolled 100 patients, out of 52% were males and 48% were females, mean age of all the patients were 41.86 ± 16.56 years also mean body mass index of the patient was 19.23 ± 6.45. Other parameters shown in the bellow table number 1

Table 1: Demographic Distribution of study population

Parameters	Frequency/Mean	Percentage/SD
Gender		
Male	52	52
Female	48	48
Age Groups		
≤20	7	7
21 - 40 Years	49	49
41 - 60 Years	26	26
>60 Years	18	18
Mean ± SD	41.86 ± 16.56	
Body Mass Index		
<18.5	37	37
18.5 - 24.9	57	37
≥25	6	3
Mean ± SD	19.23 ± 6.45	
Diabeic Status		
Diabetic	18	18
Non-Diabetic	82	82
HIV Status		
Reactive	15	15
Non-Reactive	85	85
Tabaco Users		
Yes	15	15

No	85	85
Alcohol Intake		
Yes	19	19
No	81	81
Covid-19 Status		
Negative	11	61.1
Unknown	7	38.9

Table 2: Treatment outcomes for patients started on MDR-TB treatment

Treatment Outcome	Frequency	Percent
Favourable		
Cured	59	59
Treatment Complete	18	18
Unfavourable		
Died	10	10
Treatment Regimen Changed	9	9
Lost of Follow up	3	3
Treatment Failure	1	1
Total	100	100

Above table shows that among 23% of the patients unfavorable outcomes were observed in that, 10 patients died for 9 patients treatment regimen changed, we lost follow up for 3 patients and for only one patient treatment was failed

Discussion:

This study has found that the absolute numbers of MDRTB patients receiving treatment at Department of Pulmonary Medicine, GMC Siddipet for one and half year has been increasing as well as the number of patients being cured (a total of 59 patients were cured, 77% of all patients).

Our study comprised of 76(76%) male and 24(24%) female, among male 58 were succeeded in treatment and 18 were unsuccessful, and among female 19 were succeeded and 5 were unsuccessful. There was male predominance was observed in the study Tamary Henry Leveri et al[5] comprised of 221(66.6%) were male and 111(33.4%) these results were nearly similar to our results. Another study conducted by D. Nair et al [6] observed male dominance over female, 68% of the male and 32% of the female were observed in this study. Out of all patients of 49% of the patients were lying in the age group of 21 – 40 years of age, 7% of the patients were from age group of ≤ 20 years of age. Maximum patients were lying in the age group of 21 – 60 years of age. Mean age of all the patients was 41.86 ± 16.56 years. A. Javaid et al.[7] studied observed that 81.3% of the patients were lying in the age group of 18 – 60 years of age

group also they observed the mean age in their study was 30.37 (standard deviation = 14.09) years, ranging 10 to 79 years.

Table 3: Multivariate analysis for predictors of treatment outcome..

Characteristics	Cured		Treatment Completed		Loss of Follow Up		Death	
	OR,(95% CI)	P-value	OR,(95% CI)	P-value	OR,(95% CI)	P-value	OR,(95% CI)	P-value
Age	1.64 0.7229 to 3.7552	0.23	0.72 0.2568 to 2.0253	0.53	4.52 0.2276 to 90.14	0.32	1.48 0.3599 to 6.1269	0.5846
Body Mass Index	0.0128 0.0016 to 0.1002	<0.001	0.1888 0.0610 to 0.5843	0.003*	0.5319 0.0467 to 6.0620	0.6111	0.1136 0.0461 to 0.2802	<0.01**
Diabetic Status	0.1621 0.0660 to 0.3981	0.001**	0.8933 0.2292 to 3.4812	0.8709	0.6139 0.0304 to 12.4062	0.7504	3.619 0.9035 to 14.4960	0.0693
HIV Status	0.6038 0.1794 to 2.0322	0.41	2.5357 0.6706 to 9.5884	0.17	0.8629 0.0420 to 17.7356	0.9238	11.4286 2.6524 to 49.2423	0.011**
Tobacco Users	0.1296 0.0298 to 0.5630	0.006**	6.125 1.4895 to 25.1865	0.012*	15 1.2174 to 184.8140	0.034	21.375 4.2248 to 108.1453	0.0002**
Alcohol Intake	0.0727 0.0080 to 0.6611	0.001**	16.5385 1.7697 to 154.5606	0.013*	27.5 2.0298 to 372.5819	0.012	151.6667 7.3035 to 3149.5439	0.0012**
Past History of TB	0.3008 0.1017 to 0.8897	0.02*	0.1563 0.0490 to 0.4982	0.0017*	1.62 0.086 to 32.91	0.75	0.094 0.0229 to 0.3866	0.001**
Cavitary lesions on Chest x-ray radiography	0.27 0.0990 to 0.7481	0.001**	43.57 10.06 to 188.69	<0.001*	23.15 1.14 to 467.95	0.0405	17.71 3.3868 to 92.65	0.007**

Our study showed that proportion of body mass index < 18 kg/m^2 and ≥ 18 18 kg/m^2 were equally distributed, it was 48% and 52% respectively and mean Body mass index was 18.20 ± 3.25 kg/m^2.. In the study conducted by D. Nair they observed that Being underweight, with a BMI < 18.5 kg/m2, in patients with MDR-TB has been found to be a risk factor for unfavourable outcomes, particularly mortality. Being underweight is a manifestation of severe disease and possibly poor socio-economic circumstances, and as it also impairs host immunity against mycobacteria, it is not surprising that there are higher rates of mortality in such patients. 12.4% of the patients in our study found to be reactive or positive for HIV maximum patients were non-reactive and for 10.3% of the patients had unknown status of HIV. Study conducted by Woldeyohannes D et al [8] observed that, HIV test result positive MDR TB patients were four times at risk to have unfavourable treatment outcome at any time than HIV negative patients [AHR = 3.76; 95% CI: 2.45, 5.78], these results were totally contradicting our results. Our treatment regimen found more favourable cases.

Our study found susses rate was 77%, which was favourable cases in our study, 10% of the patients were died during regimen, for 9% of the patients we have changed the treatment plan, we have lost follow up for 3% of the patients, and unlikely we failed to treat 1% of the patients completely. But from all these statistics we succeeded for maximum number of the patients. A. Javaid et al.[7] in their study they found that Treatment success rate was 75.9% in the present study, which is comparable to the 75% target treatment success rate set by the Global Plan to

Stop TB and other studies (70.77%) [9]. Our treatment success rate was better than those observed in other studies: 53% (40.70%) in 25 countries [10], 54% in Shanghai [11] and 48% in South Korea [12], but lower than Germany (80%) [13]. Possible reasons for better success rate are trained treatment supporters who provide daily directly observed treatment during treatment (>18 months) and use of individualized regimens at the highest recommended doses in the majority of patients.

In our study we found Diabetic Mellitus, Tobacco, alcohol, BMI, Cavitary lesions on Chest x-ray radiography, Past history of TB was significantly associated to cured patiets with adjusted odds ratio 0.1621, 0.1296, 0.0727, 0.0128, 0.27, 0.3008 respectively(p-value<0.05). Association of treatment completed showed the association with Tobacco, alcohol, BMI, Cavitary lesions on Chest x-ray radiography, Past history of TB, similarly Loss of follow up showed the association with Tobacco, alcohol, Cavitary lesions on Chest x-ray radiography, Past history of TB(p-value<0.05) and for death Diabetic Mellitus, Tobacco, alcohol, BMI, Cavitary lesions on Chest x-ray radiography, Past history of TB and BMI were significantly associated. (P-value<0.05) study conducted by Tamary Henry Leveri et al[5] found that Low BMI was found to be significantly related to treatment cure in this study aOR 0.59. Other studies such as the one done by Kwak did not find a significant association between BMI and MDRTB treatment success [14], a study done by Tang and colleagues found a significant association between low BMI (less than 18.5kg/m2) and poor treatment [15].

In the same study Smoking, which lowers immunity against TB, was associated with mortality (aOR 2.31). these resuts were similar to our results where use of tobacco (Smoking) was highly associated with mortality (aOR = 39.18) .Similar findings have been observed by Mollel and colleague whereby cigarette smoking and HIV positive status were both positively associated with MDRTB mortality [16]. Our study found none of the factors were associated with loss of follow up similar results were observed by Tamary Henry Leveri et al[] but in addition to this many studies have found other factors that were related to loss to follow-up such as alcohol abuse and developing adverse reactions while protective factors include receiving assistance from TB program, patients' better knowledge of TB, and trust in treating physicians and nurses [17]. A study by Javaid and colleagues found that living in rural areas had an increased risk of being loss to follow-up [18].

Conclusion:

Although the current study reports a 75% target treatment success rate as set by the Global Plan to Stop TB, a success rate of 80% is required for MDR-TB patients to achieve a tenfold reduction in MDR-TB incidence within 20 years. Despite this success rate, mortality remains high among MDR-TB patients. Strategies for early diagnosis and management of MDR-TB can improve treatment outcomes to reduce death and stop further transmission. Patients with disease resistant to second-line drugs and with XDR-TB require special attention in order to experience better treatment outcomes.

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Conflict of Interest : None

References :

1. Wright A, Zignol M. Anti-tuberculosis drug resistance in the world: fourthglobal report: the World Health Organization/International Union Against Tuberculosis and Lung Disease (WHO/UNION) global project on antituberculosis drug resistance surveillance,

2002e2007. Geneva: World Health Organization; 2008.
2. World Health Organization. Global tuberculosis report, 2015. WHO/HTM/TB/2015.22. Geneva, Switzerland: WHO, 2015.
3. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Correction: multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med 2012;9:e1001300.
4. Yang, Y., Zhou, C., Shi, L., Meng, H. & Yan, H. Prevalence and characterization of drug-resistant tuberculosis in a local hospital of Northeast China. *Int. J. Infect. Dis.* **22**, 83–86. https://doi.org/10.1016/j.ijid.2013.12.015PMID:24556164 (2014).
5. Leveri Tamary Henry, Lekule, Isack, Mollel, Edson, Lyamuya, Furaha, Kilonzo, Kajiru, Predictors of Treatment Outcomes among Multidrug Resistant Tuberculosis Patients in Tanzania, Hindawi Tuberculosis Research and Treatment, Volume 2019, Article ID 3569018.
6. Nair D, Velauutham B., Kannan T, Tripathi J P, Harries A D, Natrajan M, Saminathan S, International Union Against Tuberculosis and Lung Disease, (2017) Volume 7, Pp. 32-38(7).
7. A. Javaid, I Ullah, H. Masud, A. Basit, W. Ahmad, Z.A. Butt , M. Qasim, Predictors of poor treatment outcomes in multidrug-resistant tuberculosis patients: a retrospective cohort study, Clinical Microbiology and Infection 24 (2018) 612e617.
8. Woldeyohannes D, Assefa T, Aman R, Tekalegn Y, Hailemariam Z (2019) Predictors of time to unfavorable treatment outcomes among patients with multidrug resistant tuberculosis in Oromia region, Ethiopia. PLoS ONE 14(10): e0224025.
9. L€onnroth K, Migliori GB, Abubakar I, D'Ambrosio L, De Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. Eur Respir J 2015;45:928e52.
10. Falzon D, Mirzayev F, Wares F, Baena IG, Zignol M, Linh N, et al. Multidrugresistant tuberculosis around the world: what progress has been made? Eur Respir J 2015;45:150e60.
11. Zhao M, Li X, Xu P, Shen X, Gui X, Wang L, et al. Transmission of MDR and XDR tuberculosis in Shanghai, China. PLoS One 2009;4:e4370.
12. Park SK, Lee WC, Lee DH, Mitnick CD, Han L, Seung KJ. Self-administered, standardized regimens for multidrug-resistant tuberculosis in South Korea. Int J Tuberc Lung Dis 2004;8:361e8.
13. Diel R, Niemann S. Outcome of tuberculosis treatment in Hamburg: a survey. Int J Tuberc Lung Dis 1997;7:124e31.
14. N. Kwak, H. Kim, C. Yoo, Y. W. Kim, S. K. Han, and J. Yim, "Changes in treatment outcomes of multidrug-resistant tuberculosis,"*The International Journal of Tuberculosis and Lung Disease*, vol. 19, no. 5, pp. 525–530, 2015.
15. S. Tang, S. Tan, L. Yao et al., "Risk factors for poor treatment outcomes in patients with MDR-TB and XDR-TB in China: retrospective multi-center investigation," *PLoS ONE*, vol. 8, no. 12, Article ID e82943, pp. 1–8, 2013.
16. E. W. Mollel and J. O. Chilongola, "Predictors for mortality among multidrug-resistant tuberculosis patients in tanzania," *Journal of Tropical Medicine*, vol. 2017, Article ID 9241238, 6 pages, 2017.
17. T. E. Tupasi, A. M. Garfin, E.V. Kurbatova et al., "Factors associated with loss to follow-up during treatment for multidrugresistant tuberculosis, the philippines, 2012–2014," *Emerging Infectious Diseases*, vol. 22, no. 3, pp. 491–502, 2016.
18. Javaid, Z. Shaheen, M. Shafqat, A. H. Khan, and N. Ahmad, "Risk factors for high death and loss-to-follow-up rates among patients with multidrug-resistant tuberculosis at a programmatic management unit," *American Journal of Infection Control*, vol. 45, no. 2, pp. 190–193, 2017.