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Treatment outcome of drug-resistant tuberculosis (DR-TB) following uptake of universal drug susceptibility testing: A record review from a nodal DR-TB center

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ABSTRACT

Background: There has been delay evident in diagnosing the drug resistance and non-initiation of appropriate treatment based on drug susceptibility pattern resulting in poor treatment outcome of drug-resistant tuberculosis (DR-TB). **Aims and Objectives:** The aims of this study were to examine the treatment outcomes for DR-TB patients following universal drug susceptibility testing (UDST) and to examine the association of sociodemographic, behavioral factors, or comorbidities with outcome. **Materials and Methods:** A retrospective study at a nodal DR-TB center was done for the past 2 years (2018–2019) following the district's adoption of UDST. The study comprised patients registered between January 2018 and December 2019. Transferred out cases were excluded from the analysis. Cured or treatment completed were assigned as successful, whereas the treatment failed, lost to follow-up or died were adverse treatment outcome. **Results: A** total of 201 patients were initiated on suitable DOTS regime and they continued the treatment from the center, during the study period. Altogether 129 (64.2%) patients had successful treatment outcome. None of the examined variable (age, sex, SES, Body mass index, and comorbidity) is found to have statistically significant association with outcome ($P>0.05$). **Conclusion**: The UDST may be the reason for success rate shown here, higher than in literature published. Although a better stance is possible only by comparing the treatment outcome of pre- and post-uptake of UDST from same setting.

Key words: Treatment outcome; Drug-resistant tuberculosis; Tuberculosis; Universal drug susceptibility testing

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INTRODUCTION

The existence of drug-resistant tuberculosis (DR-TB) has been confirmed since the development of anti-TB chemotherapy. The global effort to successfully manage TB is now gravely threatened by DR-TB.[1] According to the Global TB Report 2021, rifampicin-resistant tuberculosis was diagnosed in 71% of people in 2020, up from 61% in 2019 to 50% in 2018.[2] The multi-DR-TB (MDR-TB) strain, which is a threat to everyone in the world, is another issue. Unfortunately, India is ahead of all the nation in contributing for TB incidence as well as mortality. The phrase "Programmatic Management of DR-TB" (PMDT) (formerly DOTS Plus) was added to the erstwhile Revised National Tuberculosis Control Program (RNTCP) to better address MDR-TB diagnosis, management, and treatment. This enhances treatment compliance, which ultimately enhances the therapeutic result.[3]

As a result, this study sought to evaluate how well treatment worked as there has been delay evident in diagnosing the drug resistance and non-initiation of appropriate treatment based on drug susceptibility pattern resulting in poor treatment outcome of DR-TB particularly. Hence, its essential to analyze treatment outcome. After adoption of the universal drug susceptibility testing (UDST) by the

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district as now we have the drug resistance profile of the patient available at the commencement of the regimen itself, which ought to improve the outcome.

Aims and objectives

To analyze the treatment outcome of DR-TB notified cases and the associated factors at drug resistant tuberculosis centre during the period of 2018–2019.

MATERIALS AND METHODS

After receiving approval from the Institutional Ethics Committee and District Tuberculosis Officer, the record-based study was carried out at the DR-TB center in Jabalpur between January 2018 and December 2019. Study participants include patients enrolled for DR-TB under PMDT guidelines. Patients with conventional MDR-TB and transferred out cases were excluded from the study, because their total length of the treatment is 24 months, which is outside the time frame of the investigation.

Operational definitions

For the present study, DR-TB includes MDR TB, pre-extensively DR-TB (pre-XDR TB), XDR-TB, and mixed pattern TB which are defined as follow:[4]

MDR-TB

A TB patient, whose biological specimen is resistant to both H and R with or without resistance to other first-line anti-TB drugs. MDR-TB patients may have additional resistance to any/all FQ or any other anti-TB drug.

Pre-XDR-TB

TB caused by mycobacterium tuberculosis strains that fulfill the definition of MDR/RR-TB and are also resistant to any fluoroquinolone.

XDR-TB

TB caused by mycobacterium tuberculosis strains that fulfill the definition of MDR/RR-TB and are also resistant to any fluoroquinolone (levofloxacin or moxifloxacin) and any second line injectable (SLI), that is, amikacin/kanamycin/capreomycin.

Mixed-pattern DR-TB

A TB patient, who found resistant with H mono+FQ/SLI/Linezolid, or with MDR/RR-TB+FQ/SLI+Linezolid resistance.

Treatment outcome was classified into following

Cure

Treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart during continuous period (CP) are negative including culture at the end of the treatment.

Treatment completed

As recommended by the national policy without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Treatment failed

Treatment terminated or need for permanent regimen change of at least two or more anti-TB drugs in CP due to lack of microbiological conversion by the end of the extended intensive phase or microbiological reversion in the continuation phase after conversion to negative or evidence of additional acquired resistance to FQ or SLI drugs or adverse drug reactions (ADR).

Died

A patient who dies for any reason during the course of the treatment.

Lost to follow-up

A patient whose treatment was interrupted for 1 month or more for any reasons before being declared as failed.

Not evaluated

A patient for whom no treatment outcome is assigned.

Regimen changed

A TB patient's need for permanent regimen change of at least one or more anti-TB drugs before being declared as failed.

NIKSHAY IDs were obtained retrospectively from the NIKSHAY portal for the period (January 2018–December 2019) quarter-wise with the help of PMDT co-ordinator that data collection for the registered patients was carried out by accessing the NIKSHAY Portal and RNTCP PMDT treatment cards to obtain information about their sociodemographic profile (age, gender, weight, place of residence, and socioeconomic status: as recorded in NIKSHAY portal as above poverty line or below poverty line), diagnostic, and treatment details.[5]

Body mass index (BMI) of the individual is taken as a surrogate marker of behavioral habits, that is, diet and physical activity. BMI categories for Asian population were considered for this study: <18.5, 18.5–23, 23–27.5, and ≥27.5 for underweight, normal weight, overweight, and obese, respectively.[6]

Statistical analysis

IBM SPSS software version 20 was used for analysis after the data were entered into a Microsoft Excel spreadsheet.

To determine the mean, median, and frequency of variables, such as age group and gender, descriptive analysis was conducted. With a 95% confidence interval, the Chi-square test was used to determine differences in proportions.

RESULTS

A total of 201 DR-TB patients (confirmed by [U-DST]) were enrolled as per inclusion, in this study. Among all, majority of patients (42.3%) belong to younger (18–30 years) age group with mean age 34.66 (±14.75) and were male (62.2%). According to the socioeconomic status, most of the DR-TB patients belong to below poverty line (62.2%). Meanwhile, only 31.3% of the DR-TB isolates had normal weight, while maximum of the isolates exists into under-weight category (59.7%). Surprisingly, 9% of the isolates had overweight too. Whereas, only small proportion (17.4%) of comorbid individuals was present in the following study, among them, majority were diabetics, and HIV covers only a minute proportion (Table 1).

Of the 201 enrolled DR-TB patients with the treatment outcomes, the majority (65) were cured followed by the treatment completed (64). The overall treatment success rate was 64.2%. However, 22 treated patients died, 28 were loss to follow-up, and treatment failure and regimen changed were observed in seven and 12 cases. From the total unsuccessful DR-TB treatment outcome cases (35.8%), three were with the outcome that could not be evaluated (Figure 1).

Out of all the patterns, 13.9% of the H mono resistant, 82.2% MDR isolates, and 3.9% XDR with mixed pattern isolates were showing favorable outcome, whereas 12.5% of H resistant, 80.5% MDR isolates, and 6.9% XDR with mixed cases shown unfavorable outcome (Table 2).

In this study, outcome has not been significantly associated (P>0.05) with any of the variables among sociodemographic (Age, sex, and SES) or behavioral characteristic (BMI) and comorbidities. It means that none of the variable had an influential impact on the success rate of the treatment and was independent for the failure rate of the treatment (Table 3).

DISCUSSION

India has been considered as a high burden nation in terms of DR-TB, which is creating a galloping pace over the period of time. In this study, we determined the treatment outcome of the DR-TB patients and the predictors associated with it.

Males in the present study are more likely to have favorable treatment outcomes (62.2%) than females (37.8%); in addition, the mean age (SD) of the study subjects was 34.46 (14.62); however, there was no statistically significant association with either sex or age group. El Hamdouni et al., from Morocco and other researchers from India as well produced equivalent results.[5,7,8] This age group of young adults (18–30 years) (31.8%) demonstrated unfavorable treatment outcomes which may have certain possibilities like exposed to more infectious pathogens, poor treatment compliance as a result of the lengthy treatment period, and having to forgo high-risk behaviors such as smoking and alcoholism, which weakens the immunity, ultimately led to poor treatment adherence, which has been shown to have negative effects on health, while Belachew et al., from Ethiopia in a 10 year retrospective review, found old age to be significantly associated with unsuccessful treatment outcome.[9] Small sample size in the above cited studies

Table 1: Sociodemographic profile and clinical characteristics of the study population (n=201)

Variable	Frequency (n)	Percent
Age in completed years		
<18	18	9.0
18–30	85	42.3
31–59	81	40.3
≥60	17	8.5
Sex		
Male	125	62.2
Female	76	37.8
Socioeconomic status		
APL	16	8.0
BPL	125	62.2
Unknown	6060	29.9
BMI*		
Underweight (<18.5)	120	59.7
Normal (18.5–22.9)	63	31.3
Overweight (≥23)	18	9.0
Comorbid conditions (n=35)		
Diabetes	33	94.3
HIV	2	5.7

*BMI is classified according to the South-East Asia classification of obesity.
APL: Above poverty line, BPL: Below poverty line

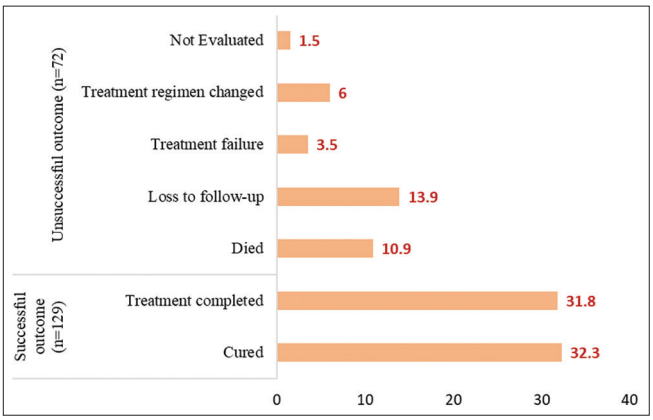

Figure 1: Treatment outcome among patients of DR-TB (n=201)

Table 2: Distribution among pattern of drug-resistant tuberculosis according to treatment outcome (n=201)

Treatment outcome	H Mono (n=27)	MDR (n=164)	XDR (n=7)	Mixed DR (n=3)	Total (n=201)
Favorable treatment outcome (n=129)					
Cured	7 (10.8)	54 (83.1)	3 (4.6)	1 (1.5)	65
Treatment completed	11 (17.2)	52 (81.2)	0 (0.0)	1 (1.6)	64
Unfavorable treatment outcome (n=72)					
Died	2 (9.1)	19 (86.4)	0 (0.0)	1 (4.5)	22
Loss to follow-up	5 (17.9)	21 (75.0)	2 (7.1)	0 (0.0)	28
Treatment failure	0 (0.0)	7 (100.0)	0 (0.0)	0 (0.0)	7
Treatment regimen changed	1 (8.3)	9 (75.0)	2 (16.7)	0 (0.0)	12
Not evaluated	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	3

*MDR: Multidrug resistant, XDR: Extensively drug resistant

Table 3: Association of sociodemographic and clinical factors with the treatment outcome

Variables	#Favorable treatment outcome (n=129)	#Unfavorable treatment outcome (n=72)	Chi-square P value
Age-group			1.802; 0.614
<18 (n=18)	12 (66.7)	6 (33.3)	
18–30 (n=85)	58 (68.2)	27 (31.8)	
31–59(n=81)	50 (61.7)	31 (38.3)	
≥60 (n=17)	9 (52.9)	8 (47.1)	
Sex			0.138; 0.710
Male (n=125)	79 (63.2)	46 (36.8)	
Female (n=76)	50 (65.8)	26 (34.2)	
Socioeconomic status			0.601; 0.741
APL (n=16)	9 (56.2)	7 (43.8)	
BPL (n=125)	80 (64.0)	45 (36.0)	
BMI			1.463; 0.481
<18.5 (n=129)	81 (62.5)	39 (32.5)	
18.5–22.9 (n=71)	37 (58.7)	26 (41.3)	
≥23 (n=21)	11 (61.1)	7 (38.9)	
Comorbidity			4.491; 0.034
Present (n=35)	17	18	
Absent (n=166)	112	54	

#Favorable=cured+treatment completed, #Unfavorable=treatment failure, loss to follow-up, treatment regimen changed

and the present study could be a reason for not getting enough power to demonstrate the effect of age or sex on treatment outcome.[5,7,8]

Majority of the DR-TB isolates in this study belong to below poverty line (62.2%), although, showed treatment success rate on higher side, not statistically significant with the treatment outcome, and might be with the reason of timely and adequate implementation of the U-DST to provide accurate diagnostic services and modification of the treatment regimen. However, no other study found the association of socioeconomic status to the treatment outcome. Comorbidity was observed only in 17.4% patients, but there was no significant (P>0.05) association between comorbidity and treatment outcome, due to limited sample size in the present study, so require more pursuit for further research thereafter.[10]

Around 60% of the participants in the present study were underweight (BMI <18), which is comparable to the results of other investigations.[5,7,10,11,12] However, the majority of them responded well to treatment (62.5%). Meanwhile, 32.5% of the patients had poor treatment outcomes, which may have resulted from factors such as inadequate nutrition, weakened immunity, exposure to extremely toxic medications, poor treatment adherence, necessary treatment regimen changes, lost follow-up, or failure to respond to treatment. However, the present investigation did not find a significant (P>0.05) association between BMI and treatment outcomes unlike the evidences favor the low BMI to be associated with poor treatment outcome.[12]

In the present study, maximum isolates showed successful treatment outcome (64%), which is quite higher (57%) than the recent national figures being depicted in the India TB report 2021 for the treatment success rate.[13] Similar cure rate (44–75%) was also obtained in other countries such as South Korea, China, and Taiwan.[14-19] On the contrary to our study, other researchers reported the unfavorable treatment outcome as high as 62%, primary reasons being ADR, frequent regime modification, higher default/death rate, and late diagnosis of DR cases as diagnostic services were

not accessible.[20] Moreover, another study by Mulisa et al., reported an extremely high unfavorable treatment outcome rate (81%), due to driven factors such as behavioral factors like alcoholism, chat chewing, then concurrent chronic disease, previous history of tuberculosis, and irrational antacid use for gastritis while being treated for tuberculosis.[21] Nevertheless, except these mentioned reasons, one of the most important reasons for this poor treatment outcome could be the non-implementation of U-DST, which somewhere causes more sufferings, affects patient compliance, and eventually landed up into unfortunate treatment outcome.[10,21-24] Unfavorable treatment outcome in this study (died, loss to follow-up, failure, regimen changed, and not evaluated) was 35.8%. The reason for this might be complicated regimens with less efficacious drugs for a long (≥20 months) duration, frequent adverse events, migration of patients, and lack of awareness among patients.[21,25,26]

Limitations of the study

As this is a retrospective study, we were able to analyze the data available within the treatment cards and web-based NIKSHAY portal, with a possibility of information bias. Determinants like comorbidities (e.g., COPD, hypertension, cardiomyopathies, and liver diseases) which may be associated with the treatment outcome could not be analyzed in our study.

CONCLUSION

Although the study's success rate was higher than that of other studies, this may be attributed to the proper UDST implementation, which improves treatment adherence. Adequate attention was also given to promptly identifying and managing any necessary modifications to the treatment plan to reduce patient noncompliance and poor treatment adherence. To decrease loss to follow-up/missing cases and death, it is advised to increase U-DST, timely access to health-care services, and treatment adherence initiatives.

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AB- Reviewed the literature, data collection, statistical analysis and interpretation of results, prepared first draft of the manuscript; **AT-** Concept and design of the study, interpretation of results, preparation and revision of manuscript; **RT-** Concept and co-ordination for the study, revised and finalized the manuscript.

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