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Research Article

Patterns of Drug-Resistant Tuberculosis in Smear Positive Pulmonary Tubercular Patients Taking Drug Sensitive Anti-Tubercular Medications under the DOTS or Non-DOTS Category at the Tertiary Care Hospital in Western Uttar Pradesh State

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Abstract

Introduction: More than half of patients with tuberculosis in India are cared for in the non-government sector. The use of inappropriate tuberculosis (TB) diagnostic and treatment measures is still seen among patients getting treatment with private practitioners, which may contribute to the problem of controlling TB and may lead to the development of resistant TB strains.

Objective: To study and compare patterns of drug-resistant tuberculosis (DR-TB) among those receiving drug-sensitive tuberculosis (DS-TB) regimens among within-DOTS and outside-DOTS cohorts.

Materials and Methods: Prospective observational type study, performed at the tertiary care center (Agra), on patients of eligible category. Rapid molecular diagnostic-based drug resistance testing and drug susceptibility testing (DST) of colonies grown in liquid culture media were conducted on sputum specimens.

Results: RR, MDR, Pre-XDR and XDR rates are higher in the outside-DOTS cohort (i.e., those patients under the care of private practitioners on one or the other DS-TB regimen), while H mono/poly resistance pattern is higher in within-DOTS cohort (i.e., those patients under the care of the government DS-TB regimen under NTEP). The overall prevalence of DR-TB is higher among those outside the DOTS category than within the DOTS category**.**

Conclusion: The overall prevalence of DR-TB with Pre-XDR and XDR forms of DR-TB is more in outside DOTS than within the DOTS cohort and further studies to suggest better policies in public-private partnerships to achieve the goal of tuberculosis elimination.

Keywords: Tuberculosis, Rifampicin resistance, Tuberculosis elimination.

Introduction

Drug-resistant TB (DR-TB) is still a threat to public health in India and the world. The 2022 estimates showed that multidrug-resistant/rifampicin-resistant (MDR/RR) TB was 3.3% (95% UI: 2.6–4.0%) among newly diagnosed cases and was around 17% (95% UI: 11–23%) among previous adequately treated cases.[1]

Frequently the first point of contact for patients with tuberculosis (TB) in India are private practitioners.[2,3] India's National TB Elimination Program (NTEP) provides TB healthcare services free of cost to all patients. Still, in urban settings, patients first seek health-related services from private practitioners, and around half of the TB patients ultimately get treatment outside the NTEP.[4]

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Usage of inadequate diagnostic tests to reach the diagnosis of TB, inappropriate treatment, differing from the national guidelines, and lack of compliance continue to be seen among patients getting treatment with private practitioners. This potentially contributes to delay in diagnosis of the disease, the development of resistant strains, and ongoing TB transmission.

To achieve the targeted goal of TB elimination from India by 2025, five years ahead of the global elimination plan, further research and updated assessment of the epidemic of TB are required at all levels.[5-10]

Our study was an attempt to make recommendations for the enhancement of current elimination strategies by comparing and analyzing the patterns of DR-TB among patients receiving DS-TB regimens both inside and outside of DOTS.

Material and Methods

This was a prospective observational study that was done at the Nodal DR-TB Center, Department of TB and Respiratory Diseases, S. N. Medical College, Agra, between January 2021 and June 2022. After taking informed written consent, all participants were enrolled as per the inclusion and exclusion criteria and operational definitions, and newly diagnosed smear-positive pulmonary TB patients on the DS-TB regimen were included. Patients who previously received treatment with MDR or extensively drug-resistant (XDR) tuberculosis regimens were excluded from the study.

Operational definitions

Outside DOTS

Patients under the care of private practitioners on a DSTB regimen.

Within DOTS

Patients under the care of the government DSTB regimen as per NTEP guidelines.

Participants were subjected to detailed history taking, examination, and information obtained about demography, previous history of TB or anti-TB drug intake, or any preventive therapy. The sputum specimens of the participants underwent investigations like the Cartridge-based nucleic acid amplification test (CBNAAT), line probe assay (LPA), and drug susceptibility testing (DST) at the intermediate reference laboratory (IRL) at Agra. Results of the CBNAAT were available as follows: (I) *Mycobacterium tuberculosis* (MTB) - detected or not detected and (II) Rifampicin resistance (RR) - detected or not detected or indeterminate. Sputum samples in which CBNAAT detected rifampicin resistance underwent a first-line line probe assay (FL-LPA) and, second-line line probe assay (SL-LPA) and liquid culture-drug susceptibility testing (LC-DST). When RR was not seen in CBNAAT but MTB was detected, samples underwent FL-LPA and if isoniazid (H) resistance was detected, then they were subjected to SL-LPA & LC-DST. Statistical analysis was conducted by SPSS 20 software and *p-value* <0.05 was considered statistically significant.

Results

A cohort of 147 eligible sputum acid fast bacilli (AFB) smear-positive DS-TB patients were enrolled within and outside DOTS. Among the 147, 49 (33.33%) were outside DOTS and 98 (66.77%) within DOTS category (Figure 1).

Among the 147 patients enrolled in the study, approximately half were males and half females, with a mean age of 31.6 years, with a majority of patients being in the younger age group. 32.65% of patients were severely undernourished, with

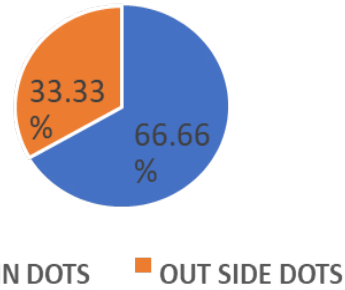
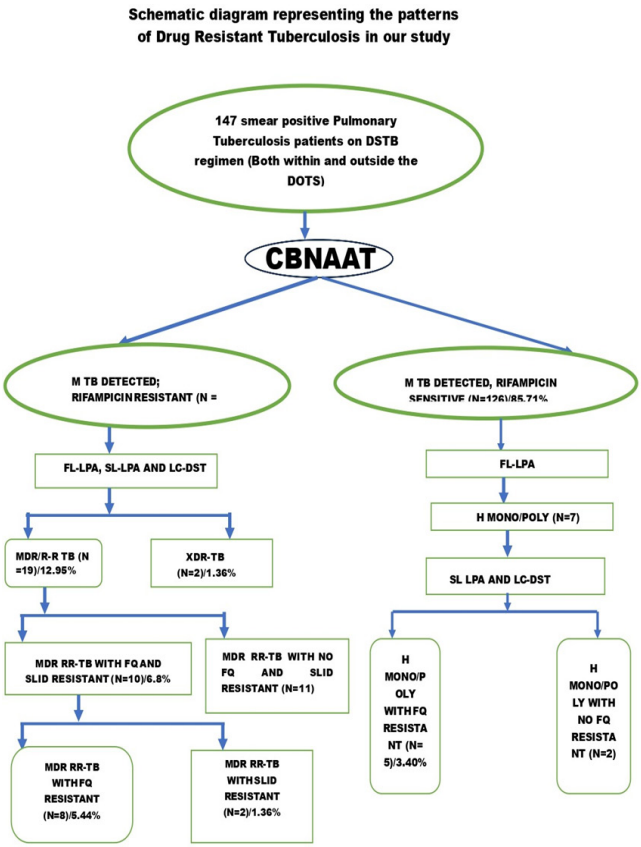


Figure 1: Distribution of Study populationaccording to DOTS profile (N = 147)



Flowchart 1: Depicting methodology and exact number of individual Tubercular of any type detected in our study.

a body mass index below 16. 68.69% of the study population had personal habits of tobacco and alcohol consumption. 42.85% of patients were categorized in class IV (upper-lower) of the Kuppuswamy socio-economic scale.

Patterns of resistance of drug

Among 147 AFB smear-positive pulmonary TB patients on a DS-TB regimen subjected to CBNAAT, 21 (14.28%) were diagnosed as rifampicin-resistant (RR), whereas 126 (85.71%) were rifampicin-sensitive (RS).

All 21 rifampicin-resistant TB patients were subjected to FL-LPA, SL-LPA, and LC-DST. Multi-drug resistant/RR-TB was detected in 19 patients, and XDR-TB was seen in 2 patients. Among the MDR/RR patients, 11 patients did not have additional fluoroquinolone (FQ) resistance or resistance to second-line injectable drug (SLID). Ten patients had resistance to FQ/SLID (eight were resistant to FQ and two to SLID). Over 126 rifampicin-sensitive patients underwent a first-line probe assay. Seven of those for whom H-mono/poly-drug resistance was detected were subjected to SL-LPA and liquid culture drug susceptibility. Out of these, five patients had no additional resistance, while two were resistant to FQ (Flowchart 1).

Discussion

This study was performed during 18 months of time interval. A cohort of 147 eligible sputum smear-positive DS-TB patients were enrolled, with 33.33% in Outside DOTS and 66.77% in Within DOTS category. The study revealed that the majority of DR-TB patients were in the younger age group. About 53.57% of the patients were of an age range of 18-25 years, while the mean age was 30.6 years, similar to other studies conducted in the public sector.[11-13] While some of the studies conducted in other parts of the southeast Asian and eastern region have slightly higher mean age. This might be because of geographical variation in prevalence of disease, variations in ethnicity and racial features and higher age of survival in the eastern countries. The overall prevalence of DR-TB obtained in our study was 19.04%, with 8.16% of patients in within-DOTS and 10.88% in the outside-DOTS category (Figure 2).

The results of our study match with that of a study conducted by Dawit Asmamaw *et al.* [14] in Addis Ababa, Ethiopia, obtaining the prevalence of 10.4% for newly diagnosed DR-TB in smear-positive patients in the public sector, and that of a study conducted by Jain A[15] at Lucknow Uttar Pradesh, India obtaining overall prevalence of 19.8% of MDR TB. One of the leading factors associated with the occurrence of DR-TB among those receiving DS-TB treatment outside the DOTS category is mainly related to economic factors: patients cannot afford medications prescribed by private practitioners for a long duration of time and are not able to afford consultation fees repeatedly, and many have sought help from local chemists for relief of their periodic symptoms. Other factors include initial relief of symptoms and discontinuation of DS-TB medications, poor accessibility from far areas, lack of knowledge about the seriousness of the illness and many times delayed treatment-seeking behavior of patients for longer-lasting symptoms.

Loss of daily wages is also a factor in 24% of patients in this category. Because of fear of loss of wages, patients ignored the initial symptoms till symptoms progressed to the level of seeking minimum health care.

Within the within-DOTS category of those receiving DS-TB treatment, the sole universal factor responsible for the development of DR-TB was the discontinuation of medications due to the initial improvement of symptoms, despite getting educated by NTEP staff about symptoms, consequences, and seriousness of the condition. In our study, we did not come across any beneficiary/patient who did not receive monthly remuneration for being on proper treatment for DS-TB. In spite of getting proper monetary remuneration, many patients discontinued DS-TB medications, which seems to be an alarming factor and needs studies in this field to explore proper reasons.

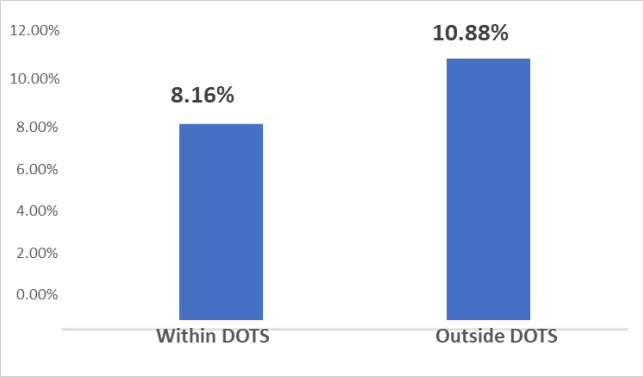


Figure 2: Prevalence of DRTB in the within DOTS category is 8.16% and outside DOTS category is 10.88%. The Chi-square is 5.711, a *p-value* is .016859 and the result is significant.

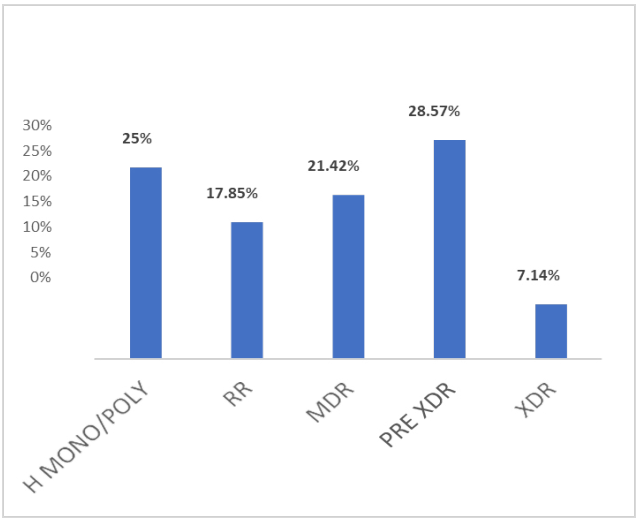


Figure 3: Drug resistance pattern of DRTB patients

Factors like the presence of poor hygiene, low socio-economic status, male sex, smoking, and alcohol consumption were related to the development of DR-TB among DS-TB patients in both categories of this study. Co-infection with HIV is also one of the important determinants of DR-TB among those having DS-TB.

Reports of DST and LPA revealed that among the 147 study participants, 28 (19.04%) were DR-TB patients. Among these 28 patients with DR-TB, 12 (42.84%) were in DOTS and 16 (57.16%) were outside the DOTS category. The drug-resistant profile of these 28 patients in our study was as follows: Isoniazid Resistance (H MONO/POLY) was in 7 (25%) cases, RR was in 5 (17.85%) cases, MDR was 6 (21.42%) cases, Pre-XDR were 8 (28.57%) cases, and XDR were 2 (7.14%) cases (Figure 3). These results are in concordance with a study conducted by Vishal Prakash Giri *et al.*[5] and the study conducted by Yuanping Pan *et al.* in Dalian, China.[16]

The mono-resistance to rifampicin was seen in 7.14%. This is higher as compared to the studies conducted in Ethiopia, quoting the ranges from 0% to 1.9% and other parts of India (1.1%), Myanmar (2%) and Cameroon (2.1%).

Finally, our study, not without limitations, has stood with almost all the concurrent studies with respect to the determination of prevalence and patterns of DR-TB among DS-TB. Some of the factors that may not co-relate or have gross differences may be due to various environmental, dietary, socio-economic and other demographic and social practices.

Limitations

Even after an extensive search online and manually, we could not get a study where specific determinations of patterns of DR-TB in the private sector. This limits us to comparing and obtaining inferences concerning the outside DOTS population. To infer and draw conclusions, we relied mainly on global, national, and regional reports and articles.

Conclusions: All patterns of DR-TB, except for H mono-resistant DR-TB, are more in the outside DOTS category. Further research is needed in this field to explore data to suggest better policies in the field of public-private partnerships to achieve the ambitious goal of elimination of tuberculosis.

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