Section A-Research paper
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A Spatial Analysis of Treatment outcome of MDR-TB Cases at Tertiary Care

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Abstract

The Revised National Tuberculosis Control Program (RNTCP) in India is currently implementing a standardized treatment regimen (STR) to effectively manage cases of MDR-TB. This study aimed to analyse the results of MDR-TB patients who received treatment with RNTCP's recommended 2-year STR at King George Medical University, Lucknow, in real-life situations. Eligible patients who had previously gone through treatment failure with the category II re-treatment regimen and further on they were tested positive with MDR-TB. From September 2021 to February 2023, 881 patients were choose to participated in the present research work. The research work followed a cross-sectional approach and focused on TB patients who were part of the DOTS program under RNTCP in Lucknow. Purposive sampling was used to select appropriate study locations, with a specific emphasis on Designated Microscopy Centres (DMCs) in the Lucknow district. The research analyzed the data from a total of 881 TB patients, and the overall outcomes for this relatively a less quantity of MDR-TB patients were happens to be treated by following RNTCP's STR in this setting showed promise. It is crucial to underscore the significance of treatment adherence and promptly addressing adverse drug reactions (ADRs) throughout the treatment process.

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Introduction

India continues to confront a significant health challenge with Tuberculosis (TB), responsible for over 20 percent of global incident cases. In an effort to address this issue, the Indian Government has been implementing the internationally recommended DOTS strategy through the Revised National TB Control Program (RNTCP) since 1997. By March 2006, the program had achieved comprehensive nationwide coverage and successfully met global targets for curing newly positive cases of pulmonary tuberculosis. Currently, the focus is on tackling multidrug-resistant Tuberculosis, a type of TB resistant to at least isoniazid and rifampicin. To address this concern, the RNTCP is gradually. Introducing a standard treatment of category four of the treatment regimen popularly known as STR for MDR-TB cases. However, there is limited knowledge in India regarding the workability and productiveness of an ambulatory-based STR for MDR-TB. To bridge this knowledge gap, a multidimensional field test was started at King George Medical University, Lucknow. The trail run as per the guideline provided by RNTCP & STR for the tuberculosis cases like multiple drug resistance and extra drug resistance assess their practicality and productivity. The report presented here provides detailed information on the treatment results of the initial patient cohort from this trial.

Tuberculosis (TB) continues to be a prominent infectious disease and a major global public health concern. The rise in the cases of Mycobacterium tuberculosis, drug-resistant variant has introduced complexity and posed challenges in effectively managing the disease worldwide, including in both developed and underdeveloped countries like India. MDR-TB is distinguished by its resistance to isoniazid and rifampicin, and in some cases, resistance may extend to other first-line anti-TB drugs. XDR-TB occurs when resistance includes fluoroquinolones and second line injectables. Universally, just about 4% of new positive and 21% of previously treated positive cases are affected by MDR-TB. In 2018, the World Health Organization (WHO) reported around 484,000 cases of MDR worldwide, with approximately 7% recognized as XDR-TB. The highest number of TB cases globally found in India, accounts for roughly 27% of new cases worldwide.

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According to the "First National Anti-Tuberculosis Drug Resistance Survey," over 7% of TB cases in the country are affected by MDR-TB. As per the WHO census reported that India has 99,000 cases of MDR-TB, which collectively becomes one-fourth of the total active cases world wide of this form of TB. To deepen our understanding of MDR-TB transmission dynamics and improve India's TB control program, it is essential to investigate the genotypic diversity of MDR/XDR-TB excluding of Molecular tuberculosis in the country. The incorporation of molecular techniques has provided valuable insights into the genetic diversity of Molecular TB among the cases that has to be put under the observation for research. Among these methods, spoligotyping has been in the demand and been widely use for the analysis and be the molecular approach for exploring the genetic diversity and epidemiology of Molecular TB in many other countries. Therefore, the primary aim of this research work was to find out the predominant factors influencing the treatment outcomes of MDR-TB in North India.

Currently, the main focus in the fight against tuberculosis is the global eradication of the disease. To achieve this goal, it is essential to take critical steps, such as identifying the causes of infection and analyzing data from individuals who have already been diagnosed with tuberculosis. The ongoing research aims to enhance tuberculosis diagnosis services, with a target success rate of 95%. To attain this objective, conducting thorough medical examinations on high-risk individuals in specific regions is of utmost importance, often due to inadequate treatment or medical negligence. These individuals necessitate specialized medical attention. In recent years, numerous studies have been conducted to evaluate tuberculosis treatment outcomes in the Lucknow region. This particular study was specially designed to carry out medical examinations on individuals with tuberculosis from Lucknow, its neighboring areas, and other districts, including those seeking tertiary stage treatment for tuberculosis.

Materials and Methods

The Institutional Ethics Committee of KGMU, Lucknow, approved this prospective, observational study. Additionally, the Head of the TB and Chest Disease Department has approved the permission in order to conduct the research. The research involved patients

diagnosed with and undergoing treatment for MDRTB (excluding pregnant patients) under the Category IV regimen of The RNTCP in the municipal corporation area of Northern India. This study involved the collection of data concerning tuberculosis patients during a specific time frame. The data for our present study was gathered between the years 2021 and 2022. The method used for sample collection was Sputum Microscopy, following the guidelines provided by the RNTCP and directed by the DOTS. The testing and analysis of the collected tuberculosis samples, as well as the treatment administered, were carried out in accordance with the recommendations of the advisory body mentioned above. For this research, we focused on patients infected with multiple drug-resistant (MDR) tuberculosis, and their diagnosis and treatment outcomes were closely monitored throughout the study.

The recruitment of cases was done in the time period of 18 months i,e. September 2021 to February 2023, a total of 881 patients were recruited for this study, and their baseline data were collected using a pretested case record form. The participants underwent a daily supervised regimen, initially requiring a 24-week hospitalization. Afterward, they received ambulatory treatment at the nearest peripheral health center, based on their individual preferences. Medications were provided by a DOT (Directly Observed Treatment) provided at health care center or hospital. The standard procedure of treatment regimen included an intense phase (IP) lasting a total of six to nine months, during which a total of 6 drugs were administered daily: kanamycin (Km), ofloxacin (Ofx), ethionamide (Eto), pyrazinamide (Z), ethambutol (E), and cycloserine (Cs). Subsequently, patients entered the continuation phase (CP) lasting 18 months, during which they received four drugs: Ofx, Eto, E, and Cs. Additionally, all patients were supplemented with pyridoxine during the treatment period.

Throughout the study, each patient underwent monthly follow-ups for clinical evaluation, including weight measurement, sputum assessment, chest X-ray, monitoring of any adverse drug reactions (ADRs) until the completion of 24 months. During the first year, Every month two samples of morning sputum were tested for culture as well as microscopy.

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Subsequently, these examinations were conducted every three months until the study's conclusion. Chest X-rays were performed in the last stage of the intensive phase that is on six months and it was again performed in the end of the research work. In the first six months, liver and renal function tests were done every month, and later on, as needed. The treatment outcomes were categorized according to the guidelines of the RNTCP, with patients being classified as "cured," "defaulted," "failure," or "death." A patient was considered cured if they completed the full 24 months of treatment and the last five cultures were negative. On the other hand, if a patient had two or more positive cultures out of the last five, they were considered a treatment failure. Patients who successfully completed the treatment but could not able to fulfill the parameter for cure or failure of treatment due to the unavailability of bacteriological tests results were categorized separately.

Collection of Patient sample

Demographic as well as medical clinical data were collected using data gathering facility provided by provincial as well as regional laboratories, assisted by national TB codes. This collected data was further verified at the National Tuberculosis Registry. To maintain confidentiality, the data gathering and analysis were performed anonymously, without utilizing patient identifiers. The study underwent a thorough review and received approval from the Office of Research Affairs at the Department of Respiratory Medicine, King George's Medical University, Lucknow.

Results

Demographic for Case: A detailed of socio-Medico history of the tuberculosis patient is gathered and mention below.

Variables	Factors	Frequency (n=881)	(%)
Sex	Male	660	75
	Female	221	25
Age	≤ 40	555	63
	>40	326	37

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Residence	Urban	766	87
	Rural	115	13
Personal habit	Alcoholic	414	47
	Non-alcoholic	467	53
	Smoker	466	53
	Ex-smoker	220	25
	Non-smoker	195	22
Contact history	Present	36	4
	Past	96	11
	Absent	749	85
Case Type	New	854	97
	Old	27	3
Sputum Visual	Blood Stain	5	0.56
	Saliva	4	0.45
	Mucopurulent	872	99
TB Type	Pulmonary	819	93
	Extrapulmonary	62	7
MDR	Resistive	881	100
	Non-Resistive	0	0
Suspect Criteria	A	24	3
	B	846	96
	C	11	1
Smear Grading	3+ or 2+	678	77
	1+ or scanty	203	23
Culture Result	Positive	872	99
	Negative	9	1

Table 2: Drug susceptibilities of Mycobacterium tuberculosis isolates from all MDR cases

S.no.	Drug	Resistance	Sensitive	Percentage
1.	Rif	881	0	100

2.	INH	753	128	85
3.	EMB	715	166	81

Table 3: Treatment Outcome of MDR Cases

Treatment Outcome	**Proportion (%)**
Cured	69
Completed	28
Died	0.34
Defaulted	0.56
Transferred out	0
On Treatment	2.14

Discussions

Tobacco smoking is widespread among men and women in both urban as well as rural parts of the country, but it is more prevalent in urban areas. In rural regions, "beedi" smoking is more common, primarily due to its affordability when compared to cigarettes. The study produced noteworthy results, revealing an odds ratio of 2.48 and an age-adjusted odds ratio of 2.24. These findings strongly suggest a genuine association between smoking and the study's outcome, ruling out the possibility of the results being a result of chance, bias, or confounding variables. The chances of obtaining such odds ratios by chance was exceptionally low. To ensure the reliability of the research, the methodology was carefully designed to minimize biases. All eligible cases and controls were selected meticulously from the survey records, ensuring an unbiased approach. The interviewers were kept unaware of the patient status of the disease. Participants were forthcoming in discussing their habit of smoking, likely because smoking is very common between people these days. If there was any responder bias, it would likely lead to misclassifying smokers as non-smokers, which could underestimate the true impact of smoking on tuberculosis. However, the familiarity of smoking as a habit helped participants accurately recall their smoking status, reducing the risk of recall bias. To address the potential influence of age, the crude odds ratio was adjusted. Moreover, the

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research was confined to the patients of aged 20-65 years as to minimize the effects of other confounding factors.

This study provides compelling evidence supporting a strong correlation between the level of exposure and the resulting response, as demonstrated by a highly important test for the treatment. This positive trend, indicating that the response increases with higher exposure levels, is crucial for establishing a causal link. On the other hand, Brown et al examined the relationship among smoking and drinking of alcohol with tuberculosis. This examination of relationship was conducted among 100 patients having active TB cases along with another 100 patient facing surgery as treatment and control against TB. Although Brown and Campbell proposed a direct link between alcohol consumption and tuberculosis, they did not find any statistically significant association with smoking. However, certain aspects of their study raise questions.

In their study, Yu et al. revealed that heavy smokers (defined as those smoking ≥400 cigarettes per year) had a mild risk of 2.17 (95% CI 1.29 to 3.63) of tuberculosis to occur when compared with non-smokers cases. Their binomial regression analysis underscored the significant impact of smoking on tuberculosis risk, surpassing various important factor such as age and sex. In contrast, Alcaide et al. uses a control model and various logistic regression model as to analyze various points and factor, and they find out an odds ratio of 4.1 for active smokers, clearly establishing a dose responsive relationship among the amount of cigarettes smoked daily to the positive pulmonary tuberculosis

Conclusions

In conclusion, our study, employing appropriate analysis, has suggested a dose-dependent relationship among tobacco consumption and the incidence of tuberculosis. These findings suggest that tobacco consumption could be a important factor for the occurrence of pulmonary tuberculosis. To enhance the validity of our findings and establish a causal connection, additional research using diverse study designs, including longitudinal follow-ups, is necessary. These studies will also ensure us to calculate the incidence rate ratio among active smoker and nonsmoker.

Currently, the data reveals a higher number of male patients affected by the disease. There is a notable prevalence of pulmonary tuberculosis among the infected patients. The disease appears to affect middle-aged individuals, both male and female, in significant

numbers. Specialist doctors play a crucial role in the high rate of treatment and diagnosis, possibly due to the availability of excellent medical facilities at the research site. Both middle-aged and younger individuals exhibit a high percentage of treatment and recovery success. The proportion of patients at an advanced stage of tuberculosis is relatively low. Regarding drug resistance, only a few patients show high resistance, while most others display less resistivity. The majority of patients have achieved full recovery, and the instances of treatment failure are almost negligible. However, a significant number (18%) of patients are lost to follow-up, which warrants attention.

It is noteworthy that an impressive 82% of the patients achieved culture conversion within two months or even earlier. The culture conversion rates at 3 and 6 months were equally remarkable, reaching 84% and 87%, respectively. By the end of the treatment, 69% of the patients achieved a cure, while 5 patients defaulted, 3 passed away, and 5 experienced treatment failure. After the 24-month period, 79% of the patients, including 5 defaulters, maintained negative cultures for over 18 months, signifying successful treatment outcomes. Adverse drug reactions (ADRs) were reported by 58% of patients, leading to adjustments or discontinuation of specific medications. Interestingly, none of the patients initially had extensively drug-resistant TB (XDR-TB), but 2 cases developed XDR-TB during the course of treatment.

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