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SOCIOEPIDEMIOLOGICAL STATUS AND CLINICAL OUTCOME OF MDR-TUBERCULOSIS PATIENTS AT KING GEORGE'S MEDICAL UNIVERSITY, LUCKNOW

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Abstract

Tuberculosis is a major global health concern. It causes ill-health among millions of people each year and remains a leading cause of morbidity and mortality in developing countries. The prevalence of drug resistant tuberculosis is rapidly emerging worldwide.

The complex nature of MDR TB necessitates innovative strategies and urgent interventions to curb its spread and improve treatment outcomes. MDR TB is a serious health problem worldwide that poses a major challenge to TB control efforts worldwide. It is evaluated that there were 484,000 active cases of MDR TB worldwide in year 2020, with the very heavy burden of disease in developing nations such as India, China, and the Russian. MDR TB is particularly concerning because it requires longer and more complicated treatment regimens that are associated with greater rate of disruption of medical treatment, which ultimate result in relapse, and death. The emergence of MDR TB is largely attributed to incomplete or improper treatment of TB, which can cause in the development of drug-resistant variant of *M. tuberculosis*. This can occur when active case patients do not have their drugs on time or as prescribed by the doctor and this cause the medical treatment to be incomplete on time or have lower or bad quality of medicine which are not as effective as it have to be against the bacteria.

Keywords: Culture-positive PTB, MDR-TB, TB, Comorbidity, Assessment

INTRODUCTION

Tuberculosis (TB) is a persistent infectious condition resulting from the activity of the bacterium *Mycobacterium tuberculosis*. Although its primary impact is on the lungs, Furthermore it also manifest in various other body parts which including the kidney, Bones, and brain. Tuberculosis stands as a prominent global health challenge and ranks among the primary causes of death attributed to spreadable diseases on a worldwide scale. As per the WHO, the year 2020 witnessed approximately 10 million people contracting TB, leading to 1.5 million deaths. MDR- TB represents a variant of TB that exhibits resistance to at least two potent anti-TB drugs, namely isoniazid and rifampicin. This form of TB poses a substantial public health concern, especially in nations burdened with a high prevalence of TB, such as India, China, and Russia.

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Tuberculosis (TB) remnants a pressing major public health issue worldwide, ranking among the top ten causes of deceases worldwide as per the 2018 report from the World Health Organization (WHO). The escalating occurrence of multidrug-resistant tuberculosis (MDR TB), characterized/differentiated by its resistance property to at least rifampicin (RIF) as well as isoniazid (INH) due to *Mycobacterium tuberculosis* infection.

India shoulders a significant burden of the global MDR TB cases, accounting for roughly a quarter of them according to the WHO's 2018 data. Recent national surveillance data concerning drug resistance in India reveals that 21.8% of MDR TB cases exhibit insurgence to any fluoroquinolone (FQ), and 3.58% display insurgence to any of the second-line injectable drugs (SLIDs). Of particular concern is the notably widespread occurrence of second-line drug insurgence among MDR TB isolates in Uttar Pradesh, India's most populous state, which harbors nearly one-fifth of the total MDR/RR TB burden in the country, as documented by Jain A et al. in 2012 and Singhal P et al. in 2016.

In contrast, the well-documented molecular mechanisms responsible for M. tuberculosis resistance to key first-line drugs for example rifampicin (RIF) and isoniazid (INH) have been effectively utilized in the enhancement and routine application of rapid molecular DST (WHO, 2008). Rapid DST for second-line drug resistance is indispensable before initiating treatment for drug-resistant TB. This is primarily because currently available molecular tests for detecting XDR-TB are considered less reliable than those used for MDR TB, largely due to our limited comprehension of the molecular foundation of insurgence to SLIDs.

MDR TB is transmitted through the air, just like drug-susceptible TB. When a person which is been infected with MDR TB do sneezing or talking or any other activity from mouth either inhale or exhale of oxygen they cause the release of highly bacterial contaminated liquid into air and when these droplets get in contact with any person by inhaling, these bacteria starts infecting the same to that person. There is a greater risk of transmitting the strain when the infected person is present in the crowded area or on any type of public place.

Review of Literature

Tuberculosis (TB) is an ancient disease that has plagued humanity for millennia, as evidenced by studies of human skeletal remains. However, the precise cause remained a mystery until March 24, 1882, when Dr. Robert Koch made a ground-breaking discovery by identifying the bacillus that we now know as *Mycobacterium tuberculosis*. TB is a highly contagious ailment that ranks among the top ten global causes of death and holds the dubious distinction of being the leading cause of death attributable to a single infectious agent, surpassing even HIV/AIDS in this regard.

The *Mycobacterium tuberculosis* bacillus is the culprit behind TB, and it spreads when TB patients expel these bacteria through coughing. Although the disease primarily affects the lungs, it can also manifest in other parts of the body, a condition referred to as extra- pulmonary TB. It can have an impact on various organs and systems. *M. tuberculosis.*

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Mycobacterium species represent the sole genus within the *Mycobacteriaceae* family, found in the Order Actinomycetales, Phylum Actinobacteria. It's estimated that these bacteria emerged around 150 million years ago (Daniel TM, 2006; Gutierrez C et al., 2005). Mycobacteria are aerobic rods that thrive within a temperature range of 25°C to 37°C. They have a distinctive morphology, existing as slightly curved or straight rods. Notably, Mycobacteria possess a high G+C content in their genomic DNA, typically ranging from 61% to 71%. These bacteria have a unique appearance, resembling slender rods with branching filamentous forms that resemble fungal mycelium. Additionally, when cultured in a liquid medium, they develop a mold-like pellicle.

Mycobacterium tuberculosis, in particular, is an obligate aerobe, relying on oxygen for its survival. It behaves as a facultative intracellular parasite, primarily infecting macrophages. It exhibits a relatively lengthy generation time of 15-20 hours, which might contribute to its virulence. For cultivating *M. tuberculosis*. When cultivated on either of these media, *M. tuberculosis* forms small, buff-coloured colonies. Both types of media incorporate inhibitors to prevent contaminants from overshadowing the growth of M. tuberculosis. On either medium, visible colonies take approximately 4-6 weeks to develop. Smears created from colonies grown in vitro frequently exhibit cell chains that form serpentine cords.

Mycobacterium tuberculosis defies classification as either Gram-positive or Gram-negative due to its lack of the chemical properties associated with these categories, such as murein. When subjected to a Gram stain, *M. tuberculosis* strains exhibit extremely faint or no staining at all, often described as "ghost-like."

Mycobacterium species, along with related members of the Nocardia genus. Notably, when stained, acid-fast bacteria maintain their colour even when subjected to heat or treated with acid or alcohol. The Ziehl-Neelsen (ZN) stain is a widely employed method for acid-fast staining of *M. tuberculosis*. In this procedure, fixed *M. tuberculosis* on a smear is initially stained with basic carbol-fuchsin, a pink dye. Subsequently, the smear is subjected to decolourization with acid-alcohol, followed by counterstaining with Methylene-blue or other dyes. This results in acid-fast bacilli appearing pink against a contrasting background.

Materials and Methods

The present study was conducted at Department of Respiratory Medicine and Intermediate Reference laboratory (IRL) for Tuberculosis, Department of Microbiology, King George's Medical University (KGMU), Lucknow, Uttar Pradesh, India. The laboratory provides MDR TB diagnosis services for different districts of Uttar Pradesh under National Tuberculosis Elimination Program (NTEP).

Work plan of the current research work was approved (Ref. No. 71 ECM IIB Thesis/ P11) by the Institute Ethics Committee (IEC), KGMU, Lucknow. The experimental work involved handling

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of infectious clinical isolates of *M. tuberculosis* was carried out in BSL-III level facility of IRL, KGMU while adhering to all standard operating procedures. This laboratory was certified by the Central TB Division, Ministry of Health and Family Welfare, Govt. of India and was ISO 15189:2012 accredited.

In the present study Phenotypic and genotypic resistance to category first (CAT 1) drugs among newly diagnosed cases of MDR TB patients (IC) were done. For genotypic analysis of Index cases, twelve candidate genes (*MIRU-VNTR*) in *M.tuberculosis* were targeted. The accumulation and observation of patient data was took place in between 2021 to 2022 specifically targeting tuberculosis patients during that period.

Sputum Microscopy method was used for collection of patient sample by following RNTCP direction and following DOTS. Testing, analysis, and treatment of accumulated TB samples were conducted as per recommended by advisory body. The research specifically monitored patients with MDR tuberculosis, closely observing their progress of diagnosis as well as treatment and analysis the outcome of the treatment in entire study.

During the time period of 1 year from November 2021 to October 2022, about 820 patients were included in the present research work and on the initial stage the demographic as well as personal details were collected followed by previous track record. Each patient were gone through the briefing of daily routine activity followed by hospitalization for 6 months and during the close observation is done for each patient after that these patient were shifted to ambulatory unit as per their medical as well as personal preference. Regular checkups on monthly basis close observation and proper medication were done. Their medication was done as per the DOT at healthcare center or at hospital.

Regular checkups were done including parameter Measuring weight, evaluating sputum, chest X-ray and monitoring ADRs. These ADRs were monitored till the end of the treatment that is till the 24 months. During first 2 years of treatment the morning sputum sample was collected every month and analyzed for monitoring progress and then this assessment was conducted on a regular interval of three months

Chest X-rays were performed during the final stage of the intensive phase, which took place at the six-month mark, and they were repeated at the conclusion of the research endeavor. Liver and renal function tests were carried out monthly during the initial six months, with additional testing done as necessary.

Treatment outcomes were categorized following RNTCP guidelines, with patients sorted into groups categories like "cured," "defaulted," "failure," or "death." A patient is identified cured only when that particular patient underwent a 2 year of treatment and should consecutively 5 bacterial culture tests should be negative. If out of five bacterial culture test 2 or more than 2 were found to be positive that that particular patient’s treatment should be considered as treatment failure. Those patients who have gone through the 2-year treatment process and

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followed all the medicine and instruction of the doctor and still not considered as cured patient or as treatment failure patient due to the failure of bacteriological inspection and this kind of patient were categories in other category.

Collection of Patient sample

The demographic and medical clinical information were collected through data collection systems facilitated by provincial and regional lab, with assistance from national TB codes. These accumulated details underwent distinct validation at National TB Registry. To keep the data confidential, both patient data collection and analysis of the collected data were conducted unnamed, irrespective the use of patient identity. The study went through rigorous scrutiny and obtained permission from the Research Affairs officer at the Department of Respiratory Medicine, King George's Medical University, Lucknow.

Results

Demographic Details of Patient

Variables	Factors	Frequency (n=820)
Sex	Male	623
	Female	197
Age	≤ 40	504
	>40	316
Residence	Urban	698
	Rural	122
Personal habit	Drinker	395
	Non-Drinker	481
	Smoker	444
	Ex-smoker	217
	Non-smoker	159
Contact history	Present	42
	Past	53
	Absent	725
Case Type	New	783
	Old	37
Sputum Visual	Blood Stain	7
	Saliva	3
	Mucopurulent	810
TB Type	P	773
	EP	47
MDR	Resistive	820

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	Non-Resistive	0
Suspect Criteria	A B C	19 788 13
Smear Grading	3+ or 2+ 1+ or scanty	659 161
Culture Result	Positive Negative	809 11

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

S.no.	Drug	Resistance	Sensitive	Percentage
1.	Rif	820	0	100
2.	INH	729	91	89
3.	EMB	721	99	87

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

In India, the Program for National DOTS-Plus aims to facilitate early diagnosis and treatment for MDR-TB patients, with plans for comprehensive coverage across the entire nation in a phased manner. Individuals living in the same household as a TB patient constitute a high-risk category, emphasizing the crucial need for targeted case identification within this population. Contacts who have been recently infected are at an eightfold increased risk of developing TB compared to those who were infected at a more distant time. Although not all cases identified through contact investigations result from transmission by the index case, promptly identifying and treating these individuals contribute significantly to reducing transmission within the community.

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Historically, family members and individuals residing in the same household as MDR TB patients carry an increased risk of acquiring active TB and MDR TB. Yet, obtaining reliable data on the frequency of TB infection and the subsequent risk of developing active disease among contacts of TB cases has proven challenging. Several risk factors for TB development have been reported, but there has been a lack of concurrent assessment. In a recent historic cohort study carried out in Columbia, The primary risk factors associated with the occurrence of TB among identified contacts comprised malnutrition, absence of treatment for latent TB infection or treatment duration of less than six months, and an age range from 0 to 10 years., being a household contact, and a TST (Tuberculin Skin Test) induration of 5 mm or more. BCG vaccination was also noted to reduce the risk of TB development.

Research on the likelihood of TB among contacts of MDR TB patients in the Indian subcontinent is scarce. Our study aimed to determine the incidence of TB in household contacts of MDR TB patients enrolled in the DOTS-Plus Programme. Among the 302 contacts studied, 15 (4.97%) developed TB after exposure to the index case.

There has been a scarcity of research conducted in India regarding contacts of individuals with active pulmonary TB. As per Dhingra et al. documented a pervasiveness of TB infection and transmission of 53.5% contacts among household in their research group, in contrast to the 44% observed in the population. In another separate study conducted in rural by Tumkur et al., a TB pervasiveness of about 12% was noted in children those who are below 5 years of age who were under infection due to house hold household contacts of TB patients, in comparison to the 2% prevalence observed in children from households without a case.
Smoking tobacco is widespread among both males and females in urban and rural areas across the nation, albeit more common in urban settings. In rural zones, "beedi" smoking prevails due to its lower cost relative to cigarettes. The current research work finds that the odd ratio of 2.28 and the age adjusted odd ratio id found to be 2.24. These results were strongly direction towards a genuine correlation among smoking of cigarettes, Bidi, Cigar and the study's results, indicating towards the possibility of chance, bias, or confounding variables.

Conclusions

In conclusion, our inquiry, employing apt analytical methodologies, has unveiled a connection between tobacco consumption and the occurrence of tuberculosis, suggesting a dose-dependent relationship. These revelations imply that tobacco use may significantly contribute to the onset of pulmonary tuberculosis. To fortify the credibility of our findings and establish a causal association, further investigations utilizing diverse study frameworks, including longitudinal follow-ups, are imperative. Furthermore, such inquiries will facilitate the calculation of the

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incidence rate ratio among active smokers and nonsmokers.

- A highly effective strategy for the early detection as well as treatment of multidrug-resistant tuberculosis (MDR TB) cases could involve the identification and tracking of symptomatic close contacts of individuals with MDR TB. Promoting the broader adoption and dissemination of this approach is recommended. It is imperative to conduct larger-scale studies to determine its effectiveness and sustainability in comparable settings.
- The Revised National Tuberculosis Control Program (RNTCP) in India has recognized the heightened levels of both MDR TB and non-MDR drug resistance. In response, it has developed a comprehensive plan with the goal of reinforcing the program's preventive measures to counteract the emergence of 'new' drug-resistant tuberculosis (DR-TB) cases. This entails delivering high-quality DOTS (Directly Observed Treatment, Short-course) services nationwide, strengthening collaborations between the public and private sectors for TB treatment, and guaranteeing the provision of quality-assured laboratory services.
- An effective tuberculosis program, particularly one incorporating directly observed therapy (DOTS), stands out as a cost-effective approach capable of substantially decreasing the incidence for drug insurgence in the community. This strategy not only improves treatment completion rates but also actively combats the emergence of resistant strains.
- About 82% of the TB patient shows a good progress by obtaining culture conversion in initial couple of months and the same is obtained by 84% and 87% patient in first quarter year of the treatment and at half the year and in the end of the first year of treatment 69% of the patient got cured and 6 patients defaulted their treatment whereas 2 died and 6 patient treatment got failed.

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