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Original Research Article

A Study on Prevalence of MDR TB Among Pulmonary TB Cases at a Tertiary Care Hospital in Southern Odisha

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Conflict of interest: Nil

Abstract

Introduction: Tuberculosis (TB) is a highly infectious disease caused by *Mycobacterium tuberculosis*. In India, more than 40% of the population is infected, and 1.8 million new cases occur every year, with over 70% affecting the economically productive age group. Multidrug-resistant TB (MDR-TB) refers to TB strains resistant to Isoniazid and Rifampicin. MDR-TB remains a major public health threat, with India accounting for over one-fourth of the global TB burden.

Aims and objectives: This study aims to detect TB and determine MDR-TB prevalence using fluorescence staining, culture, and nucleic acid amplification tests.

Methods: This prospective study was conducted at the Department of Microbiology and Department of Pulmonary Medicine, MKCG MCH, Berhampur, Odisha and Anti-TB Demonstration Centre, SCB Medical College, Cuttack. Sputum, bronchoalveolar lavage, or pleural fluid samples from suspected pulmonary TB patients were collected and screened for acid-fast bacilli using fluorescence microscopy and ZN staining. Positive samples underwent nucleic acid testing to confirm the presence of Mycobacterium tuberculosis.

Results: The analysis of Rifampicin and Isoniazid resistance genes showed that MUT3 (S450L) of the rpoB gene and katG MUT1(S351T) were responsible for 100% of the MDR-TB cases in the study. MDR-TB was more common in previously treated patients, but it could also occur as a primary infection in new patients.

Conclusion: MDR TB was a growing threat to global TB control programs, with previous TB treatment as a key risk factor. Early detection of drug resistance was crucial to prevent its rapid spread.

Keywords: Prevalence, MDR TB, Pulmonary TB, Rifampicin, Isoniazid.

Introduction

Tuberculosis (TB) remains a significant public health concern in India, with a high burden of cases and deaths **[1]**. India alone accounts for a quarter of the global TB incidence, and the disease predominantly affects adults, particularly men. Despite the high prevalence of TB infection in the population, only a small percentage of infected individuals progress to the active disease each year [1]. However, the infectious nature of the disease means that even a single case can spread the disease to multiple individuals, with potentially severe consequences for public health.

Efforts to control TB in India have included widespread testing, antibiotic treatment, and public health education campaigns to raise awareness of the disease and reduce stigma [2]. Despite these efforts, challenges remain in identifying and treating all cases of TB, particularly in marginalized populations and rural areas with limited access to healthcare services. The COVID-19 pandemic has also impacted TB control efforts, with disruptions to healthcare services and reduced access to testing and treatment. To reduce the burden of TB in India, continued investment in public health infrastructure and innovative approaches to TB diagnosis, treatment, and prevention are necessary [3]. This includes increasing access to high-quality healthcare services, improving diagnostic methods, promoting treatment adherence, and addressing social and economic factors contributing to the disease's spread. By working towards comprehensive and sustainable strategies to address TB, India can progress towards eliminating this major public health threat [4,5].

Tuberculosis (TB) remains a significant global public health challenge, particularly due to the emergence and spread of drug-resistant strains of the TB bacillus. The World Health Organization (WHO) and governments worldwide are taking great efforts to prevent and control TB. However, drug-resistant TB strains pose a major hurdle in TB control programs, with MDR and XDR-TB being the most severe forms. The estimated number of MDR and XDR-TB cases in 2021 was 4 per 100,000 and 1 per 100,000 population, respectively [1]. India has also seen a gradual increase in MDR-TB cases, with MDR-TB amongst new cases estimated at 2.84% and amongst re-treatment cases at 11.6%.

The irregular use of primary drugs for both drug-sensitive and resistant TB cases has led to the emergence of mutant TB bacilli acquiring resistance to primary drugs, making the treatment of MDR-TB more challenging. The treatment of MDR-TB is costly, involves potentially toxic drugs with more side effects, and requires a longer duration than the Directly Observed Treatment Short-course (DOTS) chemotherapy used for drug-sensitive TB [1]. Although MDR-TB occurs more frequently in patients who have taken primary anti-TB drugs in the past, it is also slowly being reported from new TB-suspected patients.

On the other hand, MDR-TB may replace all the drug-sensitive population of TB bacilli, rendering primary anti-TB drugs totally ineffective. Furthermore, the drug resistance can become more extensive, involving those drugs used to treat MDR-TB, leading to XDR-TB. The concept of XDR-TB was introduced by the Centre for Disease Control and Prevention (CDC) in March 2005. Early detection and appropriate treatment with second-line anti-tubercular drugs can prevent the emergence of XDR-TB [5].

Furthermore, drug-resistant TB poses a significant challenge to TB control programs, with MDR and XDR-TB being the most severe forms [4]. The irregular use of primary drugs for both drug-sensitive and resistant TB cases has led to the

emergence of mutant TB bacilli acquiring resistance to primary drugs, making the treatment of MDR-TB more challenging [4]. Early detection and appropriate treatment with second-line anti-tubercular drugs can prevent the emergence of XDR-TB. Therefore, it is essential to continue efforts to prevent and control TB, promote the appropriate use of anti-TB drugs, and monitor the emergence and spread of drug-resistant TB strains [6,7,8]. This study aims to detect Mycobacterium tuberculosis in clinical samples of suspected Pulmonary TB patients and determine the sensitivity of isolates to first-line anti-tubercular drugs such as INH and RIF. Additionally, the study aims to determine the prevalence of MDR-TB cases among the study population.

Patients and Methods

Research Design

This Cross-sectional observational study was carried out on participants who went to the Department of Microbiology of our hospital. Throughout these 693 Sputum samples collection process of Pulmonary Tuberculosis at the TB-Chest department. This conventional technique detects MTB, and Drug Susceptibility Testing (DST) was carried out at the Department of Microbiology. Based on the given information, this clinical study aimed at analyzing the sputum of patients. This study involves collecting two sputum samples, one in the morning and the other on the spot, from each patient. The volume of each sample is required to be at least 5 ml, and the collection should be done in sterile wide-capped containers before eating or drinking anything. This study also specifies the method for collecting sputum, which involves instructing the subjects to breathe deeply and cough low and deep to bring up the material from their lungs and deposit it into the container. This systematic approach for collecting and analyzing sputum samples from patients for further analysis or diagnostic purposes.

Inclusion and Exclusion criteria

The inclusion criteria refer to patients suspected of Pulmonary TB, who would typically need to meet certain inclusion criteria. The patient should have symptoms of TB, and the patient should have chest X-ray or CT scan results indicating suspected pulmonary TB. Pulmonary tuberculosis (TB) exclusion criteria refer that a person suspected of having TB may not be diagnosed. Some of these exclusion criteria include Anti Tuberculosis Treatment Extra pulmonary tuberculosis and absence of risk factors for TB exposure.

Statistical Analysis

The study used SPSS 25 for effective analysis. The continuous data have been expressed as mean +- SD, while prescript data have been expressed as frequencies and respective percentages. The study employed ANOVA as a tool for analyzing between several organizations was made using the total results, an estimate of sputum samples, and suspected Pulmonary TB. A significant value of 0.05 was the deduction for data to be considered significant.

Ethical Approval

The study was conducted at Maharaja Krishna Chandra Gajapati Medical and Hospital (MKCG MCH) in Berhampur, which was provided ethical clearance by Institutional Ethical Committee (IEC).

Results

Table 1 provides basic demographic information about the study participants. It shows that out of the 693 participants, 64% were male, and 36% were female. The age distribution of the participants shows that 8% were between 0-20 years, 38% were between 21-40 years, 27% were between 41-60 years, and 27% were above 60 years of age. Another sub-table shows the gender and age-wise distribution of patients whose samples were culture positive, with 74% male and 26% female.

Table 1: Baseline characteristics of Study Participants (N=693)

Gender-wise Distribution				
Gender	**Frequency**	**Percentage (%)**		
Male	442	64		
Female	251	36		
Total	693	100		
Gender-wise Distribution				
Age group (Years)	**Frequency**	**Percentage (%)**		
0-20	56	8		
21-40	263	38		
41-60	190	27		
Above 60	184	27		
Total	693	100		
Patients Whose Samples Were Culture Positive (N=168)				
Gender	**Frequency (Culture positive)**	**Percentage (%)**		
Male	**124**	74		
Female	44	26		
Total	168	100		
Age (in years)				
0-20	14	8		
21-40	52	31		
41-60	**76**	45		
> 60 years	26	16		
Total	168	100		
Participants Based on Sociodemographic Characteristics and Culture Positivity Status				
Gender	**Culture positive**	**Culture negative**	**p-value**	**Remarks (p<0.05: Significant)**
Male	124	318	0.001888	Significant
Female	44	207		
Age (in years)				
0-20	14	42		
21-40	52	211	0.00001	Significant
41-60	76	114		
> 60 years	26	158		

Table 2 provides information on the presence or absence of various risk factors in the study participants, including co-morbid conditions such as Diabetes Mellitus (DM), HIV positivity, Chronic Obstructive Pulmonary Disease (COPD), known history of contact with TB patients, and hypertension (HTN). The table shows that 74 participants had DM, 17 had HIV positivity, 23 had COPD, 42 had a known history of contact with TB patients, and 56 had hypertension. The p-values are also shown to indicate statistical significance, with values less than 0.05 indicating a significant association.

Table 2: Associated Risk Factors in Study Participants(N=693)

Risk Factors In Study Participants (N=693)				
Co-morbid condition	**Present**	**Absent**	**p-value**	**Remarks (p<0.05: Significant)**
Diabetic Mellitus (DM)	74	619	0.00001	Significant
HIV Positivity	17	676		
Chronic Obstructive Pulmonary Disease (COPD)	23	670		
Known History of Contact with TB patients	42	651		
Hypertension (HTN)	56	637		

Categories Of Patients as Per RNTCP Guidelines (N =693)					
New case	**Previously treated case**				**Total**
	Completely cured	Defaulter	Treatment failure	Relapse	
582	77	16	7	11	693

Table 3 provides information on the Ziehl-Neelsen (ZN) smear positivity status of the study participants, classified by smear grade (scanty, 1+, 2+, 3+) and new or previously treated cases. The table shows that out of the 218 participants, 178 were new cases, and 40 were previously treated cases. The ZN smear positivity rates were highest for participants with a smear grade of 3+ (28%) and lowest for those with a scanty (18%).

Table 3: ZN Smear Positivity Status of Study Participants (N=218)

Smear grade	**Category**		**Frequency (%)**
	New	**Previously treated**	
Scanty	34	6	40(18)
1+	49	9	58(27)
2+	45	13	58(27)
3+	50	12	62(28)
Total	178	40	218(100)

Pattern Of Growth on LJ Medium (N=693)		
Pattern of growth	**Frequency**	**Percentage (%)**
No growth	458	66
Contaminants	67	10
Mycobacterium tuberculosis	**168**	24
Total	693	100

: ZN Smear Status and Culture Status of Sputum Samples (NEW + PREVIOUSLY TREATED)					
Smear grade	**No. of samples**	**No. of culture positive on LJ**	**No. of culture-negative on LJ**	**% of Positivity**	**p-value**
Negative	475	6	469	1.3	0.00001
Scanty	40	22	18	55	
1+	58	42	16	72.4	
2+	58	44	14	75.9	
3+	62	54	8	87.1	
Total	693	168	525	24.2	
Total Positivity rate: 168/693 x 100 = 24.2%					

Table 4 provides information on the ZN smear and culture status of sputum samples, classified by smear grade (scanty, 1+, 2+, 3+) and new or previously treated cases. The table shows that out of the 582 new cases, 140 were culture positive, with a positivity rate of 24%. In contrast, out of the 111 previously treated cases, 28 were culture positive, with a positivity rate of 25%. The p-values are also shown to indicate statistical significance, with values less than 0.05 indicating a significant association.

Table 4: ZN Smear Status and Culture Status Of Sputum Samples (New Cases and Previously Treated Cases)

Smear grade	No. of samples	No. of culture positive on LJ	No. of culture-negative on LJ	% of Positivity	p-value	Remarks (p<0.05: Significant)
Negative	404	5	399	1	0.00001	Significant
Scanty	34	20	14	59		
1+	49	37	12	76		
2+	45	34	11	76		
3+	50	44	6	88		
Total	582	140	442	24		
Total Positivity rate: 140/582 x 100 = 24%						
Smear grade	**No. of samples**	**No. of culture positive on LJ**	**No. of culture-negative on LJ**	**% of Positivity**	**p-value**	**Remarks (p<0.05: Significant)**
Negative	71	1	70	1.4	0.00001	Significant
Scanty	6	2	4	33.3		
1+	9	5	4	55.5		
2+	13	10	3	76.9		
3+	12	10	2	83.3		
Total	111	28	83	25		
Total Positivity rate: 28/111 x 100 = 25%						

Discussion

The present study was conducted in the Department of Microbiology, M.K.C.G. Medical College, Berhampur, in collaboration with the Department of Pulmonary Medicine, MKCG MCH, Berhampur, and Anti-TB Demonstration & training centre (ATD & TC), Cuttack from September 2020 to August 2022, aimed to investigate the resistance patterns of Rifampicin and Isoniazid in clinically suspected Pulmonary TB patients. The study group included 693 patients, of which 64% were male, 36% were female, and the majority of the patients were 21-40 years old. Various co-morbidities encountered in the patients were Diabetes mellitus, HIV/AIDS, Hypertension, Chronic obstructive pulmonary disease, and known history of contact with TB patients.

The present study's findings were consistent with the study conducted by Sethi et al. in 2013, where the majority of the patients were males between 21-50 years of age [11]. They reported a total of 9.23% of patients to be seropositive for HIV. Christopher et al. [12] 2020 reported an increasing prevalence of diabetes in TB patients. In their study, 24% of the TB patients had diabetes. Gupta et al. [13]. in a study among rural South Indians, reported a higher prevalence of coexisting DM than HIV. The study highlights the need to screen and manage co-morbidities in TB patients to improve treatment outcomes [14]. This study reports a 74% positive

culture rate for smear-positive sputum samples after 8 weeks, which is lower than other studies that have reported positive rates ranging from 81% to 93% [15]. The discrepancies in culture positivity rates could be due to various factors, including patient population characteristics, sample collection and handling methods, and laboratory procedures. A negative culture result in a specimen with tubercle bacilli could be due to several reasons, such as treatment-induced loss of bacilli viability, low bacilli count, or laboratory contamination [15-17]. Therefore, clinicians should interpret negative culture results in the context of other diagnostic tests and patient characteristics to avoid missing a tuberculosis diagnosis [18,19].

Tuberculosis (TB) is a major public health problem in India. Several studies have investigated TB's relationship with age, sex, and drug resistance [20-22]. The present study revealed that patients aged 41-60 years were the most affected, followed by the age group of 21-40 years. Drug resistance is a major concern in the treatment of TB [23]. The present study found that the prevalence of MDR-TB was none in new patients and 2(7.1%) among previously treated patients [24-27]. The results showed that MDR-TB was more prevalent in previously treated patients, with a prevalence of 7.1%. This agrees with previous studies by Prakash Satpathy et al 20., Dasarathi et al.21, Chakraborty et al.22, and Shivekar et al23. This is comparable with previous studies conducted in various parts of Odisha. Large population-based studies conducted by RNTCP in states like Gujarat, Maharashtra, and Andhra Pradesh have estimated the prevalence of MDR-TB to be higher in retreatment cases than in newly diagnosed cases [30]. However, our findings are by observations from previous studies in India.

Some studies have reported a high prevalence of MDR-TB among new TB cases. For example, a study in the Sahariya tribe of Madhya Pradesh showed that, despite high TB prevalence, MDR-TB prevalence was 2.2% in newly diagnosed cases. However, in a few urban areas of Mumbai, the prevalence of MDR-TB in new cases was reported to be 24%. These findings highlight the importance of conducting regular surveillance of drug resistance patterns in different regions of the country [31]. The present study provides valuable insights into the relationship of TB with age, sex, and drug resistance in the study population. These findings can inform the development of targeted interventions to reduce the burden of TB in India. However, further studies are needed to investigate the prevalence of MDR-TB in different regions of the country, especially in new TB cases [14].

This study investigated the prevalence of drug-resistant tuberculosis (TB) among new and previously treated TB cases [32]. The TB rate was higher in males than in females, which may be related to the social behaviour of males in our society. None of the new TB cases was found to have MDR-TB. Resistance to any first-line anti-tubercular drug was observed in 1.4% of new cases and 28.6% of previously treated cases. The most common mutation associated with rifampicin resistance was the codon S450L(MUT3) in the rpoB gene, which was found in all cases of rifampicin resistance. The katG S351T mutation was associated with the two cases of isoniazid drug resistance [33]. The FL-LPA results were concordant with the drug resistance study by proportion method. These findings suggest that drug-resistant TB remains a significant public health concern, particularly among previously treated cases. The study's use of FL-LPA demonstrated its potential as a rapid and accurate method for identifying drug-resistance mutations. However, further research is needed to explore the effectiveness of FL-LPA in larger and more diverse populations [34].

Conclusion

In conclusion, controlling DR-TB is imperative for TB elimination as a whole. Early diagnosis of MDR-TB cases, improved case detection, treatment, and awareness among TB patients are necessary to maintain the area's low level of MDR-TB prevalence. The diagnosis of drug resistance should be standardized, and a multi-pronged approach, including universal MDR testing, scaling up DST for all first-line drugs, and incorporating testing facilities, should be implemented to combat this growing epidemic. This study has limitations, including potential bias in estimating drug resistance in previously treated cases, non-representativeness of the national population, and small sample sizes. Nonetheless, the study suggests the persistence of a low level of MDR-TB prevalence in the area. A multi-pronged approach is required to address the problem of the high burden of DR-TB in India. Universal MDR testing of TB patients needs to be rapidly scaled up to combat this growing epidemic. As an immediate measure, MDR testing of previously treated patients using CBNAAT/LPA should be prioritized over other risk groups. In the long run, universal testing should be employed to detect resistance against all first-line drugs and incorporate testing facilities for the same after careful consideration of cost and accessibility to reduce the turnaround time

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