

## A Study on Clinical Profile of Patients with Drug Resistant Tuberculosis in a Tertiary Care Hospital.

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### BACKGROUND:

Drug resistant TB is a global health problem and is a menacing threat especially in developing countries like India. The emergence of drug resistant TB is due to incomplete or improper treatment, resulting in a hindrance in the TB controlling programs in India. The most common causes of acquired drug resistance in *M.tuberculosis* are inadequate chemotherapeutic regimens and noncompliance by patients during therapy.

Cartridge-based nucleic acid amplification test (CBNAAT) is a recently introduced polymerase chain reaction (PCR) based method for detection of TB.

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### I. Introduction:

Decades after the discovery of the *Mycobacterium tuberculosis* (MTB) organism, tuberculosis (TB) remains a major cause of morbidity and mortality in several developing countries. In the 1990s, control of TB has been further complicated by an increase in the incidence of drug-resistant strains of *M.tuberculosis* which have been found in both developing and industrialized countries.

Multidrug resistant tuberculosis (MDR-TB) is tuberculosis resistant to isoniazid and rifampicin.

3.7% of new cases and 20% of previously treated cases were estimated to have multi-drug resistant tuberculosis worldwide. In India MDR-TB in new cases has been reported to be nearly 3% and in treated patients has been reported to be 12%.

The use of molecular methods has increased the yield of diagnosis of drug resistant tuberculosis exponentially.

CBNAAT is a *Mycobacterium tuberculosis*-specific automated, cartridge based nucleic acid amplification assay, having fully integrated and automated amplification and detection using real-time PCR, providing results within 100 minutes. It is a highly specific test as it uses 3 specific primers and 5 unique molecular probes to target the *rpoB* gene of *M. tuberculosis*, which is the critical gene associated with rifampicin resistance. It also detects rifampicin resistance as it targets the *rpoB* gene of mycobacteria.

No cross-reactions have been observed with many other bacterial species tested, including a comprehensive panel of mycobacteria, thereby excluding non-tubercular mycobacteria (NTM).

Being a PCR based method, clinical validation trials done in four distinctly diverse settings have shown that 92.2 percent of culture-positive patients were detected by a single CBNAAT test with a specificity of 99 percent as compared to the sensitivity of a single direct sputum smear of 59.5%.

### II. Aims and objectives:

- ❖ To study the demographic profile in patients with drug resistant TB.
- ❖ To study the history of TB treatment in drug resistant cases and their comorbidity profile.
- ❖ To study the drug resistance pattern.

### III. Methods and Methodology:

#### STUDY DESIGN:

This is a hospital record based retrospective study.

#### STUDY SUBJECTS AND STUDY PERIOD:

50 patients who were admitted in medical wards and diagnosed as Drug resistant TB during the period of January 2019 to June 2019 formed the study subjects.

#### STUDY SETTINGS:

Medical wards, DOTSCentre in SVRRGGH, TIRUPATI.

**METHODOLOGY:**

All cases who were diagnosed as drug resistant tuberculosis by Cartridge based nucleic acid amplification test,irrespective of type of tuberculosis were included in this study,after the approval of local institutional ethics committee.

The details of patients were obtained from the concerned records and relevant history is retrieved,specifically any past history of tuberculosis.

The relevant information on drug resistance,as proved by gene expert testing is noted.It is a record based study.Confidentiality of the patients was maintained.

Sputum for CBNAAT- One sputum sample of 1 ml was collected in a sterile container and was analysed by CBNAAT on Xpert® MTB/RIF manufactured by Cepheid, endorsed by WHO (2010).

The sample was diluted with three times the reagent, incubated at room temperature and loaded into the cartridge for automated analysis with results in 100 minutes.

Detection of mycobacteria and rifampicin resistance was carried-out in the same setting.

Rifampicin resistant samples were further analysed by Line Probe Assay(LPA).

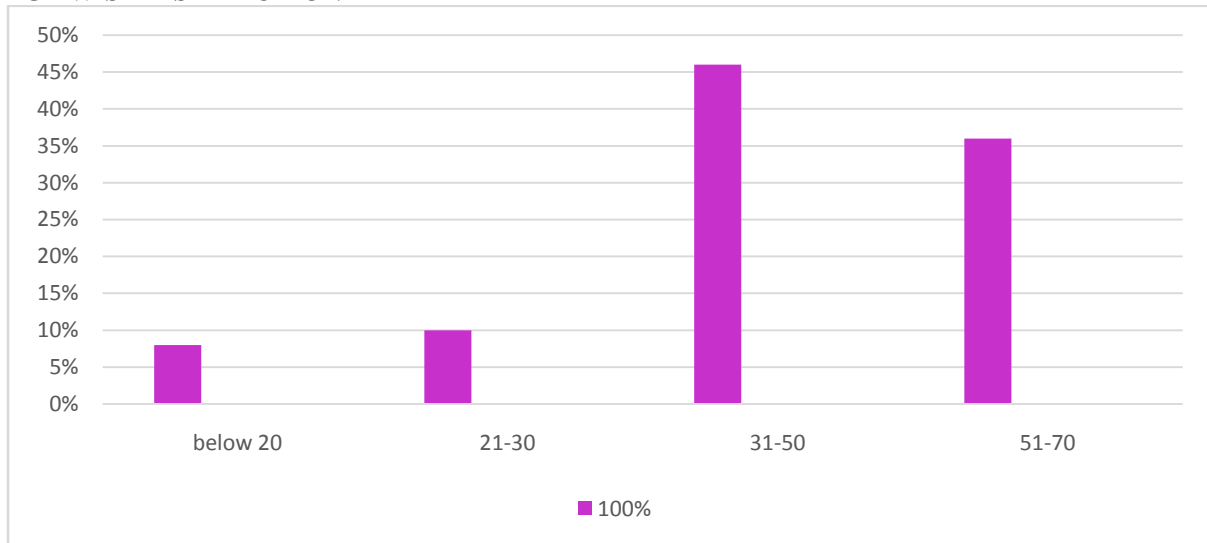
**STATISTICALANALYSIS:**The data was analysed using excel sheet and SPSS software.

**GENDERWISE DISTRIBUTION**

	frequency	percent
Female	14	28%
Male	36	72%
Total	50	100

There was a predominance of males (72%) as against females (28%).

**AGE WISE DISTRIBUTION**



About 46% are in age group between(31-50)years.This was the economically productive age group.

**DISTRIBUTIONOF TYPEOF TP PATIENTS**

	Frequency	percent
Newly diagnosed	28	56
Previously treated	22	44

	Frequency	percent
Defaulters	9	18
Relapse	8	16
Treatment failure	5	10

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44% of patients were previously treated for TB. Out of them, 18% were defaulters, 16% relapse and 10% were treatment failure cases.

**DIABETIC STATUS OF PATIENTS**

frequency	
Patients with DM	31
Patients without DM	19

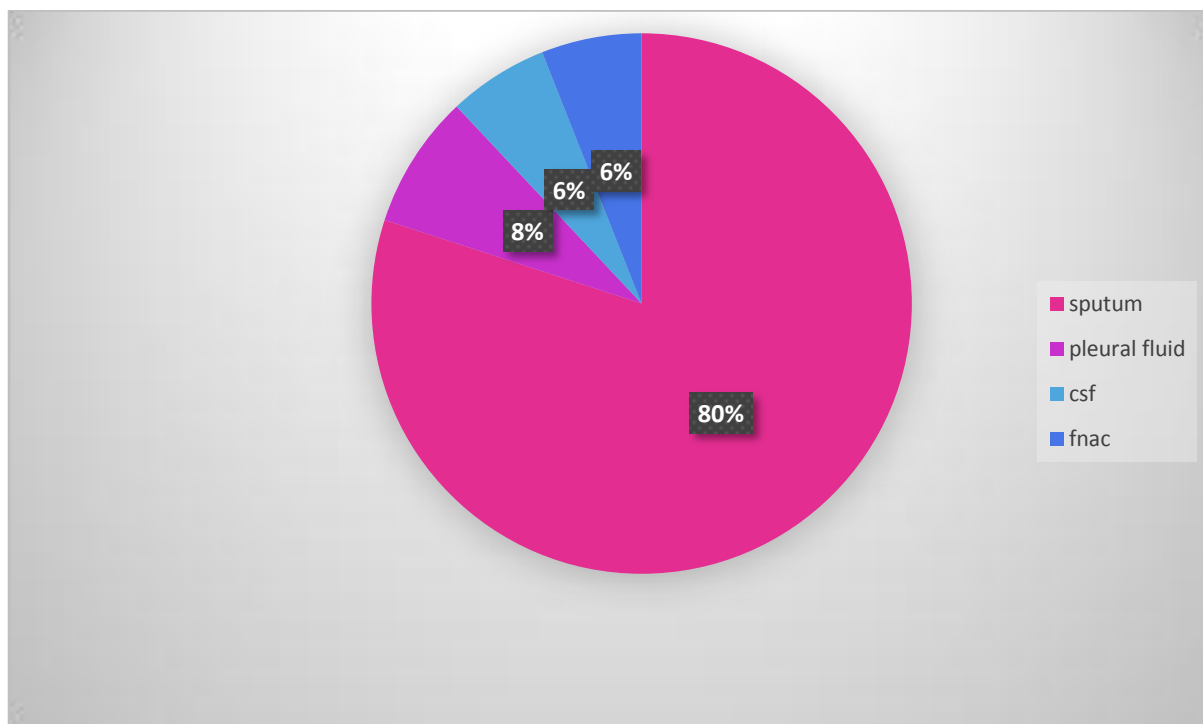
62% of patients were diabetic

**HIV STATUS OF PATIENTS**

	frequency	percent
HIV positive	5	10
HIV negative	45	90

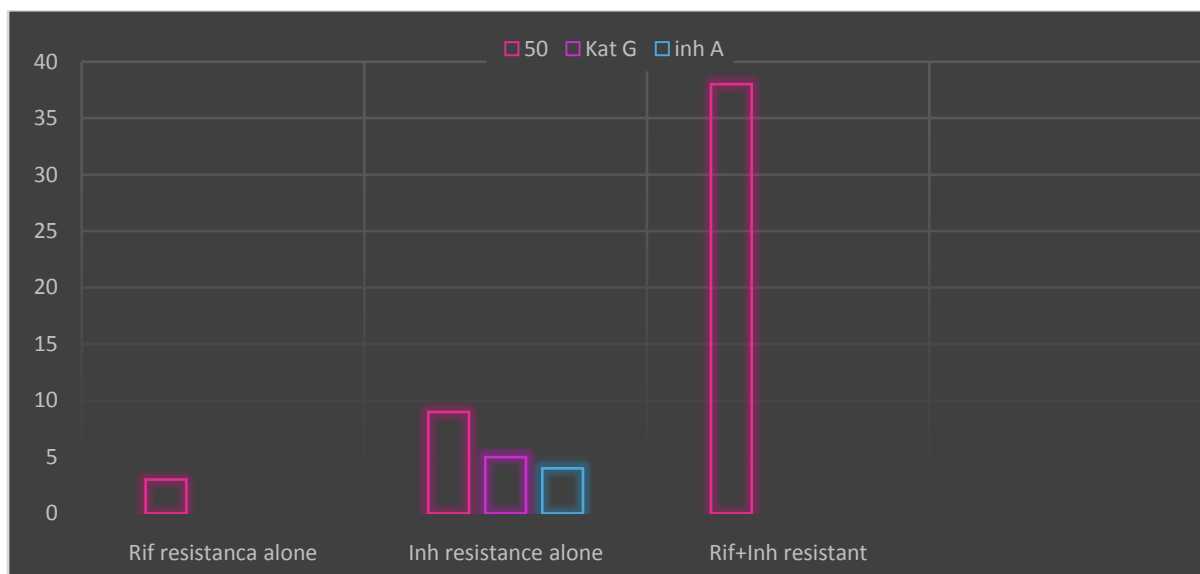
Only 10% of patients were HIV positive.

**SITE OF DRUG RESISTANT TUBERCULOSIS**



There were 40 cases of pulmonary tuberculosis, while 10 were extrapulmonary TB cases involving tuberculous pleural effusion, TB meningitis and lymph node.

## DRUG RESISTANCE PATTERNS



### IV. Results:

A total of 50 patients were included in this study. All patients who were diagnosed as drug resistant TB by CBNAAT of samples including sputum, pleural fluid, cerebrospinal fluid, lymph node were included in this study.

Among 50 patients, 72% are males comparatively more than females (28%).

Age of patients range from 12-72 years with mean age 42.9. About half (46%) of the patients are in productive age group of 30-50 years.

HIV positive patients are found to be 10%, while patients with Diabetes state are 62%

44% of patients were previously treated for TB. Among them, 40.9% were defaulters, 36.3% relapse and 22.7% were treatment failure cases. All these 44% received treatment under DOTS.

Of the samples found to be positive with CBNAAT, 80% were sputum samples, 8% pleural fluid, 6% Cerebrospinal fluid, and lymph node 6%.

Drug resistance patterns observed are 76% Isoniazid and Rifampicin resistance, 18% are only Isoniazid resistant and only 6% are found to be resistance to Rifampicin alone. Of the isoniazid resistant patients, 55.5% are found to be having resistance to KatG gene and 44.4% for inhA gene.

### V. Discussion:

Drug resistant TB is a global health problem and is a menacing threat especially in developing countries like India.

The emergence of drug resistant TB is due to incomplete or improper treatment, resulting in a hindrance in the TB controlling programs in India.

The demographic profile of MDR-TB patients in our study was similar to other studies, with majority of male patients in the economically productive age group (31-50 years). Concentration of the patients in this most productive age group gives the idea regarding adverse social and economical consequences for their affected families, communities, states and country as a whole.

About 44% patients were previously being treated under RNTCP (under CAT II) i.e. these patients were first treated under CAT I, but due to either failure or relapse or default, they were being retreated under CAT II. Out of these 22 patients, 22.72% were included under CAT II due to CAT I treatment failure, 36.36% due to relapse after successfully completing CAT I treatment and 40.9% due to defaulting CAT I treatment.

In our study, we observed that among previously treated patients, near equal proportion of cases were observed for relapse and defaulters followed by treatment failure.

Sharma S. K et al in their study reported that among previously treated drug resistant TB patients, maximum (75.00%) were of relapse followed by 16.8% defaulter and of failure (8.2%).

In another study by Bhatt G et al revealed almost equal proportion of relapse (30.9%), defaulter (28.4%) and failure (27.2%) patients among previously treated drug resistant TB patients.

Among all 50 resistant TB patients, only 10.00% were HIV positive and rest 90.00% were HIV negative. Very less proportion of HIV positive patients among drug resistant TB patients is also recorded by Kapadia VK et al (1.2%), Bhatt G et al (6.34%), CeatanoMota P et al (11%).

Additionally all of them found no significant statistical association between HIV status of patients and treatment outcome.

Out of those 50 patients treated, 38 (76.00%) had MDR TB (resistant to both isoniazid and rifampicin) and remaining 3 (6.0%) were resistant to only rifampicin and not to isoniazid. Past studies on drug resistance have shown that rifampicin resistance is seldom detected alone and 90 % of rifampicin resistant patients turn out to be MDR-TB. Similar findings were reported in a study by Kalpesh Jain et al where 93.00% patients had MDR TB and 7.00 % were resistant to only rifampicin. They also observed that the pattern of drug resistance was not significantly associated with the outcome of treatment with STR.

Of the 9 cases of isoniazid monoresistance, 55.5% were found to be resistant to katG gene and 44.4% for inhA gene. According to Georghiou et al, nearly 90% of INH resistance in India is caused by *KatG* mutations, associated with high-level resistance and poor treatment outcomes.

In general, multidrug resistance is acquired in two steps, with the first step being the development of isoniazid resistance rather than rifampin resistance, suggesting that rifampin resistance can be used as a surrogate marker for the detection of MDR *M. tuberculosis*.

RNTCP adopted CBNAAT in India in April 2012. In the government set up, CBNAAT was launched in 2012 as a pilot project in Maharashtra by the State tuberculosis department. By the end of 2012, under EXPAND-TB project, 12 CBNAAT labs were established all over India across different states. CBNAAT is currently being made available at more centres with the aim to establish it at every hospital associated with a medical college throughout the country and also in private institutions under RNTCP. Impact study on CBNAAT found that additional 2,493 patients were diagnosed of pulmonary TB by CBNAAT in 2012 among more than 30,000 TB suspects as compared to sputum microscopy.

The WHO policy guidance on the use of CBNAAT was issued in December 2010. The recommendations were that it should be used as the initial diagnostic test in individuals at risk of having MDR-TB or HIV-associated TB, and that it could be used as a follow-on test to microscopy in settings where MDR and/ or HIV is of lesser concern, especially in smear-negative specimens

## VI. Conclusion:

Drug resistant tuberculosis affects the economically productive age group. Pulmonary drug resistant cases exceed Extra-pulmonary cases. Primary drug resistant cases exceed acquired drug resistant cases. The efficacy of daily DOTS regimen in reducing the burden of DR-TB is yet to be studied.

The burden of this globally increasing health problem can be reduced by stringent measures like early diagnosis, early treatment, and improving drug compliance

## LIMITATIONS:

Our study has a limitation as it has small number of patients, and patients with DR-TB proved by CBNAAT but not culture proven were not included in the study. Thus, we may have missed out on some patients who may have had DR-TB.

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