



## Original Research Article

# Determinants of MDR-TB in a metropolitan city of Karnataka: A case control study

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### ABSTRACT

**Introduction:** In India with its current prevalence of 2.8% and 12% among newly diagnosed and previously treated TB cases respectively, MDR-TB poses a greater challenge in the management; requiring longer duration of treatment, use of second-line drugs that are more costly with severe side effects.

**Objective:** To study the determinants of MDR-TB in a metropolitan city.

**Methodology:** A Case Control study was conducted in Bengaluru, Karnataka between April 2014-February 2015 on 52 MDR-TB cases and 53 controls (Non MDR-TB cases). Univariate analysis including descriptive statistics along with Chi-square test and Multivariate logistic regression were used to analyse the data.

**Results:** Proportion of having  $\geq 2$  previous episodes of TB among MDR-TB cases were 65.3% as compared to 40.8% among non MDR-TB cases (AOR 2.9; 95% CI 1.15-7.51), proportion of treatment default/treatment failure in the previous first episode of TB among MDR-TB cases was 67.3% as compared to 46.9% among non MDR-TB cases (AOR 6.0; 95% CI 2.0-18.2).

**Conclusion:** Two or more previous episodes of TB and treatment default/treatment failure in the previous first episode of TB were found to be independent determinants of MDR-TB. Hence a prompt approach in treating TB and early diagnosis of MDR-TB will reduce the disease severity.

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## 1. Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the 2 most effective first-line anti-TB drugs. MDR-TB is treatable and curable by using second-line drugs. However, second-line treatment options are limited and require extensive chemotherapy (for at least 9 months and up to 2 years) with medicines that are expensive and toxic and hence need to be supported by counselling and monitoring for adverse events.

In 2019, MDR-TB remains a public health crisis and a health security threat. A global total of 2,06,030 people with multidrug- or rifampicin-resistant TB (MDR/RR-TB) were detected and notified in 2019, a 10% increase from 1,86,883

in 2018. About half of the global burden of MDR-TB is in 3 countries – India, China and the Russian Federation.<sup>1</sup> The current prevalence of MDR-TB in India is 2.8% and 12% among newly diagnosed and previously treated TB cases respectively. In 2018, India had an estimated 130,000 drug resistant TB cases of which, only 44.8% (around 58,347) were diagnosed. Of these 46,569 or around 35.8% received treatment.<sup>2</sup> In order to meet the SDG Target 3.3 to end TB epidemic by 2030, we need to reduce TB incidence rate by 80% and TB deaths by 90% as compared with levels in 2015. There is an urgent need to speed up and broaden access to effective treatment through expansion of Drug Susceptibility Testing (DST) and patient centred models of care. This will not only save lives but can also reduce the risk of transmission in the community, including the family members. Studying the determinants of MDR-TB will help identify the factors that could have probably

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contributed to the development of drug resistance and in turn help the policy makers and programme managers to address the problem of MDR-TB more effectively.

## 2. Objective

To study the determinants of MDR-TB in a metropolitan city of Karnataka.

## 3. Materials and Methods

### 3.1. Study design

A case control study was conducted between April 2014-February 2015 at District TB Centre (DTC), Bengaluru, Karnataka under the Bruhath Bengaluru Mahanagara Palike (BBMP) – city municipal corporation, covering 14 Tuberculosis Units (TUs). Cases were MDR-TB cases diagnosed with culture and drug susceptibility test (DST) at the Intermediate Reference Laboratory (IRL), Bengaluru & registered in BBMP for MDR-TB treatment during the period January 2013- June 2014. Controls were Non MDR-TB cases (confirmed with culture and DST at the IRL, Bengaluru) on treatment in the same BBMP area during the same period. All cases were aged  $\geq 14$  years.

### 3.2. Sample size

Among the various determinants of MDR-TB, it was found that poor compliance to previous treatment was one of the important determinants of drug resistance. In a study conducted by Sharma et al.,<sup>2</sup> it was observed that poor compliance to previous treatment was one of the important risk factors associated with MDR-TB. The study reported the proportion of poor compliance to previous treatment among MDR-TB cases to be 63% as compared to 9% in non MDR-TB cases. Multivariate analysis identified poor past compliance to treatment (OR 6.6; 95% CI 2.0-21.5) as an independent predictor of MDR-TB. In our study, expecting similar results, keeping the power of the study at 95% and 95% Confidence level, the study required a minimum of 52 subjects in each group. Cases and controls were selected at least in the ratio of 1:1.

### 3.3. Data collection

Ethical clearance was taken from the Institutional Ethical Committee. Prior permission was obtained from the District Tuberculosis Officer (DTO) of Bengaluru DTC. Cases and controls were identified from the DTC registry and traced to their residence with the help of Senior Treatment Supervisor (STS) STS, Health Visitor (HV) and DOTS provider of the respective TU, DMC and PHI. Care was taken to select the controls from the same TU area where the case was identified. Confidentiality of the patient's personal details was assured by the interviewer. Both cases and controls were interviewed at their residence or at the

nearest TU/ PHI (based on subject's choice) after assessing the environmental determinants of the residence. After obtaining written consent, a pre-designed, semi structured questionnaire consisting of questions on socio-demographic and clinical determinants was administered to the study subjects.

### 3.4. Statistical analysis

All qualitative variables like age group, gender religion, educational status, marital status, employment status, socio economic status etc., were expressed in terms of proportions. Univariate analysis using Chi square test was done to find out the association between the various determinants of MDR-TB in cases and controls. Odds ratio and 95% C.I were estimated. All those variables which had a p value  $\leq 0.2$  were included in the Forward Logistic regression analysis, to find out the independent determinants of MDR-TB. Determinants with  $P < 0.05$  was considered as having a significant association with MDR-TB and AOR with 95% CI was used to measure a degree of association.

## 4. Results

A total of 105 subjects were studied which included 52 MDR-TB cases and 53 non MDR-TB cases. Median age was 35 [IQR: 26-50] years among MDR-TB cases and 37[IQR: 28-47] years among non MDR-TB cases. Females were 26 (50%) and 14 (26.4%) among MDR-TB and non MDR-TB cases respectively. (Table 1)

On univariate analysis, proportion of females among MDR-TB cases were 50% as compared to 26.4% among controls. Further lower socio-economic class was found to be protective. (Table 1)

On univariate analysis, proportion of  $\geq 2$  previous episodes of TB among MDR-TB cases was 65.3% as compared to 40.8% among controls. Proportion of TB patients who had approached private health care facility during previous first episode of TB was 40.8% among MDR-TB cases as compared to 20.4% among controls. Proportion of TB patients with history of treatment default/failure in previous first episode of TB was 67.3% among MDR-TB cases as compared to 46.9% among controls. (Table 2)

$N=49$ . Stepwise forward logistic regression analysis,  $P < 0.05$  is considered statistically significant., \*\*  $p=0.001$  to  $<0.01$  Adjusted for gender, religion, employment status, socio-economic status, smoking, alcohol consumption, tobacco chewing, HIV status and health care facility approached during previous first episode of TB.

On multivariate logistic regression analysis, numbers of previous episodes of TB and treatment outcome of first episode of TB were found to be independent determinants of MDR-TB. TB patients with two or more previous episodes of TB were 2.9 times at higher risk of developing MDR-TB

**Table 1:** Socio-demographic characteristics of MDR-TB cases and controls

Determinant	Level	MDR-TB (N=52)	Non MDR-TB (N=53)	Unadjusted	
		n (%)	n (%)	OR(95% CI)	p value
Age (years)	≤ 36	27 (51.9)	26 (49.1)	1.1(0.52-2.41)	0.769
	> 36	25 (48.1)	27 (50.9)	1	
Gender	Female	26 (50)	14 (26.4)	2.8(1.23-6.31)	0.013
	Male	26 (50)	39 (73.6)	1	
Religion	Others	22 (42.3)	16 (30.2)	1.7(0.8-3.8)	0.12
	Hindus	30 (57.7)	37 (69.8)	1	
Education	Not literate	9 (17)	9 (17.3)	1.0(0.37-2.82)	0.965
	Literate*	43 (82.7)	44 (83)	1	
Employment status	Not gainfully employed §	25 (48.1)	16(30.2)	2.1(0.96-4.77)	0.06
	Gainfully employed	27 (51.9)	37 (69.8)	1	
Socio economic status <sup>§</sup>	Lower	35 (67.3)	47 (88.7)	0.3(0.09-0.74)	0.008
	Upper	17 (32.7)	6 (11.3)	1	
Marital status	Others #	17 (32.7)	17 (32.1)	1.0(0.45-2.33)	0.946
	Married	35 (67.3)	36 (67.9)	1	
Type of family	Non-nuclear <sup>@</sup>	23 (44.2)	20 (37.7)	1.3(0.6-2.85)	0.5
	Nuclear	29 (55.8)	33 (62.3)	1	
Type of house	Semi pucca/ kaccha	19 (36.5)	23 (43.4)	0.8(0.34-1.64)	0.473
	Pucca	33 (63.5)	30 (56.6)	1	
Type of residence	Rented/ Immigrated	30 (57.7)	29 (54.7)	1.1(0.52-2.44)	0.76
	Own house	22 (42.3)	24 (45.3)	1	

\*Primary to intermediate/diploma/graduate & above, §home maker/student/unemployed, §upper class = upper + upper middle, lower class = lower middle + upper lower + lower, #never married /widow/ widower / separated/divorced, @joint family/three generation family/others OR – odds ratio, CI- confidence interval, Chi square test. P<0.05 is considered statistically significant

**Table 2:** Clinical characteristics of MDR-TB cases and controls

Determinant	Level	MDR-TB (N=52)	Non MDR-TB (N=53)	Unadjusted	
		n (%)	n (%)	OR (95% CI)	P value
Diabetes mellitus	Present	13(25)	11(20.8)	1.3(0.51-3.17)	0.604
	Absent	39(75)	42(79.2)	1	
H/o Close contact with TB patients	Present	23(44.2)	21(39.6)	1.3(0.60-2.82)	0.512
	Absent	29(55.8)	32(60.4)	1	
No. of previous episodes of TB*	≥2	32(65.3)	20(40.8)	2.7(1.20-6.19)	0.015
	1	17(34.7)	29(59.2)	1	
Health care facility approached in previous first episode of TB*	Private	20(40.8)	10(20.4)	2.7(1.09-6.61)	0.028
	Govt./ RNTCP	29(59.2)	39(79.6)	1	
Duration of delay in diagnosing previous first episode of TB *	>1month	42(85.7)	38(77.6)	1.7(0.61-4.94)	0.3
	≤1month	7(14.3)	11(22.4)	1	
Duration of previous first anti TB treatment*	<6 months	7(14.3)	8(16.3)	0.9(0.28-2.57)	0.8
	≥6 months	42(85.7)	41(83.7)	1	
Treatment outcome of previous first episode of TB *	failure/ discontinued	33(67.3)	23(46.9)	2.3(1.03-5.29)	0.041
	Cured/ completed	16(32.7)	26(53.1)	1	

\* N=49, @ family/ relatives, §workplace/neighbours/servants, &N= 23 in cases and N=21 in control I, OR – odds ratio, CI- confidence interval. Chi square test. P<0.05 is considered statistically significant

**Table 3:** Multivariate logistic regression analysis of determinants of MDR-TB (cases) as compared with Non MDR-TB (controls)

Determinant Level		MDR-TB (N=52) n (%)	Non MDR-TB (N=53) n (%)	Odds ratio (95% C.I)	
				Crude	Adjusted
No. of previous episodes of TB*	≥2	32(65.3)	20(40.8)	2.7(1.20-6.19)	2.9(1.15-7.51)**
	1	17(34.7)	29(59.2)	1	1
Treatment outcome of previous first episode of TB *	Treatment failure/ discontinued	33(67.3)	23(46.9)	2.3(1.03-5.29)	6.0(2.0-18.2)**
	Cured/ treatment completed	16(32.7)	26(53.1)	1	1

as compared to those with just one previous episode of TB. Also TB patients who had either discontinued treatment or had treatment failure at previous first episode of TB were 6 times at higher risk of developing MDR-TB as compared to those who were either declared cured or had completed treatment.

## 5. Discussion

In the present study, the median age among MDR-TB cases was 35[26-50] years, of which 51.9% belonged to 20-39 years age group, indicating that younger age groups were more likely to develop MDR-TB than their older counterparts. With the introduction of Rifampicin in recent decades, TB in the young is more likely to be acquired at time when MDR strains are more widely circulated. Age-related differences in treatment adherence are also possible, as younger patients are often occupied by study, work or other activities on a daily basis, in contrast with the more sedentary lifestyle post-retirement.<sup>3</sup> Similarly in several other studies<sup>4-9</sup> it was found that younger age groups (<40 years) i.e., between 25–44 years were more likely to develop MDR-TB.

In our study, females were found to be 2.8 times at higher risk of developing MDR-TB as compared to males. Association of female gender with MDR-TB could be related to the fact that women spend a long period of time caring for other family members with MDR-TB in the households. The increased number of females contracting MDR-TB could also be explained by the fact that the diseased women participation is lessened in household activities and they avoid seeking treatment unless and until the disease is far advanced and beyond control.<sup>10-12</sup> The social stigma attached with the disease leads to delay in TB diagnosis and DST, making treatment more difficult and inappropriate chemotherapeutic regimens more likely.<sup>11</sup>

In the present study, 35(67.3%) of the MDR-TB cases belonged to lower socioeconomic status compared to 25 (47.2%) among controls. But it is also worthwhile to notice that, 32.7% of MDR-TB cases belonged to upper class (upper or upper middle class) compared to 11.3% among controls. This indicates that the prevalence of MDR-TB is rising even among upper socio-economic class. This observation is related to the higher educational status

observed among the cases. Higher education, higher SES leads to more people seeking private health care which might lead to delay in diagnosis and prompt treatment. Moreover patient compliance is also questionable, as there is no way of cross checking them.

In the present study, TB patients with two or more previous episodes of TB had 2.9 times higher risk of developing MDR-TB than those with single or no previous episode of TB (AOR 2.9; 95% CI 1.15- 7.51, P= 0.001) This could have led to drug resistance in these patients over the course of time. A study conducted by Wahab et al.<sup>8</sup> and Chen et al in China<sup>13</sup> showed that more than three prior episodes of anti-TB treatment (more than 2 months of continuous treatment as one episode) (AOR 5.57, 95% CI 2.38–13.00) associated with MDR-TB in previously treated TB patients. Various studies have revealed that previous treatment of tuberculosis creates an opportunity for resistant MTB mutant to dominate; resulting in management of cases a challenge and hence was strongly associated with MDR TB.<sup>3,4,9,14-17</sup> Also prior anti-TB exposure suppresses the growth of susceptible bacilli, but on the other side, it could permit suitable circumstances for the multiplication of pre-existing drug resistant mutants. Non-compliance was probably due to lower education, awareness about the disease and lower socioeconomic status.

Our study also revealed that subjects who had either discontinued their treatment or had treatment failure of previous first episode of TB were 6 times at higher risk of developing MDR-TB compared to those who were either declared cured or had completed treatment (AOR = 6; 95% CI 2.0-18.2, p <0.01). This is similar to a study conducted by Tenzin et al.<sup>18</sup> and Biru et al.<sup>19</sup> which revealed that treatment failure TB cases (AOR: 4.2, 95% CI: 1.1–15.5) and relapsed TB cases (AOR: 4.8, 95% CI: 1.3–18.1) were independent factors associated with DR-TB. Rigorous patient follow-up and monitoring, improving patient counselling and communication, alternative supervision and choice of DOTS provider, and family member education may help promote compliance.<sup>18</sup>

## 6. Conclusion

Two or more previous episodes of TB and treatment default/treatment failure in the previous first episode of TB

were found to be independent determinants of MDR-TB. Hence a prompt approach in treating TB and early diagnosis of MDR-TB will reduce the disease severity.

## 7. Source of Funding

None.

## 8. Conflict of Interest

The authors declare that there is no conflict of interest.

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