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Study of drug resistance in pulmonary tuberculosis cases in south coastal Karnataka

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Abstract The present cross-sectional study was conducted for the first time from the Udupi district of coastal Karnataka to know the prevalence of drug resistance and comparative analysis of MDR and non-MDR cases of pulmonary tuberculosis. Details of 862 smear positive cases of pulmonary tuberculosis with age ≥ 15 years from 12 designated microscopy centres of the Udupi district were studied. Initially 2 sputum samples trailed by one follow-up sample were collected from each patient and processed for culture and drug sensitivity on the Lowenstein-Jensen medium. A total resistance of 33.4% was observed that includes the mono-resistance of 22.5%, multidrug resistance (MDR) of 6.3% and extensive drug resistance (XDR) of 0.3%. Significant odds ratio (OR) was observed in category 2 cases (OR 3.9) for the development of MDR tuberculosis. A significant statistical association was observed using Fisher's exact test while comparing mortality rate (19.3% vs. 1.8%), treatment failure (8.8% vs. 3.8%) and cure rate (68.4% vs. 85.4%) between MDR and non-MDR cases ($p < 0.001$). Category 2 patients are important risk factors for the development of MDR in pulmonary tuberculosis. Due to high mortality and low cure rate in MDR

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cases it is imperative to know the drug sensitivity report before institution of anti-tubercular treatment.

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1. Introduction

Tuberculosis (TB) a disease caused by *Mycobacterium tuberculosis* complex remains the cause of highest mortality in humans, leading to three million deaths annually, about five deaths every minute [1]. Pulmonary tuberculosis (PTB), the commonest form of TB is characterised by the involvement of lung parenchyma resulting in nodule formation in the lungs. India on an average accounts for nearly 25% of the global burden of tuberculosis and 29% of mortality due to tuberculosis [1].

Although the phenomenon of drug resistance in *M. tuberculosis* was observed as early as 50 years ago, the spread of multi-drug resistant tuberculosis (MDR) and emergence of extensively drug resistant tuberculosis (XDR) is threatening to destabilize global tuberculosis control [2]. India is also witnessing an increase in the number of MDR cases being reported from many parts of the country [3,4]. An updated report from WHO in 2013 estimated prevalence of 3.6% MDR tuberculosis in newly diagnosed cases and 20% in previously treated cases [5]. Though there is an increase in drug resistance, testing for MDR status is done in very few centres. Rowland has reported that fewer than 5% of new or retreatment cases are tested for drug sensitivity and an estimated 16% of the patients with MDR tuberculosis are receiving inappropriate treatment [6].

There are few well planned epidemiological studies from the states of Tamil Nadu, Maharashtra [7] and Gujarat [8]. However, studies available from the referral hospitals of Karnataka [9,10] show a much higher burden of MDR TB and it cannot be extrapolated to the community. The knowledge of drug resistance in PTB cases helps us to know the exact burden of MDR status in this area and assists in future to plan national control measures and the treatment strategies in the case of pulmonary tuberculosis.

Hence, a first community level study was undertaken to study the prevalence of drug resistance, comparison of MDR and non-MDR cases and to know the outcomes of treatment in PTB patients of the Udupi district in the south-western coastal area of Karnataka.

2. Methodology

2.1. Study settings

The cross-sectional study was carried out in the Department of Microbiology of a tertiary care centre of south-west coastal Karnataka in liaison with the district tuberculosis office during the period of September 2011–August 2014. Ethical clearance for the study was obtained from the institutional ethics committee.

2.2. Sample collection

A total number of 990 cases of smear positive PTB patients with ages ≥ 15 years from Designated Microscopy Centres of the Udupi district (including centres of three talukas and district tuberculosis centre), Karnataka were included in the study. Out of the 990 cases, cultures of samples from 28 cases had been contaminated, data could not be collected completely for 33 cases who denied participation, 37 cases were lost to follow up either due to mortality or switching over to private treatment and about 30 samples were culture negative after eight weeks of incubation. Hence the data for the remaining 862 cases as per the sample size calculation are presented in the study. Two sputum samples-one spot and one early morning sample were initially collected from each patient and the follow-up sample was collected after 3 months of the anti-tuberculosis therapy (ATT). The HIV status was determined for all the patients without failure under the revised national tuberculosis control programme with a spot test (Comb Aids, Span Diagnostics, India). The demographic data of all the cases were obtained by the interviewer through a pre-designed questionnaire. No other forms of tuberculosis were evaluated in the study.

2.3. Sample processing

All the sputum samples were transported to our lab in the cold chain. Decontamination and concentration of the samples were done using the modified Petroff's method [11]. Samples were cultured on Lowenstein-Jensen media, incubated for 4–8 weeks and the growth was confirmed with the help of MPT 64 antigen detection kit as

M. tuberculosis. (SD Bioline TB Ag MPT64, Standard Diagnostics, Inc., Korea).

2.4. Drug sensitivity testing

First line drugs streptomycin (4 µg), isoniazid (0.2 µg), rifampicin (40 µg), and ethambutol (2 µg) and second line drugs capreomycin (40 µg), kanamycin (30 µg), amikacin (40 µg), ofloxacin (2 µg), and ethionamide (40 µg and 57 µg), were used for the 1% proportionate drug sensitivity testing as per the WHO guidelines 2008 [12].

2.5. Statistical evaluation

All the cases were classified in two groups: MDR and non-MDR. The association of demographical and clinical parameters for these groups was analysed using logistic regression. The prevalence of MDR and outcomes of treatment are reported in percentages with 95% confidence interval. The treatment outcomes of MDR and non-MDR cases were compared using Fisher's exact test. Risk was estimated using odds ratio (OR) with 95% confidence interval (CI).

2.6. Important definitions

Category 1: Newly diagnosed case of PTB with no history of previous treatment with ATT.

Category 2: Cases of PTB previously diagnosed and treated with ATT includes failure/relapse/defaulters.

Taluka: It is an area of land with a city or town that serves as its administrative centre, with possible additional towns, and usually a number of villages.

Grey collar worker: Refers to people with occupations like farming, other forms of agribusiness, fishing, security, catering and skilled and semi-skilled labour.

MDR-TB: Resistance to two of the most important first line drugs, isoniazid and rifampicin.

XDR-TB: Resistance to any one of the second line injectable drugs along with fluoroquinolone in addition to isoniazid and rifampicin.

3. Results

The recruited 862 cases of PTB had a male to female ratio of 3:1 with 473 (54.9%) cases in the age group of 15–45 years. There were 705 cases in category 1 and 157 cases in category 2 with a ratio of 4:1. Nearly 70% of the study population belonged to the lower socio-economic status whose family per capita income was less than INR 1600 per month. Monthly per capita income was calculated as per modified Kuppuswamy's socioeconomic scale for the year 2012 [13]. High proportion of the

cases belonged to grey collar workers (60%) followed by unskilled labourers (18%), house wives (14%) and unemployed people (5%).

Commonest presenting symptoms of recruited cases were cough in 858 (99.5%) followed by fever in 725 (84%), weight loss in 666 (77.3%), chest pain in 449 (52%) and haemoptysis in 74 (9%). Alcohol consumption was noticed in 437 (51%) of the study population, of whom about 420 (96%) were consuming more than 50 ml of alcohol per day. History of smoking was present in 316 (37%) cases that comprise nearly 172 (54.4%) cases that had 3–5 smoking pack years.

Nearly 167 (19.3%) cases had a history of previously diagnosed and treatment completion for PTB and about 156 (18%) newly diagnosed cases gave contact history with the TB patients within or around the house hold.

Table 1 shows total resistance in 288 (33.5%) cases of PTB, which includes the mono-resistance in 194 (67.4%) and resistance to various combinations of anti-tubercular drugs in 94 (32.6%) cases. MDR in category 1 and 2 cases was observed in 32 (4.5%) and 25 (15.8%) respectively as shown in Table 2.

Table 2 shows the association of demographic and risk factors with MDR status. Significant odds ratio was observed only in category 2 cases [OR 3.9, 95% CI – 2.26, 6.87] for the development of MDR-TB using univariate regression. A multivariate logistic regression model was done using parameters such as age, gender, socioeconomic status, alcoholism, smoking and categorisation. The step wise regression model identified category 2 as a single predictor to be associated with MDR status

Table 1 Drug susceptibility results of the total 862 cases.

Drug susceptibility pattern	Numbers	%
Pan sensitive	574	66.5
Total resistance	288	33.5
Mono-resistance		
Streptomycin (S)	144	16.7
Isoniazid (H)	40	4.4
Rifampicin (R)	7	1
Ethambutol (E)	3	0.3
Resistance to combination of drugs		
S + H	24	2.8
S + R	5	0.6
S + E	3	0.3
R + E	4	0.5
S + H + E	1	0.1
MDR	54	6.3
XDR	3	0.3

Table 2 Regression analysis of MDR and non-MDR cases of PTB in the study population.

Characteristics	Total (862) (n, %)	MDR (57) (n, %)	Non MDR (805) (n, %)	95% CI for OR	OR	P value
<i>Gender</i>						
Male	657 (76)	42 (6.4%)	615 (93.6%)	(0.46, 1.59)	0.86	0.64
Female	205 (24)	15 (7.4%)	190 (92.6%)			
<i>Age (years)</i>						
15–30	201 (23.4)	17 (8.4%)	184 (91.6%)	(0.35, 1.45)	0.72	0.36
31–45	272 (31.4)	17 (6.2%)	255 (93.8%)			
>45	389 (45.1)	23 (5.9%)	366 (94.1%)			
<i>Category</i>						
Cat 1	705 (81.8)	32 (4.5%)	673 (95.5%)	(2.26, 6.87)	3.9	<0.001
Cat 2	157 (18.2)	25 (15.8%)	132 (84.2%)			
<i>Per capita income (INR/mth)</i>						
<1600	600 (69.5)	35 (5.8%)	565 (94.2%)	(0.06, 0.782)	0.20	0.02
1601–4800	248 (28.7)	19 (7.6%)	229 (92.4%)	(0.07, 1.09)	0.27	0.06
>4801	14 (2)	3 (21%)	11 (79%)			
<i>Co-morbidities</i>						
Bronchial asthma	40 (4.6)	2 (5%)	38 (95%)	(0.17, 3.12)	0.73	0.67
Diabetes	106 (12.3)	9 (8.5%)	97 (91.5%)	(0.65, 2.87)	1.36	0.4
HIV co-infection	68 (8)	3 (4.4%)	65 (95.6%)	(0.09, 1.70)	0.21	0.4
<i>Smoking</i>						
Non smokers	546 (63)	41 (7.5%)	505 (92.5%)	(0.36, 1.19)	0.65	0.16
Smokers	316 (37)	16 (5%)	300 (95%)			
<i>Alcoholism</i>						
Non alcoholics	425 (49)	38 (8.9%)	387 (99.1%)	(0.26, 0.81)	0.46	0.008
Alcoholics	437 (51)	19 (4.3%)	418 (95.7%)			

with an adjusted odds ratio of 3.9 (CI – 2.26, 6.87). Since only a single variable figured as a statistically significant predictor of outcome in multivariate model, the odds ratio remained the same as univariate.

Cure rate of treatment among the MDR and non-MDR cases was detected as 68.4% and 85.4% respectively. Mortality was observed in 19.3% of MDR cases including 2 out of 3 cases infected with XDR-TB. However, one XDR-TB case was successfully cured after treatment. The mortality in non-MDR cases was noticed as 1.8% (Table 3).

Significant statistical association was observed using Fisher's exact test while comparing mortality rate (19.3% vs. 1.8%), treatment failure (8.8% vs.

3.8%) and cure rate (68.4% vs. 85.4%) between MDR and non-MDR cases ($p < 0.001$).

4. Discussion

The drug resistance in TB is the man-made problem, mainly due to inadequate treatment, defaulting by the patient or poor quality of drugs. Moreover, patients infected with MDR-TB need prolonged treatment with second line anti-tubercular drugs. The present study is the first study from the Udupi district of coastal Karnataka showing the results of drug resistance in PTB cases. A total resistance of 33.5% was observed in the study population that includes 6.3% of MDR cases. Primary

Table 3 Analysis of treatment outcome of MDR and non-MDR cases.

Outcomes	Total N (%)	Non-MDR N (%)	MDR N (%)	P-value
Cured	718 (84.3)	679 (85.4)	39 (68.4)	<0.001
Defaulter	35 (4.1)	33 (4.2)	2 (3.5)	
Relapse	39 (4.6)	39 (4.9)	0	
Treatment failure	35 (4.1)	30 (3.8)	5 (8.8)	
Death	25 (2.9)	14 (1.8)	11 (19.3)	

drug resistance of 4.3% and secondary drug resistance of 15.8% were observed in the current study. According to WHO data 2011 and TB India 2013, MDR cases among notified PTB cases ranged from 3.6 to 6.2% that comprises newly diagnosed cases in the range of 1.5–2.7% and retreatment cases up to 17% [14]. A surveillance study conducted in the state of Gujarat by Ramachandran et al., found 2.4% of MDR-TB in the newly diagnosed cases and 17.4% of MDR-TB in previously treated cases [8]. Joseph et al., from Kerala reported a MDR of 2% in newly diagnosed cases [15]. Dutta et al. from Kashmir reported an initial drug resistance of 5.4% and a secondary drug resistance of 36.5% among the study population [4]. A small cohort study from Mangalore by Bhat et al., reported a prevalence of 4% MDR-TB in patients in 2010 [16].

Out of the 57 MDR-TB isolates in our study, 3 (5.2%) were XDR isolates. Thomas et al. from Chennai in 2003 reported 1.5% XDR-TB isolates [17] and Ramachandra et al. from Gujarat in 2006 reported 3.8% of the XDR isolates in the surveillance studies [8]. On the contrary, Singh et al. [18] from New Delhi in 2006 reported 33% and James et al. [19] from Vellore in the year 2007 reported 60% of the MDR isolates to be XDR. This high proportion of XDR isolates can be explained as these two reports are from tertiary care reference centres. Dutta et al. from Kashmir in the year 2007 reported about 15.3% of the MDR-TB isolates in their study as extensively drug resistant [4].

The present study has highlighted the association of category 2 cases (OR 3.9) for the development of MDR-TB. Previous treatment in TB is the strongest risk factor which includes failed previous TB treatment, relapsed after treatment or default during previous treatment, for the development of MDR-TB [20]. A study by Prasad et al. on the drug sensitivity pattern of culture positive category 2 cases reported nearly 58% had MDR tuberculosis [21]. Though the predisposition of a population having type 2 diabetes mellitus (DM) with an odd's of 1.5 and 1.7 for MDR-TB has been reported by Fisher–Hoch et al. from Texas and Mexico [22], Subhash from southern India did not see any association of drug resistance with diagnosis or duration of diabetes mellitus among the 26% MDR tuberculosis cases [23] which also supports our study.

High proportion (85%) of cases in the study were from lower socioeconomic groups like labourers, unemployed and house wives with an index of 2 according to the modified Kuppuswamy's socioeconomic status classification of 2012 with a mean household of 5 members. Sethi et al., found that nearly 70% of their study population belonged to

the lower socioeconomic group [24]. About 37% of the cases reported smoking tobacco in our study. Smoking is known to cause impaired clearance of mucosal secretion, reduced phagocytic ability of alveolar macrophages, and decrease in the immune response and/or CD4 + lymphopenia due to the nicotine in the cigarettes have been given as reasons for increased susceptibility to PTB [25]. Nearly 51% of the cases self-reported to consume more than 40 ml of alcohol upon questioning. A systematic review by Lonroth et al., showed the relative risk of 2.94 in pooled studies for the development of tuberculosis where the subjects reported to consume more than 40 ml of alcohol per day [26]. This may be through direct toxic effects of alcohol on the immune system, or indirectly through micro- and macronutrient deficiency, or other alcohol-related medical conditions such as malignancies and depression. Jethani et al. on the contrary reported 57% tobacco smoking and 35% of alcoholism in their study population [27]. Although, these risk factors have been proved to be significant in the development of TB as seen in the literature, we did not see any association of these risk factors in the development of drug resistant TB. But some studies by Gaude et al. from Karnataka [10] and Fleming et al. from Russia [28] have shown a significant association of ($p < 0.05$) for alcoholism in development of drug resistance. This may be explained due to not revealing their alcoholic status by some of the studied population. Other reasons may be due to high level of literacy (86%) and public awareness which has resulted in lesser percentage of population being addicted to alcoholism and smoking compared to other parts of Karnataka.

The study observed a higher rate of mortality and treatment failure, but a low cure rate after ATT in MDR cases as compared to non-MDR cases ($p < 0.001$). Mortality was noticed in 19.3% MDR cases (including XDR cases) against 1.8% in the non-MDR tuberculosis cases. WHO global report of 2013, estimates an odd's of 2.3 for mortality among MDR-TB cases [5]. Among 3 XDR-TB infected cases, mortality was 66.6%. O'Donnell reported a mortality of 42% among the XDR-TB infected cases [29] and Gandhi NR in the South African region reported a mortality rate of 80% among the HIV co-infected population with XDR tuberculosis [30].

5. Conclusions

Category 2 patients of PTB are at higher risk of developing MDR-TB. Higher chances of treatment

failure, more mortality and less cure rate in MDR cases necessitates the need for drug sensitivity testing before institution of anti-tubercular treatment. Appropriate therapeutic management can help to reduce the spread of MDR strains.

6. Strengths of the study

This was the first community level study from our tertiary care centre with public–private participation to determine the status of drug resistant PTB in this region of the country. Our study supports the national data of drug resistance in PTB for both the categories.

With less number of defaulters, our study highlights the awareness and effective therapeutic management of the PTB cases by RNTCP in this part of the country with a higher literacy level and better access to medical facilities.

7. Limitations of the study

The study included only the population covered under the DOTS programme. Part of the population seeking private medical care is not included in the study.

The study only concentrated on the smear positive PTB cases while smear negative PTB cases may have been undiagnosed.

Lack of association between MDR-TB and risk factors may be due to the failure to reveal the habits of alcoholism and smoking, which explains the social stigma attached with it leading to social desirability bias.

Conflict of interest

None declared.

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