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A Cross sectional study on Drug resistance patterns amongst newly diagnosed cases of Pulmonary MDR-TB

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Abstract

Back Ground: The World Health Organization (WHO) recommends baseline testing for FQ and AM only among the second-line drugs due to availability of standardized tests and as these two groups of drugs are an important part of MDR-TB treatment regimens across the globe. In our study, we have aimed to find the prevalence of Pre XDR-TB and XDR-TB amongst newly diagnosed cases of pulmonary MDR-TB with various risk factors.

Methodology: A cross sectional study was carried out from JAN 2018 to JULY 2019, in the Nodal DR TB center Guntur (which involves districts Krishna and Guntur of Andhra Pradesh) for Drug Resistant Tuberculosis cases after acquiring ethics committee approval from the institutional ethics Committee. A total no of 349 Pulmonary MDR-TB patients with Primary Drug resistance attending to Nodal DR TB center were included in the study

Results: Among 349 patients of pulmonary Drug resistant-TB 253 (72.49%) were males and 96 (27.50%) were females. The prevalence of H-MONO, MDR-TB, Pre-XDR (FQ) , Pre-XDR (SLI) and XDR -TB between the age group of 15-50 yrs is 108 (40.29 %) , 150 (55.97%),8(2.98%), 0 %,2 (0.74%) respectively. In the study, 140 study participants were smokers of which H-MONO, MDR-TB, Pre-XDR (FQ), Pre-XDR (SLI)and XDR are 68(48.5%), 68(48.5%), 4(2.85%), 0, 0 respectively and 139 were alcoholic of which H-MONO, MDR-TB, Pre-XDR (FQ), Pre-XDR (SLI)and XDR$ are 65(46.7%), 70(50.3%), 4(2.8%), 0, 0. Diabetes was present in 71 patients of which H-MONO, MDR-TB, Pre-XDR (FQ), Pre-XDR (SLI)and XDR$ are 31, 38, 2, 0, 0

Conclusion: There is low prevalence of Pre-XDR (3.15%) and XDR TB (0.57%) in the current study when compared to other studies. Although usage of Fluoroquinolones and aminoglycosides is on par with the other parts of the country certain genetic factors and demographic factors might be playing a hidden role which needs to be investigated.

Keywords: Drug resistant TB, Primary Multidrug resistance, Pre XDR, XDR.

Introduction

Tuberculosis is a disease caused by Mycobacterium Tuberculosis (MTB). Globally, an estimated 10.0 million (range, 9.0–11.1 million) people fell ill with TB in 2018, a number that has been relatively stable in recent years. The burden of disease varies enormously among countries, from fewer than five to more than 500 new cases per 100 000 population per year, with the global average being around 130[1].

Geographically, most TB cases in 2018 were in the WHO regions of South-East Asia (44%), Africa (24%) and the Western Pacific (18%), with smaller percentages in the Eastern Mediterranean (8%), the Americas (3%) and Europe (3%). Eight countries accounted for two thirds of the global total: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). These and 22 other countries in the WHO's list of 30 high TB burden countries accounted for 87% of the world's cases[1]

In India according to the Estimates of TB burden 2018[1] the MDR/RR-TB incidence is 130 (77–198) i.e. 9.6 (5.7–15) per 1 lakh population. Multidrug Resistant Tuberculosis (MDR-TB) is defined when TB bacilli become resistant to both isoniazid and rifampicin or mono-resistant to rifampicin. Pre-extensively drug resistant tuberculosis (pre-XDR-TB) is defined as TB with resistance to rifampicin (RMP) and isoniazid (INH) with additional resistance to either a FLQ (Fluoroquinolone) or ISL (Injectable second line) agent but not against both these drugs simultaneously[2]. XDR-TB is defined as TB resistant to RMP and INH (MDR-TB) with additional resistance to second line anti-TB drugs i.e. to any Fluoroquinolones(FQ), and to at least one of the three injectable second-line drugs (SLI) naming amikacin, kanamycin and Capreomycin (AM= aminoglycosides)

Estimated MDR/RR-TB cases among notified pulmonary TB cases are 65,00. Estimated % of TB cases with MDR/RR-TB in new cases is 2.8% and in Previously treated cases is 12%. The prevalence of XDR-TB is 8.5% worldwide[1]. n a country like India where TB is endemic and FQs and aminoglycosides are routinely used it may be important to know the prevalence of resistance to FQs and aminoglycosides in Mycobacterium tuberculosis isolates.[3] Prevalence of XDR TB among new cases in India is 2.30% and 0.91% among previously treated cases[4]. Prevalence of Pre XDR (FQ) resistance in India among new cases is 24.14% and among Previously detected cases is 20.91 %[4].

MDR-TB patients form a heterogeneous group with two predominant subgroups, one consisting of those who have not been previously treated with second-line drugs and the other consisting of those who have been previously treated with second-line drugs. Treatment of XDR-TB is complicated, as it requires the use of second-line drugs that are less effective and more toxic, thus demanding longer treatment duration. Detection of pre-XDR-TB cases among MDR-TB patients is an important step in the prevention of treatment failure of MDR-TB and in addition, it helps to take appropriate measures to halt the progression

towards XDR-TB. World Health Organization (WHO) recommends baseline testing for FQ and AM only among the second-line drugs due to availability of standardized tests and as these two groups of drugs are an important part of MDR-TB treatment regimens across the globe. Data is scarce on the baseline resistance patterns to FQ and AM in the previously not treated group. In our study, we have aimed to find the prevalence of Pre XDR-TB and XDR-TB amongst newly diagnosed cases of pulmonary MDR-TB with various risk factors.

Materials and Methods

A cross sectional study was carried out from JAN 2018 to JULY 2019, in the Nodal DR TB center Guntur (which involves districts Krishna and Guntur of Andhra Pradesh) for Drug Resistant Tuberculosis cases after acquiring ethics committee approval from the institutional ethics Committee. A total no of 349 Pulmonary MDR-TB patients with Primary Drug resistance attending to Nodal DR TB center were included in the study.

Inclusion criteria: Pulmonary MDR TB cases detected by gene expert MTB/Rifampicin assay and Line Probe assay during the study period.

Exclusion Criteria: Extra Pulmonary MDR-TB patients, Previously Treated MDR TB and Pre-XDR patients and Patients unwilling to give consent.

Two sputum samples were collected and one is subjected to CBNAAT (cartridge based nucleic acid amplification test), and classified based on its report as RR or RS TB (Rifampicin Sensitive TB). Second sample was sent to DST laboratory. First line LPA test (Line Probe Assay test) performed for RS TB and Second line LPA for RR TB: Gene expert or CBNAAT detects only R resistance, first-line Line Probe Assay (LPA) detects H and R resistance and Second line detects Fluoroquinolones and Second Line Injectable drug resistance.

A detailed history was taken to rule out previous exposure to second-line drugs in the form of anti-tuberculous therapy. On the basis of the available DST, patients were grouped into- 1) MDR-TB, 2) MDR-TB with FQ resistance {Pre XDR-TB (FQ)}, 3) MDR-TB with SLI resistance {Pre XDR-TB (SLI)}, 4) XDR-TB. 5) H. Mono.

Statistical analysis: Data collected was tabulated using Excel 2013 and analyzed using SPSS v16. The final data was reported as prevalence of MDR TB, Pre XDR-TB (FQ), Pre XDR-TB (SLI) and XDR-TB in cases of pulmonary MDR-TB with relation to various risk factors. Chi-square tests were used to see if there were any significant differences in relation to various risk factors for patients with MDR-TB. The patients were treated according to national “Programmatic Management of Drug Resistant TB” (PMDT).

Results

Among 349 patients of pulmonary Drug resistant-TB 253 (72.49%) were males and 96 (27.50%) were females. First line LPA suggested 144 (41.26%) patients were resistant to Isoniazid (H). Second line LPA report suggested 192 (55.01%) were MDR TB sensitive to both the second-line drugs i.e. FQ and SLI, 11(3.15%) had Pre XDR-TB (FQ), none had Pre XDR-TB (SLI), 2(0.57%) had XDR-TB. Thus the prevalence of H-MONO drug resistance, MDR-TB, Pre XDR-TB and XDR-TB was 41.26% ,55.01%, 3.15% and 0.57% respectively. (Table 1).

Table 1: Gender Distribution

Patients	Males	Females	Total	Percentage
MDR - TB	128 (66.66%)	64 (33.33%)	192	55.01%
PRE-XDR (FQ)	8 (72.77%)	3 (27.23%)	11	3.15%
PRE-XDR (SLI)	0	0	0	0
XDR	0	2(100%)	2	0.57%
H MONO	117 (81.25%)	27 (18.75%)	144	41.26%
TOTAL	253	96	349	100%

The prevalence of H-MONO, MDR-TB, Pre-XDR (FQ) , Pre-XDR (SLI) and XDR -TB between the age group of 15-50 yrs is 108 (40.29 %) , 150 (55.97%),8(2.98%), 0 %,2 (0.74%) respectively.(Table 2) . The prevalence of H-MONO, MDR-TB, Pre-XDR (FQ) , Pre-XDR (SLI) and XDR -TB in the age group of >50yrs yrs is 36 (44.44 %) , 42 (51.85%), 3(3.70%), 0 %, 0 % respectively. The prevalence of H-MONO, MDR-TB, Pre-XDR (FQ), Pre-XDR (SLI), XDR among age group of 15-50 and >50 is almost similar. (Table 2)

Table 2: Age distribution

Patients	15 - 50 Years	Percentage	>50 Years	Percentage
MDR - TB	150	55.97%	42	51.85%
PRE-XDR (FQ)	8	2.98%	3	3.70%
PRE-XDR (SLI)	0	0	0	0
XDR	2	0.74%	0	0
H MONO	108	40.29%	36	44.44%

Prevalence of DR TB

Among 144 H-MONO cases ,117(81.25%) are males ,27(18.75%) are females, among 192 MDR –TB case ,128(66.66%) are males ,64 (33.33%) are females, in 11 cases of Pre-XDR (FQ) 8 (72.77%) are males and 3 (3.75 %) are females, XDR was noted in females only. The prevalence of any drug resistance in total 349 cases 253 were males and 96 were females with 72.49% and 27.50% respectively. The difference of prevalence of drug resistance is statistically significant between both genders with P value 0.003 (<0.05) suggesting more in males.

Among 349 Drug Resistant patients 140 are smokers of which H-MONO, MDR-TB, Pre-XDR (FQ), Pre-XDR (SLI)and XDR are 68(48.5%), 68(48.5%), 4(2.85%), 0, 0 respectively and 139 are alcoholic of which H-MONO, MDR-TB, Pre-XDR (FQ), Pre-XDR (SLI)and XDR$ are 65(46.7%), 70(50.3%), 4(2.8%), 0, 0.

Diabetes present in 71 patients of which H-MONO, MDR-TB, Pre-XDR (FQ), Pre-XDR (SLI)and XDR$ are 31, 38, 2, 0, 0. Of the 349 patients in the study 59 were HIV infected of which H-MONO, MDR-TB, Pre-XDR (FQ), Pre-XDR (SLI)and XDR$ are 13, 44, 2, 0, 0. With all the Risk factors combined the prevalence of Pre-XDR and XDR has not been found to be high.

Table 3:

	MDR	PRE XDR (FQ)	PRE XDR (SLI)	XDR	H MONO	TOTAL
DIABETES	38	2	0	0	31	71
HIV	44	2	0	0	13	59
15 - 50 YEARS	150	8	0	2	108	268
>50 YEARS	42	3	0	0	36	81
MALES	128	8	0	0	117	253
FEMALES	64	3	0	2	27	96
SMOKER	68	4	0	0	68	140
ALCOHOLIC	70	4	0	0	65	139

Discussion

The study was a cross sectional study conducted to estimate the prevalence of Pre-XDR and XDR among the Pulmonary MDR who have not been exposed to

anti Tuberculosis therapy. The prevalence is found to be 3.15% and 0.57% respectively for Pre-XDR and XDR. The national prevalence in New cases for Pre-XDR (FQ) and Pre-XDR (SLI) is found to be 24.14% (15.60-34.50) and 6.9% (2.57-14.41) respectively[4]. In previous studies from various part of India Pre-XDR (FQ) resistance ranges from 3-35%. [4,5,6,7,8,9]. Our study value of 3.15% for Pre-XDR (FQ) is in concordance with lower range of the prevalence reported in the previous studies [5.]

The higher prevalence in various studies was attributed to the rampant usage of fluoroquinolones in common infections leading to resistance. Although Fluoroquinolones usage is on par with other parts of India, the prevalence is found to be on lower side possibly due to underlying genetic alterations prevalent in local population for FQ resistance which need to be investigated.

Certain unknown demographic factors may also play a role in low FQ resistance patterns as found in some studies.[10] our study did not report any Pre-XDR (SLI) cases. The low prevalence of Pre-XDR (SLI) when compared to Pre-XDR (FQ) could be due to less usage of aminoglycosides to common infections as they are available in injectable forms.[11] The XDR TB prevalence in our study (0.57%) is similar to the national range (0.28-8.6%).[4]

The prevalence of H-Mono drug resistance in our study is 41.26%, this is similar to other previous studies conducted in Northern India by Sinha et al (38.8%) [12]

The prevalence of MDR/RR in our study was 55.01%. According to National drug resistance survey in the year 2016, MDR/RR-TB prevalence was 4% in India and 1.8% in Andhra Pradesh. The very high percentage of prevalence in our study was attributed to the introduction of CBNAAT in the year 2018 Jan into the RNTCP program which led to higher detection of Rifampicin resistant TB cases. Previously AFB smear negative cases were not sent to LPA for resistance detection in screened cases and high sensitivity of CBNAAT over Sputum AFB has led to increased detection rate of drug resistance patterns as more number of cases were sent to LPA.

The prevalence of resistance patterns in males compared with females for H-mono (81.25% vs 18.75%), MDR-TB (66.66% vs 33.33%), Pre-XDR (FQ)(72.77% vs 27.23%) respectively suggesting more in males which is similar to other studies[13.] Sethi et al study showed with in any particular age group males were found to be having high prevalence of drug resistance.[14]. The difference of prevalence of drug resistance is statistically significant between both genders with P-value 0.003 (<0.05) suggesting more in males. Of the total number of cases the XDR prevalence in our study was seen only in females. Sameer et al study showed male to female ratio for XDR TB as 63.63% vs 36.37%. The difference in gender related prevalence of different resistance patterns may be due to 1.) women may have reduced access to health care [15] 2.) difference in health seeking patterns [15,16,17] 3.) patient delay (women showed more patient in delay) [16,18,19] 4.) sociocultural and economic barriers to access TB care.[19,20,21,22] 5.) Knowledge about TB, which is less common among females resulting in reduced health seeking behaviour 6.) Men have a more active life when compared to women, thereby men having increased chances of exposure to drug resistant contacts.

Smoking exposure was found to be associated with higher incidence of Drug resistant TB in our study with H-mono and MDR/RR TB prevalence as 48.5% and 48.5% respectively. TB patients who had a history of

smoking (regardless of current or ex-smokers) are 1.57 times in risk of DR-TB according to Alena Skrahina et al study[23]. Ming-Gui Wang et al study also showed smoking as an independent risk factor for drug resistant TB[24].The major cytokine involved in granuloma formation is TNF-α, which is released by macrophages immediately after exposure to M. tuberculosis antigens. The TNF-α activates macrophages and dendritic cells. In smokers, nicotine, acting through the α7 nicotinic receptor, reduces the production of TNF-α by macrophages, thereby preventing its protective action and favoring the development of tuberculosis.[25,26]

Alcohol exposure was also found to be associated with higher incidence of drug resistant TB in our study with H-mono, MDR/RR-TB and pre-XDR(FQ) prevalence as 46.7%, 50.3% ,2.8%. According to Dessisa F et al.[27] alcohol is considered as an independent risk factor for drug resistant tuberculosis. Several reports, including one from WHO, indicated that the use of alcohol increases the risk of developing drug resistant tuberculosis due to impaired immune responses[28,29,30.] In the alveolar space, chronic alcohol ingestion causes severe oxidative stress and depletes antioxidants which are critical for Alveolar macrophage function[30].

We studied two common comorbidities of HIV and DM(diabetes) among MDR-TB patients. Of the 349 patients, 71 (20.3%) had Diabetes mellitus, which is higher than the prevalence of DM in the general population in south India[31] . In a study conducted by Sharma D et al.[32] the prevalence of diabetes among DR-TB patients showed 13.1%. Similar results were reported in earlier studies by Singla et al.,[33] Raghuraman et al.,[34] with 25%, 29%, respectively. It was widely accepted that DM was a major risk factor of TB infection as a result of a weakened immune system[35,36,37] for example, DM patients tended to be accompanied with abnormally regulated cytokine responses to Mycobacterium tuberculosis. The combination of impaired immune system in DM and bacterial genetics might be a reasonable explanation for primary MDR. It has been reported that poor glucose control is often associated with dysfunction of phagocytosis, reactive oxygen species (ROS) production, chemotaxis and T-cell reaction in DM patients[38]. On the other hand, MDR strains are shown to be less virulent due to heterogeneous mutations and they are less likely to lead to secondary TB cases compared with drug sensitive strains. Then the less fit MDR strains are more likely to flourish in immunocompromised DM patients, which lead to the higher primary MDR-TB in those patients.59 of our study patients were HIV infected which is approximately 16.9%. This is higher than the prevalence of national adult HIV in India is 0.22% as per NACO 2017. Balaji et al[39]and Rajasekharan et al[40] had reported similar prevalence of 27.9% and 13.9% HIV MDR-TB co-infected patients.

The limitation of our study is that the observed prevalence does not necessarily reflect the prevalence in the community since this was a tertiary care center and in general, referral basis can lead to wide variations in the observed prevalence amongst different centers. Data from the recent widespread availability of baseline second-line DST to FQ and AM under the aegis of PMDT should further provide the felt need of a large population based study.

Conclusion

The study showed high prevalence of MDR/RR (55.01%) among newly diagnosed TB cases, which may be attributed to increased detection rate, by introduction of CBNAAT into the RNTCP program. There is low prevalence of Pre-XDR (3.15%) and XDR

TB (0.57%) in the study when compared to other studies. Although usage of Fluoroquinolones and aminoglycosides is on par with the other parts of the country certain genetic factors and demographic factors might be playing a hidden role which are need to be investigated.

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