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A COMPARATIVE STUDY ON PREDISPOSING FACTORS FOR THE DEVELOPMENT OF DRUG SUSCEPTIBLE AND DRUG RESISTANT CASES IN PULMONARY TB RETREATMENT CASES AT GOVERNMENT CHEST DISEASES AND TB HOSPITAL, HANUMAKONDA

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Abstract

Background: Drug-resistant tuberculosis (DR-TB) remains a major challenge to tuberculosis control programmes, particularly among retreatment pulmonary TB cases. Identifying factors associated with the development of drug resistance is essential for improving treatment outcomes and preventing transmission. Materials and Methods: This analytical observational cross-sectional study was conducted over 24 months (May 2023–April 2025) at Government Chest Diseases and Tuberculosis Hospital, Hanumakonda. A total of 100 pulmonary TB retreatment cases aged ≥18 years were included, comprising 50 drug-resistant (DR-TB) and 50 drug-sensitive (DS-TB) cases. Demographic, clinical, microbiological, radiological, and treatment-related factors were assessed. Data were analyzed using SPSS software, and associations were evaluated using the Chi-square test, with $p<0.05$ considered statistically significant. Results: Significant factors associated with DR-TB included older age (p=0.037), male gender (88% vs. 68%, p=0.0158), illiteracy (26% vs. 10%, p=0.0373), alcohol consumption (84% vs. 62%, p=0.013), smoking (p=0.0001), multiple previous TB episodes (26% vs. 10%, p=0.037), longer interval between TB episodes (p=0.0004), previous loss to follow-up (64% vs. 42%, p=0.027), and default during the intensive phase of prior treatment (p=0.007). Undernutrition and anaemia were highly prevalent and significantly associated with disease status. HIV, diabetes mellitus, hypoproteinemia, sputum smear positivity, and radiological severity did not show significant association with drug resistance. Conclusion: Male gender, poor education, smoking, alcohol use, multiple TB episodes, and treatment default were important predictors of DR-TB. Strengthening counselling, adherence monitoring, nutritional rehabilitation, and tobacco/alcohol cessation interventions may help reduce the burden of drug-resistant tuberculosis.

Keywords: Pulmonary Tuberculosis, Retreatment Tuberculosis Cases, Tuberculosis Risk Factors, Treatment Default, Smoking and Tuberculosis, Tuberculosis Recurrence

INTRODUCTION

Drug resistant tuberculosis (DR-TB) is one of the major impediments to achieving the goal of National strategic plan of ending TB in India. DR-TB is also emerging as a growing threat to TB control programs worldwide. Multidrug resistant (MDR) TB is defined resistance to both isoniazid and rifampicin with or without resistance to other first line anti-TB drugs. MDR-TB patients may have resistance to any/all fluroquinolones or any/all second line injectable anti-TB drugs. MDR-TB is associated with a two-to-four-fold increase in period of treatment, psychological problems, economic wastage, poor treatment adherence and consequently, treatment failure1.

According to the Global TB report, there have been 8,456,395 notified TB cases in 2023, of which, 188,990 are MDR-TB cases. Thus, MDR-TB accounts for around 2.2% of TB cases worldwide. TB incidence in India is 195/100000 population in 2023, of which 106,672 were MDR-TB cases. The prevalence of MDR TB is about 2.46% in new pulmonary bacteriologically confirmed cases and 12.8% in previously treated pulmonary bacteriologically confirmed cases2.

In developing countries, due to poverty, less awareness, and various other risk factors including HIV, the incidence and spread of MDR-TB remains persistently high. India accounts for about 27% of the global MDR-TB case burden. In the perspective of public health, the study of risk factors linked to MDR-TB is important to break the transmission cycle of the same, improve the implementation of TB control programs and expand better diagnostic and treatment. As Government Chest diseases and TB hospital, Hanmakonda is a Nodal DR-TB centre, this study was to assess the attributability of various risk factors for the development of drug-resistant tuberculosis.

Tuberculosis is the most common cause of death due to single infectious agent worldwide in adults, with majority of diseases occurring in developing countries.

The World Health Organization (WHO), in 1993, declared TB to be a global emergency and has been publishing the Global TB report, annually, since the year 1997. Though the disease was known since ancient times, organism causing TB was identified only a century ago, by Robert Koch on March 24, 1882. This day, is celebrated as World TB Day since the year 1982. Modern chemotherapy for TB began with the discovery of Streptomycin by Walksman, in 1944. Drug resistant TB was recognised shortly after the introduction of effective chemotherapy in the late 1940s. As per the 2024 Global TB report, there were an estimated 300,000 MDR-TB cases worldwide, with India carrying the highest burden of 27% of the cases2.

The burden of TB morbidity and mortality in the world, as a whole impinges on people of developing countries, and disproportionately on the poor and other disadvantaged populations. No country in the world today, rich or poor, can claim to be free of tuberculosis. The prospect of an increase in the number of drug-resistant cases remains a concern, even if the total TB cases in the world has been declining. India initiated the Programmatic Management of Drug-resistant TB (PMDT) in 2007 to address the emerging problem of drug-resistant tuberculosis, and the PMDT scale up was achieved in March 2013. The treatment success rate among MDR-TB patients in India is consistently about 46% and the death rate is about 20% according to the first National anti-tuberculosis Drug Resistance Survey (NDRS)1. The first NDRS revealed that 28% of TB patients were resistant to any drugs and 6.19% had MDR-TB. Any Isoniazid resistance is a driver for Rifampicin resistance.

PATIENTS AND METHODS

This analytical observational cross-sectional study was conducted over a period of 24 months, from May 2023 to April 2025, at the Government Chest Diseases and Tuberculosis Hospital, Hanmakonda. A total of 100 pulmonary tuberculosis retreatment cases were included in the study.

Pulmonary TB retreatment cases aged ≥18 years were eligible for inclusion. Retreatment was defined as patients previously treated for TB and classified as relapse, treatment after failure, treatment after loss to follow-up, or other previously treated cases. Patients with exclusively extrapulmonary TB, those aged <18 years, and patients unwilling to provide informed consent were excluded.

Patients attending the outpatient department or admitted as inpatients to the Department of Respiratory Medicine were enrolled. An equal number of drug-sensitive and drug-resistant TB cases were included. After obtaining informed consent, demographic and anthropometric details were recorded. A detailed clinical history was obtained, including occupation, area of residence, presenting symptoms, smoking and alcohol consumption, comorbidities, current medications, and prior history of tuberculosis, including previous treatment outcomes and treatment interruptions.

All patients underwent sputum examination for acid-fast bacilli using fluorescent microscopy, CBNAAT testing, and chest radiography. Baseline laboratory investigations included complete blood picture, liver and renal function tests, random, fasting and post-prandial blood glucose levels, and HbA1c. Nutritional status was assessed using body mass index (BMI), calculated as weight in kilograms divided by height in meters

squared. Hemoglobin levels were used to classify anemia severity, and serum protein levels <6 g/dl were considered indicative of hypoproteinemia.
Risk factors assessed included age, gender, number of previous TB episodes, interval between first and current TB infection, previous treatment outcomes (cure, treatment failure, or loss to follow-up), phase of treatment during which loss to follow-up occurred (intensive or continuation phase), diabetic status, alcohol intake, smoking history, HIV status, educational status, sputum smear grading, radiological presentation, chest X-ray severity, nutritional status, anemia, hypoproteinemia, and socioeconomic status. Diabetes mellitus was diagnosed based on fasting blood sugar, post-prandial blood sugar, and HbA1c values as per standard criteria. Alcohol consumption and smoking status were classified using standard definitions. Socioeconomic status was assessed using the modified Kuppuswamy scale (2022).
Radiological evaluation focused on predominant chest X-ray patterns, including nodules, consolidation, cavities, and fibrosis. Disease severity was categorized as minimal, moderately advanced, or far advanced, and the association between cavitary disease and drug-resistant TB was specifically analyzed.

Statistical Analysis
Data were entered and analyzed using SPSS software. Categorical variables were analyzed using the Chi-square test to assess associations between risk factors and drug resistance. A p-value of <0.05 was considered statistically significant, and the null hypothesis was rejected accordingly.

RESULTS
A total of 100 pulmonary tuberculosis retreatment patients were included, comprising 50 drug-resistant (DR-TB) and 50 drug-sensitive (DS-TB) cases. The age distribution differed significantly between the two groups (p = 0.037), with a higher proportion of DR-TB patients in the 46–55 and 66–75 year age groups, whereas DS-TB cases were more common in the 36–45 year age group (shown in table 1). Male predominance was observed overall; however, males were significantly more common in the DR-TB group compared to the DS-TB group (88% vs. 68%, p = 0.0158). Illiteracy was significantly higher among DR-TB patients (26%) than DS-TB patients (10%) (p = 0.0373). Socioeconomic status, assessed using the Kuppuswamy scale, did not show a statistically significant difference between the two groups (p = 0.151).
Clinical characteristics (shown in table 2) revealed a significantly higher prevalence of alcohol consumption among DR-TB patients compared to DS-TB patients (84% vs. 62%, p = 0.013). Smoking was also more frequent in the DR-TB group, whereas exclusive tobacco use was observed only among DS-TB patients, with an overall significant association (p = 0.0001). Undernutrition was common in both groups but was significantly higher among DS-TB patients (96%) compared to DR-TB patients (84%) (p = 0.045). Anaemia was prevalent across the cohort, with a significantly higher proportion among DS-TB patients (96% vs. 82%, p = 0.025). Hypoproteinemia, HIV status, and diabetes mellitus did not differ significantly between the two groups.
DR-TB patients more frequently had multiple previous TB episodes compared to DS-TB patients (26% vs. 10%), and this difference was statistically significant (p = 0.037). A shorter interval between TB episodes (≤24 months) was significantly associated with DS-TB, whereas longer gaps (25–48 months) were more common among DR-TB patients (p = 0.0004). Loss to follow-up during prior treatment was significantly higher in the DR-TB group (64% vs. 42%, p = 0.027). Among patients with prior loss to follow-up, default during the intensive phase was significantly more common in DR-TB patients, while DS-TB patients more often defaulted during the continuation phase (p = 0.007) (shown in table 3).
Current sputum smear positivity was higher among DS-TB patients compared to DR-TB patients; however, this difference did not reach statistical significance (p = 0.071). Cavitary disease on chest radiograph was more frequently observed in the DS-TB group, though the association was not statistically significant (p = 0.130). Chest X-ray severity, categorized as minimal, moderately advanced, or far advanced disease, showed no significant difference between the two groups (p = 0.446) (shown in table 4).

Table 1Distribution of study population according to demographic characteristics

Variable	**DR (n=50)**		**DS (n=50)**			**p value**
Age group	**Frequency**	**Percentage**	**Frequency**	**Percentage**	**Row total**	
18-25	3	6	6	12	9	0.0370
26-35	8	16	8	16	16	
36-45	6	12	16	32	22	
46-55	19	38	9	18	28	

56-65	5	10	8	16	13	
66-75	8	16	2	4	10	
76-85	1	2	1	2	2	
Sex						
Male	44	88	34	68	78	0.0158
Female	6	12	16	32	22	
Education Level						
Illiterate	13	26	5	10	18	0.0373
Literate	37	74	45	90	82	
SES						
Below 3	34	68	27	54	61	0.1512
Above 3	16	32	23	46	39	

Table 2 Distribution of study participants based on clinical characteristics

Variable	**DR (n=50)**		**DS (n=50)**			**p value**
	Frequency	**Percentage**	**Frequency**	**Percentage**		
Alcohol intake						
Non-alcoholic	8	16	19	38	27	0.0132
Alcoholic	42	84	31	62	73	
Smoking status						
Non smoker	26	52	25	50	51	0.0001
Smoker	24	48	11	22	35	
Tobacco usage	0	0	14	28	14	
Nutrition Status						
Underweight	42	84	48	96	90	0.0455
Others	8	16	2	4	10	
Haemoglobin Status						
Non-anaemic	9	18	2	4	11	0.0253
Anaemic	41	82	48	96	89	
Hypoproteinaemia						
Positive	6	12	8	16	14	0.5644
Negative	44	88	42	84	86	
HIV						
Positive	4	8	3	6	7	0.6951
Negative	46	92	47	94	93	
Diabetic status						
Non diabetic	42	84	44	88	86	0.5644
Diabetic	8	16	6	12	14	

Table 3 Distribution of study population based on past history of Pulmonary tuberculosis

Variable	DR (n=50)		DS (n=50)			p value
	Frequency	Percentage	Frequency	Percentage		
No. of Previous Episodes of PTB						
1 episode	37	74	45	90	82	0.0373
>1 episode	13	26	5	10	18	
Gap between TB episodes (months)						
0–24	18	36	39	78	57	0.0004
25–48	20	40	6	12	26	
49–72	4	8	1	2	5	
>72	8	16	4	8	12	
Treatment outcome						
LTFU	32	64	21	42	53	0.0275
Completed treatment	18	36	29	58	47	
Phase of LTFU						
Intensive phase	24	75	8	38.10	32	0.0072
Continuation phase	8	25	13	61.90	21	
Total	32		21		53	

Table 4 Distribution of study population based on current sputum AFB smear and Chest X-ray

Variable	DR (n=50)		DS (n=50)			p value
	Frequency	Percentage	Frequency	Percentage		
Sputum						
Sputum Negative	28	56	19	38	47	0.0713
Sputum Positive	22	44	31	62	53	
Radiological presentation						
Cavity Present	12	24	19	38	31	0.1301
No Cavity	38	76	31	62	69	
Chest X-Ray severiy						
Minimal	18	36	13	26	31	0.4464
Moderately advanced	19	38	19	38	38	
Far Advanced	13	26	18	36	31	

DISCUSSION

AGE

Age plays an important role in the development of drug resistance. In the current study, majority of the patients in the DR group were between 46-55 years age group (38%) and in DS group were 36-45 years (32%) With a mean age of 49.50+/-15.04years for DR TB and 45.04+/-13.94 years for DS TB.

This is in corelation with another study conducted by Getahun et al , on all Tuberculosis cases in their place of study, showing a significant association between age and DR TB with majority of their study population between 26-45 years (70.9%) mean age of 32+/-10.9 years3.

A similar study conducted by Kurnia Fajar Chasanah et al.showed no significance between age and DR TB with a mean sample population age of 42 years4. A study by Abdelfattah et al dismissed age as a risk factor with mean age for DR group in their study sample being 39.09+/-14.89years and for DS group being 35.13+/-

17.05 years.5
On the contrary, in a study conducted by Cecile et al, the most represented age group in DR TB was 29-43 years(43.7%) with a mean age of 35 years.6
Higher mean age in the present study may be attributed to inclusion of only retreatment cases of pulmonary TB.

GENDER
In the current study, there were 78 male patients of which 44(56.4%) were in the DR group. There were 22 female patients of which majority 16(72.2%) were in the DS group. There was significant association between male gender and DR TB.
This was supporting various other studies. In the study by Getahun et al3, 55.1% of DR TB cases and 54.9% of DS TB cases of their study population were males. In the study conducted by Cecile et al6, of the 122 participants in DR group, male was predominant with 78(63.9%) against 44(36.06%) females, both studies dismissed age as a risk factor for DR TB. In a study by Madaki et al, 55% were male, with 1.22 times more likelihood of DR-TB in males.7
On the contrary, in the study conducted by Abdelfattah et al5, sex was significantly different between groups. Females were more in the DR group (54.5%) than in DS group (26.2%), whereas males were less in DR group (45.5%) than in DS group (73.8%). However, the study enrolled only 11 participants in the DR group.

EDUCATION STATUS
Low education serves as a risk factor for TB as it is associated with lower level of awareness regarding the disease, poor treatment adherence and poor follow up rates and a higher exposure to poor socioeconomic conditions.
This study found a statistically significant association between low education and DR TB. (p value=0.037). Among DR TB patients, 26% were illiterate, compared only 10% among the DS TB group. Conversely, a higher proportion of DS TB patients had completed high school (32%) or held a degree (4%). Several studies showed low education or illiteracy to be significantly associated with DR TB. On the contrary, study by Abdelfattah et al showed that a higher proportion (72.2%) of DR TB patients had low education but the result was not statistically significant5.
These results signify the need for targeted educational interventions, literacy and awareness programmes as a step towards mitigating the burden of DR TB and improving treatment outcome.

SOCIOECONOMIC STATUS
Low socio-economic status has been identified as a risk factor for development of TB. In the present study education, employment status and per capita income of the family were taken as determinants of SES, according to modified Kuppuswamy classification.
In the present study, majority of patients in both DR group (68%) and the DS group (54%) belonged to lesser than class 3 SES. This was in corelation with various other studies.
In a study by Cecile et al6 of the 304 participants, 158 (51.9%) had a monthly income below the minimum wage known as the Guaranteed Minimum Interprofessional Salary-GMIS, which showed that this group of individuals was more at risk of developing MDR-TB (OR 1.607; 95% CI 1.01–2.55; P = 0.045)
A study by Soundararajan et al showed that low socio-economic status (OR=11.362,95% CI (10.312-35.174)) was significantly associated with MDR TB.8 A study by Admassu et al showed that rural residence was significantly associated with MDR TB. (54.43%) OR=4.71 (3.13 to 9.58), p value=0.032.9
However, in the current study the difference in SES between the two groups was not statistically significant. This could be due to the fact that majority of the study participants belonged to less than class 3 SES in both DR and DS groups.

NUMBER OF PREVIOUS TB INFECTION
As the number of past episodes of TB increases, the chance of acquired drug resistance increases. It also tends to raise concerns regarding immune status of the patient, adherence to medications and effectiveness of TB eradication programmes.
In the current study, 82 patients had a single past tuberculosis history while 18 patients had past tuberculosis more than once. Out of this 18, 13 patients (26%) were in the DR group while 5 (10%) were in the DS group. More than one previous TB episode was statistically associated with DR-TB. (p value=0.03)
This was in agreement with another study conducted by Rifat et al, where only pulmonary TB retreatment cases were included, among the previously treated patients with MDR-TB, 64.5% had been treated more than once and all patients without MDR-TB had only one episode of treatment previously (p value<0.0001)10

Getahun et al showed that history previous TB treatment was significantly associated with DR TB (p value<0.001).3 In the study by Cecile et al, 117 (38.5%) had a history of TB of which 80 (68.3%) developed MDR-TB compared to 42 (22.4%)6. The result was statistically significant.

INTERVAL BETWEEN FIRST AND CURRENT TB EPISODE

Although there are various studies emphasising previous TB treatment as a risk factor for the development of DR TB, there are limited studies emphasising on interval between TB infections as a risk factor.

In the current study, there was a significant association between interval between first and current TB episode with DR TB. Majority (78%) of the DS cases occurred within a 24-month interval from the first episode while majority of the DR cases (64%) occurred at an interval of 72 months. This suggest that monitoring the interval between TB episodes could help identify patients at higher risk for MDR-TB, warranting closer follow-up and possibly more aggressive diagnostic and treatment strategies.

In a study by Sharma et al, majority of patients (38.1%) had a gap of more than 24 months between diagnosis of current MDR TB and first episode of TB, with a mean gap of 28.7 months between the episodes.11

PREVIOUS DS-TB TREATMENT OUTCOME – LTFU AS A RISK FACTOR

In the current study, the majority of DR cases (64%) had a history of being lost to follow-up, compared to 42% in DS cases. A higher proportion of DS cases (54%) had been previously cured, compared to DR cases (34%). Both DR and DS groups had low rates of previous treatment failure, but the proportion is slightly higher in the DS group (4%). There was significant association between LTFU and development of DR TB. (p value=0.02)

Similarly, in a study conducted by Zereabruk et al, LTFU comprised 9.4% of the DR group and 4.1% of the DS group. MDR-TB was significantly associated with return after lost follow-up with an AOR of 5.4 (1.69 to 17 95% CI) and p value=0.004.12 In a study by Sharma et al, LTFU was found to be a significant risk factor with majority of patients (n=112, 45.4%) in the group, OR=7.51((95% CI), p value=0.01.11

On the contrary, in the study by Rifat et al, treatment failure was higher among the patients with MDR-TB compared with patients without MDR-TB (68.4% and 28.6%, respectively) during their previous treatment, with a significant association between treatment failure and DR TB.10 In a study by Baya et al, previous treatment failure was 88.81% among MDR-TB and 67.5% in Non MDR-TB, OR = 3.82, 95% CI (1.87–7.79), p = 0.0002.13

PHASE OF LTFU

It is important to emphasise on the time of LTFU because, the earlier a patient defaults, more will be the chances of persistent smear-positive status and risk of drug resistance. Patients who are smear positive at the end of intensive phase have an increased risk of failure of treatment.

The present study demonstrates a significant association between the phase of LTFU during previous TB treatment and the risk of developing DR-TB. Of the total LTFU cases (53), the majority (24) of DR-TB cases (75%) in the study sample had LTFU during the IP phase of their prior TB treatment, whereas LTFU in the CP phase was more commonly observed among DS-TB cases (61.9%). The statistical analysis confirmed this relationship ($\chi^2 = 7.22$, $p = 0.007$).

Similarly, in a study by Geetha Pardeshi, on a cohort of patients registered under DOTS, in DTC, Yavatmal, in category I, maximum default is seen in the first month of treatment, i.e., 2.11%. The cumulative default rate at the end of IP phase was 3.91%; and at the end of CP phase, 6.23%.14

In a study by Kaona et al, which included 400 patients registered under DOTS, showed that about a third of the respondents (33.9% males and 39.1% females) indicated that they stopped taking anti-TB drugs within the first two months of starting treatment. However, in the above studies, the significance between time of default and development of drug resistance had not been worked up.15

SMOKING

Smoking increases the risk of tuberculosis overall mainly by impairment of macrophage function including anti-microbial activity and phagocytosis.

This study found a statistically significant association between smoking status and the development of DR-TB. Nearly half of the DR-TB patients in the study sample were smokers (48%), compared to only 22% in the DS-TB group. Additionally, tobacco consumption was observed exclusively among 14 DS-TB patients (28%). The association was highly significant ($\chi^2 = 18.85$, $p = 0.0001$). This was in corelation with other studies like Cecile et al6, which showed 0.84 times higher odds for smokers to get DR TB. Similarly, in studies by Getahun et al3 and Chasanah et al4, the odds ratios were 2.29 and 1.57 respectively. This was also in corelation with studes by Wotale et al16 and Wang et al17 which showed significant association between

smoking and development of DR TB.
These observations suggest that integrating tobacco cessation interventions into TB control programs may help in reducing the burden of drug-resistant TB.

ALCOHOL
This study found a statistically significant association between alcohol intake and TB drug resistance status ($\chi 2$=4., p=0.0275). Among patients with DR-TB, 84% reported alcohol use, compared to 62% in the DS-TB group. Conversely, non-alcoholic status was more common in DS-TB (38%) than DR-TB (16%). Various other studies, Cecile et al6, Chasanah et al4, Wotale et al16,showed alcohol consumption is a significant risk factor towards developing DR TB. On the other hand, study by Baya et al13, dismissed alcohol as a risk factor for DR TB.
These observations call for a targeted counselling for alcohol cessation in patients promoting better adherence and treatment outcome.

DIABETES
Diabetes has been known to be a risk factor for development of TB overall due to impaired granulocyte chemotaxis, phagocytosis, bactericidal activity, and superoxide production
In this study, diabetes was present in 16% of DR-TB and 12% of DS-TB patients, with no statistically significant association between diabetes status and DR TB (p = 0.5644). This was contradicting many studies such as studies by Cecile et al6, Chasanah et al4, meta-analysis by Liu et al18, diabetes was a significant risk factor for development of DR TB. The lack of significance in the present study may be due to low number of diabetic patients in either group. These findings highlight the need for larger studies to clarify the relationship between diabetes and DR TB

HIV
HIV is a risk factor for both DS and DR TB. HIV-TB co-infection is a deadly combination where one disease perpetuates the other with high morbidity and mortality rates. In DR TB, it leads to faster disease progression and high mortality rates.19 In a study by Gandhi et al, out of MDR tuberculosis in 221 patients, of whom 53 had XDR tuberculosis, all patients with XDR tuberculosis who were tested for HIV were co-infected. 52 of 53 patients with XDR tuberculosis died, with median survival of 16 days from time of diagnosis.20
In the present study, the prevalence of HIV among DR group was 8% and 6% in the DS group. The difference was not statistically significant (p value=0.695). This is in contrary to the existing literature and is expected to be because of a low number of HIV infected patients in either group. This was not corelating with other studies.
Various studies have showed significant association of HIV and DR TB. A meta-analysis of 1214 studies by Song et al showed an odds ratio of 2.78 (95 % CI: 1.07–7.20) between HIV/AIDS and MDR-TB indicating a significant positive correlation (p value=0.05)21. Another meta-analysis by Mesfin et al showed that HIV is associated with a marginal increased risk of MDR TB (estimated Pooled OR 1.24; 95%, 1.04–1.43). and effect estimates were higher (Pooled OR 2.28; 95%, 1.52–3.04) for primary MDR TB.22
Admassu et al, in their case control study showed a higher proportion of HIV positive patients in DR TB group (12.66%) compared to DS TB group (3.83%)9
Getahun et al, in their study showed that People who were co-infected with HIV were 4.4 times more likely to develop MDR-TB than those TB patients who were HIV negatives AOR=4.38; 95%CI: (1.85,10.38)].(p value=0.001).3
Prioritization of CBNAAT as the first diagnostic modality for diagnosing tuberculosis in PLHIV helps in earlier diagnosis of drug resistance and helps initiation of early treatment thereby hindering the progression of both diseases.

NUTRITIONAL STATUS (BMI)
In the present study, a significantly higher proportion of undernutrition was observed among DR-TB patients (96%) compared to DS-TB patients (84%), with the difference being statistically significant (χ^2=4.00, p=0.0455). None of the DR-TB patients were overweight or obese, while 4% of DS-TB patients fell into these categories
This was in corelation with a study by Vyawahare et al, all patients in the DR group (n=36,26.08%) fell into the low BMI category and low BMI was significantly associated with DR TB (p value- 0.000)23. Similarly, in a multivariable analysis, by Adamashvili et al, low weight (BMI < 18.5 kg/m2) at treatment initiation (aHR 3.2, 95% CI 2.2–4.7) was associated with all-cause mortality.24

On the contrary, in a study by Song et al, overweight were positively associated with MDR-TB (OR 1.603, 95% CI 1.002–2.566; aOR 1.639, 95% CI 1.02–2.633), isoniazid + rifampicin + streptomycin resistance (OR 1.948, 95% confidence interval (CI): 1.061–3.577; aOR 2.113, 95% CI 1.141–3.912), Any isoniazid + streptomycin resistance (OR 1.472, 95% CI 1.013–2.14; aOR 1.483, 95% CI 1.017–2.164), $P < 0.05$. This was attributed to presence of co-morbidities such as COPD, diabetes, cancer, etc., in the overweight group.21

ANEMIA

Anemia, especially due to iron deficiency increases the risk of TB infection by impairing oxidative burst of monocytes, macrophage phagocytosis, impaired T-Cell mediated immunity and an increases Th2 type of immune response promoting clinical TB disease. It also leads to poor treatment outcomes and increases mortality.

In the present study, majority of patients were anemic with 48 (96%) in DR and 41 (82%) in the DS group with anemia. Non anemic patients were rare in both groups; 2 (4%) in DR and 9 (18%) in DS group were anemic. The difference was statistically significant ($p = 0.025$), indicating a strong association between anemia and drug resistance in TB.

Another study by Beshaw et al reported that a significant number of patients with DR TB had anemia. Of the 331 patients, 51.4% had baseline anaemia, of which 5.7%, 15.7% and 29.9% had severe, moderate and mild anaemia, respectively. The study detailed the severity and associated factors of anemia among these patients, indicating that anemia is highly prevalent in the MDR-TB population25

6.16 HYPOPROTEINEMIA

Protein deficiency has been well described in the context of TB, and albumin and prealbumin have been found to be useful markers both for the diagnosis of deficiency as well as the monitoring of its reversal.9 However, there are limited studies on literature signifying hypoproteinemia as a risk factor of DR TB.

In the present study, 12% of DR TB and 16% of DS TB patients had hypoproteinemia at presentation. However, there was no significant association between hypoproteinemia and development of drug resistance.

6.17 SPUTUM AFB SMEAR

Higher grades of sputum AFB smear is associated with drug resistance. As a rule of thumb, the average frequency of resistant mutants is ~1 in 10^6 to isoniazid and ~1 in 10^8 to rifampicin. This occurs due to spontaneous genetic mutations that confers resistance to a particular drug occurring in a proportion of wild strain bacilli.26

However, in the present study, a higher proportion of sputum AFB smear positive patients were in the DS group (62%) compared to the DR group (44%).The result was not statistically significant.

This was contradicting many studies. A meta-analysis by Xi et al assessing 3152 MDR-TB and 52715 DS-TB cases showed that. the pooled ORs were 1.478 (95%CI 1.077–2.028) for positive sputum AFB smear ,with p value 0.005 showing that a positive smear status is significantly associated with DR TB.27

Similarly, a study by Kassa et al showed that ,of all 520 bacteriological confirmed pulmonary DR-TB patients in their study; more than one third (34.42%) had 3+, 15.77% had 2+, 18.27% had 1+, 15.19% had scanty, and 16.35% had negative sputum smear grading results signifying the presence of high bacillary loads in DR TB.28 Baya et al, in their study showed that sputum smear microscopy positive with 3+ bacilli was reported in 64.18% (84/134) of MDR-TB and 47.5% (38/80) of Non MDR-TB, OR = 1.98, 95% CI (1.13–3.48), $p = 0.02$, with significant association between high bacillary load and DR TB.13

These contradicting results could be attributed to frequent sputum NAAT tests performed at the peripheral centres at early stages of the disease, leading to earlier diagnosis of DR TB and initiation of treatment

6.18 CAVITY ON CHEST X-RAY

Presence of cavities significantly increases the risk of drug resistance. Drugs administered orally or intravenously attain sub-optimal concentrations inside the cavity leading to drug resistance subsequently.27

In the present study, the most common presentation of DR TB group was nodularity (36%) followed by cavity (24%). Cavity was found to be more predominant in the DS group (38%) and the result was not statistically significant (p value=0.13)

Similarly, in a study by Rifani et al, 37.6% of DR patients and 30.4% of DS patients had cavity on chest x-ray. But significance of cavity as a risk factor was not established (p value=0.369). Although, size and number of cavity was not considered in the study.29

This study corelated with a study by Majdawati et al, significant association was found between the presence of nodularity and MDR-TB (p value=0.001)30

On the contrary, various other studies showed cavity as a risk factor for DR TB.A study by Wu et al showed that the risk of MDR-TB in individuals with pulmonary cavity is 2.736 times higher than in individuals without pulmonary cavity (OR = 2.736, 95% CI: 1.832–4.115, $p < 0.01$)31 A meta-analysis by Xi et al showed that MDR-TB occurrence is elevated in individuals with lung cavities in comparison with those with no lung cavities (OR = 1.716, 95%CI 1.149–2.564)27.Similarly, a study by Tao et al showed that cavity (aOR: 1.55, 95% CI 1.22 to 1.97) was associated with increased risk of DR TB in retreatment cases.32

CHEST X-RAY SEVERITY

There have been a lot of studies suggesting that MDR TB is associated with more extensive and larger lesions on the chest X-ray. Longer duration of the disease, more extensive tissue damage and a larger surrounding inflammatory response have all been suggested as reasons for the same33.

However, in the present study, the most common presentation was a moderately severe chest x-ray in both DR 19 (38%) and DS 19 (38%) groups. 36% of DR-TB patients had minimal chest X-ray changes, compared to 26% of DS-TB patients. Conversely, 36% of DS-TB patients had far-advanced radiological lesions, versus 26% of DR-TB patients. There was no statistically significant association between CXR severity and drug resistance ($\chi^2 = 1.61$, $df = 2$, $p = 0.446$).

This result was contradicting various studies. A study by Majdawati et al showed a significant association between presence of advanced lesions on chest xray and MDR TB(p value=0.000)30 A study by Icksan et al showed that 96% of MDR patients in their study had large lesions when compared to small and medium sized lesions.34 A study by Rifani et al showed that MDR TB had more extensive or moderate lesions than DS TB 89.8% vs 72.4%.29 This could be attributed to an earlier diagnosis of DR TB or a possible variability in the scoring system.

SUMMARY

In this study, age, male gender, illiteracy, more than one previous TB episode, previous history of LTFU, LTFU in the IP phase, smoking, alcohol, under nourishment, anemia, were all found to be significantly associated with the development of DR TB. Low socioeconomic status was prevalent in both DR and DS TB. Although the number of diabetic patients were less in number, a majority of diabetics in the DR group had poor glycemic control. HIV, hypoproteinemia, sputum AFB smear status and radiological presentation were not found to be significantly associated with DR TB. However, larger, multi-centre studies are needed to establish a strong association of these factors with the development of drug resistance. A majority of patients were found to have defaulted treatment because of unawareness regarding the disease and treatment process. Adverse drug reactions also seem to be one of the major causes for treatment default.

CONCLUSION

From these observations, it is suggested that, apart from pharmacological management of tuberculosis, various other interventions like-

- Age and gender targeted counselling
- Special emphasis on counselling regarding various reasons of treatment default and its prevention
- Integration of tobacco and alcohol cessation programmes with TB treatment
- Nutritional rehabilitation
- Social, economic and emotional support along with counselling of family members
- Early and prompt diagnosis and management of co-morbidities
- HIV screening

are all essential to prevent drug resistance, reduce disease related morbidity and mortality and for better treatment outcome. These factors ultimately promote and sustain a successful TB control programme.

LIMITATIONS

- Limited sample size with inadequate sample for individual risk factor eg- individual number of diabetics and HIV positive patients in the study sample was very low.
- Extra pulmonary TB cases were not included in the study.
- Severity of certain risk factors such as HbA1c, smoking index, CD4 count were not analysed.
- Radiological classification was done based on chest X-ray only and not based on CT-chest.

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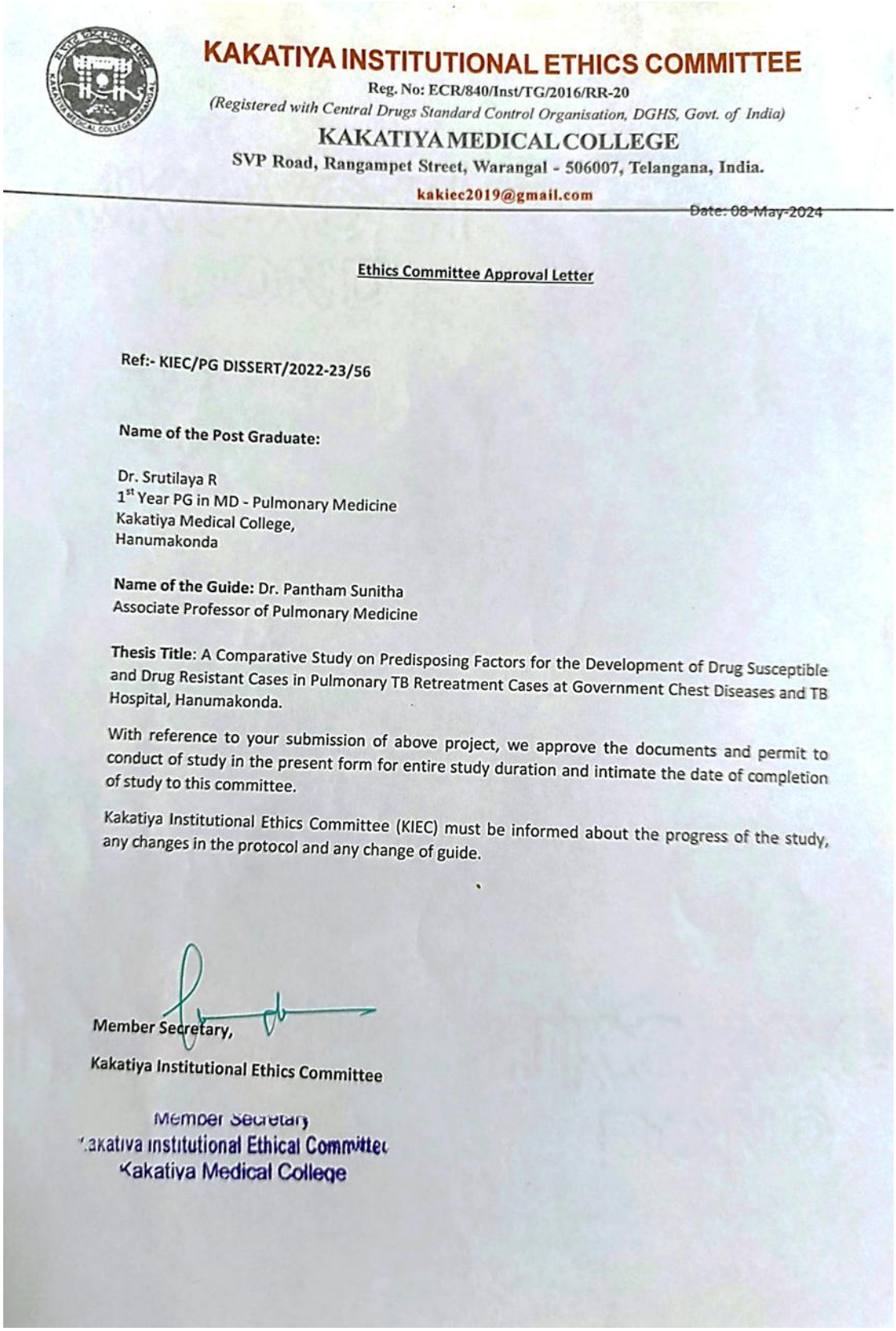
Dr. SRUTILAYA.R

ETHICS COMMITTEE APPROVAL LETTER



KAKATIYA INSTITUTIONAL ETHICS COMMITTEE

Reg. No: ECR/840/Inst/TG/2016/RR-20

(Registered with Central Drugs Standard Control Organisation, DGHS, Govt. of India)

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Ethics Committee Approval Letter

Ref:- KIEC/PG DISSERT/2022-23/56

Name of the Post Graduate:

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Hanumakonda

Name of the Guide: Dr. Pantham Sunitha
Associate Professor of Pulmonary Medicine

Thesis Title: A Comparative Study on Predisposing Factors for the Development of Drug Susceptible and Drug Resistant Cases in Pulmonary TB Retreatment Cases at Government Chest Diseases and TB Hospital, Hanumakonda.

With reference to your submission of above project, we approve the documents and permit to conduct of study in the present form for entire study duration and intimate the date of completion of study to this committee.

Kakatiya Institutional Ethics Committee (KIEC) must be informed about the progress of the study, any changes in the protocol and any change of guide.

Member Secretary,
Kakatiya Institutional Ethics Committee

Member Secretary
Kakatiya Institutional Ethical Committee
Kakatiya Medical College