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# CLINICAL FEATURES IN MULTI DRUG RESISTANT TUBERCULOSIS PATIENTS IN A TERTIARY CARE HOSPITAL IN HARYANA

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**ABSTRACT**
Multidrug resistant (MDR) tuberculosis (TB) has important implications for individual patients and tuberculosis control programmes. Tuberculosis morbidity and mortality rates remain high, and delay in diagnosis and effective treatment can further increase these rates because of disease progression and development of complications such as disseminated TB and tuberculous meningitis (TBM). In the case of drug resistant tuberculosis this delay in initiating effective treatment can be even longer, especially if the attending physician does not consider the diagnosis specially based on clinical features. So, this study was done to assess the clinical features in MDR TB.

**KEYWORDS:** Multidrug resistant (MDR) tuberculosis (TB).

## INTRODUCTION

Tuberculosis (TB) has been considered a worldwide public health problem by the World Health Organization (WHO) since 1993, and global actions have been taken to control this disease.[1,2] However, in recent years, epidemiological indicators have pointed to a low effectiveness of TB prevention and control activities in regions where HIV rates are high and where drug-resistant (DR), multidrug-resistant (MDR), or extensively drug-resistant (XDR) TB has been identified.[3-5] Cure rates of only 58% to 67% have been achieved in these settings, according to systematic reviews and meta-analyses.[3-5]

Since the launch of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance in 1994 by WHO, a large volume of drug resistance data from several countries has been collected and analysed.[3] However, drug resistance surveys have provided little information on clinical features in patients with a diagnosis of DR-TB or MDR-TB.[6] So, this study was done to assess the clinical features prevalent in MDR resistant Tuberculosis.

## MATERIAL AND METHOD

The study was conducted in the department of Respiratory Medicine, MMIMSR between for period of two years, 100 patients of PTB who were admitted in the Respiratory Medicine ward or reported in OPD and who had fulfilled the criteria that is they were sputum positive pulmonary TB or sputum negative retreatment cases were considered for the study. The patients who fulfilled inclusion criteria and after verifying the exclusion criteria were finally taken up for the study.

**Inclusion Criteria (Based on PMDT Guidelines)**
**Criteria A**
1. All failures of new TB cases.
2. Smear +ve previously treated cases who remain smear +ve at 4th month onwards.
3. All pulmonary TB cases who are contacts of known MDR TB case.

**Criteria B – in addition to Criteria A**
1. All smear +ve previously treated pulmonary TB cases at diagnosis.
2. Any smear +ve follow up result in new or previously treated cases.

**Criteria C – in addition to Criteria B**
1. All smear -ve previously treated pulmonary TB cases at diagnosis.

**Exclusion criteria**
1. Presence of immunodeficiency conditions such as
a. HIV / AIDS.
b. Organ transplantation.
c. Malignancy

2. Extra-pulmonary TB and/or patients requiring surgical intervention.
3. Patients unwilling to take part in study.

**Study Sequence:** Hundred patients who were smear positive or sputum negative retreatment cases were selected for the study. A written consent was obtained from each of these patients or their close relatives. These 100 patients were asked to submit their two sputum samples at least one morning and one spot sample. Up to 5 ml of sputum samples were collected in 50 ml falcon tubes marked A and B. The tubes were sealed with parafilm and labeled mentioning name of patient, sample A and sample B and date of collection on the specified rectangular space provided on the side of falcon tube using permanent marker pen. Annexure I was filled up mentioning the detail of patients. The duly labeled samples were individually packed in zip lock poly bags and placed in thermocol boxes after ice-gel packs below and above falcon tube packs following international guidelines for transportation of infectious substances. Annexure I was kept in separate poly bag inside the box. Then these samples are handed over to designated courier agency hired by District TB Officer, Ambala immediately so as to reach IRL Haryana Govt. Public Health Laboratory, Karnal within 72 hours of collection. These samples are received in the designated laboratory. Date of receipt was mentioned on the box and soon afterwards the samples are processed for evaluation of drug susceptibility pattern by MTB RIF/INH Line Probe Assay method. The tuberculosis patients admitted as inpatients or visited O.P.D. were subjected to thorough history taking, regarding clinical features and previous treatment. Patients who satisfied the inclusion criteria were included in the study with their consent. They were examined in detail and the study Performa was filled .Similar exercise was carried out with the outpatients, who were examined on their firstvisit and were regularly followed up. All the patients underwent HIV testing, chest x-ray imaging and sputum microscopy.

**Classification of Sputum.**

| Zn staining grading (RNTCP) | Reporting/ grading |
|---|---|
| >10 AFB per field after examination of 20 fields | Positive 3+ |
| 1-10 AFB per field after examination of 50 fields | Positive 2+ |
| 10-99 AFB per 100 fields | Positive 1+ |
| 1-9 AFB / 100 fields | Positive scanty |
| No AFB per 100 fields | negative |

**Sputum Samples Collection guidelines**

Collection container : 50 ml sterile falcon tube

Storage Requirements : Room temperature 15-20 degrees Celcius refrigeration temperature.

Transport Conditions : Thermocol boxes with cold chain system maintaining temperature 15-20 degrees Celcius. If delay in transport of more than 1 hour expected, then samples were to be refrigerated.

If the Sample quantity was less than 2 ml, Samples containing frank blood and New Pulmonary TB cases were rejected.

Patients were instructed to rinse the mouth and gargle with warm or fresh water prior to sputum collection. Also, two sputum samples were to be collected in falcon tubes provided, both morning samples or at least one morning sample and one spot sample. No food particles should have been there in the samples and approximately 5 ml of sample was needed for processing. Fresh mucoid material (free of salivary secretions) produced by deep coughing was collected with the patient being supervised as needed and deliver promptly to the laboratory.

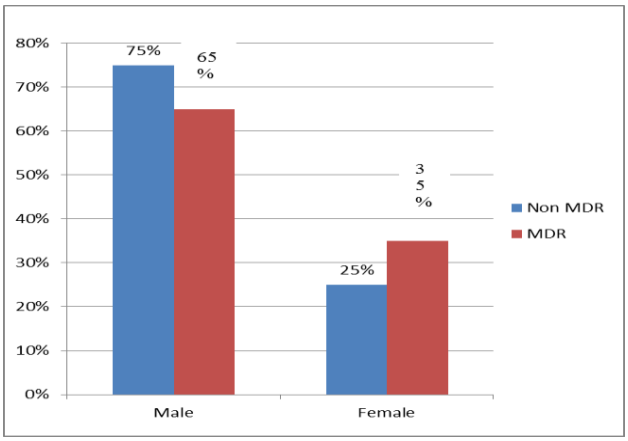
## RESULTS

This study done was done in MMIMSR Hospital for a period of two years. It incorporated a sum of 100 (n-100) category II pulmonary TB patients. Sputum positive as well as negative. Patient populace was partitioned into two gatherings of MDR (n-20) and Non MDR (n-80) as indicated by the drug susceptibility results. After that the prevalence of MDR was determined which was **20% (n=20).**These two gatherings were then examined to search for measurable association and statistically significant association between groups.

**Table No. 1: Gender distribution**.

| | MDR | | Non MDR | |
|---|---|---|---|---|
| **Gender** | **n** | **%** | **n** | **%** |
| Male | 13 | 65% | 60 | 75% |
| Female | 7 | 35% | 20 | 25% |
| Total | 20 | 100% | 80 | 100% |

Out of 100 patients, 73 were male and 27 were female. Out of 20 MDR patients 13 (65%) were male and 7 (35%) were females. In Non MDR group of 80, 60 (75%) were male and 20 (25%) were females. Male: Female proportion in MDR group was 1.9:1.




**Graph No. 1: Gender Distribution between MDR and Non MD.**

**Table No. 2: Mean ages (yrs.) according to gender.**

| Group | SEX | Mean | N | Std. Deviation | Median | Minimum | Maximum | Std. Error of Mean |
|---|---|---|---|---|---|---|---|---|
| MDR | Male | 47.38 | 13 | 14.992 | 45.00 | 28 | 70 | 4.158 |
| | Female | 32.71 | 7 | 13.338 | 28.00 | 14 | 52 | 5.041 |
| | Total | 42.25 | 20 | 15.801 | 40.00 | 14 | 70 | 3.533 |
| Non-MDR | Male | 45.38 | 60 | 16.090 | 44.50 | 18 | 85 | 2.077 |
| | Female | 41.25 | 20 | 17.305 | 39.00 | 14 | 80 | 3.869 |
| | Total | 44.35 | 80 | 16.389 | 42.00 | 14 | 85 | 1.832 |
| Total | Male | 45.74 | 73 | 15.818 | 45.00 | 18 | 85 | 1.851 |
| | Female | 39.04 | 27 | 16.566 | 38.00 | 14 | 80 | 3.188 |
| | Total | 43.93 | 100 | 16.216 | 40.00 | 14 | 85 | 1.622 |

Mean age figured sexual orientation shows that in the MDR group mean age with SD for males was 47.38 ± 14.99 with maximum age being 70yrs., and minimum being 28 years. Whereas for females, mean with SD was 32.71 ± 13.33 with maximum age being 52 yr, minimum being 14yrs. Total mean age in MDR group was 42.25±15.80. In Non MDR group, mean age with SD for males was 45.38±16.09 with maximum age being 85 yrs. and, least being 18yrs. though for females, mean with SD was 41.25±17.30, maximum age was 80 yrs, and minimum was 14 years. Over all mean age was 43.93±16.21.With overall mean male age, 45±15.81and female age, 39.04±16.566.

**Table No. 3: Clinical features in the groups: (Chi-square test).**

| Clinical Features | | MDR | | Non MDR | | $X^2$ | P - Value |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | | |
| | Present | 20 | 100% | 58 | 73% | 7.0513 | 0.007921 |
| Fever | Absent | 0 | 0% | 22 | 28% | | |
| | Present | 20 | 100% | 80 | 100% | ----- | ----- |
| Cough | Absent | 0 | 0% | 0 | 0% | | |
| | Present | 20 | 100% | 80 | 100% | ------ | ----- |
| Expectoration | Absent | 0 | 0% | 0 | 0% | | |
| | Present | 12 | 60% | 26 | 32% | 5.13 | 0.023 |
| Breathlessness | Absent | 8 | 40% | 54 | 68% | | |
| | Present | 12 | 60% | 32 | 40% | 2.5974 | 0.107039 |
| Chest Pain | Absent | 8 | 40% | 48 | 60% | | |
| | Present | 7 | 35% | 12 | 15% | 4.159 | 0.041 |
| Haemoptysis | Absent | 13 | 65% | 68 | 85% | | |
| | Present | 5 | 25% | 15 | 19% | 0.3906 | 0.531971 |
| Night Sweats | Absent | 15 | 75% | 65 | 81% | | |
| | Present | 17 | 85% | 52 | 65% | 2.992 | 0.084 |
| Weight Loss | Absent | 3 | 15% | 38 | 48% | | |
| | Present | 4 | 20% | 7 | 9% | 2.0684 | 0.150376 |
| Lymph Nodes | Absent | 16 | 80% | 73 | 91% | | |

Significant association was found between fever and the groups (p value -0.007), hemoptysis and the groups (p value-0.041), breathlessness and groups(p value 0.023).cough and expectoration was found in every patient in both groups where as fever was found in all patients in MDR group and 73 % in Non MDR group.

**Table No. 4: Respiratory system findings.**

| | MDR | | Non MDR | |
|---|---|---|---|---|
| RS | n | % | n | % |
| CREPTS | 6 | 30% | 32 | 40% |
| BRONCHIAL | 12 | 60% | 37 | 46% |
| RHONCHI | 2 | 10% | 9 | 11% |
| VBS | 0 | 0% | 2 | 3% |

Most common finding in MDR group was Bronchial breath sounds (n=12) 60%, crepts were present in 30% (n=6),Rhonchi was present in 10%(n=2) in MDR group, no patient in MDR group had vesicular breath sounds. In Non MDR group 46% had bronchial breath sounds on examination(n=37),40% (n=32) had crepts,11% had Rhonchi (n=9),and 3%(n=2) had vesicular breath sounds.

**Table No. 5: Drug susceptibility pattern (Total no of patients-100).**

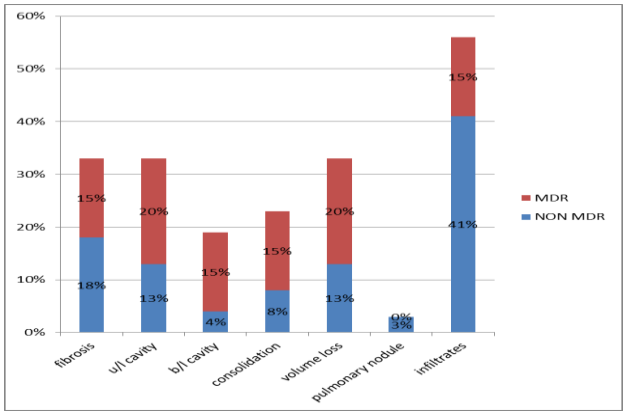
| Drugs | No. of patients | % |
|---|---|---|
| $ISONIAZID_{(only)}$ | 2 | 2% |
| $RIFAMPICIN_{(only)}$ | 0 | 0% |
| H+R | 20 | 20% |

20 patients out of 100 had resistance to Isoniazid and Rifampicin that is MDR TB and 2 patients had mono resistance to Isoniazid. None of the patients in our study showed mono resistance to Rifampicin.

**Table No. 6: Chest X-Ray findings.**

| Chest X-Ray | MDR | | Non MDR | |
|---|---|---|---|---|
| | n | % | n | % |
| fibrosis | 3 | 15% | 14 | 18% |
| infiltrates | 3 | 15% | 33 | 41% |
| u/l cavity | 4 | 20% | 11 | 13% |
| volume loss | 4 | 20% | 11 | 13% |
| b/l cavity | 3 | 15% | 3 | 4% |
| consolidation | 3 | 15% | 6 | 8% |
| pulmonary nodule | 0 | 0% | 2 | 3% |
| Total | 20 | 100% | 80 | 100% |

35 % of patient in MDR group had Cavitatory(n=7) lesion 20% unilateral(n=4) and 15% bilateral(n=3) ,20 % had volume loss(n=5),15%(n=3) had infiltrates,15% had consolidation(n=3) and 15% had fibrosis (n=3).No patient of pulmonary nodule was seen in MDR group. In Non MDR group 41 %(n=33) had infiltrates, 3 %( n=2) had pulmonary nodule, 13% had volume loss (n=11), 8% had consolidation(n. 6), 4% had b/l cavity in Non MDR group (n=3), 13% had u/l cavity (n=11), 18 %had fibrosis (n=14).




**Graph. No.7 Chest X-Ray findings between MDR and non MDR group.**

Graph no 7 shows classification of chest X-ray findings into categories acc to National Tuberculosis Association USA. 30 %(n=24)in Non MDR group were in minimally advanced group based on Chest X-ray findings, 10 %(n=2) in MDR group were in minimally advanced group, 40 %(n=32) in Non MDR group were in moderately advanced group 35%(n=7) in MDR group were in moderately advanced group .30 %(n=24) in Non MDR group were in far advanced group as compared to 55 % in MDR group.

## DISCUSSION

In a study conducted by Sharma et al[7] at Delhi the mean age of MDR TB patients was (33.25±12.04) (18-55) years in our study age was (42.25±15.80) (14-70) in MDR group. The mean age and maximum age in our study was found to be higher but the minimum age was lower than study by Sharma et al[7] similarly in another study by Dholakia et al[8] mean age was 31 (15-61) once again our study had higher mean age and maximum age though minimum age was lower than study by Dholakia et al.[8]

In our study n=13 (65%) MDR patients were male, whereas n=7(35%) were female with male female ratio of 1.9:1. In study done by Sharma et al[7] male female ratio was 3.4:1 and in Dholakia et al[8] male female ratio was 1:1. So there is lot of variability but taking all studies in account there is a slight male predominance in MDR populations.

The following symptoms were seen in patients of study group fever, cough, expectoration, breathlessness, night sweats weight loss/ anorexia, statistically significant association was seen only in fever, hemoptysis, breathlessness in MDR group with p value of p=0.0079, p=0.041, p=0.023 respectively, fever was present in 100%(n=20) in MDR group as compared to 73%(n=58) in MDR group, cough was present in all patients in MDR and Non MDR group, expectoration was present in all patients across both groups, breathlessness was present in 60%(n=12) in MDR group and 32 %(n=26) in non MDR group. chest pain was present in 60% (n=12) in MDR group and 40%(n=32) in non MDR group. Hemoptysis was present in 35% (n=7) in MDR group and 15% (n=12) in non MDR group. Night sweats were present 25% (n=5) in MDR group and 19 %(n=15) in non MDR group. Similarly weight loss was present 85 % (n=17) in MDR group and 65%(n=52) in Non MDR group. Similarly lymphadenopathy was 20 % in MDR group and 9% in Non MDR group. Most common finding in MDR group was bronchial breath sounds;

bronchial breath sounds denote consolidation, cavitation and atelectasis. It was found in 55 % patients as opposed to 46 % in non MDR group. Crepts was second most common finding in MDR group with 30% having crepts, In Non MDR group 40 % had crepts. Rhonci was found in 10 % in MDR group and 11 % in non MDR group which means there was some obstructive component along with tuberculosis.

In our study 15 %(n=3) patients had infiltrates in MDR group compared with 41 % (n=33),MDR group had 35% patients with cavitatory lesions (20% u/l cavity, 15 % b/l cavities) in Non MDR group only 17 % had cavitatory lesions (13% u/l cavity, 4% b/l cavities).15 % in MDR group had fibrosis compared with 18 % in Non MDR group , volume loss was 20 % in MDR group compared with 13 % in Non MDR group. Consolidation was 15 % in MDR group and 8 % in Non MDR group. Pulmonary nodule was 0 % in MDR group and 3 % In Non MDR group**. So in our study predominant chest x-ray finding was cavitatory lesions and volume loss.** In study done by Dholakia N et al[8], a total of 20(80%) patient had cavitatory lesion, it is safe to deduce that cavitatory lesions and volume loss points to extensive disease. Also we classified our chest x ray findings by National Tuberculosis Association USA Guidelines which showed more number of cases 55% in MDR group in very advanced disease as compared to 40% in Non MDR group. Similarly 30% patient in Non MDR group had minimally advanced disease as compared to 10 % in MDR group.

Sputum monitoring and culture conversion have been shown to be good indicators of treatment outcome in drug-sensitive TB, but those indicators have not been validated for MDR-TB.[9-11] Among MDR-TB patients, persistent positive sputum cultures at month 6 of treatment had a high negative predictive value for failure and relapse, but only a modest positive predictive value (< 60%).[9,10] Horne et al. analyzed 20 studies where drug sensitivity testing (DST) was available, and found that both sputum-smear microscopy and mycobacterial culture during TB treatment have low sensitivity and modest specificity for predicting failure and relapse.[9] Brust et al.[12], evaluating a cohort of 56 patients with MDR-TB from a rural area of South Africa, found that the only independent predictor of culture conversion at 6 months was smear positivity.

## CONCLUSION

As concluded by our study the MDR prevalence is 20 % which is comparable to other hospital based studies, nationwide studies as well and the data obtained by WHO. TB, though it is a small scale hospital based study, with referral bias and exclusion criteria, more extensive studies on topic may put more light on subject. An association was found between fever and MDR TB, hemoptysis and MDR TB, and breathlessness and MDR TB but once again sample size being only 100 and this being a hospital based study more nationwide studies are need of the hour. Another point of serious concern is MDR TB in sputum negative individuals we found a single case of patient having sputum negative state and being MDR TB in DST, since PMDT now has made sputum negative retreatment cases eligible for DST, more studies including smear negative retreatment cases must be included into the fold now.

## REFERENCES

1. Word Health Organization. Anti-tuberculosis drug resistance in the world. Geneva: WHO Press, 1997.
2. World Health Organization. The stop TB strategy: building on and enhancing DOTS to meet the TB related Millennium Development Goals. Geneva: WHO Press, 2006.
3. World Health Organization. Guidelines for the programatic management of drug-resistant tuberculosis. Emergency update. WHO/HTM/TB/2008.402. Geneva, Switzerand: WHO, 2009.
4. Mesfin YM, Hailemariam D, Biadgilign S, Kibret KT. Association between HIV/AIDS and multi-drug resistance tuberculosis: a systematic review and meta-analysis. PLoS One, 2014; 9: e822-35.
5. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med., 2012; 9: e1001300.
6. Johnston JC, Shahidi NC, Sadatsafavi M, FitzGerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and metaanalysis. PLoS One, 2009; 4: e6914.
7. Surendra K. Sharma et al. Prevalence of multidrug-resistant tuberculosis amongCategory II pulmonary tuberculosis patients; Indian J Med Res., 133, March 2011; 312-15.
8. Dholakia YN, Shah DP. Clinical profile and treatment outcomes of drug-resistanttuberculosis before directly observed treatment strategy plus: Lessons for the program.Lung India, 2013; 30: 316-20.
9. Horne DJ, Royce SE, Gooze L, Narita M, Hopewell PC, Nahid P, et al. Sputum monitoring during tuberculosis treatment for predicting outcome: systematic review and meta-analysis. Lancet Infect Dis., 2010; 10: 387-394.
10. Qazi F, Khan U, Khowaja S, Javaid M, Ahmed A, Salahuddin N, et al. Predictors of delayed culture conversion in patients treated for multidrug-resistant tuberculosis in Pakistan. Int J Tuberc Lung Dis., 2011; 11: 1556-1559.
11. Kurbatova EV, Gammino VM, Bayona J, Becerra MC, Danilovitz M, Falzon D, et al. Predictors of sputum culture conversion among patients treated for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis., 2012; 16: 1335-1343.
12. Brust JC, Berman AR, Zalta B, Haramati LB, Ning Y, Heo M, et al. Chest radiograph findings and time

to culture conversion in patients with multidrug-resistant tuberculosis and HIV in Tugela Ferry, South Africa. PLoS One, 2013; 8: e73975.