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# Risk Factors of Multi Drug Resistant Tuberculosis among TB Patients in Surat District, Gujarat, India: A Case Control Study

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***Abstract:***
***Context:*** *The emergence of Multi-Drug Resistant Tuberculosis (MDR-TB), has become a significant public health problem and an obstacle to effective TB control. In India prevalence of Primary MDR-TB is 2.2% (1.9–2.6%) and Secondary MDR-TB is 15% (11–19%).So the factors responsible for Causation and Emergence of MDR-TB need to be assessed.*
***Aims:*** *Investigating the factors associated with Multi Drug Resistant-Tuberculosis.*
***Setting & Design:*** *An Unmatched Case Control Study, Purposively Recruited 68 MDR-TB Patients as Cases from DOTs Plus Site, NCH (New Civil Hospital) Surat and 136 Non - MDR-TB Patients on DOTS Therapy from Tuberculosis Ward, NCH Surat and UHC (Urban health Centre) and PHC (Primary health Centre) from Surat District as Control.*
***Material & Methods:*** *A pre-tested standardized semi-structured questionnaire was used. Data was collected and analysed by Bivariate Analysis for the categorical variables followed by Multivariate Analysis and model making by Binary Logistic Regression Method.*
***Results:*** *A Statistical Model prepared (having Nagelkerke $R^2$ -0.563) which showed Below poverty line (OR-6.250), HIV-AIDS status (OR-5.913), Industrial work (OR-7.249), Non-Industrial work (OR-0.075), Duration of stay at Present address 1-10 Years (OR-4.762) were factors found to be significantly (P value<0.05) associated with MDR-TB. Smoking, Inadequate DOTs Therapy and Previous history of Tuberculosis have not been detected as risk factors.*
***Conclusions:*** *Multivariate analysis showed important Risk factors for MDR-TB. Study findings will guide the policy makers in planning and implementing effective strategies for control of MDR-TB.*
***Keywords:*** *multi drug resistant tuberculosis, risk factors, case control*

## I. Introduction

The rapid expansion of multidrug-resistant tuberculosis (MDR-TB; i.e., resistance to Isoniazid and Rifampicin) has jeopardized global control of TB. MDR-TB exacerbates the existing grim TB epidemic, poses a great threat to global TB control and incurs a huge burden on developing countries due to its difficult, expensive, less effective and toxic treatment.[1]

World Health Organization estimates that there were about 450,000 new (incident) MDR-TB cases in the world in the year 2012. More than one half of these cases occurred in China, India, and the Russian Federation. About 170,000 MDR-TB deaths are estimated to have occurred in the year 2012. The biggest increases were in India, South Africa and Ukraine.[2]

A study by James C.M. Brust et al. published in year 2010 showed that out of the 1209 patients with known MDR TB treatment outcomes, 491 (41%) were cured, 35 (3%) completed treatment, 208 (17%) failed treatment, 223 (18%) died while on treatment, and 252 (21%) defaulted on treatment. Overall, 526 (44%) had a favourable outcome (cure or completed), while 683 (56.5%) had an unfavourable outcome (failed, died, defaulted)[3]

In India, MDR-TB prevalence among notified new pulmonary TB Patients is 2.2% (1.9–2.6%) and among notified Re-treatment pulmonary TB patients is 15% (11–19%).[2]

Since time it is emphasized that MDR TB is a man-made phenomenon, **poor drug, poor treatment, poor compliance** leads to its emergence.[4]So, the factors responsible for its causation and emergence of drug resistance tuberculosis need to be assessed. This study is done to assess the factors associated with MDR-TB, So that necessary action can be taken to reduce the disease burden of MDR-TB.

## II. Aim & objective

To investigate the factors associated with causation & emergence of Multi Drug Resistance Tuberculosis.

## III. Subjects and Methods

**3.1 Study Design:** Unmatched Case Control study.
**3.2 Study Setting:** Cases were selected from the indoor ward of the Department of Pulmonary Medicine and controls were selected from the UHCs and PHCs of Surat City and District respectively.
**3.3 Study duration:** From October 2013 - June 2014.
**3.4 Study Tool:** A pre-tested standardized semi-structured questionnaire was used.
**3.5 Sampling Technique:** Purposive Sampling
**3.6 Sample Size:** History of smoking has been found to be the important risk factor for development of MDR-TB, having significant association (p value0.032) as well least odds ratio (2.350) was taken in to account while calculating sample size.[5] Interviews of 10 controls was taken before starting the actual data collection and found 3 (30%) controls having the history of smoking. Taking the same (30%) as expected frequency of history of smoking in control groups, at desired Confidence Level of 95 %, at desired Power of 80 %, taking Controls to Cases ratio of 2:1 and taking 2.350 as the Smallest OR that we would like to be able to detect; desired sample size came out to be 68 Cases and 136 Controls as calculated by Open Epi software according to Fiess method.
**3.7 Selection of Cases and Controls:** Drug sensitivity testing was carried out at DTC Surat. CBNAAT method is used in which Rifampicin Drug sensitivity testing was done. Those patients whose sputum was found resistant to Rifampicin sensitivity testing were considered as cases and those patients whose sputum was found to be sensitive to Rifampicin sensitivity testing were considered as controls if they fulfil inclusion and exclusion criteria of our study.
**3.7.1. Inclusion criteria for Cases and Controls:**
Only those patients whose sputum samples have been tested for Drug Sensitivity Testing (under MDR suspect criteria) during the study duration were enrolled as cases & controls.
**3.7.2. Exclusion criteria for Cases and Controls:**
Previously diagnosed MDR TB patients on DOTS Plus therapy.
**3.8 Assumption:** We assumed that all those patients who were diagnosed to be suffering from MDR-TB (Cases) and admitted at Pulmonary Medicine Department of New Civil Hospital, Surat came from the same source population as that of Non MDR-TB Patient (Controls).
**3.9 Bias:** Being a case control study, the study was subjected to Recall Bias, Interview Bias, Selection Bias, and Sampling Bias. Since sampling technique was purposive sampling which is being a non-probability sampling, so the findings of this study cannot be generalised.
**3.10 Data Collection:** All the Study Participants were asked about their socio demographic profile, residence, economic status, social behaviour, addictions and variables related to TB treatment. Occupations is divided into Industrialised Worker, Non-Industrialised worker, Housewife, Student and Unemployed, Type of Family is defined as Joint Family, Nuclear Family, Three Generations Family and Household.
**3.11. Data Entry and Analysis:** Data entry and some of the preliminary analysis was done with the help of Microsoft excel 2003. At first, bivariate analysis was conducted in Epi Info 3.5.1.0. Bivariate and Multivariate analyses were conducted and all possible interactions were assessed. All the explanatory significant variables were entered in to the Multiple Logistic Regression model using Enter wise method and model was prepared in SPSS 19.0 software.

**3.12. Limitation of the study:**

Being a case control study, the study was subjected to Recall Bias, Interview Bias, Selection Bias. Since sampling technique was purposive sampling which being a non-probability sampling, so the findings of this study cannot be generalised.
**3.13 Ethical Consideration:** Study was approved by Human Research Ethics Committee of Government Medical College, Surat

## IV. Results

**4.1. Distribution sf study subjects as per their Socio-Demographic Attributes and MDR-TB.**

In our study, about 72 % (146) of the participants were male and rest were female. Nearly 84 % (171) participants belonged to the age group of 18 – 45 years with the Mean age among 35.09±12.1 years. Majority of participants (66.66 %) have received up to primary education and rest have received higher than primary education. About 91 % of the participants belonged to the Hindu religion, 50 % belonged to nuclear family and about 76 % were married.

After the Bivariate analysis of all the socio demographic variables studied, Male Gender (OR-1.76) and education up to primary school (OR-1.78) have showed significant association (p value < 0. 05) with MDR-TB. (as mentioned in Table 1)

**Table 1:** Distribution of Study Subjects as Per their Socio-Demographic Attributes and MDR-TB.

| Variables | | Case (N=68) N ( % ) | Control (N=136) N( % ) | P VALUE | OR | 95% CI |
|---|---|---|---|---|---|---|
| **Gender** | **Male** | 40(58.8) | 106(77.9) | **0.004** | **1.762** | **1.211-2.564** |
| | **Female** | 28(41.2) | 30(22.1) | **Reference** | | |
| **Age In Years** | **18-30 Years** | 38(55.8) | 48(35.3) | 0.666 | 1.794 | 0.126-25.586 |
| | **31-45 Years** | 21(30.9) | 64(47.1) | 0.980 | 0.968 | .071-13.242 |
| | **46-60 Years** | 8(11.8) | 18(13.2) | 0.875 | 1.243 | 0.083-18.542 |
| | **More Than 60** | 1(1.5) | 6(4.4) | **Reference** | | |
| **Education Status** | **Up to Primary Education** | 36(52.9) | 100(73.5) | **0.003** | **1.778** | **1.220-2.591** |
| | **Higher Than Primary Education** | 32(47.1) | 36(26.5) | **Reference** | | |
| **Caste** | **SC** | 14(20.6) | 46(33.8) | 0.296 | 1.9.5 | 0.569-6.374 |
| | **ST** | 6(8.8) | 5(3.7) | 0.058 | 5.571 | 0.946-32.804 |
| | **SEBC** | 24(35.3) | 36(26.5) | 0.130 | 2.368 | 0.777-7.223 |
| | **General** | 17(25) | 23(16.9) | 0.50 | 3.363 | 1.002-11.288 |
| | **Do Not Know** | 7(10.3) | 26(19.1) | **REFERENCE** | | |
| **Type of Family** | **Nuclear** | 36(52.9) | 65(47.8) | 0.086 | 3.045 | 0.853-10.871 |
| | **Joint** | 18(26.5) | 31(22.8) | 0.177 | 2.825 | 0.626-12.742 |
| | **Three Generation** | 10(14.7) | 19(14) | 0.105 | 3.051 | 0.793-11.746 |
| | **Household** | 4(5.9) | 21(15.4) | **REFERENCE** | | |
| **Religion** | **Hindu** | 58(85.3) | 127(93.4) | 0.05 | 0.375 | 0.140-1.007 |
| | **Non-Hindu** | 10(14.7) | 09(6.6) | **REFERENCE** | | |
| **Marital Status** | **Married** | 52(76.5) | 104(76.5) | 0.986 | 1.006 | 0.506-2.002 |
| | **Unmarried/Others** | 16(23.5) | 32(23.5) | **REFERENCE** | | |

### 4.2. Distribution of Residence Variables and their association with MDR-TB.

Majority of participants (52 %) were residing in urban area, 35 % were residing in peri-urban area and about 13 % were residing in rural area. Duration of stay at present residence for less than 1 year (OR-4.187) & Duration of stay at present residence for 1-10 years (OR-4.762) were found to have significant association with MDR-TB when compared to duration of stay more than 20 years, Migration among study participants is also found to be significantly associated with causation of MDR-TB (OR-1.86) In contrast to this, peri-urban residency has significant protective association (OR-O.24) with MDR-TB. (as mentioned in Table 2)

**Table 2:** Distribution of Residence Variables and their association with MDR-TB.

| Variables | | Cases (N=68) N( % ) | Control (N=136) N( % ) | P Value | OR | 95% CI |
|---|---|---|---|---|---|---|
| **Present residence** | **Periurban** | 18(26.5) | 53(39) | 0.049 | 0.249 | 0.062-0.995 |
| | **Urban** | 36(52.9) | 70(51.5) | 0.387 | 0.573 | 0.162-2.024 |
| | **Rural** | 14(20.6) | 13(9.6) | **Reference** | | |
| **Duration of stay at present residence** | **1(<1 Year)** | 12(17.6) | 10(7.4) | 0.020 | 4.762 | 1.275-17.803 |
| | **2(1-10 Years)** | 22(32.4) | 32(23.5) | 0.016 | 4.187 | 1.304-13.444 |
| | **3(10-20Years)** | 14(20.6) | 35(25.7) | 0.423 | 1.613 | 0.501-5.198 |
| | **4(>20 years)** | 20(29.4) | 59(43.4) | **REFERENCE** | | |
| **Migration** | **Yes** | 13((19.2) | 10(7.4) | 0.012 | 1.860 | 1.221-2.833 |
| | **No** | 55(80.8) | 126(92.6) | **REFERENCE** | | |

**4.3. Distribution of Economic Variables, Addictive Behaviour and Comorbidities and Their Association With MDR-TB.**

Majority of study participants (36 %) were non-industrial worker followed by industrial worker (23 %) and house wife (22 %). About 17 % of the participants were unemployed & 3 % were students. Industrial workers were mainly Textile factory& Diamond Industry workers. Other variables like Socio economic status based on Per capita monthly income by modified BG Prasad's classification shows that majority of study participants belonged to Socio-economic class IV(35 %) followed by class V (27 %), class III (25 %), class II (12 %) and class I (1 %) In a bivariate analysis, Industrial work among study participants was found to be significantly associated with MDR-TB (OR-7.249) while non industrial work was found to have protective association with MDR-TB (OR-0.117).BPL(Below Poverty Line) category study participants were found to be more at risk of acquiring MDR-TB (OR-6.057) as compared to APL (Above Poverty line)category study participants. Socio Economic status as per modified BG Prasad's classification (updated October 2014) is found to have no significant association with MDR-TB. (as mentioned in Table 3)

**Table 3:** Distribution of Economic Variables and their association with MDR-TB.

| Variables | | Cases ( N= 68 ) N( % ) | Controls (N= 136 ) N( % ) | P Value | OR | 95% CI |
|---|---|---|---|---|---|---|
| **Occupation** | **Industrial worker** | 30 (44.1) | 16 (11.8) | **0.002** | **7.249** | **2.009-26.53** |
| | **Non industrial worker** | 4 (5.9) | 69 (50.7) | **0.008** | **0.117** | **0.024-0.573** |
| | **Housewife** | 22 (32.4) | 23 (16.9) | 0.131 | 2.675 | 0.746-9.591 |
| | **Student** | 5 (7.4) | 1 ( 0.7) | 0.099 | 10.188 | 0.648-160.125 |
| | **Unemployed** | 7 (9.3) | 27 (19.9) | **REFERENCE** | | |
| **Whether Belong to BPL Category** | **Yes** | 28 (41.2) | 40 ( 29.4) | **0.041** | **6.057** | **1.074-34.168** |
| | **No** | 35 (51.5) | 83 ( 61 ) | 0.225 | 2.647 | 0.550-12.746 |
| | **Don't know** | 05 (7.3) | 13 ( 9.6 ) | **REFERENCE** | | |
| **Socio-Economic Status** | **1** | 01 (1.5) | 02 ( 1.5 ) | 0.590 | 0.426 | 0.019-9.490 |
| | **2** | 09(13.2) | 15( 11 ) | 0.511 | 0.616 | 0.145-2.613 |
| | **3** | 20(29.4) | 31( 22.8) | 0.799 | 1.169 | 0.351-3.891 |
| | **4** | 20(29.4) | 51( 37.5) | 0.573 | 1.377 | 0.452-4.200 |
| | **5** | 18(26.5) | 37(27.2) | **REFERENCE** | | |

Among study participants, about 38 % of the participants were addicted to alcohol, 38 % were addicted to tobacco chewing & 22 % were addicted to smoking. Co-morbidities like HIV-AIDS and Diabetes Mellitus were found in only 16 % and 6 % of the participants respectively.

On bivariate analysis, alcohol addiction is found to have significant association (OR-2.012) with MDR-TB. Among co-morbidities sero-positive status for HIV-AIDS is also found to be significantly associated with MDR-TB (OR-5.193). Other Behavioural risk Factors like Smoking (which is an important risk factor for Tuberculosis), Habit of Tobacco chewing, and Co-Morbidities like Diabetes Mellitus were not found to have any significant association with MDR-TB.

**4.4. Distribution of Tuberculosis Treatment Related Variables and their association with MDR-TB.**

Among study participant's majority of Cases (64.7%) and Control group (63.2%) were suspected to be suffering from MDR-TB under criteria B1. It indicates that majority of emergence of cases of MDR-TB is suspected among re-treatment case of Tuberculosis.

In our study, about 62 % of the participants have followed DOTS regularly while about 33 % of the participants have discontinued their treatment at least once during their previous treatment. About 64 % of the study participants were diagnosed as having tuberculosis at Government Health Facility.

In about 35 % of the participants, family members were also affected of Tuberculosis while about 80 % of the participants have past history of Tuberculosis.

After analysis of variables related to Tuberculosis and it Treatment, two variables like Tuberculosis Diagnosis at Government health facility (OR-0.569) and family history of Tuberculosis (OR-0.614) were found to have a significant protective association with MDR-TB. (as mentioned in Table 4)

**Table 4:** Distribution of Tuberculosis Treatment Related Variables and their association with MDR-TB.

| Variables | | Case ( N= 68 ) N( % ) | Controls (N= 136 ) N( % ) | P Value | OR | 95% CI |
|---|---|---|---|---|---|---|
| **DOTS Followed** | **YES** | 36(53) | 90(66.3) | 0.067 | 1.436 | 0.979-2.107 |
| | **NO** | 32(47) | 46(33.7) | **REFERENCE** | | |
| **Discontinued Treatment** | **Yes** | 26(38.2) | 41(30.1) | 0.295 | 2.040 | 0.537-7.750 |
| | **No** | 33(48.5) | 65(47.8) | 0.264 | 2.087 | 0.574-7.585 |
| | **NA** | 9(13.3) | 30(22.1) | **REFERENCE** | | |
| **Health facility of diagnosis** | **Government** | 34(50) | 96(70.6) | **0.004** | **0.569** | **0.389-0.832** |
| | **Non-Government** | 34(50) | 40(29.4) | **REFERENCE** | | |
| **Family history of Tuberculosis** | **Yes** | 32(47.1%) | 40(29.4%) | **0.013** | **0.614** | **0.420-0.897** |
| | **No** | 36(52.9%) | 96(70.6%) | **REFERENCE** | | |
| **Past history of Tuberculosis** | **Yes** | 58(85.3%) | 106(77.9%) | 0.212 | 0.707 | 0.398-1.257 |
| | **No** | 10(14.7%) | 30(22.1%) | **REFERENCE** | | |

### 4.5. Adjusted association of exposure variables with MDR TB (Multivariate analysis)

In Bivariate analysis, thirteen exposure variables (Gender, Education, Industrial work, Non- Industrial work, Place of residence, Duration of stay at Present address<1 year, Duration of stay at present address 1-10years, HIV-AIDS status, Migration, BPL category, Alcohol consumption, health facility of TB Diagnosis, family history of tuberculosis) were found to be significantly associated with MDR TB. In multivariate analysis of these significant variables, five factors (duration of stay at present address 1-10 years, Industrial Work, Non-Industrial Work, BPL category, HIV-AIDS status) were found to be the independent risk factors for MDR TB after controlling for other variables.

Multivariate analysis shows that there are five factors which are consistently significant with p value < 0.05. Among these five factors, the highest strength of association was for having HIV-AIDS positive status with an Odds Ratio of 11.3, followed by Industrial Work (OR- 5.816), BPL category (OR- 6.25), Duration of stay at present address for 1-10 years (OR -3.56). In contrast to this Non-Industrial work was found to have protective association with MDR TB with an Odds ratio of 0.75. (as mentioned in Table 5)

This model explained 56.3% of the independent variables (Nagelkerke R Square was 0.563). Hosmer and Lemeshow statistic was 0.693.

**Table 5:** Significant Variables that remained in The Final Model of Binary Logistic Regression analysis using Enter Method in Scenario.

| Significant Variables in the final model | B | S.E. | P | OR | 95% CI for aOR | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| **Duration of Stay at present address (1-10 years)** | 1.272 | 0.613 | **0.038** | **3.569** | **1.072** | **11.872** |
| **Occupation –Industrial Work** | 1.761 | 0.664 | **0.008** | **5.816** | **1.582** | **21.373** |
| **Occupation –Non-Industrial Worker** | -2.591 | 0.855 | **0.002** | **0.075** | **0.014** | **0.401** |
| **Belong to Below poverty line** | 1.833 | 0.874 | **0.036** | **6.250** | **1.128** | **34.631** |
| **HIV status** | 2.427 | 0.883 | **0.006** | **11.328** | **2.008** | **63.870** |
| **Constant** | -3.998 | 1.986 | 0.044 | 0.018 | | |

## V. Discussion

In the present study, after the bivariate analysis of all the socio demographic variables we found male Gender showed significant association with MDR-TB. (p value-0.004, OR-1.762), this finding is supported by study by Selamawit Hirpa1 et al.[6] which showed that male gender is having significant association with MDR-TB (OR -2.7). Participants with education up to primary school have 1.78 times higher chances of developing MDR-TB (p value-0.003, OR-1.778). These findings were supported by study conducted at DOTs clinic in Nepal by Neha Deo et al.[7] and similar studies by Chen a,y et al. in China [8] and Gajanan S. Gaude et al. in India .[9] which showed that no formal education has significant association with MDR-TB. Analysis also showed that there is significant association with occurrence of MDR-TB (p value-0.012, OR-1.860.) among migrant population. These findings were supported by Study by Shen X et al. which showed that being an urban migrant and residence in an urban area of Shanghai were independently associated with resistance to any first-line drug and MDR in new cases, as well in previously treated cases.[10]

Duration of stay at present address for less than 1 year (OR-4.187) & duration of stay at present address for 1-10 years (OR-4.762) are found to have significant association with MDR-TB. Peri-urban residence was found to have significant protective association (p value-0.049, OR-0.249,) with MDR-TB. Contrast to the

present study, a study by Neha et al. (adjusted OR 3.06 with 95% CI: 1.11-8.41) showed positive association with peri-urban residence and incidence of MDR-TB. The reason given by the study was immigration issue, unhealthy life style among residence places.[7]Study Participants belonging to BPL Category have significant association with MDR-TB ( p value-0.041,OR-6.057). Study by Neha Deo et al. found that Wealth status was found to be associated with MDR-TB; where people belonging to the lower wealth group were 1.7 times more likely to get MDR-TB as compared to those belonging in the upper wealth category (OR-1.7).[7] In the present study, industrial work among study participants was found to be significantly associated with MDR-TB (OR-7.249) while non-industrial work was found to have protective association with MDR-TB (OR-0.117).

Relationship of social behavior with MDR-TB shows that Alcohol addiction is found to have 2 times higher chances of acquiring MDR-TB as compared to non -alcoholics (P value-0.002, OR-2.012). These finding is supported by a Study done at Belarus by Skrahina A et al. which showed alcohol abuse has positive association with MDR-TB. (OR: 1.3).[5]

Among study participants, co-morbidities like HIV-AIDS showed significant association with MDR-TB (P value-0.001, OR-5.193). Similar finding was seen in a study by Casal M et al. which was published in 2005 which showed positive association of AIDS (OR-1.96) with MDR-TB.[11]Tuberculosis Diagnosis at Govt. health facility (p value- 0.004, OR-0.569) was found to have protective association with MDR TB. A study done published in 2013 by Selamawit Hirpa et al. showed that participants those who were always observed during treatment, were four times less likely to develop MDR-TB than those who were never observed.[6] Another variable which showed protective association with MDR TB was family history of Tuberculosis (p value-0.013, OR-0.614). Contrast to this a study done by Casal M et al. tuberculosis contacts (OR-2.01) has positive association with MDR-TB.[11]

## VI. Conclusion

In the final model, among the thirteen exposure variables which came significant by bivariate analysis, five factors were found to be the independent risk factors for MDR-TB after controlling for other variables.
Below mentioned is the equation which depicts the P(Y) i.e. Probability of occurrence of MDR-TB by the five variables which were found to be significant associated by Multivariate binary logistic regression elimination method.

There is a need to undertake similar studies in variety of settings to establish role of other determinants. Association of MDR-TB with poverty indicates that we need to execute variety of welfare activities and pro poor schemes effectively for uplifting the economic standards of under privileged people.

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