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Research Article

**RISK FACTORS FOR MDR TB IN VULNERABLE PATIENTS**Dr Salik Ahmed Cheema<sup>1</sup>, Dr Mohammad Mustafa<sup>2</sup>, Dr Muhammad Abdul Rehman<sup>3</sup><sup>1</sup> King Edward Medical University, Lahore<sup>2</sup> Saidu Medical College, Swat<sup>3</sup> Punjab Medical College, Faisalabad

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**Abstract:**

**Objective:** The objective of our study was to determine the frequency of risk factors for MDR TB in vulnerable groups.

**Methodology:** 80 patients of MDR-TB who presented to the Out Patient Department (OPD), were recruited into six vulnerable groups namely; Prisoners, Immigrants, Pregnant Women, Drug Addicts, Diabetics and Children. A detailed questionnaire containing a list of the possible risk factors for MDR TB in each group was administered to the relevant participant. Information regarding socioeconomic status, comorbidity, patient compliance, drug availability (free or purchased), and their contacts was obtained and analyzed through SPSS Software. Descriptive analysis and cross tabs were used to obtain the results.

**Results:** Of the 80 participants 93.8% had low socioeconomic status, 66.2% had acquired only primary education, 40% had contact history and 30% could not complete DOTS regimen. Crowded living, delayed diagnosis of disease and inadequate nutrition were also found to be significant risk factors for MDR TB. Specific risk factors found in diabetics were lack of lifestyle modifications and irregularity in checking blood sugar levels. For drug abusers, most of whom resorted to oral drugs and half to intravenous, smoking and alcoholism were found to be potential predisposing factors for MDR TB.

**Conclusion:** Our study shows the challenges involved in treating MDR TB and the complications that arise when comorbidities and social and financial restrictions are taken into account. Studies with longer time spans, larger sample size for individual groups and controlled trials can better highlight these aspects in future studies.

**Key words:** MDR-TB. Multi-drug resistant tuberculosis. Factors.

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**INTRODUCTION:**

Tuberculosis(TB), the eighth leading cause of death worldwide, is a potentially fatal contagious disease primarily affecting lungs, caused by Mycobacterial species.<sup>[1]</sup> It can be divided into pulmonary and non-pulmonary tuberculosis, both of which on the basis of positivity or negativity of smear test can be drug sensitive or resistant.<sup>[2]</sup> Failure to control TB is due to HIV infection, epidemics of tuberculosis, and emergence of multidrug-resistant strains of tuberculosis.<sup>[3]</sup> Multidrug-resistant tuberculosis [MDR-TB] is defined as tuberculosis infection which is resistant to at least isoniazid and rifampin.<sup>[4]</sup> Vulnerability to TB can be due to adverse health and socioeconomic states, and geographic distribution.<sup>[5]</sup> Especially vulnerable are marginalized communities such as immigrants, homeless people, HIV positive patients, health care workers, prisoners, close contacts of tuberculosis patients, pregnant women, alcoholics and cross-border populations.<sup>[6,7,8]</sup> According to WHO, over 95% tuberculosis related deaths occur in low- and middle-income countries and tuberculosis is ranked among the top 5 causes of death for women aged 15 to 44. In 2014, 9.6 million people contracted the disease, with the death toll reaching 1.5 million, while approximately 480 000 people developed multidrug-resistant tuberculosis.<sup>[9]</sup> It is the leading killer of HIV-infected persons worldwide, causing 400 000 of the 1.2 million HIV deaths reported in 2014.<sup>[10,11]</sup> In a study conducted in the United States 85% of the tuberculosis patients were found to be foreign-born.<sup>[12]</sup> MDR TB costs 50-200 times more than non-resistant TB in treatment.<sup>[13]</sup> In a research in Rawalpindi, certain risk factors found were: over crowdedness (73.3%), illiteracy (60%), unemployment (60%); low monthly income - less than Rs 5000 (60%), smoking(60%) and patients suffering from one or more pulmonary diseases or complications (83.3%), patients with non-pulmonary diseases (23.4%).<sup>[14]</sup> Moreover, fear of infection from tuberculosis has made it one of the worst stigmas of the population, a fact which strongly hinders tuberculosis control.<sup>[15]</sup> In 2010, 431/100,000 cases of TB in Tibetan refugees in India were reported( compared with 181/100.000 cases in general population).<sup>[16]</sup> Russian study (2005) showed that MDR prisoners were nearly twice as likely to be resistant to isoniazid (rate ratio (RR) 1.9 (95% CI 1.3 to 2.6)), rifampicin (RR 1.6 (95% CI 1.0 to 2.6)), or to have MDR TB (RR 1.9 (95% CI 1.1 to 3.2)) <sup>[17]</sup> A study in Thailand revealed 5.8 times increased risk of MDR TB development in diabetics and hypertensives.<sup>[18]</sup> Approximately 32 000 children fall sick each year with MDR-TB, the children being more vulnerable than adults to contract it from an affected relative.<sup>[19]</sup>

In Pakistan, though qualitative studies identifying risk factors in vulnerable groups are abundant but not quantitative, because high risk groups are not reporting promptly in Health Care Units. This is due to fear of stigmatization, unawareness and lack of facilities of proper accommodation, cheaper drugs, coordination amongst health care providers and welfare funds for these predominantly poor people. For widespread awareness and better health care provision, we need to identify risk factors in them, reach out to them ourselves and also implement prophylactic measures. Only via identifying risk factors can we proceed to developing ways to fight and minimize them and root out this malady from our tuberculosis plagued country.

**METHODOLOGY:**

For this cross sectional study, 80 known MDR TB patients who presented to the OPD of Department of Chest Medicine, Mayo Hospital Lahore and fulfilled the criteria for inclusion were recruited by simple random sampling. MDR cases were those who were resistant to two or more first line drugs, namely Rifampin and Isoniazid, as diagnosed by Gene Xpert testing. We made six groups with vulnerability to MDR TB, a vulnerable person being an individual who carries a higher chance of acquiring a multidrug-resistant tuberculosis infection. These were namely prisoners, immigrants, pregnant women, drug addicts, diabetics and children, whereby a prisoner was defined as a person who has spent time in prison; pregnant woman, as a woman in second or third trimester of pregnancy; drug addict as an abuser of drugs, in any form, who uses the drugs daily for more than 6 months; child, an individual, male or female, under 14 years of age ; and Immigrant, a person who has lived in a TB endemic area for >3 months. We reviewed the patients' medical records from the department database (retrospectively) to find out the vulnerable group to which each patient belonged and to determine certain characteristics that each group had: socioeconomic status, comorbidity, patient compliance, drug availability (free or purchased), and information about their contacts. A detailed questionnaire was prepared containing a list of the possible risk factors for MDR TB in each group, and each patient was interviewed and evaluated through it. Data obtained from the questionnaires was analyzed through SPSS Software version 16. Descriptive analysis and cross tabs were used to obtain the results.

**RESULTS:**

The gender ratio was 1.1 (42 females):1 (38 males). Mean age was 38.45 yrs. Mean age for males was 40.32. Mean age for females was 36.76. A total of 80

participants were further categorized into subgroups. Prisoners (n=2), Immigrants (n=1), Pregnant (n=3), Diabetics (n=47), Addicts (n=17) and Children (n=14).

For the whole study group, 66.2% (n=53) were educated only up to primary level and 93.8% (n=75) belonged to a low socioeconomic status. 40% (n=32) had had a contact with a person having TB. 70 % (n=65) affirmed to have completed the DOTS

regimen. Crowding in their residence was inquired, with 65% (n=52) residing in houses with less than 3 rooms and 35% (n=28) having 10 or more members living with them. 100% (n=80) had received BCG vaccination and got subsidized medication from hospitals/NGOs. 65% (n=52) had no difficulty in accessing a healthcare facility and did not ascribe social stigma or laziness in availing medical help. With regards to nutrition, 62.5% (n=50) had adequate protein in their diets.

		Frequency	Percentage
1	Gender		
	Male	38	47.5
	Female	42	52.5
2	Education		
	Primary	53	66.2
	Secondary	14	17.5
	higher	7	8.8
	Not educated	6	7.5
3	No of rooms in house		
	3 or less	52	65
	4 or more	28	35
4	No of family members		
	10 or less	52	65
	10 or more	28	35
5	Socioeconomic status		
	Lower	75	93.8
	Middle	5	6.2
6	Any other disease?		
	Yes	54	67.5
	No	26	32.5
7	Does any contact have TB?		
	Yes	32	40
	No	48	60
8	Have you had BCG vaccine?		
	Yes	80	100
	No	0	0
9	Where did you get medicine from ?		
	Hospital/NGO(yes)	80	100
	Yourself(no)	0	0
10	Did you complete DOT?		
	Yes	56	70
	No	24	30
11	Are you a prisoner?		
	Yes	2	2.5
	No	78	97.5
12	Do you get adequate proteins in diet?		
	Yes	50	62.5
	No	30	37.5

In the diabetics subgroup (n=47), mean age=47 yrs, 76.6% (n=36) had only primary education and 95.7% (n=45) belonged to a lower socioeconomic status. 87.2% (n=41) had completed the DOTS regimen. 38.3% (n=18) had a contact with a person having TB. 76.6% (n=36) resided in houses with less than 3 rooms and 36.2% (n=17) had 10 or more people living with them. Specific questions directed to the Diabetics subgroup showed that all of them

(100%, n=47) took medication for diabetes but their lifestyle measures showed that 65.9% (n=31) did not exercise regularly, 44.7% (n=21) did not control their diets and 74.5% (n=35) did not check their blood sugar levels.

<b>Diabetics( Total 47)</b>		
		frequency
1	Education	
	Primary	36
	Secondary	7
	higher	3
	Not educated	1
2	No of rooms in house	
	3 or less	36
	4 or more	11
3	No of family members	
	10 or less	30
	10 or more	17
4	Socioeconomic status	
	Lower	45
	Middle	2
5	Any other disease?	
	Yes	47
	No	0
6	Does any contact have TB?	
	Yes	18
	No	29
7	Have you had BCG vaccine?	
	Yes	47
	No	0
8	Where did you get medicine from ?	
	Hospital/NGO(yes)	47
	Yourself(no)	0
9	Did you complete DOT?	
	Yes	41
	No	6
10	Do you get adequate protein diet?	
	Yes	29
	No	18
11	What is your BMI?	
	<30	40
	>30	7
12	Do you control sugar in diet?	
	Yes	26
	No	21
13	Do you take 20-30 min exercise daily?	
	Yes	16
	No	31
14	Do you take medicine for diabetes?	
	Yes	47
	No	0
15	Do you regularly check blood sugar?	
	Yes	12
	No	35

In the addicts subgroup (n=17), 70.6% (n=12) only had primary education and 88.2% (n=15) belonged to a lower socioeconomic status. 41.2% (n=7) confirmed to have a contact having TB. Only 47.1% (n=9) completed the DOTS regimen. 76.5% (n=13) resided in houses with less than 3 rooms with 29.4% (n=5) living with 10 or more people. Apart from MDR-TB, 70.6% (n=12) replied affirmatively to having a co-morbidity. Varied addictions were noted, with 94.1% (n=16) partaking in oral substance abuse and cigarette smoking. 47.1% (n=8) of the addicts were also alcoholics.

<b>Addicts( 17)</b>		
1	Education	
	Primary	12
	Secondary	2
	higher	0
	Not educated	0
2	No of rooms in house	
	3 or less	13
	4 or more	4
3	No of family members	
	10 or less	12
	10 or more	5
4	Socioeconomic status	
	Lower	15
	Middle	2
5	Any other disease?	
	Yes	12
	No	5
6	Does any contact have TB?	
	Yes	7
	No	10
7	Have you had BCG vaccine?	
	Yes	17
	No	0
8	Where did you get medicine from ?	
	Hospital/NGO(yes)	17
	Yourself(no)	0
9	Did you complete DOT?	
	Yes	8
	No	9
10	Do you get adequate protein diet?	
	Yes	13
	No	4
11	Is the substance of abuse oral?	
	Yes	16
	No	1
12	Is the substance of abuse I/V?	
	Yes	7
	No	10
13	Do you smoke?	
	Yes	16
	No	1
14	Are you alcoholic?	
	Yes	8
	No	9

In the children (n=14) subgroup, there was a uniform distribution in education levels with primary and secondary education recording 28.6% (n=4) participants each whereas both higher education and uneducated showing 21.4% (n=3). 92.9% (n=13) belonged to a lower socioeconomic status. 57.2% (n=8) completed the DOTS regimen and 42.9% (n=6) had a contact with a person having TB. 35.8% (n=8) resided in houses with less than 3 rooms with the members being 10 or more for 42.9% (n=6). In this sub-group, the respondents who declared having adequate protein in diet were 50% (n=8) which was below average compared with other subgroups. No co-morbidity was present amongst the participants (100%, n=14). 42.9% (n=6) thought themselves to be weak as compared to their peers.

Children ( total 14)		
1	Education	
	Primary	4
	Secondary	4
	higher	3
	Not educated	3
2	No of rooms in house	
	3 or less	5
	4 or more	9
3	No of family members	
	10 or less	8
	10 or more	6
4	Socioeconomic status	
	Lower	13
	Middle	1
5	Any other disease?	
	Yes	0
	No	14
6	Does any contact have TB?	
	Yes	6
	No	8
7	Have you had BCG vaccine?	
	Yes	14
	No	0
8	Where did you get medicine from ?	
	Hospital/NGO(yes)	14
	Yourself(no)	0
9	Did you complete DOT?	
	Yes	8
	No	6
10	Do you get adequate protein diet?	
	Yes	7
	No	7
11	Are you weaker than normal kids?	
	Yes	6
	No	8
12	Do you often acquire flu?	
	Yes	2
	No	12

In the prisoners subgroup (n=2), 100% (n=2) only had primary education and belonged to a lower socioeconomic status. 50% (n=1) confirmed to have a contact having TB. 100% (n=2) completed the DOTS regimen. 50% (n=1) resided in houses with less than 3 rooms with 100% (n=2) living with less than 10 family members. 100% (n=2) had adequate protein intake and also reported inadequate ventilation in prison.

In the pregnant women subgroup (n=3), 100% (n=3) only had primary education and belonged to a lower socioeconomic status. 33.3% (n=1) confirmed to have a contact having TB. Only 33.3% (n=1) completed the DOTS regimen. 66.6% (n=2) resided in houses with less than 3 rooms, with 66.6% (n=2) living with less than 10 family members. No significant finding was obtained other than the presence of anemia, fever and weight loss during pregnancy in 33.3% (n=1) of the patients, pointing to a decrease in immunity.

There was only one immigrant in our study group, having primary education, a low socioeconomic status and positive TB contact history. He did not complete DOTS regimen, neither did he have adequate protein diet. He reported a low health budget in his previous country, as well as diagnostic delay due to difficulty in health care access.

### DISCUSSION:

Small sample size as a whole and within the subgroups means that gender cannot be termed as a significant predictor for MDR TB in vulnerable groups. For the subgroups of prisoners, immigrants, and pregnant women, no conclusive remarks can be made on prominent indicators for MDR-TB due to inadequate number of participants. Amongst the factors that were statistically significant in being present amongst MDR-TB patients of all vulnerable groups were the education levels and socioeconomic status of the participants. Education up to primary level along with a low socioeconomic status was overwhelmingly common and dictates that physicians should take these markers into account while administering care and explaining dosage regimen. Similar results have been proved in a study carried out in Quetta, where it was seen that poverty and illiteracy directly increased the risk of TB acquisition.<sup>[20]</sup> A study done in China also correlates to these findings.<sup>[21]</sup> Patients from such backgrounds do not complete their drug regimen, being unaware of the concept of drug resistance, which is shown by low levels of DOTS completion. This finding is supported by a research carried out in Europe, which showed that irregularity in taking medication and

diagnostic delay were major risk factors for MDR TB.<sup>[22]</sup> A similar study in Brazil also pointed to these facts.<sup>[23]</sup> In addition to lack of health awareness, social stigma linked with TB is also a major reason for this lack of DOT completion as affirmed by a research done in Nepal.<sup>[24]</sup> Proper awareness of the significance of following the full treatment regimen properly is likely to improve treatment outcomes and is to be further investigated. Our study also shows that susceptibility to MDR TB is increased due to close contact with TB patients. A study carried out in Georgia showed the similar results.<sup>[25]</sup> Furthermore, living in overcrowded conditions also raises susceptibility to MDR TB infection, a finding in line with a previous study in Italian children.<sup>[26]</sup>

An exception to the low DOTS completion trend was the diabetic subgroup, which compares favorably to their rate of taking diabetic medication. An intriguing finding related to their lifestyle measures was that the percentages recorded for regular exercise, dietary control, and blood sugar monitoring were not up to the mark. Moreover, mean age of MDR TB patients with diabetes fell in older age group. Though a causal relation with old age is hard to determine, a correlation does exist which should be probed further. This relationship is signified by a study conducted in southeastern Mexico, which highlighted that mean age > 35 y, BMI > 25 and contact with TB patients were significant risk factors in diabetics.<sup>[27]</sup> A similar study carried out in India also pointed out that higher mean age, sedentary occupation and poor glycemic control increase the vulnerability of diabetics to MDR TB.<sup>[28]</sup> A multi-disciplinary approach has to be employed in treating diabetics with MDR-TB where coordination amongst the various specialists is vital to ensure that patients are adaptive to the many prolonged treatment modalities.

In the children subgroup, the diversity of education levels leads to the understanding that instructions and care would be provided by the parents/guardians, therefore negating somewhat the importance of better awareness in children themselves. Half the children were found to be taking low protein diet and almost half reported positive contact history. Two separate South African studies show supportive results for these findings.<sup>[29,30]</sup>

The data from the addiction subgroup is particularly interesting since their struggle with addiction becomes apparent with various substance abuses they partake in, which has been quantitatively recorded in the results. It is clear from results that smoking, alcoholism and drug abuse are directly linked to increased vulnerability to MDR TB In concordance, a



study in Portugal reported that intravenous drug abuse directly increases risk for MDR TB.<sup>[31]</sup> Our results are also supported by a research conducted in Amhara which linked alcohol consumption and previous TB contact to a higher risk of MDR TB acquisition, while another one carried out in India also provided similar results.<sup>[32,33]</sup> . Another aspect is that the complexity of interaction between alcohol, cigarette and drugs, when taken in combination, is bound to increase the risk for acquiring MDR-TB as compared to the risk when the abuse is of a single substance. Indeed, smoking and alcoholism combined was found to be a major risk factor in a study done in (Ceara) Brazil.<sup>[34]</sup>

An important risk factor found in the prisoner subgroup was poor ventilation and overcrowding in the prisons. This finding is supported by a research conducted on MDR TB in prisoners in Samara, Russia. However, in comparison to our study, which states that the prisoners do not have any associated comorbidities, this research points out that most patients with MDR TB also suffered from HIV and COPD.<sup>[18]</sup>

Lastly, even though a combination of retrospective and prospective techniques was employed in our study, the bias related with researches where questionnaires are the mode of data collection cannot be discounted.

The authors have no conflict of interest to report.

### CONCLUSION:

The most significant risk factors were poor socioeconomic status and low levels of education which were found to be present amongst all subgroups. Correlation of poor lifestyle adaptation in diabetics was inferred. Multiple substance abuse in addicts was found to be an important risk for MDR-TB. Our study shows the challenges involved in treating MDR TB and the complications that arise while dealing with the various subgroups afflicted with other morbidities or social and financial restrictions. Moreover, there is need for future studies, having longer time span and control trials that can study the propensity of risk factors between vulnerable groups and general population for MDR-TB. The current research would be improved with a larger sample size having equal number of participants in the assigned sub-groups compared with a control.

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