



Research Article

Risk Factors of Multidrug-Resistant Tuberculosis

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Abstract

Multidrug-resistant tuberculosis has been increased worldwide which is a severe problem. A case-control study was carried out among 50 MDR-TB cases and 63 drug susceptible controls to identify risk factors associated with multidrug-resistant tuberculosis (MDR-TB) in Lumbini Zone. Irregularity in taking medicine (OR=2.36), large family size (OR=2.40), farming as occupation (OR=2.83), history of TB and bovine at home (OR=6.5) were statistically associated with MDR-TB. Most of the MDR-TB cases were males (82%) and individual with the age group 21-30 years (40%) were highly infected with MDR-TB.

Keywords: Multidrug-resistant; Risk factors; Tuberculosis

Introduction

Multi-drug-resistant tuberculosis (MDR-TB) is defined as tuberculosis that is resistant to at least isoniazid (INH) and rifampicin (RMP), the two most powerful first-line treatment anti-TB drugs. Mostly MDR-TB develops when the course of antibiotics is interrupted and the levels of drug in the body are insufficient to kill 100% of bacteria. This can happen for a number of reasons: patients may feel better and halt their antibiotic course, drug supplies may run out or become scarce, patients may forget to take their medication from time to time or patients do not receive effective therapy (Paul 2001). WHO estimated that 45,000 people fell ill with MDR-TB in 2012 (WHO, 2013). Drug resistance can be detected using special laboratory tests which test the bacteria for sensitivity to the drugs or detect resistance patterns which can be molecular in type (eg, Xpert MTB/RIF) or else culture-based (WHO, 2015). China, India and the Russian Federation have the highest burden of MDR-TB followed by 24 other countries (WHO, 2013). TB infection begins when the mycobacteria reach the pulmonary alveoli, where tubercle bacilli are ingested by alveolar macrophages.

A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all people with TB are infected by the virus (WHO, 2011). This is a particular problem in sub-Saharan Africa, where rates of HIV are high (Chaisson and Martinson 2008). Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty (Lawn and Zumla, 2011).

Those at high risk thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather (e.g. prisons and homeless shelters), medically underprivileged and resource-poor communities, high-risk ethnic minorities, children in close contact with high-risk category patients, and health-care providers serving these patients (Griffith and Kerr, 1996). Other disease states can also increase the risk of developing tuberculosis. These include alcoholism (Lawn and Zumla, 2011) and diabetes mellitus (Restrepo 2007). Certain medications, such as corticosteroids and infliximab are becoming increasingly important risk

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factors, especially in the developed world (Lawn and Zumla 2011).

Materials and Methods

Study Area

The study was carried out at DOTS Plus Clinic of Lumbini Zonal Hospital, which lies in Butwal, Rupandehi from March-September 2014. Butwal is a small city of about eight thousand hector square in area, situated on the low-altitude land (Terai) near the border side to India.

Study Design

A case-control study was designed to determine the risk factors associated with MDR-TB.

Selection of Cases

Altogether 61 multidrug-resistant (MDR-TB) patients were registered in the DOTS Plus Clinic of Lumbini Zonal Hospital in the fiscal year 2014/2015. However, only 50 MDR-TB patients were selected as cases for the study by observing the hospital record.

Selection of Controls

Age and sex matched 63 drug susceptible pulmonary tuberculosis (PTB) patients undergoing DOTS Plus Clinic for the treatment were selected as controls. In case of dissimilar ages of cases and controls, sex was firstly matched and 2 or more than 2 controls were selected for single case.

Inclusion and Exclusion Criteria

Only the pulmonary MDR-TB patients from Lumbini zone registered at Lumbini Zonal Hospital were included in the study as cases. Patients unwilling to participate in the study, extra-pulmonary patients and patients not turning up at the hospital during the study period were excluded. Some patients of Gandaki Zone registered in the DOTS Plus Clinic of Lumbini Zonal Hospital were excluded.

Major Variables Assessment

Multiple variables under demographic factors, TB contact, previous treatment status, income, knowledge on DOTS, family size, number of rooms and presence of bovine at home were studied as major variables assessment.

Questionnaire Pre-Testing, Testing and Application

A structured questionnaire was firstly pre-tested among the colleagues and was modified where the patients felt uneasy to answer the questions. It also was again tested among the pulmonary tuberculosis patients (those are not included in the final questionnaire) and modification was done. Finally, questionnaire was applied to the study population.

Data Collection, Analysis and Interpretation

Data collection was done through structured interviews with the patients during visits to the DOTS Plus Clinic. After data collection, data were checked for the completeness. Statistical Package for Social Sciences (SPSS) version 21 for windows was used to analyze the data. Then, the

association between categorical variable was assessed by chi-square (χ^2) test (Marahatta *et al.* 2010). A result was considered significant at a P value <0.05 . Odd ratio (OR) were calculated to evaluate the magnitude of association between risk factors and MDR-TB (Marahatta *et al.* 2010).

Results

Distribution of MDR-TB Patients and Associated Risk Factors

A total of 61 MDR-TB patients were recorded at DOTS clinic of Lumbini Zonal Hospital. Among them, 50 patients were involved in the present study. Along with the designed case-control study to identify the possible risk factors of MDR-TB, information related to HIV co-infection, diabetic status and frequency of relapsed cases were collected.

Age and Sex Wise Distribution of MDR-TB Patients in Lumbini Zone

Out of 50 MDR-TB patients, highest percentage of MDR-TB (40%) were found within the age group 21-30 years followed by the age group 41-50 years (20%) and 31-40 years with 18% while rest of the age groups of PTB patients had developed comparatively less MDR-TB (6 to 8%) (Fig.1). Among 50 MDR-TB patients, 41 (82%) were male and 9 (18%) were female (Fig.2).

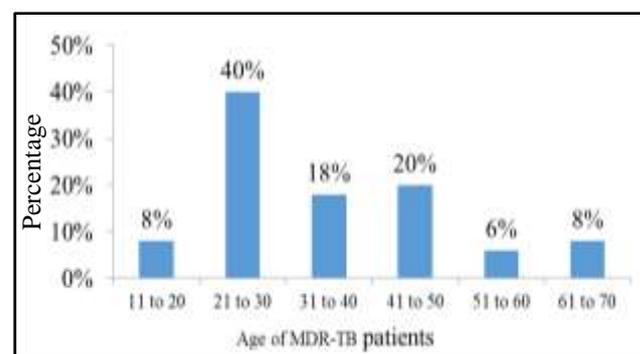


Fig. 1: Age wise distribution of the MDR-TB patients

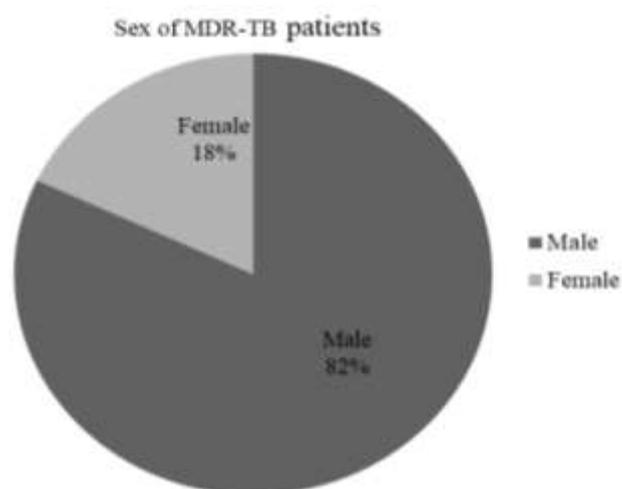


Fig. 2: Sex wise distribution of the MDR-TB patients

Risk Factors Associated With the Development of MDR-TB

A case-control study was designed to identify the risk factors for the development of MDR-TB among PTB patients. Fifty MDR-TB patients were considered as cases and 63 drug sensitive patients were considered as control. Twenty-three (46%) cases and 22 (34.92%) control had contact with TB patients either in their family or friends who had been diagnosed as TB. Habit of smoking and alcohol use was found in 23 (46%) cases. Among the control group, habit of smoking and alcohol use was found 44.44% and 60.31% respectively.

Irregularity in taking medicine was more common in cases (38%) than in controls (20.63%). Irregularity in taking medicine was significantly associated with the development of MDR-TB ($P = 0.042$). Odd ratio showed that patients with irregular intake of medicine were 2.36 times more likely to develop MDR-TB than the patients with regular intake of medicine. Fifteen (30%) of cases and 16 (25.40%) of controls had knowledge on DOTS. History of tuberculosis in the past was more common among cases (98%) than in controls (1.59%). History of tuberculosis was also significantly associated with the development of MDR-TB ($P < 0.001$). Previously who had history of TB were more likely to develop MDR-TB than who had not history of tuberculosis in the past.

Greater differences were not observed in educational attainment among the cases and controls. Among the illiterate patient, 24% were cases and 19.04% were controls.

Maximum cases (36%) and controls (28.57%) had primary education. Forty-two percent of cases and 63.49% of controls had five or less than five family members. Fifty-eight percent of cases and 36.51% of controls had more than five family members. Family size significantly contributed to the development of MDR-TB ($P = 0.023$). Large family size was 2.40 times more likely to develop MDR-TB than smaller one. Eighty-four percent of cases and 92.06% of controls had one to three rooms for whole family members.

Occupation was classified as farmer, service, business, students and housewife. Forty-four percent of cases and 34.92% of control group were service holder. Six percent of cases and 11.11% of control group had involved in business. Six percent of cases and 14.28% of controls were students. Four percent of cases and 20.63% of controls were housewife. Patients involved in farming were 40% of cases and 19.05% of control ($P = 0.01$). People involved in farming were 2.83 times more likely to develop MDR-TB than those involved in other occupation. Family income of both cases and controls ranges from 5,000 to above 15,000 per month. Development of MDR-TB was not found to be associated with their monthly family income.

Twenty-six (52%) of cases and 9 (14.29%) of controls had bovine at home. Presence of bovine at home showed significant association with MDR-TB ($P < 0.01$). Patients having bovine at home were 6.5 times more likely to develop MDR-TB than the patients with no bovine at home. About 42% of cases and 44% of control had noticed that bovine at their home coughs (Table no.1).

Table 1: Risk factors associated with MDR-TB

Characteristics	Cases n (%)	Control n (%)	Value of χ^2	Value of P	Odd ratio
Contact with TB patients	23 (46)	22 (34.92)	1.428	0.232	
Smoking	23 (46)	28 (44.44)	0.27	0.869	
Alcoholism	23 (46)	38 (60.31)	2.30	0.129	
Knowledge on DOTS	15 (30)	16 (25.40)	0.297	0.586	
Irregularity in taking medicine	19 (38)	13 (20.63)	4.141	0.042	2.36
Past history of TB	49 (98)	1 (2)	60.138	0.000	
Educational status			3.531	0.619	
Illiterate	12 (24)	12 (19.04)			
Primary level	18 (36)	18 (28.57)			
Lower secondary level	7 (14)	14 (22.22)			
Secondary level	7 (14)	11 (17.46)			
Higher secondary level	2 (4)	4 (6.35)			
Above higher secondary level	4 (8)	7 (11.11)			

Table 1: Risk factors associated with MDR-TB (Contd.)

Characteristics	Cases n (%)	Control n (%)	Value of χ^2	Value of P	Odd ratio
Family size			5.183	0.023	
≤ 5	21 (42)	40 (63.49)			0.42
>5	29 (58)	23 (36.51)			2.40
Number of rooms			1.780	0.781	
1 to 3	42 (84)	58 (92.06)			
>3	8 (16)	5 (7.94)			
Occupation			13.348	0.01	
Farmer	20 (40)	12 (19.05)			2.83
Service	22 (44)	22 (34.92)			1.46
Bussiness	3 (6)	7 (11.11)			0.51
Students	3 (6)	9 (14.28)			0.38
Housewife	2 (4)	13 (20.63)			0.16
Family income			1.082	0.781	
< 5000	8 (16)	7 (11.11)			
5000 to 10000	25 (50)	32 (50.80)			
Between 10000 to 15000	11 (22)	13 (20.63)			
>15000	6 (12)	11 (17.46%)			
Bovine at home	26 (52)	9 (14.29)	18.545	0.000	6.5
Do bovine cough			0.607	0.738	
Yes	11 (42.3)	4 (44.44)			
No	9 (34.61)	2 (22.22)			
Not noticed	6 (23.07)	3 (33.33)			

Discussion

TB has returned in a deadly form called multidrug-resistant tuberculosis. MDR-TB is microbial, clinical and programmatic issue. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective (NTP, 2009). MDR-TB cases are increasing in alarming rate and around 480,000 MDR-TB cases estimated to have occurred in 2013 (WHO, 2014). The risk of tuberculosis is greater in areas of residence characterized by crowding, poverty and lower education (Lifson *et al.*, 1999). An inadequate or poorly administered treatment regimen allows drug-resistant mutant to become the dominant strain in a patients infected with TB (NTP, 2009).

Case-control study was carried out with 50 cases and 63 controls for the identification of risk factors responsible for the development of MDR-TB. MDR-TB patients and drug susceptible PTB patients were considered as cases and control respectively. Our study showed irregularity in taking medicine, family size, occupation, past history of TB and bovine at home have a significant association with MDR-TB and regarded as the risk factors for the development of MDR-TB.

Most of the patients (98%) in our study had previous history of TB. Numerous studies had shown a very significant correlation between past history of TB and MDR-TB (Marahatta *et al.*, 2010, FMOH 2012, Hirpa *et al.*, 2013,

Biadlegene *et al.*, 2014). If the patient does not complete his/her antibiotic dose in the previous treatment or if the physician does not prescribe the proper antibiotic regimen, resistance can develop. Also, drugs that are of poor quality or less in quantity, especially in developing countries contribute to MDR-TB (Sharma and Mohan 2004). Bacteria develops the resistance to the drugs, if taken for the longer duration which leads to the development of MDR-TB.

Another important risk factor identified in present study includes irregularity in taking medicine. If the treatment is irregular, the number of bacterial death and growth cycles will be greater giving more opportunities for individual mutation of different independent genes to accumulate. According to Pant *et al.* (2009), 67% of cases missed medicine at least a few weeks during their previous treatment. Irregularity in taking medicine was shown statistically associated with MDR-TB in the study conducted by Barroso *et al.* (2003), Kritski *et al.* (2003) and Flora *et al.* (2013).

Low socio-economic status leads to poor adherence to treatment thereby leading to the development of MDR-TB. In the study conducted by Casal *et al.* (2005), Akl and Mahalli (2012) and Rifat *et al.* (2014), occupation was found to be statistically associated MDR-TB which is similar to our study. From the occupational status of TB infected patients also, higher percentage of patients has been actively involving in jobs that need to get exposed to outer environment to greater extent and need to spend more time out of home. Amin *et al.* (2009) conducted a study in Bangladesh, which showed that the highest proportion of MDR-TB cases (61.2%) were involved in occupations like agriculture, production and transport but no significant difference was obtained in income level between cases and controls. In other study done by Baghaei *et al.* (2009) and Barman *et al.* (2014) family size showed significant association with MDR-TB as in our study. Individual staying in a crowded living condition are more vulnerable to develop MDR-TB.

Family income, number of rooms, education, smoking, alcoholism, knowledge on DOTS and contact with TB patients showed no statistical association with MDR-TB while the study conducted by Antunes *et al.* (2003), HERD (2012) and Chen *et al.* (2013) had showed the co-relation between low family income and development of MDR-TB. Although family income was not statistically associated with the development of MDR-TB, most of the cases had low family income. Patients with a low family income might have more limited access to medical treatment and healthcare services. Also, their crowded and poor living conditions may facilitate the spread of infectious diseases.

Since, TB is an air-borne disease, bacteria spread through air when people who have an active TB infection expel infectious aerosol droplets. Personal contact with TB

patients and use of patients personal things play a vital role in the MDR-TB development and transmission. Several studies have shown that TB contact as strongest determinants of MDR-TB (Kliiman and Attraja, 2009; Balabanova *et al.*, 2012; Lange *et al.*, 2014), but no statistical association was observed between TB contacts and MDR-TB in the present study. The study conducted by Kritski (2003) and Skrahina *et al.* (2013) demonstrated that the smoking habit and alcoholism are strongly associated with MDR-TB. However, our finding infers that the smoking habit and alcoholism have no any co-relation with the development of MDR-TB.

Educational status was found to be statistically associated with MDR-TB in a study conducted by Li *et al.* (2015). No significant association between MDR-TB and education was observed in the study conducted by Rahman *et al.* (2005) and Amin *et al.* (2009) as in our study but most of patients were illiterate and had primary education. Poor knowledge leads to the poor adherence to the treatment which finally leads to the development of MDR-TB.

A similar study conducted by Pant *et al.* (2009) reported that 70.97% MDR-TB patients were male. Faustini *et al.* (2006) and Ahmad *et al.* (2012) found that there was statistical association between male gender and MDR-TB. But, in present study although the majority of MDR-TB patients were male, statistical association was not significant. Males get exposed to the external environment than females and are supposed to do their job outside the home while females are more restricted at home due to which mostly male gender might be infected with MDR-TB. However, Taylor and Suarez (2000), Mdivani *et al.* (2008), Lomtadze *et al.* (2009) concluded that female gender was statistically associated with MDR-TB. In a study conducted by Ukanwa and Madiba (2013) also, more females (63.6%) than males (36.4%) were infected with MDR-TB. Male gender has quick access to health care services when they get ill but females generally depend on other members of family to have access to health centres as well as they can't freely express their health problems.

Age wise observation of the MDR-TB patients showed that the highest number of patients (40%) were found in the age group 21-30 years. In the study conducted by Vander-Werf *et al.* (2012) and Lange *et al.* (2014) younger age was found to be statistically associated with MDR-TB. The highest number of MDR-TB patients of the productive age group might be due to the exposure of these age group people to different environment during their work and activities that would make their health more prone to infection by TB organisms.

Conclusion

The major risk factors identified includes: irregularity in taking medicine, family size, occupation, past history of TB and bovine at home which were statistically significant

while alcoholism, smoking, family income, education which had been identified as risk factors in previous studies were not associated with MDR-TB at Lumbini Zone. Male sex (82%) and individual of age group 21-30 years were found to be highly prone to MDR-TB infection.

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