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Risk factors for multidrug-resistant tuberculosis in urban Pakistan: A multicenter case–control study

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ABSTRACT

Objective: To evaluate risk factors for multidrug-resistant tuberculosis (MDR-TB) in an urban setting of Pakistan.

Design and methods: In this multicenter case–control study, patients aged 15 years old or older with sputum culture and sensitivity (C/S) diagnosed with pulmonary MDR-TB were defined as cases, whereas patients aged 15 years old or older with sputum C/S diagnosed and susceptible to pulmonary TB were regarded as controls. Fifty cases and 75 controls were enrolled from three tertiary-care hospitals in Karachi.

Results: Multivariable logistic regression models showed that cases were more likely to have had a TB patient in the house prior to the diagnosis of MDR-TB (adjusted odds ratio [OR_{adj}] = 3.1, 95% confidence interval [CI]: 1.2, 8.3) or had a history of prior TB treatment (OR_{adj} = 4.2, 95% CI: 1.1, 15.4). Furthermore, cases compared with controls tended to be male (OR_{adj} = 3.6, 95% CI: 1.4, 9.7), 15–25 years of age (OR_{adj} = 3.7, 95% CI: 1.2, 11.3), of Sindhi ethnicity (adjusted OR = 9.1, 95% CI: 1.9, 43.4) or with low educational attainment (OR_{adj} OR = 5.5, 95% CI: 1.7–17.6, for no formal schooling; OR_{adj} = 3.8, 95% CI: 1.1–14.1, 1 for 1–5 school years).

Conclusions: A TB patient in the house or a history of prior TB treatment was strongly associated with MDR-TB in this study. Furthermore, younger age, male gender, Sindhi ethnicity and poor educational attainment entailed a high risk for MDR-TB. Targeted educational intervention for patients and their contacts may minimize the noncompliance with prescribed TB treatment and lessen MDR-TB magnitude in settings like Karachi.

Introduction

Multidrug-resistant tuberculosis (MDR-TB) has been defined as the resistance of *Mycobacterium tuberculosis* strains to both isoniazid (INH) and rifampicin (RMP) with or without simultaneous resistance to other drugs [1]. MDR-TB poses a therapeutic and infection control challenge with significantly higher rates of morbidity and mortality [2,3]. Also, it has substantial economic implications of high treatment cost which is nearly 100 times the cost of treating a susceptible TB case [4].

A worldwide assessment in 35 countries revealed an overall prevalence of MDR-TB as 12.6% for single-drug resistance (range, 2.3–42.4%) and 2.2% for multidrug resistance (range, 0–22.1%) in all the countries surveyed [5]. About 50 million

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people were infected with multidrug resistant *M. tuberculosis* strains globally [6], and they account for 14% of the world's total TB cases [7]. In Pakistan an estimated 10–14% of TB patients are suffering from MDR-TB [8].

Spontaneous mutations leading to drug resistance occur rarely in *M. tuberculosis* [9]. Mainly, MDR-TB results from treatment that is inadequate, often because of an irregular drug supply, inappropriate regimens, or poor compliance [5]. The other known risk factors for MDR-TB include contact with a drug-resistant TB patient [10], younger age [11], lower socioeconomic status, homelessness [12], male gender with less than normal body mass index [13], and human immunodeficiency virus (HIV) infection [10,11]. However, only limited data on the role of these factors in perpetuating MDR-TB in Pakistan and other countries in the region are available. Therefore, the purpose of this case–control study was to identify risk factors for MDR-TB in an urban setting of Pakistan. Knowledge of such factors that may have been contributing in MDR-TB in this and similar settings may be used to design an effective TB control program.

Patients and methods

Study setting

Karachi is a major industrial and trade center of Pakistan. It has an estimated population of 9.8 million, which is largely multiethnic in character. Health services are provided both by public and private health care facilities in Karachi. Private sector largely consists of private practitioners, hospitals and teaching institutions, while the public sector is comprised of government hospitals and dispensaries. For this study, cases and controls were enrolled from three tertiary care health facilities of Karachi, namely, Aga Khan University Hospital, Jinnah Postgraduate Medical Center, and Ojha Institute of Chest Diseases.

Definitions and selection of cases and controls

In this study, a case was considered a patient of either gender, aged 15 years old or older, diagnosed with culture-confirmed MDR-TB and *M. tuberculosis* strain resistant to at least INH and RMP (two first-line anti-TB dugs) [1,13,14]. The control was a patient of either gender, aged 15 years old or order, diagnosed with culture-confirmed non-MDR-TB and *M. tuberculosis* strain sensitive to first-line (INH, RMP, pyrazinamide, ethambutol and streptomycin) anti-TB drugs [15]. Between January 1, 2000, and February 28, 2002, eligible cases and controls were identified through the records or in-patients of the three tertiary-care hospitals and were invited to participate in the study. Cases and controls unable to provide an interview owing to problems with speech, hearing or very poor general state of health were excluded.

Data collection

A structured and pre-tested questionnaire was administered to both cases and controls. The questionnaire comprised questions on socio-demographic characteristics, BCG vaccination, and history of prior TB treatment. It also included questions on the presence of any TB patients in the family or other possible sources of contact with TB patient(s), current therapy for TB if any, and compliance with past and present TB therapy. Two data collectors (one male and one female) and the principal author constituted the data collection team. Both the data collectors were fluent in Urdu and Sindhi – the two main locally spoken dialects – had over 12 years of formal schooling, and had previous experience in carrying out questionnaire-based interviews. Postal addresses and, where available, telephone numbers were obtained from medical records. Subjects were contacted at given addresses, and face-to-face interviews were conducted. Eligible subjects available during data collection period as in-patients were interviewed in the respective wards of the three hospitals.

Data analysis

Data were managed using EPI-INFO version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and analyzed using SPSS version 10 (Chicago, IL, USA). Descriptive statistics were computed for independent variables and compared between cases and controls using χ^2 test or Student's *t*-test as appropriate. Unadjusted association of each independent variable with the outcome variable (case/control status) was evaluated using univariable logistic regression analyses. Variables significantly ($P < 0.25$) associated with the outcome were considered for inclusion in a multivariable logistic regression model [16]. Adjusted odds ratio (OR_{adj}) and unadjusted OR for history of prior TB treatment (primary exposure of interest) were compared in the presence and absence of other variables respectively. If there was an absolute difference of 10% or more in OR_{adj} and unadjusted OR for history of prior TB treatment in the presence and absence of a given variable, it was retained in the multivariable logistic regression model. After developing a main effect model, biologically meaningful interaction terms were assessed for their statistical significance. The final model was evaluated by the Hosmer–Lemeshow goodness-of-fit test [16]. An informed consent was always requested from eligible subjects, and those consenting to participate in the study were interviewed. The study was approved by the institutional ethics review committee.

Results

Fifty cases and 75 controls were enrolled in this study. The mean (SD) age (years) of cases and controls was 31.5 (12.0) and 44.0 (19.6), respectively. The proportions of males among cases and controls were 50% and 32%, respectively. Commonly spoken dialect was Sindhi in cases (34%) and Urdu in controls (37%). Higher proportion of cases (38%) than controls (19%) had no formal schooling. More cases (64%) than controls (60%) were married and a higher proportion of cases (52%) than controls (27%) reported a monthly income less than 4000 rupees. Also, a higher proportion of cases (60%) than controls (32%) tended to live in a household size of seven or more persons (Table 1).

Smoking history was nearly similar in cases and controls, whereas a higher proportion of cases (30%) than controls

(13%) were BCG un-vaccinated. More cases (44%) than controls (23%) reportedly had a TB patient at home. Furthermore, 90% (45/50) of the cases and 73% (55/75) of the controls reportedly had a history of prior TB treatment. Among those who reported a history of prior TB treatment, 42% (19/45) of the cases and 9% (5/55) of the controls reported discontinuation of past TB treatment (Table 2). Among first-line anti-TB drugs, all 50 (100%) cases were resistant to INH and RMP. Also, 18% of the cases were resistant to streptomycin, 12% to ethambutol and 18% to pyrazinamide (Fig. 1).

Logistic regression analysis

Unadjusted logistic regression analyses showed that age, gender, ethnicity, education, total monthly household income, household size, BCG vaccination status, presence of a TB patient in the household, history of prior TB treatment, and reported history of prior TB treatment discontinuation were significantly ($P < 0.05$) associated with MDR-TB status (Tables 1 and 2). The final multivariable logistic regression model revealed that cases compared with controls were significantly more likely to have had a TB patient in the house ($OR_{adj} = 3.1$, 95% CI: 1.2–8.3) or had a history of prior TB treatment ($OR_{adj} = 4.2$, 95% CI: 1.1–15.4). Of demographic factors significantly associated with MDR-TB status were age ($OR_{adj} = 3.7$; 95% CI: 1.2–11.3 for 15–25 years old), male gender ($OR_{adj} = 3.6$; 95% CI: 1.4–9.7), Sindhi ethnicity ($OR_{adj} = 9.1$; 95% CI: 1.9–43.4), and low educational attainment (OR_{adj} OR = 5.5, 95% CI: 1.7–17.6 for no formal school years; $OR_{adj} = 3.8$, 95% CI: 1.1–14.1 for 1–5 school years). Hosmer–Lemeshow goodness-of-fit statistic for the final multivariable logistic regression model was 5.8 ($P = 0.7$) (Table 3).

Discussion

The choice of using case–control design was based on earlier recommendations to the study on the epidemiology of MDR-TB [10]. Also, the standard definitions of MDR-TB and drug susceptible TB were used to select cases and controls respectively during a comparable time frame [14,17,18].

In this study, MDR-TB cases tended to report a history of prior TB treatment more often than controls or reportedly had a TB patient in the house. Furthermore, patients with pulmonary MDR-TB compared with those with pulmonary susceptible TB tended to be younger (15–25 years old), of male gender, Sindhi ethnicity, and had only five or less years of formal schooling.

Consistent with the results of previous studies both in developed and developing countries, this study showed that a history of prior TB treatment was a significant predictor of MDR-TB [19,20]. Acquired drug resistance of *M. tuberculosis* to anti-TB drugs may occur, when there is a history of incom-

Table 1 – Distribution and univariable logistic regression analysis of demographic factors associated with multidrug-resistant tuberculosis in a case–control study, Karachi, Pakistan.

Variable	Cases, *n* (%) (*N* = 50)	Controls, *n* (%) (*N* = 75)	Crude OR	95% CI
Age (completed years)				
15–25	19 (38)	14 (19)	1.9	1.4–8.0
26–32	13 (26)	17 (22)	3.3	0.8–4.6
>32	18 (36)	44 (59)	1.0	–
Gender				
Male	25 (50)	24 (32)	2.5	1.2–5.3
Female	25 (50)	51 (68)	1.0	–
Mother tongue (ethnicity)				
Punjabi	7 (14)	10 (13)	2.2	0.6–7.4
Sindhi	17 (34)	5 (7)	10.6	3.0–39.0
Others[#]	17 (34)	32 (43)	1.7	0.6–4.3
Urdu	9 (18)	28 (37)	1.0	–
Education (years of formal schooling)				
Nil	19 (38.0)	14 (19)	3.4	1.5–7.9
1–5	13 (26.0)	17 (23)	2.6	1.0–7.2
>5	18 (36.0)	44 (59)	1.0	–
Marital status				
Married	32 (64)	45 (60)	1.2	0.6–2.5
Single	18 (36)	30 (40)	1.0	–
Household income (rupees/month)				
<4000	22 (52)	14 (27)	3.0	1.3–7.1
⩾4000	20 (48)	38 (73)	1.0	–
Household size				
>10	8 (16)	10 (13)	7.2	1.0–10.7
7–10	22 (44)	14 (19)	14.1	2.8–70.6
4–6	18 (36)	33 (44)	4.9	1.0–23.6
1–3	2 (4)	18 (24)	1.0	–

OR = odds ratio; CI = confidence interval; [#] Includes Pushto, Balochi, Gujarati, Parsi.

Table 2 – Distribution and univariable logistic regression analysis of putative risk factors associated with multidrug-resistant tuberculosis in a case–control study, Karachi, Pakistan.

Variable	Cases, *n* (%) (N = 50)	Controls, *n* (%) (N = 75)	Crude OR	95% CI
Smoking history				
Ever smoked	15 (30)	21 (28)	1.1	0.5–2.4
Never smoked	35 (70)	54 (72)	1.0	–
BCG vaccination status				
Un-vaccinated	15 (30)	10 (13)	2.8	1.1–6.8
Vaccinated	35 (70)	65 (87)	1.0	–
Presence of TB patient in household				
Yes	22 (44)	17 (23)	2.7	1.2–5.8
No	28 (56)	58 (77)	1.0	–
History of prior TB treatment				
Yes	45 (90)	55 (73)	3.3	1.1–9.4
No	5 (10)	20 (27)	1.0	–
Compliance to prior TB treatment				
Quit medication	19 (38)	5 (7)	15.2	3.2–77.5
Didn't quit medication	26 (52)	50 (67)	2.1	0.7–7.9
No past medication	5 (10)	20 (26)	1.0	–

OR = odds ratio; CI = confidence interval.

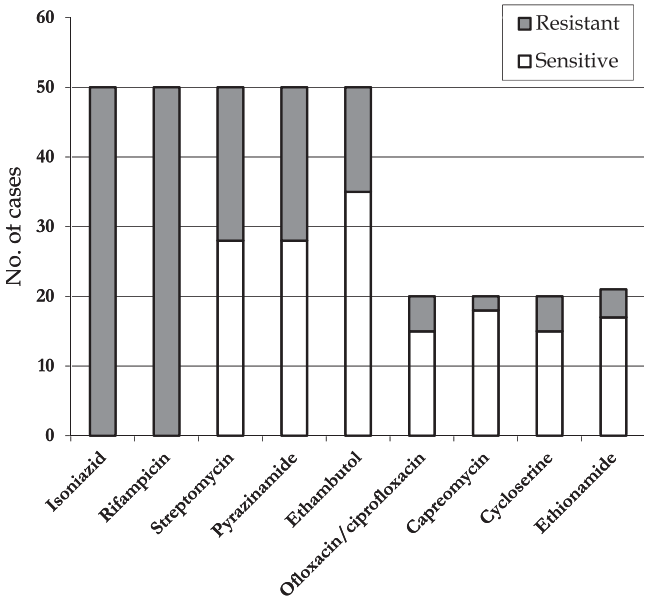

Fig. 1 – Drug resistance of *Mycobacterium tuberculosis* strains isolated from multi-drug resistant tuberculosis cases in Karachi, Pakistan 2001–2002 (N = 50).

plete or inappropriate TB treatment regimens for at least 1 month [2,21–23]. Therefore, MDR-TB patients in this study might have experienced similar conditions.

The presence of a TB patient in the household was used as a surrogate variable for a possible source for acquisition of MDR *M. tuberculosis* infection through household contact with a MDR-TB patient. Previous studies of contact tracing of MDR-TB patients have shown a clear link between prior exposure to a patient with infectious TB resistant to numerous drugs and subsequent development of TB with similar resistance patterns [17,18,24]. Sensitivity patterns against anti-TB drugs for such household members could not be ascertained owing to logistic reasons and was beyond the scope of this study. Future studies may look at this aspect.

Younger patients (15–25 years old) were more likely to suffer from MDR-TB than the patients in other age groups in this study. The association of age and MDR-TB has not been consistently identified [11]. MDR-TB in younger age groups have previously been reported [25] or older age (45–64 years) groups [26], but some other studies did not find this association [27,28]. This variation in relationship of age with MDR-TB may be a reflection of localized socio-economic factors related to exposure opportunity and development of MDR-TB.

In this study, cases were more likely to be male than controls. Significant preponderance of males towards MDR-TB has also been previously demonstrated [17,29]. Men are considered relatively more unconcerned than females regarding regular intake of medication, and this fact may have led to more males having MDR-TB in this study. Furthermore, it has been hypothesized that TB being more frequent among men may reflect gender differences in risk for *M. tuberculosis* infection or progression of TB [4]; however, such reasons for MDR-TB being more common among males have not been established and need further investigation.

Cases in this study tended to have five or less years of schooling. Patients with no or little education reportedly were more likely to default or non-comply with anti-TB treatments in Korea and elsewhere, which might have led to the development of acquired MDR-TB [30,31]. Similar patients' attitude may explain the association of low education attainment and increased likelihood of MDR-TB in this study.

Sindhi ethnicity was associated with increased odds of MDR-TB in this study. It has been shown that being an Asian was associated with an increased risk of developing MDR-TB regardless of living environment [11,17]. To substantiate this finding, there is a need to further explore this association with regard to diverse lifestyles and practices among different ethnicities in Pakistan.

Table 3 – Multivariable logistic regression model of patient and household characteristics associated with multidrug-resistant tuberculosis in a case–control study, Karachi, Pakistan.

Variable	Adjusted odds ratio	95% Confidence interval
Age (completed years)		
15–25	3.7	1.2–11.3
26–32	2.7	0.8–9.1
>32	1.0	–
Gender		
Male	3.6	1.4–9.7
Female	1.0	–
Mother tongue		
Punjabi	1.3	0.3–5.8
Sindhi	9.1	1.9–43.4
Others[#]	0.7	0.2–2.4
Urdu	1.0	–
Education (completed school years)		
Nil	5.5	1.7–17.6
1–5	3.8	1.1–14.1
>5	1.0	–
Presence of TB patient in household		
Yes	3.1	1.2–8.3
No	1.0	–
History of prior TB treatment		
Yes	4.2	1.1–15.4
No	1.0	–

[#] Includes Pushto, Balochi, Gujarati, Parsi .

Some limitations in this study are worth mentioning: First, potential recall bias is an inherent characteristic of a case–control design [32], therefore, some recall bias might have crept in while responding to a history of prior anti-TB treatment. However, misclassification of exposures of interest – if indeed it has occurred – was expected to be non-differential. Secondly, it could not empirically be determined whether MDR-TB cases in this study have had primary drug resistance or were acquired through inadequate and/or incomplete prior TB treatment. However, it is believed that MDR *M. tuberculosis* strains have relatively low transmissibility [9]. Future studies may look at this aspect of study design. Thirdly, this study was somewhat under-powered; therefore, several established risk factors – notably smoking, monthly income, household size, etc. – turned out to be non-significantly related with MDR-TB status. This issue of limited sample size needs to be addressed in any such future evaluation. Finally, this study was carried out in urban settings; therefore, generalization of these results to a population segment residing in rural areas wherein over 60% of the country's population lives needs to be done with care.

In conclusion, this study showed that a history of prior TB treatment, the presence of a TB patient in the house, younger age, male gender, Sindhi ethnicity and low educational attainment were all associated with MDR-TB in an urban setting of Pakistan. Targeted educational intervention at patients with identified characteristics and their household contacts may minimize the noncompliance with the prescribed treatment and thereby lower the magnitude of MDR-TB in this and similar settings. Future studies to evaluate the public health impact of such educational intervention on the burden of MDR-TB are indicated.

Conflict of interest

Declared none.

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