Original Article

The Factors Associated with Tuberculosis Recurrence in the Northwest and West of Iran

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Abstract

Background: **Identifying the factors associated with the recurrence of *Mycobacterium tuberculosis* (MTB) can help in tuberculosis disease prevention and reducing the burden on the health care system. This study was designed to identify the factors associated with recurrence in MTB patients in five border provinces of Iran.**

Methods: **In a cross-sectional study (2010 to 2012), clinical, economic, and social factors associated with the recurrence of tuberculosis were evaluated. The data were collected by a questionnaire and survey of medical records. Simple and multiple logistic regression analyses were performed using SPSS V.18.**

Results: **A total of 300 patients with an average age of 51.9 years (SD 24.2) were randomly selected. Overall, 7.2% of the patients were diagnosed with a recurrence of tuberculosis. Sixty-four percent (n = 151) of the patients were in a low-income class. The migration from a village to a city (OR = 8.4) and weight loss (OR = 1.5) were significantly associated with an increased chance of recurrence.**

Conclusion: **In this study, the selected provinces of Iran had moderate rates of tuberculosis recurrence in comparison to global reports. Further studies on the relationship of both weight loss and the immigration from a village to a city with tuberculosis recurrence are necessary.**

Keywords: *mycobacterium tuberculosis, recurrence, epidemiology*

Introduction

Reports of drug resistance in the treatment of tuberculosis date back to 1948, only four years after the isolation of streptomycin (1). After two decades (1970–1990), multiple drug-resistant tuberculosis (MDR-TB) with resistance to isoniazid and rifampicin has been discovered (2,3). MDR-TB became an important concern of the global effort to eradicate tuberculosis (4). Since the human immunodeficiency virus (HIV) pandemic, tuberculosis has once again emerged as a global health issue. The World Health Organization (WHO) report in 2008 indicated that each year, approximately 500 000 people are diagnosed with MDR-TB (5).

The treatment of MDR-TB requires the use of second-line drugs. The second-line anti-TB drugs cost almost 100 times more than the regular treatment plans used to treat drug-susceptible tuberculosis but have reduced efficacy and increased toxicity over their long treatment courses (6). The Iran national manual for the treatment of tuberculosis (5) suggests that patients in category I receive the first-line drugs for the treatment of tuberculosis. The category I treatment group is defined as patients with a pulmonary infection of tuberculosis and a positive sputum smear for the bacilli and who have never received tuberculosis treatment or have received treatment for fewer than four weeks. The treatment is initiated with a combination of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and etambutul (EMB) for two months and is continued with four months of INH and RMP (maintenance treatment) (5). Patients who have

been previously diagnosed with tuberculosis infection or who have received the first-line drugs but have experienced failure, relapse or drug resistance during treatment are considered to belong to category II or the recurrent group (5). Patients in category II should receive the second-line drugs: initially INH, RMP, PZA, EMB and streptomycin for five months, followed by one month of INH, RMP, EMB, and PZA and then four months of INH, EMB, and RMP (maintenance treatment) (5). The directly observed treatment short-course (DOTS) program of the ministry of health in Iran regulates the treatment of patients with tuberculosis (5).

The WHO reports that the rate of tuberculosis re-infection ranges from 0 to 100% (6) in different countries, with the recurrence rate in low-middle income countries estimated to be approximately 10-20% (7). In 2004, approximately 6.8% of the patients in Iran were in the recurrent group. In comparison, in the Azerbaijan Republic and Iraq, two neighbouring countries of Iran, 22% and 8% of patients were in the retreatment group, respectively (8). The global incidence of MDR-TB is estimated to be approximately 3.7%; however, the rate is higher (20%) in patients receiving retreatment (9). The prevention of tuberculosis recurrence not only reduces the burden of tuberculosis on national health care systems but also decreases the rate of new MDR-TB cases.

The DOTS is a globally renowned program that aims to reduce the failure of and problems with the treatment of tuberculosis (5). Several factors, including environmental factors, gender, alcohol consumption, cigarette smoking, immigration and the strains of *Mycobacterium tuberculosis*, are associated with the recurrence of tuberculosis (10–16). The aim of this study was to identify the clinical, environmental, and demographic factors affecting the recurrence of MTB in five border provinces of Iran.

Materials and Methods

In a cross-sectional study, patients with pulmonary tuberculosis and a positive sputum smear examination in the five border provinces of East-Azerbaijan, West-Azerbaijan, Ardebil, Kermanshah and Kurdistan in Iran between 2010 and 2012 were selected as the target group. In random cluster sampling, the provinces were considered as clusters. Three hundred native Iranian pulmonary tuberculosis patients with a negative HIV test and under the care of the DOTS were randomly selected. The number of patients from each province was selected to be proportional to the total number of patients in that province. Overall, 87 (29.0%) patients from East-Azerbaijan, 63 (21.0%) patients from Kermanshah, 58 patients (19.3%) from West-Azerbaijan, 53 (17.7%) patients from Kurdistan and 39 patients (13.0%) from Ardebil were randomly selected.

Sputum-positive pulmonary TB was defined as TB in a patient with at least two initial sputum smear examinations positive for acid-fast bacilli (AFB) or one sputum smear test positive for AFB and radiographic abnormalities consistent with active pulmonary TB or one sputum smear specimen positive for AFB and a culture positive for the *mycobacterium tuberculosis* (18). MTB complex was identified by also culturing on LJ medium containing p-nitro benzoic acid (PNB), where growth indicates the bacilli that are not part of the MTB complex. The samples containing non-tuberculosis mycobacterium were excluded from this study.

A questionnaire was designed to gather the demographic, socio-economic, environmental and clinical data of the patients. Information concerning patients under 15 years of age was obtained from the parents. The internal consistency of the questionnaire was confirmed in a pilot study of 35 patients from East-Azerbaijan, with a Cronbach's alpha of 0.74. The validity of the questionnaire was assessed by specialists. Additional information on the treatment, disease or other data was gathered by surveying medical records and with the help of the physician in charge of the treatment of tuberculosis in each province or city.

The variables were described using frequencies and percentages. Simple and multiple logistic regressions were used to compare the demographic, environmental, housing and clinical factors of the recurrent patients using the SPSS 18 software (233 South Wacker Drive, 11th Floor, Chicago, USA). The variables that had *P* values of less than 0.3 in the simple logistic regression analysis were entered into a model of multiple logistic regression analysis. *P* values of less than 0.05 (2-sided) were considered statistically significant

Results

Overall, 300 patients with positive sputum smears for tuberculosis were randomly selected, including 158 males (52.7%) and 142 (47.3%) females. The average age was 54.48 years (SD 24.85) for the males and 48.97 years (SD 23.17) for the females. Sixty-nine patients (23.1%) identified

with the Sunni branch of Islam, 229 cases were Shi'a, and two patients (0.6%) were members of a Christian religion. The average weight of the patients (≥ 18 years old) was 57.05 kg (SD 10.26). The patients' demographic data are shown in Table 1.

Among the selected cases, 18 patients died due to different aetiologies. In the present study, 235 patients met the criteria for category I (newly infected TB cases who received the 1st line treatment), while 20 patients fulfilled the criteria for category II (recurrent TB cases who received the 2nd line treatment). Tuberculosis recurrence was detected in 6 patients from East-Azerbaijan, 3 patients from West-Azerbaijan, 4 patients from Ardebil, 4 patients from Kermanshah and 3 patients from Kurdistan. The main clinical features of the patients are shown in Table 2.

Thirty-four patients were cigarette smokers, 65 patients had chronic illnesses (cardiovascular disease, renal problems, liver dysfunction, diabetes, respiratory illness and cancer) and only 25.2% of the patients had a history of proper vaccination.

The distribution of the patients' symptoms and their treatment groups are shown in Table 3. The most common clinical feature of the infection was a complaint of sputum, which was recorded

Table 1: Frequency distribution of demographic and Home environment variables in pulmonary tuberculosis patients

Variables		n (%)	Variables		n (%)
Gender	Male	158 (52. 7)	Number of people in house	1–3	101 (42.1)
	Female	142 (47.3)		4–6	104 (43.3)
				More than 6	35 (14.6)
Age (y)	0–4	9 (3.4)	Home type	Private	204 (82.6)
	5–18	9 (3.4)		Rental	43 (17.4)
	19–65	151 (56.8)			
	> 65	97 (36.4)			
Provinces	East Azerbaijan	87 (29.0)	Number of room in house	1–2	168 (70.6)
	West Azerbaijan	58 (19.3)		> 2	70 (29.4)
	Ardabil	39 (13.0)			
	Kermanshah	63 (21.0)			
	Kurdistan	53 (17.7)			
Marital status	Single	53 (21.4)	Antiquity of house (Y)	1–4	44 (18.2)
	Married	151 (60.9)		5–9	28 (11.6)
	Divorced	40 (16.1)		10–19	62 (25.6)
	widowed	4 (1.6)		≥ 20	108 (44.6)
Job (upper 18 Y)	Staff	23 (9.1)	monthly income (U.S. dollar)	< 117	151 (69.6)
	Skilled worker	15 (6.0)		117–156	35 (16.1)
	Unskilled worker	79 (31.3)		157-313	21 (9.7)
	House worker & student unemployment	117 (46.4)		313	10 (4.6)
		18 (7.2)			
Education status (upper 7 Y)	Upper diploma	14 (5.9)	Ventilation house status	Good	196 (81.7)
	Diploma- student	25 (10.5)		Bad	44 (18.3)
	middle	35 (14.8)			
	Reading	40 (16.9)			
	Illiterate	123 (51.9)			
Number of child	0	33 (15.3)	Migration history	Yes	62 (22.3)
	1–2	22 (10.3)		No	216 (77.7)
	3–4	49 (22.8)			
	≥ 5	111 (51.6)			

in 63.9% (n = 131), followed by chronic cough (59.3%, n = 116). However, in category I patients, sputum was the most common symptom of the disease. Sputum and weight loss were the most common symptoms of the category II patients (87.5% and 75%, respectively) (Table 3).

In the simple logistic regression analyses, the only variable that was significantly associated with the treatment type was weight loss. Weight loss was significantly lower in the retreatment group (OR = 3.2, CI 95%: 1.1–9.1), as shown in Table 4.

Table 2: Frequency distribution of clinical characteristics in pulmonary tuberculosis patients

Variables		n (%)	Variables		n (%)
Treatment Patients Status	Category I	235 (92.2)	Liver disease	Yes	24 (9.8)
	Category II	20 (7.8)		No	220 (90.2)
Smokes Tobacco	Yes	34 (29.3)	Diabetes	Yes	24 (10.2)
	No	82 (70.7)		No	220 (89.8)
Addiction	Yes	6 (5)	Parasite	Yes	4 (1.7)
	No	115 (95)		No	231 (98.3)
Drinks Alcohol	Yes	3 (1.4)	Asthma	Yes	27 (11.5)
	No	226 (98.6)		No	208 (88.5)
			Cardiac	Yes	17 (92.8)
				No	218 (7.2)
Chronic Disease	Yes	65 (25.5)	Blood disease	Yes	8 (3.4)
	No	190 (74.5)		No	227 (96.6)
Family History	Yes	18 (5.9)	Vaccination history	Yes	60 (25.2)
	No	286 (94.1)		No	178 (74.8)
PPD	< 5	152 (83.5)	Vaccination scar	Yes	46 (18.9)
	5–9	19 (10.4)		No	197 (81.1)
	> 10	11 (6.1)			

Table 3: Frequency distribution of clinical symptom in pulmonary tuberculosis patients

Clinical Symptoms	Category I patients* Frequency (%)	Category II patients* Frequency (%)
Have cough (Yes)	99 (63.5)	13 (72.2)
Chest Pain (Yes)	89 (53.9)	11 (61.1)
Appetite (Yes)	71 (55.5)	3 (25.0)
Wheezing (Yes)	88 (53.7)	6 (33.3)
Weightless (Yes)	108 (65.9)	14 (77.8)
Quick Fatigue (Yes)	68 (41.5)	11 (61.1)
Hemoptysis (Yes)	50 (30.5)	4 (22.2)
Fever (Yes)	81 (49.1)	11 (61.1)
Weakness (Yes)	93 (56.4)	5 (27.8)
Sputum (Yes)	115 (69.7)	14 (77.8)
Dyspnea (Yes)	96 (58.2)	9 (50.0)

*Category I patients : Pulmonary infection of tuberculosis and positive sputum smear for the patients that have never received a tuberculosis treatment or have received the treatment for fewer than four weeks to receive first line drugs in treatment of tuberculosis.
**Category II patients : Patients who are either diagnosed with previous infection of tuberculosis or have received the first line drugs but have faced failure, relapse or drug resistance during the treatment, had shortage access to drugs or have encountered faults in receiving the treatment plan by the health care providers.

Table 4: Relationship between demographical, environmental and clinical factors with re-current tuberculosis patients by simple logistic regression

Variables		Crude OR	CI95% (OR)	*P* value
Sex	Male	1		0.221
	female	0.5	0.2, 1.4	
Age (year)	0–14	1		
	15–34	0.2	0.0, 2.2	0.202
	35–63	0.2	0.0, 1.9	0.305
	64 ≥	1.9	0.0, 6.3	0.231
Province	East Azerbaijan	1		
	West Azerbaijan	0.8	0.2, 3.3	0.754
	Ardabil	1.6	0.4, 6.2	0.465
	Kermanshah	1.6	0.4, 6.2	0.280
	Kurdistan	1.7	0.4, 7.4	0.225
Religion	Shia	1		
	Sunni	1.6	0.6, 4.7	0.312
Married status	Single	1		
	Married	4.9	0.6, 39.0	0.081
	Divorced/died	2.1	0.2, 24.0	0.475
Migration history (village to city)	No	1		0.668
	Yes	1.4	0.5, 3.9	
Home type	Private	1		
	Rental	0.2	0.0, 1.8	0.155
Number of room in house	1–2	1		
	2 >	1.2	0.4, 3.3	0.072
Number of households	1–3	1		
	4–6	0.6	0.3, 2.1	0.485
	6 >	0.2	0.0, 2.3	0.197
Number of child	0	1		
	1–2	0.8	0.1, 23.4	0.823
	3–4	0.8	0.4, 30.4	0.278
	5 >	0.3	0.4, 24.3	0.306
Having Chronic disease	No	1		
	Yes	0.6	0.2, 2.2	0.263
Vaccination history	No	1		
	Yes	0.9	0.3, 2.6	0.193
Vaccination scar	No			
	Yes	0.4	0.1, 2.0	0.316
PPD (mm)	< 5	1		
	5–9	0.7	0.1, 5.3	0.692
	> 10	2.6	0.5, 13.7	0.261
Family History	No	1		
	Yes	1.5	0.3, 7.1	0.172
Smoking	No	1		
	Yes	0.5	0.1, 1.9	0.298
SES*	5–10	1		
	11–15	0.2	0.0 to1.4	0.113
	16–22	1.2	0.4 to 3.1	0.294

(Table 2 continue)

(Table 2 continued)

Clinical Symptoms				
Cough	No	1		
	Yes	1.8	0.5, 5.7	0.348
Chest pain	No	1		
	Yes	1.9	0.6, 5.6	0.269
Appetite	No	1		
	Yes	0.2	0. 7, 1.3	0.323
Wheezing	No	1		
	Yes	0.4	0.1–1.2	0.102
Weightless	No	1		
	Yes	2.5	1.5–9.4	*0.033
Quick fatigue	No	1		
	Yes	2.4	0.8, 6.9	0.114
Hemoptysis	No	1		
	Yes	0.54	0.2, 1.9	0.348
Fever	No	1		
	Yes	1.8	0.6, 5.0	0.298
weakness	No	1		
	Yes	0.3	0.1, 0.9	*0.027
Sputum	No	1		
	Yes	1.7	0.7, 10.6	0.310
Dyspnea	No	1		
	Yes	0.73	0.3, 2.0	0.543

*SES;Social–economic status combining of patient Job (Regardless housekeeper job) and education status, spouse Job (Regardless house keeper job) and education status and family income among married patients.(grading: Job; 1:unemployment, 2: unskilled worker,3:semi and skilled worker,4: staff education . Education status; 1:illiterate, 2: reading, 3: middle school, 4: diploma, 5: upper diploma. Family income; 1: < 117 USD, 2:117–156 USD, 3: 157–313 USD, 4:> 313 USD.

In the simple regression analyses, there were several variables that presented a *P* Value less than 0.3, including the demographic data on age, gender, province of residence, socioeconomic state, family size, type of house, previous history of tuberculosis infection in the family, comorbidity with chronic illness, weight loss, vaccination history, immigration status and the number of children; these variables were entered into the multiple analysis (Table 5).

In the multiple logistic regression analysis, the category II patients had a higher odds regarding the immigration from a village to a city (OR = 5.4, CI 95%: 1.3 to 20.4) and weight loss (OR = 2.38, CI 95%: 1.92 to 33.3). The other variables did not show any significant association with the recurrence of tuberculosis.

Discussion

This study was designed to explore the relationship of multiple effective socioeconomic and clinical variables with the recurrence rate of tuberculosis in MTB patients of five major border provinces in the north and northwest of Iran. The use of a standard treatment regime in patients suffering a recurrence of tuberculosis remains a challenge for the health care systems of countries with less-developed economies (19). The tuberculosis re-infection ratio (the number of cases of tuberculosis re-infection divided by the number of newly diagnosed patients) in 2012 was 7.3% of patients in Iran, 8% in Iraq, 50% in Russia, 37% in Azerbaijan, 24% in India, and 6% in England. In Africa, these ratios can be as high as 47.4% (20). In the present study, the ratio of re-infection to new infections of tuberculosis was 8.5%, which is consistent with the ratios reported in Iraq (8). However, the estimated ratios in the Azerbaijan Republic were higher than the global average and did not agree with the results of our study. A possible aetiology for re-infection lies in the isolated strain of *M. tuberculosis*. In previous studies, the Beijing strains of *M. tuberculosis*,

Table 5: Relationship between demographical, environmental and clinical factors with re-current tuberculosis patients by multiple logistic regression

Variables		Adjusted OR	CI95% (OR)	*P* value
Age	0–14	1		
	15–34	0.1	0.0, 3.7	0.194
	35–63	0.0	0.0, 0.0	0.997
	64 ≥	0.2	0.0, 2.7	0.234
sex	Male	1	0.1, 3.1	0.423
	Female	0.5		
SES*	5–10	1		
	11–15	0.2	0.0, 2.5	0.368
	16–22	1.0	0.9, 11.0	0.185
		8.4	0.1, 11.0	0.990
Home type	Private	1		
	Rental	0.1	0.0, 2.6	0.181
Migration history (village to city)	No	1		
	Yes	8.4	1.0, 19.8	*0.047
Family history	No	1		
	Yes	0.8	0.0, 54.0	0.936
comorbidity with Chronic disease	No	1		
	Yes	0.3	0.0, 4.8	0.358
Vaccination history	No	1		
	Yes	7.8	0.5, 134.1	0.156
Number of room in house	1-2	1		
	2>	1.6	0.2–13.7	0.673
Weightless	No	1		
	Yes	1.5	1.1–20.4	*0.044
Chest pain	No	1		
	Yes	6.9	0.7–65.4	0.092
weakness	No	1		
	Yes	0.3	0.0, 2.1	0.216
Quick fatigue	No	1		
	Yes	7.2	0.8, 83.9	0.063
Wheezing	No	1		
	Yes	0.4	0.1, 2.3	0.286

*SES;Social-economic status combining of patient Job (Regardless housekeeper job) and education status, spouse Job(Regardless house keeper job) and education status and family income among married patients.(grading: Job; 1:unemployment, 2: unskilled worker,3:semi and skilled worker,4: staff education . Education status; 1:illiterate, 2: reading, 3: middle school, 4: diploma, 5: upper diploma. Family income ;1: < 117 USD, 2:117–156 USD, 3: 157–313 USD, 4:> 313 USD.

which are relatively frequent in the Azerbaijan Republic, were associated with higher rates of re-infection (21). Considering the relatively long border between Iran and the Azerbaijan Republic and the high number of travellers between these two countries, a new trend of recurrence and MDR-TB infection in the north of Iran is predicted. In the assessment of socioeconomic status, gender, age, marital status and residency in the provinces, none of the variables showed a significant association with the rate of recurrence (the socioeconomic score was assessed using a multiple scoring system considering the job, salary, and education level of the patient and his/her spouse). These findings are, however, contradictory to those reported by previous studies. In studies by Sindra et al. (20) and Tomas et al. (22), the gender, age and socioeconomic status of the patients were not associated with the rate of recurrence. However, in studies by

Dooley et al. (7), Comolet et al. (13), Mishra (14), Mphothulo in Africa (19) and Santa (23), males had higher rates of recurrence, which was not correlated with the patients' marital status. None of the environmental factors, such as the ownership of a house and the number of rooms per house, were associated with the rate of recurrence in this study. These finding are in concordance with the results of the study by Mphothulo on the ownership of a house and the number of rooms per house with respect to the rate of tuberculosis re-infection in Africa (19).

The present study failed to reveal a significant association between cigarette smoking and the recurrence of tuberculosis. Several studies have reported controversial results on this issue. Altet (10), Wang (11) and Santa (23) have shown an increased likelihood of re-infection with cigarette smoking; however, Singla (20) reported no correlation between cigarette smoking and tuberculosis recurrence. In this study, the immigration from a village to a city was found to be significantly correlated with higher rates of re-infection. This correlation remained statistically significant even with when the socio-economic variable was considered as a confounding factor. In studies by Comolet and Mishra, patients with tuberculosis re-infection were also found to have an immigration history (13,14). According to the patients' clinical data, the vaccination history, PPD size, scar from the BCG vaccination, comorbidity with chronic illnesses and family history of tuberculosis were not associated with the rate of recurrence. Although there are studies on the role of the BCG vaccination in the prevention of tuberculosis reactivation (23), the literature lacks sufficient data on the effect of the Bacillus Calmette-Guerin (BCG) vaccination on the recurrence of tuberculosis.

The only clinical symptom of MTB that was associated with tuberculosis recurrence was weight loss. Weight loss is a common feature in tuberculosis infection, mainly due to the loss of appetite from various causes, such as fever, a decrease in respiratory function and the adverse effects of the drugs. Designing a cohort study to evaluate the effect of weight loss on the rate of tuberculosis recurrence requires further research. Most of the people with tuberculosis infection are in a low-income societal class and have a limited food supply. Thus, providing economic support to these patients may be a practical plan to help them with maintaining a healthy diet and preventing recurrence. This study is limited with regard to the data of alcohol usage and opium addiction, and thus, these factors could not be analysed with regard to the recurrence of tuberculosis. The data on the drug resistance pattern of *M. tuberculosis* were not available during the study time, which limited the study analyses. Genomic fingerprinting of *M. tuberculosis* is suggested for to identify different strains of the bacilli and determine what role they play regarding the re-infection rate. The regulation of screening plans for travellers to and from neighbouring countries could facilitate controlling tuberculosis recurrence.

Conclusion

The studied border provinces of Iran had moderate recurrence rates (8.5%) in comparison to the globally available rates of recurrence (10-20%). This study revealed that in Iran, migrating from village to city and weight loss was associated with higher recurrence rates of tuberculosis. More literature lacks sufficient data on effect of BCG vaccination in recurrence of tuberculosis. Organised and continuous control of tuberculosis, drug resistance screening, and proper treatment of patients with tuberculosis is required at bordering cities of Iran.

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Conflict of Interest

None.

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Authors' Contributions

Conception and design: MS
Analysis and interpretation of the data: LS
Drafting of the article: LS, MS, AM
Critical revision of the article for the important intellectual content: LS, SF
Final approval of the article: LS, AM
Provision of study materials or patient: SSM
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