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RESEARCH ARTICLE

Factors Associated with Treatment Failure among Smear Positive TB Patients in Khorasan-e-Razavi and Sistan-Baluchistan Provinces, Iran

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ABSTRACT

Introduction: Tuberculosis (TB) treatment failure is one of the major problems of the health sector in developing countries. Poor treatment of patients leads to drug resistance, relapse, death, and ultimately prevents TB control programs. This study was conducted to determine the factors affecting tuberculosis treatment failure in Khorasan and Sistan- Balochistan regions which have a high prevalence of TB.

Methods: In this case - control study 270 patients with tuberculosis (90 cases, 180 controls) were analyzed. New TB patients registered with failure to treatment according to the national protocol between March 2008 - March 2012 were chosen as cases and new TB patients with negative sputum smear in the same time frame were enrolled as control group. Demographic data and clinical treatment outcomes were collected through interviews and file records. Multivariate logistic regression analysis was used to determine the predictors of treatment failure in SPSS 19.

Results: Independent factors and predictors of failure treatment included illiteracy, a three plus positive sputum smear, positive sputum smear at end of the second month, non-implementation of the Directly Observed Treatment Short strategy by healthcare staff, history of addiction and history of diabetes.

Conclusion: Intervention programs for early detection and control of diabetes, drug control programs, giving priority to providing DOTS by health care workers, more individual care and attention to patients with initial smear p + 3 or those that remain sputum positive at the end of the second month or those who are less educated is necessary. *J Microbiol Infect Dis 2016;6(4): 172-178*

Key words: Tuberculosis, Treatment failure, Iran.

INTRODUCTION

Nearly one third of the world population (about 2 billion people) is contaminated with Mycobacterium tuberculosis or is threatened by it. Each year approximately 9 million people are infected with Mycobacterium and about 1.5 million people die as a result of this infectious disease. Pulmonary tuberculosis (TB) forms 66% of TB infections and it is often associated with positive sputum smear (sputum containing AFB) among the adults, which in this case it becomes highly contagious. With the ascending spread of TB, in 1991, the World Health Organization (WHO) announced TB as a global emergency and announced that the immediate reduction of TB prevalence, the mortality caused by it and consequently its incidence as one of its general goals to be followed by all countries. The WHO also determined short term goals such as achieving a 70% patient detection and 85% treatment success for the world states by 2000, and implementing the Directly Observed Treatment Short (DOTS) strategy into the healthcare system in order to control and reach its goals partially [1].

Poor treatment of TB patients would certainly lead to the risk of drug resistance, failure of treatment, relapse, death, continuous existence of infection, and finally could abate successful implementation of TB control programs. In general, countries

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which implement DOTS program in order to ensure patient treatment show increased treatment success and less treatment absence. Hence, patient's regular use of drugs must be guaranteed by implementing DOTS [2].

IV drug abusers, individuals who work or live at places where contaminated people are concentrated (such as prisons and homeless shelters), and poor people with no access to proper medical care are at risk of getting TB. Compared with nonsmokers, smokers are nearly more than twice as likely at risk of getting TB. Other diseases, such as alcoholism and diabetes mellitus, can increase the risk of TB by three times. Studies have revealed a significant increased treatment failure in diabetic TB patients compared with non-diabetic ones [2-4].

In recent years, the number of treatment failures has been above the average level in Khorasan-e-Razavi Province. However, apparently no study has been conducted about the factors associated with treatment failure so far in this region. In this study, the researchers have investigated variables which have not been previously investigated in the province even in the previously conducted descriptive studies. This study has taken into account the effects of occupation, place of residence, imprisonment, addiction and education in treatment failure. The current study delves into the factors associated with treatment failure among smear positive patients in Khorasan-e Razavi and Sistan-Baluchistan Provinces in Iran.

MATERIALS AND METHODS

The study population included two provinces with a high incidence of tuberculosis in Iran. Khorasan-e-Razavi with a population over 5,990,000 as well as 118,854 square kilometers of area is among the biggest provinces of Iran. This study included all 22 cities covered by Mashhad University of Medical Sciences including 19 sputum smear labs and 243 healthcare centers.

The second research area included the city of Zahedan, in Sistan-Baluchistan Province and its suburbs with an area of 36,581 square kilometers and nearly 660,000 inhabitants. This city has 15 healthcare centers and four sputum smear diagnosis labs.

The two provinces have a common border in the east with two countries with a high incidence of TB, i.e. Afghanistan and Pakistan. The smear positive cases registered in the database were recruited based on definitions given in national instructions.

According to the definitions, a smear positive pulmonary TB patient is one that has at least two AFB smear-positive sputum lab results, or a patient that has one positive sputum smear test in terms of AFB and whose chest radiographic changes confirm pulmonary TB. In addition, a patient that has only one AFB smear positive sputum as well as one AFB positive sputum culture. The treatment failure case is a pulmonary TB patient with smear positive sputum for which the direct sputum test is still positive after five months (or more) from the start of treatment or it gets positive in this time span after becoming negative. Also, if at any time during the treatment of a patient, the diagnosis of MDR-TB is confirmed, the result of his treatment should be registered as treatment failure [1].

In the present study, a new patient is one who has never received anti-TB treatment in the past or has used anti-TB drugs less than four weeks.

In the present study a case is a smear positive patient whose treatment result was registered as "treatment failure" during March 21, 2010 until February19, 2012 according to national TB guidelines. Here, the controls were new smear positive patients whose result of treatment according to the national TB protocol was labelled as "cured" in the same time-span.

Cases imported from other provinces or countries, patients whose result of treatment was registered as absent, patients transferred to other provinces and cases with incorrect diagnosis (cases of Non-tuberculosis Mycobacteria that were wrongly diagnosed as tuberculosis are registered as incorrect diagnosis in the database) were excluded from the total number of patients due to lack of access to their information. Regarding the fact that in this study one of the variables under investigation was DOTS and no DOTS was conducted for patients with smear negative pulmonary TB in the healthcare system; therefore smear negative patients and cases of smear negative treatment failure were excluded from the study as well.

In this study, all new smear positive pulmonary TB patients of Khorasan-e- Razavi province and Zahedan city and its suburbs during March 21, 2010 until February 19, 2012 were extracted from the relevant TB database. Cases and controls were selected randomly from these patients. Then, information was collected through file records and interviews. The interviewers were given face to face training for correct data collection. In all the cities, interviews were conducted in company of autho-

rized personnel of the relevant healthcare center of the urban or rural area to ensure patient cooperation. Moreover, in different stages of data collection, patients were assured about the confidentiality of their personal information.

Based on a research by Viswanathan et al [4], the prevalence of treatment failure in diabetic patients with positive smear was 0.188 and in controls (smear positive non-diabetic patients) was 0.0256. Therefore, with the power of 90% and first type error equal to 5% at least 71 cases in each group for this case control study were calculated [5]. In the present study, 90 cases and for each case two controls (180 controls) and totally 270 new smear positive patients were enrolled and the power increased up to 97%.

Data analysis was performed by SPSS 19. Primarily t-test and chi-sqaure tests were performed. Then, univariate and multivariate backward logistic regression was performed.

RESULTS

From the 270 patients (90 cases and 180 controls), information about 82 cases and 169 controls were collected correctly and completely. The address of 8 cases and 11 controls was not found, and their information was not complete, therefore they were excluded from our study. Eventually, the information of 251 patients was included into the research.

The demographics of the two groups could be seen in Table 1.

Table 1. Demographic characteristics of the cases and controls, in two provinces

Qualitative variables	**Khorasan-e-Razavi**			**Sistan-Baluchistan**			**Total Patients**		
	Controls:n (%)	Cases: n (%)	p-value	Controls:n(%)	Cases: n (%)	p-value	Controls:n (%)	Cases: n(%)	p-value
Sex (M)	73/123 (59.3)	27/60 (45)	0.067	34/46 (73.9)	12/22 (54.5)	0.116	107/169 (63.3)	39/82 (47.6)	0.018
Nationality (Iranian)	103/123 (83.7)	43/60 (71.7)	0.056	29/46 (63)	18/22 (81.8)	0.115	132/169 (78.1)	61/82 (74.4)	0.512
Rural Residence	21/123 (17.1)	6/60 (10)	0.257	12/46 (26.1)	1/22 (4.5)	0.035	33 /169 (19.5)	8/82 (8.5)	0.026
Prisonment history	123/123 (100)	57/60 (95)	0.012	44/46 (95.7)	19 /22 (86.4)	0.173	2 /169 (98.8)	6/82 (92.7)	0.009
Occupation (Insured employee)	27/123 (22)	6/60 (6)	0.025	0/46 (0)	1/22 (4.5)	0.345	27/169 (16)	7/82 (8.5)	0.071
Level of education (uneducated)	51/123 (41.5)	33/60 (55)	0.195	29/46 (63)	15/22 (68.2)	0.673	80/169 (47.3)	48/82 (58.5)	0.218
Household Monthly income (0-3500000 Rials)	38/123 (30.9)	30/60 (50)	0.038	29/46 (63)	11/22 (50)	0.062	67/169 (39.6)	41/82 (50)	0.218
The degree of sputum smear positivity (p+1patients)	27/123 (22)	6/60 (10)	0.012	21/46 (45.7)	3/22 (13.6)	0.019	48/169 (28.4)	9/82 (11)	<0.001
The result of the smear at the end of the second month (Smear negativity)	94/123 (76.4)	12/60 (20)	<0.001	35/46 (76.1)	3/22 (13.6)	<0.001	(76.3)129	40/82 (18.3)	<0.001
DOTS (Provided by the health care staff)	95/123 (77.2)	29/60 (48.3)	<0.001	35/46 (76.1)	11/22 (50)	0.054	130/169 (76.9)	40/82 (48.8)	<0.001
Smoking history (not Smoking)	108/123 (87.8)	44/60 (73.3)	0.014	40/46 (87)	15/22 (68.2)	0.065	148/169 (87.6)	59/82 (72)	0.002
Addiction history (not Addicted)	110/123 (89.4)	41/60 (68.3)	<0.001	37/46 (80.4)	15/22 (68.2)	0.264	147/169 (87)	56/82 (68.3)	<0.001
History of Diabetes (no Diabetes)	108/123 (76.4)	46/60 (20)	0.053	42/46 (91.3)	14/22 (63.6)	0.005	150/169 (88.8)	60/82 (73.2)	0.002
Quantitative variables	**mean ± standard deviation**		**p-value**	**mean ± standard deviation**		**p-value**	**mean ± standard deviation**		**p-value**
Age	54.4 ± 23.2	17.3 ± 49.5	0.112	22 ± 49.5	18 ± 53.5	0.646	22.9 ± 53.1	17.5 ± 50.5	0.334
Weight	12.3±53.6	11.4± 50.9	0.145	15.1±49.3	11.6± 51.7	0.514	13.2±52.5	11.4± 51.1	0.423
Delay in treatment	5.3± 2.7	2.4±9.2	0.724	0.8± 0.4	0.63±8.0	0.262	4.7± 2.1	1.9 ± 6.2	0.816
Patient's received DOTS (days provided by healthcare staff)	18.5±42	20.6±31.6	0.001	16.9±40.9	18.3±33.8	0.115	18±41.7	19.9±32.2	<0.001

The average age and weight in the case group was respectively 50.6 ± 17.5 years and 51.14 ± 11.45 kg. The same variables were respectively 53.12±22.9 years and 52.5±13.27 kilograms in the control group. The differences were not significant. The number of days delay in treatment was not significant either, but the number of days the patient's received DOTS by the healthcare staff was significantly different (p-value=0.0001). Thus, receiving DOTS can probably be considered as one of the predictors of treatment failure.

Men and urban patients had a significantly higher chance of treatment failure as well. There were no significant differences between treatment failure and patients' occupation. However, treatment failure was higher in p+3 patients than others. Positive smear at the end of the second month in patients was also associated with more treatment failure. Having a history of prison, smoking, addiction and diabetes significantly increased the risk of treatment failure in the patients, but nationality, education and the level of monthly income had no significant difference in the two groups (Table 1). The results of multivariate logistic regression analysis can be seen in Table 2.

Table 2. Univariate and Multivariate Logistic Regression of factors affecting treatment failure in TB patients

Qualitative variables		Crude OR (%95CI)	p-value	Adjusted OR (95%CI)	p-value
Sex	Men (compared to women)	1.9 (1.11-3.25)	0.018	1.52(0.8-2.89)	0.200
Nationality	Afghan (compared to Iranian)	1.23 (0.66-2.27)	0.512	1.33 (0.5-3.5)	0.567
Place of Residence	Urban (compared to Rural)	2.59 (1.09-6.01)	0.033	2.13 (0.69-6.5)	0.189
Prison record	Prison (compared to unprisoned)	6.59 (1.3-33.42)	0.023	2.22 (0.3-16.03)	0.429
Occupation	Housewife (compared to Insured employee)	1.67 (0.67-4.16)	0.165	2.29 (0.7-7.47)	0.163
	Worker (compared to Insured employee)	2.67 (1.05-6.79)	0.043	2.81 (0.85-9.28)	0.089
Level of education	Below high school diploma (compared to uneducated)	0.66 (0.38-1.15)	0.142	0.33 (0.14-0.76)	0.011
	Academic education(compared to uneducated)	0.45 (0.12-1.71)	0.245	0.64 (0.08-4.73)	0.664
Household Monthly income	3500000-5200000 Rials (compared to 0-3500000 Rials)	0.54 (0.27-1.09)	0.091	0.68 (0.26-1.82)	0.455
	above 5200000 Rials(compared to 0-3500000 Rials)	0.74 (0.4-1.36)	0.343	1.11 (0.43-2.87)	0.817
The degree of sputum smear positivity	p+2 patients (compared to Insured p+1 patients)	1.88 (0.77-4.59)	0.165	1.53 (0.48-4.89)	0.473
	p+3 patients(compared to Insured p+1 patients)	4.19 (1.9-9.27)	<0.001	2.89 (1.01-8.24)	0.047
The result of the smear at the end of second month	Smear positivity (compared to Smear negativity)	14.4 (7.42-27.9)	<0.001	14.33 (6.77-30.33)	<0.001
DOTS	Shared with the family (compared to Provided by the healthcare staff)	4.16 (2.21-7.82)	<0.001	4.03 (1.66-9.81)	0.002
	By the patient's family(compared to provided by the healthcare staff)	(0.96-5.63)2.32	0.062	4.19 (1.18-14.83)	0.026
Smoking history	Smoking (compared to not Smoking)	2.75 (1.41-5.34)	0.003	1.12 (0.33-3.75)	0.853
Addiction history	Addiction (compared to no Addiction)	3.1 (1.63-5.92)	0.003	2.9 (1.14-7.37)	0.025
Diabetes history	Diabetes (compared to no Diabetes)	2.89 (1.46-5.73)	0.002	2.92 (1.11-7.67)	0.033
Quantitative variables	Age	0.99 (0.98-1.007)	0.381	0.97 (0.95-1.002)	0.071
	Weight	0.99 (0.97-1.01)	0.425	1.009 (0.97-1.04)	0.582
	Delay in treatment	0.99 (0.93-1.06)	0.815	1.002 (0.91-1.1)	0.963
	Patient's received DOTS (days provided by the healthcare staff)	0.97 (0.96-0.98)	<0.001	1.02(0.67-1.11)	0.511

DISCUSSION

This case-control study shows a number of factors as the main risk factors in treatment failure of smear positive pulmonary TB patients. Despite the high incidence of TB in Sistan-Baluchistan, the percentage of treatment failure has been lower there compared with Khorasan-e Razavi and the national average level [6].

Based on the findings of this study, independent risk factors and important predictors for TB treatment failure include level of education, the degree of sputum smear positivity, the positivity of the sputum smear at the end of the second month, the DOTS implementation strategy, history of addiction, as well as diabetes.

The present study highlights the positive sputum smear at the end of the second month as the strongest predictor of treatment failure. This finding is in line with the results of the researches conducted in southern Delhi [7], Yunnan province of China [8] as well as a study performed in Uganda [9].

DOTS has been implemented in many countries to ensure proper treatment of TB patients and has yielded effective results in increasing success of the treatment and reducing absence from treatment [2]. Multivariate analysis in this study showed that DOTS given jointly by the patient's family and the health care staff and the one provided only by the patient's family, each increases the chance of treatment failure compared with DOTS presented only by healthcare staff. In a study by Narayanan et al [2], about the factors associated with failure and absence from treatment in southern India, the chance of treatment failure in patients to which DOTS was presented irregularly was 4.3 more than the chance for treatment failure in patients who had received complete DOTS from the healthcare system. In another study by Jianzho et al [8], conducted in China, a significant difference in treatment related to DOTS was observed. In this study, the chance for treatment failure in a group on which the DOTS was implemented in cooperation with the patient's family was 3.1 times higher than the group which DOTS was provided by the healthcare staff.

The findings of the present research showed that uneducated people are at a higher risk of treatment failure in such a way that patients with an educational level below high school diploma have less chance for treatment failure compared with the uneducated ones. In the present study, a small ratio of patients (5.6%), were in the tertiary educated class and most of the patients under investigation in the present study belonged to the less educated members of the society. It is noteworthy to mention that approximately 75% of the patients investigated in the present study were either uneducated or only had elementary education.

In studies conducted in Uganda [9] and China [8], no significant difference was shown between patients with upper-intermediate level of education and the reference group (elementary and uneducated ones). However, in the Uganda study the ratio of educated people in the case and control groups was exactly the same. In a research by Narayannan et al [2] in southern India, the chance of treatment failure in uneducated patients was not significant compared with educated patients. Also, in a research by Satyanarayana et al [10] in India and as well as in a study from Egypt [11], contrary to the results of the present study, there was no significant difference in treatment failure between the educated and uneducated patients. It is worthy to note that in all of these studies, education was merely categorized into two groups (educated vs. uneducated) while in our study it was categorized in three levels.

Consistent with the results of Jianzhao et al in China, in this study those with initial 3+ smear positivity had a higher chance of treatment failure compared with others. In Jianzhao et al's study the odds ratio for those with 2+ or more initial smear positivity compared with patients with a sputum smear below 2+ was 2.7 (CI 95% 1.1-7.1). But Singla et al's research in southern Dehli [7] showed no significant difference in treatment failure in the 3+ group compared with other patients.

The present work found a significant relation between history of addiction and treatment failure which is in line with the research conducted in Zabol, Iran by Adineh et al [12] in which the odds ratio obtained was OR=25.61 (CI 95% 5.23-123.91).

The current study also showed a significant relationship between history of diabetes and treatment failure. Treatment failure in diabetics was higher than non-diabetics which is also in line with the result of the study conducted by Shibin et al [13] in India in which the odd ratio was 2.4 (P-value=0.022).

Age was not significantly related to treatment failure in our study. This was in line with the studies carried out in Angula (in which the subjects were divided into two subcategories of ≤32 and >32years of age) [9] as well as a study by Satyanarayana et al [10] in India. Also in a study by Morsy et al [11] in Egypt, no significant relationship existed between treatment failures in patients under 25 years of age

compared with the other subgroups. Despite the different age-based categorization of the patients in the above research, none of them found a significant relation between treatment failure and age.

Furthermore, in line with the findings of the present study that did not find a relation between treatment failure and occupation, Mosry et al [11] revealed no significant difference between those occupied with household or manual jobs compared with those doing other kinds of work in Egypt.

Patient's weight was not significant in this study. In Dooly et al's study [14] in Morocco weight was not related to treatment failure either.

Gender was a significant variable in some studies including the one conducted by Satyanarayana et al [10] in India. In Satyanarayana et al's study men were more prone to treatment failure. But it was not significant in the researches carried in southern Dehli [7], Egypt [11] and China [8]. In our study although treatment failure was higher in men, but this difference was not significant in multivariate logistic regression.

Smoking was not significant in this study and confirmed the results of a study by Singla et al [7] in southern Dehli, but Garcia et al [3] in southern Mexico got different results. Garcia et al classified patients into three groups (non-smokers, light smokers and heavy smokers). Treatment failure was significantly higher in light and heavy smoking groups.

Inconsistent with the findings of the study by Jianzhao et al in China [8], monthly income of the families was also not significant in our study. However, it is worth mentioning that in Jianzhao et al's study the number of people with low, medium and high incomes were similar. But, in the current study almost all subjects (controls and cases) had a low income.

The current study had some limitations. Due to the few cases of patients with HIV+ (only 4 patients), this variable was excluded from our study. Variables such as alcohol use, chest radiography results, weight gain during the first two months of treatment, distance between the patient's residence and the service center, support by family and others, and finally the level of knowledge of family members and the TB patient about TB and other diseases like blood pressure and hepatitis were also among the variables excluded from this research. These variables were excluded due to the increased study workload, time limitation and lack of sufficient samples. The effects of other variables on treatment failure are suggested to be investigated in future research.

In conclusion, intervention programs for early detection and control of diabetes, rehab for addicts, providing DOTS to patients by health care staff, more individual care and attention to patients with an initial3+ smear or cases who remain sputum smear positive at the end of the second month as well as to the less educated patients are necessary to successfully treat TB in Iran.

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