

ORIGINAL ARTICLE

Risk Factors Associated with unsuccessful treatment outcomes among Patients with smear positive pulmonary tuberculosis in Iran: A Logistic Regression Model

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ABSTRACT:

Objective: Tuberculosis is still one of the principal infectious main of disease and death worldwide. The aims of this study were to evaluate the treatment outcome for new smear positive pulmonary TB cases registered in North of Iran and to identify factors associated with non-successful treatment.

Methodology: The study of Present was conducted longitudinal (2005-2011). A checklist containing research variables was applied for data collection. 683 smear-positive pulmonary TB patients were included in the study. Data were analyzed using classical statistical test and logistic regression for adjusting variables effect.

Results: The mean age of patients was 49.73±21.57 years. 57.5% of patients were male and 57.4 % of them were urban residents. The treatment outcome of these patients was as followed: treatment success 87.8%, defaulted treatment 2.6%, death 4.4%, failure 2% and transferred out 3.1%. In multivariate regression analysis, patients with non-Iranian nationality, self-administered therapy and positive sputum at the end of the second month of treatment were considered as significant determinants for non-successful treatment.

Discussion and conclusion: Assessment of treatment results of studied smear-positive pulmonary tuberculosis patients are desirable according to the goals set by the World Health Organization (cure at least 85% of new sputum smear-positive pulmonary TB). Application of Directly Observed Therapy increases treatment success in all patients, especially patients who are at risk of low treatment success rate.

Keywords: tuberculosis, cure, Dots, treatment success, treatment failure,

INTRODUCTION:

Tuberculosis (TB) still is recognized as one of the main causes of disease and death worldwide, especially, in middle and low-income countries¹. Despite the widespread availability of cheap, effective treatment, TB remains a major cause of severe illness and death, with an estimated nine million new cases and two million annual deaths².

According to millennium development goals, morbidity and mortality of this disease must decrease by 50% till 2015 compared to 1990 and the countries must eliminate this disease till 2050; it will be possible through improving case finding and success rate of TB treatment³. However, even in many industrialized countries, in spite of good treatment facilities and a secured supply of drugs free of charge for patients, treatment results have not reached the targets set by WHO⁴⁻⁵.

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The WHO reports worldwide success rates for TB treatment ranging from 20–87%^{6,7}. Several factors such as physician awareness of TB diagnosis, treatment and DOTS

strategy are associated with treatment success⁸⁻⁹. The key to TB control is to detect the disease as early as possible and to ensure that those diagnosed, complete their treatment and get cured¹.

However, treatment is challenging for both patients and providers because it requires taking multiple medications for a minimum of 6 months^{10, 11}, which frequently results in patients taking their medications erratically or not at all¹². Non-adherence to TB medications decreases the chances of cure, increases the risk of relapse after treatment, and selects for drug-resistant TB strains¹³. Noncompliance has been identified as being associated with recurrence of TB¹⁴.

Recurrence of TB causes significant threats like MDR-TB. Moreover, MDR-TB and HIV-associated TB can be counted as problems resulted from improper TB treatment¹⁵.

Therefore, treatment outcome monitoring is a core part of surveillance necessary to succeed in TB elimination¹⁶.

Recognizing factors affecting unsuccessful treatment of people with TB is of great importance in improving treatment strategy. For this we aimed to study the results of response to treatment of smear-positive pulmonary TB, and to determine factors related to unsuccessful treatment in Mazandaran (north of Iran).

Material and methods:

The location of the study was Mazandaran, a province in the north of Iran with approximately 2450000 inhabitants in the year of the study. A longitudinal study design was performed to assess treatment outcomes of patients. Data was extracted from the Iran Surveillance System of TB historical database. A data collection checklist collected data on variables such as outcome treatment, gender, age, residing area, sputum smear status at the beginning of Treatment and after 2 months, nationality, category of treatment and TB treatment under DOTS.

We included all patients with smear positive TB who were reported to the TB Control Section of the Department of disease control of Mazandaran university of medical sciences from March, 1, 2005 through March 29, 2010(683 cases).

All patients who were sputum smear-positive at the initiation of treatment were followed up until the completion of treatment. TB cases were diagnosed with sputum smear-positive tests using the Ziehl–Nielsen technique. We excluded patients with extra pulmonary TB and those with smear-negative TB.

Treatment regime and procedures, including laboratory diagnosis, were guided by the national policy on TB Control; all of the TB cases underwent a 6 or 8-month treatment regimen according to the WHO protocol¹⁶⁻¹⁸

Sputum samples were taken at the end of the second month and the beginning of the fifth month. Patients who were smear-positive after the second month had an extra month on the four-medicine regimen. Those who were smear-positive at the beginning of the 5th month were considered as treatment failures.

The treatment outcome was divided into seven categories according to WHO guidelines, with some modifications¹⁶: Cure rate, Completion of treatment,

Successful Treatment (The sum of Cure rate and Completion of treatment), Died, Transferred out, Treatment failure, Defaulted (a patient who did not come back to complete chemotherapy).

The outcome was categorized as favorable (Treatment success) and unfavorable¹⁶. We used SPSS 16 for data analysis. Chi-square test was used to evaluate differences in categorical variables and The Fisher's exact test was used when cell sizes were < 5 (For univariate results). Logistic regression analysis was performed to identify predictors of poor treatment outcome. To estimate the odds ratio for treatment outcome (success vs. non-success) Variables such as gender, age, residing area, sputum smear status after 2 months and at the beginning of the first month, nationality, category of treatment and TB treatment under DOTS were entered into both univariate and multivariate logistic regression models.

The ethics approval for this study was acquired from the medical ethics committee of Mazandaran University of medical sciences before embarking on the study.

Results:

Mean of smear-positive TB and pulmonary TB incidence in the studied population was 9.1 and 4.3 in hundred thousand respectively. Frequency of all TB cases in males and females was 51.5% and 48.5% respectively. ($P=0.0001$, $OR=1.62$, $95\%CI=1.3-2.01$); while these figures were 54.6 and 45.4 percent respectively for pulmonary TB cases ($P=0.0001$, $OR=1.1$, $95\%CI=1.1-1.2$); and frequency of smear-positive pulmonary TB cases in males and females was 48.1 and 51.9% respectively ($P=0.003$, $OR=0.87$, $95\%CI=0.79-0.95$). 683 patients with smear-positive pulmonary TB were diagnosed from 2004 to 2009 and their mean age was 49.73 ± 21.57 ; no significant difference was observed in patients' age in terms of their gender ($P=0.8$). 57.4% cases lived in urban regions and 93.3% of diagnosed cases belonged to the new cases disease group. 50.5% of patients were cured using DOTS (Directly Observed Treatment, Short-Course).

Results of treatment suggests 87.8% successful treatment, 2.6% defaulted, 2% failure in treatment, 4.4% death and 3.1% transferred. Successful treatment rate in females was higher than that of males; however, defaulted, failure, death and transferred cases were higher in males. According to chi square results, effect of gender on treatment results was significant ($P=0.01$) however according to multiple regression test, gender was not a predictor of treatment results ($OR=1.2$, $95\%CI=0.4-1.06$, $P=0.08$). Moreover, treatment success rate in rural areas was higher than that of urban areas ($OR=0.8$, $95\%CI=0.5-1.3$, $P=0.4$) and treatment success rate of new patients was higher than that of retreatment patients; however, the observed difference wasn't significant ($OR=1.2$, $95\%CI=0.5-2.9$, $P=0.7$). Treatment success rate of Iranian patients was significantly ($OR=4.2$, $95\%CI=1.6-10.8$, $P=0.003$) higher than that of non- Iranian patients and it was significantly higher in patients underwent DOTS ($OR=1.9$, $95\%CI=1.1-3.2$, $P=0.02$) than patients with Self-administered therapy. Successful treatment in age group 31-45 and 75 years and more age group was less than 85% (see table 1)

Discussions

Treatment success rate of people with smear-positive pulmonary TB was 87.8% and unsuccessful treatment rate was 12.8%. In another Iranian study, the level of negative response to TB treatment was 35.5%¹⁹. In a study in Finland, 441 patients

were cured successfully (70.1%), 108 patients died (17.2%) and 80 patients were in one of "failure in treatment, defaulted and transferred" groups (23%)²⁰. Treatment success rate in European Union for all new cases and retreatment cases of pulmonary TB in 2007 was 73.8 and 79.5% respectively²¹. In determining factors related to TB results in south part of Ethiopia, 74.8% were classified in successfully treated group and 16.7% in weakly treated group; of the latter group, 60.9% were classified as defaulted, 36.9% in death group and 2.2% in failure group²². This indicates, treatment status of patients with TB in Mazandaran Province (Iran) is more desirable than that of the mentioned studies.

When interpreting the desirable treatment outcomes, in addition to better services provided for tubercular patients, it should be mentioned that the results of treatment of patients with smear-positive pulmonary TB were based on direct sputum smear tests which are performed in laboratories of Health and Treatment networks. This way, if the tools aren't appropriate, if the personnel performing the tests aren't skillful enough and if enough time isn't allocated to study the slides, the possibility of existence of false negative reports for sputum smear results will increase and possibility of relapsing the disease in far future will be expectable. Understanding the fact that most patients with smear-positive pulmonary TB are diagnosed by laboratories other than health networks laboratories, raise questions about accuracy of the tests of second month and end of treatment.

In this study, treatment results in females were more desirable than males and the possibility of unsuccessful treatment in males was 1.7 times higher than females. However, in another Iranian study, no significant statistical relationship was found between gender and treatment consequences²³, but, in a study in south of Ethiopia, gender (male) was one of the factors related to undesirable results of treatment²⁴. Same results were observed in Finland where, gender (male) was regarded among risk factors contributing to unsuccessful treatment²⁰.

It has been shown that smoking and HIV/AIDS in males are higher than in females and both are considered as important risk factors in mortality of patients with TB²⁴⁻²⁶. Hence, successful treatment of males with TB is harder and less effective than females due to some reasons including working out of the house, working in different shifts, lower sensitivity and attention to health, using narcotics, reluctance to medicine consumption for a long time and faster recovery.

In the present research, unsuccessful treatment rate in urban dwellers was 1.25 times higher than that of people who live in rural areas. In Ethiopia, low attention of health centers located in the disease-stricken regions was one of the factors related to undesirable treatment results²². More desirable treatment results in rural areas can be attributed to the presence of health personnel (physician, midwives, health practioners and Behvarzs), health and treatment centers, health posts and good health activities in Iran's health network at rural areas.

According to research data, treatment of Iranian patients was better and more desirable than that of non-Iranians ($P=0.001$). Comparison of treatment results of Iranian and non-Iranian patients with smear-positive pulmonary TB in Isfahan revealed that recovery rate, success in treatment, death and transferred cases were

75.8, 6.5, 8.37 and 1.95 percent higher in Iranian patients in comparison with non-Iranians respectively; however, failure in treatment was 5.89 percent and defaulted cases were 10.65 percent in non-Iranians²⁷. In another Iranian study in Mashhad, total recovery and successful treatment of Iranians were 70.2 and 72.8% respectively and 68 and 69.7% in emigrants²⁸ which match the results of this research. Some factors including economical and cultural poverty and lack of access to health facilities might be the main reasons of unsuccessful treatment in non-Iranians patients in comparison with their Iranians counterparts. To treat non-Iranians patients more effectively, observing them carefully and having enough information about their living places in Iran and their own countries is of great importance.

The possibility of unsuccessful treatment of patients with Self-Administered Therapy was 1.9 times more than those with directly Observed therapy (DOTS) ($P=0.02$). In a study carried out on 149 patients with directly Observed therapy and on 223 patients with Self-Administered therapy, treatment results of directly observed patients was more desirable ($P<0.002$)²⁹. In another study in Turkey, DOTS increased success rate of all patients especially those with unsuccessful treatment risk factors³⁰. In a study on effectiveness of DOTS strategy in recovery or failure of treatment of pulmonary TB, failure rate in DOTS group was 1.7% while it was 7.3% in control group³¹. Taking anti-TB medicine correctly and regularly with direct observation and supervision of skillful personnel decreases the failure and relapse of disease. Results of all of the above-mentioned studies, regarding application of DOTS, conform to the results of the present study.

In this research, possibility of unsuccessful treatment in patients who were treated for the second time was 1.2 times more than new patients ($P=0.7$). Successful and unsuccessful treatment rates in patients with tuberculosis in territories covered by Shaheed Beheshti University of Medical Science were not statistically significant in relation to variable of new treatment or retreatment cases²³. Also previous experience with receiving anti-TB treatment has been reported to be a weak risk factor for death of patients³². In another research, retreatment was reported to be a factor related to undesirable result of treatment²². Results of some of the mentioned studies match and some contradict the result of the present study regarding specific role of therapeutic group (new treatment or retreatment). However, the most important point here is the effective treatment management of this group of patients because prevalence of resistant TB in this group is high.

Research findings showed that treatment success is weak in patients whose sputum smear remained positive at the end of the second month of treatment. Unsuccessful treatment in those whose sputum smear was positive at the end of the second month of treatment was 16.9 times more than those whose sputum smear was negative at the end of the second month ($P=0.0001$). However Kheirkhah et al²³ did not find any significant relation between laboratory result and successful and unsuccessful rate of disease outcome. But, in the study in south of Ethiopia, positive sputum smear at the end of the second month of treatment was considered as a factor related to undesirable result in treatment²⁴ which is in line with our study.

Positive sputum smear reflects some issues like timely diagnosis or delayed diagnosis, creation of cavity on lungs and patient's infecting power which must be taken into consideration in evaluating the performance of the plan and in evaluating treatment status.

This study indicated that results of treatment outcome varies based on age groups; unsuccessful treatment rate in age group of 35-45 and over 75 was higher than other age groups. Accordingly, Manissero et, reported older age as a risk factor in undesirable treatment of TB. Additionally, it has been shown that mortality rate in TB patients increases with age and the highest mortality rate is observed in people aged 65 and more²¹. In an Indian study³³ a significant difference was observed in treatment result in terms of age group (P=0.02) and age group more than 40 were considered as an important risk factor for death of TB patient. Older age groups show weaker response to treatment in comparison with younger (under 40) due to some reasons like immunity disorders, frequency of diabetes and renal diseases, etc³⁴.

Conclusion:

Main objective of TB control program is to decrease TB diseases significantly through reducing mortality and morbidity of disease and then through reducing disease prevalence in society so that this disease won't be considered a health problem in society anymore and TB can be eradicated. However, increased HIV/AIDS, side effects of anti-TB medicines, addiction and increased MDR TB in this region are serious threat for TB program and if these conditions are ignored and no suitable decisions are made, an undesirable future will appear for this program. Thus, reviewing the related workforce structure fundamentally, supporting and strengthening the strategy of DOTS, paying attention to motivational issues of personnel related to program and having effective relationship with physicians of private section to follow anti-TB treatment protocol in Iran, which needs a comprehensive attempt and sensitivity of all related authorities, are effective steps in controlling and finally eradicating this disease until 2050.

Table I: comparing the effect of studied variables on treatment results of patients with smear-positive pulmonary tuberculosis based on classical analysis and regression model

Variables		<i>Logistic regression</i>			<i>Chi square test</i>			
		<i>test</i>	OR	CI	Treatment success (%)	Treatment failure (%)	X2	P
Gender	Male	-	-	-	85.2	14.8	5.9	0.01
	Female	0.08	0.6	0.4-1.06	91.4	8.6		
Residential area	Urban	-	-	-	87.2	12.8	0.3	0.6
	Rural	0.4	0.8	0.5-1.3	88.7	11.3		

Disease case	New	-	-	-	88.2	11.8	1.1	0.3
	Old	0.7	1.2	0.5-2.9	83	17		
Dots Strateg y	Yes	-	-	-	92	8	12.3	0.0001
	No	0.02	1.9	1.1-3.2	83.2	16.8		
Age group	16>	-	-	-	100	0	9.5	0.09
	16-30	0.999	-	-	88	12		
	31-45	0.999	-	-	84	16		
	46-60	0.999	-	-	94.1	5.9		
	61-75	0.999	-	-	88.5	11.5		
	75<	0.999	-	-	82.7	17.3		
Positive level of sputum smear at the beginning of treatment	Basil 1-9	-	-	-	77.8	22.3	3.6	0.3
	1 ⁺	0.2	0.5	0.2-1.5	89.8	10.2		
	2 ⁺	0.4	0.6	0.2-1.9	87.2	12.8		
	3 ⁺	0.2	0.5	0.2-1.5	87.3	12.7		
Results of sputum smear at the end of second month of treatment	Negative	-	-	-	91	9	54.6	0.0001
	Basil 1-9	0.000	6.6	2.3-19.01	52.9	47.1		
	1 ⁺	0.01	2.6	1.2-5.5	75.9	24.1		
	2 ⁺	0.02	4.3	1.2-15.2	71.4	28.6		
	3 ⁺	0.000	16.9	3.6-79.3	37.5	62.5		
Nationality	Iranian	-	-	-	89	11	16.5	0.0001
	Non-Iranian	0.003	4.2	1.6-10.8	64.5	35.5		

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