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Smoking Effects on Clinical Manifestations and Drug Resistance Patterns in Pulmonary TB Patients

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ABSTRACT

Background: *Considering the rising trend of tuberculosis (TB) and cigarette smoking, an evaluation of the clinical manifestations and drug resistance patterns in TB patients with regard to smoking status seemed beneficial.*

Materials and Methods: *Clinical manifestations and drug resistance patterns were studied in 872 new pulmonary TB patients classified as non-smokers, ever-smokers, and passive smokers during 3 years at the National Research Institute of Tuberculosis and Lung Disease. Both univariate and multivariate analyses were performed.*

Results: *Ever-smokers were mostly male (p<0.001), Iranian (p<0.001), and drug and alcohol users (p<0.001). They were found to have a longer patient delay (15.9 versus 8.7 and 6.3 days, p=0.008), shorter diagnostic delay (106.8 versus 132.6 and 156 days, p=0.01), greater weight loss (p=0.01), and higher sputum expectoration (p<0.001). Notably, the degree of smear positivity was associated with smoking (p<0.001) in both univariate and multivariate analyses. No statistical significance was found for the aforementioned factors among non-smokers and passive smokers.*

Conclusion: *Some of the clinical manifestations of TB are significantly different with regard to the patients' smoking status. The degree of sputum smear positivity for acid fast bacilli was higher and patient delay was longer in ever-smoker patients.*
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Key words: *Clinical manifestations, Drug resistance, Smoking, Tuberculosis*

INTRODUCTION

Annually, two million deaths worldwide are attributed to tuberculosis (TB) alone. With 8.8 million new cases each year, TB is still a public health problem, especially in developing countries (1,2). Smoking is also a major health concern and is responsible for the death of one in ten adults (3). According to the "World Health Organization" (WHO), tobacco consumption is the second cause of death worldwide (4) and ranks fourth among ten risks to human health (5).

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Studies have shown that both active and passive smoking increase the risk of tuberculosis (6,7). A portion of the research in this field shows a significant association between cigarette smoking and TB. Meta-analyses report that smoking has an effect on TB infection, TB disease, (6,8) and mortality (9). However, conclusive results have not been reached regarding the effects of cigarette smoke on drug resistance patterns and clinical manifestations of tuberculosis. While some studies report a correlation, (9, 10, 11) others do not present significant association. (8,12) Therefore, further investigation is necessary in this respect.

This study aimed to compare the clinical manifestations and drug resistance patterns in TB patients with regard to their smoking status (as non-smokers, ever- smokers, and passive smokers).

MATERIALS AND METHODS

Settings:

A retrospective study of pulmonary tuberculosis patients was conducted between March 2003 and February 2006 at the National Research Institute of Tuberculosis and Lung Disease (NRITLD), Masih Daneshvari Hospital, the WHO collaborating center for the Eastern Mediterranean Region. It is located in northeastern Tehran, Iran and is a tertiary referral care center for TB and lung disease. This research has been reviewed and approved by the Ethical Committee of the center.

Patient Recruitment:

Subjects were all new pulmonary TB patients (smear or culture positive) older than 14 years of age.

Patients were classified into three categories: ever-smokers, passive smokers and non-smokers. Ever-smoker was defined as a person, who has smoked more than 100 cigarettes during his or her life. Passive smoker was defined as a person who had continuous exposure to tobacco smoke, either in his/her workplace or household. 0thers who had no history of smoking or less than 100 cigarettes during their life were classified as non-smokers.

Demographic characteristics such as age, sex, nationality, place of residence, alcohol use, drug use, patient delay, and diagnostic delay as well as the clinical factors including tuberculin skin test (TST), erythrocyte sedimentation rate (ESR), serum albumin level, degree of sputum smear positivity, sputum culture, drug susceptibility test (DST) and adverse effects were collected from existing data and studied in three smoking groups. Patient delay is defined as the time between the onset of symptoms and the initial visit. Diagnostic delay is the time between the first visit and TB diagnosis.

Tuberculin skin tests were performed on all patients according to the protocols outlined by the WHO (13).

The sputum smear and culture of patients were analyzed in the "National Mycobacteriology Reference laboratory (NRL), which is supervised by the Swedish Institute for Infectious Disease Control (Solna, Sweden) and the Research Institute of Tuberculosis of the Japan Anti-Tuberculosis Association (Tokyo, Japan). Sputum smear degree was determined according to the WHO guidelines (14). It is of note that, although sputum culture had been performed for all patients, until 2003 DSTs were not routinely performed on all new pulmonary TB cases and as such, this information was unavailable for 280 patients in this study. After 2003, if the culture test was positive, a DST was performed.

All patients received a treatment of isoniazid (INH), rifampin (RIF), ethambutol (ETB), and pyrazinamide (PZA) for two months and continued INH and RIF treatment for four months afterwards. In cases where the DST showed resistance to any of the above four drugs, treatment was changed according to WHO guidelines (15). Drugs that caused adverse effects were either discontinued or replaced

by an alternative drug. After patients were discharged from the hospital, public health centers continued the DOTS treatment.

Statistical Analysis:

In this cross-sectional study, 872 new case of pulmonary TB were studied. Continuous data are expressed as mean ± SD. The primary outcome variables were age, sex, nationality, place of residence, alcohol use, drug use, patient delay, diagnostic delay, tuberculin skin test (TST), erythrocyte sedimentation rate (ESR), serum albumin level, degree of sputum smear positivity, sputum culture, drug susceptibility test (DST) and adverse effects. The null hypothesis states that there is no difference in these variables among the three states of smoking.

Chi-square test without Yates' correction, Fisher's exact test, the Student's t-test and the Mann-Whitney U test were used as appropriate. All reported p-values were two-sided. A p-value less than 0.05 was considered statistically significant. Further analyses were done by multiple logistic regression to control the effects of sex, age, drug and alcohol use and other confounding variables that could contribute to the existence of any interaction.

Statistical analyses were performed using SPSS software, version 15.5.

RESULTS

In this study, 872 new cases of pulmonary tuberculosis (PTB) were enrolled out of which, 431 (49.4%) were males and 441 (50.6%) were females. Iranians accounted for 680 (78.0%) patients and 192 (22.0%) were not Iranian. The mean age of patients was 51.8±21.4 years (range 14 to 90 years).

Patients were classified into three groups: 504 (57.8%) non-smokers, 232 (26.6%) ever-smokers, and 136 (15.6%) passive smokers. The mean age was 54±22 years among non-smokers, 48±18 years among ever-smokers, and 48±22 years among passive smokers; non-smokers were significantly older than others (p<0.001). A total of 134(15.4%) patients were drug abusers and 74 (8.5%) had a history of alcohol use. Twenty eight patients (3.2%) were HIV positive and they all were smokers. Ninety-three were culture negative and DSTs were performed for 499 patients. Sixty-seven (7.7%) patients suffered from pulmonary and extra pulmonary TB simultaneously. Smear positive and smear negative cases accounted for 766 (88.0%) and 106 (12.0%) patients, respectively.

Demographic, epidemiological, and clinical factors for each of the three groups are summarized in Tables 1 and 2.

A univariate analysis showed that significantly more males were ever-smokers compared to females (p<0.001). Nationality, drug abuse, and alcohol use were all found to be significantly different among the three groups (p<0.001), with ever-smokers being more likely to engage in drug and alcohol use. Interestingly, patient delay was longer in ever-smokers than in non-smokers and passive smokers (15.9 days versus 8.7 and 6.3 days, p=0.008), whereas diagnostic delay in ever-smokers was shorter than in the other groups (106.8 days versus 132 and 156 days, p=0.01). Passive smokers had a shorter patient delay and longer diagnostic delay than non-smokers although this correlation was not significant. Weight loss (p=0.01) and sputum production (p<0.001) were greater among ever-smokers. Ever-smokers were more likely to be smear positive (p=0.021) and had a higher degree of smear positivity (p<0.001) than the other two groups. In addition, ESR was greater (p=0.02) and serum albumin levels were lower (p<0.001) in ever-smokers. Drug-induced hepatitis and extra-pulmonary TB were not found to be more common among any group. Furthermore, no association was detected between the smoking group and pattern of drug resistance.

Based on multivariate analysis, only higher degree of smear positivity had a significant correlation with smoking status.

Table 1. Demographic and epidemiological factors of patients

	Non-smokers N=504 n(%)	Passive smokers N=136 n(%)	Ever-smokers N=232 n(%)	p-value
Sex				
Male	186 (36.9%)	30 (22.1%)	215 (92.7%)	<0.001*
Female	318 (63.1%)	106 (77.9%)	17 (7.3%)	
Age (years)	54 ± 22	48 ± 22	48 ± 18	<0.001*
Nationality				<0.001*
Iranian	371 (73.6%)	104 (76.5%)	205 (88.4%)	
Non- Iranian	133 (26.4%)	32 (23.5%)	27 (11.6%)	
Residence				NS
Urban	419 (83.0%)	113 (83.7%)	203 (87.5%)	
Rural	86 (17.0%)	22 (16.3%)	29 (12.5%)	
Alcohol abuse	5 (1.0%)	0 (0.0%)	69 (29.7%)	<0.001*
Drug addiction	6 (1.2%)	2 (1.5%)	126 (45.7%)	<0.001*
Patient delay (days)	8.7 ± 45.6	6.3 ± 18.6	15.9 ± 61.8	0.008*
Diagnostic delay (days)	132.6 ± 156.3	156 ± 212.7	106.8 ± 126	0.01*

*Statistically significant results

Table 2. Clinical factors in patients.

Clinical characteristics:	Non-smokers N=504 n(%)	Passive smokers N=136 n(%)	Ever-smokers N=232 n(%)	p-value
Cough	486 (96.0%)	126 (92.6%)	217 (93.5%)	NS
Sputum	366 (72.6%)	100 (73.5%)	202 (87.4%)	<0.001*
Hemoptysis	99 (19.6%)	22 (16.2%)	50 (21.6%)	NS
Dyspnea	320 (63.5%)	87 (64.0%)	162 (70.4%)	NS
Anorexia	369 (73.2%)	94 (69.1%)	180 (77.9%)	NS
Diaphoresis	355 (70.4%)	165 (77.2%)	179 (77.2%)	NS
Fever	398 (79.0%)	106 (77.9%)	188 (81.0%)	NS
Weight loss	426 (84.7%)	117 (86.0%)	215 (92.7%)	0.01*
EPTB†	37 (7.3%)	12 (8.8%)	18 (7.8%)	NS
ESR	57 ± 30	56 ± 31	63 ± 31	0.02*
Albumin level	3.39 ± 0.45	3.51 ± 0.50	3.11 ± 0.52	<0.001*
TST (mm)	7.4 ± 7.4	7.0 ± 7.0	6.1 ± 6.6	NS
Smear positive				
Yes	430 (85.5%)	120 (88.2%)	215 (92.7%)	0.021*
No	73 (14.5%)	16 (11.8%)	17 (7.3%)	
Degree of smear positivity				
0	73 (14.5%)	16 (11.8%)	17 (7.3%)	
Scanty	40 (8.0%)	11 (8.1%)	12 (5.2%)	
1	130 (25.8%)	32 (23.5%)	43 (18.5%)	<0.001*
2	97 (19.3%)	33 (24.3%)	45 (19.4%)	
3	163 (32.4%)	44 (32.4%)	115 (49.6%)	
DST				
Sensitive	222 (75.8%)	62 (79.5%)	86 (67.2%)	
MDR	4 (1.4%)	1 (1.3%)	4 (3.1%)	NS
Mono-drug	50 (17.1%)	8 (10.3%)	25 (19.5%)	
Poly-drug	17 (5.8%)	7 (9.0%)	13 (10.2%)	
Any drug resistance	71 (24.2%)	16 (20.5%)	42 (32.8%)	
Drug-induced hepatitis	57 (11.4%)	13 (9.6%)	28 (12.1%)	NS

*Statistically significant results

†Extra-pulmonary tuberculosis (patients with both pulmonary and extra pulmonary TB)

DISCUSSION

Based on the obtained results, ever-smokers were mostly males (92.7% versus 7.3%) and passive smokers were mostly females (77.9% versus 22.1%). This sex distribution was also reported in other studies (7,16). Among our patients, the mean age was lower in ever-smokers than in non-smokers (48 versus 54 yrs) but Wang et al. found that smokers affected with TB were older than non-smokers (7). This may be due to the increasing prevalence of smoking among younger people (17).

This study showed that there was a greater frequency of alcohol use among ever-smokers. Evidence shows alcohol has further effects on TB development; (18) thus in our study, the presence of alcohol use in patients may have additive effects on TB infection and development. This association is also supported by Altet-Goméz et al (16).

HIV tests were performed for patients with any risk factor for HIV infection. Interestingly, those who were HIV positive were all smokers. This trend is probably due to the fact that the most common route of HIV transmission in Iran is through intravenous drug use (19) and such drug users are presumably smokers as well. Smoking may be a risk factor for HIV (20) and may cause a higher frequency of opportunistic diseases such as TB in HIV positive smokers than in non-smokers (21). It is known that cigarette smoke alters the pulmonary macrophages, making them less capable of fighting against microorganisms and thus, compromising the individual's cellular immunity (22). Altet-Goméz et al. did not find a significant difference in the prevalence of HIV in TB patients who were smokers and those who were non-smokers, (16) and this may be because epidemiological factors and HIV transmission pathways vary in different study settings.

Interestingly, patient delay was longer in ever-smokers than in the other two groups, most likely because smokers who experience TB symptoms, such as cough and sputum, may assume that these symptoms arose from cigarette smoke and do not require medical attention. Although multivariate analysis did not confirm this significant difference, the univariate results are sufficient enough to encourage public health education in this field, which can increase public awareness about TB manifestations, decrease patient delay and at the same time, decrease the period during which a TB patient unknowingly transmits the disease to others. Conversely, diagnostic delay was shorter in ever-smokers and longer in the other groups. It can be argued that an earlier diagnosis in smokers may be due to the fact that medics may initially suspect serious conditions such as cancer and immediately perform a chest x-ray, which leads to the earlier detection of TB. However, little is known about the reason why diagnosis in passive smokers occurs later. Perhaps the symptoms of passive smokers are initially assumed to be the result of contact to smoke. Again, diagnostic delay did not reach statistical significance in the multivariate analysis.

With regard to clinical manifestations, sputum expectoration and weight loss were greater in ever-smokers than in the other groups, although based on a study done by Leung et al, smokers were also more likely to have cough and dyspnea (22). The multivariate analysis showed that the only variable that influenced sputum expectoration was age and similarly, weight loss was affected only by addiction.

The higher frequency of smear-positive cases among ever-smokers is likely due to higher rates of sputum production in these individuals. While other studies have reported such results, (16, 22) Wang et al. found no association between smoking and being smear-positive (7). It is of note that in our study,

multivariate results matched those of Wang et al in that we also did not find a significant correlation between smoking and being smear-positive.

Both univariate and multivariate analyses showed higher degree of sputum smear positivity in ever-smokers and this may be indicative of a higher rate of infectivity (23). Therefore, early diagnosis of TB in smokers is essential so that others are less exposed to the disease. Although we did not compare presence of cavitary lesions in three groups, another study performed in our center in 2002 found that smoker TB patients were more likely to have cavitary lesions than those who were non-smokers ($p<0.001$) and this finding may explain higher infectivity (24). Other studies reported the same results as well (7,16,22).

Few studies have been conducted thus far regarding drug resistance patterns in TB patients who smoke. One such study (7) found that there was no significant relationship in this regard, a finding that was supported by our research as well. Given that all patients in the study were new TB cases and had no history of TB treatment, the effect of smoking on drug resistance development may be shown more directly. In other reports such as that of Chiang et al. study (6), smoking was linked with acquired MDR-TB and isoniazid mono-drug resistance. Additional researches are needed to clarify any relation between smoking and TB drug resistance.

Although passive smoking has been identified as a risk factor for TB especially among children and adolescents, (6, 7, 25) a 2007 meta-analysis reported that active smoking served as a much greater risk factor (26). In our study, no significant difference was found between the clinical manifestations and drug resistance patterns of passive smokers and non smokers.

There were some limitations in this study. Primarily, our center is a referral center and thus, there may have been a bias toward patients with more severe forms of TB. In order to minimize this bias, we recruited only new TB cases**.** Secondarily, due to the retrospective nature of the study, the patients' data on smoking were collected from their medical records, and hence we could not differentiate ex-smokers form current smokers. Another drawback is that the length and amount of cigarette usage, and cigarette type were not considered for ever-smokers. Furthermore, the length and amount of exposure to cigarette smoke were not noted for passive smokers. The extent of contact with smoke varies in each patient and obtaining such information proves challenging. We suggest that a prospective study be performed that takes into consideration these factors to maximize result accuracy.

CONCLUSION

This study conducted on 872 new pulmonary TB patients who were non-smokers, ever-smokers, or passive smokers showed significant differences in some factors of clinical manifestations and drug resistance patterns among the three groups. In both univariate and multivariate analyses, a higher degree of sputum positivity was found in ever-smokers. The higher degree for AFB may mean that smokers expectorate larger loads of bacilli and probably can infect other healthy people easier. However, no significant difference was found between the clinical and laboratory characteristics of non-smokers and passive smokers.

Given the higher load of bacilli and the longer patient delay in ever-smokers, it is beneficial to pay more attention to education and smoking cessation programs in general population and TB patients. Additional studies are required to further assess the epidemiology, and clinical manifestations of TB in passive smokers.

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