Risk Factors for Recurrent Tuberculosis among Successfully Treated Patients in Israel, 1999–2011

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ABSTRACT: **Background:** Recurrent tuberculosis (TB) is one of the indices used to assess the effectiveness of the National TB Program.

Objectives: To estimate the incidence of recurrent TB in Israel and to identify the associated risk factors.

Methods: We conducted a retrospective cohort study that included all TB patients who were Israeli citizens and diagnosed between 1999 and 2011 with a treatment outcome recorded as "success." We compared those who had recurrent TB with those who did not. In addition, a nested case-control study included all those who had recurrent TB with a random sample from this cohort matched by age, gender, and year of TB diagnosis.

Results: Of 3515 TB patients diagnosed between 1999 and 2011, 37 (1.05%) had recurrent TB during the follow-up period, with an incidence rate of 1.55 cases per 1000 person-years. Male gender [hazard ratio (HR) 3.2, 95% confidence interval (95%CI) 1.4–7.4], human immunodeficiency virus (HIV) infection (HR 3.9, 95%CI 1.5–10.4), positive sputum culture [odds ratios (OR) 2.7, 95%CI 1.1–6.9], and low adherence to anti-TB treatment (OR 3.2, 95%CI 1.0–10.3) were found to be risk factors for recurrent TB.

Conclusions: Male gender, HIV infection, positive sputum culture, and low adherence to anti-TB drugs during the initial TB episode were risk factors for developing recurrent TB.

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KEY WORDS: adherence, recurrent tuberculosis (TB), human immunodeficiency virus (HIV), Israel

In recent years, the Israeli health care system has encountered a number of challenges in the eradication of tuberculosis (TB). Some of the factors that limit disease elimination include human immunodeficiency virus (HIV) co-infection, mycobacterial resistance, migration from countries with a high prevalence of TB, and events of TB recurrence [1-4]. According to the World Health Organization (WHO), recurrent TB is a new event of TB among patients who were previously treated for TB and declared "success", which include those who were cured or whose treatment was completed by the end of their most recent course of treatment [5]. Recurrent TB compromises the patient's health and also may expose other contacts to *Mycobacterium tuberculosis*. Furthermore, the recurrence of the disease can undermine the credibility of the health care system, lead to low adherence, and overburden the health care system financially. Therefore, recurrent TB is defined by the WHO as one of the indices to assess the efficacy of the Israeli National TB Program (NTP) [5].

Recurrent TB can be either the result of a new infection (exogenous re-infection), or a reactivation of the TB strain that was responsible for the original episode of disease (endogenous reactivation) [5]. In low-incidence settings (defined as countries with an incidence rate of < 20 cases per 100,000 population or < 10 cases in total) [5], recurrent TB is usually caused by reactivation. In contrast, in high-incidence settings, the disease mostly occurs due to re-infection [6]. It was suggested that the probability of exposure to *M. tuberculosis* of various strains in high-incidence settings is higher than in low-incidence settings.

The most common risk factors for recurrent TB in previous studies included low treatment compliance [6-8], substance abuse [9,10], smoking [8,10,11], and HIV co-infection [7,8,10,12-14]. Recurrent disease has also been associated with male gender, immigrant status [9], positive sputum culture, and pyrazinamide resistance [13].

TB incidence in Israel in 2012 was 7.6 cases per 100,000 people; 1.4% of all cases were recurrent TB [5]. No data have been published on recurrent TB in Israel, and to the best of our knowledge, no national investigation has yet been conducted. The purpose of the current study was to estimate the incidence of recurrent TB during a long period in Israel and to examine its associated risk factors.

PATIENTS AND METHODS

Retrospective cohort and nested matched case-control studies were conducted to examine risk factors for recurrent TB in Israel between 1 January 1999 and 1 June 2011.

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STUDY POPULATION

The cohort included all patients who were Israeli citizens, had been initially diagnosed with TB, and whose treatment outcome was recorded as "success" at the end of the therapy period. The follow-up period lasted until 31 December 2011, or until recurrent TB was diagnosed or the patient died, whichever occurred first. To identify those who died during the follow-up period, the national TB registry was cross-matched with the civil population census. Patients without Israeli citizenship were excluded from the study as it was unclear whether they had left the country or died during the follow-up period.

The nested matched case-control study included all recurrent TB patients in the study arm, while patients who had not developed recurrent TB were included in the control group. The groups were matched by age, gender, and year of initial TB diagnosis.

DEFINITIONS

Treatment success was defined as a bacteriological confirmation of cure and/or documentation that the anti-TB treatment was completed. Recurrent TB was defined as a new episode of disease in people who had been diagnosed with TB during the study period and treatment success was recorded. TB patients in Israel are treated with directly observed therapy (DOT) for the entire duration of treatment. We defined low adherence to anti-TB treatment with DOT as meeting the following criteria: ≥ 2 consecutive weeks of therapy were missed, and/or ≥ 25% of planned doses were missed.

DATA SOURCE

The national TB registry, which is managed by the Ministry of Health, was used to collect the data for the retrospective cohort study. The data included gender, age, citizenship, country of birth, date of immigration to Israel, date of TB diagnosis, site of disease, initial sputum smear and culture, drug resistance profile, treatment end date, and treatment outcome as defined by the WHO and reported from the health departments and TB clinics. The national TB registry and HIV registry were cross-matched to define the HIV status for each TB patient.

The case-control study used patients' records from all the various TB clinics and health departments in Israel to access additional data, including behavioral characteristics (smoking, alcohol and drug abuse), clinical signs, imaging findings, chronic morbidity, adherence to treatment, side effects of treatment, and DOT characteristics.

STATISTICAL ANALYSIS

The incidence rate of recurrent TB was calculated in the cohort as the number of recurrent TB cases per 1000 person-years (PY) of follow-up. Since none of the quantitative variables had normal distributions, the Mann-Whitney test was carried out to compare continuous variables between recurrent and non-recurrent TB cases and the chi-square test was used for categorical variables. The final model included those variables with a P value < 0.1 in the univariate analysis. A Cox proportional hazard model was performed for the multivariate analysis for the cohort study and logistic regression for the case-control study to identify characteristics predicting recurrent TB. All analyses were conducted using SPSS software (SPSS Inc., version 17, Chicago, IL, USA).

The study was approved by the institutional review board of the Wolfson Medical Center, Holon, Israel (WOMC-0130-11).

RESULTS

Of the 5096 TB cases that were reported during the study period, 3515 (69%) were Israeli citizens and included in the cohort which was followed for a total of 23,805 PY. Of the entire cohort, 37 patients (1.05%) developed recurrent TB, generating an incidence rate of 1.55 cases per 1000 PY. The total number of patients with positive sputum culture was 2440, while 28 (1.15%) were recurrent cases with an incidence rate of 5.2 per 1000 PY. The median time from start of follow-up to recurrence was 2.6 years (interquartile range, IQR, 0.7–5.3 years), while 12 (32.4%) cases recurred during the 1st year of follow-up [Figure 1].

In the univariate analysis, higher rates of TB recurrence were found among male patients, those born in the former Soviet Union, patients who had mycobacterial resistance to rifampicin or multi-drug resistance, and those who were co-infected with HIV [Table 1]. In the multivariate analysis, only male gender [hazard ratio (HR) 3.2, 95% confidence interval (95%CI) 1.4–7.4] and HIV co-infection (HR 3.9, 95%CI 1.5–10.4) were statistically significant in predicting recurrence.

Patients who were not Israeli citizens, including migrant workers, asylum seekers and tourists, were excluded from the study. They were younger (P < 0.001) than Israeli citizens, more commonly male (P = 0.02), but less likely to have multi-drug resistance (P = 0.02). There was no significant difference in recurrent TB rate between Israeli and non-Israeli patients.

Figure 1. Percentage of all tuberculosis recurrence in Israel by year of follow-up from initial episode, 1999–2011

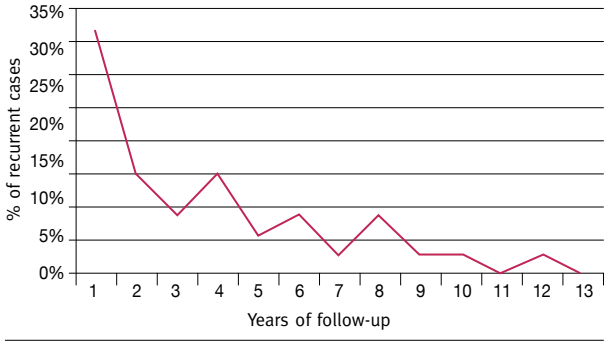

Table 1. Univariate analysis comparing recurrent and non-recurrent patients of all tuberculosis cases in Israel, 1999–2011 and multivariate Cox regression model for recurrent tuberculosis

		Univariate			Multivariate		
		Recurrence N=37 (%)	**No recurrence N=3478 (%)**	***P* value**	***HR***	**95%CI**	***P* value**
Demographics	Age (median, IQR)	42 (28–66)	44 (28–65)	1.0	1.0	1.0-1.02	0.7
	Male	30 (81.1)	1907 (54.8)	0.001	3.2	1.4-7.4	0.005
	Place of birth Former Soviet Union Horn of Africa Israel Other places	 18 (48.6) 11 (29.7) 4 (10.8) 4 (10.8)	 1193 (34.3) 1042 (30) 633 (18.2) 610 (17.5)	 0.07 1.0 0.2 0.3	 1.7 – – –	 0.9-3.3 – – –	 0.1 – – –
Clinical	Pulmonary tuberculosis	32 (86.5)	2784 (80)	0.3	–	–	–
	HIV co-infection	5 (13.5)	129 (3.7)	0.002	3.9	1.5–10.4	0.005
	Duration of treatment (median months and IQR)	8 (6–10)	8 (6–10)	0.3	–	–	–
Laboratory	Positive sputum smear	19 (51.4)	1429 (41.1)	0.2	–	–	–
	Positive sputum culture	28 (75.7)	2412 (69.4)	0.4	–	–	–
	Multi-drug resistance	4 (10.8)	111 (3.2)	0.01	2.8	1.0-8.1	0.06

IQR = interquartile range, TB = tuberculosis, HIV = human immunodeficiency virus, HR = hazard ratio, CI = confidence interval

The nested matched case-control study included 37 recurrent TB cases and 107 controls who had not developed recurrent TB during the follow-up period. In the univariate analysis, those who had positive sputum culture, treatment duration longer than the median time of therapy, smoked, and whose adherence to treatment was low more often had recurrent TB [Table 2]. In the multivariate analysis, positive sputum culture [odds ratio (OR) 2.7, 95%CI 1.1–6.9] and low adherence to treatment (OR 3.2, 95%CI 1.0–10.3) were significantly associated with TB recurrence.

DISCUSSION

During 13 years of follow-up, the incidence rate of recurrent TB was 1.55 cases per 1000 PY. This rate is higher than the mean national TB incidence rate in the general population of Israel (an annual average of 6.2 cases per 100,000 persons in 1999–2011) [15]. Male gender, HIV infection, positive sputum culture, and low adherence to treatment were found to be risk factors for recurrent TB.

The present study demonstrated that 32% of all recurrent cases occurred during the 1st year of the follow-up period, whereas studies performed in Brazil and England found that 65% and 46%, respectively, recurred during the 1st year [11,12]. The relatively low recurrence rate in Israel may be due to different treatment regimens used in other countries [7,8,11,16,17]. The following regimen is usually administered in Israel when the *Mycobacterium* is sensitive to all drugs: isoniazid (INH) + rifampicin (RIF) + pyrazinamide (PZA) + ethambutol (EMB) for 2 months and INH + RIF for another 4 months [16] provided by DOT for the entire treatment period. The same regimen is recommended by the National Institute for Health and Care Excellence (NICE) in the United Kingdom, but DOT is not usually implemented [17]. In Brazil, the treatment is self-administered and consists of INH + RIF + PZA for 2 months and INH + RIF for another 4 months [7,11].

Male gender was associated with recurrent TB, in line with a report from a Spanish study [9]. A higher risk for TB recurrence in men may be due to occupational or social exposure and also to other behavioral characteristics, such as smoking and alcohol abuse, which are more prevalent in males and may result in decreased immunity [18].

HIV co-infection is an additional recognized risk factor for recurrence of TB [7,8,10,12-14]. HIV tests are recommended for all TB patients in Israel, and the average estimated HIV testing coverage during the study period was 88.4% [2]. The presence of *M. tuberculosis* in pulmonary tissue encourages the migration of monocytes that proliferate to macrophages and form a granuloma. HIV replicates within activated T lymphocytes, and macrophages that had formed the granuloma eventually cause cell apoptosis that leads to granuloma dysfunction and *Mycobacterium* dissemination [19]. Effective antiretroviral treatment with anti-TB treatment among HIV co-infected TB patients was suggested to reduce the risk of recurrent TB [20,21]. In order to reduce cases of recurrent TB among HIV co-infected patients, a prolonged anti-TB treatment is recommended [12]. However, longer anti-TB treatment among HIV co-infected patients did not reduce the risk of recurrence in our study.

In this study, we observed that positive sputum culture in the initial episode of TB was a risk factor for recurrence. This finding is unique to this study, as other publications included positive-culture patients only [6-10,13,14]. The association between positive sputum culture and TB recurrence is poorly

Table 2. Univariate analysis comparing demographic, behavioral, clinical, and laboratory characteristics of tuberculosis patients with and without recurrence in a case-control sample in Israel, 1999–2011, and multivariate logistic regression model for recurrent tuberculosis

		Univariate			Multivariate		
		Recurrence 37 (%)	No recurrence 107 (%)	*P* value	OR	95%CI	*P* value
Demographics	Age (median and IQR)	42 (28–66)	42 (27–60)	0.8	–	–	–
	Male	30 (81.1)	83 (77.6)	0.6	–	–	–
	Born in the former Soviet Union	18 (48.6)	39 (36.4)	0.2	–	–	–
Behavioral	Smoking	16 (43.2)	29 (27.1)	0.07	1.1	0.5-2.8	0.8
	Alcohol abuse	3 (8.1)	12 (11.2)	0.6	–	–	–
	Drug abuse	3 (8.1)	3 (2.8)	0.2	–	–	–
Clinical	Pulmonary tuberculosis	32 (86.5)	86 (80.4)	0.4	–	–	–
	Any clinical sign*	33 (89.2)	82 (76.6)	0.1	–	–	–
	Cavitation in X-ray	9 (26.5)	16 (16.8)	0.2	–	–	–
Laboratory	Positive sputum smear	19 (51.4)	39 (36.4)	0.1	–	–	–
	Positive sputum culture	28 (75.7)	57 (53.3)	0.02	2.7	1.1-6.9	0.04
	Multi-drug resistance	4 (10.8)	0 (0)	0.004	–	–	–
Treatment	Duration of treatment (months, median, IQR)	8.5 (6.7–10.9)	7.1 (6.2–9.2)	0.09	–	–	–
	Low treatment adherence	8 (22.9)	7 (7.4)	0.02	3.2	1.0-10.3	0.05
	Low clinic visit adherence	4 (10.8)	16 (15)	0.5	–	–	–
	Treatment side effects†	11 (29.7)	23 (21.5)	0.3	–	–	–
Co-morbidity	HIV co-infection	5 (13.5)	9 (8.4)	0.4	–	–	–
	Chronic disease§	20 (54.1)	51 (47.7)	0.5	–	–	–

*Cough, fever, weight loss, night sweats, hemoptysis, weakness

†Diabetes mellitus, cancer, chronic pulmonary infection, and other generalized chronic illnesses

§Any side effect that was mentioned in the medical record

IQR = interquartile range, OR = odds ratios, CI = confidence interval

understood and further examination is essential to assess its influence on TB recurrence.

Low treatment adherence is associated with a higher risk of TB recurrence [7,22]. Treatment adherence is necessary for recovery, prevention of TB spread, and reduction of the risk of drug resistance [23,24]. Non-adherence appears to be related to a multiplicity of factors involving the patient and the health-care services [25]. Patients should be instructed about the side effects of drugs and the duration of treatment during medical follow-up. They should be offered financial benefits and should also be educated about the consequences of irregular treatment or premature discontinuation of treatment.

Unlike previous studies, no association was found between recurrent TB and behavioral factors or chronic morbidity [8-11]. This finding may be related to the low frequency of these risk factors in our sample.

To the best of our knowledge, this is the first study of recurrent TB in Israel. However, it is subject to several limitations. First is the limited number of recurrent TB cases, even though the long follow-up period lasted for 13 years. Second, there was a short follow-up period for the patients who were diagnosed closer to the end of the investigation period. We therefore performed survival analysis to control for the different follow-up periods of the patients. Third, laboratory data of molecular DNA genotype were not available for the entire study period, and consequently we were not able to distinguish recurrent cases due to reactivation and those due to re-infection.

CONCLUSIONS

Risk factors for recurrent TB included male gender, HIV co-infection, positive sputum culture, and low adherence to treatment during the initial TB event. These determinants should increase physicians' awareness during the active phase of TB to implement monitoring after the completion of the treatment in order to prevent recurrence.

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