Letter to the Editor

Follow-up Study of Retreatment TB Patients with Sputum Smear and/or Culture Positive Two Years after They were Declared Cured with First-line Anti-TB Drugs in Shandong Province^{*}



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This study aimed to learn the recurrence rate in the retreatment TB patients with sputum smear and/or culture positive (ss+ and/or c+) two years after they were declared cured, and to explore causes of recurrence in order to improve long-time treatment outcome. 5 cities were selected as research locations. Recurrence of TB was judged by chest X-ray examination together with sputum smear and culture examination. Questionnaire was carried out to collect data on treatment history. demographics and possible risk factors. Chi-square test and logistic regression were conducted using SPSS in this study. As the result, 99 active TB patients were identified and the recurrence rate was 16.67% and irregular medicine and smoking were the causes of the recurrence. The retreatment TB patients with sputum smear and/or culture positive in this study had higher recurrence rate and health education work on regular medication and smoking should be strengthened.

Shandong province is located in eastern China with a population of 95.79 million. In the past 20 years, major efforts have been made in order to reduce the burden of tuberculosis (TB). The average TB notification rate was 70.54% during 2001-2010 and this rate had reached the Millennium development goals. However, the recurrence rate for retreatment TB patient is still higher than that for new TB^[1]. Treatment regimens recommended by WHO for retreatment TB patients whose smear and/or culture results were positive (ss+ and/or c+) had been adopted for nearly 20 years and cure rate of retreatment TB patients (ss+) was from 90.57% to 91.78% in Shandong province during 2008-2011.

However, long-term recurrence rate of the retreated patients who were cured was seldomly reported in this province. The follow-up was therefore needed in order to evaluate the recurrence and the treatment outcome for the retreatment patients who were cured according to the current definition of cure outcome. Hence, a retrospective survey was conducted in order to learn long-term outcomes and causes of recurrence for retreatment TB patients (ss+ and/or c+) in Shandong province.

5 cities (Binzhou, Linyi, Dezhou, Zaozhuang, and Liaocheng) were selected as research locations and definite cluster sampling of non-probability was applied for the selection. Sputum culture was available in said location due to the implementation of China global fund TB program on multidrug resistant tuberculosis. 400 cases calculated by simple proportion with absolute precision were needed [α =0.05, β =0.2, p_0 (recurrence rate and death rate estimated)=10%, d (allowable error)=0.10]. However, The sample size was doubled to 1000 due to clustering sampling and probable 20% lost rate of follow up.

Survey objects were defined as the retreatment TB patients (ss+ and/or c+) who were not drug-resistance and had declared to be cured after 8-month retreatment for more than 2 years by Jan 1^{st} , 2011. Most of these objects started the retreatment from Jan 1^{st} , 2007 to Mar 31^{st} , 2007. Their sputum smear or culture was negative in the fifth and the last month of the retreatment and they were declared to be cured over 2 years by Jan 1^{st} , 2011. They signed informed consent and then were enrolled in the retrospective cohort. Standard

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treatment regimen used for retreatment (ss+ and/or c+) TB patients refers to chemotherapy regimens recommended by Guidelines for Implementing the National Tuberculosis Control Program in China (2008), namely 2H₃R₃Z₃E₃S₃/6H₃R₃E₃ or 2HRZES/6HRE. A few patients from them didn't receive standard treatment regimen. They received individualized regimens, adding Levofloxacin (Lfx).

Chest PA X-ray examination was conducted for the follow-up patients and also chest LAT when necessarily. On-spot sputum, morning sputum, and night sputum of the follow-up patients were collected. Thyroid sputum, blood sputum, or mucous sputum are the criteria for qualified sputum sample. If sputum sample was unqualified, physicians gave guidance for recollection of sputum sample. Criteria for reporting of Direct sputum smear microscopy of the Ziehl-Neelson stain with optical microscope (10×ocular piece, 100×oil lens) is the criteria for reporting. Morning sputum and night sputum were used to *Mycobacterium* culture with LJ medium. Outcome were defined based on Infectious Tuberculosis Diagnostic Criteria and Principles^[2].

The patients were chosen as the study subjects when recurrence was diagnosed based on the X-ray and sputum examination. Diagnosis was made by radiology doctors and respiratory doctors together. The survey was conducted by the trained interviewers with face-to-face questionnaire to collect data on treatment history, demographics, and health behaviors. Lose or death of study objects were recorded with conformation with their families or village doctors.

Variables such as age, gender, marriage, income, living areas, smoking and alcohol drinking, inregular medication, standard treatment regimen, supervisor for regular medication and complication were used in order to analyze the association between variables and the recurrence for the present study, and classification standards were as follows (Table 1).

Variable Classification	Variables	Classification Standard
Dependent variable	Relapse	0=Non-recurrence, 1=Recurrence
Independent variable	Sex	1=Male, 2=Female
	Age group (years)	1=<30, 2=30-, 3=40-, 4=50-, 5=60-, 6=70-, 7=80-
	Marriage	1=single, 2=married, 3=divorced, and widowed
	Average family income per capita (yuan)	1=<500, 2=500-999, 3=1000-1499, 4=1500-1999 5=2000-2999, 6=3000-4999, 7=≥5,000
	Living areas per Capita (square meters)	1=<30, 2=30-49, 3=50-69, 4=70-89, 5≥90
	Smoking history	0=Non-smoker 1=Ex-smokers refers to continuous or cumulative smoking more than six months before, but didn't smoke at least 1 year 3=Smokers refers to continuous or cumulative smoking more than six months during lifetime
	Drinking history	0=Non-drinker or people drank for less than 1 year before the enrollment date 1=Ex-drinkers refers to people drank for at least 1 year and quit drinking for at least 1 year before the enrollment date 2=Drinkers refers to people drank for at least 1 year and either never quit drinking or quit drinking less than 1 year before the enrollment date
	Taking medicine regularly	1=Taking medicine regularly refers to TB patients who can complete full course of chemotherapy as prescribed and ensure high adherence to therapy, without forgetting or discontinuance 2=Taking medicine irregularly means forgetting, discontinuance and even stop taking medicines during therapy
	Supervisor of taking medicines	1=Medical staff as supervisor 2=Family members as supervisor 3=Self-medication
	Standard treatment regimen	1=Standard treatment regimen refers to chemotherapy regimens for retreatment ss+ TB patients recommended by Guidelines for Implementing the National Tuberculosis Control Program in China (2008), namely $2H_3R_3Z_3E_3S_3/6H_3R_3E_3$ or $2HRZES/6HRE$ 2=TB patients who didn't use standard treatment regimen refers to using individualized regimens, adding accord line anti TB drugs.

Table 1. Variable Description in This Study

test was conducted the Chi-square and difference in the distribution of the various variables between the dependent variable and the independent variables was studied. The variables with significant differences were selected for multiple factors analysis. Whether relapse was considered as dependent variable and multivariate logistic regression model (forward stepwise) was fitted to test and adjust for confounders (a=0.05). All data were double entered in EpiData3.1 and were analyzed by SPSS 16.0.

Of 1230 patients enrolled in the study, 869 patients were confirmed to be not the Multi-drug resistance TB and are 683 males (73.62%) and 231 females (26.58%), 747 (85.96%) older than 40 and 461 (53.05%) older than 60. 265 patients (21.5%) died and 96 patients (7.8%) lost. Total TB recurrence rate of retreatment TB patients (ss+ and/or c+) was 16.67% (189/1134). These include 99 active TB patients (11.39%) among 869 patients received TB screening and 90 death (33.96%) caused by TB among 265 patients died. Among the 99 active TB patients, 21 (21.21%) were sputum positive. Other major causes of death were due to cardiovascular disease, cancer, pulmonary heart disease, etc. Recurrence rates were significantly different between male (12.85%) and female (7.36%) (P<0.05). Among 869 patients, recurrence rate was higher in age group of 40 years and older. Among newly detected TB patients, those who took medicine irregularly during previous treatment were more

likely to relapse than those who took medicine regularly (χ^2 =4.440, *P*=0.035). Ex-smokers were more likely to be recurrent than non-smokers (χ^2 =12.979, *P*<0.001), but the comparison between smokers and ex-smokers was not significant (χ^2 =1.746, *P*=0.186). Besides, the more cigarettes the patients smoked, the more likely the recurrence of the patients (χ^2 =14.971, *P*=0.01). Drinkers and ex-drinkers were more likely to relapse than non-drinkers (χ^2 =4.376, *P*=0.036) and the comparison between drinkers and ex-drinkers was not significant (χ^2 =1.821, *P*=0.177) (Table 2). Statistical analysis also showed that marital status, income, living areas, supervisor of medication and standard treatment regimen, had no significant impact on recurrence rates (*P*>0.05).

Single factor analysis was conducted to select significant factors and variables such as sex, age, smoking, alcohol drinking, and irregular medication had significant impact to the recurrence rate. These 5 variables were selected as independent variables. Relapse was selected as dependent variable. Sex and age as the adjusted variables were fixed in the logistic regression model by enter method, and smoking, alcohol drinking and irregular medication were entered in the logistic regression model to study the causal factors by back ward LR method. However, smoking and irregular medication were associated with an increased recurrence adjusted by other factors. Adjusted by other variables, the risk on recurrence for the retreated TB patients who took irregular medication was 2.828 times (95% CI

Factors	Category	Survey Numbers	Patient Detected	Recurrence Rate (%)	OR	χ²	Р
Taking medicines	regularly	842	92	10.93	0.35		0.026*
	irregularly	27	7	25.93	-	-	0.020
Smoking history	Smokers	130	15	11.54	1.52	1.650	0.199
	Ex-smokers	297	49	16.50	2.30	12.979	<0.001
	Non-smokers	442	35	7.92	-	-	
Number of cigarette per day	<10	68	7	10.29	-	14.971	0.011
	10-	121	14	11.57	1.14		
	20-	140	19	13.57	1.37		
	30-	30	7	23.33	2.70		
	40-	41	12	29.27	3.57		
	50-	14	5	35.71	4.76		
Drinking history	Drinkers	159	18	11.32	1.21		
	Ex-drinkers	209	34	16.27	1.84	6.540	0.038
	Non-drinkers	493	47	9.53	-		

Table 2. Recurrence Rates of Retreatment TB Patients (ss+ and/or c+) after beCured Two Years among Different Populations

Note. ^{*}Fisher's exact test.

1.147-6.971) higher than that of the retreated TB patients who took regular medication. Furthermore, adjusted by other variables, the risk on recurrence for smokers and ex-smokers were 1.403 times (95% Cl 1.073-1.835) higher than that of non-smokers (Table 3).

As reported in China, the cure rates of retreatment TB patients (ss+) were from 63.8% to 95%^[3-6]. The same rate in Shandong province was within the said range. As reported, up to 7% of the patients with TB who were cured after short-course treatment in trial condition had recurrent and they need retreatment within 1 to 2 years^[7]. However, the exact recurrence rate of retreatment TB patients was not clear in Shandong province. This study was therefore conducted to collect retrospectively the data on recurrence outcome as the independent variable in order to obtain the recurrence rate of retreatment TB patients to the recurrence in Shandong province at the first time.

In the present study, we found that retreatment TB patients (ss+ and/or c+) who were declared to be cured with retreatment regimen over two years, had higher rate of TB recurrence than that of general population and they were more likely to be sputum-smear-positive than those from general population. The standardized prevalence rate of general population and the rate of TB (ss+ and/or c+) were $337.15/10^{6}$ and $36.85/10^{6}$ respectively in 2010 in Shandong province. Compared to the survey in 2010, the prevalence rate and bacteriologic positive rate for cured retreatment TB patients over two years from this study were 33.79 and 65.58 times more than those in general population. TB patients (ss+ and/or c+) counted for 10.93% among all new TB patients in general population. Nevertheless, recurrent TB patients (ss+ and/or c+) who were cured for retreatment over 2 years counted for 21.21% among total recurrent TB patients. The proportion of bacteriologic positive patients among recurrent cases of cured retreatment patients were higher than that of among new TB cases (P<0.05). Simultaneously, the recurrence rate of cured retreatment TB patients (ss+ and/or c+) (16.67%) from this study was similar to that (12%) for recurrent tuberculosis in Haiti^[8].

Retreatment TB patients (ss+ and/or c+) who took irregular medication during previous treatment or/and were smokers, were more likely to be recurrent. This was consistent with the result of initial treatment relapse^[8-9]. Compliance was suggested to be increased for patients who took irregular medication during previous treatment because they were more likely to be recurrent than those who took regular medication. As the smokers and ex-smokers were more likely to be recurrent non-smokers and non-drinkers, than health education activities for good behavior of no-smoke and no-drink must be strengthened to the general public. As the comparison of TB recurrence among retreatment TB patients between smokers and ex-smokers, drinkers and ex-drinkers were not statistically significant, it was late for giving up smoking and stop alcohol drinking to reduce the risk on recurrence among retreatment TB patients.

Only one more drug is added in the current treatment regimen for retreatment TB patients (ss+) compared with the initial treatment regimen. Limitations may exist based on anti-TB drug treatment principles. All of the 99 recurrent TB patients adopted standard treatment regimen for retreatment TB patients (ss+) in this survey, but all of the 17 patients who didn't adopt standard treatment regimen didn't relapse. Therfore, the standard treatment regimen for retreatment TB patients (ss+) should be modified and perfected. As observed in other studies^[5], the classification of recurrence is not taken into account in the standard treatment regimen for retreatment TB patients (ss+ and/or c+) and same to whether the patients took regular medication during previous treatment but still failed,

Factors	в	0	OR -	95% Cl for OR		
		P		Lower	Upper	
Constant	-2.866	0.000	0.057	-	-	
Sex	0.180	0.572	1.198	0.641	2.239	
Age group	0.213	0.202	1.237	0.892	1.716	
Taking medicines	1.039	0.024	2.828	1.147	6.971	
Smoking history	0.339	0.013	1.403	1.073	1.835	

Table 3. Logistic Regression Outcome

medication time and outcome of drug susceptibility testing (DST). Long-term of single, non-selection standard treatment regimen for retreatment TB patients (ss+) can't catch up with the change of TB control strategies. However, retaining the current standard treatment regimen, adding appropriate second-line anti-TB drugs in the new treatment regimen can be helpful to prevent the recurrence of retreatment TB patients and reduce developing tuberculosis^[5]. multidrug resistant Treatment regimens for retreatment TB patients (ss+) had been adopted for many years and had a high recurrence rate^[10]. The implementation of sputum culture in county-level ΤВ institution and DST in prefecture-level institution make it possible to individualized treatment regimen based on outcomes of DST and to increase cure rate of retreatment TB patients (ss+ and/or c+).

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