

Factors affecting smear conversion in tuberculosis management

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Abstract

Inpatient clinic at Ministry of Health Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital To identify risk factors associated with persistent sputum positivity at the end of 2 months of direct observed treatment. Retrospective cohort study concerning evaluation of medical records of 547 patients with smear positive tuberculosis treated at our clinic from January 2004 to December 2005 Of 547 patients with AFB positive smears, late conversion occurred in 11.9% while early conversion in 88.1%. Males composed 54.7% of the population, 31.9% of the population was ≤ 25 years old, 37.5% had exposure to tobacco, 15.7% had any drug resistance, 8.9% had co-morbid diabetes mellitus and 16.0% had extensive radiologic involvement. Upon univariate analysis, significant association was found between late sputum smear conversion and smoking for more than 20 package/year (<0.001), being over 40 years old (<0.001), being male (<0.001) and having extended radiological involvement (0.007). However, multivariate logistic regression analysis revealed smoking >20 package/year (OR=4.11; 95% CI=2.13-7.94) and extended radiological findings (OR=2.3; 95% CI=1.21-4.37) to be statistically significant predictors of late sputum smear conversion.

Our findings confirm the relationship between TB and tobacco and indicate smoking >20 package/year and extended radiological findings as significant independent predictors of late sputum smear conversion.

Key words: Tuberculosis, smoking, risk factor, sputum smear

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Introduction

Tuberculosis (TB) is a chronic pulmonary disease associated with high morbidity and mortality rates. The estimates of the global burden of TB in 2009 indicated to be 9.4 million incident cases [1].

Short course chemotherapy (SCC) achieves a favorable response, as defined by culture negativity at the end of the treatment in 97-100% of the treated population, whereas the identification of practical regimens with low (<5%) relapse rates has been the main therapeutic challenge [2]. Late sputum smear conversion after 2 or 3 months of treatment has been considered as a good predictor of eventual cure if treatment is completed [3].

A positive sputum smear at the end of the intensive phase may indicate poor supervision of the initial phase of therapy, poor patient adherence, poor quality of anti-TB drugs, use of anti-TB drugs at doses below the recommended range, slow resolution due to extensive cavitation and a heavy initial bacillary load, presence of co-morbid conditions that interfere either with adherence or with response, presence of drug-resistant *M. tuberculosis* that is not responding to first-line treatment and the evidence of non-viable bacteria that remain visible by microscopic examination [4].

A few meta-analysis and systematic reviews summarized the evidence association between exposure to tobacco smoke and three TB outcomes including TB infection, active TB disease and mortality due to TB. There has been insufficient evidence to support an association of smoking with delay, default, and slower smear conversion, greater severity of disease or drug-resistant TB [5-8].

If potential factors associated with the persistent sputum positivity at the end of 2-month therapy are known, they may be helpful in stratifying patients according to risk of adverse outcome. This current study was performed to identify risk factors associated with persistent sputum positivity at the end of 2 months of direct observed treatment (DOT), which could be used under programmed conditions in low-income countries.

Study Population and Methods

A total of 547 patients with smear positive tuberculosis treated in our clinic Ministry of Health Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital from January 2004 to December 2005 were included in this retrospective cohort study. Patients' medical records were evaluated retrospectively with respect to age groups (group 1: < 25 years old, group 2: 26-40 years old, Group 3: $\geq$ 40 years old), gender, exposure of tobacco (group 1: never smoking, group 2: $\leq$ 20 packets/year, Group 3: > 20 packets/year), category of disease (Category I and Category II), presence of co-morbid diabetes mellitus, extended radiological involvement, presence of any drug resistance and any HR (isoniasid, rifampicin) drug resistance. Smoking exposure was calculated based on number of packets/day/ year. Radiologic extensive involvement was considered in case of >75% involvement of hemithorax.

TB treatment

Categorization and appropriate treatment of tuberculosis was performed according the WHO guidelines [5-6]. Category I was defined to be composed of tuberculosis patients with new smear-positivity, new smear-negative pulmonary tuberculosis with extensive parenchymal involvement and severe forms of extra-pulmonary TB (EPTB). Category II was defined to be composed of tuberculosis patients with previously treated sputum smear-positive pulmonary TB (PTB) including relapse, treatment after interruption and treatment failure.

Treatment regime administered in Category I composed of two phases including initial phase of 2 months with isoniasid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) therapy under direct observation followed by continuation phase including 4 months self-administration of HR therapy. Category II treatment regime composed of initial phase of 2 months "HRZE and streptomycin (S)" followed by 1 month HRZE under direct observation and continuation phase of 5 months self-administration of HRE therapy.

In case of failure of therapy in category I patients, category II treatment was initiated while the treatment failure in category II patients was managed by administration of second-line drug

Study procedures

In case of identification of positive sputum examination at the end of the initial phase one month extension was performed during the treatment of Category I patients. Then, at the end of this additional month, if the smear sputum was still positive, the continuing phase was started with two major drugs (HR) under supervision at monthly check-ups. Patients were hospitalized until the sputum conversion was achieved. After discharge, sputum samples of patients were checked at the second month, fifth month and at the end of the treatment regime.

Bacteriological testing was based on three sputum samples per patient or a gastric aspiration sample if the patient could not produce sputum. The sputum and gastric aspiration samples were evaluated for acid-fast bacillus (AFB) by Erlich Ziehl Neelsen (EZN). Sputum smear examination was performed at least once in a month during treatment until achievement of sputum conversion and following discharge of the patient.

Sputum culture was performed on a monthly basis via Löwenstein-Jensen medium for *M.tuberculosis*. Routine drug sensitivity tests were performed for H, R, E, and S at the beginning of the treatment in all patients identified with culture positivity. Drug susceptibility tests (DST) were performed by proportion method but without an external laboratory quality control system. DST was not used to lead the management of the patients.

Assessment of early and late sputum conversion

‘Early conversion’ was defined as sputum smear conversion evident within the first two months and ‘late conversion’ as sputum smear conversion appearing later than the first two months.

Statistical analysis

Statistical analysis was made using computer software (SPSS version 14.0, SPSS Inc. Chicago, IL, USA). An initial one-way analysis was conducted to assess the distribution for each variable. Group differences for categorical variables were evaluated using the chi-square test. Final analysis was performed via multivariate logistic regression for dichotomous outcomes. Data were expressed as “mean (standard deviation; SD)” for normally distributed variables, median and quartiles for non-

normally distributed variables and percent (%) for categorical variables. $p < 0.05$ was considered statistically significant.

Results

Of 1024 tuberculosis patients treated in Ministry of Health Sureyyapasa Chest Diseases and Thoracic Surgery Education and Research Hospital from January 2004 to December 2005, 630 patients were identified to have Acid Fast Bacilli (AFB) positive smear.

Of these 630 patients, 83 patients were excluded from this study due to missing data ($n=21$), default or death ($n=48$), or evidence of treatment failure ($n=14$) leading 547 cases to be subject to final analysis.

Of 547 patients with AFB positive smears, late conversion occurred in 11.9% ($n=65$), while early conversion in 88.1% ($n=482$). Males and females composed 54.7% ($n=299$) and 45.3% ($n=248$) of the smear positive population, respectively. Late and early conversion was identified in 16.7% ($n=50$) and 83.3% ($n=249$) of male patients, respectively.

Of 547 patients with AFB positive smears, 449 (82.0%) were new cases, 98 (17.9%) were previously treated for tuberculosis. Early and late and conversion was identified in 89.8% ($n=403$) and 10.2% ($n=46$) of 449 new cases. In previously treated 98 cases, 80.6% ($n=79$) of cases had early conversion while 19.4% ($n=19$) had late conversion.

Of 547 patients with AFB smear positivity, 31.9% ($n=175$) were ≤ 25 years old while late and early conversion were identified in 7.4% ($n=13$) and 92.6% ($n=162$) of these patients, respectively. Of 167 (30.5%) cases in 26-40 years of age, late and early conversion were identified in 7.2% ($n=12$) and 92.8% ($n=155$), respectively. Of 205 (37.5%) patients ≥ 40 years old, 165 (80.5%) had early conversion while 40 (19.5%) had late conversion.

Of 266 (48.6%) of cases with no exposure to tobacco, 8.3% ($n=22$) had late conversion and 91.7% ($n=244$) had early conversion. Of 157 (37.5%) cases with exposure to tobacco for ≤ 20 packet-years, 8.3% ($n=13$) had late conversion while 91.7% ($n=144$) had early conversion. Of 124 (22.7%) cases with exposure to tobacco for >20 packet-years, 24.2% ($n=30$) had late conversion and 75.8% ($n=94$) had early conversion.

Of 86 (15.7%) cases having any drug resistance, 10 (11.6%) had late conversion while 76 (88.4%) had early conversion. Isoniasid (H) and Rifampicin (RMP) drug resistance was identified in 4.9% (n=27) of patients with smear positivity, while late and early conversion was evident in 7.4% (n=2) and 92.6% (n=25) of these patients, respectively.

Table 1. Evaluation of factors influencing early and late conversion in tuberculosis patients

		Early conversion (first 2 months)	Late conversion (≥3 months)	Total	p
Gender n (%)	Male	249 (83.3)	50 (16.7)	299 (100.0)	<0.001
	Female	233 (94.0)	15 (6.0)	248 (100.0)	
Category n (%)	I	403 (89.8)	46 (10.2)	449 (100.0)	0.016
	II	79 (80.6)	19 (19.4)	98 (100.0)	
Age groups n (%)	≤25 years	162 (92.6)	13 (7.4)	175 (100.0)	<0.001
	26-40 years	155 (92.8)	12 (7.2)	167 (100.0)	
	≥41 years	165 (80.5)	40 (19.5)	205 (100.0)	
Smoking status n (%)	Non-smoker	244 (91.7)	22 (8.3)	266 (100.0)	<0.001
	≤20 packets/year	144 (91.7)	13 (8.3)	157 (100.0)	
	>20 packets/year	94 (75.8)	30 (24.2)	124 (100.0)	
Any drug resistance n (%)	Absent	406 (88.1)	55 (11.9)	461 (100.0)	1.000
	Present	76 (88.4)	10 (11.6)	86 (100.0)	
HR resistance n (%)	Absent	457 (87.9)	63 (12.1)	520 (100.0)	0.759
	Present	25 (92.6)	2 (7.4)	27 (100.0)	
Diabetes mellitus n (%)	Absent	442 (88.8)	56 (11.2)	498 (100.0)	0.162
	Present	40 (81.6)	9 (18.4)	49 (100.0)	
Radiological evaluation n (%)	Limited	383 (90.1)	42 (9.9)	425 (100.0)	0.007
	Extended	64 (79.0)	17 (21.0)	81 (100.0)	
	Missing data	35	6	41	
Total		482 (%88.1)	65 (%11.9)	547 (100.0)	

Co-morbid diabetes mellitus was evident in 8.9% (n=49) of patients with smear positivity, while late and early conversion was evident in 18.4% (n=9) and 81.6% (n=40) of these patients, respectively.

Of 506 patients with data on radiological evaluation, 81 (16.0%) had extensive radiologic involvement with late and early conversion in 21.0% (n=17) and 79.0% (n=64) of these patients, respectively.

Table 2. Predictors of late sputum smear conversion in tuberculosis patients

	OR	%95 CI	p
Smoking status			
Non-smoker			
≤20 packets/year	2.16	0.54; 2.50	0.698
>20 packets/year	4.11	2.13; 7.94	<0.001
Radiological findings			
Limited			
Extended	2.30	1.21; 4.37	0.012

CI: confidence interval; OR: Odds ratio;

Upon univariate analysis, significant association was found between late sputum smear conversion and smoking for more than 20 package/year (<0.001), being over 40 years old (<0.001), being male (<0.001) and having extended radiological involvement (0.007). However, multivariate logistic regression analysis revealed smoking >20 package/year (OR=4.11; 95% CI=2.13-7.94) and extended radiological findings (OR=2.3; 95% CI=1.21-4.37) to be statistically significant predictors of late sputum smear conversion (Table 2).

Discussion

Examination of smear-positive patients in 2 months, 5 months, and at the end of treatment provides a better indication of the success of treatment in large-scale treatment programs [9]. The proportion of smear-positive patients with late sputum smear conversion at the end of the intensive phase has also been considered as an indicator of TB program performance [4]. However, at the end of the second month of therapy, skilled laboratory technicians can often detect low grades of positivity, while the positivity rate can still be as high as 25%, even if the initial phase of treatment is well supervised and the drugs are of good quality [3].

Smear status at the end of the intensive phase is a poor predictor of relapse development. Frequency of relapse rate with standardized short-course chemotherapy was reported to be around 3-7%. Approximately 80% of the relapses have been considered to occur within the first 6 months of treatment withdrawal while after 3-5 years, the risk in both groups diminishes appreciably [10].

Horne et al. performed a systemic review and meta-analysis to evaluate the accuracy of a positive sputum smear or culture during treatment with standardized regimen with rifampicin in the initial phase for predicting failure or relapse in pulmonary TB. As a result, both culture and smear had low PPV (positive predictive value) ranging from 9 to 18% in predicting poor outcome. In contrast, NPV (negative predictive value) were high (at least 93%) [11].

Previous WHO Guideline recommends that whatever the reason, if the sputum is positive at the end of the second month, the initial phase is prolonged for a third month [12]. But according to the latest WHO guideline, in patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended [4].

Risk factors such as higher age, male gender, higher smear grading, presence of cavitary disease, extensive disease; co-morbid conditions like diabetes mellitus have been considered to be associated with a delay in smear conversion among TB patients [13-17].

Accordingly, in our study population while smoking for more than 20 package/year (<0.001), being over 40 years old (<0.001), being male (<0.001) and having extended radiological involvement (0.007) were significantly associated with the likelihood of late sputum smear

conversion, logistic regression analysis revealed only smoking >20 package/year (OR=4.11; 95% CI=2.13-7.94) and extended radiological findings (OR=2.3; 95% CI=1.21-4.37) to be statistically significant predictors of late sputum smear conversion with 4.11 and 2.30 fold increase in likelihood of late conversion, respectively. Although male gender was consistently reported as a significant predictor of late sputum smear conversion, possibly in relation to higher incidence of smoking and alcohol consumption in this group [13-17], male gender was not a significant predictor of late sputum conversion in our population.

Significant delay in sputum conversion with advanced age [13,15-17] has been linked to physical disability resulting in increased delay clearing the bacilli probably due to decreasing immunity and also delay in seeking care and diagnosis which might lead progression of the disease [18].

In line with our findings, extensive radiologic involvement was consistently reported to predict later occurrence of sputum smear conversion in the literature [13,15-17,19].

Likewise, smoking was reported to be associated with late sputum smear or culture conversion, after 2 months of anti-tuberculosis treatment [20,21]. In a past clinical trial on immunotherapy with *M.vaccae* in the treatment of pulmonary tuberculosis by Durban Immunotherapy Trial Group identification of time to sputum conversion using multivariate Cox's proportional hazards regression revealed time to conversion to be longer among smokers than non-smokers [22].

While a significant relationship between diabetes and TB was reported in some studies [13-23], Rekha et al. showed that at the end of initial phase, the smear and culture conversion rates were similar in diabetes mellitus and HIV groups [18], alike to our findings.

Additionally, Fitzwater et al. [24] reported that delayed culture conversion was associated with multidrug resistance. Persistent day 60 smear positivity yielded positive and negative predictive values of 67% and 92%, respectively, for detecting multidrug resistance. In our study, drug resistance was not associated with late smear conversion.

The significant association between being previously treated (category II) and late sputum smear conversion in univariate analysis ($p=0.016$) in our population was not confirmed in the multivariate analysis. In fact, higher likelihood of having more extended radiologic

involvement among patients with past history of anti-tuberculosis treatment in our study population was determined to underlie the occurrence of late sputum conversion.

The major limitation of the present study seems to be the lack of correlation between times of culture and smear conversion. Secondly, since data on treatment outcome of patients following discharge were not available, we had no chance to evaluate the correlation of the time of smear conversion to treatment outcome among our patients.

Conclusions

In conclusion, our findings confirmed the consistent relationship between TB and tobacco, both of which have been considered among major health concerns in developing countries. Tobacco consumption is an important risk factor for TB so that TB control programs must address tobacco control as potential preventive intervention by implementing tobacco cessation and prevention programs as part of global TB control efforts. Our findings indicate smoking >20 package/year and extended radiological findings as significant independent predictors of late sputum smear conversion. Finally, therapeutic modifications in the management of sputum smear positive patients seem unnecessary in the presence of these independent factors since late conversion seems not to have a significant impact on treatment outcome, except in cases of treatment failure.

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