Original Article

Predicting Factors of Treatment Failure in Smear Positive Pulmonary Tuberculosis: A Retrospective Cohort Study in Bangkok Using a Combination of Symptoms and Sputum Smear/Chest Radiography

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Background: A successful outcome of smear positive pulmonary tuberculosis [SPPTB] used as an indicator of TB control program performance is necessary for monitoring program achievement.

Objective: To study outcomes of SPPTB and to investigate factors associated with treatment failure.

Materials and Methods: A retrospective study was conducted to identify outcomes and factors associated with failure in HIV-seronegative, SPPTB adult patients at Prasarnmit Hospital, Bangkok, Thailand between 2003 and 2012.

Results: Two hundred ninety-one patients were enrolled. The following outcomes were notes, 78.7% cure, 1.7% completed treatment, 5.5% failure, 10% transfer out, 3.8% default, and 0.3% died. In multiple logistic regression, the failures were statistically associated with age over 50 years (OR 3.99, 95% CI 1.06 to 15.07), sputum smear 3+ at diagnosis (OR 6.34, 95% CI 1.71 to 23.55), and drug resistance (OR 23.58, 95% CI 6.11 to 90.97). To predict failure, symptoms and basic laboratory results as well as sputum smear and chest radiography [CXR] were combined. The symptoms of cough, fever, and hemoptysis plus sputum smear 3+ showed high odd ratios of 5.17 (95% CI 1.50 to 18.67), 8.88 (95% CI 1.46 to 68.75), and 18.57 (95% CI 1.82 to 456.86), respectively. When combining symptoms with cavitary lesion(s) in CXR, only hemoptysis in combination with cavitary lesion(s) showed a significant association with failure (OR 8.54, 95% CI 0.87 to 205.19).

Conclusion: The WHO goal of success rate in SPPTB was not achieved. However, the risk factors of failure were identified by using symptoms plus simple laboratory tests, which can be useful in resource-limited areas.

Keywords: Predicting failure, Smear positive pulmonary tuberculosis, Tuberculosis, Treatment outcome, Thailand

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Globally, tuberculosis [TB] is considered one of the major public health burdens and causes enormous economic impacts, particularly in developing countries. The World Health Organization [WHO] goals of 50% and 90% reduction of TB prevalence within the year 2015 and 2035, respectively, require strengthening of TB control programs in all member states[(1)]. Thailand has been listed as one of the top 22 highest burdened countries with the incidence rate of 119 per 100,000 population in 2013[(1)]. Although the estimated TB incidence rate has decreased globally, that of Thailand remains relatively constant[(2)].

Smear positive pulmonary tuberculosis [SPPTB] is the most contagious form of TB, and treatment outcomes of SPPTB have been used as an indicator of efforts in TB control[(2,3)]. Thus, the WHO has emphasized close monitoring of treatment outcomes of SPPTB and has set a success rate of 85% as the target. In 2013, the overall global treatment success rate among new pulmonary tuberculosis [PTB] cases was 86%[(1)]. Many studies that vary in location and time of treatment outcomes of TB have been carried out, but few studies

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have specifically targeted treatment outcomes in HIV-negative SPPTB patients. This specific population is more contagious compared with the smear-negative TB and has better outcomes compared with HIV-infected patients[4-6]. Thus, evaluating the treatment outcomes of these patients and determining factors associated with poor outcomes will help clinicians to improve treatment and control the infectiousness of the disease, especially in endemic areas such as Thailand.

Therefore, the primary aim of the present study was to determine the cure rate of anti-TB treatment in new SPPTB and retreated SPPTB patients who were treated with WHO-recommended regimens. The authors also investigated factors associated with treatment failure outcomes to help clinicians predict the high-risk patients that need close monitoring and care.

Materials and Methods

Study setting

Prasarnmit Hospital, formerly called the Bangkok Chest Hospital, has a good reputation in the diagnosis and treatment of patients with TB and other respiratory diseases. The Anti-Tuberculosis Association of Thailand under the Royal Patronage of H.M. the King is located here. All of the TB cases are treated in the Outpatient Care Unit by experienced doctors. According to the National TB guidelines, sputum Ziehl-Neelsen stain [AFB] is routinely performed on the date of the diagnosis and at the second, third, and fifth months of the course of treatment. Chest radiography [CXR] is also routinely taken on the date of diagnosis and at the fifth month of treatment. The mycobacterial sputum culture (Lowenstein-Jensen media) is routinely done at the first diagnosis as well as at third and fifth months of treatment. Drug sensitivity test [DST] is also routinely done in all *Mycobacterium tuberculosis* [MTB] positive cultures. Although the Direct Observed Treatment, Short Course [DOTS] is not performed in this center, the compliance is ensured by self-reported drug administration. The experienced nurses provide health education and call for follow-up.

Study design and data collection

A retrospective review of medical records of patients who fulfilled the eligibility criteria for SPPTB was performed. The inclusion criteria were patients aged more than 18 years old, SPPTB cases, and treatment with standard short course regimens (CAT1) or receiving the 8-month retreatment regimen (CAT2). Extra-pulmonary TB cases were excluded as well as HIV-infected patients, pregnant women, and patients with changed regimens for any reason.

The sample size for primary outcome was 186 cases, calculated based on the previous WHO report[7]. The medical records were screened in reverse chronological order, starting in 2012 and ending in 2003. The study protocol was reviewed and approved by the Ethical Committee of the Faculty of Tropical Medicine, Mahidol University.

Definitions

The definitions and treatment outcomes were defined by the WHO treatment guideline 2010: 1) cure, 2) completed treatment, 3) treatment failure, 4) died, 5) default, and 6) transferred out[8]. The cure and completed treatment groups were classified as a successful outcome while others were classified as an unsuccessful outcome. High grade smear positive TB was defined as AFB 3+ or higher. Treatment compliance was categorized as good (no missing visits) and as poor (one or more missing visits).

Statistical analysis

The data were analyzed with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). To determine the factors associated with treatment failure, a cross-tabulation technique was used and corresponding *p*-value was assessed by Pearson's Chi-square or Fisher's exact test as appropriate. Binary logistic regression with odds ratio and 95% confidence interval [CI] were calculated to identify the independent risk factors for treatment failure. The criterion for inclusion of variables in the forward stepwise multivariate logistic regression analysis was *p*-value less than 0.10 in the univariate analysis. A two-sided *p*-value of less than 0.05 was considered statistically significant for all tests.

Results

Eight-hundred and ten cases were screened, and 291 patients were enrolled. Among these, there were 205 males (70.4%) and 86 females (29.6%). Other baseline demographic data are shown in Table 1. Two hundred seventy-one cases (93.1%) were new SPPTB cases, and 20 cases were retreated PTB (6.9%). Underlying diseases were reported in 42 of 249 patients (16.9%). The most common disease was diabetes mellitus (73.8%), followed by hypertension (9.5%) and chronic kidney diseases (9.5%). Symptoms were reported in 268 cases (92.1%), while 23 asymptomatic patients sought medical treatment due to abnormal CXR. The commonly reported symptoms were cough, fever,

and chest pain in 256, 121, and 90 cases, respectively. Eighty-one patients complained of hemoptysis. All 291 enrolled patients had abnormal CXR findings. Among 277 cases with available data on type of CXR abnormality, 108 patients (39.0%) had a cavitary lesion(s). Gradings of sputum were 1+, 2+, and 3+. The number of patient with gradings of sputum AFB were 146 (50.2%) with grade 1+, 59 (20.3%) with grade 2+, and 86 (29.5%) with grade 3+. The mycobacterial sputum culture were performed in all cases; however, four cases were no growth, and five cases had no data of drug susceptibility. There were 38 cases (13.5%) of drug resistant strains. Among these, 13 cases were multidrug resistant TB [MDR-TB]. The percentages of MDR-TB among new cases and retreated cases were 2.2% and 10%, respectively.

Of the 291 enrolled patients, the treatment outcomes were cure in 229 (78.7%), complete in five (1.7%), failure in 16 (5.5%), transfer out in 29 (10.0%), default in 11 (3.8%), and died in one (0.3%). The one death was reported as suicide. The success rate in new SPPTB patients was documented in 224 of 271 patients (82.7%), encompassing 219 (80.8%) cure and five (1.8%) treatment completed cases. The success rate in the retreatment group was established in 10 of 20 cases (50%). The overall rate of success was 80.4% (234 of 291 patients) (Table 2).

Only failure cases were compared with successful ones, namely cure and complete, to examine the factors associated with treatment failure (Table 3). The transfer out cases were not included in the analysis of factors associated with treatment failure. Univariate analysis revealed that age over 50 years was statistically significant associated with failure ($p = 0.005$). Patients with underlying co-morbid conditions were less likely to achieve a target success rate than those without any underlying disease, but this was not statistically significant. Although treatment success rate in the retreatment group was lower (10 of 12 patients, 83.3%) than in the new treatment group (224 of 238 patients, 94.1%), there was no statistical significance ($p = 0.348$).

The grading of sputum smear at initial visit expressed a statistically significant association ($p = 0.002$). Patient with a sputum smear reported as grade 1+ had a greater probability of success than those reported as grade 2+ or 3+. However, the cavitary lesion(s) in CXR at first visit showed no statistically significant association with failure ($p = 0.320$).

Among the 282 cases with available data of drug susceptibility testing, 30 patients were reported to have a drug resistant strain of MTB. The success rate in the drug resistant patients was statistically significant lower (19 of 30 patients, 63.3%) than the drug sensitive cases (209 of 214 patients, 97.7%) ($p<0.001$). Treatment compliance in patients visiting regularly had a statistically significant higher success rate (95.6%) than those who did not ($p = 0.032$).

Multiple logistic regression analysis (Table 4) revealed that older age (more than 50 years old), high grade sputum smear, and having drug resistant strain of MTB were statistically significant associated with treatment failure, with adjusted odds ratios of 3.99 (95% CI 1.06 to 15.07), 6.344 (95% CI 1.71 to 23.55), and 23.58 (95% CI 6.11 to 90.97), respectively.

Symptoms including fever, cough, chest pain,

Table 1. Baseline characteristic (n = 291)

Variable	n (%)
Age group (years)	
18 to 30	97 (33.3)
31 to 40	71 (24.4)
41 to 50	60 (20.6)
51 to 60	40 (13.8)
>60	23 (7.9)
Age (years), mean ±SD	39.3±13.9
Sex: male	205 (70.4)
Place of residence: Bangkok	198 (68.0)
Nationality: Thai	286 (98.3)
Having underlying diseases	42 (16.9)
Status: new cases	271 (93.1)
Sputum smear on the first visit	
AFB 1+	146 (50.2)
AFB 2+	59 (20.3)
AFB 3+	86 (29.5)
Mycobacterial sputum culture: positive	287 (98.6)
Sensitive	244 (86.5)
Mono-drug resistant	25 (8.9)
MDR-TB	13 (4.6)
CXR on the first visit: cavitary lesion	108 (39.0)

AFB = sputum Ziehl-Neelsen stain; MDR-TB = multidrug resistant tuberculosis; CXR = chest radiography

Table 2. Treatment outcomes

Treatment outcomes	New case (n = 271) n (%)	Retreated case (n = 20) n (%)	Overall (n = 291) n (%)
Successful	224 (82.7)	10 (50.0)	234 (80.4)
Cured	219 (80.8)	10 (50.0)	229 (78.7)
Treatment completed	5 (1.8)	0 (0.0)	5 (1.7)
Unsuccessful	47 (17.3)	10 (50.0)	57 (19.6)
Treatment failure	14 (5.2)	2 (20.0)	16 (5.5)
Died	1 (0.4)	0 (0.0)	1 (0.3)
Default	8 (2.9)	3 (30.0)	11 (3.8)
Transfer out	24 (8.8)	5 (50.0)	29 (10.0)

Table 3. Factors associated with treatment failure: univariate analysis

Factors	n (%)	Treatment outcomes		*p*-value
		Successful, n (%)	Failure, n (%)	
Age category (years)				0.005**
18 to 50	194 (77.6)	187 (96.4)	7 (3.6)	
>50	56 (22.4)	47 (83.9)	9 (16.1)	
Gender				0.548
Male	173 (69.2)	163 (94.2)	10 (5.8)	
Female	77 (30.8)	71 (92.2)	6 (7.8)	
Smoking				0.177
Currently	52 (20.8)	51 (98.1)	1 (1.9)	
Previously	37 (14.8)	32 (86.5)	5 (13.5)	
No smoking	54 (21.6)	52 (94.4)	3 (5.6)	
Unknown	107 (42.8)	100 (93.5)	7 (6.5)	
Underlying disease				0.121**
Yes	38 (15.2)	32 (84.2)	6 (15.8)	
No	106 (42.4)	100 (94.3)	6 (5.7)	
Unknown	106 (42.4)	102 (96.2)	4 (3.8)	
Status of the disease				0.348**
New case	238 (95.2)	224 (94.1)	14 (5.9)	
Retreatment case	12 (4.8)	10 (83.3)	2 (16.7)	
Sputum smear on the first visit				0.002
AFB 1+	131 (52.4)	128 (97.7)	3 (2.3)	
AFB 2+	53 (21.2)	50 (94.3)	3 (5.7)	
AFB 3+	66 (26.4)	56 (84.8)	10 (15.2)	
CXR on the first visit				0.320**
Cavitary lesion	86 (34.4)	78 (90.7)	8 (9.3)	
Non cavitary lesion	157 (62.8)	149 (94.9)	8 (5.1)	
No data	7 (2.8)	7 (100)	0 (0.0)	
Drug susceptibility				<0.001
Sensitive	214 (85.6)	209 (97.7)	5 (2.3)	
Resistant	30 (12.0)	19 (63.3)	11 (36.7)	
- Mono-drug resistance	22	19 (86.4)	3 (13.6)	
- Multi drug resistance	8	0 (0.0)	8 (100)	
No data/no growth	6 (2.4)	6 (100)	0 (0.0)	
Symptoms				
Cough (n = 229)				0.310
- Yes	223	209	14	
- No	6	5	1	
Fever (n = 165)				0.753
- Yes	103	95	8	
- No	62	58	4	
Chest pain (n = 136)				0.242
- Yes	78	75	3	
- No	58	53	5	
Hemoptysis (n = 137)				0.380
- Yes	72	66	6	
- No	65	62	3	
Weight loss (n = 118)				0.325
- Yes	54	49	5	
- No	64	61	3	
Treatment compliance*				0.032**
Yes	203 (81.2)	194 (95.6)	9 (4.4)	
No	47 (14.8)	40 (85.1)	7 (14.9)	

AFB = sputum Ziehl-Neelsen stain; CXR = chest radiography

* Treatment compliance: yes, medicine taken regularly; no, missed medication taken >1 week

** Two-tailed *p*-value Fisher's exact test

hemoptysis, and weight loss were not associated with treatment failure. Combinations of symptoms and basic laboratory results such as grading of sputum smear or cavitary lesion(s) in CXR were used in analysis. Interestingly, some combinations of symptoms and findings showed statistically significant associations with treatment failure. Patients presenting with cough, fever, or hemoptysis with a smear of 3+ had a significantly higher risk of failure compared with those having a smear of 1+ and 2+ with odds ratios of 5.17 (95% CI 1.50 to 18.67), 8.88 (95% CI 1.46 to 68.75), and 18.57 (95% CI 1.82 to 456.86), respectively (Table 5). However, the combinations of chest pain and weight loss with the grading of sputum AFB were not significantly associated with failure. The same analysis was done with CXR results. Only patients who complained of hemoptysis with CXR that reported cavitary lesions were statistically significant more likely to fail than patients suffering from the same symptom with non-cavitary lesions, $p = 0.038$ (Table 5). Other symptoms including cough, fever, chest pain, and weight loss were evaluated, but no significant associations were noted.

Discussion

The successful treatment outcomes of the present study were in the same range as previous studies, but lower than the WHO target. These previous studies that focused on outcomes and factors associated with outcomes of SPPTB are summarized in Table 6. The low success rate in the present study might be explained by the high rate of transfer out. Because this center is one of the reference centers for TB treatment, many patients sought diagnoses and the early period of treatment before transferring out to continue treatment at local centers. The death rate was low in the present study due to the non HIV-infected population. It is well known that HIV-infected patients with TB have poorer outcomes and higher mortality compared with HIV-seronegative patients[6,9,10]. There were low percentages of deaths and defaulters as well as high percentages of transfer out due to the nature of this center. When comparing the treatment failure group with the success group, predicting factors associated with failure were age more than 50 years, AFB 3+ at first visit, drug-resistant strain, and poor compliance. These factors were similar to previous studies (Table 6).

Table 4. Factors associated with treatment failure: multivariate analysis

Factors	Crude OR (95% CI)	Adjusted OR (95% CI)
Old age group (>50 year)	5.12 (1.81 to 14.85)	3.996 (1.060 to 15.066)
High grade sputum smear at diagnosis (3+)	5.30 (1.84 to 15.22)	6.344 (1.709 to 23.549)
Drug resistance	24.20 (7.61 to 76.94)	23.583 (6.114 to 90.968)
Non excellent compliance	3.77 (1.33 to 10.72)	1.353 (0.313 to 5.858)

CI = confidence interval; OR = odds ratio

Table 5. Treatment outcomes classified by symptoms and a positive sputum smear/abnormal chest radiography at the first visit

Symptoms	Total (n)	Treatment outcome		Crude OR (95% CI)	CXR on the first visit	Total (n)	Treatment outcome		Crude OR (95% CI)
		Failure	Success				Failure	Success	
Cough	223					218			
AFB 3+	63	9	54	5.17 (1.50 to 18.67)	Cavitary	83	7	76	1.78 (0.54 to 5.90)
AFB 1+/2+	160	5	155	Reference	Non cavitary	135	7	128	Reference
Fever	103					100			
AFB 3+	30	6	24	8.88 (1.46 to 68.75)	Cavitary	40	4	36	1.56 (0.30 to 8.04)
AFB 1+/2+	73	2	71	Reference	Non cavitary	60	4	56	Reference
Hemoptysis	72					71			
AFB 3+	19	5	14	18.57 (1.82 to 456.86)	Cavitary	29	5	24	8.54 (0.87 to 205.19)
AFB 1+/2+	53	1	52	Reference	Non cavitary	42	1	41	Reference
Chest pain	78					76			
AFB 3+	18	2	16	7.48 (0.48 to 220.74)	Cavitary	29	1	28	0.80 (0.03 to 12.15)
AFB 1+/2+	60	1	59	Reference	Non cavitary	47	2	45	Reference
Weight loss	54					51			
AFB 3+	23	4	19	6.32 (0.58 to 160.43)	Cavitary	23	3	20	1.95 (0.23 to 18.81)
AFB 1+/2+	31	1	30	Reference	Non cavitary	28	2	26	Reference

AFB = sputum Ziehl-Neelsen stain; CI = confidence interval; OR = odds ratio

Table 6. Summary of outcomes of smear positive pulmonary tuberculosis in previous studies

	The present study	Lienhardt et al.[9], 1998	Joseph et al.[14], 2011	Berhe et al.[3], 2012	Tweya et al.[6] 2013	Alobu et al.[12], 2014	Atif et al.[16], 2014	Reechaipichitkul et al.[19], 2014
Population (n)	291 Thailand	1,357 The Gambia	286 South India	407 Northern Ethiopia	2,361 Malawi	985 Southeastern Nigeria	336 Malaysia	322 Northeastern Thailand
HIV positive (%)	0	6.3	N/A	8.6	56	13.8	4.76	7.77
Resistance rate (%)	13.2 (MDR 4.5)	N/A	N/A	N/A	N/A	N/A	N/A	3.6% in new case, 22.92% in previously treated
Treatment success rate (%)	80.4	79.6	N/A	89.2	87	N/A	67.26	74.2% in new cases, 76% in previously treated
Factor associated with poor outcome	-Age >50 years -High grade sputum smear -Drug resistance -Poor adherence	High grade sputum	-Retreatment cases -Old age (in new cases)	-Age >40 years -Unemployed -Retreatment cases -Family size equal or more than 5 persons	N/A	-Age >40 years -Male -Retreatment cases -No smear conversion at 2 months	-Male -Low education -Foreigners	N/A

HIV = human immunodeficiency virus; N/A = not available

The cut points of older age have varied among studies in the literature. For example, the cut-off is 65 to 79 years old in a study from Taiwan[11], 40 years and over in a study from Africa[3,12], and more than 45 years in an Indian study[13]. Apart from having lower immunity than young adults, the elderly might have impairment in absorption of drugs[14,15], higher rate of loss to follow-up, and higher rate of side effect related to anti-TB drugs[15]. Thus, the elderly with PTB need special attention and close monitoring in treatment.

Initial smear grading is well recognized as a predicting factor of poor outcomes as well as a risk factor for death in Atif et al's study[16]. Increasing initial smear grading was also associated with a decrease in smear conversion rate[13]. Although DOTS was not provided in our center, compliance by using irregularity of visits and self-reported drug administration could be used to predict the outcome in the present study. Additionally, a meta-analysis by Pasipanodya and Gumbo showed that DOTS was not significantly better than self-administration in preventing microbiological failure and relapse as well as preventing acquired drug resistance[17].

The global rate of MDR-TB among new cases was 3.5% in 2013. The national survey of Thailand in 2006 reported that 1.7% were new cases PTB, and 34.5% were retreated cases[18]. The rate of MDR-TB in the present study was 2% that were new cases, which is similar to the result from the national survey, but the rate of MDR among retreated group was much lower than in the national survey. This might be explained by the small number of retreated cases in the present study (20 cases, 6.9%). Although the present study reported that drug resistant MTB was a strong predictor of treatment failure in SPPTB patients, it might not be practical in clinical practice due to the time consumed to test for it and resource limitations in clinical practice in remote areas.

In the present study, the presence or absence of symptoms such as fever, cough, hemoptysis, chest pain, and weight loss were not associated with treatment outcome. However, the finding of symptomatic patients who were evaluated by sputum smear and CXR result on the first visit revealed that patients who presented with cough, fever, or hemoptysis with sputum smear AFB 3+ had statistically significant associations with failure. In addition, patients with hemoptysis and the presence of cavitary lesions on CXR on the first visit had a statistically significant higher risk of treatment failure than those who had hemoptysis with non-cavitary lesions. To the best of our knowledge, there have been no reports of a combination of clinical findings and basic laboratory results to predict outcomes similar to our study. These findings will help clinicians to pay particular attention to the appropriate management and follow-up of patients presented with the symptoms stated above in addition to AFB 3+ or hemoptysis with cavitary lesions. To confirm these findings, further prospective studies should be carried out.

There are some limitations in the present study. Firstly, the retrospective nature of the study gave incomplete data on some socioeconomic factors. Secondly, data from this single center might not be applicable to other settings. The information of underlying diseases such as HIV and diabetes mellitus were mostly self-reported. Anti-HIV and fasting blood sugar tests were not routinely done in all cases. These tests were performed only in cases with an index of

suspicion from history and physical examination. Thus, some asymptomatic cases might have been missed.

Conclusion

The SPPTB success rate of 80.4% in the present study did not reach the WHO target. Failure was statistically associated with age over 50 years, sputum smear 3+ at diagnosis, and drug resistance. Furthermore, combinations of certain symptoms and basic laboratory investigations such as sputum smear grading and CXR can be used to predict failure. This approach may be useful in resource-limited settings. More studies that focus on predicting the factors associated with unfavorable outcomes of SPPTB should be conducted on a larger scale, together with studies of strategies to improve outcomes of patients with problematic factors.

What is already known on this topic?

The common factors associated with failure or unfavorable outcome in SPPTB are elderly, male, high grade smear positive, drug resistant strains, retreatment cases, poor compliance, and low education.

What this study adds?

Using symptoms plus simple laboratory tests at first visits could significantly identify risk factors of failure with high odd ratio in SPPTB patient. This approach is compatible with the setting of resource-limited TB clinics/centers in Thailand. In addition, a good nursing support team and self-reported drug administration strategies (without DOTS) could reflect the compliance of patients and be used effectively at the TB center. This will decrease the burden on health care providers.

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Potential conflicts of interest

The authors declare no conflict of interest.

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