TREATMENT OUTCOMES AMONG DIABETIC PATIENTS WITH TUBERCULOSIS IN THAILAND

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Abstract. Tuberculosis (TB) is common in Thailand and the prevalence of diabetes mellitus (DM) is increasing. We conducted this study to determine the impact of DM on the outcome of pulmonary TB treatment in northern Thailand by retrospectively reviewing TB registry data. Data for all pulmonary TB patients being treated at 95 TB clinics in eight provinces from northern Thailand during January 2010-December 2012 were retrospectively analyzed. TB treatment outcomes were assessed by sputum tests at 2 months and 6 months after starting treatment, and the overall success rate at the end of the treatment course was determined. Factors associated with treatment outcome were evaluated. A total of 7,807 new pulmonary TB patients were included in the analysis. Among those, 555 (7%) had history of diabetes. At 2-month after the intensive phase treatment, a negative sputum result was found in 85% of all tested patients. The proportion of negative sputum at 2-month was similar in both TB with and without DM (85%). The overall treatment success rate was 77%. TB treatment outcomes were not significantly different between TB patients with DM (84%) and without DM (77%). In conclusion, having DM did not affect the TB treatment outcome in the studied population. More detailed studies of TB treatment outcome and level of DM control are underway.

Keywords: tuberculosis, diabetes mellitus, treatment outcome, smear positive, Thailand

INTRODUCTION

Tuberculosis (TB) is a public health concern worldwide (WHO, 2011). The pulmonary TB treatment success rate varies by country and ranges from 67% in developing countries to 90% in developed countries (Jasmer *et al*, 2004; Chung *et al*, 2007; Joseph *et al*, 2011; Getahun *et al*, 2013; Tweya *et al*, 2013; Atif *et al*, 2014). Factors associated with poor pulmonary TB treatment outcomes include advanced age, smoking, male sex, low socioeconomic status, and comorbidities

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such as HIV infection and diabetes mellitus (DM) (Gadkowski and Stout, 2008; Low *et al*, 2009; Shen *et al*, 2009; Wang *et al*, 2009; Dooley *et al*, 2011; Jianzhao *et al*, 2011; Moolphate *et al*, 2011).

In developing countries, the prevalence of DM is projected to increase by 69% from 2010 to 2030 (Shaw *et al*, 2010). DM has been reported to increase the risk of TB infection and clinical TB (Jayawardena and Samarathunga, 2008; Chang *et al*, 2011), and affect treatment outcome of TB patients (Alisjahbana *et al*, 2007;Pajankar *et al*, 2008). In Sri Lanka and Taiwan, TB patients with DM were more likely to have severe TB infections, higher mycobacterial loads, higher probability of developing multidrug resistance, and a higher treatment failure rate than TB patients without DM (Jayawardena and Samarathunga, 2008; Chang *et al*, 2011). However, the effect of DM on pulmonary TB treatment outcomes is not consistent (Alisjahbana *et al*, 2007; Pajankar *et al*, 2008).

TB is common in Thailand. In 2012, the estimated prevalence and incidence rates for all forms of TB were 159 and 119 per 100,000 population, respectively (WHO, 2013). TB is particularly common in northern Thailand. Despite a major effort to control TB, the overall TB treatment success rate is < 80% (Pokaew, 2011). DM has become a public health problem in Thailand (Shaw *et al*, 2010). According to a National Health Examination Survey in Thailand, the prevalence of DM among adults aged ≥15 years was 2.3% in 1991 and 6.9% in 2009 (Deerochanawong and Ferrario, 2013). In 2014, the prevalence of DM in Thailand was reported as 8.5% (International Diabetes Federation, 2014). An increase in the prevalence of DM may result in an increase number of TB patients with underlying DM. However, screening for DM has not been added to the standard procedures or guidelines for TB management in Thailand due to a lack of evidence on the impact of DM on TB treatment outcomes.

The aim of this study was to determine the association between having DM and pulmonary TB treatment outcome retrospectively using TB treatment data from northern Thailand. Findings from this study can inform clinicians treating pulmonary TB among patients with DM in this study population.

MATERIALS AND METHODS

We conducted a retrospective cohort study using data from a TB registry for northern Thailand. New pulmonary TB patients aged ≥18 years with a positive sputum smear for acid-fast bacilli between 2010 and 2012 were included in the study. All patients were treated following National TB Treatment Guidelines from the Ministry of Public Health, Thailand (Bureau of Tuberculosis, 2008).

Source of data

Data were obtained from the TB Clinic Management Program (TBCM), a web-based TB registration database. All new TB cases diagnosed in all public hospitals in the eight provinces of northern Thailand must be recorded in the TBCM program (Fig 1). The program, in use since 1999, is managed by the Office of Disease Prevention and Control Region 1 (DPC1), Ministry of Public Health, Thailand. The database contains demographic data, clinical characteristics, diagnosis, treatment, and treatment outcomes for all TB patients. Since 2010, data regarding comorbidities, such as DM, hypertension (HT), and chronic obstructive pulmonary disease (COPD), have been added because of an increase awareness of the need for management of TB and comorbidities. DM

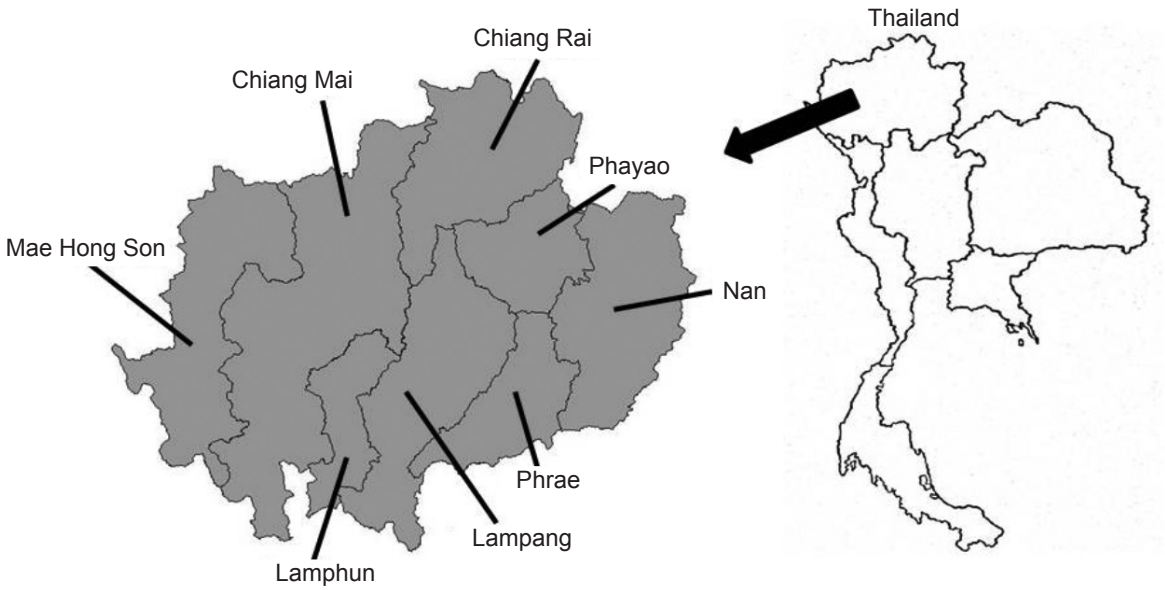

Fig 1–Map of eight study areas from northern Thailand; 95 tuberculosis clinics.

data are mostly based on a medical history of having an abnormal fasting blood sugar level (existing cases), since there is no guideline for DM screening among newly diagnosed TB cases.

Statistical analysis

The demographic and clinical characteristics of TB patients were described and compared between TB patients with and without DM using the chi-square test. The final treatment outcome was classified as successful (treatment complete or cure) or unsuccessful (died, defaulted, treatment failure or transferred out). A treatment cure was defined as a negative sputum smear or culture in the last month of treatment and a negative sputum on at least one previous occasion. Treatment complete was defined as completing standard treatment but having no sputum smear result available. Died was defined as a death due to any cause. Defaulted on treatment was defined as treatment interuption for at least 2 consecutive months. Treatment failure was defined as a sputum smear or culture still positive after at least 5 months of treatment. Transferred out was defined as a patient referred to another facility. Relative risk (RR) and 95% confidence interval (95%CI) were calculated to identify factors associated with treatment outcome. Data analysis was performed using SPSS, version 15 (SPSS, Chicago, IL).

Ethical considerations

This study was approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University, Thailand. Permission to use the data was granted by the Director of the DPC10. Patient consent was not obtained due to the anonymous nature of the data.

RESULTS

A total of 12,008 newly diagnosed pulmonary TB patients from 95 TB clinics were recorded in the TBCM system during the study period. Of these, 7,807 patients

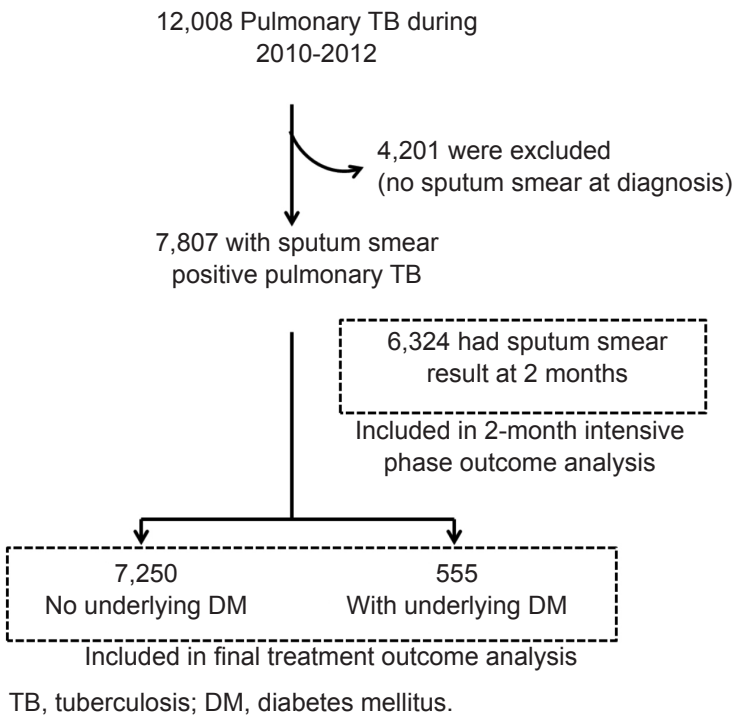

Fig 2–Flow diagram of case enrollment and patients with sputum smear data in the study.

had an acid-fast bacillus positive sputum smear obtained before treatment; these were included in our study. Of these, 1,483 patients did not have a sputum smear result after 2 months of treatment and were excluded from the 2-month sputum result analysis (Fig 2).

Patient characteristics

Seventy-two percent of patients were male and 55% were aged >50 years. A lung cavity lesion was found of chest x-ray in 40% of patients. Fifty-nine percent of patients had a TB sputum smear of 2+ or more at diagnosis. Human immunodeficiency virus (HIV) infection and other chronic diseases, such as hypertension and chronic obstructive pulmonary disease (COPD) were recorded to be present in 10% of patients. DM was found in 7% of patients (555/7,807). TB patients with DM comorbidity were more likely to be female, older, and have other chronic diseases. HIV infection was less prevalent among TB patients with DM than TB patients without DM (Table 1).

Sputum smear results after 2 months treatment

Of the 6,324 patients for whom sputum smear data after 2 months of treatment were available, 953 (15%) still had a positive sputum smear. The presence of DM was not significantly associated with the sputum result (adjusted RR=1.00; 95%CI: 0.77-1.30). A positive sputum test at 2 months was significantly associated with male sex (adjusted RR = 1.36; 95%CI: 1.12-1.64), older age (adjusted RR=1.41; 95%CI: 1.04-1.91), and high bacterial grade

Table 1
Characteristics of pulmonary TB patients by DM status (*N*=7,807).

Characteristic	Total No. (%)	Pulmonary TB patients		*p*-value
		With DM (*n*=555) No. (%)	Without DM (*n*=7,250) No. (%)	
Sex				
Male	5,650 (72)	354 (64)	5,296 (73)	<0.001
Female	2,155 (28)	201 (36)	1,954 (27)	
Age group (years)				
18-30	895 (12)	10 (2)	885 (12)	<0.001
31-40	1,148 (15)	42 (8)	1,106 (15)	
41-50	1,510 (19)	122 (22)	1,388 (19)	
51-60	1,700 (22)	180 (32)	1,520 (21)	
>60	2,554 (33)	201 (36)	2,353 (33)	
Occupational status				
Employed	3,344 (78)	227 (78)	3,117 (78)	
Unemployed	931 (22)	63 (22)	868 (22)	0.982
Lung cavity lesion				
No	4,278 (60)	324 (62)	3,954 (60)	
Yes	2,830 (40)	199 (38)	2,631 (40)	0.392
TB smear grading before treatment				
Low (<2+)	3,190 (41)	233 (42)	2,957 (41)	0.577
High (≥2+)	4,617 (59)	322 (58)	4,295 (59)	
HIV				
Negative	6,330 (88)	505 (98)	5,825 (88)	
Positive	844 (12)	10 (2)	834 (12)	<0.001
Comorbidity				
No	6,926 (89)	364 (66)	6,562 (90)	
Yes	881 (11)	191 (34)	690 (10)	<0.001
Hypertension				
No	7,279 (93)	384 (69)	6,895 (95)	
Yes	528 (7)	171 (31)	357 (5)	<0.001
COPD				
No	7,527 (96)	543 (98)	6,984 (96)	
Yes	280 (4)	12 (2)	268 (4)	0.061
Drug treatment				
Separate drugs	3,180 (52)	271 (51)	2,909 (52)	
Fixed drug combination	2,912 (48)	259 (49)	2,653 (48)	0.607
Hospital level				
Primary	5,410 (69)	373 (67)	5,037 (70)	
Secondary	1,418 (18)	113 (20)	1,305 (18)	
Tertiary	977 (13)	69 (13)	908 (12)	0.374

COPD, chronic obstructive pulmonary disease.

Table 2
Factors associated with sputum smear results after 2 months of treatment (*N*=6,324).

	Total No. (%)	Sputum at second month		RR	95%CI	Adjusted RR	95%CI
		Positive No. (%)	Negative No. (%)				
Total	6,324	953 (15)	5,371 (85)				
DM							
No	5,850 (93)	883 (15)	4,967 (85)	1		1	
Yes	474 (7)	70 (15)	404 (85)	0.99	0.77-1.25	1.00	0.77-1.30
Gender							
Female	1,748 (28)	192 (11)	1,556 (89)	1		1	
Male	4,575 (72)	761 (17)	3,814 (83)	1.51	1.29-1.77	1.36	1.12-1.64
Age group (years)							
18-30	763 (12)	81 (11)	682 (89)	1		1	
31-40	941 (15)	122 (13)	819 (87)	1.22	0.92-1.62	1.26	0.87-1.73
41-50	1,300 (20)	223 (17)	1,077 (83)	1.62	1.25-2.08	1.51	1.11-2.05
51-60	1,456 (23)	252 (17)	1,204 (83)	1.63	1.27-2.09	1.41	1.04-1.91
>60	1,864 (30)	275 (15)	1,589 (85)	1.39	1.09-1.78	1.31	0.97-1.77
Occupation							
Employed	2,770 (81)	405 (15)	2,365 (85)	1			
Unemployed	668 (19)	96 (14)	572 (86)	0.98	0.80-1.23		
Lung cavity lesion							
No	3,469 (60)	566 (16)	2,903 (84)	1		1	
Yes	2,337 (40)	319 (14)	2,018 (86)	0.84	0.73-0.96	0.79	0.67-0.93
TB smear grading before treatment							
Low (<2+)	2,560 (59)	232 (9)	2,328 (91)	1		1	
High (≥2+)	3,764 (41)	721 (19)	3,043 (81)	2.11	1.82-2.45	2.08	1.74-2.49
HIV							
Negative	5,292 (89)	839 (16)	4,453 (84)	1		1	
Positive	637 (11)	45 (7)	592 (93)	0.45	0.33-0.59	0.52	0.36-0.75
Comorbidity							
No	5,673 (90)	846 (15)	4,827 (85)	1			
Yes	651 (10)	107 (16)	544 (84)	1.10	0.90-1.35		
Drug treatment							
Separate drugs	2,609 (52)	347 (13)	2,262 (87)	1		1	
Fixed drug combination	2,386 (48)	414 (17)	1,972 (83)	1.30	1.13-1.51	1.27	1.08-1.49
Hospital level							
Primary	4,436 (70)	705 (16)	3,731 (84)	1		1	
Secondary	1,187 (19)	137 (12)	1,050 (88)	0.73	0.61-0.87	0.54	0.61-0.93
Tertiary	699 (11)	111 (16)	588 (84)	1.00	0.82-1.22	1.28	1.98-1.65

(≥2+) before treatment (adjusted RR=2.08; 95%CI=1.74-2.49). Patients with a cavitary lung lesion or HIV were significantly less likely to have a positive sputum test (adjusted RR=0.79 and adjusted RR = 0.52 for cavitary lung and HIV infection, respectively). Patients who received a fixed-dose combination treatment for TB were 1.27 times more likely to have a positive sputum test for TB at 2 months compared

Table 3
Final pulmonary TB treatment outcome among study subjects (*N*=7807).

Treatment outcome	Total No. (%)	TB No. (%)	TB-DM No. (%)
Successful	6,034 (77)	5,569 (77)	465 (84)
Cure	5,716 (73)	5,266 (73)	450 (81)
Complete	318 (4)	303 (4)	15 (3)
Unsuccessful	1,773 (23)	1,683 (23)	90 (16)
Death	1,174 (15)	1,107 (15)	67 (12)
Default	258 (3)	252 (3)	6 (1)
Failure	127 (2)	121 (2)	6 (1)
Transferred out	214 (3)	203 (3)	11 (2)

with those who received separate drugs (adjusted RR=1.27; 95%CI: 1.08-1.49). Employment status, comorbidities including HT and COPD, and the level of hospital were not significantly associated with the sputum results after 2 months treatment (Table 2).

About 19% (*n*=1,483) of our study subjects did not have a sputum smear result at 2 months. Of these, 60% had died by the 2 months; this proportion was not different between those with or without DM.

Final treatment outcome of pulmonary TB cases

The overall success rate of TB treatment was 77%, with cure in 73% and treatment completion in 4%. The success rate was not significantly different among TB patients with DM (84%) compared with TB patients without DM (77%). Death was the major cause of unsuccessful treatment (15%). Among unsuccessful cases, death occurred more frequently but not significantly among TB patients without DM (15%) than in those with DM (12%). Defaulted (treatment interuption for at least 2 consecutive months) was observed in 1% and 3% of TB patients with and without DM, respectively. Treatment failure was found in 2% of TB patients (Table 3).

DM was not significantly associated with final TB treatment outcome (adjusted RR=1.04; 95% CI: 0.89-1.20). Age >60 years, unemployment status, HIV or other comorbidity including HT and COPD, were not significantly associated with successful TB treatment after adjusting for other potential confounding variables. The 2-month sputum results and other clinical factors were also not associated with final treatment outcome (Table 4).

DISCUSSION

Some studies found the presence of DM can affect treatment outcomes of bacterial TB infection (Alisjahbana *et al*, 2007; Pajankar *et al*, 2008; Jayawardena and Samarathunga, 2008; Chang *et al*, 2011). However, in Thailand, screening for DM is not required in the management of TB. The prevalence of DM among newly diagnosed TB patients in our study was 7%; lower than the prevalence of DM in the general population (8.5%) (International Diabetes Federation, 2014). Previous studies conducted in Peru and Turkey have shown that TB patients with DM are more likely to be female, older, and have other comorbidities, such as hypertension

Table 4
Evaluation of association between selected variables and TB treatment outcome among study subjects (*N*=7,807).

	No. (%)	Treatment response		RR	95%CI	Adjusted RR	95%CI
		Successful No. (%)	Unsuccessful No. (%)				
Total	7,807	6,034 (77)	1,773 (23)				
DM							
No	7,252 (93)	5,569 (77)	1,683 (23)	1		1	
Yes	555 (7)	465 (84)	90 (16)	1.09	0.99-1.20	1.04	0.89-1.20
Sex							
Female	2,155 (28)	1,683 (78)	472 (22)	1			
Male	5,650 (72)	4,350 (77)	1,300 (23)	0.99	0.93-1.04		
Age group (years)							
18-30	895 (11)	730 (82)	165 (18)	1		1	
31-40	1,148 (15)	886 (77)	262 (23)	0.95	0.86-1.04	0.99	0.88-1.12
41-50	1,510 (19)	1,254 (83)	256 (17)	1.02	0.93-1.12	1.00	0.88-1.13
51-60	1,700 (22)	1,438 (85)	262 (15)	1.04	0.95-1.34	1.01	0.90-1.14
>60	2,554 (33)	1,726 (68)	828 (32)	0.83	0.76-0.90	0.96	0.85-1.08
Occupation							
Employed	3,344 (78)	2,636 (79)	708 (21)	1		1	
Unemployed	931 (22)	598 (64)	333 (36)	0.82	0.75-0.89	0.96	0.87-1.06
Lung cavity lesion							
No	4,278 (84)	3,306 (77)	972 (23)	1			
Yes	2,830 (36)	2,242 (79)	588 (21)	1.03	0.97-1.08		
Sputum smear before treatment							
Low <+2	3,190 (41)	2,443 (77)	747 (23)	1			
High ≥+2	4,617 (59)	3,591 (78)	1,026 (22)	1.02	0.97-1.07		
HIV							
Negative	6,330 (88)	5,095 (81)	1,235 (19)	1		1	
Positive	844 (12)	571 (68)	273 (32)	0.84	0.77-0.92	0.89	0.79-1.00
Comorbidity							
No	6,926 (89)	5,431 (78)	1,495 (22)	1			
Yes	881 (11)	603 (68)	278 (32)	0.87	0.80-0.95		
AFB at 2nd month							
Negative	5,371 (85)	4,914 (92)	457 (8)	1		1	
Positive	953 (15)	807 (85)	146 (15)	0.93	0.86-1.00	0.92	0.83-1.03
Drug treatment							
Separate drugs	3,180 (52)	2,517 (79)	663 (21)	1			
Fixed drug combination	2,912(48)	2,243 (77)	669 (23)	0.97	0.92-1.03		
Hospital level							
Primary	5,410 (69)	4,259 (79)	1,151 (21)	1		1	
Secondary	1,418 (18)	1,132 (80)	286 (20)	1.01	0.95-1.08	1.01	0.93-1.10
Tertiary	977 (13)	641 (66)	336 (34)	0.83	0.77-0.91	0.92	0.82-1.05

(Ocal *et al*, 2009; Magee *et al*, 2013). In our study, TB patients with DM were less likely to have a lung cavity lesion. Bacterial grading before treatment was likely to be higher among TB patients with DM. Findings on clinical features of TB among DM patients varied among different studies. In Taiwan a study suggested that lung cavity lesions and a high bacterial grade (≥ 2+) were observed more often among TB patients with DM (Chang *et al*, 2011). A study from Indonesia found pulmonary lesion and sputum mycobacterial load were not significantly different between TB patients with and without DM (Alisjahbana *et al*, 2007). These variable findings for the association between DM and TB treatment outcomes may be due to varying levels of blood sugar control. In our study, nearly all the DM cases had been diagnosed with DM before TB occurrence. Screening for DM does not currently practice in TB management. These DM patients may have had well-controlled blood sugar, causing the DM to have less of an effect on the clinical course and manifestation of TB.

For the total cohort, the overall success rate of TB treatment was 77%. The success rate was slightly higher, but not significantly different, in TB patients with DM (84%), compared with those without DM (77%). The success rate of 77% in our study was lower than the target success rate of 90% suggested by the WHO SEARO (2014). The major cause (about 70%) of unsuccessful in our study was death due to all causes. Confirmed treatment failure was seen in only 2% of all TB cases.

DM and other comorbidities were not significantly associated with the 2-month sputum results or the final treatment outcome. Previous studies have reported varying results for TB treatment outcomes and the presence of DM (Singla *et al*, 2006; Jayawardena and Samarathunga, 2008; Chang *et al*, 2011). The effect of DM on TB treatment response seen in some studies and not others, including our study, may be due to clinical condition of the patient before TB treatment and treatment compliance. The complications of DM depend mainly on how well blood sugar is controlled (Leung *et al*, 2008; Dooley and Chaisson, 2009; Park *et al*, 2012). The blood sugar level may be a better indicator to determine an effect on TB treatment outcome, rather than DM status alone. Since blood sugar level was not included in the TB reporting system, the effect of blood sugar level was not evaluated in our study. We are conducting a prospective study to explore this factor. Compliance to TB treatment is the most important indicator for successful TB treatment (Patel *et al*, 2010). DM is a chronic disease; diabetic patients are usually familiar with the need for compliance with long-term medication. Adherence to treatment may be greater among those with chronic disease, which can lead to a good treatment success rate (Patel *et al*, 2010).

Male sex and older age were associated with a positive sputum test at 2 months. Males may be more likely to have high risk behavior such as smoking or substance abuse. Previous study showed that smoking and alcohol drinking are associated with delay sputum conversion time (Jayawardena and Samarathunga, 2008). Advanced age has been widely shown to be associated with poor TB treatment response (Low *et al*, 2009; Shen *et al*, 2009; Jianzhao *et al*, 2011; Moolphate *et al*, 2011). Adverse effects to TB drugs are more common among older people and may lead to poor treatment outcome during the intensive phase (Storla *et al*, 2008, Shen *et al*, 2009).

We found a cavitary lung lesion,

bacterial grade ≥2+, and HIV co-infection were associated with treatment response only during the intensive phase (first 2 months of treatment), but not with the final treatment success. Patients with severe infection or a high bacterial grade (≥2+) at diagnosis may require a longer duration of intensive treatment (Park *et al*, 2012). However, with effective treatment, the final treatment outcome was not associated with the baseline TB severity in this study.

The type of TB medication was also associated with treatment response in the intensive phase. Patients who received a fixed dose combination were less likely to have sputum smear for AFB negative after 2 months of treatment. A fixed dose combination has been reported to have adverse effects more often than separate drug preparations; therefore, patients may be less likely to tolerate and be compliant with a fixed dose combination medication regimen (Bangalore *et al*, 2007).

There were several limitations in this study. The study was a retrospective evaluation of data in a TB registry. Screening for DM is not a recommended test for treating TB patients. Only those with previously diagnosed DM were included in the study in the diabetic group. This would likely underestimate the prevalence of DM. The prevalence of DM among Thai adults has been reported to be 8.5% (Internation Diabetes Federation, 2014) but the prevalence of DM observed in this study was 7%. This suggests that the underestimation of the prevalence of DM among TB patients in this study may not be large. Previous studies in India and Germany, where the prevalence of diabetes is >20%, suggest DM screening should be performed in the management of TB patients, since a number of patients may remain undiagnosed (Rathmann *et al*, 2003; Balakrishnan *et al*, 2012). We will be conducting a follow-up prospective study with DM screening among all newly diagnosed TB cases to estimate the actual prevalence of DM in the study population.

Our current study included only newly diagnosed sputum smear positive pulmonary tuberculosis patients. Patients with extra-pulmonary TB and those with sputum smear negative pulmonary TB may have different clinical characteristics and outcomes; therefore, the results of this study cannot be applied to them.

This study evaluated the effect of having DM on the outcome of patients with pulmonary TB in northern Thailand, where the prevalence of TB is the highest in Thailand (Bureau of Epidemiology, 2016). Underlying DM was not associated with the TB treatment response in this study. Since our study did not take into consideration for level of diabetes control, the impact of DM control on TB treatment response could not be determined. A further study will be conducted to examine this issue more closely.

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