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Non-communicable diseases increased risk of recurrent tuberculosis in epidemic area of Human Immunodeficiency Virus infection, Thailand

Tipayamongkholgul, M.[1*], Marin, W.[2], Sujirarat, D.[1], Pokaew, P.[3] and Pungrassami, P.[4]
[1]Department of Epidemiology, Faculty of Public Health, Mahidol University, 420/1 Rajavithi Road, Rajthewee, Bangkok, 10400 Thailand
[2]Nan Provincial Office of Public Health, Worrawichai Road, Muang District, Nan Province, 55000 Thailand
[3]Regional Office of Prevention and Control 10, Muang District, Chaingmai Province, 50000 Thailand
[4]Department of Disease Control, Ministry of Public Health, Tiwanon Road, Nonthaburi, 11000 Thailand
[*]Corresponding author e-mail: mathuros.tip@mahidol.ac.th
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Abstract. In recent decades, many countries in Southeast Asia such as Thailand reported an increase of non-communicable diseases (NCDs) and are faced with double burden of NCDs and communicable diseases such as tuberculosis. Recurrent tuberculosis (TB) has been reported in association with Human Immunodeficiency Virus infection (HIV) and diabetes mellitus, however the association between recurrent TB and other NCDs has not been well investigated in this region. A retrospective cohort study was conducted to determine risk of recurrent TB associated with NCDs in an endemic area of HIV in Thailand. Of 1,444 pulmonary TB patients who are registered and had completed a course of treatment during 2003-2012, 99 were diagnosed for recurrent TB (1.954 per 100 TB cases-year). After adjusting for HIV, age, sex, and previous TB treatment outcome, Poisson regression revealed significant risk of recurrent TB among patient with diabetes mellitus (RR=2.76; 95% CI=1.66-4.59), with chronic obstructive pulmonary disease (RR=2.16; 95% CI=1.33-3.49) and with liver cirrhosis (RR=4.45; 95% CI=2.23-8.87). Regular routine screening for TB among patients with liver cirrhosis, diabetes mellitus and chronic obstructive pulmonary disease should be established to improve prevention and control of TB in endemic areas of TB and HIV.

INTRODUCTION

Tuberculosis (TB), an infectious disease, has been a major public health problem in developing countries; it has threatened millions of human lives each year (WHO, 2014). In the 1990s, an epidemic of human immunodeficiency virus infection (HIV) worsened the TB situation worldwide (Fitzgerald *et al.*, 2000). Fortunately, introduction of highly active antiretroviral therapy (HAART) has mitigated the burden of dual infection (TB/HIV) (LÕnnroth *et al.*, 2010). In recent decades, an increased prevalence of non-communicable diseases (NCDs) such as diabetes mellitus (DM) have risen in developing countries and complicated the situation of TB/HIV (Abegunde *et al.*, 2007; Hossain *et al.*, 2007; Laniado-Laborý´n, 2009; Marais *et al.*, 2013; Miranda *et al.*, 2008; Sharma *et al.*, 2013; Stevenson *et al.*, 2007; Van Zyl Smit *et al.*, 2010).

Thailand, although no longer considered a developing country, has large epidemics of TB and HIV (WHO, 2014) particularly in the northern region. In past decades, an increased trend of NCDs has been reported continually (Bureau of policy and strategy, 2013). The prevalence of NCDs and TB was higher for the low socioeconomic population than middle class population (Bureau of policy and strategy, 2013). A growing body of evidence describes a link between TB and

NCDs reported in many countries (Creswell *et al*., 2011; Jeon *et al*., 2008; Lee *et al*., 2013; Lin *et al*., 2007; Lin *et al*., 2014), the association between NCDs and recurrent TB has not been well investigated.

Recurrent TB is a significant threat to TB prevention and control due to its association with drug resistance and being more expensive to treat than first episode TB. Related factors of recurrent TB include having HIV (Lo *et al*., 2011; Panjabi *et al*., 2007), sputum smear remaining positive at 2 months, and poor adherence to TB treatment (Yen *et al*., 2014). In high epidemic areas of both TB and HIV, discovering a link between NCDs and recurrent TB may be significant information for TB management. Therefore, this study aimed to investigate the risk of NCDs on recurrent TB in epidemic areas of TB and HIV.

MATERIALS AND METHODS

Study population and data source

We conducted a retrospective cohort study among pulmonary tuberculosis (PTB) patients aged ≥15 years old in Nan Province, northern Thailand. We retrieved data from TB clinic management programs covering TB patients registered as new smear positive for PTB treatment at 15 public hospitals in Nan Province from 2003-2012. All successfully treated patients were followed-up at least 2 years. Treatment outcome was recorded regarding WHO guideline for tuberculosis treatment (WHO, 2010) as completed treatment (completed the treatment course but did not have result of sputum test at month 5) or cured (completed the treatment course and had negative result of sputum test at month 5). The follow-up time began at completion of previous treatment and ended at date of recurrent TB diagnosis or at the end of the study period. We excluded patients with TB drug resistance and uncompleted comorbidity data. Recurrent TB in this study was not categorized as reinfected or relapsed TB because in Thailand DNA fingerprinting is not a routine practice.

Study variables

Recurrence TB comprised eligible subjects diagnosed with PTB during the study period. Demographic data, clinical factors of TB, comorbidity statuses such as DM, HIV, liver cirrhosis, chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) were diagnosed by a physician and recorded in the TB clinic management program. These exposures were defined at the date of diagnosis or at the end of previous TB treatment. To complete recurrent TB events among eligible cases, we encrypted identification of TB cases to check all TB registries in the north for recurrent TB diagnosis of all eligible subjects and checked death certificates of the Ministry of the Interior to ensure all eligible subjects were still alive at the period of study.

Data analysis

All recurrent cases were calculated at the rate of person per year. Kaplan-Mier was used to compare time to recurrent TB. Poisson regression was used to identify determinants of the TB recurrence rate by calculating rate ratio. The significant level was 0.05. This study was approved by Review Board Institute of Mahidol University (PHMU82/2556).

RESULTS

Of 1,444 eligible cases, follow-up time was at least 2 years. Of 5,065.11 persons-year, the recurrent rate was 1.954 per 100 TB cases-year. The rate of recurrent TB in females was higher than among males (2.020 and 1.926 of 100 TB cases-year, respectively). Of 99 recurrent TB cases, 79.8% occurred within 2 years. Those aged younger than 65 years had a higher rate of recurrence than those aged 65 and older. Regarding previous TB treatment, higher recurrent rates were observed among patients with complete treatment and smear positive at the end of initial phase (Table 1). Patients with comorbidities had recurrent rates higher than those without. Median time to recurrent TB was 1.2 year (IQR=2.2 years).

Table 1. Factor-specific recurrence rate

Factors		Number of recurrent cases	Person-Year	Recurrent rate/ 100 persons-year	P-value
General characteristics					
Sex					0.001
	Female	31	1534.29	2.020	
	Male	68	3530.82	1.926	
Age(Year)					<0.001
	< 65	78	3869.77	2.016	
	≥ 65	21	1195.34	1.757	
Previous TB treatment					
Treatment outcome					0.019
	Complete	42	1592.50	2.637	
	Cure	57	3472.62	1.641	
Sputum conversed at 2 month					0.009
	No	18	447.44	4.023	
	Yes	69	3853.29	1.791	
	Unknown	12	764.38	1.570	
Comorbidity condition					
HIV					0.001
	Positive	30	522.81	5.738	
	Negative	59	3266.01	1.806	
	Unknown	10	1276.29	0.784	
DM					<0.001
	Yes	20	385.44	5.189	
	No	79	4679.68	1.688	
COPD					<0.001
	Yes	22	567.96	3.874	
	No	77	4497.15	1.712	
CKD					0.534
	Yes	1	94.3	1.060	
	No	98	4970.81	1.972	
Liver cirrhosis					<0.001
	Yes	13	100.00	13.000	
	No	86	4965.11	1.732	

Note: HIV is Human immunodeficiency virus infection, DM is diabetes mellitus, COPD is Chronic Obstructive Pulmonary Disease, CKD is Chronic Kidney Disease. P-value by chi-square test

After adjusting for HIV, age, sex, and previous TB treatment outcome, DM, COPD and liver cirrhosis showed significantly increased rates of recurrent TB (Table 2). DM and COPD patients were more likely to develop second episodes of TB compared with non-DM and non-COPD patients by 2.764 times (95% CI = 1.661-4.599) and 2.155 times (95% CI = 2.232-8.870), respectively. Liver cirrhosis presented a strong risk of recurrent TB, RR=4.450 (95% CI 2.232-8.870)

Table 2. Adjusted relative rate of Non-communicable diseases on TB recurrent

Comorbidity	Adj. RR	95% CI of Adj. RR	P-value
DM	2.764	1.661 – 4.599	<0.001
COPD	2.155	1.328 – 3.496	0.002
CKD	2.340	0.322 – 17.015	0.401
Liver cirrhosis	4.450	2.232 – 8.870	<0.001

Note: Adjusted for HIV status, Age, Sex, Sputum conversion, Treatment outcome of previous treatment; P-value by chi-square test and <0.05 is significant.

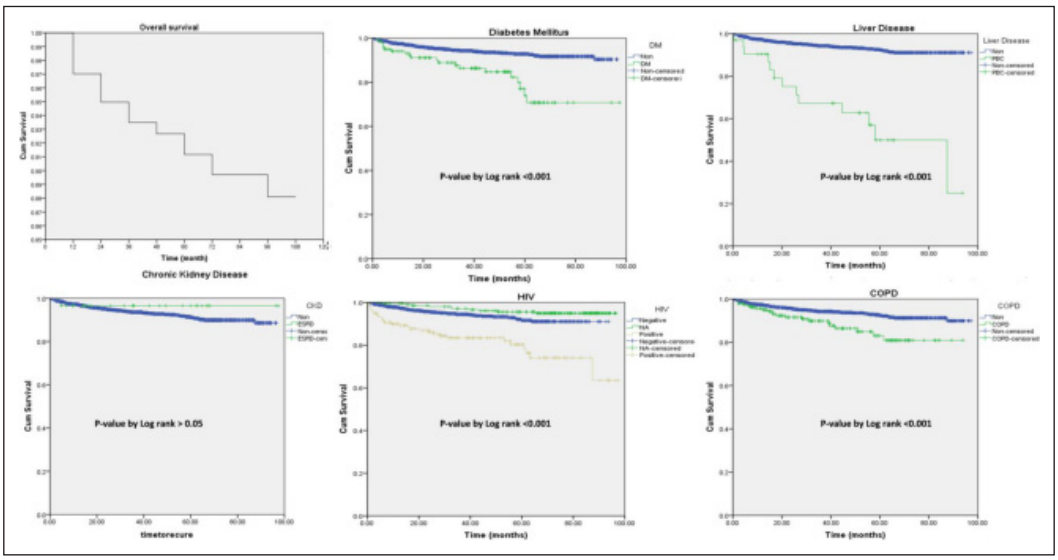

Figure 1. Time of TB recurrent cases by types of comorbidity

DISCUSSION

This retrospective cohort study revealed high rates of recurrent TB (1.954 per 100 TB cases-year), and demonstrated a risk of recurrent TB among NCDs patients. The recurrent rate in this study was ten times higher than studies in Taiwan (Yen *et al.*, 2014) and USA (Pettit *et al.*, 2011) but lower than studies in many developing countries (Fitzgerald *et al.*, 2000; Panjabi *et al.*, 2007). Our study emphasized that DM, COPD and liver cirrhosis increased risk of recurrent TB after adjusting for HIV, age, sex, sputum conversion and treatment outcome of previous TB treatment. Of 99 recurrent cases, 79.8% occurred within 2 years after completing previous TB treatment.

DM increased risk of recurrent TB by 2.764 times (95%CI 1.661-4.599) compared with non-DM patients after adjusting for confounders. The results of the study was consistent with many studies in Europe and Asia (Baker *et al.*, 2012; Jeon & Murray, 2008; Jimenez-Corona *et al.*, 2013; Sharma *et al.*, 2013; Stevenson *et al.*, 2007; Vijay *et al.*, 2012). Reports of recurrent TB were more common among DM patients than non-DM patients (Jeon & Murray, 2008; Stevenson *et al.*, 2007). A study in India reported higher TB incidence among DM patient than non-DM patient by three times (Vijay *et al.*, 2002). Risk of recurrent TB among DM patients could be explained by an association between glucose control and cell-mediated immunity. An experimental study and a mouse model

experiment (Gomez *et al*., 2013; Sugawara *et al*., 2004) revealed dysfunction of cell-mediated immunity which is a main system for tuberculosis pathogen clearance among a hyperglycemia sample and likely led to invasion of TB pathogens to human cells. In contrast to a study in Denmark, a case-control study did not find any association between DM and TB (Leegaard *et al*., 2011). An alteration of DM's effect on TB may relate with the magnitude of TB prevalence. The previous study was conducted in a low TB incidence area (Leegaard *et al*., 2011), different from this present study. Our study emphasized the risk of COPD on recurrent TB (RR = 2.155 (95%CI 1.328–3.496)), consistent with a nested case-control study in the USA (OR= 5.28, 95%CI 1.16–24.04) (Pettit *et al*., 2011). Similarly to two large cohort study in Sweden and Taiwan reported the risk of recurrent TB among COPD patients (Inghammar *et al*., 2010; Lee *et al*., 2013). Increased risk of recurrent TB in COPD patient can be explained by physical condition of COPD patients. First COPD patients mostly have an impaired function of muco-ciliary in airway which compromised body function against TB pathogen and COPD patients are high exposed to cortisol, a risk factor of TB (Sethi & Murphy, 2008).

Our study emphasized the risk of TB among cirrhosis patient, consistency to the cohort study in Taiwan investigating risk of liver cirrhosis on TB (Lin *et al*., 2014). Cirrhosis is related to dysfunction of the cell mediated immune response and decreased production of cytokine, which helps to prevent TB (Schirren *et al*., 1997; Thulstrup *et al*., 2000). The impairment of the cell mediated immune response likely allows TB pathogens to invade human cells and develop TB in cirrhosis patients (Flynn & Ernst, 2000; Kaufmann, 2002; van Crevel *et al*., 2002).

Although our study revealed significant knowledge for TB management, our study had some limitations. We did not collect data of unhealthy lifestyles such as tobacco smoking and alcohol consumption, which previous studies reported in association with TB. Another limitation was we did not have available data to identify reinfected and relapsed TB. Another limitation was unavailable data on other liver diseases such as hepatitis infection.

Based on our knowledge, this study is one of a very few on NCDs and recurrent TB in Asia. Almost all recurrent cases were diagnosed within 2 years. Recurrent rates in this high epidemic area of TB and HIV were very high. DM, COPD and liver cirrhosis increased risk of TB at least twice. An intensive follow-up in first 2 years after the end of previous treatment is needed. Among DM, COPD and alcohol misuse patients, routine TB screening might improve TB prevention and control within the setting double burdened by communicable and NCDs.

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