SCREENING SCHEME DEVELOPMENT FOR ACTIVE TB PREDICTION AMONG HIV-INFECTED PATIENTS

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Abstract. The objective of this study was to develop and evaluate a simple scoring scheme to screen for active tuberculosis (TB) among HIV-infected patients. Two hundred fifty-seven HIV-infected patients were enrolled in the study between April 2009 and May 2010 from Mae Sai District Hospital and Lampang Regional Hospital**.** Participants underwent routine evaluations to diagnose TB. Data collection included demographics, medical history, signs and symptoms and laboratory results. Of the 257 HIV-infected patients enrolled, 66 (25.7%) were diagnosed with active TB. Six variables were statistically significant predictors of active TB ($p<0.05$): BMI ≤19 kg/m^2, cough >2 weeks, shaking chills ≥1 week, not taking antiretroviral drugs, a CD4+ cell count level ≤200 cells/µl, and had a history of TB. A risk score (ranging from 0 to 16) gave a 92.1% sensitivity of being associated with active TB. A low risk score (≤ 2.0), a moderate risk score (3.0-7.0), and a high risk score (>7.0) gave positive likelihood ratios (LHR+) of 0.04 (95%CI 0.01-0.24), 2.56 (95%CI 1.71-3.85), and 11.72 (95%CI 4.91-27.96), respectively. This screening tool may be useful to identify patients who should have further diagnostic testing for TB, but requires further validation before adoption due to the variability of predicting factors and the prevalence of TB in the target population.

Keywords: HIV, tuberculosis, screening tool

INTRODUCTION

Tuberculosis (TB) in Thailand is a public health burden that has been exacerbated by the HIV pandemic. There were 12,890 TB deaths reported in 2009. A main contributing factor to death was HIV co-infection, which was present in 17% of TB deaths; the highest in Southeast Asia, followed by old age (Jittimanee *et al*, 2009; WHO, 2009). The Thai Ministry of Public Health has made an effort to reduce its ranking as number 18 of top 22 countries in the world with a high TB burden. The treatment success rate for Thailand has never reached the WHO target (WHO, 2009). Delayed or missed diagnosis is an important factor contributing to the high rate of transmission and mortality with TB infection.

Like other developing countries with

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a high TB/HIV burden, the diagnosis of active TB in Thailand has depended on clinical features, chest radiographs, AFB smear results and lack of response to non-antimycobacterial antibiotics, instead of relying on TB cultures or biopsy results, which are often unavailable due to the cost of equipment, availability of skilled technicians, or the long waiting time for results (Adjei *et al*, 2003). However, many HIV-infected patients have undiagnosed TB due to the atypical characteristics of TB in immune suppressed HIV patients. Suppression of immunity leads to sensitivity reduction in diagnostics tests and can delay diagnosis (Harries *et al*, 1998).

Early identification and timely adequate treatment are crucial in TB control programs. Intensified case findings (ICF) using the screening tool of a simple questionnaire asking about symptoms related to TB in HIV-infected patients should be developed and validated (The World Health Organization Stop TB Department, 2008). The screening tool is the first step towards making a diagnosis of TB. Previous studies have proposed a constellation of signs and symptoms for TB, including loss of appetite, cough, weight loss, difficulty breathing, fatigue, fever, shaking chills, night sweats, chest pain, abdominal pain, nausea/vomiting; and signs such as temperature >37.5°C (or 38), a body mass index <18.5, lymphadenopathy size, hemoglobin <10, tuberculin skin test positive, hospitalized at enrollment, not on antiretroviral therapy (ART), and chest X-ray abnormality (The World Health Organization Stop TB Department, 2008).

In Thailand, active TB case finding is promoted. All HIV-infected patients receive TB screening. However, for HIV-infected patients, who are more likely to have a suppressed immune response to TB, a specific TB screening tool has not been available. The goal of the present study was to develop a simple scoring scheme and evaluate its performance for identifying suspected active TB among HIV-infected patients. The tool may be used to identify patients who require further evaluation for TB and subsequently facilitate early diagnosis and initiation of treatment.

MATERIALS AND METHODS

HIV-infected patients aged ≥18 years old on the day of enrollment were eligible for the study. They were recruited from the antiretroviral (ARV) clinic, TB clinic, outpatient and inpatient departments regardless of the signs and symptoms of active TB. Two hundred fifty-seven patients were investigated at Mae Sai District Hospital, and Lampang Regional Hospital between April 2009 and May 2010. HIV-infected patients were excluded if they were receiving TB treatment or isoniazid preventive therapy (IPT) during the enrollment period or during one year prior to enrollment. Enrolled HIV-infected patients received routine TB diagnosis evaluations, and blood was sampled for CD4+ cell counts. Available TB diagnostic procedures were performed, including chest radiographs, ultrasound examinations, CT scans, three consecutive sputum collections for AFB smear and sputum cultures. An active TB case was defined as positivity of either smear or culture of sputum or other specimens for TB, or was based on positive clinical or radiological response to anti-TB treatment, or characteristic histology seen on biopsy specimens. Non-TB diseases were diagnosed using standard clinical practices.

Patients who gave informed consent were interviewed by trained staff using a specific case record form. Data collected were age, sex, Body Mass Index (BMI),

and type of employment. Clinical data included medical history, history of TB diagnosis, history of TB exposure, history of opportunistic diseases, and treatment with ARV drugs. Duration of signs and symptoms were assessed for cough, cough with sputum, hemoptysis, fever, diarrhea, weight loss, night sweats, dyspnea, chest pain, nausea, vomiting, abdominal pain, loss of appetite, fatigue, shaking chills, and size of lymphadenopathy. Laboratory tests obtained on the day of enrollment were white blood cell (WBC) counts, hemoglobins, hematocrits, platelet counts, and CD4+ cell counts. Chest radiography results were recorded. All enrolled patients were followed for two months.

The study was approved by two institutional review boards: the Faculty of Medicine, Chiang Mai University, and Lampang Regional Hospital.

Statistical analysis

Statistical analysis used a two-stage procedure. The first stage compared the characteristics of HIV-infected patients with and without active TB. Either a chi-square or Fisher's exact test were used for categorical data analysis. *T*-tests or rank-sum tests were performed to analyze continuous data. Predictors with a *p*-value <0.25 were selected for second stage analysis. Multivariable logistic regression with backward elimination was used for second stage analysis to identify independent predictors. Only variables which reached statistical significance ($p<0.05$) were included in the final evaluation. Each variable was weighted by an odds ratio (OR) coefficient, and transformed to an item score. Cut-off points were determined by statistical significance and the results of the receiver operating characteristic curve (ROC) value. The ability of the "total score" to predict TB was determined by a relative operating characteristic (ROC) plot. The likelihood ratio for a positive result was presented with cut-off points for the total score to categorize patients into low, moderate and high risk groups. Statistical significance level was set at $p<0.05$ for type I error.

Estimation of samples was based on the result of a previous study with the smallest OR of 9.6 and 17% in the non-TB comparison group (Mohammed *et al*, 2004). The sample size needed to ensure an adequate power of 90% and a significance <0.05 was 18 active TB patients. One hundred six HIV-infected patients were needed with a presumed active TB prevalence in the study population of 17% (WHO, 2009). To compensate for missing data, an additional 20% more cases was included. Therefore, at least 128 HIV-infected patients were required for the present study.

RESULTS

Of the 257 eligible HIV-infected patients included in the final analysis, 66 patients (25.7%) were diagnosed with active TB. Of whom, 52 patients (78.8%) had pulmonary TB (PTB) and 14 patients (21.2%) had extra-pulmonary TB (ETB). The non-TB group was comprised of one patient with asthma, 19 with bronchitis, one with lung cancer, one with fever of unknown origin, one with a lung abscess, one with neuritis, 6 with PCP, one with penicilinosis, 6 with pneumonia, and 153 without chest disease.

Comparing the demographic characteristics of the patients with active TB and without active TB, the former group had a lower mean BMI, were more likely to be unemployed, and were less likely to have received ARV therapy. Gender, age, co-morbidity and history of opportunistic

Table 1
Characteristics of HIV infected patients (*N*=257).

Characteristic	Subjects with TB (*n*=66)	Subjects without TB (*n*=191)	*p*-value
Male	35 (53.9)	92 (48.4)	0.475
Age, mean (SD) (years)	39.8 (9.8)	37.5 (11.1)	0.125
BMI, mean (SD) (kg/m^2)	19.1 (3.4)	21.0 (3.0)	<0.001
Other nationality[a]	26 (43.3)	58 (31.5)	0.169
Unemployment	16 (24.2)	16 (8.5)	0.001
Occupation with little skill	37 (62.7)	162 (90.5)	<0.001
Any co-morbidity[a]	5 (7.6)	19 (10.0)	0.561
Diabetes mellitus	1 (1.5)	7 (3.7)	0.684
Hypertension	7 (3.7)	0 (0)	0.196
Liver disease	1 (1.5)	2 (1.1)	0.764
Lung disease	1 (1.5)	5 (2.6)	0.606
Other underlying diseases	2 (3.0)	2 (1.1)	0.274
ARV therapy received	20 (30.3)	151 (79.1)	<0.001
History of opportunisitic infection (OI)	10 (15.4)	41 (21.5)	0.289
Medication use for OI	40 (61.5)	100 (52.4)	0.199
History of TB diagnosis	9 (13.6)	18 (9.5)	0.233
History of TB exposure[a]	7 (10.6)	7 (3.7)	0.054
Abnormal chest features[a]	31 (77.5)	38 (23.9)	<0.001
Cavity	4 (10.5)	4 (2.5)	0.046
Pleural	1 (2.7)	2 (1.3)	0.468
Miliary	2 (5.4)	1 (0.6)	0.092
Mass or nodule	0 (0.0)	1 (0.6)	1.000
Hilar	3 (8.1)	1 (0.6)	0.022
CD4+ cell count, cells/µl			
Median (range)[b]	90 (4-559)	371.5 (6-1,293)	<0.001
<200	31 (73.8)	43 (24.7)	<0.001
WBC count, 1,000 cells/dl[b]	6.3 (1-23.2)	6.1 (1-24)	<0.001
Hemoglobin level, g/dl [b]	10.0 (4.4-14.7)	12.0 (2.1-17.1)	0.835
Hematocrit, median (range)[b]	31.0 (2.6-45.7)	37.6 (8.5-49.9)	0.002
Platelet count, median cells x 1,000/ml (range)[b]	267 (69-612)	315 (28-912)	0.066

[a] Fisher's exact test; [b] Rank-sum test

infection were not statistically different between the two groups. The active TB group had a significantly larger number of abnormal chest radiographs. They also had a significantly higher median WBC count, a lower mean CD4+ cell count and a lower mean hematocrit level (Table 1).

Patients with TB had significantly more days with cough, cough with sputum, hemoptysis, fever, diarrhea, weight loss, night sweats, dyspnea, chest pain, nausea, vomiting, abdominal pain, loss of appetite, fatigue, shaking chills, and greater lymphadenopathy size (Table 2).

Table 2
Signs and symptoms (*N*=257).

Signs and symptoms[a] (days)	Subjects with TB (*n*=66)	Subjects without TB (*n*=191)	*p*-value[b]
Cough duration	30.8 ± 53.1	4.6 ± 15.6	<0.001
Median (range)	14.0 (0-365)	0 (0-150)	
Cough with sputum	23.6 ± 52.4	2.3 ± 7.0	<0.001
Median (range)	7 (0-365)	0 (0-60)	
Hemoptysis	1.4 ± 5.5	0.1 ± 1.5	<0.001
Median (range)	0 (0-30)	0 (0-21)	
Fever	11.0 ± 18.3	1.6 ± 6.9	<0.001
Median (range)	0 (0-90)	3 (0-60)	
Diarrhea	1.1 ± 3.0	0.7 ± 4.8	0.001
Median (range)	0 (0-14)	0 (0-60)	
Weight loss	21.0 ± 31.6	5.7 ± 18.2	<0.001
Median (range)	7.5 (0-150)	0 (0-150)	
Night sweats	5.8 ± 17.3	0.9 ± 4.9	0.004
Median (range)	0 (0-120)	0 (0-60)	
Dyspnea	10.4 ± 46.3	1.4 ± 4.5	<0.001
Median (range)	0 (0-365)	0 (0-30)	
Chest pain	10.9 ± 26.3	1.3 ± 5.6	<0.001
Median (range)	2 (0-180)	0 (0-60)	
Nausea/vomiting	1.9 ± 7.9	0.2 ± 1.1	0.009
Median (range)	0 (0-60)	0 (0-10)	
Abdominal pain	2.1 ± 7.3	0.8 ± 3.9	<0.018
Median (range)	0 (0-45)	0 (0-30)	
Loss of appetite	9.0 ± 19.5	1.9 ± 5.6	<0.001
Median (range)	0 (0-90)	0 (0-30)	
Fatigue	18.1 ± 34.1	2.2 ± 7.3	<0.001
Median (range)	3 (0-150)	0 (0-60)	
Shaking chills	5.1 ± 12.5	0.7 ± 4.9	<0.001
Median (range)	0 (0-60)	0 (0-60)	
Lymphadenopathy size (cm)	0.4 ± 1.3	0.0 ± 0.1	<0.001
Median (range)	0 (0-5)	0 (0-1)	

[a] Mean ± SD otherwise indicated; [b]Rank-sum test

Significantly different characteristics were selected as potential predictors for further evaluation. Using multivariable backward elimination logistic regression, 6 variables were retained in the final model. BMI ≤19 kg/m^2, cough >2 weeks, shaking chills ≥1 week, not receiving ARV drug, having a CD4+ cell count level ≤200 cells/µl, and having a history of TB were found to be statistically significant predictors of active TB($p<0.05$) (Table 3). A risk score for each variable was calculated from coefficients from the multivariable logistic model and transformed by dividing with the smallest coefficient from CD4+ cell count (1.33). A final score was

Table 3
Logistic regression coefficient, adjusted OR and 95%CI of selected predictor for active TB.

Predictors	Coefficient	Adjusted OR (95%CI)	*p*-value
BMI			0.008
≥19.0	-	1.0	
<19.0	1.38	3.99 (1.45-11.03)	
Cough			0.002
≤2 weeks	-	1	
>2 weeks	1.82	6.16 (1.98-19.18)	
Shaking chills			0.016
<1 week	-	1.0	
≥1 week	1.94	6.95 (1.43-33.75)	
ARV received			<0.001
Yes	-	1	
No	1.85	6.37 (2.27-17.83)	
CD4+ cell count level			0.011
>200	-	1.0	
≤200	1.33	3.79 (1.36-10.52)	
History of TB			0.001
No	-	1.0	
Yes	2.23	9.31 (2.64-32.78)	

Table 4
Item scoring scheme for predictors of active TB derived from logistic regression coefficient.

Predictors	Coefficient	Transformed score	Assigned score
BMI			
≥19.0	-	0	0
<19.0	1.38	1.04	2.0
Cough			
≤2 weeks	-	0	0
>2 weeks	1.82	1.37	3.0
Shaking chills			
<1 week	-	0	0
≥1 week	1.94	1.46	3.0
ARV received			
Yes	-	0	0
No	1.85	1.39	3.0
CD4+ cell count level			
>200	-	0	0
≤200	1.33	1	2.0
History of TB diagnosis			
No	-	0	0
Yes	2.23	1.68	3.0

Table 5
Risk category among patients with or without TB, LHR+ and 95% CI (ROC=0.897)

Risk category	TB *n* (%)		LHR+(95% CI)	*p*-value
	Yes	No		
Low (≤2)	1 (2.6)	125 (74.8)	0.04 (0.01-0.24)	<0.001
Moderate (3-7)	21 (55.3)	36 (21.6)	2.56 (1.71-3.85)	<0.001
High (>7)	16 (42.1)	6 (3.6)	11.72 (4.91-27.96)	<0.001

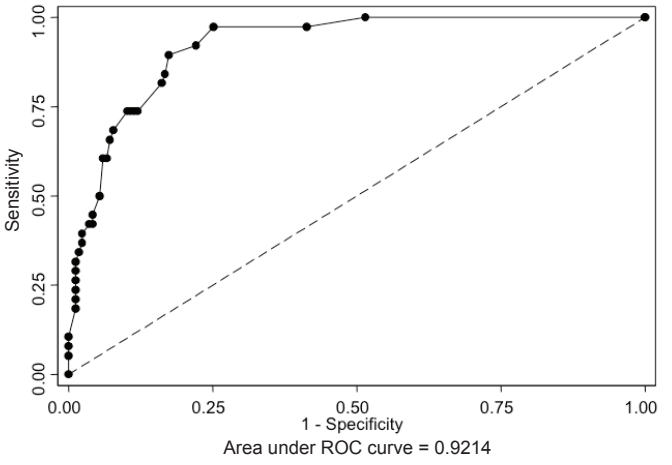

Fig 1–Receiver operating characteristic (ROC) curve of risk for TB predicted by risk scoring scheme.

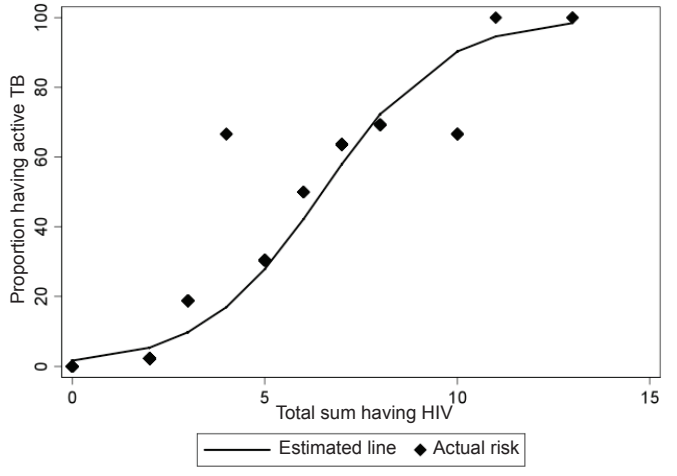

Fig 2–Actual score predicted risk (dots) and logistic estimated risk (solid line) for TB using the total score.

determined by rounding up to the nearest whole number (Table 4). Total scores ranged from 0 to 16. The scoring scheme gave the probability of detecting active TB of 92.1% as the area under the ROC curve (Fig 1). The total scores were then categorized into low risk (≤2), moderate risk (3-7), and high risk (>7). The likelihood ratio of positivity (LHR+) in low risk subjects was 0.04 (95%CI 0.01-0.24), in moderate risk patients was 2.56 (95%CI 1.71-3.85), and in high risk patients was 11.72 (95%CI 4.91-27.96) (Table 5). The proportion of participants with active TB *versus* the total score was plotted, showing the estimated risk corresponded well with the actual risk (Fig 2).

DISCUSSION

In this study, the best combination of predictors of active TB in HIV infected patients were BMI ≤19 kg/m^2, cough >2 weeks, shaking chills ≥1 week, not receiving ARV drugs, a CD4+ cell count level ≤200 cells/µl and a history of TB. A BMI ≤18 kg/m^2 (Day *et al*, 2006), and cough >2 weeks were similar findings to that of

Mohammed *et al* (2004). Coughing duration with the most controversial predictor, and has been found inconsistently across studies (Day *et al*, 2006; Were *et al*, 2009; Cain *et al*, 2010). Some predictors found associated with active TB in other studies but did not reach significance in this study were weight loss (Mohammed *et al*, 2004; Day *et al*, 2006), night sweats (Mohammed *et al*, 2004; Day *et al*, 2006; Cain *et al*, 2010), fever (Mohammed *et al*, 2004; Were *et al*, 2009; Cain *et al*, 2010), lymphadenopathy (Were *et al*, 2009), and general weakness (Were *et al*, 2009). An abnormal chest X-ray has been used as a predictor (Were *et al*, 2009; Cain *et al*, 2010) and helped to increase the sensitivity of active TB detection in some studies. However, we excluded an abnormal chest X-ray as a predictor because having it was one of the criteria defining active TB, which could introduce incorporation bias. Discrepancy in the result could be due to differences in study populations. Three medical history indicators-receiving ARV therapy, having a CD4+ cell count level <200 and having a history of TB selected for screening in this current study were not predictors but were used for stratification of signs and symptoms.

Most studies chose signs and symptoms giving the best diagnostic value for predicting active TB in HIV infected patients: sensitivity, specificity, PPV, NPV, or LHR+. One recent study (Cain *et al*, 2010) recommended the optimal number of predictors is 3. Unlike other similar studies, we scored potential predictors, elements of patient characteristics, signs and symptoms, and medical history, by weighting each predictor with the probability of forecasting active TB. We finally calculated a total score giving good predictivity demonstrated by the area under an ROC curve of a total score of 92.1%. We then defined the cut-off points to divide patients into low, moderate, and high risk groups for having active TB, with an accuracy of 89%. This scoring scheme can effectively identify patients who require further evaluation with the use of specific diagnostic tests, or "intention-to-diagnose", a high risk group. Patients in the low risk group (61.5%) need not be investigated further resulting in a cost savings.

One limitation of the current study was not consistently using the gold standard for diagnosing TB by a positive culture for *M. tuberculosis* or positive biopsy results. We used standard procedures available in Thailand, which are clinical and radiological features, AFB smears and lack of response to non-antimycobacterial antibiotics due to limited availability of cultures in some areas. The high positive predictive value of the model reflects discrepancy between our study population and other similar studies. TB/HIV co-infected patients used in studies often present with advance stage disease. The prevalence of active TB in the study area is the highest in Thailand. Thus, the generalizability of this study may be limited. The screening tool developed may be used in HIV infected adults in areas similar to our study. The tool should be validated in other health care facilities before application because of variability of predicting factors and the prevalence of TB in the target population.

A strength of this study was that it prospectively followed patients for up to two months. The diagnosis of TB is less prone to misclassification bias. There is the possibility of other non-tuberculous mycobacteria (NTM) contamination because the TB diagnostic criteria used did not exclude NTM. Even using response to antimycobacterial treatment does not

exclude NTM, especially with microbacterium avium complex (MAC) infection. However, NTM contamination is unlikely due to its low incidence (less than 1%) in the study setting. None of the TB cases had a change in diagnosis after two months due to MAC infection.

The screening tool predicted active TB using a simple scoring scheme with six predictors. The accuracy of the scoring scheme was high for categorizing patients into low, moderate, and high risk groups. The tool is easily administered by medical staff using simple questions.

The screening tool may be useful for physicians to identify patients who require further evaluation using specific diagnostic tests for TB. Appropriateness and frequency of use of the screening tool should be determined in future research.

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