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Thai drug-resistant tuberculosis predictive scores

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ABSTRACT

Introduction: This study aimed to determine the prevalence and risk factors of drug-resistant tuberculosis (TB), and to develop a diagnostic algorithm for newly-diagnosed TB patients.

Methods: This is a retrospective medical chart review of 290 patients who were diagnosed with bacteriological-proven pulmonary TB between 2000 and 2006 in Ramathibodi Hospital, Thailand. Patient characteristics, radiological and microbiological findings, as well as a history of previous TB disease and treatment, were included in the analysis of predictive factors of drug resistance. Predictive scores were derived from statistically significant factors at the cut-off point of the receiver-operating curve that yielded the best area under the curve.

Results: The resistance rate to each of these drugs among 290 patients was: isoniazid, 6.9 percent; rifampicin, 4.5 percent; either isoniazid or rifampicin, 9.0 percent; and multidrug resistance, 2.4 percent. Far advanced TB was an independent risk factor for isoniazid resistance. Rifampicin resistance was associated with recurrent TB within six months after the completion of treatment and prior incomplete TB treatment. A drug-resistant TB predictive score of either isoniazid or rifampicin resistance was developed based on the aforementioned factors. The cut-off score of greater than or equal to 3 yielded the least error of classification in differentiating patients with the resistant strain from those with the susceptible strain at a sensitivity of 57.7 percent, a specificity of 67.8 percent, a positive predictive value of 15 percent and a negative predictive value of 94.2 percent.

Conclusion: Our study suggested a drug-resistant TB predictive score for the exclusion of either isoniazid or rifampicin resistance, and provides a decisional guide for the clinician on whether to send a patient's respiratory specimen for sputum culture and drug susceptibility testing.

Keywords: drug-resistant tuberculosis, drug susceptibility testing, tuberculosis

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INTRODUCTION

Tuberculosis (TB) remains a global public health concern. In Thailand, the incidence of TB has been rising over the past decade due to the dramatic increase in the human immunodeficiency virus (HIV)-infected population.[1] In 2003, the incidence rate of all TB cases and new smear-positive pulmonary TB cases was 142 and 63 cases/100,000 population, respectively,[2] where the prevalence rate of HIV seropositivity was 8.7%. Despite this, the prevalence of drug-resistant TB (DR-TB) has declined. Based on the national surveillance for drug resistance, multidrug-resistant (MDR) TB has decreased from 2.02% in 1997 to 0.9% in 2003.[2] Similar results were also found for each antituberculous drug during this period of time.[2-5] The reduction in DR-TB might be explained by an improvement in patient compliance and strict adherence to the treatment programme. The standard short-course chemotherapy over a six-month period has been recommended to every newly diagnosed TB patient and treatment is directly observed by the healthcare worker, village health volunteer or supervised family member, on the basis of Directly Observed Treatment, Short-course (DOTS).[6] The Ministry of Public Health relaunched the National Tuberculosis Programme, through which DOTS has been adopted since 1996, and countrywide DOTS coverage was achieved in 2001. The cure rate for TB in Thailand was approximately 76% in 2003, slight lower than the World Health Organisation (WHO) target cure rate of 85%. Even though the number of DR-TB cases is low and decreasing, it may impact the outcomes of standardised short-course anti-TB chemotherapy. Either isoniazid or rifampicin resistance have been reported to be risk factors for relapse and treatment failure.[7-9] In Thailand, Yoshiyama et al found that 11 out of 13 cases resistant to isoniazid or rifampicin at first registration became MDR after treatment with standardised short-course chemotherapy.[10]

Standard recommendations for mycobacterial culture

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and drug susceptibility testing (DST) are still conflicting. The American Thoracic Society (ATS), Center for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) recommend that all patients suspected of having TB should have appropriate specimens collected for microscopic examination, and mycobacterial culture and DST for isoniazid, rifampicin and ethambutol should be performed on a positive initial culture.[11] In contrast, the WHO and International Union against Tuberculosis and Lung Disease (IUATLD), which document target countries in which mycobacterial culture and susceptibility testing and radiographical examinations are not widely available, do not recommend routine susceptibility testing for new patients because of cost, limited applicability and a lack of facilities.[12,13] The Thai guidelines for the diagnosis and treatment of TB[14], adopted closely from the WHO's guidelines for the treatment of TB, also does not recommend routine susceptibility testing for new patients. The identification of risk factors for DR-TB would be useful and DST should be performed in selected patients who carry any of these factors. We therefore sought to determine the prevalence and risk factors for DR-TB, and develop a diagnostic algorithm for patients with newly-diagnosed TB.

METHODS

We retrospectively analysed all consecutive patients who were ≥ 15 years of age with *Mycobacterium* (*M.*) *tuberculosis* culture-positive from respiratory specimens including sputum and bronchoalveolar lavage fluid, and who received treatment at Ramathibodi Hospital, a tertiary university referral hospital in Bangkok, Thailand, between January 1, 2000 and November 30, 2006. During this time period, the sending of respiratory specimens for culture was based on the physicians' judgment. All cases of TB included in our study had culture specimens collected at the beginning of treatment. Cases of culture-negative TB were excluded. Only one positive culture specimen for each patient was included. The study protocol was approved by the Ethics Committee on Human Experimentation at the Ramathibodi Hospital, Thailand.

Respiratory specimens were decontaminated by the addition of N-acetyl-L-cysteine, 5% NaOH and 2.9% sodium citrate, centrifuged, and then inoculated on Löwenstein-Jensen media. Cultures were incubated in air at 37°C. The specimens were then examined on a twice-weekly basis until a growth was detected. Cultures were reported as negative if there was no growth after eight weeks. Cultures with a visible growth were tested for definitive biochemical identification at the species level. Once identified, all *M. tuberculosis* isolates were prepared for DST. Susceptibility testing was performed for isoniazid, rifampicin, ethambutol, ofloxacin and streptomycin, using the absolute concentration method on Middlebrook 7H9 medium. Susceptibility was determined on the basis of the following drugs and concentrations: minimum inhibitory concentration (MIC) of isoniazid, 0.5 μg/ml; MIC of rifampicin, 1.0 μg/ml; MIC of ethambutol, 2.0 μg/ml; MIC of ofloxacin, 2.0 μg/ml and MIC of streptomycin, 2.0 μg/ml. Pyrazinamide susceptibility was not tested.

Clinical data was collected via chart reviews that included the following: general demographical information, HIV status, underlying comorbid condition, history of previous TB disease and treatment, sputum acid fast bacilli (AFB) smear result, chest radiographical finding and DST results for each drug. The radiographical extent of disease was classified according to the criteria established by the National Tuberculosis and Respiratory Disease Association.[15] Subjects were classified as having minimal disease if lesions were non-cavitary lesions, of slight to moderate density, and involved a small part of one or both lungs. The total extent was required to be less than the volume of one lung above the second chondrosternal junction and the spine of the fourth or body of the fifth thoracic vertebrae. Subjects were classified as having moderately advanced disease if they had more than minimal disease but had a total extent of slight or moderately dense lesions limited to the total volume of one lung, and that of dense lesions limited to one-third the volume of one lung. Cavitary lesions were required to be < 4 cm in diameter. Subjects were classified as having far advanced disease if lesions were more extensive than the moderately advanced disease.

Statistical analyses were performed using the Statisical Package for Social Sciences 11.5 (SPSS Inc, Chicago, IL, USA). All values were expressed as mean ± standard deviation for continuous variables, and as frequencies for categorical variables. Between-group comparisons for continuous variables were performed using the Student's two-tailed *t*-test or nonparametric Mann-Whitney U-test when appropriate. Chi-square and Fisher's exact tests were used to analyse differences among categorical variables. We then included variables that were statistically significantly associated with drug resistance in univariate analysis in a multivariate logistic regression model. All statistical tests were two-sided, and $p < 0.05$ was considered to be statistically significant.

In order to create a simple diagnostic tool to identify DR-TB patients, a predictive score was developed from the significant variables identified by multivariate analysis according to the regression coefficients in the final model, with one point corresponding to a value close to the

Table I. Characteristics of 290 patients with culture-positive tuberculosis and comparisons between drug-susceptible and drug-resistant tuberculosis cases tested for resistance to isoniazid and rifampicin.

Variables*	Total	Isoniazid			Rifampicin		
		Sensitive	Resistant	p-value	Sensitive	Resistant	p-value
Age† (years)	47.7 (16.9)	47.5 (16.8)	51.0 (18.9)	0.373	47.8 (17.2)	45.5 (10.6)	0.472
Gender, male	153 (52.8)	143 (93.5)	10 (6.5)	0.798	145 (94.8)	8 (5.2)	0.516
Region							
Bangkok	189 (65.2)	175 (92.6)	14 (7.4)	0.721	180 (95.2)	9 (4.8)	0.724
North	16 (5.5)	14 (87.5)	2 (12.5)		16 (100.0)	0 (0.0)	
Central	43 (14.8)	40 (93.0)	3 (7.0)		40 (93.0)	3 (7.0)	
Northeast	21 (7.2)	21 (100.0)	0 (0.0)		21 (100.0)	0 (0.0)	
East	6 (2.1)	6 (100.0)	0 (0.0)		6 (100.0)	0 (0.0)	
South	15 (5.2)	14 (93.3)	1 (6.7)		14 (93.3)	1 (6.7)	
Underlying disease							
Diabetes mellitus	42 (14.5)	39 (92.9)	3 (7.1)	0.946	41 (97.6)	1 (2.4)	0.477
Chronic lung disease	29 (10.0)	26 (89.7)	3 (10.3)	0.440	28 (96.6)	1 (3.4)	0.777
Chronic kidney disease	13 (4.5)	12 (92.3)	1 (7.7)	0.911	12 (92.3)	1 (7.7)	0.570
Cirrhosis	4 (1.4)	4 (100.0)	0 (0.0)	0.584	4 (100.0)	0 (0.0)	0.663
HIV serology							
Positive	45 (15.5)	42 (93.3)	3 (6.7)	0.584	42 (93.3)	3 (6.7)	0.451
Negative	158 (54.5)	149 (94.3)	9 (5.7)		150 (94.9)	8 (5.1)	
Unknown	87 (30.0)	79 (90.8)	8 (9.2)		85 (97.7)	2 (2.3)	
Systemic steroid use	26 (9.0)	24 (92.3)	2 (7.7)	0.867	25 (96.2)	1 (3.8)	0.869
Smoking	98 (33.8)	91 (92.9)	7 (7.7)	0.906	93 (94.9)	5 (5.1)	0.716
Alcohol consumption							
Teetotaller	209 (72.0)	194 (92.8)	15 (7.2)	0.856	201 (96.2)	8 (3.8)	0.153
Social drinker	24 (8.3)	23 (95.8)	1 (4.2)		24 (100.0)	0 (0.0)	
Moderate to heavy drinker	57 (19.7)	53 (93.0)	4 (7.0)		52 (91.2)	5 (8.8)	
History of contact tuberculosis	24 (8.3)	22 (91.7)	2 (8.3)	0.817	24 (100.0)	0 (0.0)	0.263
Injecting drug use	8 (2.8)	8 (100.0)	0 (0.0)	0.435	7 (87.5)	1 (12.5)	0.266
History of imprisonment	4 (1.4)	4 (100.0)	0 (0.0)	0.584	4 (100.0)	0 (0.0)	0.663
Medical personnel	7 (2.4)	6 (85.7)	1 (14.3)	0.435	6 (85.7)	1 (14.3)	0.205
Prior tuberculosis	45 (15.5)	40 (88.9)	5 (11.1)	0.225	40 (88.9)	5 (11.1)	0.019
Prior tuberculosis treatment							
Complete	33 (73.3)	30 (90.9)	3 (9.1)	0.627	32 (97.0)	1 (3.0)	0.014
Incomplete							
Treatment < 2 mths	4 (8.9)	3 (75.0)	1 (25.0)		3 (75.0)	1 (25.0)	
Treatment ≥ 2 mths	8 (17.8)	7 (87.5)	1 (12.5)		5 (62.5)	3 (37.5)	
Relapse after previous treatment							
≤ 6 mths	6 (13.3)	5 (83.3)	1 (16.7)	0.405	4 (66.7)	2 (33.3)	0.001
> 6 mths	39 (86.7)	35 (89.7)	4 (10.3)		36 (92.3)	3 (7.7)	
Prior drug susceptibility testing							
Unknown	43 (95.6)	38 (88.4)	5 (11.6)	0.391	39 (90.7)	4 (9.3)	0.002
Sensitive	2 (4.4)	2 (100.0)	0 (0.0)		1 (50.0)	1 (50.0)	
Resistant	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Sputum acid fast bacilli result							
Negative	107 (36.9)	101 (94.4)	6 (5.6)	0.217	102 (95.3)	5 (4.7)	0.863
Positive 1–2+	107 (36.9)	95 (88.8)	12 (11.2)		101 (94.4)	6 (5.6)	
Positive 3–4+	59 (20.3)	57 (96.6)	2 (3.4)		57 (96.6)	2 (3.4)	
Could not collect	12 (4.1)	12 (100.0)	0 (0.0)		12 (100.0)	0 (0.0)	
Not collected	5 (1.7)	5 (100.0)	0 (0.0)		5 (100.0)	0 (0.0)	
Chest radiograph							
Cavity	91 (31.4)	83 (91.2)	8 (8.8)	0.620	88 (96.7)	3 (3.3)	0.709
Extent of lesion							
Minimal	83 (28.6)	80 (96.4)	3 (3.6)	0.048	79 (95.2)	4 (4.8)	0.043
Moderately advanced	129 (44.5)	122 (94.6)	7 (5.4)		127 (98.4)	2 (1.6)	
Far advanced	78 (26.9)	68 (87.2)	10 (12.8)		71 (91.0)	7 (9.0)	

* Data is expressed as no. (%) unless otherwise indicated.
† Age is expressed as mean ± standard deviation.

smallest regression coefficient and serving as the lowest common denominator for assigning point values for the score items. We then computed the score for each patient, performed a receiver operating characteristic (ROC) curve analysis, and computed the area under the ROC curve and its corresponding 95% confidence interval (CI). Finally, we chose the cut-off value that discriminated among the drug susceptible and resistant strains by comparison of the score's sensitivity, specificity and positive and negative predictive values across different cut-off scores.

Table II. Drug susceptibility testing in *Mycobacterium tuberculosis* isolates (n = 290), comparing between primary and acquired drug resistance.

Drug	No. (%) total resistance	No. (%) of new cases	No. (%) with history of previous treatment	p-value
Any resistance to:				
Isoniazid	20 (6.9)	15 (6.1)	5 (11.1)	0.225
Rifampicin	13 (4.5)	8 (3.3)	5 (11.1)	0.019
Ethambutol	14 (4.8)	10 (4.1)	4 (8.9)	0.167
Streptomycin	18 (6.2)	12 (4.9)	6 (13.3)	0.031
Ofloxacin	4 (1.4)	4 (1.6)	0 (0.0)	0.388
Isoniazid or rifampicin	26 (9.0)	18 (7.3)	8 (17.8)	0.024
Multidrug resistance*	7 (2.4)	5 (2.0)	2 (4.4)	0.334
Resistance to:				
1 drug	23 (7.9)	15 (6.1)	8 (17.8)	0.015
2 drugs	9 (3.1)	5 (2.0)	4 (8.9)	
3 drugs	1 (0.3)	1 (0.4)	0 (0.0)	
4 drugs	5 (1.7)	4 (1.6)	1 (2.2)	
5 drugs	1 (0.3)	1 (0.4)	0 (0.0)	
Any drug resistance	39 (13.4)	26 (10.6)	13 (28.9)	0.001

Any resistance: resistance to stated drug with or without resistance to other drugs.
*Resistance to at least isoniazid and rifampicin.

RESULTS

A total of 12,429 respiratory specimens were sent for mycobacterial culture during the period between January 1, 2000 and November 30, 2006. Of these, 290 culture-proven TB patients were diagnosed by at least one positive culture specimen. Each patient provided only one positive culture specimen for analysis. The characteristics of these patients are summarised in Table I. Of these, 153 were male. The mean age of the patients in the cohort was 47.7 years. 203 cases (70.0%) had been through a HIV-serology test and 45 cases (15.5%) were reported to have a HIV infection. 45 patients (15.5%) had a history of previous treatment. Of these 45 patients, 33 (73.3%) had prior complete treatment. Only six cases relapsed within six months after previous treatment. Known prior DST as resistance for any anti-TB medication was not found in our patients.

Of the total number of culture-positive cases, specimens were sent for AFB stain in 273 (94.1%) cases, where 166 (60.8%) had microscopically-detected AFB. The incidence of smear-negative, culture-positive TB in our study was 39.2%. The radiographical extent of disease, classified by the National Tuberculosis and Respiratory Disease Association's criteria,[15] included 83 (28.6%) cases of minimal disease, 129 (44.5%) of moderately advanced disease and 78 (26.9%) cases of far advanced disease. Cavitary lesions were found in 91 (31.4%) patients.

Detailed drug susceptibility results of all subjects are shown in Table II. 251 (86.6%) had TB that was susceptible to all drugs, and 39 (13.4%) were resistant to at least one antimicrobial agent. Of these patients with resistance, 20 (6.9%) showed resistance to isoniazid, 13 (4.5%) showed resistance to rifampicin, 26 (9.0%) showed resistance to isoniazid or rifampicin, and seven (2.4%) were resistant to at least isoniazid and rifampicin. Five (71%) of seven MDR-TB isolates were susceptible to ofloxacin, whereas only two (29%) were susceptible to streptomycin.

The results of the sensitivity tests in the patients with TB classified according to their history of previous treatment are also shown in Table II. The prevalence of rifampicin resistance was significantly different between the patients with a history and those without a history of previous treatment (OR 3.70; 95% CI 1.15–11.89; p = 0.019). However, this difference was not found in isoniazid (OR 1.92; 95% CI 0.66–5.57; p = 0.225). Furthermore, patients with a history of previous treatment had a markedly higher rate of resistance to any drug (OR 3.42; 95% CI 1.59–7.33; p = 0.001).

Statistical analyses were performed to identify clinical features associated with either isoniazid or rifampicin resistance. For isoniazid, far advanced disease was only an independent factor associated with isoniazid resistance (OR 3.92; 95% CI 1.04–14.83; p = 0.044). Factors associated with rifampicin resistance, in a multivariate logistic regression model, were relapse after previous treatment within six months and a history of incomplete prior treatment (OR 14.81; 95% CI 2.36–93.06; p = 0.004 and OR 9.00; 95% CI 1.40–57.94; p = 0.021, respectively).

We assigned points for the scores according to the regression coefficients, including three variables that were independently associated with either isoniazid or rifampicin resistance. Table III presents the scores to predict DR-TB. Then, we retrospectively computed the scores in our patients; the area under the ROC curve was 0.65; CI 0.53– 0.76) (Fig.1). Using the DR-TB predictive score, the

Table III. Predictive scoring system.

Variables	Regression coefficients	Score
Chest radiograph		
Moderately advanced	0.42	1
Far advanced	1.36	3
Relapse after previous treatment		
≤ six mths	2.69	5
> six mths	0.90	2
Prior tuberculosis treatment		
Incomplete treatment	2.19	4

cut-off score of ≥ 3 yielded the least error of classification in differentiating patients with the resistant strain from those with the susceptible strain at a sensitivity of 57.7%, specificity of 67.8%, positive predictive value of 15%, and negative predictive value of 94.2%. Of the 290 cases, 190 (65.5%) had a score of < 3 and 100 (34.5%) had a score of ≥ 3.

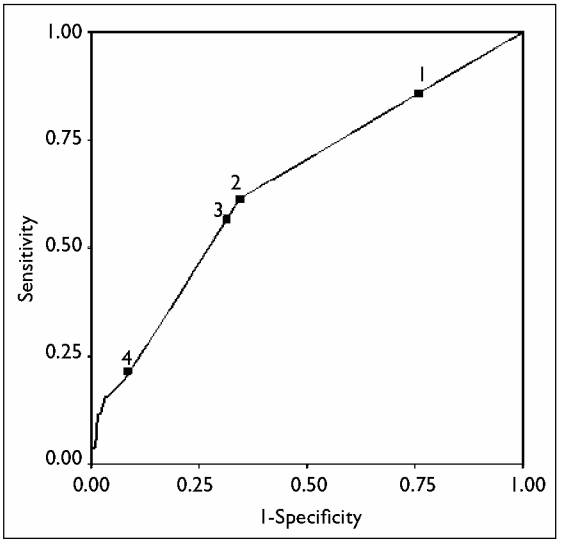

Fig. 1 Receiver operating characteristic curve for the drug-resistant TB predictive score and isoniazid or rifampicin resistance.

DISCUSSION

The prevalence of DR-TB is increasing worldwide.[7-9,16-18] Patients harbouring strains of *M. tuberculosis* that are resistant to either isoniazid or rifampicin are at high risk for treatment failure and further acquired resistance.[7-9,16,17,19] However, drug resistance can be proven only by drug-susceptibility testing performed in a competent laboratory. Because of this, the ATS, CDC and IDSA recommend that susceptibility testing should be performed on an initial isolate from all patients from whom *M. tuberculosis* is recovered.[11] In contrast, the WHO and IUATLD do not recommend susceptibility testing for all new patients in low income, high incidence countries.[12,13] Hence, in Thailand, which is one of the low income, high incidence TB countries, DST should be recommended to be performed in selected patients who have risk factors for DR-TB, for early identification and appropriate treatment of such cases.

Various risk factors associated with DR-TB have been identified in several studies including younger age, male gender, being HIV positive, previous imprisonment, a history of prior TB, and advanced radiological abnormalities.[17,18,20-23] However, all of these factors are not included in any one study. Different geographical, demographical and treatment strategies may provide an explanation. For example, it has been amply demonstrated that a well-implemented DOTS-based TB control programme is associated with a decreased rate of emergence of drug resistance.[21,24-26] Therefore, risk factors for DR-TB may be different in each country.

In Thailand, DOTS was adopted in 1996 and countrywide coverage has been achieved since 2001. Even though the incidence rate of all TB cases is on the increase, the prevalence of DR-TB is decreasing.[2] In our study, any resistance to an anti-TB drug was at 13.4%. Any resistance to each of these drugs was: isoniazid, 6.9%; rifampicin, 4.5%; ethambutol, 4.8%; ofloxacin, 1.4%; streptomycin, 6.2%; and either isoniazid or rifampicin, 9.0%. As expected, the MDR rate in our institution was 2.4%, higher than the national average. However, compared to previous reports from our institution,[4,5] a 53% decline in the proportion of MDR-TB was observed from 5.2% in 1990–2000 to 2.4% in our study period. This finding underlines the success of DOTS implementation in Thailand.

Our study focused on risk factors associated with either isoniazid- or rifampicin-resistant TB. Far advanced disease on chest radiographical findings was associated with isoniazid resistance. Tubercle bacilli are continually undergoing spontaneous mutations that create resistance to individual anti-TB drugs. Resistance to isoniazid exists more commonly at a rate of one in 10^6 bacilli.[27] Thus, the development of drug resistance most commonly occurs when there is a large bacillary population, such as in pulmonary cavities and far advanced disease.[28] Ben-Dov and Mason have found that resistance rates are higher if cavitary disease is present on radiographs.[29] Similarly, Granich et al found that cases of DR-TB are twice as likely to have cavitary lesions compared with non-DR-TB cases.[18] However, our study was able to demonstrate the risk factor of isoniazid resistance only in far advanced disease, not in a cavitary lesion, which was classified as moderately advanced disease. The prevalence of rifampicin resistance was significantly different between the patients with a history and those without a history of previous treatment. Of those who had prior TB, patients who relapsed after previous treatment within six months and who had a

history of incomplete prior treatment, carried a higher risk of rifampicin resistance. In agreement with our findings, recent studies have clearly indicated that a prior history of TB is the factor most strongly associated with rifampicin resistance.[17,18,20-22]

HIV infection has been found to be a risk factor associated with DR-TB in various studies,[21,22] though some studies have not been able to demonstrate this association.[17,18,23,30] In Thailand, few studies have confirmed HIV infection as a risk factor for DR-TB,[31] while most studies including ours have not.[3,5,32,33] Because of the small number of cases with a history of imprisonment, we were unable to ascertain the importance of this risk factor. The prevalence of new smear positive pulmonary TB among prisoners in Bangkok is 1,226 cases/100,000 prisoners. Tansuphasiri et al reported that 49.7% of 165 TB strains among prisoners in three prisons in Bangkok are resistant to at least one antimicrobial agent. Of these patients with resistance, 35.8% showed resistance to isoniazid, 19.4% to rifampicin, 36.4% to either isoniazid or rifampicin, and 18.8% were MDR.[33] Thus, a history of imprisonment should be considered as an important risk factor for DR-TB in Thailand.

We propose a DR-TB predictive score comprising of three parameters as risk factors of either isoniazid or rifampicin. The DR-TB predictive score provides a tool for differentiating patients with the resistant strain from those with the susceptible strain. From Table III, a score of ≥ 3 was considered to be a positive test with a high negative predictive value of 94.2, which excluded the low risk for DR-TB patients. In other words, DST may not need to be performed if the predictive score is ≤ 2. However, this high negative predictive value might be driven by the low DR-TB prevalence in our population.[34] It should be noted that the accuracy of this predictive score might change when applied in a population with a different prevalence level. Furthermore, this predictive score may not be applicable to patients from different geographical or demographical populations because of different significant risk factors, as mentioned above.

One of the study limitations was the retrospective nature of the analysis. Hence, data was incomplete in terms of exact number of culture-negative TB and culture-"might be"-positive TB, as respiratory specimens for these cases were not collected. Our hospital is a tertiary university referral hospital, where the decision to send for mycobacterial culture depended on the physician in charge of patient care. This might have resulted in a selection bias in favour of including only patients more likely to have worse disease and drug resistance. This may explain the higher incidence of DR-TB in our institute compared to the national average. Another limitation could also result from the relatively small number of cases. Only culture-proven TB cases were eligible and this study was retrospectively reviewed in one centre, which may have biased the study population towards worse patterns of disease and resistance than are prevalent in the country as a whole. Pooling of data from several centres could add statistical power to an analysis of risk factors of drug resistance. Finally, some important variables have been missed, such as HIV-serology test and sputum AFB stain as well as the drug regimen administered in previous treatment of relapsed cases.

In summary, our study has suggested a DR-TB predictive score for the exclusion of either isoniazid or rifampicin resistance, and also provides a decisional guide for clinicians to send specimens for sputum culture and drug susceptibility testing. With its strength in the high negative predictive value, DST may not need to be performed in cases of low predictive scores. However, this predictive score may not be applicable to patients from different geographical or demographical populations because of different significant risk factors, as mentioned above. A follow-up prospective study needs to validate this scoring system in a larger, more generalisable population, to help assess its potential contribution to a national TB control programme.

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