ORIGINAL ARTICLE

Influence of Co-Morbidity in the Interpretation of Tuberculin Skin Reactivity in Multi-Ethnic Adult Patients With Tuberculosis

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Summary

In the Malaysian setting of multi-ethnicity and high BCG coverage, interpretation of Tuberculin Skin Testing (TST) may be difficult. Between January 2001 and December 2003, a retrospective study on all adult patients with documented TST results treated for tuberculosis (TB) in chest clinics of two government hospitals was conducted to determine the reliability of TST and factors affecting its interpretation. One hundred and three patients [mean age (SD): 43 (17); male: 67%] were eligible for data collection: 72% and 57% of patients had positive TST results based on cut-off points of 10mm and 15mm respectively. The only significant univariate association with TST results was the severity of co-morbidity. A patient with co-morbidity score of 3 defined as those with any cancer, end-stage renal or liver disease, or HIV disease, was more likely to have a negative TST results [10mm cut-off point: Odd Ratio (95% CI) 6.6 (1.82 to 24.35), p=0.003; 15mm cut-off point: 4.8 (1.21 to 18.95), p=0.012]. A TST reading of 10mm had a higher sensitivity than 15mm as the cut-off point in diagnosing TB infection. Considering all possible confounding factors like ethnicity, prior BCG vaccination and TB burden in the population, severity of co-morbidity remains strongly predictive of a negative TST. Caution should be exercised in interpreting TST in these patients.

Key Words: Tuberculin Skin Testing, Tuberculosis, Co-morbidity, Malaysia

Introduction

Tuberculosis (TB) continues to be a significant global public health challenge[1]. Tuberculin skin testing (TST) is a useful diagnostic tool for latent TB infection (LTBI) but appropriate interpretation of the TST requires knowledge of the nature of skin test used, possible confounding factors such as prior BCG vaccination, and the local prevalence of TB infection[2,3,4]. Most clinical practice guidelines[5,6] including that in Malaysia[7], generally recommend that a TST reading of ≥10mm induration is indicative of TB infection. However, interpretation of TST continues to be a practical problem among many clinicians who are concerned about either over-treating patients who do not have LTBI with potentially hazardous ant-TB chemotherapy or under-treating those who have the disease that carries the potential of death and continuing spread in the community.

Malaysia is a multiracial country with a TB notification rate of 68.1 per 100 000 population and with an estimated incidence at 112 per 100 000 population[8,9] based crudely on the calculation that there are at least an estimated 1.22 cases of 'smear negative' pulmonary or extrapulmonary TB to every 'smear positive' case in countries with low HIV incidence[10]. Currently, The World Health Organization has categorized Malaysia as

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a region of intermediate high TB burden. Malaysia is also one of the countries that has implemented the policy of primary BCG vaccination in infants and newborns since 1961. The policy has been extended to include all residents under the age of 20 years for primary vaccination from 1969[11]. These three factors of multi-ethnicity, relatively high TB burden and extensive BCG coverage in the general population must be taken into consideration when interpreting TST.

To study the reliability of TST and identify the possible factors that influence its interpretation, we undertook a retrospective study on all patients with TB with documented TST results, treated in the chest clinics of two government hospitals in the state. The reliability of TST is assessed based on 10mm and 15mm cut-off points.

Materials and Methods

All case notes of patients treated for TB in the chest clinics of two government hospitals (Seremban Hospital and Kuala Pilah Hospital) between January 2001 and December 2003 were screened for eligibility to enter this study. Patients included were those who were confirmed to have TB (either microbially or following successful empirical therapy) and with documented TST discrete results (i.e. recorded numerical figure for the induration size of TST). Both pulmonary and non-pulmonary TB cases were accepted. Clinico-demographic characteristics of patients including the extent of radiological involvement and the number of BCG scars, were collected using a structured record sheet.

TST were performed by designated nurses in the chest clinics. The procedure involved an intradermal injection of 2 Tuberculin Units (TU) of PPD RT-23 (Statens Serum Institute, Denmark), administered into the volar surface of the forearm with disposable syringes and 27-gauge needles. Skin reactivity was defined as the maximum induration in millimeters (mm) after 48 to 72 hours of administration and this was read by the same nurses using the ballpoint method. A physician (LCL) who was blind to the outcome, classified retrospectively co-morbidity into three categories (score between 1 and 3) based on past medical history. A co-morbidity score of 1 indicated no important chronic illness; 2 indicated moderate or severe disease of the heart, lungs, gastrointestinal tract and endocrine system, and 3 indicated the presence of any cancer (except skin), end-stage renal or liver disease, or HIV infection. This classification of comorbidity was based on a study by Brancati et al[12] on prognosis in community-acquired pneumonia with slight modification.

Statistical analysis was performed according to whether patients had positive or negative TST using cut-off points of 10mm and 15mm induration. The groups were compared by means of unpaired t test for continuous data, and *Chi square* test for categorical data. Correlation between the induration size and the clinical variables that could affect TST was assessed using Spearman rank test. Six clinical variables selected were age, degree of sputum smear positivity, BCG scars, number and severity of co-morbidity and the extent of pulmonary involvement. For variables that showed univariate association with the results of TST using 10mm or 15mm cut-off points, odd ratios with 95% confidence interval, specificity, sensitivity, positive and negative predictive values, were calculated to determine the usefulness of these variables as predictors of TST results. All computations were made using statistical package SPSS version 11.5 for Windows (Chicago, Illinois, USA). In all cases, the statistical significance was defined at the 5% level and all associations assessed with two-tailed tests.

Results

A total of 865 case notes were screened for the purpose of this study, and 103 cases [mean age (SD) 43 (17); male 67%] were eligible for data collection. The vast majority of cases were rejected because TST were either not done or recorded. The patient clinico-demographic and radiological characteristics are shown in Table I.

Based on 10mm cut-off point, 74 patients (72%) were considered to have a positive TST test. When 15mm was used as cut-off point, the number of patients with a positive TST was reduced to 59 (57%). Except for co-morbidity score, there were no variables that were associated with either positive or negative TST results, irrespective of whether 10mm or 15mm was used as the cut-off point. Based on 10mm cut-off point, only 5% of patients with a positive test had co-morbidity scoring 3, compared to 27% of patients with a negative tests, [p=0.003]. Similarly, when 15mm cut-off point was used, only 5% of patients with a positive test had co-morbidity scoring 3, compared to 20 patients with a negative test, [p=0.012] [Table I].

There was no correlation between the TST induration size and the six selected clinical variables, indicating that the absolute induration size had little association with these variables [Table II].

Based on 10mm cut-off point, a patient with a co-morbidity score of 3, was six times more likely to have a negative TST result [Odd ratio (95% CI) 6.6 (1.82 to 24.35). p=0.003]. When 15mm cut-off point was used, the likelihood of a negative TST result was reduced to four times [4.8 (1.21 to 18.95); p=0.001]. The specificity of a co-morbidity score of 3 for a negative TST result was 94% for both cut-off points while the sensitivity was below 30%. The positive and negative predictor values for both cut-off points were similar [66% vs 76% for 10mm and 75% vs 61% for 15mm] [Table III].

In view of the significant association with the co-morbidity score, further analysis of the twelve patients (11.7%) with a score of 3 was carried out. Six patients had HIV infection [Mean induration size: 10.3mm]; 3 patients had end-stage renal disease [all TST were negative]; 2 patients had chronic liver disease [mean: 8.5mm], and 1 patient, in whom the TST was negative, had combined HIV and chronic hepatitis B and C diseases [Table IV].

Table I: Clinico-demographic and radiological characteristics of patients with tuberculosis infection based on two different cut-off points of Tuberculin Skin Test (TST)

	Entire Group	10 mm cut-off point		15 mm cut-off point	
		¶Positive/ Negative TST	**p	¶Positive/ Negative TST	**p
n (%)	103	74 (72)/29 (28)	-	59 (57)/44 (43)	-
Mean age (SD), yrs	43 (17)	41 (17)/ 47 (17)	0.116	41 (17)/45 (17)	0.283
Male	67	62/79	0.096	61/75	0.135
Ethnic groups					
Malays	54	55/51	0.736	42/50	0.442
Chinese	22	21/24	0.783	23/20	0.693
Indians	19	18/20	0.838	13/27	0.082
Pulmonary TB	81	81/82	0.843	81/81	0.952
Extrapulmonary TB	18	18/17	0.843	18/18	0.952
Positive sputum smear	35	35/34	0.950	35/34	0.874
Sputum smear positivity‡					
+1 to +2	71.4	77/75	-	78/75	-
+3 to +4	28.6	23/24	0.900	22/25	0.725
BCG scars					
None	43.7	39/55	-	42/45	-
One	43.7	47/34	-	50/34	-
Two	12.6	13/10	0.338	6/20	0.067
Any chronic illness	38.8	37/41	0.740	40/36	0.657
Co-morbidity score*					
1	61	62/58	-	59/63	-
2	27	32/13	-	35/15	-
3	11	5/27	0.003	5/20	0.012
Radiological involvement					
None	18.4	18/17	-	18/18	-
One to two lobes	51.5	54/44	-	49/54	-
Three or more lobes	30.1	27/37	0.549	32/27	0.840

Values are percentages unless otherwise stated
‡ in those with pulmonary TB only
* Co-morbidity score [12]: 1= no important chronic illness; 2=moderate/severe disease of heart, lungs, GI tract; Endocrine System 3= any cancer (except skin), end stage renal/liver disease/HIV disease
¶ Positive and negative TST defined as ≥ and < the cut-off points respectively
** between patients with TST positive and TST negative.

Table II: Correlation between skin induration sizes of Tuberculin Skin Test with potential clinical predictors

Potential Clinical Predictors	Spearman correlation, r	p values
Age	-0.108	0.279
Degree of sputum smear positivity (from 0 to +4)	-0.046	0.646
Number of BCG scars (from 0 to 2)	-0.022	0.826
Number of comorbidity*	-0.033	0.739
Co-morbidity scoring (from 1 to 3)*	-0.077	0.440
Extent of pulmonary involvement (grading from 0 to 8)**	-0.057	0.565

*Co-morbidity score [12]: 1= no important chronic illness; 2= moderate/severe disease of heart, lungs, GI tract; Endocrine System 3= any cancer (except skin), end stage renal/liver disease/HIV disease

** Involvement of pulmonary lobes ranging from 1 to 6. Involvement of pleural space on each side numbered 1.

Table III: Ability of co-morbidity severity to predict a negative Tuberculin Skin Test based on cut-off point of 10mm and 15mm

	OR (95% CI)	Sensitivity	Specificity	PPV	NPV
10mm cut-off point	6.6	27	94	66	76
Co-morbidity Score 3	(1.82 to 24.35)				
15mm cut-off point	4.8	20	94	75	61
Co-morbidity Score 3	(1.21 to 18.95)				

Values (except for OR) are in percentage

OR= odd ratio; CI= confidence interval; PPV= positive predictive value; NPV= negative predictive value

Co-morbidity score 12: 1= no important chronic illness; 2= moderate/severe disease of heart, lungs, GI tract; Endocrine System 3= any cancer (except skin), end stage renal/liver disease/HIV disease

Table IV: Diseases with Co-morbidity Score 3 (n=12) and their TST sizes

Diseases	n	Individual TST sizes (mm)	Mean
HIV	6	18, 18, 15, 9, 2, 0	10.3
End-stage renal disease	3	0, 0, 0	0
Chronic liver disease	2 (1 Hep B; 1 Hep C)	3, 14	8.5
HIV plus chronic liver disease (Hep B and C)	1	0	0

Hep= Hepatitis

Discussion

In our retrospective study of 103 multi-ethnic patients with TB, we showed that 72% and 57% of patients had positive TST results based on cut-off points of 10mm and 15mm respectively. The only significant association with the TST result was the severity of co-morbidity. This was present with both cut-off points, although the association was greater when a 10mm cut-off point was used. A patient with a co-morbidity of 3, defined as those with any cancer (except skin), end-stage renal or liver disease, or HIV disease, was six times and four times more likely to have a negative TST result based on 10mm and 15mm cut-off points.

The main weakness of our study lies in its retrospective nature, as the accuracy and comprehensiveness of patient case records may be lacking. It is possible, for

example, that co-morbidity in some patients' notes was not clearly recorded and therefore missed during data collection. Another important consideration is that the vast majority of TST records of the patients were not available or unclear, resulting in many being excluded from the study. It is therefore unclear as to whether the sample data collected is sufficiently representative of the whole patient population. The findings also suggest that TST was not commonly requested for.

We only included patients with confirmed TB. This was important to ensure that patients who did not respond to empirical anti-TB therapy were excluded from the study. The fact that only 35% and 18% patients were smear-positive and had extrapulmonary TB respectively, suggests that a large number of the patients in our study were treated empirically. This may explain why TST were carried out more often in these patients. The fact that TST were administered and read by the same designated nurses should reduce any inter-subject procedural variation that is well recognised [13,14].

Much had been published regarding the diagnostic reliability and practical problems associated with TST and its interpretation. Within the Malaysian context, several considerations are important. Firstly, multi-ethnicity may contribute to differences in TST reactivity. An early study in a large teaching hospital in northern peninsular Malaysia[15] showed that only 42% of the 468 patients with active TB infection had positive TST tests and the low sensitivity of the test was attributed to differences in tuberculin test profiles among the various ethnic communities. Except for a possible association with Indian ethnicity at 15mm cut-off point (p=0.08), our study did not suggest that ethnicity (defined as the three main races in Malaysia) led to differences in TST reactivity. Clinical practice guidelines[5] recognize the possible role of ethnicity in influencing TST reactivity.

Secondly, the local TB burden in Malaysia may influence TST interpretation. The predictive value of a positive test is usually low in low prevalence populations because a positive result in the absence of risk factors is likely to be falsely positive[16]. Hence, higher cut-off points for low-risk population and lower cut-off points for high-risk groups may be more appropriate[5]. Our finding that a 10mm cut-off point yields a higher positive rate than the 15mm cut-off point indicates that 10mm is more appropriate. In India where the TB burden is higher than in Malaysia, the national TB control programme recommends a 10mm cut-off point as being both appropriate and relevant for its population [17].

Finally, is the issue of prior BCG vaccination. The proportion of individuals with previous BCG vaccination who test positive for TST has been reported to vary from 0%[18] to 90%[19]. TST reactivity can vary depending on the dose of vaccination [20], manufacturer of the vaccine[19], age when vaccinated [21], and the interval between vaccination and skin testing [21]. A recent meta-analysis[3] that included pooled data from 117, 507 subjects concluded that patients who had received prior BCG vaccination were at least twice more likely to have a positive TST, based on 10mm cut-off point, compared to those who were not vaccinated. The analysis also showed that a TST of ≥ 15mm induration was more likely to be the result of TB infection rather than prior BCG vaccination. However, we did not find that proportionately more patients became TST positive if the 15mm cut-off point was used instead of 10mm. Perhaps a proportion of our patients was not vaccinated or did not mount an adequate immune response as reflected by the absence of BCG scars in almost 40% of the patients. The same meta-analysis also showed that the effect of BCG vaccination on TST lessens after 15 years. This may also explain our findings as our study involved adult patients, two thirds of whom were over 30 years of age.

Our study showed what we have intuitively known-that severe co-morbidity has a negative impact on TST reactivity [5,6] by virtue of its effect on immuno-competence. This highly significant association was present irrespective of whether the cut-off point was 10mm or 15mm in a relatively heterogeneous group of patients, with different ethnicity and perhaps varying uptake rates of BCG vaccination. As such, co-morbidity could possibly be the single most important consideration in the interpretation of the TST in the Malaysian context. Further analysis of the data of patients with a co-morbidity of 3 showed that significant variance of TST reactivity, reflecting the heterogeneity of immuno-competency within each disease. We were not able to show any correlation between induration size and other clinical variables such as age, degree of TB involvement reflected by sputum smear positivity and radiological involvement. The explanation for this is unclear and it may be due to the lack of sufficient number of cases for analysis of this nature. Given the complexity of TST reactivity and its interpretation, it is obvious that more research is required, and prospective studies relevant to local

practice settings would help to improve our understanding on how best we can make use of TST in the diagnosis of latent TB infection, especially with re-emergence of TB worldwide now.

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