A clinical risk score to distinguish tuberculosis From non-specific cervical lymphadenitis in children

Jayanton Patumanond[1], Apichart Visitwong[2], Chamaiporn Tawichasri[3]

[1] Clinical Epidemiology Unit, Faculty of Medicine,
Chiang Mai University. Chiang Mai 50200, THAILAND
e-mail: jpatumanond@gmail.com
[2] Department of Pediatrics, Nakorn Sawan Hospital,
Nakorn Sawan 60000, THAILAND
e-mail: apichartvis@hotmail.com
[3] Clinical Epidemiology Unit, Faculty of Medicine,
Chiang Mai University, Chiang Mai 50200, THAILAND
e-mail: ctawichasri@yahoo.com

Corresponding Author:
Prof. Dr. Jayanton Patumanond
Clinical Epidemiology Unit, Faculty of Medicine,
Chiang Mai University, Chiang Mai 50200, THAILAND
Phone: 66+53+946306, Fax: 66+53+945476
e-mail: jpatumanond@gmail.com

Summary

Objective: To propose a simple clinical risk score to distinguish tuberculosis from non-specific infection in children with cervical lymphadenitis.
Methods: Six-year retrospective data of 284 children initially diagnosed with cervical lymphadenitis in a large university affiliated hospital were analyzed. Cases were children eventually diagnosed with tuberculosis by fine needle aspiration cytology (FNAC) and/or excisional biopsy (n=58), controls were children diagnosed with non-specific cervical lymph node infection (n =57). Scores were assigned to clinical characteristics statistically significant under the multivariable logistic regression.
Results: Age group, history of contact to TB case, positive tuberculin skin test, duration of enlargement, the number of nodes and size of the largest node were significant predictors. When classified the total scores into three categories, the likelihood ratio of positive for tuberculosis increases from 0.07 (p<.001) in low probability category (score below three) to 9.17 (p<.001) in high category (score above nine).
Conclusions: General practitioners may use this simple clinical risk score to help recognizing and distinguishing tuberculosis from non-specific cervical lymphadenitis. Children with low scores may be handled with empirical treatment. Children with high scores may be referred to specialists for proper investigation and treatment. Those with intermediate scores may be evaluated appropriately.

KEY WORDS: *Tuberculosis; Infection; Lymphadenitis; Lymph Node Tuberculosis; Differential Diagnosis; Neck.*

Background

Cervical lymphadenitis is a common clinical presentation in general practice (1). In developing countries where pulmonary tuberculosis (TB) is prevalent, lymph node TB is not uncommon in children presenting with swollen head and neck lymph nodes, and should be included in the differential diagnosis (2).
In children, fine needle aspiration cytology (FNAC) is acceptable as a very useful diagnostic tool, accurate, speedy, inexpensive and easy to perform (1,3,4). FNAC, however, requires patients' co-operation. Some children resist the procedure and have to end up with undesirable sedation, causing a high level of anxiety among parents. A lot of FNAC performed in children suspicious of lymph node TB turned out to be non-specific infection or inconclusive. Without FNAC, these children could otherwise have been successfully treated with empirical antibiotics.
Although more investigative procedures help clinicians diagnose TB with more confidence (1,5,6), it is not feasible or practical to apply all the dia-

gnostic procedures in all patients, as this would be time consuming and expensive. In order to gain high disease likelihood, but still spending minimal resources, a simple clinical risk score to predict which children are more likely to gain benefit from full investigation for lymph node TB is required.

Methods

Setting

A 653 beds university-affiliated, regional hospital in Nakorn Sawan, a province located 240 kilometers to the north from Bangkok, captures 1.1 million population around the upper central part and the lower northern part of Thailand. The prevalence of TB is 558 per 100 000 population. Approximately 6.2% are children 15 year-old or under. Of those, 53.9% is extra-pulmonary and 70.1% out of which is at the head or neck area.

Patients and data collection

Children initially diagnosed with cervical lymphadenitis at the pediatric, surgical and ear, nose and throat departments between fiscal years 2004-2009 were identified. Children without further FNAC investigation were excluded. TB cases were defined as children who, after FNAC and/or excisional biopsy were either; 1. positive for *Mycobacterium tuberculosis* on culture or, 2. positive for acid fast bacilli (AFB) or, 3. reported as caseating granuloma or granulomatous changes compatible with TB. This definition was based on routine clinical practice.

Non-TB cases were defined as the remaining children who did not fulfill any of the above conditions and were clinically diagnosed with and treated as non-specific lymph node infection, who responded to treatment with empirical antibiotics, or were surgically removed and were finally diagnosed with non-specific lymph node infection.

Potential predictor variables used in our study included demographic information (gender and age), clinical history (duration of enlarged nodes, history of contact with TB cases), physical examination (number and size of lymph nodes) and tuberculin skin test.

The size of the largest node recorded was used in this study. Tuberculin skin testing was performed under the routine basis in most of the children suspicious of TB. A positive reaction required induration of $\geq$15 mm. All information was extracted from the medical records.

Other potential predictors were also considered, but were not included in the analysis. Sites of lymph nodes were vaguely defined, pain or fever was interfered with analgesic or antipyretic premedication and therefore not used in the study, as well as the consistency of nodes which rarely existed in the records.

The final outcome of the investigation was lymph node TB diagnosed by means of FNAC and/or excisional biopsy. All aspirations were done by board certified pathologists. All excisional biopsies were done by board certified surgeons. Cytology or histology of specimens was interpreted by the same set of pathologists, who were unaware of the clinical manifestations.

The research protocol and data collection was approved by Nakorn Sawan Hospital Research Ethics Committee. Patient informed consents were not required in this retrospective data collection.

Statistical analysis

Characteristics of TB and non-TB cases were compared by exact probability tests or t-tests as appropriate. All p values were two-sided. Continuous variable (age, duration of symptom, number and size of nodes) were categorized into groups to enhance meaningful clinical interpretation. The points of categorization were decided after careful examination of the relationship between each continuous variable and the log odds of being cases. A univariable, multivariable odds ratio and beta coefficient for sub-level of each characteristic was calculated by logistic regression clustering (gender). Beta coefficient was divided by the smallest value among all beta coefficients in the model and rounded up or down to the nearest 0.5 decimal points to achieve an item score. Each item score was added up to obtain a total score. The total score was used as the only predictor in the logistic regression. The area under the receiver operating characteristic (AuROC) curve and its 95% confidence interval were calculated. The total score was classified and ranked into three probability categories, low, moderate and high. The likelihood ratio of positive test (LHR+) was calculated for each probability category.

Results

Characteristics of patients and diagnosis

During 2004-2009 there were 284 children who were initially diagnosed with cervical lymphadenitis. One hundred and sixty five cases resolved after close observation or after treatment with empirical antibiotics without further investigation. Among the remaining 119, FNAC was scheduled in 102 cases, from which two cases of malignancy were reported (one Hodgkin's disease and one neuroblastoma). Two cases were lost before FNAC was scheduled. These four latter cases were excluded. Four of the 98 cases set for FNAC were also sent for excisional biopsy, three of which were diagnosed with TB and one infected brachial cyst. Among the other 94 cases set for FNAC alone, 47 were professionally diagnosed with and successfully treated as TB. There were 17 cases who were initially scheduled for excision biopsy alone, eight turned out as TB, the rest were non-specific lymphadenitis or other benign conditions (histiocytic necrotizing lymphadenitis). The total number of cytologically and/or histologically proved lymph node TB cases in this study was therefore 58. The remaining 57 cases were included as non-TB cases. These 115 children were from the pediatrics (n=104), surgery (n=7) and ear, nose and throat (n=4) departments. None of the children had HIV-infection nor other immune-compromising conditions.

Tuberculosis and non-TB cases were different with respect to age group, duration of node enlargement, history of contact to TB case, number of nodes and size of the largest node and tuberculin skin test (Table I).

Table 1. Characteristics of children with and without tuberculosis (TB), odds ratio (OR) and 95% confidence interval (CI).

Characteristics	Children with TB (58) n (%)		Children without TB (57) n (%)		OR	95% CI	p
Gender							
Male	37	(64)	32	(56)	1.4	0.6, 3.1	0.45
Female	21	(36)	25	(44)	1	(reference)	
Age group (month)							
<36	14	(24)	5	(9)	7.2	1.7, 32.1	<0.01
36-72	9	(16)	23	(40)	1	(reference)	
>72	35	(60)	29	(51)	3.1	1.1, 8.7	0.02
Mean (SE)	97.8	(7.4)	85.3	(6.1)	-		0.19
Duration of nodes (week)							
1-3	19	(33)	8	(14)	3.0	1.1, 8.7	0.03
>3	39	(67)	49	(86)	1	(reference)	
Mean (SE)	15.7	(4.0)	28.8	(6.9)	-		0.10
History of TB case contact							
No	39	(67)	30	(53)	1	(reference)	
Undetermined	9	(16)	23	(40)	0.3	0.1, 0.8	0.01
Yes	10	(17)	4	(7)	1.9	0.5, 9.2	0.38
Number of nodes							
1	32	(55)	26	(46)	1	(reference)	
2	16	(28)	29	(51)	0.4	0.2, 1.1.	0.07
3, matted or chained	10	(17)	2	(3)	4.1	0.8, 40.7	0.11
Size of largest node (cm)							
<2	15	(26)	39	(69)	1	(reference)	
2-2.9	24	(41)	11	(19)	5.7	2.0, 16.1	<0.001
3 and over	19	(33)	7	(12)	7.1	2.2, 23.6	<0.001
Mean (SE)	2.5	(0.2)	1.6	(0.1)	-		<0.001
Tuberculin skin test							
Negative	20	(34)	23	(40)	1	(reference)	
Undetermined	23	(40)	31	(55)	0.9	0.4, 2.1	0.84
Positive	15	(26)	3	(5)	5.8	1.3, 34.5	0.01

OR, univariable odds ratio.

Table 2. Predictors, odds ratio (OR), 95% confidence interval (CI), regression beta coefficient (β) and the assigned score.

Predictors	OR	95% CI	p		Score
Age group (month)					
<36	9.4	5.1, 17.6	<0.001	2.24	5
36-72	1	(reference)	-	-	0
>72	1.6	0.7, 3.7	0.29	0.45	1
Duration of nodes (week)					
0-3	1.8	1.0, 3.1	0.05	0.58	1.5
>3	1	(reference)	-	-	0
History of TB case contact					
No/undetermined	1	(reference)	-	-	0
Yes	5.1	4.4, 6.0	<0.001	1.64	3.5
Number of nodes					
1-2	1	(reference)	-	-	0
>2, matted or chained	8.2	3.4, 19.6	<0.001	2.10	4.5
Size of largest node (cm)					
<2	1	(reference)	-	-	0
2-2.9	9.3	1.0, 84.3	0.05	2.23	5
3 and over	15.1	2.8, 81.9	<0.01	2.72	6
Tuberculin skin test					
Negative/undetermined	1	(reference)	-	-	0
Positive	7.4	1.7, 32.8	<0.01	2.00	4.5

OR, multivariable odds ratio from logistic regression clustering (gender).

Development of clinical risk score

Under the logistic regression clustering (gender), all predictors were significant at 0.05 with relatively high odds ratios. The AuROC curve for the full model was 86.5 (95% confidence interval: 79.8, 93.1). The item-specific score transformed from beta coefficient varied between zero and six (Table II) and the summary scores ranged from zero to 17.5 (Figure 1). When the summary score was used as the only predictor in the logistic model, the AuROC curve was 86.8 (95% confidence interval: 80.3, 93.2) (Figure 2).

The score predicted probability of TB increased with an increase in summary scores (Figure 3). When classifying the summary score into three probability categories at the probability of 20% and

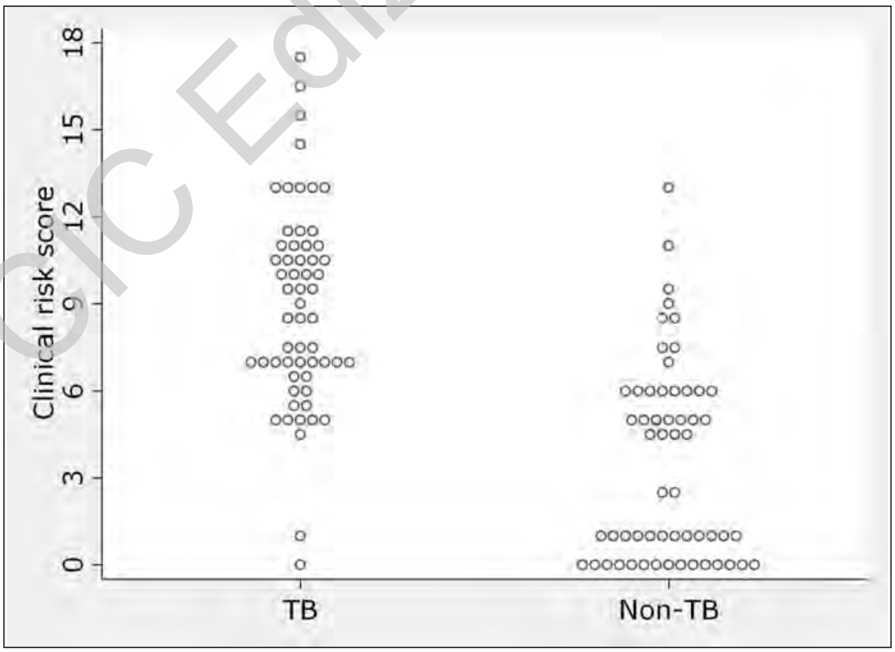

Figure 1. Clinical risk score distribution of children with and without tuberculosis (TB).

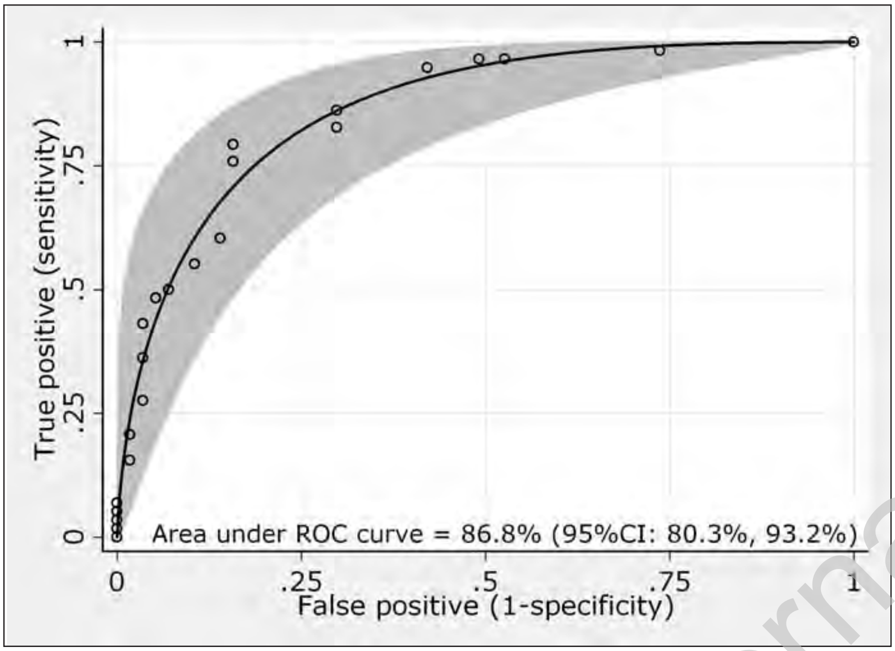

Figure 2. Performance of the clinical risk score, area under the receiver operating characteristics (ROC) curve and 95% confidence band.

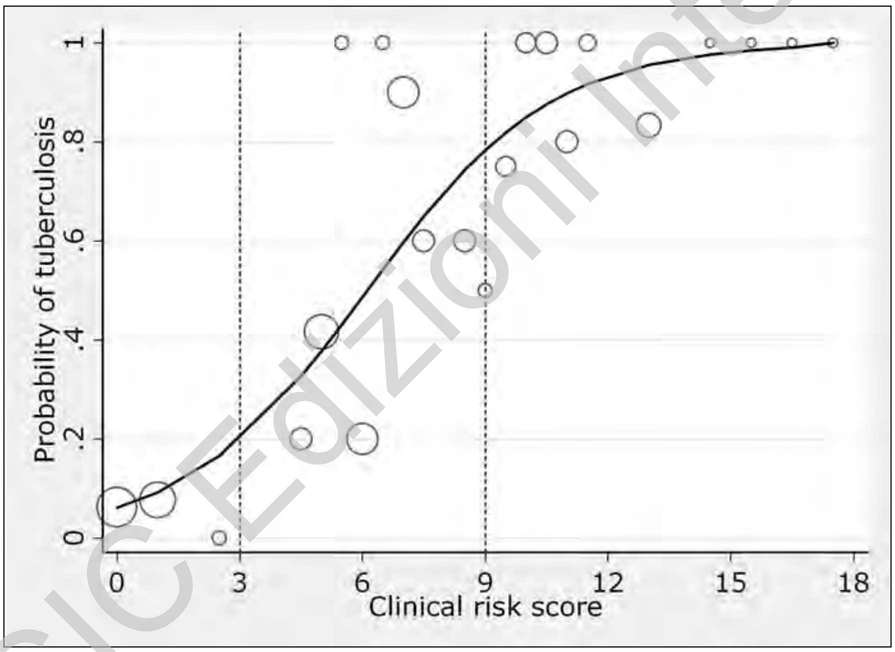

Figure 3. Predicted (solid line) and observed (circle) probability of tuberculosis (TB) at each score. Area of circles represents numbers of children at each score. Vertical dotted lines classify children into low (<20%), moderate (20%-80%) and high (>80%) probability of tuberculosis.

80%, the corresponding cut-point value of the scores was at three and nine.
The likelihood ratio of positive for TB increases from 0.07 (95% confidence interval: 0.02, 0.27) in the low risk category (score <3), to 1.10 (95% confidence interval: 0.74, 1.64) in the moderate (score 3-9) and 9.17 (95% confidence interval: 2.95, 28.48) in the high risk category (score >9) (Table III).

Discussion

Predictors of tuberculosis

To make these clinical risk score most feasible and applicable, we selected the predictors from only demographic characteristics, clinical history and diagnostic investigation that were available on a routine basis. Extra-pulmonary TB is more common in children than adults, mostly occurring in

Table 3. Distribution of cases by probability categories, likelihood ratio of positive (LHR+) and 95% confidence interval (CI).

Probability categories	Score	Children with TB (58) n (%)	Children without TB (57) n (%)	LHR+	95% CI	p
Low	<3	2 (4)	29 (51)	0.07	0.02, 0.27	<0.001
Moderate	3-9	28 (48)	25 (44)	1.10	0.74, 1.64	0.71
High	>9	28 (48)	3 (5)	9.17	2.95, 28.48	<0.001
Mean (SE)	-	8.9 (0.5)	3.5 (0.4)	-	-	<0.001

those who are less than 4 years old (2), or less than 2 years in some areas (7). In our study, the likelihood of TB is more common in children <3 years old and >6 years old compared to those in between. This may be the case in areas where pulmonary TB is common, where small children are usually kept unintentionally in households with adult TB cases while pre-school children are allowed to stay outdoor. Older children may contract infection from TB cases in the community. There was already some evidence that children may be infected either in the community or in the household (8).

Surprisingly, we found that early presentation of enlarged lymph nodes was more likely to be TB than later ones. Enlargement of cervical lymph nodes of very short duration is more likely to be acute infection such as Streptococcal or Staphylococcal infection, while in less acute conditions, lymph node TB should be considered. One of the most common causes of sub-acute lymph node infection is mycobacterial infection (3). This discrepancy needs further explanation.

A history of contact to TB cases, whenever reported, increased the likelihood of TB by five times. History of contact was reported in one-fourth of lymph node TB pediatric cases (9). Differential diagnosis with cervical lymph node TB should be considered when there is any history of exposure to TB (3). Tuberculosis infection and clinical disease among children in household contact with adult patients is more prevalent than in general population (7), and is 34 times higher among children with positive history of TB contact than those without (10).

Cervical region was the commonest site affected among all lymph node TB. In the majority of cases, glands were multiple and/or matted (11). Multiple cervical lymph nodes, size >2 cm, and matting were the characteristic clinical features (10,12). From our findings, more than two, matted or chained lymph glands increase the probability of TB by eight times, while nodes sized 2-2.9 cm and larger than 3 cm are nine and 15 times more likely to be TB.

In the majority of TB, positive tuberculin skin test could be obtained (2). A differential diagnosis with cervical lymph node TB should be considered when tuberculin test reaction is >15 mm (3). When combined with tuberculin test, the sensitivity of FNAC increased from 69% to 85% (13). From our analysis, children with positive tuberculin reaction are seven times more likely to have TB.

Other clinical prediction rules

There have been attempts to use a mathematically derived clinical prediction rule for TB in a variety of patients. Most of them confined to pulmonary tuberculosis (14-21). There are only few reports of clinical prediction rule for lymph node TB (12,22). A simple model was proposed to select adolescents and young adults with peripheral lymphadenopathy for biopsy (23,24). One study attempted to help diagnose lymph node TB in remote peripheral areas, where the facility for FNAC or biopsy is restricted (22). These models included a combination of TB risk factors, signs and symptoms, physical examination and investigations. Unfortunately, there was only one clinical guideline specifically designed for TB in children (25).

Model specification

It should be understood that any clinical prediction rules should be considered space and time specific. For TB, the baseline prevalence of tuberculosis in the community and the diversity of human behaviors modify the degree of tuberculosis transmission. Therefore, external validation of the present rule is essential. However, a clinical risk score like the one we proposed, could easily be derived from clinical parameters which are important to each specific area.

Conclusions

A simple clinical risk score may be used to classify children initially diagnosed with cervical lymphadenitis into three groups, those with low, intermediate and high scores. General practitioners may use this rule to help recognizing and distinguish tuberculosis from non-specific cervical lymphadenitis. Children with low scores may be handled with empirical treatment. Children with high scores may be referred to specialists for proper investigation and treatment. Those with intermediate scores may be evaluated appropriately.

Acknowledgements

The authors wish to thank Dr Chaninya Patanasakpinyo (senior pathologist, Nakorn Sawan Hospital), for her compilation of pathological reports of all the FNAC preparation.

Declaration of interest:

We (the authors) have no financial support, nor conflicts of interest to declare.

References

1. Jordan N, Tyrrell J. Management of enlarged cervical lymph nodes. Current Paediatrics 2004;14:154-159.
2. Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. Lancet Infect Dis 2003;3:624-632.
3. Leung AK, Robson WL. Childhood cervical lymphadenopathy. J Pediatr Health Care 2004;18:3-7.
4. Wright CA, Hesseling AC, Bamford C, Burgess SM, Warren R, Marais BJ. Fine-needle aspiration biopsy: a first-line diagnostic procedure in paediatric tuberculosis suspects with peripheral lymphadenopathy? Int J Tuberc Lung Dis 2009;13:1373-1379.
5. Mudduwa LK, Nagahawatte Ade S. Diagnosis of tuberculous lymphadenitis: combining cytomorphology, microbiology and molecular techniques - a study from Sri Lanka. Indian J Pathol Microbiol 2008;51:195-197.
6. Nataraj G, Kurup S, Pandit A, Mehta P. Correlation of fine needle aspiration cytology, smear and culture in tuberculous lymphadenitis: a prospective study. J Postgrad Med 2002;48:113-116.
7. Singh M, Mynak ML, Kumar L, Mathew JL, Jindal SK. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. Arch Dis Child 2005;90:624-628.
8. Schaaf HS, Michaelis IA, Richardson M, Booysen CN, Gie RP, Warren R, et al. Adult-to-child transmission of tuberculosis: household or community contact? Int J Tuberc Lung Dis 2003;7:426-431.
9. Khan RA, Wahab S, Chana RS, Naseem S, Siddique S. Children with significant cervical lymphadenopathy: clinicopathological analysis and role of fine-needle aspiration in Indian setup. J Pediatr (Rio J) 2008;84:449-454.
10. Narang P, Narang R, Narang R, Mendiratta DK, Sharma SM, Tyagi NK. Prevalence of tuberculous lymphadenitis in children in Wardha district, Maharashtra State, India. Int J Tuberc Lung Dis 2005;9:188-194.
11. Hussain M, Rizvi N. Clinical and morphological evaluation of tuberculous peripheral lymphadenopathy. J Coll Physicians Surg Pak 2003;13:694-696.
12. Purohit SD, Gupta ML, Sarkar SK, Gupta PR, Tanwar KL, Jain D. A novel clinical scoring method for diagnosis of tubercular cervical lymphadenitis. Indian J Tuberc 1987;34:22-25.
13. Khan FY. Clinical pattern of tuberculous adenitis in Qatar: experience with 35 patients. Scand J Infect Dis 2009;41:128-134.
14. Mello FC, Bastos LG, Soares SL, Rezende VM, Conde MB, Chaisson RE, et al. Predicting smear negative pulmonary tuberculosis with classification trees and logistic regression: a cross-sectional study. BMC Public Health 2006;6:43-50.
15. Wang CS, Chen HC, Chong IW, Hwang JJ, Huang MS. Predictors for identifying the most infectious pulmonary tuberculosis patient. J Formos Med Assoc 2008;107:13-20.
16. Le Minor O, Germani Y, Chartier L, Lan NH, Lan NT, Duc NH, et al. Predictors of pneumocystosis or tuberculosis in HIV-infected Asian patients with AFB smear-negative sputum pneumonia. J Acquir Immune Defic Syndr 2008;48:620-627.
17. Kanaya AM, Glidden DV, Chambers HF. Identifying pulmonary tuberculosis in patients with negative sputum smear results. Chest 2001;120:349-355.
18. Rakoczy KS, Cohen SH, Nguyen HH. Derivation and validation of a clinical prediction score for isolation of inpatients with suspected pulmonary tuberculosis. Infect Control Hosp Epidemiol 2008;29:927-932.
19. Wisnivesky JP, Henschke C, Balentine J, Willner C, Deloire AM, McGinn TG . Prospective validation of a prediction model for isolating inpatients with suspected pulmonary tuberculosis. Arch Intern Med 2005;165:453-457.
20. Wisnivesky JP, Serebrisky D, Moore C, Sacks HS, Iannuzzi MC, McGinn T. Validity of clinical prediction rules for isolating inpatients with suspected tuberculosis. A systematic review. J Gen Intern Med 2005;20:947-952.
21. Solari L, Acuna-Villaorduna C, Soto A, Agapito J, Perez F, Samalvides F, et al. A clinical prediction rule for pulmonary tuberculosis in emergency departments. Int J Tuberc Lung Dis 2008;12:619-624.

22. Purohit SD, Purohit V, Mathur ML. A clinical scoring system as useful as FNAC in the diagnosis of tuberculous lymphadenitis in HIV positive patients. Curr HIV Res 2006;4:459-462.
23. Slap GB, Brooks JSJ, Schwartz JS. When to perform biopsies of enlarged peripheral lymph nodes in young patients. JAMA 1984;252:1321-1326.
24. Vassilakopoulos TP, Pangalis GA. Application of a prediction rule to select which patients presenting with lymphadenopathy should undergo a lymph node biopsy. Medicine (Baltimore) 2000;79:338-347.
25. Marais BJ, Wright CA, Schaaf HS, Gie RP, Hesseling AC, Enarson DA, et al. Tuberculous lymphadenitis as a cause of persistent cervical lymphadenopathy in children from a tuberculosis-endemic area. Pediatr Infect Dis J 2006;25;142-146.