

Multi-Centric Meta-Analysis on Pulmonary Tuberculosis (PTB) Diagnostic Accuracy index for Diagnosis of PTB- A Problem Solving tools in Health Care Delivery System in Developing Countries.

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Abstract

Diagnostic dilemma in terms of availability, accessibility, accuracy and cost of diagnostic tests are still major drawback for the diagnosis of pulmonary tuberculosis. It is one of the single most important limitation of national tuberculosis programme. With that in mind, in this randomized clinical trial, we are proposing a new scoring system for the diagnosis of PTB in our clinical practice. The results of this study strongly suggest that Pulmonary Tuberculosis (PTB) diagnostic accuracy index is a reliable and cost-effect scoring system in terms of sensitivity, specificity, positive predictive value, negative predictive value, accuracy, positive likelihood ratio, negative likelihood ratio, k (Kappa statistic), agreement with sputum culture, intra and inter-observer variation. Thus, hereby, by this study, we are suggesting that this scoring index should be included in national tuberculosis programme of different countries, especially of the developing countries where health care cost is a big problem.

Keywords: Pulmonary Tuberculosis; Diagnosis; Accuracy index; Sensitivity; Specificity

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Introduction

M. tuberculosis infects a third of the world's populations. World Health Organization estimates 13.7 million prevalent TB cases globally during 2007. There were approximately 9.27 million new TB cases during 2007. Among these an estimated 44% (4.1 million) were new smear positive cases. Asia (the South East Asia and Western Pacific regions) accounts for 55% of the global TB cases. Among 9.27 million incident cases reported during 2007 about 1.37 million (14.8%) were HIV positive. Similarly, during 2007 an estimated 1.776 million deaths were due to TB among these 456,000 were among HIV positive people¹. An individual's risk of infection depends on the intensity and duration of exposure to droplet nuclei and susceptibility to infection. The risk of infection of a susceptible individual is therefore high with close, prolonged, indoor exposure to a person with sputum smear-positive pulmonary tuberculosis (PTB) [1].

TB is an airborne communicable disease. It is spread primarily by tiny airborne particles (droplet nuclei) expelled by a person who has infectious TB. If another person inhales air containing these droplet nuclei, infection may occur. Infection begins with the multiplication of

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tubercle bacilli in alveolar macrophages, some of which spread through the bloodstream; however, the immune system response usually prevents the development of disease². Persons who are infected, but who do not have TB disease, are asymptomatic and not infectious. Such persons usually have a positive reaction to the tuberculin skin test. About 10% of infected persons will develop TB disease at some time in their lives, but the risk is considerably higher for persons who are immunosuppressed, especially those with HIV infection [1,2].

The highest priority for TB control is the identification and cure of the infectious cases, i.e. patients with sputum smear-positive PTB. Therefore all patients with clinical features suggesting PTB must submit sputum for diagnostic sputum smear microscopy. Most TB suspects are ambulatory. The diagnosis of PTB is therefore usually on an out-patient basis. A few TB suspects are severely ill and/or bed-bound and therefore need investigation as in-patients [3].

The diagnosis of TB depends on numerous factors namely; self-presentation of persons with TB symptoms to health care facility, high index of TB suspicion among health care professionals, TB screening practices in health facilities, sensitivity and specificity of diagnostic test used, turnaround time for delivery of laboratory results, and the capacity to trace people with positive results and start them on treatment⁴. Traditionally, TB services have relied on passive, self-presentation of persons with TB symptoms to the health care facilities. Increasing community awareness of TB symptoms will cause more persons with TB symptoms to present earlier to a health care facility for investigation for TB. It is also possible to look for persons with TB through active, community or facility based interventions such as community outreach events to schools, places of work, or through screening or investigating persons who have had contact with someone with recently diagnosed TB. The aim is to screen every person for TB annually [2,4].

Clinical screening by assessment of symptoms identifies PTB suspects among patients attending health facilities. The most cost-effective method of screening PTB suspects in high-prevalence countries is by sputum smear microscopy. When a suspect has a positive sputum smear, the person has sputum smear-positive PTB. Register this person with the appropriate health authority and start treatment. In most cases, a chest X-ray is unnecessary. In populations with a high TB prevalence, the tuberculin skin test is of little value in the diagnosis of TB in adults. A positive tuberculin skin test does not by itself distinguish *M. tuberculosis* infection from tuberculosis disease. Previous exposure to environmental mycobacteria may also result in a false-positive test result. Conversely, the tuberculin skin test result may be negative, even when the patient does have TB. Conditions often associated with a false-negative tuberculin skin test include HIV infection, severe malnutrition and military TB [3].

Culture is more sensitive than smear microscopy, detecting a higher proportion of cases among patients with symptoms. However, it is an expensive and slow diagnostic technique, not accessible to some patients. Time to positive results depends on bacillary load and should be positive by 4 weeks in most cases; however a culture is only reported as negative at the end of 6 weeks incubation. Culture is however an important diagnostic tool in patients with paucibacillary tuberculosis, such as HIV positive patients with smear negative pulmonary tuberculosis and children [5].

For increasing the diagnostic accuracy, in this randomized clinical trial, we are proposing a new scoring system for diagnosis of PTB in our clinical practice.

Pulmonary Tuberculosis (PTB) diagnostic accuracy index:

<i>PTB Diagnostic Accuracy Index (Step A)</i>		
<i>Sl No.</i>	<i>Components</i>	<i>Score</i>
1.	Cough more than 3 consecutive weeks	2
2.	Other clinical feature/features of PTB	1
3.	Unresponsiveness of optimal medication for > 7 days	1

4.	Close contact with PTB patient	1
5.	Clinician's judgement*	2
	Total	7

*Clinician must be at least qualified with MBBS or equivalent academic qualification and must be competent enough to treat respective patients (PTB) regularly at least for continuous last 06 months.

PTB Diagnostic Accuracy Index (Step B)

Threshold score	Advice
4 or more	Refer to Step B

PTB Diagnostic Accuracy Index (Step B)			
Sl No.	Components	Split score	Total score
1.	Complete blood count (CBC): • High ESR • Lymphocytosis	1 1	2
2.	Mantoux test (MT): • Positive • Equivocal • Negative	2 1 0	2
3.	Sputum for acid fast bacillus (AFB): • 2 or 3 slides positive out of 3 • 1 slide positive out of 3 • All slide negative (3)	6 5 0	6
4.	Chest X ray: (Digital): • Strongly suggestive • Equivocal • Non-specific change • Essentially normal	6 3 2 1 0	6
5.	Clinician's judgement**: (+ Reconsideration of Step A score) • First opinion positive • Second opinion positive	1 1	2
			18

**Clinician must be at least qualified with MBBS or equivalent academic qualification and must be competent enough to treat respective patients (PTB) regularly at least for continuous last 06 months.

Score	Interpretation	Advice
6 or more	Indication	Anti-TB chemotherapy.
4 – 5	Equivocal	C/S of sputum. Follow up (F/U) after 7-14 days with Step A±B.
3 or less	Non-specific	No specific treatment plan for TB. Exclusion of other causes.

6 or more with B (5) = 0	Equivocal high score	Refer to step C.
4 -5 (F/U)	Equivocal on F/U	C/S of sputum. Refer to step C.

PTB Diagnostic Accuracy Index (Step C)
GeneXpert TB Test

Methology

This multi-centric randomized clinical trial was conducted among the total 17723 patents of 4 different centres of 3 different levels of health care delivery system of Bangladesh from a period of June 2012 to July 2016. Patients with persistent cough and suspicion of pulmonary tuberculosis were included as study population. Respected patients with other intractable medical problems like severe uncontrolled concomitant co-morbidity of respiratory system, bronchogenic carcinoma, severe sepsis etc. were excluded from study population. Systemic random sampling was done to select the study population. No blinding was done. Data of different centres (2 primary, 1 secondary and 1 tertiary centres of health care delivery system) were processed, presented in tabulated form and discussed with compare & comparison on the basis of statistical analysis.

Results

Results in (UHC, Dighalia) Upazila Health Complex (including all Union Sub-centers and Satellite Clinics), Dighalia, Khulna, Bangladesh (Primary level of health care delivery system):

During the study period, a total 7601 patients were evaluated by Step A of PTB Diagnostic Accuracy Index and out of them, initially 2035 (26.8%) were referred for Step B. Among these total 2035 patients, 119 (5.8%) were dropped out at different phases of Step B and were excluded from the study. In case of 30 (0.4%) patients, those were initially negative to Step A, but referred to Step B later on, on subsequent follow-ups, were included and a total number 1946 (25.6%) patients were referred to Step B.

PTB Diagnostic Accuracy Index (Step B)	Sputum Culture		Total
	Positive	Negative	
Positive	231 (TP)	03 (FP)	234 (TP+FP)
Negative	04 (FN)	1708 (TN)	1712 (FN+TN)
Total	236 (TP+FN)	1711 (FP+TN)	1946 (TP+FP+ FN+TN)

Sensitivity = $TP / (TP + FN) \times 100 = (231/236) \times 100 = 97.9\%$

Specificity = $TN / (FP + TN) \times 100 = (1708/1711) \times 100 = 99.8\%$

Positive predictive value = $TP / (TP + FP) \times 100 = (231/234) \times 100 = 98.7\%$

Negative predictive value = $TN / (FN + TN) \times 100 = (1708/1712) \times 100 = 99.8\%$

Accuracy = $(TP+TN) / Total \times 100 = (1939/1946) \times 100 = 99.6\%$

Positive likelihood ratio = $Sensitivity / (100 - Specificity) = 97.9 / (100 - 99.8) = 489.5$

Negative likelihood ratio = $(100 - Sensitivity) / Specificity = (100 - 97.9) / 99.8 = 0.02$

Agreement (reliability/precision/reproducibility/repeatability) test of clinical measurements (between PTB Diagnostic Accuracy Index and sputum culture):

Observed agreement = $(231 + 1708) / 1946 = 0.996$

Expected value of 231 = $(234 \times 236) / 1946 = 28.4$

Expected value of 1708 = $(1712 \times 1711) / 1946 = 1505.4$

Agreement expected by chance = $(28.4 + 1505.4)/1946 = 0.788$

k (Kappa statistic) = $(\text{Observed agreement} - \text{Agreement expected by chance}) / (1 - \text{Agreement expected by chance}) = (0.996 - 0.788) / (1 - 0.788) = 0.98$

Interpretation: Excellent agreement between PTB Diagnostic Accuracy Index and sputum culture.

Results in (UHC, Katiadi) Upazila Health Complex (including all Union Sub-centers and Satellite Clinics), Katiadi, Kishoreganj, Bangladesh (Primary level of health care delivery system):

During the study period, a total 4520 patients were evaluated by Step A of PTB Diagnostic Accuracy Index and out of them, initially 1401 (31.0%) were referred for Step B. Among these total 1401 patients, 67 (4.8%) were dropped out at different phases of Step B and were excluded from the study. In case of 23 (0.5%) patients, those were initially negative to Step A, but referred to Step B later on, on subsequent follow-ups, were included and a total number 1357 (30.0%) patients were referred to Step B.

PTB Diagnostic Accuracy Index (Step B)	Sputum Culture		Total
	Positive	Negative	
Positive	197 (TP)	04 (FP)	201 (TP+FP)
Negative	03 (FN)	1153 (TN)	1156 (FN+TN)
Total	200 (TP+FN)	1157 (FP+TN)	1357 (TP+FP+ FN+TN)

Sensitivity = $TP / (TP + FN) \times 100 = (197/200) \times 100 = 98.5\%$

Specificity = $TN / (FP + TN) \times 100 = (1153/1157) \times 100 = 99.7\%$

Positive predictive value = $TP / (TP + FP) \times 100 = (197/201) \times 100 = 98.0\%$

Negative predictive value = $TN / (FN + TN) \times 100 = (1153/1156) \times 100 = 99.7\%$

Accuracy = $(TP+TN) / \text{Total} \times 100 = (1350/1357) \times 100 = 99.5\%$

Positive likelihood ratio = $\text{Sensitivity} / (100 - \text{Specificity}) = 98.5 / (100 - 99.7) = 328.3$

Negative likelihood ratio = $(100 - \text{Sensitivity}) / \text{Specificity} = (100 - 98.5) / 99.7 = 0.02$

Agreement (reliability/precision/reproducibility/repeatability) test of clinical measurements (between PTB Diagnostic Accuracy Index and sputum culture):

Observed agreement = $(197 + 1153) / 1357 = 0.995$

Expected value of 197 = $(201 \times 200) / 1357 = 29.9$

Expected value of 1753 = $(1156 \times 1157) / 1357 = 985.6$

Agreement expected by chance = $(29.9 + 985.6) / 1357 = 0.748$

k (Kappa statistic) = $(\text{Observed agreement} - \text{Agreement expected by chance}) / (1 - \text{Agreement expected by chance}) = (0.995 - 0.748) / (1 - 0.748) = 0.98$

Interpretation: Excellent agreement between PTB Diagnostic Accuracy Index and sputum culture.

Results in Khulna medical College Hospital (KMCH), Bangladesh (Tertiary level of health care delivery system):

During the study period, a total 3310 patients were evaluated by Step A of PTB Diagnostic Accuracy Index and out of them, initially 1497 (45.2%) were referred for Step B. Among these total 1497 patients, 50 (3.3%) were dropped out at different phases of Step B and were excluded from the study. In case of 12 (0.4%) patients, those were initially negative to Step A, but referred to Step B later on, on subsequent follow-ups, were included and a total number 1459 (44.1%) patients were referred to Step B.

PTB Diagnostic Accuracy Index (Step B)	Sputum culture		Total
	Positive	Negative	
Positive	113 (TP)	04 (FP)	117 (TP+FP)
Negative	02 (FN)	805 (TN)	807 (FN+TN)
Total	115 (TP+FN)	809 (FP+TN)	924 (TP+FP+ FN+TN)

Sensitivity = $TP / (TP + FN) \times 100 = (113/115) \times 100 = 98.3\%$

Specificity = $TN / (FP + TN) \times 100 = (805/809) \times 100 = 99.5\%$

Positive predictive value = $TP / (TP + FP) \times 100 = (113/117) \times 100 = 96.6\%$

Negative predictive value = $TN / (FN + TN) \times 100 = (805/807) \times 100 = 99.8\%$

Accuracy = $(TP + TN) / \text{Total} \times 100 = 99.4\%$

Positive likelihood ratio = $\text{Sensitivity} / (100 - \text{Specificity}) = 98.3 / (100 - 99.5) = 196.6$

Negative likelihood ratio = $(100 - \text{Sensitivity}) / \text{Specificity} = (100 - 98.3) / 99.5 = 0.02$

Agreement (reliability/ precision/ reproducibility/ repeatability) test of clinical measurements (between PTB Diagnostic Accuracy Index and sputum culture):

Observed agreement = $(113 + 805) / 924 = 0.994$

Expected value of 113 = $(117 \times 115) / 924 = 14.6$

Expected value of 805 = $(807 \times 809) / 924 = 706.6$

Agreement expected by chance = $(14.6 + 706.6) / 924 = 0.781$

k (Kappa statistic) = $(\text{Observed agreement} - \text{Agreement expected by chance}) / (1 - \text{Agreement expected by chance}) = (0.994 - 0.781) / (1 - 0.781) = 0.97$

Interpretation: Excellent agreement between PTB Diagnostic Accuracy Index and sputum culture.

Results in Khulna medical College Hospital (KMCH), Bangladesh (Tertiary level of health care delivery system):

During the study period, a total 3310 patients were evaluated by Step A of PTB Diagnostic Accuracy Index and out of them, initially 1497 (45.2%) were referred for Step B. Among these total 1497 patients, 50 (3.3%) were dropped out at different phases of Step B and were excluded from the study. In case of 12 (0.4%) patients, those were initially negative to Step A, but referred to Step B later on, on subsequent follow-ups, were included and a total number 1459 (44.1%) patients were referred to Step B.

PTB Diagnostic Accuracy Index (Step B)	Sputum culture		Total
	Positive	Negative	
Positive	145 (TP)	05 (FP)	150 (TP+FP)
Negative	04 (FN)	1300 (TN)	1304 (FN+TN)
Total	149 (TP+FN)	1305 (FP+TN)	1459 (TP+FP+ FN+TN)

Sensitivity = $TP / (TP + FN) \times 100 = (145/149) \times 100 = 97.3\%$

Specificity = $TN / (FP+TN) \times 100 = (1300/1305) \times 100 = 99.6\%$

Positive predictive value = $TP / (TP+FP) \times 100 = (145/150) \times 100 = 96.7\%$

Negative predictive value = $TN / (FN + TN) \times 100 = (1300/1304) \times 100 = 99.7\%$

Accuracy = $(TP + TN) / \text{Total} \times 100 = 99.0\%$

Positive likelihood ratio = $\text{Sensitivity} / (100 - \text{Specificity}) = 97.3 / (100 - 99.6) = 243.3$

Negative likelihood ratio = $(100 - \text{Sensitivity}) / \text{Specificity} = (100 - 97.3) / 99.6 = 0.03$

Agreement (reliability/precision/reproducibility/repeatability) test of clinical measurements (between PTB Diagnostic Accuracy Index and sputum culture):

$$\text{Observed agreement} = (145 + 1300)/1459 = 0.990$$

$$\text{Expected value of 145} = (150 \times 149)/1459 = 15.3$$

$$\text{Expected value of 1300} = (1304 \times 1305)/1459 = 1166.4$$

$$\text{Agreement expected by chance} = (15.3 + 1166.4)/1459 = 0.810$$

$$k \text{ (Kappa statistic)} = (\text{Observed agreement} - \text{Agreement expected by chance}) / (1 - \text{Agreement expected by chance}) = (0.990 - 0.810) / (1 - 0.810) = 0.95$$

Interpretation: Excellent agreement between PTB Diagnostic Accuracy Index and sputum culture.

Overall integrated result:

Different demographic characteristics and data regarding the study population in different centres are depicted in table 1.

Demographic data	Centres			
	UHC, Dighalia	UHC, Katiadi	KGH	KMCH
Total patients	7601	4520	2292	3310
Step B refer (n)	1946	1357	924	1459
Step B refer rate (%)	25.6%	30.0%	40.3%	44.1%
Dropout at Step B (n)	119	67	83	50
Dropout rate at Step B (%)	5.8%	4.8%	8.3%	3.3%
(-)ve to (+)ve at Step A (n)	30	23	16	12
(-)ve to (+)ve rate at Step A (%)	0.4%	0.5%	0.7%	0.4%

Table 1: Demographic data regarding the study population in all centres.

Different statistical parameters of newly proposed PTB diagnostic accuracy index are tabulated in table 2.

Parameters	Centres			
	UHC, Dighalia	UHC, Katiadi	KGH	KMCH
Sensitivity	97.9%	98.5%	98.3%	97.3%
Specificity	99.8%	99.7%	99.5%	99.6%
Positive predictive value	98.7%	98.0%	96.6%	96.7%
Negative predictive value	99.8%	99.7%	99.8%	99.7%
Accuracy	99.6%	99.5%	99.4%	99.0%
Positive likelihood ratio	489.5	328.3	196.6	243.3
Negative likelihood ratio	0.02	0.02	0.02	0.03
k (Kappa statistic)	0.98	0.98	0.97	0.95
Agreement with sputum culture	Excellent	Excellent	Excellent	Excellent
Intra-observer variation	0.3%	0.4%	0.4%	0.4%
Inter-observer variation	0.2%	0.1%	0.2%	0.1%

Table 2: Different statistical parameters of the score (Step B).

Discussion

In this research study, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the our newly proposed PTB diagnostic accuracy index (Step B) were 97.9%, 99.8%, 98.7%, 99.8% & 99.6% respectively in respect to sputum culture in UHC, Dighalia, Khulna and were 98.5%, 99.7%, 98.0%, 99.7% & 99.5% respectively (table 2) in UHC, Katiadi, kishoreganj (Primary/grass root level of health care delivery system). At secondary level these were 98.3%, 99.5%, 96.6%, 99.8% & 99.4% (Khulna General Hospital, Bangladesh) and at tertiary level these were 97.3%, 99.6%, 96.7%, 99.7% & 99.0% respectively (Khulna Medical College Hospital, Bangladesh). In all centres, the values of k (Kappa statistic) were in between 0.95 to 0.98, which suggest excellent Agreement of PTB diagnostic accuracy index (Step B) with sputum culture statistically (table 2). Intra-observer variation of results was within satisfactory level (in between 0.3% to 0.4%). And Inter-observer variation of results was also negligible (in between 0.1% to 0.2%). So, the parameters of this new scoring index for diagnosis pulmonary TB are quite statistically up to the mark and is gold standard and cost effective.

Other research studies suggest that for the diagnosis of PTB the detection of Acid Fast Bacilli (AFB) in expectorated sputum is still crucial, especially in developing countries, where other facilities including sputum culture for Mycobacterium Tuberculosis (MTB) are unavailable or are prohibitively expensive. When AFB is detected in sputum, the diagnosis of PTB is certain. However diagnostic problem start when patients with suspected PTB have a negative sputum smear [6,7]. It has always been recognized that a majority proportion of patients are sputum smear negative using the Ziehl-Nelsen (ZN) stain, the commonly used stain in most laboratories in the region to detect AFB in sputum. This is a simple, rapid and cheap test but lacks sensitivity of a single sputum test⁷. About 5000 bacilli per milliliter of sputum must be present for it to be positive. However it has been reported that multiple sputum tests in a good laboratory can give a sensitivity of about 90% [5]. Chest radiography is not always helpful in smear negative patients. The radiographic distinction between active and inactive tuberculosis can be difficult [6,7].

In fact, substantial numbers of patients are treated for tuberculosis without definitive diagnostic criteria⁸. In countries where resources are limited, and where the use of chest X-rays may be inadequate due to the cost as well as atypical presentation found in HIV infected patients, clinical and/or laboratory characteristics which are able to identify smear negative but culture positive PTB are required. The Tanzania National TB and Leprosy Programme uses a smear negative PTB diagnostic algorithm adopted from the World Health Organization (WHO) [6,9]. The usefulness of a new rapid diagnostic test (Patho-TB) using antibodies specific to mycobacterial antigens was evaluated for the rapid discrimination between pulmonary tuberculosis (TB) and non-TB pulmonary diseases on sputa. The sensitivity, specificity, positive predictive value, and negative predictive value of the Patho-TB test were 95%, 100%, 100%, and 84%, respectively. Patho-TB test is simple, quick, and easy to perform. Its sensitivity, specificity, and positive predictive value are satisfactory. Therefore, it could be used as a screening test in poorly equipped laboratories of TB endemic areas [10].

Conclusion

Pulmonary Tuberculosis (PTB) diagnostic accuracy index is a reliable and cost-effect scoring system in terms of sensitivity, specificity, positive predictive value, negative predictive value, accuracy, positive likelihood ratio, negative likelihood ratio, k (Kappa statistic), agreement with sputum culture, intra and inter-observer variation. This scoring index should be merge in national tuberculosis programme of different countries, especially of the developing countries where health care budget is a tremendous issue, after proper re-evaluation of this scoring system.

Recommendations

In conclusion of this study, it can be also said that however, this study was done in a comparatively limited number of study population and a narrow time scale, more research studies in this relation involving multiple centres and level of different countries should be performed with sufficient number study population with a wider time scale to depict the original scenario in the clinical setup.

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