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Diagnostic Accuracy and Clinical Role of Rapid C-Reactive Protein Testing in HIV-infected TB Suspects in South Africa

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Abstract

Objective—We sought to determine the accuracy and role of rapid C-reactive protein (CRP) testing in HIV-infected tuberculosis suspects.

Design—We enrolled HIV-infected adults (> 18 years) with a cough for > 2 weeks and negative sputum smears for acid-fast bacilli (AFB) in KwaZulu-Natal, South Africa. Participants were evaluated for pulmonary tuberculosis by a nurse with rapid CRP, and independently by a physician with a chest radiograph. Rapid CRP test results were compared to laboratory CRP and sputum sent for confirmation of tuberculosis.

Results—Among 93 participants, 55 (59%) were female, mean age was 35 years, and median CD4 count was 177/mm³. Forty-five (54%) participants were diagnosed with pulmonary tuberculosis. Diagnostic sensitivity and specificity were 95% (95% CI 74–99%) and 51% (95% CI 35–66%) for rapid CRP > 8 mg/l, 87% (95% CI 73–96%) and 53% (95% CI 38–68%) for nurse assessment, and 69% (95% CI 52–83%) and 76% (95% CI 61–87%) for physician examination. Combining a positive rapid CRP (> 8 mg/l) to nurse and physician assessments decreased post-test probability of pulmonary tuberculosis from 22% to 6% and 32% to 6%, respectively.

Conclusion—Rapid CRP testing helped exclude pulmonary tuberculosis, and may be a valuable test to assist nurses and physicians in tuberculosis-endemic regions.

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Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

Keywords

Tuberculosis; C-reactive protein; HIV/AIDS; point-of-care test; diagnostic testing; South Africa

Introduction

Tuberculosis is a leading cause of AIDS-related deaths worldwide.¹ In South Africa, nearly half a million new cases of tuberculosis are diagnosed annually, and over two-thirds of those people are living with HIV.² The World Health Organization promotes intensified case finding for tuberculosis in adults living with HIV, and suggests evaluating persons with a cough, fever, weight loss, or night sweats for pulmonary tuberculosis.^{3,4} Conducting microbiological testing for all patients who present with any of those common symptoms may overburden existing infrastructure, and a rapid, clinic-based test to exclude tuberculosis may be valuable.

Existing tests have low diagnostic sensitivity, or a high false negative rate, for detecting pulmonary tuberculosis among HIV-infected adults.⁵ Sputum smear microscopy for acid-fast bacilli (AFB) has poor sensitivity (9–33%) among HIV-infected adults with culture-confirmed pulmonary tuberculosis.^{6–8} Mycobacterial culture, which takes weeks to months to obtain results, is not accessible to many health facilities in sub-Saharan Africa.⁹ The Xpert MTB/RIF assay, which is more sensitive than smear microscopy, has lower diagnostic sensitivity for both sputum- smear negative and HIV-infected adults.^{10,11} Furthermore, placement in centralized reference laboratories has reduced its potential clinical impact.¹² Urine lipoarabinomannan has moderate sensitivity and high specificity for detecting active tuberculosis, so it may be valuable as a ‘rule-in’ test.^{13,14} A rapid, clinic-based test that could exclude active tuberculosis might improve patient outcomes.^{5,15}

C-reactive protein (CRP), a non-specific acute phase serum protein, is elevated in both HIV-infected and -uninfected people with active tuberculosis,^{16–19} and has been proposed as a biomarker for active tuberculosis.⁵ Rapid CRP tests have been developed, but their performance has not been evaluated in HIV-infected adults with suspected pulmonary tuberculosis. We sought to determine the diagnostic accuracy and clinical role of rapid CRP testing in HIV-infected tuberculosis suspects in a tuberculosis-endemic region.

Methods

Study design and participant selection

We conducted a study of HIV-infected tuberculosis suspects referred to Edendale Hospital in KwaZulu-Natal, South Africa from August 2009 to October 2010. Edendale serves a population with a high HIV prevalence and tuberculosis incidence.^{20,21} Eligible participants were referred from a primary care facility, were ≥ 18 years old, HIV-seropositive, had a cough for ≥ 2 weeks, and were either unable to produce a respiratory sputum sample or had ≥ 2 negative sputum smear microscopy for AFB samples. We excluded people who had taken antituberculosis medications within 3 months. Participants received a 5-day course of

amoxicillin/clavulanic acid or doxycycline before enrollment, in accordance with South African guidelines for sputum smear-negative tuberculosis suspects.²²

The Research Ethic Committee of the University of KwaZulu-Natal and the KwaZulu-Natal Department of Health approved the study. All participants provided written informed consent prior to enrollment.

Study Procedures

Upon enrollment, a study nurse performed a clinical assessment for pulmonary tuberculosis using a standardized questionnaire for tuberculosis symptoms. A nurse obtained venous blood for laboratory-based CRP and CD4 count testing, and one sputum sample for smear microscopy and mycobacterial culture from all participants (using an ultrasonic nebulizer with 5% hypertonic saline if cough was non-productive). A nurse obtained approximately 5 L of whole blood by finger prick of the index finger and performed rapid CRP testing using the NycoCard CRP test (Axis-Shield; Oslo, Norway), according to the manufacturer's specifications.²³ The finger-prick whole blood drop is placed on a card, which is then read by the machine. The test provided a quantitative CRP result ranging from 8–200 mg/liter (l). The NycoCard kit included a positive control test, and this calibration step was performed each morning before participant CRP testing.

Immediately after the study nurse visit, all participants had a same-day, single-view chest radiograph, symptom review and a targeted physical examination, including chest auscultation and lymph node palpation, by a physician who was blinded to the rapid CRP result. Participants were offered antiretroviral therapy in accordance with South African guidelines.²⁰

Laboratory Testing

Direct microscopy of AFB was performed with both Ziehl-Nielsen and Auramine fluorescent staining. All specimens sent for mycobacterial culture were cultured in liquid culture media (BACTEC™ MGIT™ BD, Sparks, MD, USA) and solid culture media. Positive cultures were identified as *M. tuberculosis* using a niacin test. Some AFB positive specimens were not cultured due to limited capacity. All laboratory investigations were performed at accredited laboratories by technicians registered with the Health Professions Council of South Africa.

Laboratory-based high-sensitivity CRP testing was performed using a Dimension RXL analyzer from Dade-Behring (Deerfield, IL, USA). The machine had a range of 0.7-400 mg/L with good precision.²⁴

Clinical Diagnosis of Tuberculosis

A study nurse classified participants as having pulmonary tuberculosis with presence of cough, an elevated rapid CRP test result (> 8 mg/L), and at least one of the following tuberculosis-related symptoms: fever, night sweats, or weight loss. Therefore, the diagnostic classification from the study nurse was a designated *a priori* algorithm that utilized both

symptom-based screening and rapid CRP result. The physician, who was blinded to CRP results, reviewed participants clinically and evaluated the chest radiograph.

Statistical Analysis

Culture-confirmed *M. tuberculosis* was used as the reference-standard diagnostic test for pulmonary tuberculosis. Participants with positive sputum smear microscopy and who did not have a sputum culture result were also classified as having pulmonary tuberculosis. We determined the correlation between the lab-based and rapid CRP results using correlation coefficients and receiver operating curves. We calculated sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios for lab-based CRP and rapid CRP testing using thresholds of > 8, 25, and 50 mg/l. We also calculated sensitivity and specificity for combinations of tuberculosis symptoms, nurse assessment, and physician assessment, both with and without rapid CRP testing. Exact 95% confidence intervals were calculated for test characteristics. We then assessed the change in clinical pre-test probability by multiplying the pre-test odds by the positive or negative likelihood ratio and then converting back to a post-test probability, when using various diagnostic strategies. All reported p-values were two-tailed with $\alpha=0.05$. We conducted analyses using SAS (version 9.2; SAS Institute, Cary, USA).

Results

Among 93 participants, mean age was 34.7 years [standard deviation (SD) ± 8.2], and 55 participants (59.1%) were female (Table 1). The mean duration of cough was 7.5 weeks (SD ± 3.6), and most participants reported fevers (94.6%), night sweats (88.2%), or weight loss (92.5%). Mean weight was 56.3 kg (SD ± 11.5), and median Karnofsky Performance score was 80 [Interquartile range (IQR) 70–80]. All participants were HIV-positive, and median CD4 count was 177/mm³ (IQR 80–256/mm³). Sixty participants (65.2%) had radiographic findings consistent with consolidation. Forty-five of 84 participants (53.6%) with bacteriology results had pulmonary tuberculosis; 37 were sputum culture positive and 8 were sputum smear positive.

Mean lab-based CRP was 70.7 mg/l (SD ± 72.1), and identified 70 participants (77.8%) as having a high value (> 5 mg/l). Mean rapid CRP was 50.7 mg/l (SD ± 54.8), and identified 64 participants (71.1%) as having a high value (> 8 mg/l). The correlation coefficient between lab-based CRP and rapid CRP was 0.79 among all observations, and 0.70 when restricting lab-based results to the range of the rapid CRP test (8–200 mg/l). The area under the receiver operating curve for the lab-based and rapid CRP tests were 0.87 (95% CI 0.79–0.95) and 0.82 (95% CI 0.74–0.91), respectively (Figure 1). Study nurses easily performed rapid CRP testing, and results were available within 5 minutes.

Diagnostic Accuracy of CRP Testing

Lab-based CRP > 8 mg/l had a diagnostic sensitivity of 97.4% (95% CI 92.5–99.9%), and specificity of 53.5% (95% CI 37.7–68.8%) (Table 2). Rapid CRP > 8 mg/l had a diagnostic sensitivity of 94.9% (95% CI 82.7–99.4%), and specificity of 51.1% (95% CI 35.8–66.3%). Using a high threshold for CRP positivity decreased sensitivity and increased specificity.

Among our cohort, rapid CRP > 8 mg/l had a positive predictive value of 62.7% (95% CI 49.2-75.0), and a negative predictive value of 92.0% (95% CI 74.0-99.0). Positive likelihood ratio (LR+) was highest (5.22) for rapid CRP \geq 50 mg/l. Negative likelihood ratio (LR-) was lowest (0.05 and 0.10) for lab-based and rapid CRP > 8 mg/l, respectively.

Diagnostic Accuracy of CRP Testing with Symptoms and/or Clinical Assessment

Among our cohort, having \geq 3 tuberculosis-related symptoms had 94.4% sensitivity (95% CI 86.5-99.9%), but only 4.4% specificity (95% CI 0.5-15.2%) (Table 3). When combined with rapid CRP > 8 mg/l, diagnostic sensitivity decreased slightly to 92.3% (95% CI 79.1-98.4%), but specificity increased to 53.3% (95% CI 37.9-68.3%). Using a higher threshold for rapid CRP decreased sensitivity and increased specificity.

Nursing assessment alone had a sensitivity of 87.2% (95% CI 72.6-95.7%) and specificity of 53.3% (95% CI 37.9-68.3) for diagnosing pulmonary tuberculosis. When using a combined testing strategy of either rapid CRP > 8 mg/l or nurse assessment positive, diagnostic sensitivity increased to 97.4% (95% CI 86.5-99.9%), but specificity decreased to 42.2% (95% CI 27.7-57.9%). Using a higher threshold for rapid CRP caused moderate decreases on diagnostic sensitivity and small increases on specificity. Likelihood ratios positive and negative were 1.87 and 0.24 for the nursing assessment alone, and 1.69 and 0.06 when using a combined strategy with rapid CRP > 8 mg/l.

Physician assessment with a chest radiograph alone had a sensitivity of 69.2% (95% CI 52.4-83.0%) and specificity of 75.6% (95% CI 60.5-87.1) for diagnosing pulmonary tuberculosis. When using a combined testing strategy of either rapid CRP > 8 mg/l or physician assessment positive, diagnostic sensitivity increased to 97.4% (95% CI 86.5-99.9%), but specificity decreased to 46.7% (95% CI 31.7-62.1%). Unlike the nursing assessment, using a higher threshold for rapid CRP appeared to have small decreases on diagnostic sensitivity, but moderate increases on specificity. Likelihood ratios positive and negative were 2.84 and 0.41 for the physician assessment alone, and 1.83 and 0.06 when using a combined strategy with rapid CRP > 8 mg/l.

Value of Rapid CRP on Post-test Probability

The use of rapid CRP test (> 8 mg/l) substantially improved a nurse or physicians ability to exclude pulmonary tuberculosis (Figure 2). The baseline prevalence (or pre-test probability) of pulmonary tuberculosis was 53.6%. When using nursing assessment alone, the post-test probability of disease was 68.3% for a positive assessment and 21.7% for a negative assessment. The inclusion of rapid CRP decreased the post-test probability of disease to 6.1% for a negative assessment, and had minimal impact (66.1%) on post-test probability for a positive assessment. Similarly, when using physician assessment alone, the post-test probability of disease was 76.6% for a positive assessment and 32.1% for a negative assessment. When either test was positive the post-test probability decreased slightly to 67.9%, but the post-test probability substantially decreased to only 6.1% when using rapid CRP testing.

Discussion

Among this cohort of HIV-infected tuberculosis suspects, a positive rapid CRP test (> 8 mg/l) had high overall sensitivity, but low specificity, for diagnosing pulmonary tuberculosis. Combining rapid CRP testing with a nurse or physician assessment provided significant value for excluding or “ruling out” pulmonary tuberculosis. The rapid CRP test, which had a strong correlation with results from the laboratory-based CRP test, was feasible of being operated at the clinical point-of-care by a nurse, was performed on whole blood obtained from a simple finger prick, and returned results within 5 minutes. Rapid, clinic-based CRP testing may be an inexpensive and valuable test to assist nurses and physicians in excluding pulmonary tuberculosis among HIV-infected adults in tuberculosis-endemic regions.

Whole blood CRP is known to correlate well with serum CRP. Testing whole blood with the rapid NycoCard CRP test, which was used in this study, has previously showed good correlation with serum in laboratory-based CRP results.²⁵ In a previous study, quantitative discrepancies began to appear at higher CRP concentrations (> 150 mg/l),²⁶ but this was not observed in our study. Our study demonstrates that nurses can accurately perform rapid CRP testing on whole blood in a clinical setting, and obtain results similar to a laboratory-based test.

Serum CRP has a positive association for the presence of pulmonary tuberculosis.^{16,27} Among a similar cohort of tuberculosis suspects, serum CRP above the upper limit of normal had a sensitivity of 98% and specificity of 59% for diagnosing either smear AFB- or culture-positive pulmonary tuberculosis, which were similar to our findings.²⁸ When used as a screening test among asymptomatic newly-diagnosed HIV-infected adults, serum CRP 10 mg/l had a sensitivity of 85% and specificity of 58% for culture-confirmed pulmonary tuberculosis.²⁹ Their findings may be different by using a different CRP machine (Quantikine; R&D Systems Inc., USA) and/or by including asymptomatic individuals. We improve on prior studies by providing the first evaluation of a rapid, clinic-based, whole blood CRP testing as a diagnostic test for pulmonary tuberculosis among HIV-infected adults in a tuberculosis-endemic region.

Our findings suggest that rapid CRP testing may be an efficient and effective method to exclude, or ‘rule out’, pulmonary tuberculosis among HIV-infected tuberculosis suspects, which has been suggested.^{28–30} In asymptomatic newly-diagnosed HIV-infected adults, CRP 10 mg/l had a negative predictive value of 95% and negative likelihood ratio of 0.3, both to which suggest potential use as a “rule out” test.²⁹ Using a similar CRP threshold among tuberculosis suspects, we previously reported a similar negative predictive value (96%), but a negative likelihood ratio of 0.04.²⁸ In our analyses, a negative rapid CRP test decreased the post-test probability of disease of the physician’s assessment by over 5-fold (32% to 6%). Thus, a negative rapid CRP test should give nurses and physicians more confidence for excluding pulmonary tuberculosis.

Several rapid quantitative and semi-quantitative CRP tests are now available. At least three tests, including the one used in this study, are small, portable, battery powered devices that

require 20 microliters of whole blood and provide a numerical readout (8–160 mg/l) within 4 minutes.³¹ Two semi-quantitative tests use a test cassette and reagent buffer, without a machine, and provide information on CRP being less than or greater than 10 mg/l.³² Although we evaluated a variety of CRP levels, we used a CRP > 8 mg/l since it is commonly used in rapid tests, has been reported in prior studies,^{33,34} and maximizes diagnostic sensitivity. In 2012, the average price of 3 rapid CRP machines was Euro (€) 1,837, and €4 per test.³⁵ However, CRP testing may decrease overall costs by reducing expensive and labor-intensive microbiological evaluations of sputum samples. Rapid exclusion of tuberculosis could also assist clinicians to initiate antiretroviral therapy more quickly, which might reduce mortality.³⁶

Our study had several limitations and strengths. We had a limited sample size, conducted the study in a single clinic, and did not assess rapid CRP with extrapulmonary tuberculosis. Sputum culture is an imperfect gold standard test and non-differential misclassification could reduce diagnostic accuracy. We also did not assess CRP as a prognostic indicator, as serum CRP > 10 mg/l and > 50 mg/l predict HIV disease progression and mortality.^{29,34} Finally, we evaluated rapid CRP as an outpatient diagnostic test among tuberculosis suspects in a tuberculosis-endemic region, and these results apply to HIV-infected sputum smear-negative tuberculosis suspects with cough for more than two weeks and may not be generalizable to other populations or areas with low tuberculosis rates. Rapid CRP testing should be evaluated in other populations, including inpatients, across a wider range of CD4 counts, and include a more diverse range of tuberculosis symptoms. Additional studies may also compare rapid, point-of-care CRP testing to the Xpert MTB/RIF assay conducted in a centralized laboratory for excluding active pulmonary tuberculosis.

In conclusion, rapid whole blood CRP testing can be performed at the clinical point-of-care, and may be an inexpensive and valuable test to assist clinicians in excluding pulmonary tuberculosis among HIV-infected tuberculosis suspects in a tuberculosis-endemic region. If CRP is a marker of tuberculosis bacillary load,²⁹ then rapid CRP testing at the clinical point-of-care, as well as repeated CRP measurement, may be a valuable host biomarker to allow for an earlier evaluation of treatment efficacy. Since rapid CRP testing has several appealing properties, including independence from microbiological laboratories, studies are warranted to determine if rapid whole blood CRP testing predicts disease relapse, treatment failure, or patient outcomes. Rapid CRP testing appears to be a promising tuberculosis test to exclude pulmonary tuberculosis at the clinical point-of-care in certain settings.

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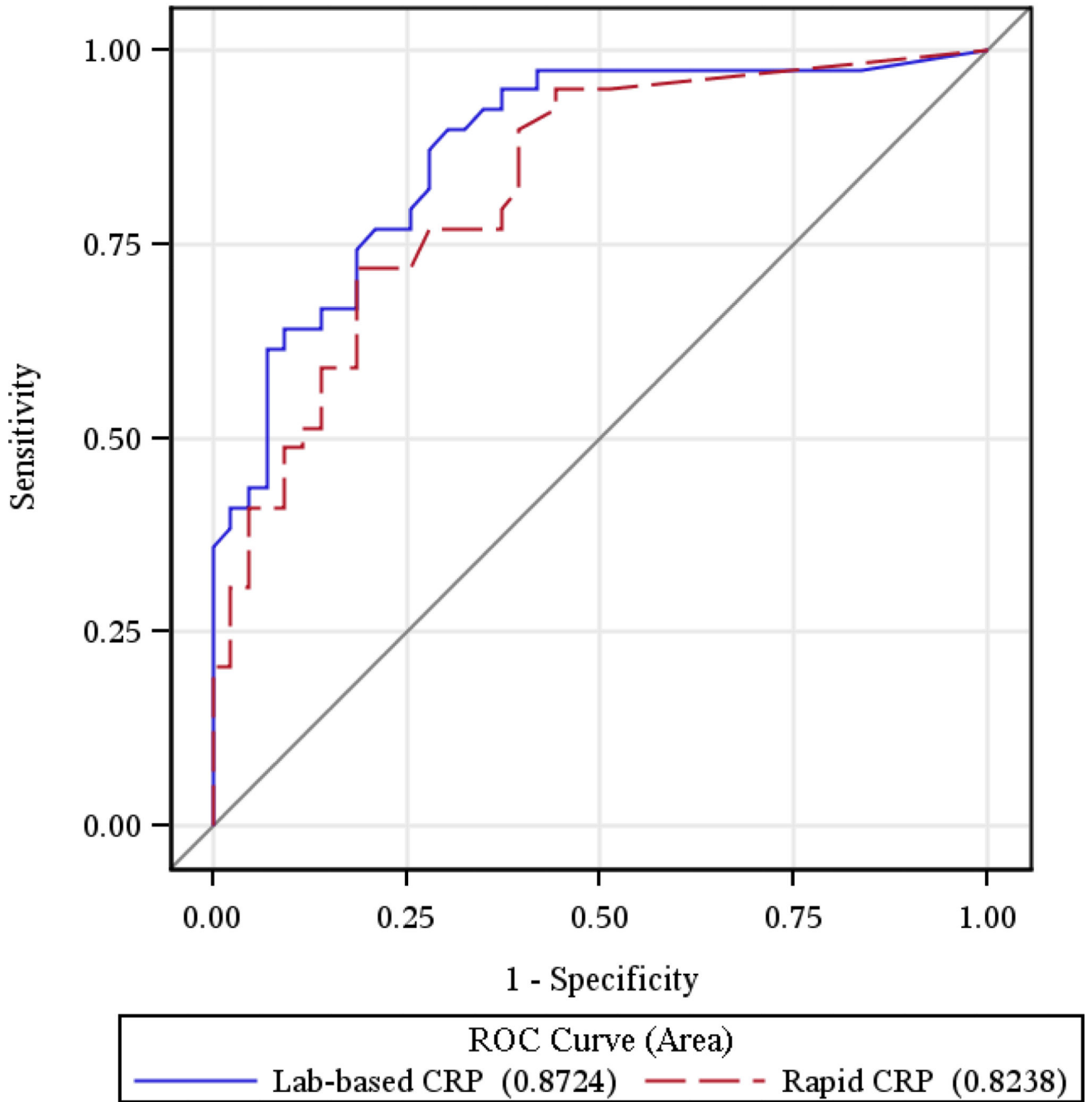


Figure 1. Receiver operating curves (ROC) for lab-based and rapid CRP tests for diagnosing active pulmonary tuberculosis.

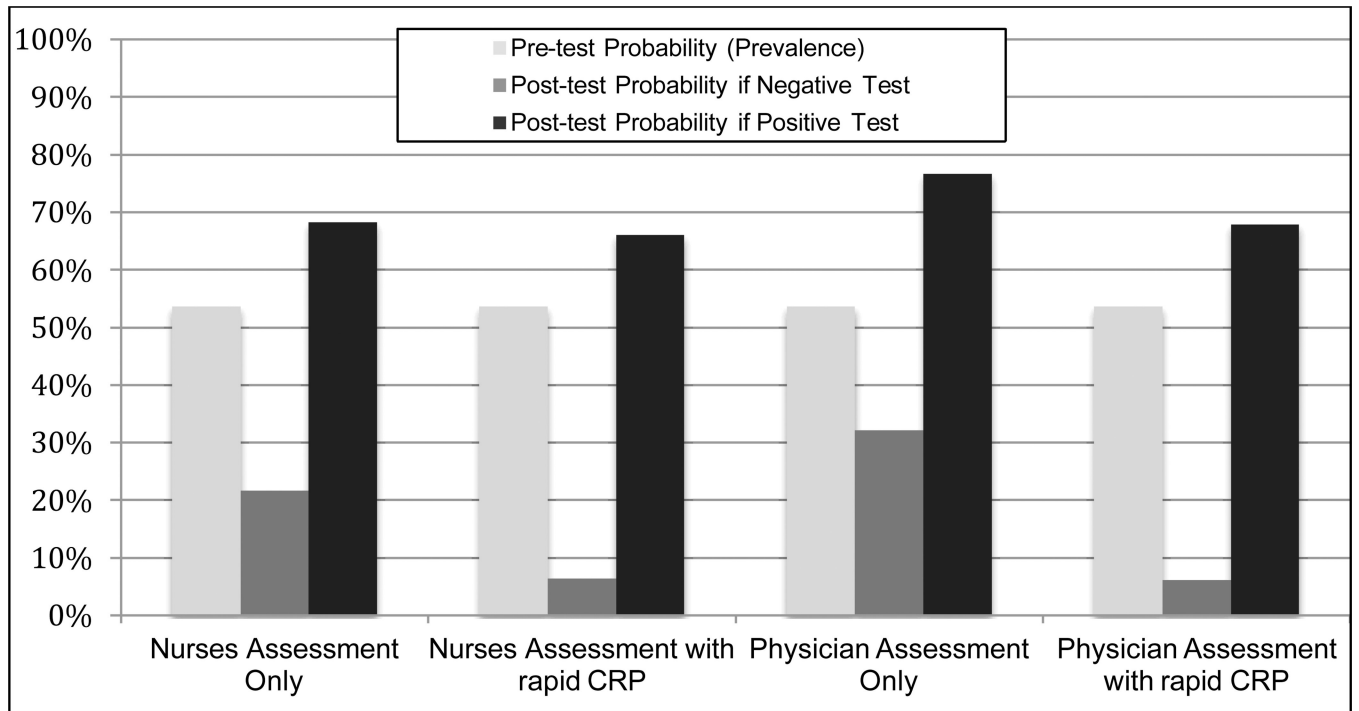


Figure 2.

Pre- and Post-test probabilities for clinical assessment, with and without rapid CRP testing (≥ 8 mg/l), among HIV-infected tuberculosis suspects in a tuberculosis-endemic region.

Table 1

Cohort characteristics of 93 HIV-infected tuberculosis suspects.

	Mean \pm SD or N (%)
Demographic	
Age (years)	34.7 \pm 8.2
Female	55 (59.1)
Tuberculosis-related Symptoms	
Cough	93 (100)
Cough Duration (weeks)	7.5 \pm 3.6
Fever	88 (94.6)
Night sweats	82 (88.2)
Weight loss	86 (92.5)
Clinical Assessment	
Weight (kg)	56.3 \pm 11.5
Karnofsky Performance Status [median, IQR]	80 [70, 80]
ECOG Performance Status [median, IQR]	1 [1, 2]
Laboratory and Radiographic	
CD4 count [median, IQR]/mm ³	177 [80, 256]
Chest X-ray with Infiltration or Miliary Pattern	60 (65.2)
Tuberculosis Diagnosis	
Sputum Microscopy or Culture Positive*	45 (53.6)

ECOG – Eastern Cooperative Oncology Group

* N=84

Table 2

Diagnostic accuracy of C-reactive protein (CRP) among HIV-infected tuberculosis suspects with bacteriology results (N=84).

	Sensitivity (%)	Specificity (%)	Positive PV (%)	Negative PV (%)	LR Positive	LR Negative
Lab-based C-reactive protein						
CRP >8 mg/l	97.4 (92.5–99.9)	53.5 (37.7–68.8)	65.5 (51.9–77.5)	95.8 (78.9–99.9)	2.18	0.05
CRP 25 mg/l	92.3 (79.1–98.4)	62.8 (46.7–77.0)	69.2 (54.9–81.3)	90.0 (73.5–97.9)	2.48	0.12
CRP 50 mg/l	76.9 (60.7–88.9)	74.4 (58.8–86.5)	73.2 (57.1–85.8)	78.1 (62.4–89.4)	3.00	0.31
Rapid C-reactive protein						
CRP >8 mg/l	94.9 (82.7–99.4)	51.1 (35.8–66.3)	62.7 (49.2–75.0)	92.0 (74.0–99.0)	1.94	0.10
CRP 25 mg/l	76.9 (60.7–88.9)	73.3 (58.1–85.4)	71.4 (55.4–84.3)	78.6 (63.2–89.7)	2.88	0.32
CRP 50 mg/l	59.0 (42.1–74.4)	86.7 (73.2–95.0)	79.3 (60.3–92.0)	70.9 (57.1–82.4)	5.22	0.47

PV = predictive value; LR = likelihood ratio.

Values in parentheses represent 95% confidence intervals.

Table 3

Rapid CRP testing to augment diagnostic accuracy of tuberculosis (TB) symptom screening, nurse assessment, and physician assessment (N=84).

	No Rapid CRP Testing		Rapid CRP >8 mg/l		Rapid CRP 25 mg/l		Rapid CRP 50 mg/l	
	Sens.(%)	Spec.(%)	Sens.(%)	Spec.(%)	Sens.(%)	Spec.(%)	Sens.(%)	Spec.(%)
Number of TB Symptoms								
2 symptoms	100(91.0–100)	2.2(0.1–11.8)	94.9(82.7–99.4)	51.1(35.8–66.3)	76.9(60.7–88.9)	73.3(58.1–85.4)	59.0(42.1–74.4)	86.7(73.2–95.0)
3 symptoms	97.4(86.5–99.9)	4.4(0.5–15.2)	92.3(79.1–98.4)	53.3(37.9–68.3)	74.4(57.9–87.0)	73.3(58.1–85.4)	56.4(39.6–72.2)	86.7(73.2–95.0)
All 4 symptoms	94.9(82.7–99.4)	28.9(16.4–44.3)	89.7(75.8–97.1)	64.4(48.8–78.1)	71.8(55.1–85.0)	82.2(68.0–92.0)	53.8(37.2–69.9)	88.9(76.0–96.3)
Nurse Assessment								
Nurse AND CRP value	--	--	84.6(69.5–94.1)	62.2(46.5–76.2)	71.8(55.1–85.0)	77.8(62.9–88.8)	56.4(39.6–72.2)	86.7(73.2–95.0)
Nurse OR CRP value*	--	--	97.4(86.5–99.9)	42.2(27.7–57.9)	92.3(79.1–98.4)	48.9(33.7–64.2)	92.3(79.1–98.4)	48.9(33.7–64.2)
Physician Assessment								
Physician with CXR AND CRP value	--	--	66.7(49.8–80.9)	80.0(65.4–90.4)	56.4(39.6–72.2)	86.7(73.2–95.0)	43.6(27.8–60.4)	88.9(76.0–96.3)
Physician with CXR OR CRP value*	--	--	97.4(86.5–99.9)	46.7(31.7–62.1)	89.7(75.8–97.1)	62.2(46.5–76.2)	84.6(69.5–94.1)	73.3(58.1–85.4)

Values in parentheses represent 95% confidence intervals.

* Test considered positive if either clinical assessment or rapid CRP >8 mg/l were positive.