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Diagnostic Outcomes After Chest Radiograph Interpretation in Patients With Suspected Tuberculosis and Negative Sputum Smears in a High-Burden Human Immunodeficiency Virus and Tuberculosis Setting

Patrick G. T. Cudahy,[1] Rodney Dawson,[2] Brian W. Allwood,[2,3] Gary Maartens,[4] and Douglas Wilson[5]

[1]Section of Infectious Disease, Department of Medicine, Yale University School of Medicine, New Haven, Connecticut; and [2]Department of Medicine, University of Cape Town Lung Institute and Division of Pulmonology, Groote Schuur Hospital, Cape Town, [3]Department of Medicine, Division of Pulmonology, Stellenbosch University/Tygerberg Academic Hospital, Stellenbosch, [4]Department of Medicine, Division of Clinical Pharmacology, University of Cape Town, Cape Town, and [5]Department of Internal Medicine, Edendale Hospital, University of KwaZulu-Natal, Pietermaritzburg, South Africa

Background. Evaluation of patients with suspected tuberculosis and negative sputum smears for acid-fast bacilli (AFB) is challenging, especially in high human immunodeficiency virus coinfection settings where sputum smears have lower sensitivity for detecting AFB.

Methods. We examined the utility of chest radiographs for detecting smear-negative pulmonary tuberculosis. Three hundred sixty sputum smear–negative patients who were referred from primary care clinics in the KwaZulu-Natal province of South Africa were evaluated. Chest radiographs were read by experienced pulmonologists using a previously validated Chest X-Ray Reading and Recording System (CRRS).

Results. Agreement between observers using CRRS was high at 91% with a Cohen's kappa of 0.64 (95% confidence interval [CI] = 0.52–0.76). Against a reference standard of sputum culture, sensitivity was 93% (95% CI = 86%–97%), whereas specificity was 14% (95% CI = 10%–19%). Performance against clinical diagnosis (following World Health Organization guidelines) was similar with sensitivity of 92% (95% CI = 88%–95%) and specificity of 20% (95% CI = 13%–28%).

Conclusion. The low specificity of CRRS in this setting indicates poor diagnostic utility for detecting pulmonary tuberculosis.

Keywords. tuberculosis; smear-negative; chest radiograph; South Africa.

Chest radiographs have been used to help detect tuberculosis for more than a century, yet their utility remains uncertain [1]. The main limitations of chest radiographs as a diagnostic investigation for tuberculosis are low specificity and low levels of interobserver agreement [2]. Certain radiographic features, such as cavities and apical disease, are considered typical for tuberculosis but have only been correlated with smear-positive disease in immunocompetent hosts [3]. Sub-Saharan Africa carries an undue burden of human immunodeficiency virus (HIV)–associated tuberculosis with 79% of the world's burden, and South Africa specifically accounts for 28% of the global burden [4]. Patients with HIV, especially those with CD4

counts <200 cells/μL, are more likely to have atypical chest radiograph findings [5]: cavities are uncommon, infiltrates do not have apical predominance, and concomitant extrapulmonary tuberculosis (pleural effusions and hilar/mediastinal lymphadenopathy) is more frequent. Advanced HIV disease is also associated with higher rates of normal chest radiographs in pulmonary tuberculosis, with rates of >20% in patients with <200 CD4 cells/μL [6].

Many settings rely on detection of acid-fast bacilli (AFB) on sputum smear microscopy as an initial diagnostic test for pulmonary tuberculosis [7]. Smear microscopy has been shown to have a low sensitivity for diagnosing active disease, especially in people living with HIV [5]. Chest radiograph interpretation remains a central component of current World Health Organization (WHO) recommendations for the diagnosis of smear-negative tuberculosis in high HIV prevalence settings [8, 9].

The Chest X-Ray Reading and Recording System (CRRS) was developed to aid in standardizing interpretation of chest radiographs [10]. Physicians who use this reporting system are trained in the use of a standardized reporting form. Previous studies have evaluated its performance in screening for tuberculosis in community surveys [10–12] and tuberculosis suspects

[13–15]. It has also been used for screening for tuberculosis in patients living with HIV who are initiating antiretrovirals [16] or isoniazid preventive therapy [17].
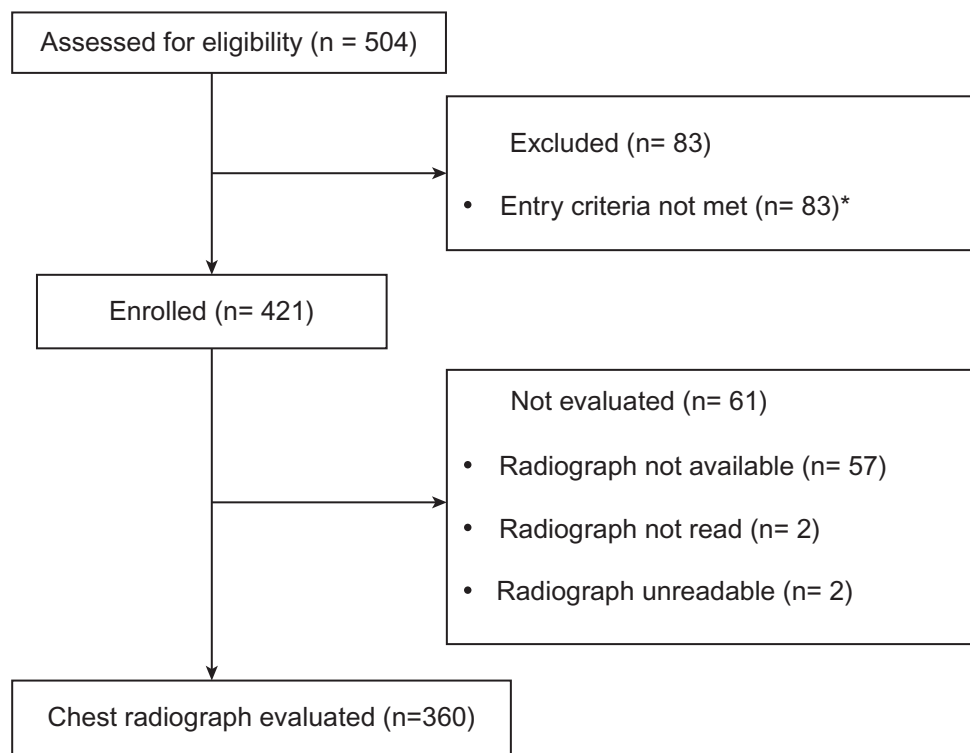
We evaluated the CRRS for detecting culture-positive tuberculosis in an adult cohort of smear-negative tuberculosis suspects in the uMgungundlovu District in the KwaZulu-Natal province of South Africa, where the annual tuberculosis incidence was 1142 per 100 000 around the time of this study in 2010 [18], and 70% of patients diagnosed with tuberculosis in South Africa were HIV coinfected [19]. In 2008 the HIV prevalence in adults aged 15–49 years was 18.8% [20].

METHODS

Ambulant adults aged ≥18 years with suspected tuberculosis and >2 negative sputum smears or inability to produce sputum were referred from primary care clinics in the uMgungundlovu District to the medical outpatient department at Edendale Hospital for further diagnostic evaluation as part of the standard district protocol for suspected smear-negative tuberculosis. Consecutive patients who met inclusion criteria were enrolled prospectively by the clinical research team between June 2005 and February 2007 (Figure 1). Inclusion criteria were >1 symptoms compatible with tuberculosis (cough, weight loss, loss of appetite, hemoptysis, fevers and chills, drenching night sweats, fatigue, chest pain, shortness of breath, swollen lymph nodes, or abdominal swelling) for >2 weeks. Exclusion criteria were Karnofsky performance score of <40, suspected tuberculosis meningitis, *Pneumocystis jirovecii* pneumonia, >1 week of antitubercular therapy, <3 months of antiretroviral therapy, or fluoroquinolone use within the past 6 months. Further details of the cohort have been published elsewhere [21]. All participants underwent standardized baseline clinical evaluation focusing on features suggesting tuberculosis and had a chest radiograph. Study physicians used standardized clinical criteria based on WHO guidelines to diagnose smear-negative tuberculosis. Participants were also referred for a pericardial and abdominal ultrasound scan if clinically indicated.

Sputum specimens were cultured in liquid culture media (BACTEC Mycobacteria Growth Indicator Tube [MGIT]; BD and Diagnostic Systems) and positive cultures were identified as *Mycobacterium tuberculosis* by the niacin test. Laboratory personnel did not have access to any other clinical information or test results. Sputum induction with hypertonic saline and an ultrasonic nebulizer was performed on participants with a nonproductive cough. Cultures from extrapulmonary sources were obtained at the clinical team's discretion. The decision

Assessed for eligibility (n = 504)

Excluded (n= 83)
- Entry criteria not met (n= 83)*

Enrolled (n= 421)

Not evaluated (n= 61)
- Radiograph not available (n= 57)
- Radiograph not read (n= 2)
- Radiograph unreadable (n= 2)

Chest radiograph evaluated (n=360)

Reasons for exclusion (n) Not able to attend for regular review - determined during screening visit (28) No active symptoms (17) Alternative medical diagnosis made at screening (14) Karnofsky Score <40 (5) Pneumocystis pneumonia (4) Informed consent not obtained (3) Sputum smear positive (3) Already on antitubercular therapy (3) Other (6).

Figure 1. Participant flow chart.

to start antitubercular therapy was made at the baseline visit using clinical and radiographic features. Participants who were not started on empiric antitubercular therapy at baseline and who were then found to be culture positive were started on antitubercular therapy during the follow-up period. Those with unknown HIV status were offered rapid antibody testing at baseline and at follow up visits 2, 4, and 8 weeks after enrollment.

Participant chest radiographs were stored at Edendale Hospital after completion of the study if not required by clinical teams for further participant treatment and care. Individuals with missing radiographs were excluded from analysis. Two expert pulmonologists trained in CRRS reporting subsequently reviewed participants' chest radiographs. The reporters were aware that all participants were smear-negative tuberculosis suspects but were blinded to culture results and individual clinical symptoms and signs. The 2 reporters reviewed the films individually and subsequently met to develop a consensus on whether the radiograph was consistent with tuberculosis without modifying the initial report.

Statistical Analysis

Sample size was determined by the needs of a larger parent study for which this was a substudy. We calculated interobserver agreement on individual chest radiograph features used in CRRS both with percentage agreement and using Cohen's kappa [22] with 95% confidence intervals (CIs). The radiographic features evaluated were parenchymal abnormalities, large opacities, small opacities, cavities, pleural abnormalities, and central abnormalities. A final assessment of the chest radiograph was evaluated as normal or abnormal and, if abnormal, suggestive of active tuberculosis. In a prespecified analysis, we calculated odds ratios, sensitivity, specificity, positive and negative predictive value, and likelihood ratios of a consensus interpretation of "abnormalities consistent with tuberculosis" by the 2 pulmonologists. Sputum tuberculosis culture was used as the reference standard. Radiograph interpretation was also compared with clinical diagnosis using WHO guidelines. Sensitivity and specificity were additionally calculated for the subgroup with known HIV disease in an exploratory analysis. Analysis was done using Jupyter version 4.2.3 (http://jupyter.org) and R version 3.3.0 (http://r-project.org).

Ethics

Written consent was obtained. The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

RESULTS

Study Population

Five hundred four patients were screened for entry into the study. Four hundred twenty-one participants with any symptom of tuberculosis, as well as negative sputum smears or without sputum production, were enrolled. Three hundred sixty-four had a chest radiograph available for CRRS reporting. Two did not have their chest radiographs read by the senior pulmonologists. Two films were assessed as unreadable by at least 1 of the readers and were excluded from further analysis. Three hundred sixty patients were in the final analysis.

As shown in Table 1, of those tested for HIV, 194 (84%) were HIV positive. One hundred twenty-eight of the 194 HIV-positive participants (66%) had a CD4 count performed at time of enrollment with a median of 135 cells/μL (range = 1–789). Only 5 participants with known HIV (2.57%) were on antiretroviral therapy at the time of enrollment. Most patients (72.8%) did not report prior tuberculosis disease.

Most patients presented with a cough of >2 weeks (92.5%). Ninety-nine percent of patients had either cough, fever, night sweats, or weight loss. One hundred twenty-one participants (34%) had sputum cultures positive for tuberculosis, and 239 (66%) had negative sputum cultures. Two hundred sixty participants (72%) were started on tuberculosis therapy.

Chest Radiograph Correlation With Sputum Culture–Positive Tuberculosis
Culture results were compared with a consensus read by the 2 senior pulmonologists of "abnormalities consistent with tuberculosis" (Table 2). The odds ratio for a chest radiograph labeled as consistent with tuberculosis for having a positive culture was 2.06 (95% CI = 0.96–4.46; $P = .06$). Sensitivity was 93% (95% CI = 86%–97%), and specificity was 14% (95% CI = 10%–19%), with a positive predictive value of 35% (95% CI = 30%–41%) and negative predictive value of 79% (95% CI = 64%–90%). The positive likelihood ratio was 1.08

Table 1. Baseline Characteristics of Participants

Characteristic	N = 360
Age, mean (SD), y	36.51 (10.23)
Male, no. (%)	198 (56.6)
BMI, mean (SD), kg/m²	27.1 (4.55)
HIV tested, no. (%)	231 (64.3)
HIV positive, no. (%)	194 (54)
CD4 T-lymphocyte count, median (IQR), cells/μL	135 (175.75)
Taking antiretroviral therapy, no. (%)	5 (2.57)
Reported prior tuberculosis diagnosis, no. (%)	98 (27.2)
Presenting symptom	
Cough for 2 weeks, no. (%)	333 (92.5)
Weight loss, no. (%)	271 (75.3)
Loss of appetite, no. (%)	251 (69.7)
Fevers/chills, no. (%)	208 (57.8)
Night sweats, no. (%)	251 (69.7)
Fatigue, no. (%)	224 (62.2)
Chest pain, no. (%)	199 (55.3)
Hemoptysis, no. (%)	398 (10.6)
Shortness of breath, no. (%)	146 (40.6)
Swollen lymph nodes, no. (%)	42 (11.7)
Abdominal swelling, no. (%)	5 (1.4)

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.

Table 2. Culture Results Versus Chest Radiograph Interpretation

Radiograph Interpretation	Sputum Culture Positive	Sputum Culture Negative	Total
Radiograph suggestive of tuberculosis	112	205	317
Radiograph not suggestive of tuberculosis	9	34	43
Total	121	239	360

(95% CI = 1.00–1.16), and the negative likelihood ratio was 0.52 (95% CI = 0.26–1.05). Of the 121 participants with positive sputum cultures, 10 (8%) were found to have a normal chest radiograph by reader 1 and 13 (11%) were found to have a normal chest radiograph by reader 2.

Interobserver Agreement

When evaluating specific features of the chest radiograph, reader 1 considered 278 (78%) chest radiographs to have parenchymal abnormalities, whereas reader 2 considered 261 (73%) chest radiographs to have parenchymal abnormalities, with a kappa of 0.63 (95% CI = 0.54–0.73). There were few small opacities, with 145 (41%) identified by reader 1 and 55 (15%) identified by reader 2, with a kappa of 0.37 (95% CI = 0.26–0.48). Cavities were identified in 74 (21%) cases by reader 1, 60 (17%) cases by reader 2, and in 46 cases (13%) by both. Agreement had a kappa of 0.62 (95% CI = 0.51–0.72) (Table 3).

Three hundred eight (86%) radiographs were read as abnormal by reader 1 and 312 (87%) were read as abnormal by reader 2. Eight radiographs were labeled as neither normal nor abnormal by reader 1, and 6 were labeled as neither normal nor abnormal by reader 2. Three hundred six (85%) chest radiographs were found to have "abnormalities consistent with tuberculosis" by reader 1, and 308 (86%) chest radiographs were found to have "abnormalities consistent with tuberculosis" by reader 2. Agreement had a kappa of 0.64 (95% CI = 0.52–0.76). When reviewed together for a consensus, 317 (88%) were found to have "abnormalities consistent with tuberculosis."

Chest Radiograph Correlation With Clinical Pulmonary Tuberculosis Diagnosis

Based on clinical assessment using WHO guidelines by study physicians, 245 participants (68%) were considered to have pulmonary tuberculosis. One hundred nine of the 245 (44%) had a positive sputum tuberculosis culture. For diagnosing culture-positive pulmonary tuberculosis, WHO guidelines had an odds ratio of 6.88 (95% CI = 3.63–13.16). Sensitivity was 90% (95% CI = 83%–95%), specificity was 43% (95% CI = 37–50), positive predictive value was 44% (95% CI = 38%–51%), negative predictive value was 90% (95% CI = 82%–94%), positive likelihood ratio was 1.58 (95% CI = 1.40–1.79), and negative likelihood ratio was 0.23 (95% CI = 0.13–0.40).

Table 3. Interobserver Agreement

Agreement Index (Reader 1/Reader2)	Parenchymal Abnormalities	Large Opacities	Small Opacifications	Cavities	Pleural Abnormalities	Central Abnormalities	Radiograph Normal	Radiograph Abnormal	Radiograph Suggests Active Tuberculosis
+/+	245	211	51	46	131	30	29	295	291
+/–	33	37	94	28	39	41	14	13	15
–/+	16	21	4	14	25	27	12	17	17
–/–	64	87	209	269	163	257	304	34	36
Agreement (95% CI)	0.86 (0.83–0.90)	0.84 (0.80–0.88)	0.73 (0.68–0.77)	0.88 (0.85–0.92)	0.82 (0.78–0.86)	0.81 (0.77–0.85)	0.93 (0.90–0.95)	0.92 (0.89–0.95)	0.91 (0.88–0.94)
Kappa (95% CI)	0.63 (0.54–0.73) Substantial agreement	0.63 (0.54–0.72) Substantial agreement	0.37 (0.26–0.48) Fair agreement	0.62 (0.51–0.72) Substantial agreement	0.64 (0.56–0.72) Substantial agreement	0.35 (0.22–0.49) Fair agreement	0.65 (0.52–0.78) Substantial agreement	0.65 (0.52–0.77) Substantial agreement	0.64 (0.52–0.76) Substantial agreement

Abbreviation: CI, confidence interval.

The clinical diagnosis, which included evidence of pulmonary tuberculosis on chest radiograph was compared with a consensus read by the 2 senior pulmonologists of "abnormalities consistent with tuberculosis." Using the clinical diagnosis as reference standard, a specialist read of a chest radiograph consistent with tuberculosis had an odds ratio of 2.81 (95% CI = 1.47–5.37; $P < .001$). Sensitivity was 92% (95% CI = 88%–95%) and specificity was 20% (95% CI = 13%–28%), with a positive predictive value of 71% (95% CI = 66%–76%) and negative predictive value of 53% (95% CI = 38%–69%). The positive likelihood ratio was 1.15 (95% CI = 1.04–1.27), and the negative likelihood ratio was 0.41 (95% CI = 0.23–0.71). Seventy-eight patients (21%) found to have radiographs consistent with pulmonary tuberculosis were not started on tuberculosis treatment.

One hundred ninety-four participants had known HIV disease. In this subset, 71 (39%) had positive sputum cultures for tuberculosis, and 123 (61%) were culture negative. Similar to the overall population, in this subset the odds ratio for a chest radiograph consistent with tuberculosis versus culture was 1.78 (95% CI = 0.71–4.43; $P = .20$).

DISCUSSION

In this study of participants in a high tuberculosis and HIV prevalence region presenting with pulmonary symptoms and negative AFB smears, a high proportion were judged by experienced pulmonologists using the CRRS system to have chest radiographs consistent with tuberculosis, but this had low specificity for either clinician-diagnosed (using WHO guidelines) or culture-proven pulmonary tuberculosis. The strengths of our study were that it evaluated chest radiographs using a systematic interpretation form by experienced pulmonologists and that it was completed in a clinical setting with the same radiology services offered to public-sector patients.

Despite 68% of participants having clinical evidence of tuberculosis and only 34% having sputum cultures positive for tuberculosis, >85% of chest radiographs were considered abnormal. In this group of mostly HIV coinfected participants with a median CD4 count of 135, the chest radiograph abnormalities could represent a range of opportunistic infections or comorbidities. The performance of CRRS in diagnosing tuberculosis did not differ significantly in the subgroup of patients with confirmed HIV. The high number of abnormal chest radiographs could also be in part due to prior scarring because nearly 30% of participants reported a history of prior tuberculosis. Despite the high rates of abnormal chest radiographs, between 8% and 11% of those with sputum culture–positive tuberculosis had chest radiographs read as normal.

Smear-negative tuberculosis remains a challenge to diagnose even as the introduction of rapid molecular tests such as the Xpert MTB/RIF are replacing the sputum smear as a front-line diagnostic. These too have had limited sensitivity in smear-negative disease, especially in HIV coinfected suspects [23]. New developments such as the Xpert Ultra have increased sensitivity for detecting smear-negative disease but have not yet been rolled out on a large scale. Given the currently limited ability of these tools to definitively diagnose tuberculosis in a resource-poor setting, clinicians still regularly rely on chest radiographs. In our particular setting, tuberculosis incidence and HIV prevalence have remained high in the 10 years since this study was conducted, with 678 tuberculosis cases per 100 000 persons and an HIV prevalence in adults aged 15–49 years of 18.9% reported in 2016 [24, 25]. Even with improved diagnostic tools, our results remain relevant, and improved diagnostics are needed for the diagnosis of smear-negative pulmonary tuberculosis to reduce the role of the chest radiograph in diagnostic algorithms.

For most of the features evaluated, interobserver agreement had a kappa >60%. This is generally considered to be substantial agreement [26]. The only outliers were in judging small opacifications and central abnormalities, for which there was only fair agreement. This is similar to other evaluations of the CRRS with trained readers [16]. There was good agreement on the presence of cavities, with a kappa of 0.61. In older studies, cavities have been highly correlated with smear-positive disease [27]. Our findings of a relatively high proportion (13%) of cavities in smear-negative disease were concordant with a study in Uganda with a similar population of HIV-seropositive tuberculosis patients with low CD4 counts [13]. It is possible that some cavities could be the result of prior tuberculosis rather than representative of active disease.

Limitations of our study were that further investigations for tuberculosis, such as bronchoscopy or polymerase chain reaction–based diagnostics such as Xpert MTB/RIF, were not obtained on patients with abnormal radiographs but negative sputum cultures to further rule out tuberculosis. The generalizability of the study was limited by being conducted in a setting with a very high incidence of both HIV and tuberculosis. Diagnosis was made strictly on WHO criteria at a centralized treatment site and not at the peripheral referring clinics.

Chest radiographs were evaluated in our study by specialist pulmonologists and not front-line clinicians. Presumably the performance of the CRRS by nonspecialists would be worse at detecting tuberculosis. Henostroza et al compared CRRS use by medical officers with >10 years of experience in treating tuberculosis versus less experienced clinical officers in a similar high-burden setting and found that the clinical officers had lower interobserver agreement and lower specificity for diagnosing tuberculosis [12]. The CRRS may also increase the time for interpreting a chest radiograph in a front-line setting. Although actual time taken to interpret each film was not measured, other studies have recorded a CRRS read at up to 4 minutes per chest radiograph [15]. These limitations would further limit the utility of the CRRS by primary care clinicians.

There was also not a large enough population of HIV-negative patients to evaluate as a subgroup and in general HIV testing uptake was low, with only 64% of participants having a result. Fourteen percent of the participants enrolled in the study did not have chest radiographs available and were excluded from the study. The largest identified factor in having a missing chest radiograph was the continued use of the radiographs by clinical teams for further treatment, potentially introducing bias by preferentially excluding sicker patients.

In conclusion, we found that in a setting with high rates of tuberculosis and HIV coinfection, the CRRS had little diagnostic utility in patients presenting with symptoms of tuberculosis and a negative sputum smear.

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