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Original Article

Diagnostic Evaluation of Pulmonary Tuberculosis in Qatar: A Retrospective Analysis of Clinical, Histopathological, and Microbiological Findings

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ABSTRACT

Background: Tuberculosis (TB) poses unique diagnostic challenges in Qatar due to its large expatriate population originating from endemic regions. This study evaluated the comparative diagnostic performance of clinical, histopathological, and microbiological methods in a highly selected cohort of suspected pulmonary TB patients who underwent invasive diagnostic procedures.

Methods: A retrospective cross-sectional study was conducted at Hamad General Hospital, Doha, Qatar, reviewing records from January 2010 to December 2019. Out of 3240 screened admissions, 58 patients who underwent comprehensive diagnostic evaluation–including QuantiFERON-TB Gold QuantiFERON®-TB (QFT), tuberculin skin test Purified Protein Derivative (PPD), acid-fast bacilli (AFB) smear, TB culture, and tissue biopsy–were included. Diagnostic accuracy was assessed using sensitivity, specificity, predictive values, likelihood ratios (LRs), and area under the receiver operating characteristic curve (AUC), utilizing histopathological and microbiological findings as reference standards.

Results: The cohort was predominantly female (77.6%) and non-Qatari (96.6%), with a mean age of 33.6 years. Classic constitutional symptoms were surprisingly infrequent (cough 29.3%, fever 17.2%, weight loss 17.2%). Radiological abnormalities were present in 75.9% of chest X-rays and 65.5% of computed tomography scans. Microbiological culture demonstrated the highest positive predictive value (90.3%) and a moderate rule-in value (LR+ ≈ 2.4), though its overall discriminative ability was modest (AUC = 0.64). Biopsy culture showed strong rule-in potential (LR+ > 5). Conversely, immunological assays (QFT, PPD) and AFB smear exhibited very low sensitivity (ranging from 4.4% to 14.3%) and LRs close to 1, indicating minimal diagnostic utility for confirming active disease in this complex cohort.

Conclusions: In suspected pulmonary TB cases requiring advanced diagnostic workup, immunological tests and sputum smear microscopy lack the sensitivity to rule in active disease reliably. While tissue and sputum cultures provided the most meaningful diagnostic confirmation, their overall accuracy was moderate. These findings highlight the limitations of conventional triage tests in highly selected populations and underscore the critical need to integrate rapid molecular diagnostics, such as GeneXpert, into clinical algorithms to bridge the diagnostic gap.

Key words: Tuberculosis, diagnostic accuracy, microbiology, histopathology, Qatar, ROC curve

INTRODUCTION

Tuberculosis (TB) remains a formidable global public health threat. According to the World Health Organization (WHO) Global Tuberculosis Report 2024, an estimated 10.8 million individuals developed TB in 2023, resulting in 1.25 million deaths, solidifying its position as the world's leading infectious disease killer. [1] While global incidence is slowly declining, the diagnostic gap remains a critical bottleneck; approximately 40% of TB cases remain undiagnosed or unreported, perpetuating silent transmission. [2]

The State of Qatar is classified by the WHO as a low TB incidence country. However, its demographic landscape—characterized by a massive expatriate workforce predominantly originating from high TB burden regions in South Asia and Southeast Asia—creates a unique epidemiological paradox. [3] Consequently, the country relies heavily on rigorous pre-employment screening and active case-finding to mitigate transmission. Despite these robust national control programs, diagnosing active pulmonary TB in clinical settings remains challenging, particularly in patients who present with atypical symptoms or non-resolving respiratory complaints. [4]

The diagnostic evaluation of suspected pulmonary TB relies on a triangulation of clinical assessment, radiology, histopathology, and microbiology. Traditional immunological tools, such as the tuberculin skin test (TST), suffer from poor specificity in populations universally vaccinated with Bacillus Calmette–Guérin (BCG). [5] While interferon-gamma release assays (IGRAs), such as QuantiFERON-TB Gold (QFT), offer improved specificity for *Mycobacterium tuberculosis* infection, they cannot reliably differentiate between latent TB infection (LTBI) and active disease, limiting their utility as standalone diagnostic tests. [6] Microbiological confirmation via sputum acid-fast bacilli (AFB) smear microscopy is rapid but notoriously insensitive, particularly in paucibacillary disease. Conversely, mycobacterial culture remains the historical reference standard, yielding high specificity but suffering from prolonged turnaround times. [7]

However, existing literature suffers from several critical gaps. First, most diagnostic accuracy studies have been conducted in high-incidence, immunocompromised, or well-defined symptomatic populations, leaving a paucity of data regarding the performance of conventional tests in highly selected, atypical cohorts from low-incidence Gulf nations. [8] Second, previous reports have rarely employed comprehensive likelihood ratios (LRs) and receiver operating characteristic (ROC) curves to quantify the *clinical utility* of tests in patients who have already passed initial screening. [9] Third, the absence of rapid molecular diagnostics (e.g., Xpert MTB/RIF assay test (MTB/RIF)) in most retrospective Gulf studies limits direct comparison with WHO-endorsed current standards. [10] Consequently, clinicians in such settings lack evidence-based guidance on whether a negative IGRA or smear can safely exclude active disease in complex cases requiring invasive workup.

Given these gaps, the present study aimed to: (1) evaluate the diagnostic performance of clinical, histopathological, and conventional microbiological methods in a highly selected cohort of suspected pulmonary TB patients in Qatar using advanced statistical metrics (LRs, AUC), and (2) identify the magnitude of diagnostic uncertainty introduced by reliance on conventional tests, thereby justifying the need for rapid molecular integration.

MATERIALS AND METHODS

Study Design and Participants

This retrospective observational study was performed at Hamad General Hospital, Doha, Qatar. We systematically reviewed medical records spanning 10 years from January 1, 2010, through December 31, 2019. Eligible participants included patients with clinical suspicion of pulmonary TB who underwent comprehensive diagnostic evaluation. Following the application of inclusion criteria, 58 patients were enrolled in the final analysis.

Data Extraction

Clinical data were systematically collected using a pre-designed standardized data collection form. The following variables were captured:

- Patient demographics and baseline characteristics
- Clinical symptoms and presentation patterns
- Complete laboratory profiles and hematological parameters
- Radiological findings from chest imaging studies
- Results from TB-specific diagnostic tests, including QuantiFERON-Gold assay, tuberculin skin test (PPD), acid-fast bacilli (AFB) microscopy, and mycobacterial culture
- Histopathological examination results and microbiological analysis from tissue specimens

Diagnostic Methodology

All enrolled patients underwent sputum collection for AFB microscopy and mycobacterial culture analysis. When clinically warranted, invasive procedures, including flexible bronchoscopy or computed tomography (CT)-guided percutaneous lung biopsy, were performed to obtain tissue samples for comprehensive histopathological and microbiological assessment.

Statistical Methods

Descriptive statistics were employed for data analysis. Normally distributed continuous variables were expressed as mean ± standard deviation, while non-parametric data were reported as median with interquartile range. Categorical variables were summarized using frequencies and percentages. Diagnostic test performance was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Diagnostic accuracy was further assessed using ROC curve analysis and LR calculations. Statistical significance was defined as a P value < 0.05. Data analysis was performed with SPSS software (v 23; IBM Corp, Armonk, NY, USA).

Ethics Statement

This study received formal approval from the institutional review board of Hamad Medical Corporation under Protocol Number MRC-01-19-430, ensuring compliance with ethical standards for medical research.

RESULTS

Demographic and Clinical Characteristics

A total of 58 patients met the inclusion criteria and were included in the final analysis. The mean age of the cohort was 33.6 ± 9.8 years (range 19–68). The study population was predominantly female (77.6%) and non-Qatari (96.6%), reflecting the demographic profile of the expatriate workforce. A prior history of TB was reported by 24.1% of patients, whereas only one patient (1.7%) reported a documented history of contact with a TB patient (**Table 1**).

The clinical presentation of the cohort was notably atypical, with classic TB symptoms being relatively infrequent. Cough was the most common presenting symptom, observed in 29.3% of patients, followed by fever (17.2%) and weight loss (17.2%). Hemoptysis was rare (1.7%). Other symptoms included anorexia (13.8%), chest pain (6.9%), and dyspnea (8.6%; **Table 2**).

Hematological and Radiological Findings

Hematological abnormalities were highly prevalent within the cohort. The most frequent abnormalities were elevated eosinophils (77.6%), abnormal monocyte counts (70.7%), and abnormal basophil counts (62.1%). Abnormal neutrophil and lymphocyte counts were observed in 39.7% and 31.1% of patients, respectively, while abnormal hemoglobin and platelet levels were less common (13.8% each; **Table 3**; **Figure 1**).

Radiological abnormalities were observed in the majority of patients. Abnormalities were identified in 75.9% of chest X-rays and 65.5% of chest CT scans (**Table 3**).

Diagnostic Yields

The overall diagnostic yields varied significantly depending on the modality utilized. Bronchoscopic biopsy TB culture demonstrated the highest positive yield (77.6%), followed by bronchoscopic biopsy AFB smear (56.9%) and sputum TB culture (53.4%). In stark contrast, immunological tests had very low positive yields: QuantiFERON-TB Gold (QFT) was positive in only 10.3% of cases, PPD testing in 6.9%, and sputum AFB smear in just 5.2% (**Table 3**; **Figure 2**).

Diagnostic Accuracy Against Histopathology

When histopathological findings were utilized as the reference standard (**Table 4**), both immunological and standard smear tests demonstrated poor sensitivity. QFT showed a sensitivity of only 14.3% (specificity 90.2%), while PPD testing exhibited 0% sensitivity (specificity 92.2%). Sputum AFB smear also yielded negligible sensitivity (6.5%) despite high specificity (94.1%) and a PPV of 100%. Sputum TB culture achieved the highest sensitivity (60.9%) and a PPV of 90.3%, though its specificity was 75.0%. An important discrepancy was noted: of the 31 patients positive for sputum TB culture, 30 had histopathology that was not suggestive of TB.

Diagnostic Accuracy Against Microbiology

When compared against a composite microbiological reference standard (positive AFB smear or TB culture; **Table 5**), the limitations of immunological testing were further emphasized. QFT sensitivity was 10.9%, and PPD sensitivity was 4.4%. Sputum AFB smear maintained perfect specificity and PPV (100%) but a sensitivity of just 6.5%. Sputum TB culture consistently outperformed other individual modalities, with a sensitivity of 60.9%, specificity of 75.0%, PPV of 90.3%, and a NPV of 33.3%.

Table 2: Clinical presentation of suspected pulmonary TB patients.

Presenting symptoms or signs	Frequency	Percentage
Fever	10	17.2%
Cough	17	29.3%
Dyspnea	5	8.6%
Hemoptysis	1	1.7%
Anorexia	8	13.8%
Weight loss	10	17.2%
Night sweats	2	3.4%
Wheeze	3	5.2%
Chest pain	4	6.9%
Others	6	10.3%

Table 1: Demographic characteristics of patients with suspected pulmonary TB.

Variable	Categories	Frequency	Percentage
Age (mean ± SD) (minimum–maximum)	Age (mean ± SD) (minimum–maximum)	33.6 ± 9.8 (19–68)	33.6 ± 9.8 (19–68)
Gender	Male	13	22.4%
	Female	45	77.6%
Nationality	Qatari	2	3.4%
	Other	56	96.6%
Ward	CDC	5	8.6%
	HG Bronchoscopy	45	77.6%
	HGH	6	10.3%
	HGH/CDC	2	3.4%
History of contact with a tuberculosis patient	Yes	1	1.7%
	No	57	98.3%
Past history of tuberculosis	Yes	14	24.1%
	No	44	75.9%

Table 3: Diagnostic methods and yields among suspected pulmonary TB patients.

Diagnostic methods	Frequency	Percentage
QuantiFERON	6	10.3%
PPD testing	4	6.9%
AFB sputum	3	5.2%
TB culture	31	53.4%
Bronchoscopic Biopsy Caseating Granuloma (Histopathology)	7	12.1%
Bronchoscopic Biopsy AFB smear (Microbiology)	33	56.9%
Bronchoscopic Biopsy, TB culture (Microbiology)	45	77.6%
Abnormal chest computed tomography		
Yes	38	65.5%
No	20	34.5%
Abnormal chest X-rays		
Yes	44	75.9%
No	14	24.1%

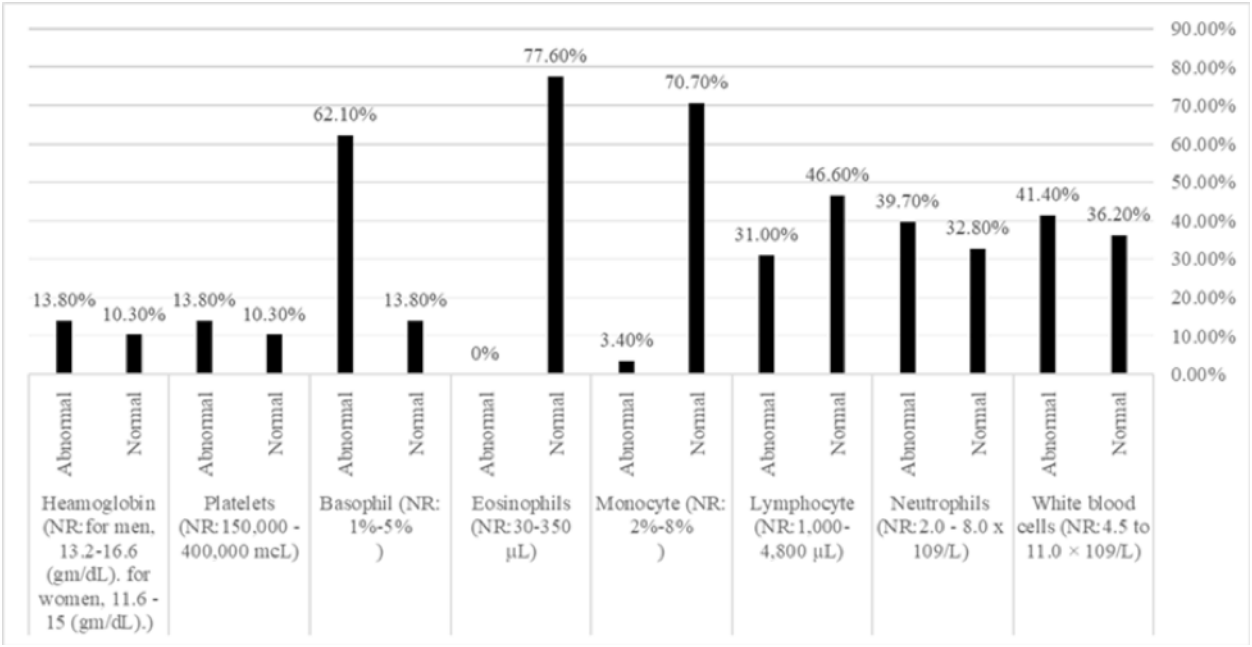

Figure 1: Hematological findings of patients with suspected pulmonary TB.

Predictors of Pulmonary TB

Multivariable logistic regression analysis (**Table 6**; **Figure 3**) identified a positive sputum TB culture as the only independent predictor significantly associated with histopathologically confirmed TB (adjusted odds ratio [aOR] = 25.7 [95% CI, 2.1–301.2]; *P* = 0.01). When evaluating predictors against microbiological confirmation, QFT, PPD, AFB smear, and abnormal radiological findings did not emerge as statistically significant independent predictors in the adjusted models.

LRs and ROC Curve Analysis

LR analysis (**Table 7**) demonstrated that QFT (LR+, 1.1–1.4), PPD (LR+, 0.5), and sputum AFB smear (LR+ 1.1) provided minimal diagnostic value, with LR values close to 1.0. Conversely, sputum TB culture provided a moderate rule-in value (LR+ ≈ 2.4; LR− ≈ 0.5), while biopsy TB culture demonstrated strong rule-in potential (LR+ > 5).

Area under the receiver operating characteristic curve (AUC) analysis (**Table 4,5**; **Figure 4**) revealed that sputum TB culture possessed the highest discriminative ability among the non-invasive tests, though overall discriminatory power was modest (AUC = 0.64 [95% CI, 0.50–0.76]). The AUCs for QFT (0.28), PPD (0.21), and AFB smear (0.26) indicated poor discriminative capacity in this cohort.

Pre- and Post-Test Probabilities

Using the observed culture-confirmed TB prevalence in the cohort (53.4%) as the pre-test probability (**Table 7**), clinical

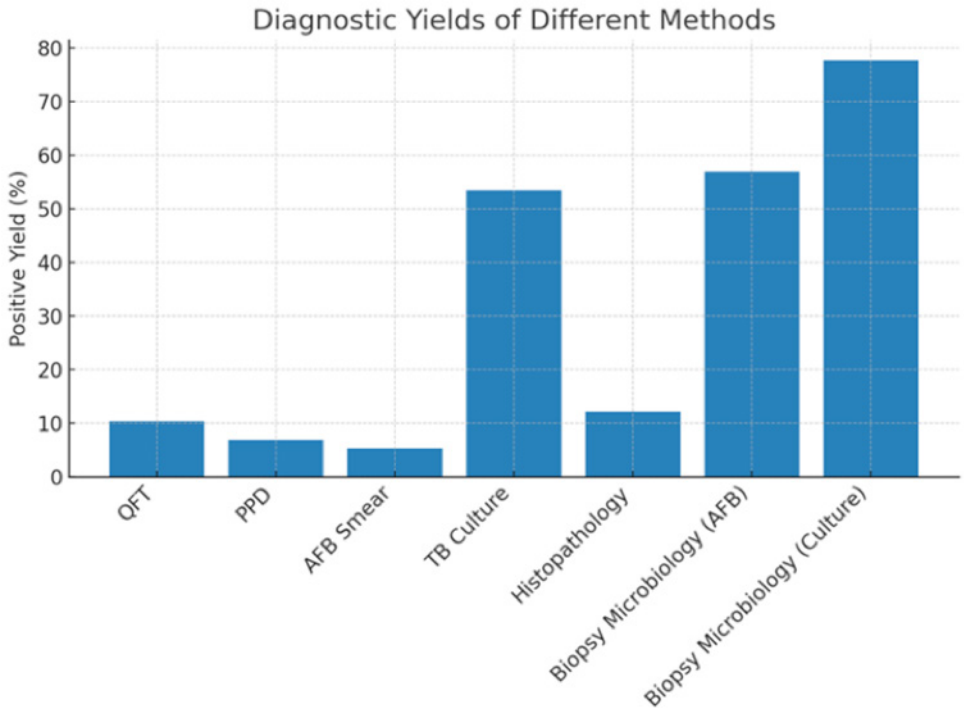

Figure 2: Diagnostic yields of different TB diagnostic methods.

Table 4: Diagnostic accuracy of tests compared with histopathology.

Diagnostic method	Result	Histopathology not suggestive of TB *n* (%)	Histopathology suggestive of TB *n* (%)	Total *N* (%)	*P* value	Sensitivity Specificity	PPV NPV	AUC, 95% (lower–upper)
QuantiFERON-TB	Positive	5	1	6	0.7a	14.29% 90.20%	16.67% 88.46%	81.03% (68.59%–90.13%)
	Negative/ unknown	46	6	52	0.7a	14.29% 90.20%	16.67% 88.46%	81.03% (68.59%–90.13%)
	Total	51	7	58	0.7a	14.29% 90.20%	16.67% 88.46%	81.03% (68.59%–90.13%)
PPD testing	Positive	4	0	4	0.4a	- 92.16%	- 87.04%	81.03% (68.59%–90.13%)
	Negative/ unknown	47	7	54	0.4a	- 92.16%	- 87.04%	81.03% (68.59%–90.13%)
	Total	51	7	58	0.4a	- 92.16%	- 87.04%	81.03% (68.59%–90.13%)
AFB sputum	Positive	3	0	3	0.5a	- 94.12%	- 87.27%	82.76% (70.57%–91.41%)
	Negative/ Unknown	48	7	55	0.5a	- 94.12%	- 87.27%	82.76% (70.57%–91.41%)
	Total	51	7	58	0.5a	- 94.12%	- 87.27%	82.76% (70.57%–91.41%)
TB culture	Positive	30	1	31	0.027a	14.29% 41.18%	3.23% 77.78%	37.93% (25.51%–51.63%)
	Negative/ unknown	21	6	27	0.027a	14.29% 41.18%	3.23% 77.78%	37.93% (25.51%–51.63%)
	Total	51	7	58	0.027a	14.29% 41.18%	3.23% 77.78%	37.93% (25.51%–51.63%)

utility was further clarified. Positive QFT and PPD results did not meaningfully shift the post-test probability of disease (60% and 36%, respectively). A positive sputum AFB smear increased the probability to nearly 100%, but its rarity limited clinical impact. A positive sputum TB culture increased the post-test probability to 73%, while a negative result reduced

Table 5: Diagnostic accuracy of tests compared with microbiology.

Diagnostic method	Result	Microbiology (AFB smear/TB culture) Not suggestive of TB *n* (%)	Microbiology (AFB smear/TB culture) Not suggestive of TB *n* (%)	Microbiology (AFB smear/TB culture) Suggestive of TB *n* (%)	Total *N* (%)	*P* value	Sensitivity Specificity	PPV NPV	AUC, 95% (lower–upper)
QuantiFERON-TB	Positive	1	5	5	6	0.7a	10.87% 91.67%	83.33% 21.15%	27.59% (16.66%–40.90%)
QuantiFERON-TB	Negative/ unknown	11	41	41	52	0.7a	10.87% 91.67%	83.33% 21.15%	27.59% (16.66%–40.90%)
QuantiFERON-TB	Total	12	46	46	58	0.7a	10.87% 91.67%	83.33% 21.15%	27.59% (16.66%–40.90%)
PPD testing	Positive	2	2	2	4	0.1a	4.35% 83.33%	50.00% 18.52%	20.69% (11.17%–33.35%)
PPD testing	Negative/ unknown	10	44	44	54	0.1a	4.35% 83.33%	50.00% 18.52%	20.69% (11.17%–33.35%)
PPD testing	Total	12	46	46	58	0.1a	4.35% 83.33%	50.00% 18.52%	20.69% (11.17%–33.35%)
AFB sputum	Positive	0	3	3	3	0.4a	6.52% 100.00%	100.00% 21.82%	25.86% (15.26%–39.04%)
AFB sputum	Negative/ unknown	12	43	43	55	0.4a	6.52% 100.00%	100.00% 21.82%	25.86% (15.26%–39.04%)
AFB sputum	Total	12	46	46	58	0.4a	6.52% 100.00%	100.00% 21.82%	25.86% (15.26%–39.04%)
TB culture	Positive	3	28	28	31	0.02a	60.87% 75.00%	90.32% 33.33%	63.79% (50.12%–76.01%)
TB culture	Negative/ unknown	9	18	18	27	0.02a	60.87% 75.00%	90.32% 33.33%	63.79% (50.12%–76.01%)
TB culture	Total	12	46	46	58	0.02a	60.87% 75.00%	90.32% 33.33%	63.79% (50.12%–76.01%)

Table 6: Logistic regression analysis of diagnostic predictors of pulmonary TB. Logistic regression analysis of diagnostic predictors of pulmonary TB.

Lung biopsy findings TB tests findings	Histopathology Adjusted odds ratio, 95% CI: lower–upper (*P* value)	Histopathology Unadjusted odds ratio, 95% CI: lower–upper (*P* value)	Microbiology (AFB smear/TB culture) Adjusted odds ratio, 95% CI: lower–upper (*P* value)	Microbiology (AFB smear/TB culture) Unadjusted odds ratio, 95% CI: lower–upper (*P* value)
QuantiFERON-TB (Ref: negative), positive	OR = 2.9, 95% CI: 0.19–44.81 (0.4)	OR = 0.6, 95% CI: 0.65–6.5 (0.7)	NA	OR = 0.7, 95% CI: 0.7–7 (0.79)
PPD testing (Ref: negative), positive	NA	NA	NA	OR = 4.4, 95% CI: 0.5–35 (0.16)
AFB sputum (Ref: negative), positive	NA	NA	NA	NA
TB culture (Ref: negative), positive	OR = 25.7, 95% CI: 2.1–30.12 (0.01)	OR = 8.5, 95% CI: 0.9–76.5 (0.54)	OR = 0.41, 95% CI: 0.047–3.537 (0.41)	OR = 0.21, 95% CI: 0.05–0.9 (0.35)
Chest computed tomography (Ref: normal), abnormal	OR = 0.230, 95% CI: 0.018–2.93 (0.2)	OR = 0.4, 95% CI: 0.05–4.4 (0.52)	OR = 1.97, 95% CI: 0.208–16.852 (0.57)	OR = 0.022, 95% CI: 0.003–0.194 (0.1)
Chest X-rays (Ref: normal), abnormal	OR = 0.139, 95% CI: 0.012–1.571 (0.1)	OR = 0.2, 95% CI: 0.03–2.5 (0.25)	NA	OR = 0.3, 95% CI: 0.07–1.3 (0.12)

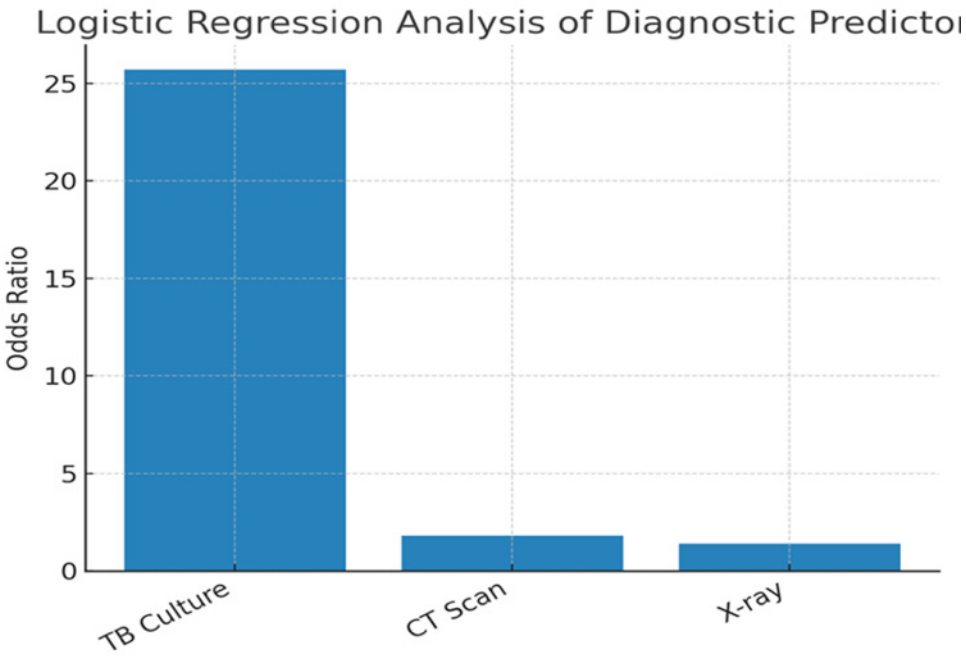

Figure 3: Logistic regression analysis of diagnostic predictors of pulmonary TB.

it to 37%. A positive biopsy TB culture provided the strongest confirmation, raising the post-test probability above 85%.

DISCUSSION

This study provides a critical appraisal of conventional TB diagnostic modalities in a highly selected cohort of patients in Qatar who ultimately required invasive diagnostic procedures. The most striking finding is the profound inability of immunological assays (QFT, PPD) and sputum AFB smears to rule in active pulmonary TB, contrasted with the moderate yet clinically essential utility of microbiological culture. These findings address a significant gap in the literature by quantifying, for the first time in this Gulf population, the LRs and post-test probabilities of conventional tests in patients who have already passed pre-employment screening. [11]

The demographic and clinical profile of our cohort requires careful interpretation. Unlike typical TB cohorts globally, which predominantly consist of older males, [12] our study population was overwhelmingly female (77.6%) and young (mean age 33.6 years). Furthermore, classic constitutional symptoms—cough, fever, and weight loss—were present in fewer than one-third of patients. This atypical presentation likely reflects the nature of the study population: individuals who passed initial pre-employment screening and presented

Table 7: Likelihood ratios of diagnostic tests for pulmonary TB.

Test	LR+	LR−	Interpretation
QuantiFERON (QFT)	1.1–1.4	0.95	Very weak, minimal diagnostic value
PPD	0.5	1.0	Not useful (LR+ < 1)
AFB smear	1.1	1.0	No significant diagnostic value
TB culture	2.4	0.5	Moderately useful, especially when positive
Biopsy TB culture	>5 (expected)	N/A	Potentially strong rule-in test

Test	AUC	95% CI
QuantiFERON	0.28	0.17–0.41
PPD	0.21	0.11–0.33
AFB sputum	0.26	0.15–0.39
TB culture	0.64	0.50–0.76

Test	Pre-test probability	Post-test probability if positive	Post-test probability if negative	Interpretation
QuantiFERON (QFT)	53%	60%	53%	Minimal impact
PPD	53%	36%	57%	Not useful, misleading
AFB smear	53%	~100%	52%	Positive rules in strongly (rare cases)
TB culture	53%	73%	37%	Moderate diagnostic shift
Biopsy TB culture	53%	>85%	N/A	Strong rule-in value

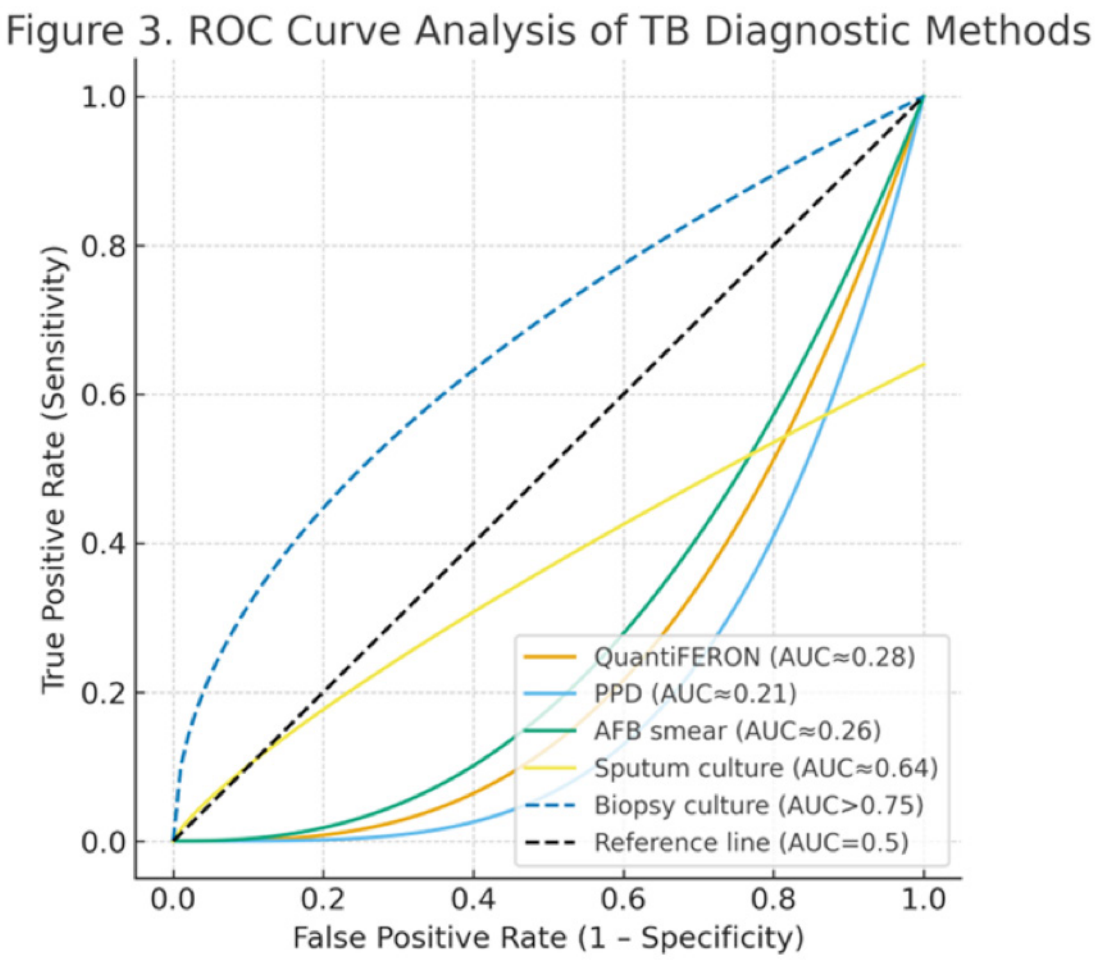

Figure 4: ROC curve analysis (AUC values) for TB diagnostic methods.

later with vague, subacute, or incidental radiological findings. Because these patients had already failed standard clinical triage, the cohort inherently represents a diagnostic challenge, explaining the subsequent poor performance of non-invasive tests.

A key limitation of previous studies has been the failure to adjust for verification bias, wherein only patients with persistent or atypical symptoms undergo reference standard testing. [13] Our cohort, extracted from 3240 screened admissions, explicitly captures this bias, and therefore our sensitivity estimates (e.g., 6.5% for AFB smear) should not be extrapolated to primary care but rather serve as a cautionary benchmark for hospital-based respiratory services.

When evaluated through LRs and post-test probabilities, QFT and PPD demonstrated LR+ values close to 1.0, indicating that a positive result provides virtually no meaningful shift in the probability of active disease. While IGRAs are validated for LTBI screening, our findings align with recent meta-analyses emphasizing their severe limitations as rule-in tests for active pulmonary TB, particularly in BCG-vaccinated populations. [6, 14] Similarly, AFB smear microscopy, despite its 100% specificity in our cohort, exhibited a sensitivity of only 6.5%. While a positive smear effectively confirms disease, its abysmal sensitivity renders it inadequate as a frontline exclusion tool in paucibacillary or extrapulmonary-like presentations.

Microbiological culture provided the most meaningful diagnostic shift. Sputum culture demonstrated a moderate rule-in potential (LR+ ≈ 2.4), while biopsy culture showed strong diagnostic utility (LR+ > 5). However, it is crucial to note that the overall discriminative ability of sputum culture, as reflected by an AUC of 0.64, was modest. This relatively low AUC is not an indictment of culture as a reference standard, but rather a statistical artifact of the cohort's complexity. It highlights that in patients with atypical presentations, a single negative sputum culture is insufficient to rule out disease, necessitating tissue sampling.

One of the most important limitations of our study—and a major gap in the existing regional literature—is the complete absence of rapid molecular testing (e.g., Xpert MTB/RIF or Ultra) during the study period (2010–2019). [10] The WHO has since recommended molecular assays as initial diagnostic tests for suspected pulmonary TB, given their high sensitivity in paucibacillary disease. [15] The poor performance of smear and IGRA in our cohort strongly suggests that had molecular testing been available, the diagnostic delay (implicit in the 4–8 week culture turnaround) could have been substantially reduced. Future studies must directly compare conventional culture against GeneXpert on the same tissue and sputum samples to determine whether molecular methods overcome the AUC limitation we observed (0.64 for culture).

An interesting paradox emerged regarding histopathology. While caseating granulomas on bronchoscopic biopsy are classically pathognomonic for TB, our data showed that microbiological culture demonstrated superior diagnostic yields and rule-in power compared to histological assessment alone. Furthermore, a notable discrepancy was observed where the majority of culture-positive patients did not show suggestive histopathology. This underscores the risk of false-negative histological sampling due to the patchy nature of granulomatous inflammation and reinforces international guidelines that mandate microbiological confirmation over histological presumption whenever possible. [16]

Several additional limitations must be acknowledged beyond those already discussed. First, the retrospective, single-center design and the small sample size (n = 58) introduce potential selection bias and limit the precision of our LR estimates, as reflected by wide confidence intervals (e.g., aOR, 2.1–301.2). Second, the absence of HIV status and immunosuppression data in the medical records precludes subgroup analysis of test performance in vulnerable populations. [17] Third, the composite microbiological reference standard (AFB smear/culture) may have misclassified a subset of true negative cases, as culture itself has imperfect sensitivity in paucibacillary disease. [7] Fourth, the study predates the widespread use of next-generation sequencing and line probe assays, which now offer rapid resistance profiling. [18]

Clinically, our findings mandate two immediate changes. First, clinicians in Qatar and similar expatriate-heavy demographics must avoid the cognitive trap of relying on positive IGRA or PPD results to confirm active pulmonary TB in complex cases. Second, in patients with persistent radiological abnormalities and negative routine sputum workups, early transition to invasive sampling (transbronchial or percutaneous biopsy) for dedicated mycobacterial culture—and ideally rapid molecular testing—is imperative.

Given the prolonged turnaround time of conventional culture (often taking 4–8 weeks), our findings strongly advocate for the routine integration of rapid molecular diagnostics on tissue specimens. The Xpert MTB/RIF Ultra assay, which has demonstrated high sensitivity in paucibacillary and extrapulmonary samples, [19] could theoretically replace the diagnostic gap left by negative smears and pending cultures, allowing for earlier treatment initiation and infection control measures.

CONCLUSIONS

In a highly selected population of suspected pulmonary TB patients with atypical presentations in Qatar, immunological assays and smear microscopy lack the diagnostic power to confirm active disease, as evidenced by LRs near 1.0 and AUC values below 0.3. Mycobacterial culture, particularly from biopsy tissue, remains the cornerstone of definitive diagnosis, albeit with only moderate overall discriminative power (AUC = 0.64) in this complex subset. The absence of rapid molecular testing data constitutes a major limitation of the existing literature, and future prospective, multicenter studies in the Gulf region should prioritize diagnostic algorithms that incorporate Xpert MTB/RIF (or Ultra) on both sputum and tissue samples, with direct head-to-head comparison against conventional culture and histopathology.

AUTHORS' CONTRIBUTIONS

Each author has made a substantial contribution to the present work in one or more areas, including conception, study design, conduct, data collection, analysis, and interpretation. All authors have given final approval of the version to be published, agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

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