

The Diagnostic Efficacy of Interferon-Gamma Release Assays Combined with GeneXpert MTB/RIF Detection for Urinary Tract Tuberculosis

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Abstract

Objective: To evaluate the efficacy of the interferon-gamma release assay (IGRA) combined with GeneXpert MTB/RIF (Xpert) in the diagnosis of urinary tuberculosis. **Methods:** A total of 105 patients with clinically suspected urinary tuberculosis who visited the Affiliated Hospital of Youjiang Medical University for Nationalities from January 2022 to June 2024 were selected. Urine acid-fast bacillus smear, *Mycobacterium tuberculosis* culture, IGRA, and Xpert were performed on all patients. The diagnostic efficacy of each method was compared. **Results:** In this study, there were 59 positive cases (59/105, 56.2%) and 46 negative cases (46/105, 43.8%) of urinary tuberculosis. Among them, 19 cases (19/59, 32.2%) were confirmed by *Mycobacterium tuberculosis* culture, and the remaining 40 cases (40/59, 67.8%) were diagnosed through clinical comprehensive judgment. The detection rate of IGRA combined with Xpert (53/59, 89.8%) was significantly higher than that of smear (17/59, 28.8%), *Mycobacterium tuberculosis* culture (19/59, 32.2%), IGRA (39/59, 66.1%), and Xpert (46/59, 78.0%), and the differences were statistically significant (all $P < 0.0125$). The sensitivity, accuracy, and negative predictive value of Xpert combined with IGRA were higher than those of other methods (all $P < 0.0125$). The specificity of Xpert combined with IGRA was higher than that of smear ($P < 0.0125$), but there was no statistically significant difference compared with the other three methods (all $P > 0.0125$). The positive predictive value of Xpert + IGRA combined detection was higher than that of smear ($P < 0.003$) and single IGRA ($P < 0.0125$), but

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there was no statistically significant difference compared with culture and single Xpert (all $P > 0.0125$). In addition, the sensitivity of combined detection in 40 cases with negative culture but clinically confirmed was 87.1%. **Conclusion:** The preliminary results show that IGRA combined with Xpert has high diagnostic efficacy in the diagnosis of urinary tuberculosis. However, these conclusions are limited by the single-center and small sample size, and need to be verified by large-scale prospective studies.

Keywords

Urinary Tuberculosis, Interferon-Gamma Release Assays, GeneXpert MTB/RIF, Diagnostic Efficacy

1. Introduction

Urinary system tuberculosis caused by *Mycobacterium tuberculosis* is a common chronic infectious disease worldwide. According to the WHO 2023 report, approximately one-quarter of the global population has latent tuberculosis infection. Among them, the number of newly reported tuberculosis cases in China reached 741,000, which is equivalent to 52 cases per 100,000 Chinese citizens [1]. As a type of extrapulmonary tuberculosis, the incidence of urinary system tuberculosis accounts for about 4% of the total number of tuberculosis cases, and urinary system tuberculosis accounts for 15% - 20% of extrapulmonary tuberculosis [2]. Due to its diverse and non-specific clinical manifestations [3], it is easily confused with common urinary system diseases, leading to delayed diagnosis and posing great difficulties and challenges to clinical diagnosis [4].

Currently, the traditional diagnostic methods for urinary system tuberculosis each have limitations. A positive urine *Mycobacterium tuberculosis* culture can confirm the diagnosis, but the culture takes a long time, is prone to contamination, and has a sensitivity of only 10% - 15% [5]; the traditional acid-fast smear microscopy has a high false-positive rate [6]; imaging examinations are not effective in diagnosing early minor lesions [7]; pathological examinations are difficult to sample, invasive, and rely on the operator's experience [8]. Therefore, it is urgent to explore more efficient and accurate diagnostic methods.

The Interferon-Gamma Release Assays (IGRA), as an immunological diagnostic technique, detect tuberculosis infection based on the T-cell immune response. It can better distinguish between tuberculosis infection, Bacillus Calmette-Guérin (BCG) vaccination, and most non-tuberculous mycobacterial infections. It has high specificity and sensitivity, and blood sampling for testing is simple, which can quickly provide a diagnostic basis for clinical practice [9]. The GeneXpert MTB/RIF (Xpert), based on molecular biology, can quickly and accurately detect *Mycobacterium tuberculosis* and rifampicin resistance, providing crucial information for timely treatment [10]. Although several studies have individually evaluated the role of IGRA in genitourinary tuberculosis [11] and demonstrated the

high performance of Xpert in urine samples, systematic evidence on their combined use remains limited [12]. To our knowledge, few prospective studies have explored the synergistic diagnostic value of IGRA with Xpert specifically for urinary tract tuberculosis. This study aims to fill this gap by evaluating the incremental yield of this dual-modality approach.

In view of this, this study innovatively combines IGRA and Xpert for the diagnosis of urinary system tuberculosis. By comparing various detection methods in clinically suspected patients and analyzing the sensitivity, specificity, and accuracy of the combined detection, the aim is to evaluate the efficacy of the combined IGRA and Xpert detection in the diagnosis of urinary system tuberculosis, provide a scientific basis for the early diagnosis of this disease, promote the improvement of clinical diagnosis and treatment levels, and contribute to the global prevention and control of tuberculosis.

2. Materials and Methods

2.1. General Information

This study included patients suspected of having urinary tract tuberculosis who were admitted to the Affiliated Hospital of Youjiang Medical University for Nationalities from January 2022 to June 2024. The inclusion criteria were patients with clinical manifestations such as urinary irritation symptoms (urgency/frequency/pain), hematuria, low back pain, or abnormal urine routine. Patients with a history of anti-tuberculosis treatment, HIV-positive patients, and those with a history of urinary system surgery were excluded (to avoid postoperative inflammatory reactions interfering with the IGRA test results and to reduce the risk of false positives). The researchers comprehensively collected the demographic data and clinical characteristics of the patients (gender/age/medical history/comorbidities/involvement of the urinary system, etc.). All subjects signed informed consent forms. The study was approved by the Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities (YYFY-LL-2022-55) and complied with the ethical guidelines of the Declaration of Helsinki.

“Gold standard” for diagnosis: The diagnostic criteria were based on the “Expert Consensus on the Diagnosis of Extrapulmonary Tuberculosis” published by the Chinese Antituberculosis Association in 2022 [13]. A diagnosis was confirmed if any of the following conditions were met: 1) Positive urine *Mycobacterium tuberculosis* culture; 2) Pathological confirmation of tuberculous granulomas; 3) Typical symptoms plus supportive imaging/cystoscopic findings, along with a favorable response to anti-tuberculosis therapy. Notably, Xpert MTB/RIF results were analyzed independently and did not influence the final clinical diagnosis.

A total of 105 patients suspected of having urinary tract tuberculosis were included in this study. Finally, 59 cases (59/105, 56.2%) were diagnosed with urinary tract tuberculosis, and 46 cases (46/105, 43.8%) were non-tuberculosis patients. Data analysis showed that in the experimental group vs. the control group, there were no significant differences in age (43.13 ± 17.08 vs. 43.54 ± 14.25 years, $P =$

0.302), gender ratio (male: female = 35/24 vs. 29/17, $P = 0.124$), gender composition, age, comorbidities, and involvement of the urinary system between the two groups, as shown in **Table 1**.

To further explore the diagnostic efficacy of different combined strategies, this study evaluated the performance of the serial method (both IGRA and Xpert needed to be positive to be judged as positive) and the parallel method (either IGRA or Xpert needed to be positive to be judged as positive). The results showed that the parallel method had the highest sensitivity (89.8%), but relatively low specificity (91.3%), while the serial method had a high specificity of 97.8%, but the sensitivity decreased to 66.1%, and the risk of missed diagnosis increased significantly. Considering the principle of “early detection and avoidance of omission” in the clinical diagnosis of urinary tract tuberculosis, the parallel strategy was more practical. Therefore, this study mainly used the parallel method for analysis.

Table 1. Patient baseline characteristics.

Clinical characteristic		UTB (n = 59)	NUTB (n = 46)	Statistic	P
Gender	Male	35 (59.3%)	29 (63.0%)	$\chi^2 = 2.38$	0.124
	Female	24 (40.7%)	17 (37.0%)		
Age (years)		43.13 ± 17.08	43.54 ± 14.25	t = -0.52	0.302
Complication	Diabetes	10 (16.9%)	5 (10.9%)	OR = 1.68 (0.51 - 5.55)	0.381
	Hypertension	15 (25.4%)	8 (17.4%)	$\chi^2 = 1.00$	0.318
	Chronic kidney disease	5 (8.5%)	3 (6.5%)	OR = 1.33 (0.31 - 5.83)	0.724
Involvement of the urinary system	Kidney	31 (52.5%)	25 (54.3%)	$\chi^2 = 0.04$	0.845
	Ureter	13 (22.0%)	11 (23.9%)	OR = 0.90 (0.36 - 2.25)	0.818
	Bladder	19 (32.2%)	16 (34.8%)	$\chi^2 = 0.08$	0.779

Note: For small sample sizes, Fisher’s test is used, with the odds ratio (OR) and the 95% confidence interval (CI) provided as the statistical measures.

2.2. Empirical Method

2.2.1. Sample Collection

Collect at least 5 mL of clean midstream urine specimens from each case. For each specimen, perform smear examination for acid-fast bacilli, *Mycobacterium tuberculosis* culture, and Xpert testing. At the same time, collect 10 mL of the patient’s venous blood for IGRA testing.

2.2.2. Smear Examination for Acid-Fast Bacilli

Take an appropriate amount of sterile urine sample and evenly smear it on a glass slide to make a urine smear. Stain it with Ziehl-Neelsen staining solution (Qingdao Haibo Biotechnology; batch number: HB8284; specification: 5 ml*6). Then, use a *Mycobacterium tuberculosis* microscopic scanner (Ningbo Sunny Instru-

ments; model: FS50) to determine the result. The result is considered positive if 3 - 9 acid-fast bacilli are found in 100 fields under the oil-immersion lens [14].

2.2.3. *Mycobacterium tuberculosis* Culture

Take 2 mL of urine sample, treat it with N-acetyl-L-cysteine-sodium hydroxide (NALC-NaOH, final concentration 1.5%), and incubate it at room temperature for 15 minutes. Then, neutralize it with phosphate buffer (pH 6.8). Centrifuge the mixture at 3000×g for 15 minutes, discard the supernatant, and resuspend the precipitate in 2 mL of phosphate buffer. Take 0.5 mL of the suspension and inoculate it into an MGIT 960 culture tube. Add 0.8 mL of the mixture of nutritional additives and bacteriostatic agents (prepared according to the reagent instructions). After inoculation, place the culture tube in the fully automatic mycobacterial culture system (BD, USA; model: BACTEC MGIT 960) for incubation, and the system automatically determines the growth curve. The result is considered positive if cauliflower-like colonies are observed within 8 weeks. Use the MPB64 antigen detection kit to preliminarily screen and identify the strains to distinguish the *Mycobacterium tuberculosis* complex from non-tuberculous mycobacteria [5].

2.2.4. IGRA Testing

Collect 10 mL of venous blood and add it to a heparin-containing blood collection tube. Shake the venous blood specimen well within 16 hours and evenly distribute it into the test culture tube, positive control culture tube (stimulated by tuberculosis antigen), and negative control (Nil tube). Use a fully automatic chemiluminescence immunoassay analyzer (Xiamen Youmaike Medical Instruments; model: Caris200) and the QuantiFERON-TB Gold Plus kit (Qiagen, Germany, batch number: 2022CE123) to measure the concentration of gamma-interferon. Result judgment: The result is considered positive if the IFN- γ concentration is ≥ 0.35 IU/ml and the value in the Nil tube is < 8.0 IU/ml [15].

2.2.5. Xpert Testing: Use the Standardized Xpert Testing Process

Centrifuge 1 mL of urine sample (3000g \times 15 min) \rightarrow resuspend the precipitate add the sample to the Xpert MTB/RIF Ultra kit (Cepheid, USA), and put it into the GeneXpert system (Shanghai Cepheid; model: GX-IV R2 4-channel) for automated testing. Result judgment criteria: The result is considered positive if the Ct value of the internal control probe is ≤ 38 . If the Ct value is > 38 , it is a sample with an extremely low bacterial load, and clinical judgment is required [16].

2.3. Statistical Analysis

In this study, SPSS 22.0 was used for statistical analysis. After the continuous variables were confirmed to follow a normal distribution by the Shapiro-Wilk test, they were expressed as mean \pm standard deviation, and the independent-samples t-test was used for comparison between groups; categorical variables were expressed as frequency (percentage), and the Pearson χ^2 test or Fisher's exact test was used for comparison between groups. When comparing the detection rates of multiple detection methods, the Bonferroni correction method was used for mul-

tiple comparisons between the combined detection and each single detection, and the corrected significance level was set at $\alpha = 0.0125$. Diagnostic performance indicators were expressed as 95% confidence intervals, and the significance of differences was evaluated by the Z-test or McNemar's test. Sensitivity = number of true positives/(number of true positives + number of false negatives) \times 100%; Specificity = number of true negatives/(number of true negatives + number of false positives) \times 100%. Accuracy = (number of true positives + number of true negatives)/(number of true positives + number of true negatives + number of false positives + number of false negatives) \times 100%. Positive predictive value = number of true positives/(number of true positives + number of false positives) \times 100%; Negative predictive value = number of true negatives/(number of true negatives + number of false negatives) \times 100%.

3. Results

3.1. Results of Different Methods for Diagnosing Urinary Tuberculosis

Based on etiological testing and comprehensive clinical judgment, 59 cases (59/105, 56.2%) were diagnosed with urinary tuberculosis, and 46 cases (46/105, 43.8%) were non-tuberculosis patients. Among them, 19 cases (19/59, 32.2%) in the tuberculosis group were diagnosed by mycobacterium culture, and the remaining 40 cases (40/59, 67.8%) were diagnosed through comprehensive judgment of typical clinical manifestations, urinary system imaging findings, pathological results of cystoscopic biopsy, and the effectiveness of anti-tuberculosis drug treatment. The detection rate of Xpert combined with IGRA (53/59, 89.8%) was significantly higher than that of the smear method (17/59, 28.8%) ($\chi^2 = 45.51$, $P < 0.0125$), *Mycobacterium tuberculosis* culture (19/59, 32.2%) ($\chi^2 = 41.36$, $P < 0.0125$), IGRA (39/59, 66.1%) ($\chi^2 = 9.668$, $P < 0.0125$), and Xpert (46/59, 78.0%) ($\chi^2 = 3.07$, $P < 0.0125$), and all the differences were statistically significant (Table 2).

Table 2. Results of different detection methods in the diagnosis of urinary tuberculosis.

Method	Result	UTB (n, %)	NUTB (n, %)
Smear test for acid-fast bacilli	Positive	17 (16.19%)	9 (8.57%)
	Negative	42 (40.0%)	37 (35.24%)
Tubercle bacillus culture	Positive	19 (18.10%)	0 (0%)
	Negative	40 (38.10%)	46 (43.81%)
IGRA	Positive	39 (37.14%)	6 (5.71%)
	Negative	20 (19.05%)	40 (38.10%)
Xpert	Positive	46 (43.81%)	1 (0.95%)
	Negative	13 (12.38%)	45 (42.86%)
Xpert + IGRA	Positive	53 (50.48%)	4 (3.81%)
	Negative	6 (5.71%)	42 (40.0%)

3.2. Efficacy of Different Diagnostic Methods for the Diagnosis of Tuberculosis of the Urinary Tract

The sensitivity, accuracy, and negative predictive value of the Xpert combined with IGRA test were higher than those of other methods, and the differences were statistically significant (all $P < 0.0125$). The specificity of Xpert combined with IGRA was higher than that of the smear method, and the difference was statistically significant ($\chi^2 = 9.68$, $P < 0.0125$); there was no statistically significant difference compared with the other three methods (all $P > 0.0125$). The positive predictive value of the Xpert + IGRA combined test was higher than that of the smear method ($Z = 2.94$, $P < 0.003$) and the single IGRA method ($Z = 2.51$, $P < 0.0125$), and the differences were statistically significant; there was no statistically significant difference compared with the culture method and the single Xpert method (all $P > 0.0125$). It is worth noting that among 40 patients with negative culture results but diagnosed by comprehensive clinical judgment, the sensitivity of the IGRA combined with Xpert test reached 87.1% (34/40), suggesting that this combined method still has good recognition ability for low-bacterial-load or old infections (Table 3).

Table 3. Diagnostic efficacy of different detection methods for urinary tuberculosis.

Method	Sensitivity (%)	Specificity (%)	Accuracy rate (%)	Positive predictive value (%)	Negative predictive value (%)
Smear test for acid-fast bacilli	28.8% (18.7% - 41.4%) [17/(17 + 42)] ^a	80.4% (66.8% - 90.3%) [37/(9 + 37)] ^a	51.4% (41.5% - 61.3%) [(17 + 37)/105] ^a	65.4% (45.5% - 81.8%) [17/(17 + 9)] ^a	46.8% (35.6% - 58.2%) [37/(37 + 42)] ^a
Tubercle bacillus culture	32.2% (19.7% - 47.7%) [19/(19 + 40)] ^a	100% (91.3% - 100%) [46/(0 + 46)]	61.9% (51.5% - 71.5%) [(19 + 46)/105] ^a	100.0% (81.2% - 100%) [19/(19 + 0)]	53.5% (40.6% - 66.2%) [46/(46 + 40)] ^a
IGRA	66.1% (52.2% - 78.0%) [39/(39 + 20)] ^a	87.0% (75.1% - 94.5%) [40/(6 + 40)]	75.2% (65.9% - 83.3%) [(39 + 40)/105] ^a	86.7% (73.8% - 94.3%) [39/(39 + 6)] ^a	66.7% (53.5% - 78.2%) [40/(40 + 20)] ^a
Xpert	78.0% (65.2% - 87.7%) [46/(46 + 13)] ^a	97.8% (88.8% - 99.9%) [45/(1 + 45)]	86.6% (78.3% - 92.8%) [(46 + 45)/105] ^a	97.9% (89.1% - 99.9%) [46/(46 + 1)]	77.6% (66.7% - 86.3%) [45/(45 + 13)] ^a
Xpert + IGRA	89.8% (80.2% - 95.7%) [53/(53 + 6)]	91.3% (80.8% - 96.9%) [42/(4 + 42)]	90.5% (83.7% - 95.3%) [(53 + 42)/105]	93.0% (83.2% - 97.7%) [53/(53 + 4)]	87.5% (76.8% - 94.5%) [42/(42 + 6)]

Note: Compared with the Xpert + IGRA test, ^a $P < 0.015$ (Bonferroni correction). The data in the table represent the analysis results (n = 59).

3.3. Subgroup Analysis: Diagnostic Performance in Culture-Negative, Clinically Confirmed Cases

Among 40 patients with negative culture but clinically confirmed urinary tuberculosis, the sensitivity of the IGRA + Xpert combination was 87.1% (34/40), highlighting its utility in paucibacillary disease.

4. Conclusions

As a special type of *Mycobacterium tuberculosis* infection, urinary tract tuberculosis is characterized by a high incidence rate, complex clinical manifestations,

and a tendency to be confused with other urinary system diseases. Its clinical diagnosis faces severe challenges [1]. This study systematically evaluated the application value of the IGRA combined with Xpert detection protocol in the diagnosis of urinary tract tuberculosis, aiming to provide a more accurate and efficient diagnostic tool for clinical practice. The preliminary results showed that this combined detection strategy demonstrated significant advantages in diagnostic efficacy. Its sensitivity, accuracy, and negative predictive value were all significantly better than those of single detection techniques, which is highly consistent with the original intention of the study design.

Specifically, the sensitivity of the combined detection scheme has achieved a breakthrough improvement compared with traditional detection methods: it is 3.1 times higher than that of the smear method (28.8%), 2.8 times higher than that of *Mycobacterium tuberculosis* culture (32.2%), 35.2% higher than that of single IGRA (66.1%), and 15.1% higher than that of single Xpert (78.0%). This performance improvement stems from the complementary mechanisms of the two detection technologies: as an immunological detection technology based on the release of T-cell gamma-interferon, IGRA can capture immune response signals in the early stage of infection or in the state of low bacterial load [17]; while Xpert detection can simultaneously complete the nucleic acid amplification of *Mycobacterium tuberculosis* and the detection of rifampicin-resistant genes through real-time fluorescent quantitative PCR technology [18]. The two technologies work together to construct a two-dimensional detection system of “immune response-pathogen nucleic acid,” effectively making up for the detection limitations of a single technology in the infection window period, differences in bacterial load, and changes in the host immune status. This system constructs an efficient diagnostic pathway for urinary tuberculosis through the complementary advantages of immunological and etiological technologies. Among them, as an immunological dimension detection, IGRA confirms the immune response to tuberculosis infection by identifying the gamma-interferon released after effector T cells contact specific antigens of *Mycobacterium tuberculosis* (such as ESAT-6, CFP-10). Its core advantage is that it is not limited by the bacterial load in the sample and can effectively identify early-stage infections, latent infections, and extrapulmonary tuberculosis with extremely low bacterial counts; while Xpert MTB/RIF, as an etiological dimension detection, directly detects the DNA of *Mycobacterium tuberculosis* in the sample and simultaneously identifies rifampicin-resistant genes (rpoB mutations) based on real-time fluorescent quantitative PCR technology. With its high sensitivity and rapidity, it directly confirms active tuberculosis and drug-resistance information, but its results depend on the bacterial load in the sample [19]. The combination of the two forms a collaborative pathway of “immune response screening + etiological confirmation”, which not only optimizes the overall detection efficiency by improving the diagnostic sensitivity, accuracy, and negative predictive value (especially suitable for difficult cases), but also can meet the diagnostic needs of special populations such as immunosuppressed pa-

tients and smear-negative pulmonary tuberculosis. Through the process optimization of “IGRA indicating infection → Xpert quickly confirming the pathogen and drug-resistance”, it avoids the treatment delay caused by the time-consuming traditional culture and provides an integrated solution for the precise diagnosis and treatment of tuberculosis.

Systematic literature analysis shows that most of the existing studies focus on the single application of IGRA or Xpert. Although there is evidence supporting the specific value of IGRA in the diagnosis of genitourinary tuberculosis [20], and the high efficiency of Xpert in the detection of urine specimens [21], there are still limited systematic data on the combined application of the two. Through a prospective controlled study, this research verified the synergistic effect of the immune-molecular combined detection protocol and established a complete diagnostic chain from immune recognition to pathogen confirmation. This protocol has three clinical advantages: First, it can be used as a primary screening tool in primary-care emergency departments to reduce the risk of misdiagnosis through rapid differentiation; second, it can optimize individualized treatment plans by relying on the drug-resistance detection function of Xpert; third, it establishes a non-invasive blood-urine combined detection model to improve the accessibility of diagnosis and treatment in resource-poor areas.

Although the overall specificity of the combined IGRA + Xpert detection reached 91.3%, which was slightly lower than that of Xpert alone (97.8%) and the culture method (100%), it was still within the clinically acceptable range. The slight decrease in its specificity was mainly due to possible false-positive reactions caused by IGRA [22]. In this study, among the 6 patients with positive IGRA results but ultimately excluded from having tuberculosis, 3 had a clear history of silicosis. Situations such as silica dust (silicon dioxide dust), pregnancy, active chlamydia infection, endotoxin contamination of reagents, as well as disease states like diabetes and sepsis, or the use of immunomodulatory drugs can indeed activate macrophages and T-cells, leading to non-specific release of gamma-interferon and thus causing false-positive results in IGRA [17]. The specific mechanism is as follows: After being phagocytosed by macrophages, silica dust can activate intracellular inflammatory pathways (such as the TLR4 signaling pathway), promoting the polarization of macrophages into the M1 type and the release of pro-inflammatory cytokines (such as IL-1 β and TNF- α) [23]. This inflammatory environment further activates T-cells (especially Th1 cells), resulting in non-specific release of IFN- γ . Since IGRA relies on the detection of IFN- γ under the stimulation of tuberculosis-specific antigens to diagnose tuberculosis infection, the non-specific increase in IFN- γ caused by silica dust may interfere with the test results, leading to false positives [24]. Detailed data on potential confounding factors—such as recent infections, autoimmune conditions, or immunomodulatory therapies—were not available retrospectively for the remaining three cases. Future studies should prospectively collect comprehensive comorbidity and medication histories to better elucidate sources of false positivity. It is worth noting that while

the parallel testing strategy maximizes sensitivity—an essential goal in early UTB diagnosis where missed cases can lead to irreversible renal damage—it comes at the cost of reduced specificity (91.3% vs. 97.8% for Xpert alone). This implies a higher likelihood of false-positive results, potentially leading to unnecessary anxiety, prolonged investigations, or even unwarranted initiation of anti-tuberculosis treatment. Therefore, clinicians should interpret positive IGRA/Xpert results cautiously, especially in low-prevalence settings or high-risk populations for false positives (e.g., those with silicosis or autoimmune disorders), and always integrate findings with clinical context, imaging, and follow-up [25].

From the perspective of the significance of the research, this study provides new ideas for the early diagnosis of urinary tract tuberculosis. Compared with traditional detection methods, the combined detection scheme has significant clinical value. Traditional bacteriological tests (smear/culture) have defects such as a long detection cycle (4 - 8 weeks), a low positive rate, and a high risk of contamination. Imaging and pathological examinations also have limitations in terms of early diagnosis and sampling convenience [8]. This study confirms that the combined detection scheme not only significantly shortens the detection cycle (4 - 6 hours) but also raises the diagnostic accuracy to a new level, which is of great public health significance for achieving early diagnosis and treatment and blocking the spread of the disease.

At the clinical application level, this combined detection strategy presents three core advantages in the diagnosis and treatment of urinary tract tuberculosis: Firstly, it can be used as the first-screening scheme in emergency departments/primary-care settings, reducing the risk of misdiagnosis through rapid identification. Secondly, it can optimize chemotherapy decisions based on Xpert drug-resistance information, enhancing the ability to prevent and control drug-resistant tuberculosis. Thirdly, it constructs a non-invasive detection system by combining blood IGRA with urine Xpert, improving accessibility in resource-poor areas. The current issue of detection cost can be partially alleviated by the health-economic benefits of early diagnosis. Future technological iterations and medical insurance coverage are expected to break through the cost bottleneck.

However, this study has the following limitations:

1) Limitations in sample size and study design: The conclusions are limited by the fact that this is a single-center retrospective study. Only 105 suspected patients were included, with 59 confirmed cases. The relatively small sample size may lead to insufficient statistical power. Although there were no significant differences in baseline characteristics (age, gender) between groups, single-center data may have regional bias (such as the differences in tuberculosis epidemic characteristics between the Guangxi region and other areas), which affects the universality of the conclusions.

2) Immunocompromised populations (such as HIV-infected individuals) were not included. The sensitivity of IGRA in special populations is questionable.

3) Lack of long-term follow-up data: This study only evaluated the short-term

diagnostic efficacy of the detection method. There was no long-term follow-up of patients for 6 - 12 months after treatment. It is impossible to verify the association between the combined detection results of IGRA and Xpert and the risk of disease recurrence, and it is also difficult to evaluate the impact of this combined protocol on long-term treatment outcomes.

4) Inadequate analysis of drug-resistant genes: Although the Xpert test can simultaneously detect mutations in the rifampicin-resistant gene (*rpoB*), this study did not conduct an in-depth analysis of the correlation between the types of drug-resistant mutations (such as hotspot mutations like S531L and H526Y) and the adjustment of clinical treatment protocols. There is a lack of dynamic monitoring data of drug-resistant genes, making it difficult to clarify the guiding value of combined detection for the diagnosis and treatment of drug-resistant tuberculosis.

In response to the above problems, future research can be improved in the following directions:

1) Multi-center large-sample verification: It is recommended to conduct a multi-center, prospective cohort study, expanding the sample size to more than 500 cases, covering different regions (such as high- and low-tuberculosis-prevalence areas) and populations with different immune statuses (such as HIV-infected individuals and organ transplant recipients) to further verify the diagnostic efficacy of the combined IGRA and Xpert detection and reduce regional and population biases.

2) Long-term follow-up and prognosis analysis: Conduct at least 12-month follow-up of confirmed patients, record treatment responses (such as sputum smear conversion time and improvement in imaging), recurrence rate, and adverse events, and establish an association model between detection results and clinical prognosis to provide evidence for the long-term effectiveness of this combined protocol.

3) Correlation analysis between drug-resistant genes and treatment decisions: Combine the results of rifampicin-resistant mutations detected by Xpert and simultaneously conduct tests on drug-resistant genes of first-line drugs such as isoniazid and ethambutol (such as *katG* and *embB* genes). Analyze the correlation between drug-resistant genotypes and treatment protocol adjustments (such as whether drug-resistant patients need to be switched to second-line anti-tuberculosis drugs) to optimize individualized treatment strategies.

4) Evaluation of health economic benefits: Although this study did not directly evaluate the detection cost, from a clinical value perspective, combined detection can shorten the diagnostic cycle from 4 - 8 weeks with traditional culture to 4 - 6 hours. Early diagnosis can reduce unnecessary use of antibiotics (reducing the risk of drug resistance) and avoid renal function damage or surgical intervention caused by delayed treatment, significantly reducing medical expenses. It is recommended that subsequent studies quantify the health economic advantages of combined detection through cost-benefit analysis (such as the cost per confirmed tuberculosis case and the reduction in hospital stay) to provide a basis for inclusion

in medical insurance policies.

With the continuous advancement of science and technology, the application prospects of IGRA combined with Xpert testing in the diagnosis of urinary tuberculosis will be even broader. First, the further development of molecular biology and immunology technologies may lead to improvements in the sensitivity and specificity of the tests, thereby further enhancing the accuracy of diagnosis. Second, with the introduction of artificial intelligence and big data technologies, the analysis and interpretation of test data may become more efficient and precise, which will provide more support for clinical diagnosis [26]. In addition, the establishment of standardized procedures and optimization plans for IGRA combined with Xpert testing will contribute to its standardized application in clinical practice, providing stronger support for the early diagnosis and treatment of urinary tuberculosis [27] [28].

In conclusion, this study evaluated the application efficacy of IGRA combined with Xpert testing in the diagnosis of urinary tuberculosis and preliminarily verified the advantages of this combined testing strategy. However, its clinical application still needs to be further verified through multi-center, large-sample studies, and the evaluation should be improved by combining drug-resistant gene monitoring and long-term follow-up data. In addition, the analysis of testing costs and health economic benefits will provide a more comprehensive decision-making basis for the clinical promotion of this combined program. In the future, with the continuous optimization of technology and the further promotion of application, IGRA combined with Xpert testing is expected to become an important tool for the diagnosis of urinary tuberculosis, safeguarding the prevention and control of tuberculosis and the health of patients.

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Conflicts of Interest

All authors of this paper declare that there are no conflicts of interest.

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