

# Diagnostic Value of PCR compared to Urine Culture for Urinary Tuberculosis in Adult Women: An Evidence-Based Case Report

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## ABSTRAK

**Latar belakang:** tuberkulosis saluran kemih (GUTB) merupakan infeksi *Mycobacterium tuberculosis* pada saluran kemih dengan gejala klinis yang dapat menyerupai berbagai diagnosis pada bidang urologi. Dengan insidensi 192-232 per 100.000 individu, hanya sebagian kecil penderita GUTB yang terdiagnosa secara klinis. Kombinasi antara manifestasi yang tidak spesifik, gejala atipik, tingginya angka negatif palsu pemeriksaan bakteri tahan asam, dan lamanya waktu kultur semakin mempersulit diagnosa GUTB. **Metode:** kami melakukan pencarian literatur sistematis pada 4 basis data berbeda berdasarkan kata kunci terkait PICO dan operator Boolean untuk menjangkau hasil paling relevan. Penilaian terkait kualitas (Variability-Importance-Applicability) dilakukan pada seluruh artikel berdasarkan panduan *The Centre for Evidence-Based Medicine (CEBM)* dari Universitas Oxford. Studi telaah sistematis dan meta-analisis akan dinilai berdasarkan kriteria QFAITH. **Hasil:** sebanyak 243 artikel dijangkau dari hasil pencarian awal. Sebanyak 11 artikel yang relevan dijangkau setelah dilakukan penapisan berdasarkan judul dan abstrak. Dari jumlah tersebut 9 artikel dieksklusi karena ketidaksesuaian dengan kriteria dan penilaian akhir dilakukan terhadap 2 artikel. Dari sebuah artikel telaah sistematis didapatkan hasil yang heterogen ( $I^2 =$  tidak tersedia;  $p =$  tidak tersedia) dengan sensitivitas PCR >85% dan spesifisitas PCR >75%. Satu studi potong lintang membandingkan 2 metode PCR (primer IS6110-PCR dan 16SrRNA-PCR) dengan sensitivitas sebesar 95.99% dan 87.05% serta spesifisitas sebesar 98,11% dan 98,9%. **Kesimpulan:** bukti yang terbatas menunjukkan bahwa PCR tidak dapat digunakan secara mandiri untuk mendiagnosa TB urogenital, tetapi penggunaannya dapat dianjurkan bersama pemeriksaan lain untuk mengarahkan pilihan tatalaksana dan melakukan monitoring.

**Kata kunci:** tuberkulosis saluran kemih, diagnosis, polymerase chain reaction, bakteri tahan asam, kultur urin.

## ABSTRACT

**Background:** genitourinary tuberculosis (GUTB) refers to a *Mycobacterium tuberculosis* infection of the urinary tract with clinical manifestation masquerading as various urological diagnostic entities. With an incidence rate of 192-232 per 100,000 individuals, current diagnoses have fallen short in comparison to the total incidence. Combined with an atypical and non-specific manifestation, a high false negative rate of acid-fast bacilli (AFB) staining, and long AFB culture duration has made diagnosis difficult. We aim to gather current available evidence regarding the diagnostic performance of polymerase chain reaction (PCR) in the diagnosis of GUTB. **Methods:** a literature search was conducted in four different, well-known databases using a predetermined PICO, keywords,

and Boolean operators. All included articles will be subjected to rigorous appraisal according the University of Oxford's Centre for Evidence-Based Medicine (CEBM) Diagnostic Variability Criteria. Review and meta-analysis will be subjected to the QFAITH appraisal checklist to assess its quality. **Results:** out of a total of 243 initial search results, 11 relevant studies were determined after title and abstract screening. Additionally, nine articles were excluded based on the predetermined criteria. Two fully appraised articles were included in the study: one systematic review article, revealing a heterogenous ( $I^2 = \text{unstated}$ ;  $p = \text{unstated}$ ) result of sensitivity mean above 85% and specificity above 75%; and one cross-sectional diagnostic study that reported the use of two different PCR primers: IS6110-PCR and 16SrRNA-PCR primer with a sensitivity of 95.99% and 87.05% and specificity of 98.11% and 98.9%, respectively. **Conclusion:** current limited evidence showed that PCR could not be solely used for the diagnosis of GUTB, but its use is recommended to guide patient treatment and monitoring.

**Keywords:** genitourinary tuberculosis, diagnosis, polymerase chain reaction, acid-fast bacilli, urine culture.

## INTRODUCTION

Although tuberculosis was discovered a century ago, it is still a huge global health burden with an incidence rate of 192-232 per 100,000 individuals in the population and 19-30 deaths per 100,000 individuals per year.<sup>1</sup> Up to 90% of these individuals live in developing countries.<sup>2</sup> In Indonesia, the tuberculosis incidence rate is estimated to be 321 per 100,000 individuals, with a death rate of 47 per 100,000.<sup>3</sup> For the majority of cases, lungs account for the primary infection site, while 10-30% of cases occur as extrapulmonary.<sup>4</sup> Genitourinary tuberculosis (GUTB) is responsible for 30-40% of all extrapulmonary cases, which is second only to lymph-node involvement.<sup>4</sup> The majority of GUTB cases involves the organs of the urinary tract, and 5-30% of cases have been isolated to the women's genital organ only.<sup>5</sup> Epidemiologically, GUTB affects more men than women with a ratio of 2 to 1, at a mean age of 40.7 years.<sup>6</sup>

Hematogenic dissemination from the lung has been suspected as the main pathophysiology; however, only 36.5% of GUTB patients have had a previous diagnosis of pulmonary tuberculosis.<sup>7</sup> A study investigating GUTB from autopsies reported that 50% of patients were asymptomatic, and only 18% of patients had eventually received a diagnosis.<sup>7,8</sup> Clinically, patients with GUTB might show no specific symptoms or atypical presentations, making the diagnosis difficult, especially in patients with poor care-seeking behavior.<sup>9</sup> Clinical suspicion usually arises when manifestation of storage symptoms, pyuria, dysuria, and hematuria appeared, which

affect 50.5%, 46%, 37.9%, and 35.6% of cases, respectively.<sup>7,9</sup> This could be accompanied by back, flank, or abdominal pain, while systemic symptoms, such as fever, weight loss, and anorexia, are less common. GUTB is also known to masquerade as other well-known urological entities, such as urinary tract infection, ureteral calculus, and renal cell carcinoma, complicating the diagnosis even further.<sup>10-12</sup> Due to these reasons, GUTB may result in delayed treatment and lead to significant morbidity.<sup>11,12</sup>

To date, the isolation and culture of *Mycobacterium tuberculosis* bacilli remains as the gold standard of GUTB diagnosis. For this purpose, Ziehl-Neelsen smear examination and Lowenstein-Jensen medium culture is performed.<sup>13</sup> Ideally, all body fluid specimens from possible sites of infection and aspirates should be subjected to examination. Although, Ziehl-Neelsen smear examinations have high specificity (up to 96.7%) and are relatively quick to perform, this method has low sensitivity (42.1-52.1%).<sup>14</sup> In contrast, although considered as the gold standard, a Lowenstein-Jensen medium culture could take up to eight weeks before initiation of treatment. In recent reports, newer polymerase chain reaction (PCR) techniques have been demonstrated to be sensitive (25-93%), as well as highly specific (95-100%) in the diagnosis of extrapulmonary tuberculosis.<sup>15</sup> In this study, we aim to compare the diagnostic performance of PCR in urine culture for the diagnosis of GUTB by using the exploratory method of examining currently available evidence.

## CASE ILLUSTRATION

A 31-year-old female patient presented to the emergency department with chief complaints of unproductive right nephrostomy access seven days prior to the presentation. Initially, the patient presented with severe lower urinary tract symptoms of frequency, urgency, and nocturia with an International Prostate Symptom Score (IPSS) of 23. Initial anamnesis, physical examination, and laboratory and radiologic work up were not able to reveal any organic abnormalities. However, the patient explained that she had a history of pulmonary tuberculosis and had completed the anti-tuberculosis regimen 18 months prior to her initial presentation, in which GUTB had been suspected by the physician. Laboratory work ups for HIV infection turned out to be negative. For this reason, it was decided that an evaluation cystoscopy, a right retrograde pyelography, a right double J stent insertion plus a Barbotage procedure, and a bladder biopsy would be performed. And for diagnostic purposes, a collected urine sample was sent to the clinical pathological laboratory in which cytology examination, PCR, and a culture was ordered to detect the presence of *M. tuberculosis*.

## CLINICAL QUESTION

Is the diagnostic performance of PCR comparable with urine culture for the diagnosis of urinary tuberculosis in adult women?

## METHODS

A literature search was conducted using the related online databases, including PubMed, ScienceDirect, Cochrane, and EMBASE, in March 2020. Boolean operators were used in combination with the following search terms: “polymerase chain reaction”, “diagnosis”, “diagnostic”, “urinary tuberculosis”, “genitourinary tuberculosis”, and “urogenital tuberculosis”. In regard to discover the widest evidence available, we did not impose any limitation on publication date nor language. However, we imposed limitations on studies investigating only genital tuberculosis in women population. Also, studies without any clear gold standard comparison to urinary culture, and studies without available full manuscript were excluded.

Included articles were appraised independently by both authors according to the Oxford model of evidence-based medicine using the Validity-Importance-Applicability checklist for diagnostic studies, while the QFAITH appraisal checklist was used to appraise review articles and meta-analyses.<sup>16,17</sup> A third opinion was consulted if a consensus was not achieved by both authors.

## RESULTS

We performed a systematic literature search according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) using the related PICO criteria (**Table 1**). A Boolean search in four different databases returned 243 articles related to the keywords (**Table 2**). Title and abstract screening by the investigators returned 18 relevant studies. In total, nine articles were excluded due to inclusion

**Table 1.** PICO Criteria.

PICO	Descriptions
Population	Adult Population
Intervention	Polymerase Chain Reaction (PCR)
Comparison	Urine Mycobacterial Culture
Outcome	Diagnosis Performance of Urinary Tuberculosis

**Table 2.** Searched Database Results and Keywords

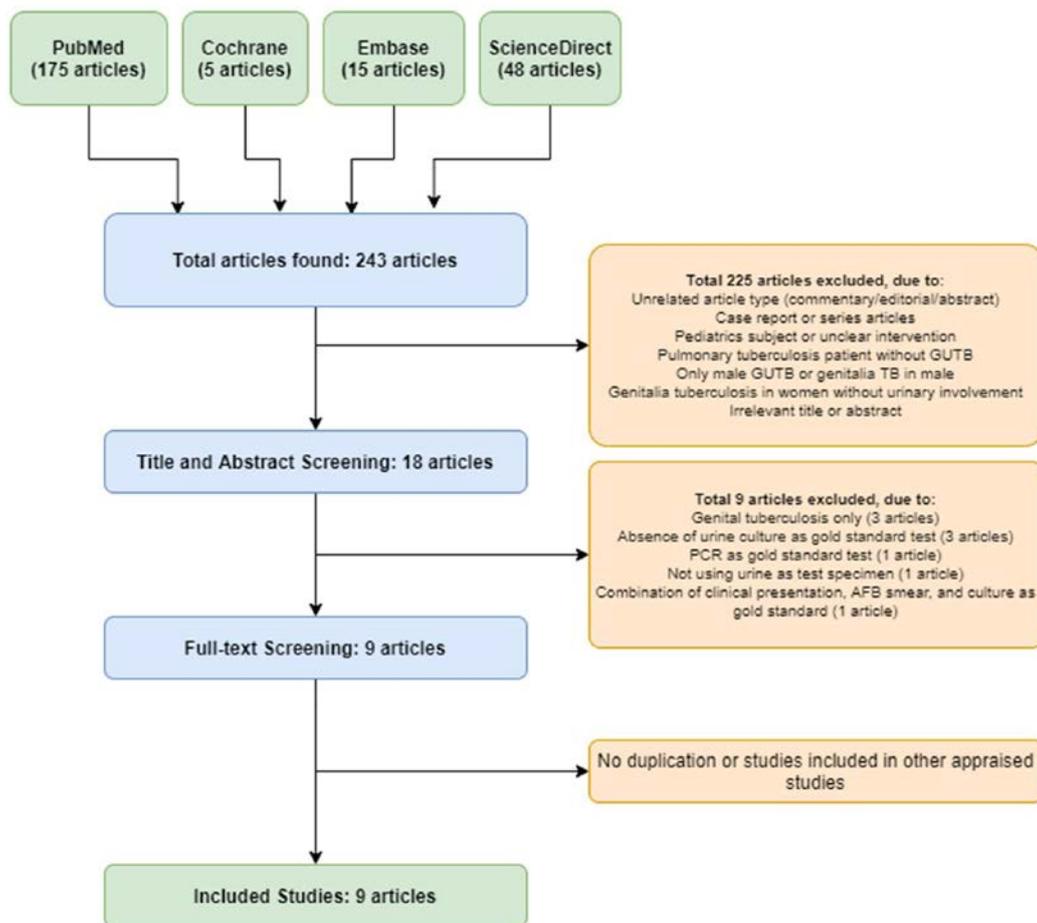
Database	Search terms and keywords	Results
PubMed	((“PCR” OR “polymerase chain reaction”) AND (“diagnosis” OR “diagnostic”) AND (“urinary tuberculosis” OR “urogenital tuberculosis” OR “genitourinary tuberculosis”))	175 articles
Cochrane	((“PCR” OR “polymerase chain reaction”) AND (“diagnosis” OR “diagnostic”) AND (“urinary tuberculosis” OR “urogenital tuberculosis” OR “genitourinary tuberculosis”))	5 articles
EMBASE	((“PCR” OR “polymerase chain reaction”) AND (“diagnosis” OR “diagnostic”) AND (“urinary tuberculosis” OR “urogenital tuberculosis” OR “genitourinary tuberculosis”))	15 articles
Science Direct	((“PCR” OR “polymerase chain reaction”) AND (“diagnosis” OR “diagnostic”) AND (“urinary tuberculosis” OR “urogenital tuberculosis” OR “genitourinary tuberculosis”))	48 articles

of only genital tuberculosis cases (three articles), the absence of urine culture as gold standard (three articles), PCR as means of primary gold standard (one article), not using urine as a test specimen (one article), and the combination of clinical presentation, acid-fast bacilli (AFB) smear, and culture as gold standard (one article). After screening for possible article duplication, nine cross-sectional studies related to the PICO question were included (**Figure 1**). The validity and risk assessment of both studies is provided in **Table 3**.

Nine cross sectional diagnostic studies are included in the final analysis,<sup>14,18-24</sup> seven of which had suitable patient selection and reference test with our PICO criteria thus scored 2 of 3 in validity assessment.<sup>18-20,22-25</sup> Two remaining studies used acid fast bacilli culture as reference test but failed to mention specific media being used thus scored 1 for validity.<sup>14,21</sup> However, none of the included studies described any mechanism

to ensure blind comparison between samples. In five studies,<sup>14,18,20,22,24</sup> authors specifically compared urine specimen from suspected adult GUTB patients while four other studies intended to compare diagnostic performance on various specimen from patient suspected for extrapulmonary tuberculosis.<sup>19,21,23,25</sup> However, all of four studies investigating extrapulmonary tuberculosis specimen also included sub analysis of urine specimen thus sub-analysis could be performed. In two studies (Moussa et al. and Khan et al.), urine specimens were collected using three consecutive morning urine samples while the remaining studies collected urine specimen either from first morning voided urine or failed to describe any collection method.<sup>20,25</sup>

Of nine studies included, majority of studies used Lowenstein-Jensen solid culture media as reference test,<sup>19-20,22-25</sup> while BACTEC was the most widely used liquid culture media reported in two studies.<sup>18-19</sup> Other solid culture



**Figure 1.** PRISMA flowchart of the literature search process. AFB: acid-fast bacilli.

**Table 3.** Validity Appraisal Result of Included Studies.

Author, year	Study Design	Level of Evidence	Validity			Validity Score*
			Patient Selection	Reference Standard	Independent Blind Comparison	
van Vollenhoven et al., <sup>18</sup> 1996	Cross sectional diagnostic study	2a	92 adult patients suspected with GUTB (male-to-female ratio of 43:40)	Bactec culture media	Not stated, no data provided	2/3
Gamboa et al., <sup>19</sup> 1998	Cross sectional diagnostic study	2a	526 adults suspected with extrapulmonary TB, with inclusion of 69 urine specimen	Lowenstein-Jensen, Coletosos, and BACTEC 13A culture media	Not stated, no data provided	2/3
Hemal et al., <sup>14</sup> 2000	Cross sectional diagnostic study	2a	42 adult patients suspected with GUTB (male-to-female ratio 25:17) with specimen collection from first morning voided urine	AFB culture (media not stated)	Not stated, no data provided	1/3
Moussa et al., <sup>20</sup> 2000	Cross sectional diagnostic study	2a	1000 adult population suspected with GUTB and urine specimen obtained	Combination of Lowenstein-Jensen, Colestos, and Middlebrook 7H10 agar	Not stated, no data provided	2/3
Garcia-Elorriaga et al., <sup>21</sup> 2009	Cross sectional diagnostic study	2a	45 adult patients suspected with extrapulmonary tuberculosis with 20 urine sample collected for GUTB	Positive bacilloscopy and culture (media not stated)	Unstated, no data provided	1/3
Khosravi et al., <sup>22</sup> 2010	Cross sectional diagnostic study	2a	200 urine samples from adult patients suspected with GUTB through clinical diagnosis	Lowenstein-Jensen culture media	Not stated, no data provided	2/3
Hillemann et al., <sup>23</sup> 2011	Cross sectional diagnostic study	2a	521 specimens from adult patients suspected with extrapulmonary tuberculosis including 91 urine specimens	Lowenstein-Jensen and Stonebrink slant	Not stated, no data provided	2/3
Tortoli et al., <sup>24</sup> 2012	Cross sectional diagnostic study	2a	1493 specimens from 1068 adult and paediatric patients suspected for extrapulmonary tuberculosis including 112 urine specimens collected from adult patients	Lowenstein-Jensen media + MGIT 960 Liquid culture	Not stated, no data provided	2/3
Khan et al., <sup>25</sup> 2013	Cross sectional diagnostic study	2a	50 adult patients suspected for GUTB with three consecutive morning urine samples collected	Lowenstein-Jensen media	Not stated, no data provided	2/3

\*Scored based on the University of Oxford's Centre for Evidence-Based Medicine (CEBM) Diagnostic Variability criteria

media reported in the studies includes Colestos agar, Middlebrook 7H10 agar, and Stonebrink slant while other liquid culture media reported includes MGIT 960 liquid culture.<sup>19-20,23-24</sup> Two studies (Hemal et al. and Garcia-Elorriaga et al.) failed to specify solid or liquid culture as reference test for GUTB.<sup>14,21</sup> To investigate PCR as index test, different PCR primer were utilized among studies to aid the amplification tuberculosis nucleotides. Both IS6110 nested PCR and GeneXpert MTB/RIF detection were the most commonly utilized detection method reported in three,<sup>20-22</sup> and two studies respectively.<sup>23,24</sup> Other studies also reported M13 mp8, MPB-64, and 16SrRNA as possible primer to aid nucleotide amplification.<sup>14,18,20</sup> Two studies reported self-developed primer but failed to report specific primer being use or specific nucleotide targeted for the PCR method.<sup>14,25</sup>

Although performed using different primer and culture media, as described in **Table 4**, all studies reported high sensitivity and specificity of TB detection using PCR method.<sup>14,18-25</sup> Reported sensitivity ranging from 78.5% to 100% while reported specificity ranging from 78.6-100%. Seven studies also reported high number of positive predictive value (PPV) and negative predictive value (NPV) which ranged from 78.6-100% and 75-100% respectively.<sup>14,18-21,24-25</sup> However, two studies failed to provide sufficient data for PPV and NPV calculation thus both numbers could not be calculated.<sup>22,23</sup> Comparing the applicability of all studies (**Table 5**), we found that three studies reported specific details regarding test methodology and reported sufficient diagnostic performance data for replication.<sup>18,20,24</sup> However, four studies did not report sufficient data but described specific index test methodology which replication might still be possible.<sup>14,21-23</sup> In remaining studies, both authors failed to mention specific primer or target being used in the study thus we regarded replication of results are not possible.<sup>19,25</sup>

## DISCUSSION

Typically, GUTB begin with a small renal cortical lesions followed by the passing down of bacilli through renal tubules, renal pelvis which eventually implanted in the urothelium.<sup>26</sup>

This descending route of infection could result in various manifestations such as stricture formation, hydroureter, hydronephrosis, or bladder contractures.<sup>27</sup> Generally, when GUTB is suspected, simple voided urine should suffice as a decent specimen.<sup>28</sup> However, patients with prostatitis-like infection might require mid-stream urine collection, while three early-morning urine samples is more suitable if renal tract tuberculosis is suspected.<sup>29</sup> Urine specimens can also be collected via catheter access to prevent contamination and is regarded as the method of choice for collecting urine from the ureter.<sup>30</sup> Bladder washing, also known as Barbotage procedure, is performed by irrigating the bladder with a saline or fixative solution. Although considered invasive, this method enables superior cellularity collection and cell preservation compared to voided urine collection.<sup>31</sup>

To date, culture is still considered the gold standard for diagnosis of tuberculosis in any site aided with AFB identification using a Ziehl-Neelsen stain.<sup>32</sup> However, the rate of positive culture results in GUTB could range widely from 10.6-80% depending on the medium and patient's gender, especially woman patient in which a low culture rate is often observed.<sup>28</sup> A more recently developed nucleic acid amplification method enabled the detection of *M. tuberculosis* DNA with smaller cut-off point of 10-20 ng (equivalent to 10,000 to 10,000,000 base pairs) and could turn positive result even without living bacilli which theoretically could offer higher sensitivity, specificity, and replicability.<sup>33</sup> Given the possible advantageous property, it is surprising that the evidence of its use in GUTB diagnosis is scarce. During our literature search process, only nine relevant articles were found as we screened for studies with suitable patient settings and characteristics. Additionally, all studies failed to described mechanism for blinding while two studies failed to specify type of PCR primer used.<sup>14,18-25</sup> This finding showed the lack of data regarding evidence in GUTB diagnosis using PCR.

Moussa et al.<sup>20</sup> reported the biggest sample among other studies. He investigated urine specimen from 1000 suspected GUTB patients

**Table 4.** Summary of Included Studies Result (Importance).

Author, year	Population	Number of Patients	Index Test	Gold-standard Test	Reported PCR characteristics compared to Gold Standard			
					Sensitivity	Specificity	PPV	NPV
van Vollenhoven et al., <sup>18</sup> 1996	Suspected adult GUTB patients (urine specimen)	83	PCR M13 mp8	Bactec Culture Medium	100	100	100	100
Gamboa et al., <sup>19</sup> 1998	Extrapulmonary TB adult patients including GUTB	69	LCx Mtb Assay	Lowenstein-Jensen, Bactec and Colestos media	78.5	100	100	93.1
Hemal et al., <sup>14</sup> 2000	Suspected adult GUTB patients	42	PCR MPB-64	AFB Culture	94	86	97	75
Moussa et al., <sup>20</sup> 2000	Suspected adult GUTB patients (morning urine specimen)	1000	Nested PCR IS6110	Lowenstein-Jensen, Colestos, and Middlebrook media	95.99	98.11	96.66	97.5
Garcia-Elorriaga et al., <sup>21</sup> 2009	Extrapulmonary TB patients including GUTB	20	Nested PCR IS6110	Positive Culture or AFB Smear	100	82	82	100
Khosravi et al., <sup>22</sup> 2010	Suspected adult GUTB patients (urine specimen) Adult	11	Nested PCR IS6110	Lowenstein-Jensen culture media	100	100	Not reported	Not reported
Hillemann et al., <sup>23</sup> 2011	extrapulmonary TB patients including GUTB (urine specimen) Adult	91	GeneXpert MTB/RIF	Lowenstein-Jensen and Stonebrink slant	100	98.6	Not reported	Not reported
Tortoli et al., <sup>24</sup> 2012	extrapulmonary TB patients including GUTB (urine specimen)	112	GeneXpert MTB/RIF	Lowenstein-Jensen media + MGIT 960 Liquid culture	84.6	97.3	78.6	98.2
Khan et al., <sup>25</sup> 2013	Suspected adult GUTB patients	32	PCR	Lowenstein-Jensen media	88.6	96.5	95.3	92.4

GUTB: Genitourinary tuberculosis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; TB: tuberculosis

with two different PCR primers (IS6110 and 16SrRNA), the authors found higher sensitivity using an IS6110-PCR primer compared to an 16SrRNA-PCR primer with results of 95.99% and 87.05%, respectively while both primer had comparable sensitivity.<sup>20</sup> Other studies with similar design on suspected GUTB patients had similar results on diagnostic performance although only smaller sample were obtained (11-83 subjects).<sup>14,18,22,24</sup> We found that smallest sensitivity and specificity were reported from suspected extrapulmonary TB patients with collected urine specimen (78.5 and 82%,

respectively).<sup>19,21</sup> However, these studies reported high number of PPV and NPV thus indicating low number of false positive and false negative detection.

We identified five studies with identical PCR primers.<sup>20-24</sup> Three studies (Moussa, et al.,<sup>20</sup> Garcia-Elloriaga, et al.,<sup>21</sup> and Khosravi, et al.<sup>22</sup>) utilized IS6110 as PCR primer targets while two studies (Hillemann, et al.,<sup>23</sup> and Tortoli, et al.<sup>24</sup>) utilized GeneXpert MTB/RIF as diagnostic methods. All three studies using IS6110 PCR primers reported similar number on sensitivity and specificity.<sup>20-22</sup> Although, Khosravi, et al.<sup>22</sup>

**Table 5.** Applicability Appraisal Result of Included Studies.

Author, year	Described sufficient detail to permit replication*	Reason
van Vollenhoven et al., <sup>18</sup> 1996	Yes	Both gold and standard test had been specifically described along with the diagnostic performance of the index test.
Gamboa et al., <sup>19</sup> 1998	No	Index test is not described. Authors failed to describe specific primer or gene targeted
Hemal et al., <sup>14</sup> 2000	Unclear	Index test and diagnostic performance had been described. However, author failed to describe specific AFB culture media used
Moussa et al., <sup>20</sup> 2000	Yes	Both gold and standard test had been specifically described along with the diagnostic performance of the index test.
Garcia-Elorriaga et al., <sup>21</sup> 2009	Unclear	Index test and diagnostic performance had been described. However, author failed to describe specific AFB culture media used
Khosravi et al., <sup>22</sup> 2010	Unclear	Both gold and standard test had been specifically described. However, the author failed to report sufficient data for PPV and NPV calculation.
Hillemann et al., <sup>23</sup> 2011	Unclear	Both gold and standard test had been specifically described. However, the author failed to report sufficient data for PPV and NPV calculation.
Tortoli et al., <sup>24</sup> 2012	Yes	Both gold and standard test had been specifically described along with the diagnostic performance of the index test.
Khan et al., <sup>25</sup> 2013	No	Index test is not described. Authors failed to describe specific primer or gene targeted

\* Scored based on the University of Oxford's Centre for Evidence-Based Medicine (CEBM) Diagnostic Variability criteria.

failed to report sufficient data for PPV and NPV calculation, both Moussa, et al.<sup>20</sup> and Garcia-Elorriaga, et al.<sup>21</sup> reported high number of PPV and NPV which we argue did not clinically different. It is important to note that Moussa, et al. and Garcia-Elorriaga, et al had different subject collection criteria (suspected GUTB vs. extrapulmonary TB with urine collection) and still resulted in a very similar result.<sup>20-21</sup>

In the two studies investigating GeneXpert MTB/RIF as index test on suspected extrapulmonary TB with urine specimen collection, both authors reported high number of sensitivity and specificity comparable with IS6110 PCR primer.<sup>23-24</sup> However, only Tortoli, et al.<sup>24</sup> reported PPV and NPV of 78.6% and 98.2%, respectively while Hillemann et al.<sup>23</sup> did not. Since GeneXpert MTB/RIF operates in a similar manner to PCR, this result should indicate the potential of PCR to be used as a GUTB diagnostic modality. Additionally, Abbara et al. also emphasized that GeneXpert MTB/RIF PCR had additional benefit compared to traditional

PCR since the modality could be used for specific genes detection and early identification of multidrug-resistant or extensively drug-resistant tuberculosis.<sup>28</sup> However, due to the difference in procedure, cost, and access limitation, we argued that GeneXpert MTB/RIF might not always be applicable especially in the developing countries.

Since Moussa, et al.<sup>20</sup> also provided diagnostic performance on two different PCR primer (IS6110 and 16SrRNA PCR Primer), it is interesting to note that PCR sensitivity could be affected by primer target. The authors argued that IS6110-PCR achieve higher sensitivity due to the ability to bind more insertions site in the *M. tuberculosis* genome, compared to the 16SrRNA-PCR primer. The authors argued that this difference could be affected by the abundant availability of IS6110 insertion site in *M. tuberculosis* genome while the specificity was not affected since insertion site could be found in almost every strain of *M. tuberculosis*.<sup>20</sup> However, he argued that both primers were required to ensure highest sensitivity and

specificity to be achieved since several strains of *M. tuberculosis* were absent from the IS6110-PCR genome insertion point.<sup>20</sup>

Although our data suggested that PCR had a somewhat high diagnostic performance compared to culture for diagnosis of GUTB from urine samples, several authors have also raised concern regarding the applicability of these results. A study by Marangu et al. suggested that high number of studies had reported the possibilities of urine PCR as a diagnostic modality for pulmonary tuberculosis.<sup>34</sup> In his review, he concluded that compared to sputum culture, urine PCR could achieve 49% sensitivity and 96% specificity for diagnosis of pulmonary tuberculosis which contrasted our findings where urine PCR is highly sensitive and specific for GUTB.<sup>34</sup> In a different report, Altez-Fernandez had discovered high heterogeneity among different studies comparing PCR with culture for extrapulmonary tuberculosis using urine samples mainly due to the difference in PCR method and primer selection.<sup>35</sup> Since our results were only based on 1.460 patients from nine different studies where publication bias in this topic has not widely assessed, we suggest to take these results in regards with specific clinical context in mind. However, the Centers for Disease Control and Prevention has begun recommending PCR as the standard practice for GUTB, and has argued that accessibility to nucleic acid amplification testing could shorten the diagnosis time.<sup>36</sup> From our quality assessment, we argue that current evidence has not been sufficient to suggest that the diagnosis of GUTB should be based solely on PCR, but instead should be complimented by urine culture as confirmatory. However, the high sensitivity, specificity, and predictive value of PCR coupled with the rapid duration and wide availability of PCR test could potentially be utilized by physician as guiding tool to initiate and monitor patient response to anti-tuberculosis drugs.

Finally, we admit that several limitations, such as full-text availability, number of databases used, and the search terms specified, might limit the overall gathered evidence in this study. Regarding the results, we suggest that authors investigating PCR and AFB culture in the diagnosis of GUTB should adhere to standard

protocol and widely used primers and media. We also suggest that patient clinical presentation, characteristics, and method of sample collection should not be ignored and be reported to allow other researchers and clinicians to infer better decisions based on the presented results and the clinical context at hand. Our findings also suggest the dire need of well-designed studies evaluating the PCR method for the diagnosis of GUTB.

## CONCLUSION

PCR offers a more rapid detection of the presence of tuberculosis DNA over longer-duration AFB culture tests to diagnose patients suspected of having GUTB. Current data suggest that the high sensitivity, specificity, and predictive value of PCR might enable it to be used as a single GUTB diagnostic modality in the future. However, limited by current evidence, we have not been able to suggest the diagnosis of GUTB based solely on PCR, but instead its use in compliment with urine culture as confirmatory. Since PCR offers relatively rapid test results, wide availability, and is routinely performed, we encourage clinicians to employ PCR as a guiding tool while initiating and monitoring patient response to anti-tuberculosis drugs. Regarding limited number of well-designed studies found during the search process, studies with high-quality and rigorous methodological bases will certainly contribute to supporting current evidence.

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## COMPETING INTEREST

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