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Clinical Features and Drug-Resistance Profile of Urinary Tuberculosis in South-Western China

A Cross-sectional Study

Yuanxin Ye, PhD, Xuejiao Hu, PhD, Yunying Shi, MD, Juan Zhou, MS, Yi Zhou, MS, Xingbo Song, MS, Yi Xie, MD, Xiaojun Lu, MS, Lanlan Wang, MD, Binwu Ying, MD, and Xuerong Chen, MD

Abstract: To investigate the epidemiology, clinical features, and drug-resistance profile of urinary tuberculosis (UTB) in south-western China to improve UTB diagnostics.

After the screening of 1036 cases of suspected UTB, 193 patients with UTB were enrolled during 2009 to 2014. Urine samples were collected for routine urinalysis, smear, tuberculosis DNA (TB-DNA) detection, and drug-resistant analysis, whereas blood samples were collected for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and renal function evaluation. Clinical features (such as symptoms and outcome) and imageology results (such as B ultrasonic, computerized tomography, intravenous pyelography, and renography) were also collected and analyzed to investigate the epidemiology, clinical features, and drug-resistance profile.

The most common presenting symptoms were urinary irritation (61.1%) and lumbago (49.2%). High proportions of microscopic hematuria (63.2%) and microscopic proteinuria (45.6%) were also observed. The positive rate for TB-DNA was 66.3%. The positive rate for culture was 13.1% and for smear it was 9.8%. The abnormal outcome rates of the computerized tomography, ultrasonography, intravenous pyelography, and the nephrogram were 76.9%, 70.1%, 29.8%, and 37.0%, respectively. The total rate of drug-resistant TB (resistant to at least 1 drug) was 39.7%, of which 20.7% was multidrug-resistance TB. The most prevalent mutation sites were *katG* S315T1, *rpoB* S531L, and *gyrA* D94G.

We observed a serious epidemic of drug-resistant UTB and a substantial number of new UTB cases with multidrug resistance TB. Molecular diagnostics is crucial in the definite diagnosis of UTB, and our finding is a supplement and further confirmation of polymerase chain reaction usage for TB diagnosis. We recommend real-time polymerase chain reaction for TB-DNA identification instead of culture, and GenoType tests (MTBDRplus and MTBDRsl assay) for drug resistance as routine assays for patients with suspected UTB.

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Abbreviations: BUN = blood urea nitrogen, CT = computerized tomography, CVKA = capreomycin, viomycin, kanamycin, and amikacin, DSTs = drug-susceptibility tests, EMB = ethambutol, EPTB = extrapulmonary tuberculosis, FLQ = fluoroquinolones, HIV = human immunodeficiency virus, INH = isoniazid, IVP = intravenous pyelography, MDR-TB = multidrug-resistance tuberculosis, MDR-TB = multidrug-resistance tuberculosis, RFP = rifampicin, SD = standard deviation, TB-DNA = tuberculosis DNA, UTB = urinary tuberculosis.

INTRODUCTION

Extrapulmonary tuberculosis (EPTB) constitutes approximately 10% to 20% of tuberculosis (TB) cases and continues to be a significant problem worldwide.[1,2] Urinary TB (UTB) is one of the most common types of EPTB, and more than 90% of EPTB cases occurred in developing nations such as China.[3,4] The nonspecific clinical features of UTB typically result in delayed diagnosis and poor management of the disease.[3] A definite diagnosis of UTB typically depends on detecting acid-fast bacilli in urine or tissue specimens. Smear microscopy is rapid and has a low cost, but it is insensitive and other factors can easily interfere with its diagnostic capabilities.[5–7] Culture identification also has limited sensitivity, with a long turnaround time for confirming the diagnosis.[3,7–11] Microbiological diagnosis has not satisfied clinical expectations.

Apart from the poor etiology confirmation, drug resistance is another impediment to TB management.[12–14] Rapid confirmation of drug resistance is a prerequisite for effectively treating TB and preventing additional resistance traits.[3,14] DNA strip assays, the GenoType MTBDRplus, and the GenoType MTBDRsl assay (Hain Lifescience, Nehren, Germany)—a combination of polymerase chain reaction (PCR) and reverse hybridization—generally provide a satisfactory rapid diagnosis of first-line and second-line drug resistance. Several studies[14–16] have provided lots of evidence that GenoType tests, which can be finished within 4 hours, have a very good coherence with drug-susceptibility testing. As GenoType tests are repaid and reliable, the World Health Organization (WHO) has also recommend GenoType tests for drug resistance test.

China has the highest annual number of cases of multidrug-resistant TB (MDR-TB) worldwide.[4] The incidence of TB in

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From the Department of Laboratory Medicine (YY, XH, JZ, YZ, XS, YX, XL, LW, BY), West China Hospital, Sichuan University, Sichuan Province; Department of Nephrology (YS), and Department of Tuberculosis (XC), West China Hospital, Sichuan University, Chengdu, The People's Republic of China.
Correspondence: Xiaojun Lu, Lanlan Wang, Binwu Ying, Department of Laboratory Medicine, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, The People's Republic of China (e-mails: luxiaojun1972@163.com; lymist1981@163.com; docbwy@126.com);
Xuerong Chen, Department of Tuberculosis, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, The People's Republic of China (e-mail: 1136121315@qq.com).
YY, XH, and YS contributed equally to this article.
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south-western China is higher than that of other areas in China.[17] To date, there are no data assessing clinical features and drug resistance of UTB in south-western China, and drug-susceptibility tests (DSTs) have not been routinely performed in most hospitals in China.[18] Therefore, this study aimed to determine the clinical features, diagnostic investigations, and drug resistance gene profile of UTB in south-western China.

METHODS

Study Design and Patient Population

A cross-sectional study was conducted in West China Hospital, Sichuan University, located in south-western China, from January 2009 to March 2014. After screening 1036 cases of suspected UTB, 271 patients were preliminarily diagnosed based on any of the positive results for mycobacterium culture, smear microscopy, real-time PCR, and histological patterns. Two hundred six of them were inpatients who were further examined to determine clinical features, radiological findings, and response to antitubercular therapy. One hundred ninety-three patients finally diagnosed with UTB were included. We also verified that the patients eventually enrolled in our study were all diagnosed with UTB by experienced urinary specialists in our team, and these special authors had access to identifying information during data collection, whereas the others were not. Figure 1 provides an overview of the cohort.

A flowchart of patients diagnosed with UTB was based on clinical features, laboratory examinations, radiological findings, and patient responses to antitubercular therapy. The diagnosis was confirmed by experienced urinary specialists.

Written informed consent was obtained from all patients included, and the study was approved by the Clinical Trials and Biomedical Ethics Committee of West China Hospital, Sichuan University. The relevant Judgement's Reference Number is No. 198 (2014).

Clinical Characteristics and Relevant Examinations

All 193 patients had demographic data, clinical history, radiological findings, selected laboratory results, and prognosis obtained from their medical records. All 193 patents had midstream morning urine collected and decontaminated (N-acetyl-L-cysteine [NALC]/NaOH method). Each sample was concentrated through centrifugation and subjected to TB-DNA, smear microscopy, and urine analysis simultaneously. Urine TB-DNA was extracted using NucliSens EasyMag (BioMérieux, Lyon, France). Real-time PCR was performed to detect mycobacterial DNA using a 'Care TB' real-time PCR kit (Qiagen China [Shenzhen] Co Ltd, Shenzhen, China) in the LightCycler 480 Real-Time PCR System (Roche Diagnostics, Germany). The result was interpreted according to reagent instructions. Urine smear microscopy was performed with the Ziehl-Neelsen acid-fast staining method, consistent with acid-fast bacilli smear standard procedures. The urine cellular and biochemical analysis was performed with an automated routine urine laboratory analyser UF-100 (Sysmex, Kobe, Japan).

Three millilitres of EDTA-anticoagulated peripheral blood was obtained from all participants for conducting a blood routine examination by automated haematology analyser XE-5000TM (Sysmex, Kobe, Japan).

Three millilitres of fasting venous blood was obtained for serum creatinine, blood urea nitrogen (BUN), and HIV testing. The renal function of all patients was evaluated by determining the level of serum creatinine and BUN using an automatic Biochemistry Analyzer Modular P800 (Roche Diagnostics, Germany). The presence of human immunodeficiency virus (HIV) antibody in the serum was examined using a Modular Analytics E170 automated immunoassay analyser (HIV Combi; Roche Diagnostics, Germany).

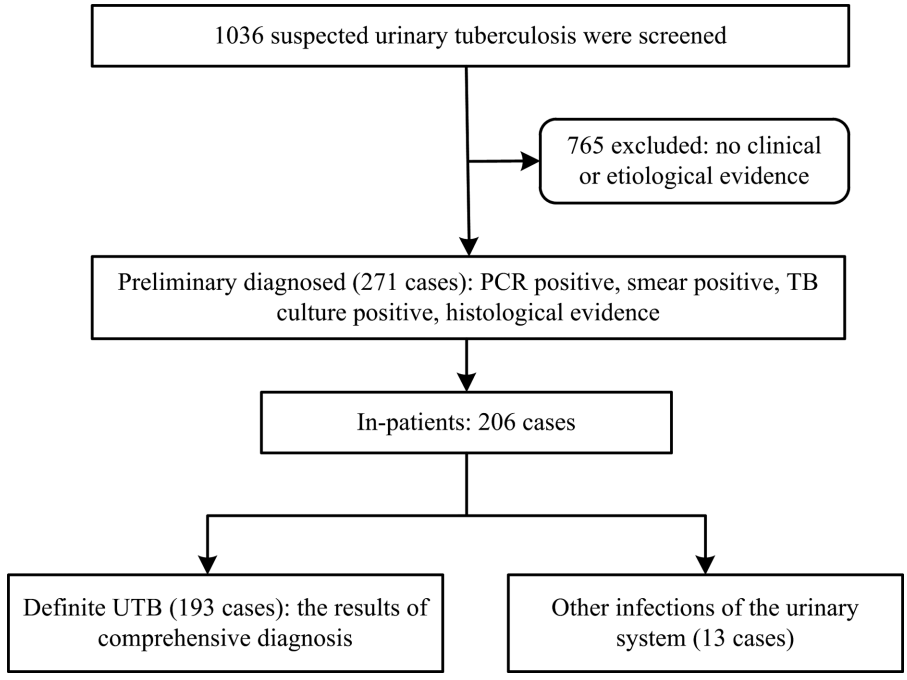

FIGURE 1. An overview of the study population.

Drug-Resistant Genotyping Analysis

Mutations in the *rpoB*, *katG*, and *inhA* genes associated with resistance to rifampicin (RFP) and isoniazid (INH) were identified using MTBDRplus kits (Hain Lifescience, Nehren, Germany). Mutations in the *gryA*, *rrs*, and *embB* genes associated with resistance to fluoroquinolones (FLQ), injectable aminoglycosides/cyclic peptides capreomycin, viomycin, kanamycin, and amikacin (CVAK), and ethambutol (EMB) were identified using MTBDRsl kits (Hain Lifescience, Nehren, Germany) according to the manufacturer's instructions. The existence of a resistant strain is signaled by the omission of a wild-type band, the appearance of mutant type bands, or both.

Statistical Analysis

Sample number was calculated with P value of 0.05 and a confidence coefficient of 0.95. Positive ratios were calculated and patients lost to follow-up were excluded. Continuous variables were described in the form of means ± standard deviation (SD); categorical variables were described with numbers and percentages. The difference between groups was analyzed using a chi-square test or the Fisher exact test. Statistical analyses were performed with SPSS software (version 17.0). Finally, statistical significance was established at an alpha level of 0.05.

RESULTS

Clinical Characteristics and Relevant Examinations in UTB Patients

The demographic data and clinical manifestations of 193 patients on admission are summarized in Table 1. Considering the differences in the reproductive systems of males and females, patients were subjected to a clinical characteristic

TABLE 1. The Clinical Features of Urinary Tuberculosis Patients

		Sex		
Clinical Characteristics	**All Patients**	**Male Patients**	**Female Patients**	***P***
Age, years (mean ± SD)	42.80 ± 14.95	43.33 ± 15.21	41.93 ± 14.57	0.529
Male	120/193 (62.2%)	120	73	—
Retreated TB	65/193 (33.7%)	43/120 (35.8%)	22/73 (30.1%)	0.454
Extra-urinary TB	70/193 (36.3%)	48/120 (40.0%)	22/73 (30.1%)	0.167
Symptoms on admission				
Urinary irritation	118/193 (61.1%)	71/120 (59.2%)	47/73 (64.4%)	0.471
Lumbago	95/193 (49.2%)	53/120 (44.2%)	42/73 (57.5%)	0.073
Night sweat	25/193 (13.0%)	17/120 (14.2%)	8/73 (11.0%)	0.520
Weight loss	21/193 (10.9%)	12/120 (10.0%)	9/73 (12.3%)	0.614
Fever	52/193 (26.4%)	36/120 (30%)	16/73 (21.9%)	0.220
Laboratory abnormalities				
Smear-positive	19/193 (9.8%)	12/120 (10.0%)	7/73 (9.6%)	0.926
TB-DNA-positive	128/193 (66.3%)	78/120 (65.0%)	50/73 (68.5%)	0.619
Culture-positive*	11/84 (13.1%)	6/53 (11.3%)	5/31 (16.1%)	0.768
Leukocytosis	25/193 (13.0%)	17/120 (14.2%)	8/73 (11.0%)	0.520
Anemia	30/193 (15.6%)	18/120 (15.0%)	12/73 (16.4%)	0.789
Microscopic hematuria	122/193 (63.2%)	79/120 (65.8%)	43/73 (58.9%)	0.333
Microscopic pyuria	37/193 (19.2%)	22/120 (18.3%)	15/73 (20.5%)	0.705
Microscopic proteinuria	88/193 (45.6%)	54/120 (45.0%)	34/73 (46.6%)	0.831
Increased BUN	45/193 (23.3%)	34/120 (28.3%)	11/73 (15.1%)	0.035
Increased creatinine	39/193 (20.2%)	29/120 (24.2%)	10/73 (13.7%)	0.079
Raised ESR*	69/97 (71.1%)	44/63 (69.8%)	25/34 (73.5%)	0.702
Elevated CRP*	53/63 (84.1%)	32/40 (80.0%)	21/23 (91.3%)	0.237
Imageology abnormalities				
CT*	133/173 (76.9%)	85/107 (79.4%)	48/66 (72.7%)	0.309
Ultrasonography*	117/167 (70.1%)	72/102 (70.6%)	45/65 (69.2%)	0.852
IVP*	31/104 (29.8%)	17/64 (26.6%)	14/40 (35.0%)	0.360
Nephrogram*	40/108 (37.0%)	19/64 (29.7%)	21/44 (47.7%)	0.056
Outcome				
Mortality	1/193 (0.5%)	1/120 (0.8%)	0/73 (0%)	>0.999
Default	4/193 (2.1%)	2/120 (1.7%)	2/73 (2.7%)	0.634
Nephrectomy (lost to follow-up)	25/193 (12.9%)	16/120 (13.3%)	9/73 (12.3%)	0.513
Recover after nephrectomy	20/21 (95.2%)	11/12 (91.7%)	9/9 (100%)	0.571
Die after nephrectomy	1/21 (4.8%)	1/12 (8.3%)	0/9 (0.0%)	0.568
Not treated	8/193 (4.2%)	4/120 (3.3%)	4/73 (5.5%)	0.480
Good recovery	134/193 (69.4%)	85/120 (70.8%)	49/73 (36.6%)	0.587

CT = computerized tomography, IVP = intravenous pyelography, TB = tuberculosis.
*Denominators are less than the total as some patients did not do the examination at the time they were diagnosed as TB.

analysis (Table 1). The participants were mostly middle-aged adults, most of whom were male. All patients were administered a similar therapeutic regimen, that is, RFP, INH, and EMB, combined with FLQ or aminoglycoside antibiotics, when necessary. More than one-third of all patients had extra UTB, and approximately one-third of all patients received repeated treatments. The most common presentation was urinary irritation (61.1%), followed by lumbago (49.2%), fever (26.4%), night sweat (13.0%), and weight loss (10.9%). No significant differences in demographic data or clinical syndromes on admission were found between male patients and female patients (P value as shown in Table 1).

Regarding the microbiological diagnostic tests, real-time PCR was more sensitive than smear microscopy and culture (66.3% vs 9.8% vs 13.1%) for the diagnosis of UTB in urine (Table 1). Abnormal urinalysis was a diagnostic clue for UTB and was common in UTB patients. More than half of all participants presented with microscopic hematuria (122/193) and/or microscopic proteinuria (88/193). Additionally, elevated CRP was observed in 84% (53/63) patients and elevated ESR was observed in 71% (69/97) patients. About 23% patients (45/193) had increased BUN and about 20% patients (39/193) had increased creatinine, which means approximately one-fourth of all patients were in danger of abnormal renal function. About 13% patients (25/193) suffered from leukocytosis and about 15% patients suffered from anemia (Table 1). Notably, all 193 patients were HIV-seronegative. There were no significant differences in the laboratory abnormalities between male and female patients, except in the proportions of increased urea ($P = 0.035$).

The abnormal outcome rates of computerized tomography (CT) were 76.9%, followed by ultrasonography, nephrograms, and IVP, with positive rates of 70.1%, 37.0%, and 29.8%, respectively. Male and female patients showed similar positive tendencies in accordance with all UTB patients' imaging results (Table 1).

For the patients' outcome, most participants were discharged from the hospital after recovery and received continuous anti-TB treatment. Nevertheless, approximately a quarter of patients (46/193) underwent a surgical excision of their nonfunctioning kidneys, and 21 of these patients were followed and 95.2% (20/21) of them recovered after surgery (Table 1). The outcomes of male and female patients were similar as shown in Table 1.

Drug-Resistance Profile in UTB Patients

One hundred twenty-eight patients with positive DNA results were subjected to TB drug-resistance detection. Interpretable results with no ambiguity were obtained in samples from 121 patients (94.5%). The results indicated that more than one-third of patients had drug-resistant TB, and approximately one-fourth of patients had MDR-TB, which manifested primarily as resistance to RFP combined with high-level resistance to INH (Table 2).

The 121 patients were divided into a de novo group (new patients) and a retreated group (previously treated patients) to elucidate whether drug resistance was correlated with previous treatment (Table 2). No significant differences in drug-resistant patterns were observed in the 2 groups ($P = 0.582$). Tables 2 and 3 showed the resistant gene profile of the drug-resistant patients. The most common mutations were INH resistance (31.4%) and RFP resistance (24.8%), followed by FLQ resistance (15.7%) (Table 2). The most prevalent mutation sites were S315T1 exchanges in *katG* codons 315, S531L exchanges in *rpoB* codons 530 to 533, and D94G exchanges in *gyrA* codons 92 to 97 (Table 3).

The clinical characteristics were compared between 48 drug-resistant patients and 73 drug-susceptible patients (Table 4). Clinical features, laboratory examinations, and radiology were similar between the 2 groups (as shown in Table 4). In general, drug-susceptible patients exhibited a better recovery rate than drug-resistant patients ($P = 0.017$).

DISCUSSION

Our study showed that UTB was a disease that primarily affects middle-aged males, often manifesting as urinary irritation and lumbago. Microscopic hematuria and microscopic

TABLE 2. Drug-Resistance Pattern of Urinary Tuberculosis Patients

		Drug-resistant UTB		
Drug-resistance Pattern	**Total UTB (n = 121)**	**De novo UTB (n = 89)**	**Retreated UTB (n = 32)**	***P***
Resistance to any drug	48 (39.7%)	34 (38.2%)	14 (43.8%)	0.582
MDR-TB	25 (20.7%)	15 (16.9%)	10 (31.3%)	0.085
XDR-TB	16 (13.2%)	10 (11.2%)	6 (18.8%)	0.440
Mono resistance to RFP	4 (3.3%)	4 (4.5%)	0 (0.0%)	0.572
Mono resistance to INH	13 (10.7%)	10 (11.2%)	3 (9.4%)	>0.999
Mono resistance to FLQ	4 (3.3%)	3 (3.4%)	1 (3.1%)	>0.999
Mono resistance to CVAK	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
Mono resistance to EMB	1 (0.8%)	1 (1.1%)	0 (0.0%)	>0.999
Resistance to RFP	30 (24.8%)	19 (21.3%)	11 (34.4%)	0.143
Resistance to INH	38 (31.4%)	25 (28.1%)	13 (40.6%)	0.283
High level	33 (27.3)	21 (23.6%)	12 (37.5%)	0.130
Low level	5 (4.1%)	4 (4.5%)	1 (3.1%)	>0.999
Resistance to FLQ	19 (15.7%)	13 (14.6%)	6 (18.8%)	0.581
Resistance to CVAK	5 (4.1%)	4 (4.5%)	1 (3.1%)	>0.999
Resistance to EMB	5 (4.1%)	4 (4.5%)	1 (3.1%)	>0.999

CVKA = capreomycin, viomycin, kanamycin, and amikacin, EMB = ethambutol, FLQ = fluoroquinolones, INH = isoniazid, MDR-TB = multidrug resistance tuberculosis, RFP = rifampicin, UTB = urinary tuberculosis, XDR-TB = X-drug resistance tuberculosis.

TABLE 3. Mutation Loci of *Mycobacterium Tuberculosis* From Urinary Tuberculosis Patients

Drug Resistance	Gene and Codon	Mutation	Resistant to Any Drug	MDR
Resistance to RFP			30	25
	rpoB526-529	H526Y	1 (3.3%)	1 (4.0%)
	rpoB526-529	H526D	3 (10.0%)	3 (12.0%)
	rpoB526-529	H526D,Y	1 (3.3%)	1 (4.0%)
	rpoB 530-533	S531L	25 (83.4%)	20 (80.0%)
Resistance to INH			38	25
High level	katG 315	S315T1	29 (76.3%)	23 (92.0%)
	katG 315	S315T2	2 (5.3%)	0 (0.0%)
	katG 315	S315T1,T2	2 (5.3%)	1 (4.0%)
Low level	inhA	C15T	5 (13.1%)	1 (4.0%)
Resistance to FLQ			19	15
	GyrA89-93	A90V	2 (10.5%)	2 (13.3%)
	GyrA92-97	D94A	1 (5.3%)	0 (0.0%)
	GyrA92-97	D94N/Y	2 (10.5%)	0 (0.0%)
	GyrA92-97	D94G	11 (57.8%)	10 (66.7%)
	GyrA92-97	D94H	1 (5.3%)	1 (6.7%)
	GyrA92-97	D94G,H	1 (5.3%)	1 (6.7%)
	GyrA89-93	S91P	1 (5.3%)	1 (6.7%)
Resistance to CVAK			5	4
	rrs1401	A1401G	3 (60.0%)	2 (50.0%)
	rrs1484	A1484G	1 (20.0%)	1 (25.0%)
	rrs1401,1484	A1401G,A1484G	1 (20.0%)	1 (25.0%)
Resistance to EMB			5	4
	embB306	M306L	2 (40.0%)	2 (40.0%)
	embB306	M306V	2 (40.0%)	1 (20.0%)
	embB306	M306L,M306V	1 (20.0%)	1 (20.0%)

CVKA = capreomycin, viomycin, kanamycin, and amikacin, EMB = ethambutol, FLQ = fluoroquinolones, INH = isoniazid, RFP = rifampicin.

proteinuria were commonly detected in the urine analysis of UTB patients. In addition, most UTB patients presented with a favorable outcome, but surgical treatment was required for advanced UTB. These results are generally consistent with previously published literature.[3,19–20] Our findings, together with the findings available in the literature, suggest that urologists should consider the possibility of TB in a urinary system for patients presenting with obstinate and progressive frequent urination with unknown causes and for middle-aged patients with retreated asymptomatic hematuria or proteinuria.

An etiology examination is crucial for facilitating a definite diagnosis of UTB. Some published studies have reported that smear microscopy possessed low variable sensitivity values (0%–40%) and could not differentiate *Mycobacterium tuberculosis* from nontuberculous mycobacteria.[5–7] Our results were in agreement with previous data and showed a low positive rate of 9.8%. Combining its simple, rapid property with insensitivity, smear microscopy is useful for screening for UTB in countries with a high incidence of TB. There are conflicting data regarding the positive rate of cultures. For instance, a study from Spain showed that the positive rate of culture was 10.7%, whereas some studies reported higher positive rates, up to 80%.[3,8–10,20] The diagnosis rate of mycobacterial culture was 13.1% in our study, which was lower than the diagnosis rate of most reported studies.[3,7–9] Possible explanations for this discordance are: the number of submissions for cultures is low because of the long time taken by the mycobacterial culture and the positive rate is low because the poor transferring live bacteria condition, insufficient clinical sample volumes and the nonuniform distribution of bacteria in urine.

Polymerase chain reaction has been evaluated largely as a high-flux method for the rapid, noninvasive diagnosis of TB. Its sensitivity has been variably reported to be approximately 45.5% to 100%.[6–7,19,21–23] In contrast to the low yield of culture and smear, PCR identified 128 UTB patients (66.3%) as harboring mycobacterial DNA in our experiment. Our findings supplement and further confirm published observations concerning the use of PCR for TB diagnosis. The positive rate of real-time PCR is higher than the positive rates of traditional methods (ie, culture and smear), but is not sufficiently high. What is more, 1 of the 11 patients who were culture-positive was negative with DNA, and 1 of the 19 patients who were smear-positive was negative with TB-DNA. Moreover, real-time PCR has disadvantages. One disadvantage is its inability to detect whether the TB infection is biologically active or in its latent phase.[24] Chakravorty et al found that DNA-extraction steps could cause a substantial loss of mycobacterial DNA.[25] However, our findings still indicate that real-time PCR is an instant and effective diagnostic tool for suspected UTB patients. Although DNA does not replace conventional diagnostic tests completely, it is an indispensable complement. Therefore, it may be more suitable for diagnosing UTB when real-time PCR is combined with traditional methods.

Our results showed that male patients were more likely to have a greater proportion of increased BUN compared with female patients. The reason for this difference remains

TABLE 4. Clinical Features of Drug-Resistant UTB Patients and Drug-Susceptible UTB Patients

Clinical Characters	Drug-resistant TB (n = 48)	Drug-susceptible TB (n = 73)	*P*
Age, years (mean ± SD)	40.79 ± 15.36	42.67 ± 14.81	0.502
Male/female	28/20	45/28	0.716
Recurrent TB	14/48 (29.2%)	18/73 (24.7%)	0.535
Extra-urinary TB	16/48 (33.3%)	22/73 (30.1%)	0.653
Symptoms on admission			
Urinary irritation	35/48 (72.9%)	43/73 (58.9%)	0.115
Lumbago	24/48 (50.0%)	39/73 (53.4%)	0.712
Night sweat	9/48 (18.8%)	11/73 (15.1%)	0.594
Lose weight	9/48 (18.8%)	9/73 (12.3%)	0.332
Fever	13/48 (27.1%)	21/73 (28.8%)	0.840
Laboratory abnormalities			
Smear-positive	5/48 (10.4%)	5/73 (6.8%)	0.486
Culture-positive*	4/24 (16.7%)	1/33 (3.0%)	0.072
Leukocytosis	6/48 (12.5%)	10/73 (13.7%)	0.849
Anemia	10/48 (20.8%)	8/73 (11.0%)	0.135
Microscopic hematuria	34/48 (70.8%)	53/73 (72.6%)	0.832
Microscopic pyuria	15/48 (31.3%)	15/73 (20.5%)	0.182
Microscopic proteinuria	26/48 (54.2%)	38/73 (52.1%)	0.820
Increased BUN	11/48 (22.9%)	18/73 (24.7%)	0.826
Increased creatinine	10/48 (20.8%)	17/73 (23.3%)	0.751
Raised ESR*	14/19 (73.7%)	29/40 (72.5%)	0.924
Elevated CRP*	12/13 (92.3%)	24/27 (88.9%)	0.736
Imageology abnormalities			
CT*	36/45 (80.0%)	48/69 (69.6%)	0.216
Ultrasonography*	31/43 (72.1%)	43/70 (61.4%)	0.247
IVP*	7/33 (21.2%)	16/57 (28.1%)	0.472
Nephrogram*	10/32 (31.3%)	10/53 (18.9%)	0.192
Outcome			
Mortality	1/48 (2.1%)	0/73 (0%)	0.397
Default	1/48 (2.1%)	0/73 (0%)	0.397
Nephrectomy (lost to follow-up)	5/48 (10.4%)	4/73 (6.8%)	0.226
Recover after nephrectomy	6/7 (85.7%)	5/5 (100.0%)	0.583
Die after nephrectomy	1/7 (14.3%)	0/5 (0.0%)	0.583
Not treated	3/48 (6.3%)	3/73 (4.1%)	0.681
Good recovery	31/48 (64.6%)	61/73 (83.6%)	0.017

CT = computerized tomography, IVP = intravenous pyelography, TB = tuberculosis.
*Denominators are less than the total as some patients did not do the examination at the time they were diagnosed as TB.

unknown, but the discrepancy implies that deteriorating renal function should be considered in diagnosing UTB in males. Further studies are required to clarify these results.

In terms of imaging findings, an abnormal outcome of iconography examination can provide a diagnostic clue for genito-UTB.[3] Our observations also demonstrated that CT and ultrasonography were important in the auxiliary diagnosis of UTB, particularly for patients suspected to have negative microbiological evidence. Given these findings and observations, a combined diagnosis is applicable in clinical practice. A systematic approach informed by attention to clinical features, laboratory investigations, radiological imaging, and even patient responses to antitubercular therapy might be particularly effective for the early diagnosis of UTB.

South-western China has a serious epidemic of drug-resistant TB. Duo et al[17] reported a high rate of MDR-TB (32.14%) in tubercular meningitis. One study of PTB in Sichuan (south-western China) showed that the prevalence of MDR-TB was 51.3%.[26] The rate of MDR-TB in this research was 20.7 %, that is, 16.9% in newly diagnosed patients and 31.3% in treated TB patients, which is higher than Zhao et al's[18] study around China (5.7%, 95% confidence interval [CI] 4.5–7.0 and 25.6%, 95% CI 21.5–29.8) and is also higher than the world level (about 4% of new TB cases and 20% of previously treated cases are estimated to have MDR-TB). Although the rate of MDR in UTB was lower than that in extra UTB, attention should be paid to its occurrence. The burden of confirmed MDR-TB indicates a serious risk for nosocomial transmission and the necessity for reinforced infection control within an inpatient setting. In addition, Zhao et al[18] found that repeated exposure to anti-TB agents might increase the likelihood of developing MDR-TB. We found that the retreated group presented with more cases of MDR-TB than did the de novo group; however, the difference was not statistically significant. We also discovered that de novo UTB patients accounted for a certain proportion of MDR-TB patients (15.7%). These new patients may have been hospitalized without MDR-TB and received inadequate treatment, thus causing them to develop MDR-TB. Alternatively, they may have developed MDR-TB through nosocomial transmission. Regardless of the specific cause, we advise both

previously treated TB patients and de novo TB patients to conduct DSTs before their treatment.

Regarding drug-resistance mutation profiles, the most prevalent mutation sites were *katG* S315T1 and *rpoB* S531L. FLQ resistance accounted for most of the second-line drug resistance, with *gyrA* D94G as the most common mutation of FLQ resistance. These results are similar to previously reported results.[27–28] The mutation sites in UTB patients were simplex, which may be ascribed to small differences in genotypes and phenotypes, and in pharmacy. Additional research is required to determine the reasons for this finding. Our study reflected that GenoType tests (the GenoType MTBDRplus and the GenoType MTBDRsl assay) were rapid and reliable methods for detecting first-line and second-line drug resistance. Hence, UTB patients may benefit from the application of these molecular linear probe techniques.

Further analysis revealed that drug-resistant patients tended towards unfavorable prognosis compared with drug-susceptible patients. Drug-resistant TB, particularly MDR-TB, was associated with long-term and complicated treatment, poor prognosis, and severe sequels,[17–18,29] in addition to imposing a tremendous emotional burden on patients and medical workers.[30] Therefore, clinicians should consider the possible diagnosis of drug-resistant TB when UTB patients complain of heavier, retreated disease or delayed healing. In such cases, conducting DSTs immediately is advised. Treatment methods should be adjusted according to the results of DSTs and the patients' medical history.

This study yielded significant findings regarding UTB diagnosis and drug resistance. First, considering the nonspecific nature and the poor etiology confirmation of UTB, urologists should evaluate clinical symptoms, laboratory results, radiological findings, and antituberculous therapy together. Second, real-time PCR diagnosis of UTB was more dependable and rapid compared with the smear and culture methods. Third, south-western China had a serious epidemic of drug-resistant UTB, which manifested commonly as MDR-TB. Fourth, our data suggest that GenoType tests (the MTBDRplus and MTBDRsl assay) may be capable of detecting drug resistance in urine samples with PCR-positive results. Therefore, we strongly recommend real-time PCR-based diagnosis and GenoType tests as routine assays for patients with suspected UTB. Finally, this study represents the first survey of the clinical features and the drug-resistance gene profile of UTB in south-western China. We hope our study will encourage more of our colleagues to conduct improved experiments to increase the early diagnosis of UTB and to reduce the spread of drug-resistant TB to populations.

This study has several limitations. First, the West China Hospital is the center of diagnosis and treatment for mysterious illnesses in south-western China. A large number of refractory patients are admitted to the hospital. Therefore, the incidence of drug-resistant TB in the region is likely overestimated. Second, because of the limited sample, further studies are required to validate our findings. Third, we did not follow up with UTB patients; thus, we intend to explore follow-ups in subsequent studies.

In conclusion, south-western China has a serious epidemic of drug-resistant UTB. A substantial number of newly and previously treated UTB patients present with MDR-TB. The diagnosis of UTB should include an evaluation of presenting symptoms, laboratory investigations, radiological findings, and patient responses to antitubercular therapy. Among laboratory examinations, molecular diagnostics achieve rapid results with relatively higher sensitivity than do smear and culture diagnoses. Accordingly, we strongly recommend real-time PCR for mycobacterial DNA and GenoType tests for drug resistance as routine inspections for patients with suspected UTB.

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