DIAGNOSTIC PERFORMANCE OF XPERT® MTB/XDR FOR DRUG-RESISTANT PULMONARY TUBERCULOSIS

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ABSTRACT

OBJECTIVES

The study aimed to determine the diagnostic accuracy of Xpert® MTB/XDR assay for drug-resistant pulmonary tuberculosis by taking conventional drug susceptibility testing (DST) as standard.

METHODOLOGY

In the cross-sectional analytical study, 1789 pulmonary TB suspects were tested for Xpert® MTB/RIF assay from November 2022 to April 2023. Of these 604 were Mycobacterium tuberculosis (MTB) positive and 57 rifampicin-resistant (RR). Two first-morning sputum specimens were collected from all RR cases. One specimen was processed for Xpert® MTB/XDR, and the other for Lowenstein Jensen (LJ) culture and conventional DST.

RESULTS

Overall mean age was 36.6±16.6 years, and gender distribution was comparable (49.1% vs. 50.9%). RR was 100.0% on Xpert® and 78.9% on DST, MDR 77.2% on Xpert® and 66.7% on DST, pre-XDR 26.3% on Xpert® and 31.6% on DST, and XDR 0.0% on Xpert® and 5.3% on DST. Compared to conventional DST, the accuracy of Xpert® was 79.0% for RR, 75.0% for MDR, 81.0% for pre-XDR, and 95.0% for XDR-TB.

CONCLUSION

The Xpert® MTB/XDR assay demonstrated greater accuracy for drug-resistant pulmonary tuberculosis, especially XDR-TB. However, more studies are needed to validate the diagnostic performance of this new modality.

KEYWORDS: *Drug Resistant, Tuberculosis, MDR, XDR, GeneXpert®*

INTRODUCTION

The contagious nature of tuberculosis (TB) and its easy transmission from person to person has set off a bunch of micro-organisms known as Mycobacterium tuberculosis complex (MTBC). On the other hand TB infection deceits among the top ten causes of morbidity and mortality through the single most communicable disease.[1] Characteristically MTBC infects the lungs in humans to cause pulmonary TB however, micro-organisms may approach every tissue in the body beyond the lungs to establish extra-pulmonary TB.[2] Currents reports of the World Health Organization (WHO) presented around eleven million patients who had been infected with TB. An estimated rate of incidence ranges from 114-140 patients 100 thousands of the general population. Geologically, around 43% global burden of TB is contained by Southeast East Asia and Pakistan ranked the 5th highest TB-loaded country around the globe stentorian 5.8% of the global load.[3] GeneXpert® MTB/RIF assay revolutionized not only in early accurate diagnosis of TB but also established the detection of drug resistance to rifampicin. Drug-resistant (DR) TB along with multidrug-resistant (MDR) TB poses a major risk to Global Health. Drug-resistant TB has also been found to be associated with various factors including non-adherence and treatment default from patients, low-quality drugs, low dosage of drugs, social stigma among patients and various programmatic deficiencies.[4] Around 518000 new TB cases were reported during 2019 in Pakistan comprising 15000 cases of Drug-resistant TB.[5] Over the past couple of decades, the emergence of DR-TB has presented an even greater challenge, leading to confusion among physicians and causing further distress for patients

affected by the disease. The options for treating DR-TB cases are already limited, and the situation could worsen if resistance develops against fluoroquinolones and at least one of the three injectable drugs (amikacin, capreomycin, or kanamycin), known as extensively drug-resistant tuberculosis (XDR-TB).[6] Implementation of End TB Strategy provides a right of universal access to patients getting their drug susceptibility testing (DST), which determines the pathogen i.e. Mycobacterium tuberculosis (MTB) being resistant or susceptible to specified anti-tubercular drugs.[3] After the success of GeneXpert® MTB/RIF assay, another rapid Xpert® MTB/XDR test also based on nucleic amplification detects TB along drug susceptibility of various drugs other than rifampicin in a single test cartridge. This test has been recommended in all intermediate and peripheral laboratories by the National TB Control Program. Like MTB/RIF assay this test also detects MTB along resistance to six drugs including isoniazid, fluoroquinolones, ethionamide, amikacin, capreomycin, and kanamycin simultaneously.[7] Xpert® MTB/XDR assay is based on real-time polymerase chain reaction (PCR) which detects drug resistance based on genetic mutations in various genes conferring resistance to respective drugs. GeneXpert® MTB/RIF assay proved to be very sensitive and accurate but MTB/XDR assay is quite new and its accuracy may vary in various regions due to differences in physical, environmental and cultural characteristics. These factors have been already proven to show their influences on genetic characteristics and mutations. Therefore it is necessary to observe its accuracy at the local level for adoption and optimization results. Thus present study aims to observe the accuracy of drug susceptibility testing by Xpert® MTB/XDR assay.

METHODOLOGY

The cross-sectional analytical study was conducted at a tertiary hospital from November 2022 to April 2023. All patients tested rifampicin-resistant (RR) by Xpert® MTB/RIF assay, aged 18 years and above, of either gender were included. Samples from 1789 pulmonary TB suspects were tested for Xpert® MTB/RIF assay, of which 604 were found to have MTB and 57 were found to have RR.A pre-designed proforma was used to collect the demographic data, presence of any other comorbidity and history of previous TB treatment. Before taking an informed consent each patient was explained about the purpose of the study. Patients (n=57) were asked to provide two first-morning sputum specimens. One sample was processed for Xpert® MTB/XDR, while the other was processed for culture and DST. Isolation of MTB was achieved by culture on Lowenstein Jensen (LJ) media further drug proportion method was used for DST. First-line drugs along their final concentration in LJ media included in DST were Isoniazid (0.2µg/ml), Rifampicin (40.0µg/ml), Ethambutol (2.0µg/ml),[8] Pyrazinamide (100.0µg/ml),[9] and Streptomycin (4.0µg/ml). Second-line drugs were Amikacin (4.0µg/ml), Kanamycin (5.0µg/ml), Capreomycin (10.0µg/ml), Ofloxacin (2.0µg/ml), Levofloxacin (1.0µg/ml), Moxifloxacin (0.5µg/ml), Ethionamide (5.0µg/ml)[8], Bedaquiline (1.0µg/ml), Delamanid (1.0µg/ml),[10] Clofazimine (1.0µg/ml), and Linezolid (1.0µg/ml).[11] MDR-TB is defined as resistance to at least isoniazid and rifampicin, and XDR-TB is defined as MDR-TB with additional resistance to any fluoroquinolone, and to at least one injectable second-line drug.[12] Data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 26.0. Categorical data was presented in frequency and percentages, while continuous data was presented in mean and standard deviation. Comparative data of DST for Xpert® MTB/XDR and conventional drug proportion phenotypic susceptibility were presented in frequency and percentages of new drug-resistant TB patients and Cat I treated patients. *The chi*-square test was also applied and p-value ≤ 0.05 was considered significant. Cross tabulation was used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy using MedCalc online software.

RESULTS

The overall mean age of respondents was 36.6±16.6 years with a higher mean age of males than females (42.9±17.3 vs. 30.5±13.7 years, p 0.004).

Table 1: Demographic Characteristics of the Study Population

		n	%
Age (years)	< 25	22	38.6%
	25-44	14	24.6%
	45-64	17	29.8%
	≥ 65	04	7.0%
Gender	Male	28	49.1%
	Female	29	50.9%
District	Lahore	46	80.7%
	Gujranwala	03	5.3%
	Sheikhupura	04	7.0%
	Other	04	7.0%
Addiction	None	50	87.7%
	Smoking	06	10.5%
	Other	01	1.8%
Comorbidity	None	42	73.7%
	Diabetes mellitus	13	22.8%
	Heart disease	01	1.8%
	Diabetes & Heart disease	01	1.8%
History of previous treatment	New	29	50.9%
	Cat I	28	49.1%
History of second-line treatment	Yes	03	5.3%
	No	54	94.7%
Treatment Regimen group	New	29	50.9%
	Others previous treated	25	43.9%
	Failure	01	1.8%
	Relapse	01	1.8%
	Transfer In	01	1.8%

The accuracy rate of Xpert® rifampicin-resistance with conventional DST has remained to be 79.0% with a sensitivity of 100.0%. However, specificity and NPV could not be calculated due to the absence of rifampicin negative on Xpert®. Isoniazid also presented an accuracy of 84.2% with Xpert®. Sensitivity, specificity, PPV, NPV and accuracy of all drugs tested through Xpert® MTB/XDR are presented in Table 2.

Table 2: Mono drug resistance by Xpert® compared to conventional DST

Drug	Sensitiviy %	Specif icity %	PPV %	NPV %	Accura cy %
Isoniazid	90.7	64.3	88.6	69.2	84.2
Rifampicin	100.0	-	78.9	-	78.9
Ethionamide	-	98.3	0	100.0	-
Ofloxacin	-	71.9	0	100.0	-
Levofloxacin	65.2	97.1	93.8	80.5	84.2
Moxifloxacin	80.0	76.9	25.0	97.6	77.2
Amikacin	0.0	100.0	-	94.7	94.7
Kanamycin	-	100.0	-	100.0	-
Capreomycin	-	100.0	-	100.0	-

RR was 100.0% on Xpert® and 78.9% on DST, MDR 77.2% on Xpert® and 66.7% on DST, pre-XDR 26.3% on Xpert® and 31.6% on DST, and XDR 0.0% on Xpert® and 5.3% on DST. Compared to conventional DST, the accuracy of Xpert® was 79.0% for RR, 75.0% for MDR, 81.0% for pre-XDR, and 95.0% for XDR-TB as shown in Table 3.

Table 3: Poly drug resistance by Xpert® compared to conventional DST

			Conventional DST		Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
			Yes	No					
Xpert	**RR**	**Yes**	45	12	100.0	0.0	78.9	0.0	78.9
		No	0	0					
	MDR	**Yes**	34	10	89.0	47.0	77.0	69.0	75.0
		No	04	09					
	Pre-XDR	**Yes**	11	04	61.0	90.0	73.0	83.0	81.0
		No	07	35					
	XDR	**Yes**	0	0	0.0	100.0	0.0	95.0	95.0
		No	03	54					

RR: Rifampicin-resistant, MDR: Multidrug-resistant, Pre-XDR: Pre-extensively drug-resistant, XDR: Extensively drug-resistant, DST: Drug susceptibility testing, PPV: Positive predictive value, NPV: Negative predictive value.

All patients presenting RR conferred mutations in the rpoB gene through GeneXpert®. The Xpert® MTB/XDR assay conferred resistance in 77.2% of the RR cases. Fluoroquinolone resistance was found in 28.1% of cases and no resistance was found in injectable drugs i.e. Amikacin, kanamycin and capreomycin as presented in Table 4. Chi-square test was applied and an insignificant difference (p-value >0.05) was found in new and Cat I treated cases.

Table 4: Drug susceptibility in New and Cat1 Treated TB cases

Xpert® Susceptibility		Previous History of Treatment				Total	
		New		Cat I			
		n	%	n	%	n	%
Isoniazid	Resistant	23	79.3	21	75.0	44	77.2
	Sensitive	06	20.7	07	25.0	13	22.8
Ethionamide	Resistant	01	3.4	0	0.0	01	1.8
	Sensitive	28	96.6	28	100.0	56	98.2
Fluoroquinolones	Resistant	07	24.1	09	32.1	16	28.1
	Sensitive	22	75.9	19	67.9	41	71.9
Amikacin, Kanamycin & Capreomycin	Resistant	0	0.0	0	0.0	0	0.0
	Sensitive	29	100.0	28	100.0	57	100.0

Conventional DST of first- and second-line drugs are presented in Table 5. Chi-square test was applied and only rifampicin showed a significant difference (p-value <0.05) of susceptibility in new and previously treated cases with Cat I, while all other drugs showed insignificant differences (p-values >0.05). For fluoroquinolones resistance, a significant difference was found for levofloxacin (p-value = 0.001) and moxifloxacin (p-value = 0.019).

Table 5: Comparison of conventional susceptibility among new and Cat I TB cases

		Previous History of Treatment				Total	
		New		Cat I			
		n	%	n	%	n	%
Rifampicin	Resistant	19	65.5	26	92.9	45	78.9
	Sensitive	10	34.5	02	7.1	12	21.1
Isoniazid	Resistant	20	69.0	23	82.1	43	75.4
	Sensitive	09	31.0	05	17.9	14	24.6
Ethambutol	Resistant	02	6.9	00	0.0	02	3.5
	Sensitive	27	93.1	28	100.0	55	96.5
Pyrazinamide	Resistant	08	27.6	03	10.7	11	19.3
	Sensitive	21	72.4	25	89.3	46	80.7
Streptomycin	Resistant	07	24.1	08	28.6	15	26.3
	Sensitive	22	75.9	20	71.4	42	73.7
Kanamycin	Resistant	00	0.0	00	0.0	00	0.0
	Sensitive	29	100.0	28	100.0	57	100.0
Amikacin	Resistant	0	0.0	03	10.7	03	5.3
	Sensitive	29	100.0	25	89.3	54	94.7
Capreomycin	Resistant	00	0.0	00	0.0	00	0.0
	Sensitive	29	100.0	28	100.0	57	100.0
Ofloxacin	Resistant	00	0.0	00	0.0	00	0.0
	Sensitive	29	100.0	28	100.0	57	100.0
Levofloxacin	Resistant	09	31.0	14	50.0	23	40.4
	Sensitive	20	69.0	14	50.0	34	59.6
Moxifloxacin	Resistant	01	3.4	04	14.3	05	8.8
	Sensitive	28	96.6	24	85.7	52	91.2
Ethionamide	Resistant	00	0.0	00	0.0	00	0.0
	Sensitive	29	100.0	28	100.0	57	100.0
Clofazimine	Resistant	01	3.4	02	7.1	03	5.3
	Sensitive	28	96.6	26	92.9	54	94.7
Bedaquiline	Resistant	01	3.4	03	10.7	04	7.0
	Sensitive	28	96.6	25	89.3	53	93.0
Delamanid	Resistant	01	3.4	01	3.6	02	3.5
	Sensitive	28	96.6	27	96.4	55	96.5
Linezolid	Resistant	00	0.0	00	0.0	00	0.0
	Sensitive	29	100.0	28	100.0	57	100.0

DISCUSSION

With the advancement in technology, man has sought after many valuable and safer technologies in the field of medical technology. The invention of the PCR technique by Kary Mullis in 1985 opened new horizons in many fields of current science including medical diagnostics. The infectious nature of various microorganisms like MTBC are great biohazard for the safety of lab personnel as the disease spreads through airborne aerosols. The great advent of Xpert® over conventional PCR is that the former uses single-step closed cassettes consisting of various chambers for DNA extraction, amplification and detection which was a great breakthrough in the diagnosis of TB as well as rifampicin resistance in just two hours. The sensitivity of Xpert® MTB RIF was further enhanced by introducing the second generation in the name Xpert® MTB Ultra.[13] A lot of literature on the accuracy of GeneXpert® diagnosis of MTB is present but the focus on comparing the conventional DST is negligible. The accuracy of rifampicin resistance (RR) in the present study remained at 78.95% when plotted against the gold standard drug proportion method on LJ media. Sensitivity in this case remained to be 100% whereas specificity could not be calculated due to the absence of rifampicin-sensitive cases on GeneXpert®. Results accuracy are though in agreement with studies presenting sensitivity of this test in the range of 61.8% to 85% among pulmonary TB patients.[14,15] Interestingly all of the sensitivity, specificity, PPV, NPV and accuracy were calculated for only Isoniazid, Levofloxacin and moxifloxacin due to the presence of all categories required in 2x2 table in this study. More amusingly conventional DST presented 23(40.4%) cases of levofloxacin resistance, 5(8.8%) moxifloxacin and none of the cases resistant to Ofloxacin. All of these three drugs belong to the same class of fluoroquinolones. Genetically *gyrA* and *gyrB* are reported to be associated with susceptibility of fluoroquinolones. Only 16(28.1%) cases were found to be resistant to Xpert®. Quinolone resistance determining region (QRDR) includes 87-95 (261-285 nucleotides) codon region for *gyrA* and codon 531-544 or 492-505 (1596-1632 nucleotides) for *gyrB* are used in Xpert® MTB/XDR.[16] Even significant differences (p-value <0.05) are reported for levofloxacin and moxifloxacin but no resistance to Ofloxacin also questioned the credibility of Xpert® MTB/XDR being used for all quinolone. Ofloxacin is a second-generation quinolone while levofloxacin and moxifloxacin belong to the third generation of quinolones. A study has presented cross-resistance among Ofloxacin, moxifloxacin and levofloxacin by finding mutations in the QRDR of *gyrA*. These mutations have also been found to have a positive correlation with higher minimum inhibitory concentrations on LJ media.[17] Debate among these three quinolones in the treatment of drug-resistant TB continuous on early bacterial activity, dosage, safety profile and side effects like higher QT interval in echocardiograph.[18] Unlike other fluoroquinolones chemical structure of Ofloxacin contains an oxazine ring which links the nitrogen at the 1st position and carbon at the 8th position of the quinolone ring thus reported to suppress the drug metabolism in-vivo.[19] Moxifloxacin bears a cyclopropyl substituent at the 1st position and methoxy substituent at the 8th position with two more differences than Ofloxacin.[20] Levofloxacin is a chiral fluorinated carboxy-quinolone which is an enantiomer of Ofloxacin.[21] Only three (5.3%) cases were resistant to amikacin in phenotypic DST whereas Xpert® MTB/XDR showed no mutation in the rrs gene at present. Domenech et al, have claimed a rare mutation in the rrs gene of MTB among

DR isolates, further exact antibiotic resistance among aminoglycosides conferring mutation in this specific gene was also not reached previously. Additionally, this gene does not converse cross-resistance among other injectables i.e. capreomycin and kanamycin. A substantial in vitro mutation fitness defect has also been claimed to hurdle in its appearance thus making it rare.[22] Mutations in *eis* promoter have also been debatable while a recent study has also claimed a novel mutation in the rrs gene in kanamycin, capreomycin and amikacin which are not comparable in this study as none of the cases conferred resistance by Xpert® MTB/XDR assay and all cases remained sensitive to kanamycin and capreomycin phenotypically. Isoniazid susceptibility presented good agreement rates of 75.4% and 77.2% among GeneXpert® RR cases phenotypically and genetically on Xpert® respectively. Conclusively only 78.9% of RR cases by GeneXpert® showed phenotypic resistance to rifampicin. Isoniazid also showed a good agreement rate and sufficient gene targets are included in the assay. Mutations in *gyrA* and *gyrB* do not generalize the resistance among all fluoroquinolones due to many differences in chemical structures, absorbance and serum bioavailability of drugs. Although Xpert® MDR-TB is a great addition to prompt diagnosis of complex DR-TB cases more work is needed to address the issues in finding genotypic drug resistance for quinolones and all injectable drugs for TB.

LIMITATIONS

The limitations of the study include observational study design, purposive enrollment of patients and small sample size.

CONCLUSIONS

The Xpert® MTB/XDR assay demonstrated greater accuracy for drug-resistant pulmonary tuberculosis, especially XDR-TB. However, more studies are needed to validate the diagnostic performance of this new modality.

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