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Original Article

Diagnostic Value of Gene-Xpert and Ziehl-Neelsen in the Detection of Pulmonary Tuberculosis

Tamer Mohamed Ibrahim[1], Safaa Ragab Askar [2], Radwa Samir Hagag [3*], Sahar Fawzy Abd El Shafy[1], Dalia Abdel-Sttar el-Embaby [1]

[1] Department of Chest diseases, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

[2] Department of Tropical Medicine, Faculty of Medicine, Ain Shams University, Cairo, Egypt.

[3] Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, Egyptian Russian University, Cairo, Egypt.

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*Corresponding author

Email: Radwahagag@yahoo.com

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Abstract

Background: Accuracy and quick diagnosis of tuberculosis [TB] is the basis to effective treatment and management. Culture using Lowenstein-Jensen [LJ] medium is considered the gold standard for the diagnosis of TB. The delay in diagnosis increases the transmission opportunities to others and the emergence of multidrug resistant TB. Newly administered Gene-Xpert MTB/RIF assay takes only a couple of hours to give the results and provide data about rifampicin resistance at the same time.

Aim of The Study: This study aimed to evaluate the diagnostic value of both Gene-Xpert in TB and Zeil-Neelson [ZN] stain versus the LJ culture in pulmonary TB. Drug susceptibility tests [DST] for first line anti-TB drugs were also performed for the resistant patients.

Patients and Methods: This observational study was conducted on 100 TB people presented to the hospital. Diagnosis of tuberculosis depended on the examination of sputum samples with Zeil-Neelson stain, Gene-Xpert test and LJ culture.

Results: Hemoglobin level and red blood cells [RBCs] count were found to be significantly lower in TB patients when compared to "No TB" patients. ZN smear positivity for TB was 55% and for Gene-Xpert was 66% of confirmed TB diagnosed cases. Sensitivity and negative predictive value of Gene-Xpert were 95.5% and 91.5%, respectively which are significantly higher as compared to ZN in which sensitivity and negative predictive value were 78.8% and 68.5%, respectively.

Conclusion: Gene-Xpert is considered a more sensitive tool than ZN stain in the early diagnosis of pulmonary tuberculosis.

Keywords: Diagnostic value; Gene-Xpert; Ziehl-Neelson stain; Tuberculosis.

INTRODUCTION

Tuberculosis [TB] is a contagious disease that is caused by *Mycobacterium* species. *Mycobacterium tuberculosis* [MTB], *Mycobacterium Africanum* and *Mycobacterium Canetti* are most common etiologic causes of TB in humans [1]. Tuberculosis is a worldwide disease that has a yearly mortality rate of 1. 4 million deaths. Sputum samples with Zeil-Neelson [ZN] negative diagnosis and culture-positive pulmonary TB diagnosis causes pulmonary TB transmission rates of 12.6% [2].

In 2021, TB incidence in Egypt, according to the WHO country profile, was 10 /100,000 people. Bacteriologically confirmed cases totaling 6907, in which 52% have confirmed pulmonary tuberculosis cases. There were roughly one-third females [aged ≥ 15], 60% males [aged ≥ 15], and 6% of children [0–14 years old] [3].

Upper Egypt is an area of highest prevalence when compared with other regions in Egypt, despite persistent efforts to reduce the national TB burden. Several factors, including limited financial and logistical resources and ecological, social, and demographic conditions, could be the cause for this [3]. Therefore, successful management of TB needs rapid and accurate diagnostic methods [4].

The best diagnostic method for TB diagnosis is the TB culture, but it takes several weeks to produce results [5]. More recently, Gene-Xpert MTB/RIF [Gene-Xpert] is one of the molecular techniques that has been implemented in the diagnosis of TB [6].

The Gene-Xpert is a technique that rapidly analyse sputum specimens, and it can detect the presence of MTBC as well as the detection of rifampicin resistance [7, 8]. TB diagnosis by ZN smear microscopy has a lower limit of detection [LOD] of 5,000 to 10,000 bacilli/ milliliter of sputum leading to missed cases and false negatives. On the other hand, Gene-Xpert technology has a LOD of 131–250 bacilli/ milliliter in sputum samples. Therefore, its use is useful for early detection of TB and then minimizing drug-resistant TB cases [2].

AIM OF THE STUDY

This study aimed to determine the diagnostic value of Gene-Xpert versus ZN stain for the early detection of pulmonary TB in pulmonary samples in Egyptian TB patients.

PATIENTS AND METHODS

Study design: This study was prospective observational, and the cases were recruited in 6 months period from pulmonary department, Ain Shams University Hospitals, Cairo, Egypt.

Methods: All suspicious cases presented to chest diseases clinic in the hospital were checked for eligibility for the study. One hundred patients met the inclusion criteria of the study. Patients were recruited from January 2024 till June 2024 and the eligible patients were consecutively enrolled in the study after giving written informed consent.

Inclusion criteria: patients were included if they met the following 1] patients with suspected TB regarding clinical symptoms; 2] production of sputum without inducement; 3] age≥18 years old, and 4] Agreement of patients to sign an informed written consent for participation in the study.

Exclusion criteria: Patients weren't included for any of the following 1] patients with extra-pulmonary tuberculosis; 2] Induced sputum sample collection, and 3] sputum sample less than 3 ml.

Diagnosis of TB was based on clinical history, physical findings, full laboratory testing [CBC, liver function test and kidney function], chest radiography and examination of sputum by ZN stain and Gene-Xpert Test. Moreover, Drug susceptibility tests [DST] for the first line anti-TB drugs and LJ culture were conducted. Flow diagram for recruitment of patients and TB diagnostic tests is shown in **Figure [1]**.

The sample transfer is the responsibility of the investigators. Ziehl-Neelson stain was performed using a sterile stick then a drop of raw sputum was placed on a grease free glass slide and spread equally. Let it dry then heat then, Ziehl-Neelson staining were performed as directed [9].

Gene-Xpert Sampling methods was performed according to manufacturer's instruction [Xpert® MTB/XDR, Cepheid inc., Solna, Sweden] and the results will be available within 2 hours. Gene-Xpert test for detection of MTB/RIF resistance was done according to the steps of the manufacturer's kit [Xpert® MTB/XDR, Cepheid inc., Solna, Sweden]. Drug susceptibility tests for first line anti TB drugs were determined by following the steps of the instructions [10]. Culture on Lowenstein Jensen medium was prepared according to the instructions [11].

Sample size calculation: Calculation of the sample size was performed using the PASS 15 program. Reviewing results from the previous study [Rahadianto et al,2021] showed that agreement between ZN smear and Gene-Xpert was very good [k=0.89], based on this finding a sample size of at least 50 patients achieves 100% power to detect a true kappa value of 0.89 in a test of H0: Kappa=kOvs. HI: Kappa ≠kO when there are 2 categories with frequencies equal to 0.46 and 0.54 [12].

Statistical methods: Patients' data were revised, tabulated, and analyzed statistically using IBM SPSS software version 22.0, IBM Corp., Chicago, USA. Data were then presented as mean ± standard deviation [SD] or number [percentages] [n [%]]. The statistical test used for comparing means is independent t-test for numerical data while comparing ordinal and categorical data is performed using Chi square test and Fisher's Exact test. Results are considered statistically significant if $p < 0.05$.

RESULTS

The present study included 100 suspected cases, 80 males [80%] and 20 females [20%] with mean age 43.3±13.3 ranging from 18-73 years old and smoking represents 63% of participants and 10% are presented with special habits [smoking and IV addiction]. **Table [1]** represents demographic characteristics, clinical findings and x-ray findings of the studied cases. **Figure [2]** shows treatment types among the studied cases.

According to the conventional tests, cases are divided to: TB and "No TB" groups. No significant differences between the 2 groups were observed regarding age, sex, special habits, symptoms and findings by X-ray. Clinical findings and x ray picture is worse

in TB group but without significant difference than "No TB" group. Data are shown in **table [2]**. **Figure [3]** gives data about differences in types of patients in Tb and "No TB" groups.

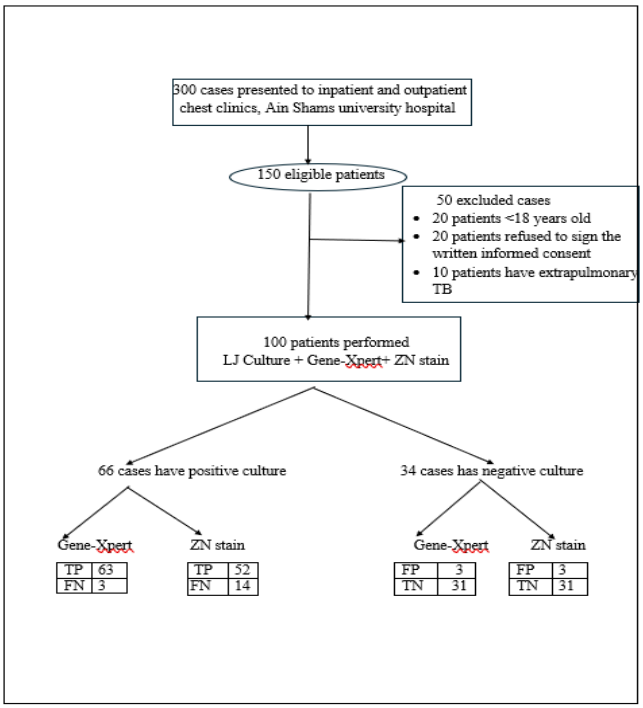

Figure [1]: Flow diagram for recruitment of patients and TB diagnostic tests. LJ culture: Lowenstein-Jensen, ZN stain: Zeil-Neelson stain, TP: true positive, FN: false negative, FP: false positive and TN: true negative.

Regarding laboratory findings, there were significant decrease of haemoglobin percent and red cells count among patients with tuberculous infection when compared to "No TB" group. Data are shown in **table [3].**

Number of TB patients diagnosed with TB using Gene-xpert 63 [95.5%] is higher than number of patients diagnosed with ZN stain 52 [78.8%]. **Table [4]** showed that there was significant low agreement between culture and ZN stain on TB diagnosis. **Table [5]** showed correlation between culture and Gene-Xpert with kappa=0.86 [0.763-0.970] and CI=95%. There was significant moderate agreement between culture and gene-Xpert on TB diagnosis. Comparison between gene-Xpert and culture on LJ media in TB diagnosis is shown in **Figure [4]**. The high diagnostic yield of Gene-Xpert MTB/RIF assay in the diagnosis of pulmonary TB in comparison to LJ media culture in TB diagnosis is shown in **table [5]**.

Results of anti-TB drug sensitivity test has showed that among 66 positive cases detected by culture, about 80% of cases were sensitive to all 4 drugs [isoniazid, rifampicin, streptomycin and ethambutol], about 13.8% of cases were resistant to all 4 drugs and about 6.15% of cases were resistant to isoniazid and rifampicin. About 92% of rifampicin resistant cases were males and about 8% of cases were females. Acquired resistance was 84.6% and primary resistance was 15.4%. Among 13 patients were detected as MDR-TB by DST, there were 12 of them were detected as MDR-TB by Gene-Xpert MTB/RIF test and 1 patient was detected as sensitive to rifampicin by Gene-Xpert test but by DST it was detected as a resistant case. Diagnostic performance of ZN stain and Gene-Xpert in TB diagnosis, and Gene-Xpert in rifampicin resistance is shown in **table [6]**. The later table also shows that Gene-Xpert has the highest sensitivity [95.5%] and Gene-Xpert in rifampicin resistance has the highest specificity percentage, negative predictive value [NPV] and positive predictive value [PPV].

Table [1]: Demographic characteristics, clinical findings and x-ray findings of the studied cases

Variables		Mean ± SD	Range
Age [years]		43.3±13.3	18.0 –73.0
		n [N=100]	**%**
Sex	**Male**	80	80.0
	Female	20	20.0
Smoking		63	63.0
I.V. Addiction		10	10.0
Clinical findings	**Dyspnea**	49	49%
	Chest pain	51	51%
	Constitutional	70	70%
	Hemoptysis	40	40%
	Consolidation	65	65%
Findings by x-ray picture	**Cavitation**	20	20%
	Nodules	11	11%
	Effusion+ Consolidation	12	12%

N: total number of patients

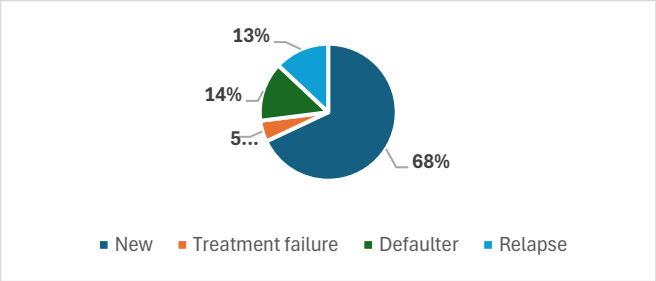

Figure [2]: Treatment types among the studied cases

Table [2]: Comparison between patients have TB and patients haven't TB [by culture] regarding demographic characteristics, clinical findings and findings by x-ray.

Findings		TB [N=66]	No TB [N=34]	P
Age [years]		42.5±12.6	44.8±14.8	^0.421
Sex	**Male**	56[84.8%]	24[70.6%]	#0.091
	Female	10[15.2%]	10[29.4%]	
Smoking		58[87.9%]	32[94.1%]	&0.487
Clinical findings	**Cough**	64[97%]	34[100%]	&0.547
	expectoration	62[93.9%]	34[100%]	&0.296
	Dyspnea	33[50%]	16[47.1%]	#0.835
	Chest pain	33[50.1%]	18[52.9%]	#0.835
	Constitutional	46[69.7%]	24[70.6%]	#0.927
	hemoptysis	27[40.9%]	13[38.2%]	#0.796
	Consolidation	40[60.6%]	25[73.5%]	#0.199
Findings x-ray picture	**Cavitation**	14[21.2%]	6[17.6%]	#0.673
	Nodules	9[13.6%]	2[5.9%]	&0.324
	Effusion+ consolidation	10[15.2%]	2[5.9%]	&0.213

Statistical tests used: ^Independent t-test, #Chi square test and &Fisher's Exact test.

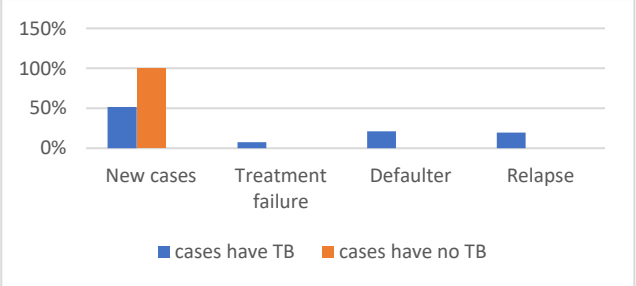

Figure [3] gives data about differences in types of patients in both groups.

Table [3]: Comparison between cases with and without TB [by culture] regarding laboratory findings

Findings	TB [N=66]	No TB [N=34]	^P
Hb [gm/dL]	10.8±0.8	11.2±0.9	0.007*
RBC [x10^6/mL]	3.6±0.4	3.9±0.4	0.003*
PLT [x10^3/mL]	293.8±28.6	299.8±52.4	0.462
WBC [x10^3/mL]	14.9±4.0	14.3±3.6	0.435
ALT [IU/L]	19.5±7.1	19.1±9.6	0.802
AST [IU/L]	23.2±7.9	22.6±10.1	0.747
Albumin [g/dL]	3.7±0.5	3.6±0.7	0.226
Urea [mg/dL]	19.8±8.3	20.3±11.5	0.799
Creatinine [mg/dL]	1.4±1.8	1.6±3.1	0.670
FBG [mg/dL]	112.8±36.0	101.5±33.3	0.132
PPBG [mg/dL]	161.1±46.0	148.8±44.0	0.203
ESR [mm/hr]	112.9±12.7	109.4±15.0	0.212

^Independent t-test, *Significant, Hb: haemoglobin, RBCs: red blood cells , PLT: platelets , WBCS:white blood cells, ALT:Alanine transaminase ,AST: Aspartate transaminase, FBG: Fasting blood glucose, PPBG:post prandial blood glucose , ESR: Erythrocte sedimentation rate.

Table [4]: Comparison between culture and ZN stain on TB diagnosis

ZN stain	Culture [golden]		Total	
	Positive	Negative		
Positive	52 [52.0%] TP	3 [3.0%] FP	**55**	
Negative	14 [14.0%] FN	31 [31.0%] TN	**45**	
Total	**34**		**100**	
Kappa [95% CI]	**0.649 [0.501–0.797]**		**P**	**<0.001***

Percentages are from the total [100], **TP**: True positive, **TN**: True negative, **FP**: False positive, **FN**: False negative, CI: Confidence interval, *Significant. Statistics were performed using Chi square test.

Table [5]: Correlation between culture and gene-Xpert on TB diagnosis

Gene-Xpert	Culture [golden]		Total	
	Positive	Negative		
Positive	63 [63.0%] TP	3 [3.0%] FP	**66**	
Negative	3 [3.0%] FN	31 [31.0%] TN	**34**	
Total	**66**	**34**	**100**	
Kappa [95% CI]	**0.866 [0.763–0.970]**		**P**	**<0.001***

Percentages are from the total [100], **TP**: True positive, **TN**: True negative, **FP**: False positive, **FN**: False negative, CI: Confidence interval, *Significant

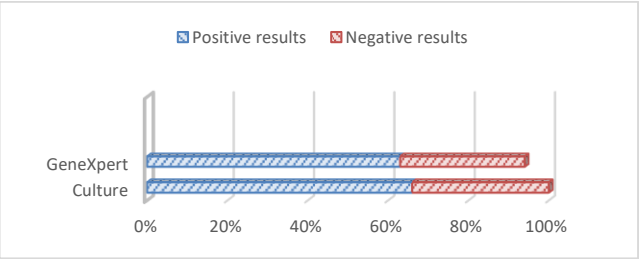

Figure [4] shows comparison between Gene-Xpert and culture on LJ media in TB diagnosis.

Table [6]: Diagnostic performance of ZN stain, Gene-Xpert in TB diagnosis and Gene-Xpert in rifampicin resistance

Method and specimen type	Positivity	Sensitivity	Specificity	PPV	NPV
ZN stain	55%	78.8%	92.1%	92.1%	68.5%
Gene-Xpert in TB diagnosis	66%	95.5%	91.2%	95.5%	91.2%
Gene-Xpert in rifampicin resistance	_____	92.3%	100%	100%	98.9%

ZN stain: Ziehl-Neelson stain, PPV: positive predictive value and NPV: negative predictive value.

DISCUSSION

The estimated incidence of TB was 10.6 million in 2022, 10.3 million in 2021 and 10.0 million in 2020 [13] although, it was reported that the incidence in TB has decreased from 7.1 to 5.8 million between 2019 and 2020 [3]. Culture-positive samples and smear-negative pulmonary TB transmissions reached 12.6% [2]. Globally, the treatment efficacy for TB was 89%, and the TB mortality was approximately 4% in 2022.

Egypt is One of countries with the lowest rates of TB worldwide. Though the annual risk of infection has decreased slightly but other factors may cause stagnant or rising incidence of TB. These factors include strong population growth, population aging, and related factors like poverty, unemployment, and overcrowding [3]. To eradicate TB in Egypt, sustained efforts in maintaining the TB control strategy are necessary, including enhancing treatment results, early diagnosis and surveillance reporting [3].

In our study, the prevalence of TB in men is higher than women. In accordance with our data, the prevalence of confirmed disease was found to be higher in males when compared with females and this is consistent with previous studies in Philippines and Indonesia [14, 15]. This is may be caused by the more exposure of males to smoking and infected animals that are considered risk factors [3].

Moreover, Men have delayed TB diagnosis since they usually have late referral compared with female TB patients who need usually fast referral [16]. Moreover, men may lack disease awareness and more often start with conventional treatment [17].

TB medical diagnosis depends on medical history, physical examination, TB blood tests or TB skin test, chest radiograph and bacteriologic examination [18].

Acid-fast bacilli [AFB] smear has a lower limit of detection [LOD] of 5x10^3 to 10 x10^3 [CFU/ml] and below this threshold might lead to missed cases and false negatives when diagnosing TB with smear microscopy. On the other hand, Gene-Xpert technology has a lower LOD in sputum samples. Also, it has the advantage of providing proper identification and assessment of the TB resistance to rifampicin [19].

Gene-Xpert has the advantages of detecting MTB and rifampicin resistance in less than 2 h while the culture takes up to detection of 28 days for MTB only [20].

Therefore. Gene-Xpert implementation is believed to permit the TB's early detection drug-resistant cases [2, 21] and this data is in parallel with our data as Gene-Xpert has 95.5% vs 78.8% sensitivity with ZN stain in the diagnostic performance.

Gene-Xpert specificity in rifampicin resistance according to our study was 100% and this is in accordance with previous studies [22, 23].

The high sensitivity of the Gene-Xpert assay doesn't differentiate between live and not alive bacteria [24] since the Gene-Xpert technique can detect dead bacteria with unbroken DNA even if the bacteria in not viable [25, 26]. Treatment decisions need to determine if bacteria are live or not to avoid drug misuse and emergence of resistant strains [27].

The Gene-Xpert MTB/RIF test has reported higher rates in TB detection among cases that were negative in ZN stain [28,29] and this is in parallel with our study that shows that the Gene-Xpert test could efficiently detect some missed cases with ZN stain.

In our study there is a strong correlation between gene-Xpert and culture results [p<0.001]. In parallel, a study has concluded that there is a concordance of [96.8%] between Gene-expert and culture results [20].

Our results have shown a false positive result with Gene-Xpert. This is in accordance with a previous case study which stated Gene-Xpert was reported to be positive in some culture negative cases after completing the suitable antitubercular therapy. Therefore, the accuracy of Gene-Xpert positive tests in patients with TB history is largely unknown, due to possible false-positive results [30]. Therefore, data should be read cautiously and be linked with clinical and treatment history of the patient [31, 32]. This phenomena can be explained by the presence of dormant viable bacteria that do not form colonies directly on culture media [33].

A commonly associated symptom in TB is anemia where certain cytokines and inflammatory markers participate in the development of anemia. Anemia in TB patients is mild-to-moderate and is simultaneously resolved after the completion of anti-tuberculosis therapy. Moreover, iron therapy during the active phase of the disease is not recommended [34].

This is in accordance with our data as mean Hb level for patients was 10.8±0.8 gm/dl which is below normal Hb level for men [14-18 g/dl] and for women [12-16 g/dl] [35].

In our study, radiographic imaging findings in TB patients has no significant differences versus "no TB" patients. In the contrary, a recent study has reported that TB patients had radiographs with at least one radiographic finding suggestive of active TB when compared to cases haven't TB [36].

This controversy may be due to the higher number of patients included in the other study [740 patients] and different nationality of the included subjects.

Conclusion: Gene-Xpert MTB/RIF assay method is more sensitive and specific in TB diagnosis when compared to ZN stain method. Therefore, we recommend the use of Gene-Xpert in early diagnosis of TB for early management of TB more effective treatment using sputum samples in Egyptian TB patients.

Limitations of the study: The low number of the included eligible patients, being a uni-center study and excluding extra pulmonary T.B. are considered the major limitations.

Recommendations: Multicenter studies with higher number of patients are required to assess the economic impact of using Gene-Xpert instead of ZN smear in the early diagnosis of TB in different regions in Egypt.

Ethics approval and consent to participate: All procedures were carried out in accordance with the Declaration of Helsinki and were given the nod of approval by Ain Shams University Hospital's research and ethics committee [No. FMASU R175/2024]. All patients who participated in the study were asked to give written informed consent.

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