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Original Research Article

Evidence based diagnosis of Pulmonary Tuberculosis in sputum smear negative patients, a practical challenge! The role of Gene-X-pert?

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Abstract

Background:

Tuberculosis is a treatable global public-health issue, causing significant morbidity and mortality. Mycobacterial detection is the gold standard for diagnosis. A large number of TB-cases are reported negative owing to the limitations of procedure and remain an inadvertent source of TB-transmission in community. Because of rapid results, we determined the diagnostic accuracy of Gene-X-pert assay for early diagnosis of these cases.

Methodology:

This analytical cross-sectional study was conducted in OPD-Gulab Devi Teaching Hospital, Lahore - Pakistan, from 01-06-2019 to 10-01-2020. 261-willing, adult-patients having two sputa negative for AFB on fluorescent microscopy were included while sputum positive and un-willing patients were excluded. 75 non-TB patients were included as control. Patients were subjected to Gene-X-pert and presumptive-TB patients were treated according to DOTS and followed up. Response to treatment was noted and considered as reference. Data was tabulated and analyzed by SPSS-24.

Results:

Of 255 clinically confirmed TB-patients, MTB was detected in 149 patients while all control were negative by Gene-X-pert. A Sensitivity 58.43%, Specificity: 92.59%, Positive Predictive Value 96.13%, Negative predictive value 41.44% and diagnostic accuracy 66.67% were obtained.

Conclusions:

Gene-X-pert assay is rapid and tremendous tool for evidence based diagnosis of pulmonary tuberculosis in sputum smear-negative patients.

Keywords: AFB-negative, Diagnosis, Evidence based, Gene-Xpert, Sputum smear negative

INTRODUCTION

Tuberculosis (TB) is a community health issue world-wide because 1/3rd population over the globe harbors Mycobacterial infection. It is responsible for significant morbidity, mortality and in fact is a preventable, curable and one of the most common infectious disease in Pakistan.[1] More than 90% patients are afflicted in low and middle income populations, resulting further financial constrain.[2] In consonance with World Health Organization (WHO) report 2019, ten million people got the disease and 1.5 million died of Tuberculosis (TB) world-wide in one year. The incidence, prevalence and mortality in Pakistan are 230/100,000, 310/100,000 and 39/100,000, respectively. Additionally, 3800 HIV-positive patients also developed TB-disease.[3] The prevalence of sputum smear-negative but culture positive-TB was 17.1% in Pakistan.[4] Pakistan is at 5th position among high burden countries of TB and 4th among high burden countries of MDR-TB, so precise diagnosis & prompt treatment is essential for an effective TB-control program.[5]

Capturing Mycobacterium Tuberculosis (MTB) in sputum is essential for an evidence based diagnosis which is made either by direct sputum smear microscopy or by culture methods. Direct smear-microscopy has low sensitivity and high false negative rates by conventional ZN-staining method.[6] Even fluorescent microscopy (FM), requiring 10^4/ml bacillary load for AFB detection, misses remarkable number of cases if bacillary load is low.[7] The gold standard is the

mycobacterial culture which is highly sensitive and requires only 10-100 viable organisms/ml for a positive report but requires six-week time for results along with special gadgets and expertise. Furthermore, on getting a sputum Acid Fast Bacillus (AFB) negative report, irrespective of limitations of bacillary load or technical compromises, patient considers himself non-tubercular and remains a source of inadvertent diseases transmission by careless coughing, sneezing, talking or spitting in surroundings.[8] According to literature, sputum negative TB cases are responsible for at least 17% spread of the disease. Precise diagnosis of such cases is mandatory for cutting down the chain of transmission for satisfactory TB-control. The limitations of conventional tools are real obstacles in having a TB-Free Pakistan and there is a dire need of a test with improved diagnostic yield, feasibility and accuracy in sputum negative patients. [9] WHO recommends the use of Gene-X-pert MTB/RIF assay for the diagnosis of TB in children, immunocompromised, suspected extra-pulmonary and drug-resistant TB, also in patients with suggestive chest X-ray changes [10,11] The threshold for bacterial detection is 136 bacilli/ml for Gene-X-pert.[10] Because the test is rapid, results can be obtained in a few hours, this study was conducted to evaluate the diagnostic yield of Gene-X-pert in sputum smear-negative patients, for early diagnosis.

Objectives

To determine the sensitivity, specificity and diagnostic accuracy of Gene-X-pert for TB-diagnosis in sputum smear-negative patients.

Methodology

This cross sectional study was conducted at the out-patient department of Gulab Devi Teaching Hospital, Lahore-Pakistan (a tertiary care hospital of the country, well known for the management of Tuberculosis). Ethical Approval was obtained from IRB of the hospital.

A case was defined as study participant presumed to have tuberculosis either by clinical or chest-x-ray findings but negative on sputum smear fluorescent microscopy while control was characterized as patient having productive cough but no clinical or radiographic suspicion of tuberculosis. The minimum sample size 270 was calculated against the prevalence of 0.31 suggested by Leeflang MM and co-workers, using formula for sample size suggested by Karimollah Hajjan Tilaki (2014). [12,13] Sample was inflated to 336 to compensate for the lost patients. 261 adult patients of both gender with two sputa negative for AFB by FM, history of productive cough of more than 03 weeks, hemoptysis, pyrexia of unknown origin (PUO), decreased appetite, weight loss, night sweating, contact with TB patients, radiographic evidence consistent with tuberculosis and willing for taking part in study were included. 75 patients with productive cough without any suspicion of TB were included as control. While AFB-positive cases and those unwilling for participation in the study were excluded.

A detailed medical history and thorough physical examination was undertaken and findings were recorded. Each patient was evaluated with Gene-X-pert and CBC with ESR. Gene-X-pert "not detected" cases were discussed in departmental conference and clinical diagnosis of sputum negative-TB was made. All TB patients were treated with anti-TB drugs according to DOTS strategy and followed up according to the guide-line. The response to treatment was noted and considered as benchmark. Patient's clinical, radiographic and hematologic findings were recorded. Facts were summarized, organized, tabulated and conclusions were drawn by statistical analysis using SPSS-24.

Quantitative variables were expressed as mean ± SD, categorical data was represented as frequency. Sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and diagnostic accuracy were calculated at 95% confidence interval. Fisher exact test was used for determining *p-value* which was considered significant at $p < .05$.

Results

Total 336 participants included 261 TB-patients and 75 controls. Age range was 15-80 years with mean age 34.33 years SD + 17.38 and Std. Error + 1.39. Male patients were 178/336 (52.97%). Female patients were 158/336 (47.02%). Male to female ratio was 1.12:1. Patients presented with typical symptoms of chronic respiratory tract infection (Table-I).

Table-1: Clinical manifestations in 261 TB-patients.

Nos.	Clinical Features	Observed cases	Percentage
1.	Cough	261	100.00%
2.	Sputum	261	100.0%
3.	Fever	221	84.67%
4.	Decreased Appetite	216	82.75%
5.	Weight loss	198	75.86%
6.	Night sweats	198	75.86%
7.	Hemoptysis	57	21.83%
8.	Shortness of Breath	52	19.92%
9.	Contact History	44	16.85%

The x-ray chest of all control participants (n=75) showed signs of chronic obstructive pulmonary disease only. No consolidation, cavitation, fibrosis or calcification was found. While in TB-patients, right sided lesion was seen in 112 cases (42.92%), left sided in 60 patients (22.98%) and bilateral lesions were found in 89 cases (34.09%).

Table-II: Radiographic features in TB-patients. n=261

Nos.	CXR-morphology	Observed cases	Percentage
1.	Upper zone predominant	128	49.04%
2.	Middle zone predominant	72	27.58%
3.	Lower zone predominant	61	23.37%
4.	Cavities	107	40.99%
5.	Infiltration	121	46.36%
6.	Consolidation	62	23.75%
7.	Collapse	02	0.76%
8.	Associated Pleural Effusion	03	1.14 %

***CXR: Chest X-Ray**

The detailed radiographic morphology was tabulated (Table-II). The Gene-X-pert results in 75 control patients were reported as "not detected" while the results of 261 smear-negative TB patients were recorded (Figure-1).

Out of total 336patients, 261 were diagnosed pulmonary tuberculosis on clinical and radiographic grounds. 255 cases were diagnosed PTB on treatment response. 06 patients were identified as fungal infection and organizing pneumonia. Out of 255 cases, Gene-X-pert diagnosed Pulmonary TB in 149 cases (58.43%) which were true positive (TP). 106 TB-cases (41.56%) were not detected by Gene-X-pert, these were false negative (FN). Non-TB patients were 06 cases- false positive (FP) and 75 control cases were true-negative (TN).

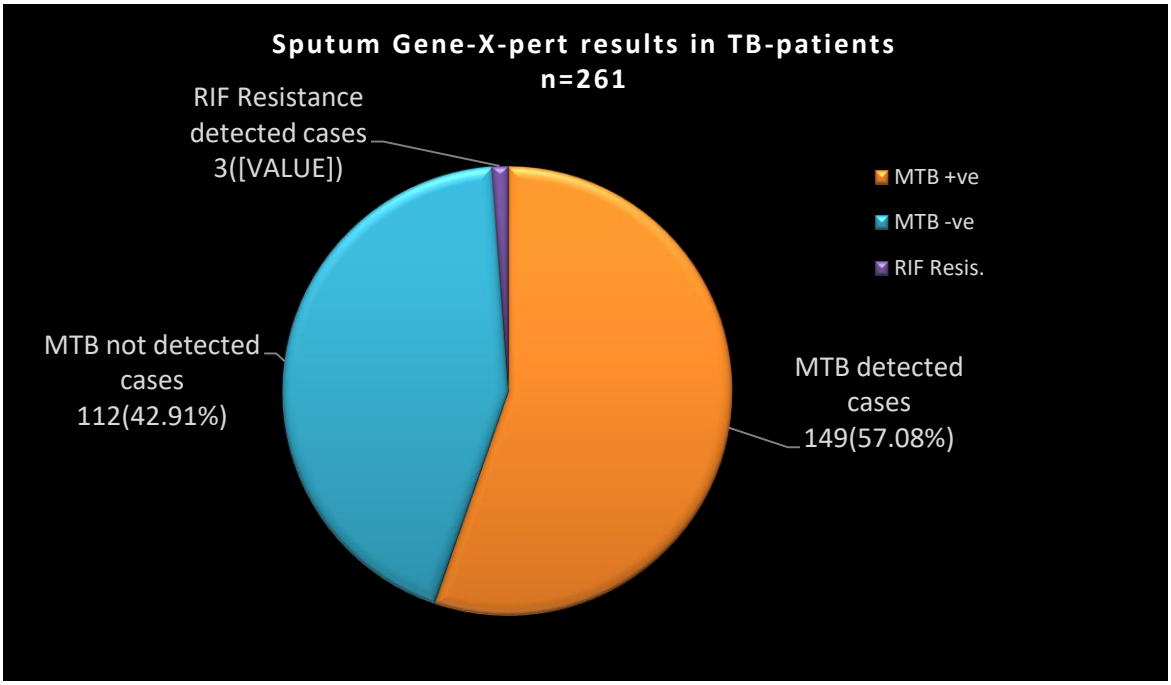

Figure-1: Sputum Gene-X-pert results in 261 smear negative, TB-patients.

Table-III: Gene-X-pert efficacy for Pulmonary TB in smear negative cases. n=255

Statistic	Value	95% CI
Sensitivity	58.43%	52.12% to 64.55%
Specificity	92.59%	84.57% to 97.23%
Positive Likelihood Ratio	7.89	3.63 to 17.15
Negative Likelihood Ratio	0.45	0.38 to 0.53
Positive Predictive Value	96.13%	91.95% to 98.18%
Negative Predictive Value	41.44%	37.66% to 45.32%
Accuracy	66.67%	61.35% to 71.69%

Gene-X-pert diagnosed 149 cases (58.43%) out of 255 TB patients while clinical trial diagnosed 255cases out of 261 patients. The Fisher exact test statistic value was 0.0002.

DISCUSSION

In-spite of all modern modalities of diagnosis and treatment, TB is still a major health hazard all over the world. Delay in diagnosis and prompt treatment is the sole cause of multiplied transmission by aerosol inhalation. [12]

In current study on 261 PTB-patients, maximum numbers of TB cases were observed in 15-40 years age group and the mean age was 34.33 years which reflects that PTB is common in younger age group. Rai and colleagues (2015) reported that most of the patients were between the age of 15 and 30 years, displaying good agreement. [14]

A male to female ratio 1.12:1 indicated the male preponderance. Our results are in concordance with those reported by Rajasekaran et al (2000) reporting 76.3% males and 23.7% females.[15] Similarly, Rai et al (2015) communicated 65.1% male and 34.9% female.[14] Sedky M et al (2018) displayed 80% male and 20.0% female but no statistically significant correlation was observed by Grover S and co-workers (2020) between TB with HIV and sex of the patient.[16,17]

The magnitude of tuberculosis is remarkably high in endemic populations due to under detection and multiplied transmission, creating remarkable hindrance in the way to disease control. Delayed diagnosis is directly related to sputum bacillary load that is why getting a sputum negative report by a TB patient is not infrequent even by fluorescent microscopy which is a high sensitivity test. Behr and associates demonstrated that sputum smear-negative-TB patients are less infectious, but can still transmit tuberculosis.[18] According to the 2015 European Centre for Disease Prevention report, in Italy, in 2014, from all TB cases, 68.1% spread was by smear-negative-TB cases. [19]

In this study, 261-patients were declared negative for tuberculosis by fluorescent microscopy, tested on two samples. But when subjected to Gene-X-pert assay, 149 patients (58.43%) were diagnosed as pulmonary TB. Identification if 03 cases of MDR out of sputum negative patients is a horrible finding. These cases are responsible for multiplication of MDR in community and increasing the burden. Although Vasall et al. (2011) showed detection rate more than 30%. [20] but our detection rate was very high, 58.43%. World Health Organization have set their goals for TB-free globe but in prevailing circumstances, it appears to be a dream only because a large number of cases including MDR, remain undiagnosed and keep on disseminating disease in the community.[21]

Current study reflected that 149/261 cases (58.43%), missed by FM were successfully captured by Gene-Xpert with sensitivity: 58.43%, Specificity: 92.59%, PPV: 96.13%, NPV: 41.44% and diagnostic accuracy: 66.67%. Rasheed W and co-workers (2019) reported 65.3% detection rate by Xpert MTB/RIF with sensitivity, specificity, PPV, NPV and diagnostic accuracy 84.48%, 100%, 100%, 65.38%, and 88%, respectively.[7] Reechaipichitkul W and associates (2016) demonstrated sensitivity 83.9%, specificity 92.1%, PPV 81.3%and NPV of 93.3%.[22] Although the sensitivity in this study is a bit low as compared to the quoted reports, even then it shows fair agreement while the specificity and PPV are in full concordance with these studies. Similarly, Malik, M. et al. (2019) manifested Sensitivity, specificity, PPV and NPV as 86.36%, 84.1%, 69.5%. 93.66% respectively in BAL samples not in sputum [23] Velen K et al. (2021) communicated rather a low sensitivity of 21.2%, specificity 98.3%, PPV 63.6% and NPV of 90.0% in sputum samples.[24] The calculated p-value 0.0002 is highly significant at $p < .05$, reflecting remarkable differentiating ability of Gene-Expert between a normal and diseased person.

Shi J et al (2018) proclaimed that X-pert outperformed mycobacterial culture on salivary sputum samples for detecting MTB.[25] Umair M and colleagues commented that sputum Gene-Xpert MTB/RIF test should be used to avoid a missed diagnosis of smear-negative Tuberculosis.[26] According to Akanbi MO and co-workers (2017), Gene-X-pert reduced the time for detection in HIV-positive TB-patients.[27] Pandey O et al conveyed that simultaneous MTB diagnosis and rifampicin resistance detection is possible by this test on the same day.[28] Khadka, P. and associates pointed out that by implementing X-pert, global disease burden can be reduced as targeted by WHO.[29] Wikman-Jorgensen PE et al recommended this test as a replacement of microscopy in high TB/HIV prevalence African setting.[30] Because the missed diagnosis of smear-negative pulmonary TB can have significant financial implications for the individuals, families, and the country as a whole, Sagili KD and workers identified its cost effectiveness for TB with high TB/HIV-burden areas. [31] WHO expressed that Gene-X-pert MTB/RIF assay is the most rapid test requiring less than two hour time for organism detection.[32] Lombardi et al (2017) concluded that Gene-X-pert can be used for early diagnosis of TB especially in smear-negative cases. [33] Kabir S and colleagues (2021) intimated that Gene-X-pert had significant impact on the challenge of sputum negative under-diagnosis.[34] Similarly, Munoz et al. reported a sensitivity of 68% for providing evidence based diagnosis of sputum smear-negative pulmonary TB.[35]

The results of this study may find very useful applications in resource-limited populations with high prevalence areas where rapid diagnosis and prompt treatment in smear-negative patients, using Gene-X-pert, can decelerate disease transmission and in turn reduce the burden of this malady in the community. As Gene-X-pert is a high specificity test, it can be used as reference in areas where AFB-culture is not available.[36]

Main limitation of this study is that it is the out-come of 336 patients and is a single centere research. By multi-centered study, with larger sample size, the subject can be explored effectively for optimized generalizability. Because response to treatment was considered as benchmark in this study, the potential of bias is not out of question. There is a

need of another ground-work, utilizing AFB-culture as gold standard to further consolidate the credibility of investigation.

This study has revealed high affinity of Gene-X-pert for AFB, substantially altering the scenario of TB-diagnosis. It is a high specificity test with adequate sensitivity, acceptable diagnostic accuracy and by using it rightly, disease can be diagnosed and treated early, thus cutting down the chain of transmission successfully. Concomitant diagnosis of RIF-resistance is also a delicate finding because these cases are a big threat to community. By correct management, according to MDR protocol, the threat of MDR-TB transmission can be restricted. As TB is a curable disease, the implementation of this diagnostic tool, can play a pivotal role in changing the complexion of TB-control over the globe.

Conclusions

As Gene-X-pert is faster than AFB-culture and even can detect rifampicin resistant strains of M. Tuberculosis simultaneously, we conclude that:

1. Gene-X-pert-MTB assay is rapid, highly specific and valuable test for evidence based diagnosis of sputum negative pulmonary tuberculosis.
2. Every patient, negative by sputum fluorescent microscopy, must be subjected to Gene-X-pert assay before labelling it as other than-TB case.
3. It provides foundations for prompt treatment of PTB and MDR cases which are lethal for public health.
4. It can be tremendously useful for a TB-control program by cutting down the chain of transmission and reducing the disease burden in community.

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