

Genexpert Positivity in Sputum Negative Cases with Clinico-radiologically Suggestive of Pulmonary Tuberculosis Infection in Tertiary Center

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Abstract

Background:

Tuberculosis is a major public health problem of world. Nearly 1/3rd of the global population is infected with mycobacterium Tuberculosis. GeneXpert is mainly indicated for early diagnosis and treatment of the pulmonary tuberculosis to prevent the TB related mortality and morbidity.

The objective of this study is to study GeneXpert result in sputum AFB negative but clinic-radiologically suggestive of pulmonary tuberculosis infection.

Methodos:

A Quantitative study was carried in the Department of Internal Medicine of National Medical College. A total of 80 cases with clinically and radiologically suggestive of PTB with AFB negative were included in this study. Data were collected for one year period and calculated the result by using SPSS.

Result:

Among the total 80 patients were included who presented in national medical college Birgunj, Parsa in the time period of 1 year.

In this study most common age group who presented with PTB were 31-45 years in 36.3% case with female predominance in 51.2% cases and male predominance of GeneXpert positive in 31 patients.

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Symptoms observed in our study was Cough>2 weeks, hemoptysis, weight loss, fever, SOB and night sweat among which most common presentation was cough >2 weeks in 81.3% cases with GeneXpert predominantly positive in 44 cases presented with cough >2 weeks.

In our study five radiological feature were observed among which most common was pleural effusion in 51 cases, 63.7% cases with predominant GeneXpert positive in 40 cases.

Conclusion:

GeneXpert testing increases the detection of pulmonary tuberculosis cases and it is also use full to diagnose and confirm the pulmonary tuberculosis in smear negative cases.

Keywords: Pulmonary Tuberculosis; Sputum two sample negative; Gene Xpert positive; Radiologically suggestive Pulmonary Tuberculosis.

1. Introduction

Tuberculosis (TB) is a major global health problem. It causes ill-health for approximately 10 million people each year and is one of the top ten causes of death worldwide. For the past 5 years, it has been leading causes of death from a single infectious agent. This disease is caused by bacillus mycobacterium tuberculosis. It typically affects the lungs (pulmonary TB or PTB) but can also affect the other sites (extrapulmonary TB)[1].

In 2016, WHO estimated that 7,18,000 deaths from TB among HIV negative men and 1,10000 among boys. There were an additional 3,78,000 deaths from TB among HIV negative women and 91,000 among girls. These numbers correspond to the 55% deaths in men, 29% in women and 16% in children[2]. In Nepal, Tuberculosis is a major public health problem. About 45% of total population is infected with TB, of which 60% are adults. Every year, 40,000 people develop active TB, of whom 20,000 have infectious pulmonary disease. These 20,000 are able to spread the disease to others. Treatment by Directly Observed Short course (DOTS) has reduced the number of deaths; however 5,000-7,000 people still die per year from TB.

High index for suspicion is very essential for the diagnosis of TB. Diagnosis can be done easily if cases present with typical symptoms and a classic chest radiograph showing upper-lobe infiltration with cavities. However, diagnosis is often difficult in an elderly or a teenager or in immunocompromised patients, including those with HIV infection, who may have “atypical” findings on chest radiography. TB is suspected in cases who presents with cough, fever, lymphadenopathy, night sweats and weight loss[3].

Clinicians often depend on alternative diagnosis based on patient symptoms and chest x-ray (CXR) findings, which have low sensitivity. This may lead to either over- or under diagnosis of PTB, with huge consequences on patient outcomes and use of limited resources. CXR cannot be used alone to diagnose smear negative PTB, as no single radiological lesion pathognomic of PTB exists[4].

These reasons limit its use in resource constrained settings. In order to obtain results in short period of time,

nucleic acid amplification test are increasingly used worldwide for rapid diagnosis of tuberculosis[5].⁶ The GeneXpert assay has been shown to have an accuracy comparable to that of culture. The sensitivity of a single Xpert result in smear- negative, culture –positive cases is 72.5%; the sensitivity increases with repeated testing[6]. In 2007, the WHO decided to improve diagnosis and management of smear-negative tuberculosis in HIV prevalent and resource constrained setting. The implementation required individuals with presumptive TB to be initially evaluated using two sputum microscopy examinations followed by clinical diagnosis such as chest x-rays in smear negative individuals. In December 2010 the WHO endorsed GeneXpert MTB/RIF (Xpert) for Mycobacterium tuberculosis detection in settings with high burden of tuberculosis[7]. WHO's 2013 policy recommendations emphasized that after evaluating the GeneXpert MTB/RIF technology, it should be used rather than conventional microscopy and culture as the initial diagnostic test in adults suspected of multi drug resistant TB or HIV associated TB.

The Xpert MTB/RIF is a cartridge-based, automated real time diagnostic test that can identify mycobacterium tuberculosis (MTB) DNA and resistance to rifampicin (RIF) by nucleic acid amplification techniques (NAAT) in less than 2 hours. It does not require special expertise[8]. Results from field demonstration studies found that a single Xpert MTB/RIF test can detect MTB in 99% of patients with smear positive PTB and more than 80% in patients with smear negative PTB[9]. The Xpert MTB/RIF assay uses a disposable cartridge with the GeneXpert Instrument system. A sputum sample is collected from the patient with suspected TB. The sputum is mixed with the reagent that is provided with the assay, and a cartridge containing this mixture is placed in the GeneXpert Machine. All processing from this point on is fully automated. High rate of undiagnosed PTB due to smear negative disease play a key role in TB transmission at community level. Early diagnosis improves treatment outcomes and reduces the risk of primary TB resistance[9].

2. Methodos

This is Descriptive cross-sectional hospital-based study conducted at National Medical College and Teaching Hospital (NMCTH), Birgunj, Parsa, Nepal over a period of 12 month from November 2016 to October 2017. Ethical approval was obtained from the Institutional Review Committee (IRC) of NMCTH prior to the start of the study. Written informed consent was obtained from patients or their relatives prior to enrolment in the study.

The objective of this study is to study GeneXpert result in sputum AFB negative but clinic-radiologically suggestive of pulmonary tuberculosis infection. On - probability purposive sampling was done and sample size was calculated to be 80 by using Solven's formula.

All patients who fulfill inclusion criteria of this study, presenting to National Medical College, Birgunj with clinico-radiological case suggestive of tuberculosis were enrolled for this study till the required sample size was achieved. The study was continued till the data analysis done and conclusion drawn and the work is submitted and approved.

All these criteria were required to be fulfilled to be included in the study. Patients aged more than 16 year visiting in an OPD and IPD of NMCTH, patients willing to provide consent in study two sample of sputum AFB

negative chest X-ray with clinical features suggestive of pulmonary tuberculosis. The following patients were excluded from the study: patients below 16 years of age, patients receiving ATT before the study, patients with extra Pulmonary TB, patients with other serious comorbid conditions like ESRD, decompensated CLD, decompensated heart failure, advanced Carcinoma.

Semi structured Performa was used to record the patient's socio demographic and clinical and profiles. Details of the patient including demographics, relevant history, symptoms and signs, physical examination findings, routine investigations and chest x-ray were performed. The patients who were having sign and symptoms of pulmonary tuberculosis chest x-ray were done. For each CXR showing features of PTB were examined for sputum AFB in National Medical college, Birgunj. All sputum negative cases were again sent for GeneXpert test of sputum at Narayani Zonal Hospital, Birgunj. Early morning sample of sputum about (15-20) ml was collected in sterile container and sent for GeneXpert examination at Narayani Zonal Hospital, Birgunj. GeneXpert examination was free of cost hence there was no burden for patient and patient party to do GeneXpert. And all the results of GeneXpert were analyzed.

3. Statistical analysis

The data were collected and processed in accordance with institutional guidelines to ensure patient privacy and confidentiality. The collected data were entered in Microsoft Excel (2007) and analyzed using Statistical Package for Social Science (SPSS) Software version 20 by using descriptive statistics (frequency and percentage). The study was continued till the data analysis done and conclusion drawn and the work was submitted and approved.

4. Result

In the present study total 80 patients were included who were present in the National Medical College and Teaching Hospital, Birgunj, Parsa in the time period of 1 year. All the patients included in the study were undergone the lab test of Sputum for AFB and the only patients included in this study were AFB negative patients suspected for tuberculosis symptomatically or radiologically.

In this study patients of all age group suspected for tuberculosis were included. Highest number patients were found in age group 31-45 (36.3%) and lowest in > 75 years (1.3%) with the mean age of 38 year and standard deviation of 1.003. Among the clinico-radiologically suspected pulmonary tuberculosis patients 41 (51.2%) patients were female and 39 (48.8%) were male. The patients included in this study presented with five symptoms among which most common symptom was cough for more than two weeks found in 81.3% patients followed by hemoptysis in 45% patients and weight loss in 41% patients. On the basis of clinical symptoms observed, it is hard to distinguish TB positive cases from TB negative cases because the observation of clinical symptoms on TB patients were statistically insignificant i.e., $p > 0.05$.

Among 80 patients five radiological features were observed during this study. Pleural effusion was the commonest feature noted in 63.7% of cases followed by the consolidation in 58.8% and upper lobe infiltration in 38.8% of cases. Least common finding was the normal finding radiologically who were suspected clinically

for pulmonary tuberculosis. Among the 80 clinico-radiologically suspected patients included in this study, 59 (74 %) patients were found to be GeneXpert positive and 21 (26 %) were GeneXpert negative.

In 80 patients included in this study, age wise distribution of GeneXpert positive tuberculosis cases. The highest number of GeneXpert positive cases were observed in 31-45 year of age i.e 23 cases. Followed by the age group 46-60 years (18 cases). Lowest age group was >75 years only one case. Among 80 cases included in this study the number of female patients 41 (51.25%) cases were more than that of the male patient 39 (48.75%) cases but the number of GeneXpert positive cases were more in male patients i.e 31(38.7%) cases. Among 80 patients, 59 patients were GeneXpert positive and 21 patients were negative with most common symptom was cough for >2 weeks in 44 patients followed by fever in 43 cases and hemoptysis in 36 cases. Weight loss seen in 24 and SOB in 19 GeneXpert positive cases. On the basis of clinical symptoms observed GeneXpert positive among the patients having cough for > 2 weeks, shortness of breath and hemoptysis were found to be statistically significant i.e $p < 0.05$.

In this study most common symptoms observed in GeneXpert positive cases were cough for more than 2 weeks in 44 cases followed by fever in 43 cases and hemoptysis in 23 cases. In this study consolidation, effusion and upper lobe infiltration were the most common observed radiological finding in TB cases and rest were the Cavitatory lesion and normal radiological finding. Among the observed features highest number of GeneXpert positive cases were found in the Effusion (40 cases) followed by consolidation (34 cases) and upper lobe infiltration (20 cases). Among the observed features are found to be statistically insignificant i.e $p > 0.05$. Among GeneXpert positive cases most common radiological finding was Pleural effusion 40 cases followed by consolidation 34 cases and upper lobe infiltration 20 cases. In this present study, maximum number of the cases of cough for more than 2 weeks were present in age group 31-45 years with maximum number 20 (33.8%) cases followed by the fever 16 (27.1%) cases in 46-60 years.

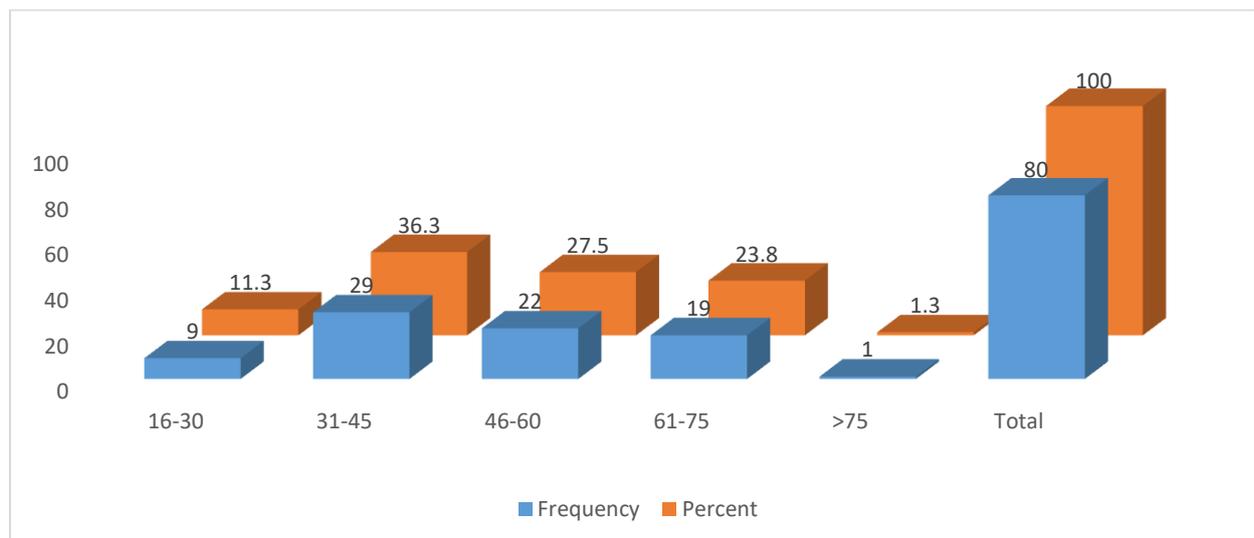


Figure 1: Age wise distribution of PTB

Table 1: Sex wise distribution of PTB

Sex	Frequency	Percent (%)
Male	39	48.8
Female	41	51.2
Total	80	100

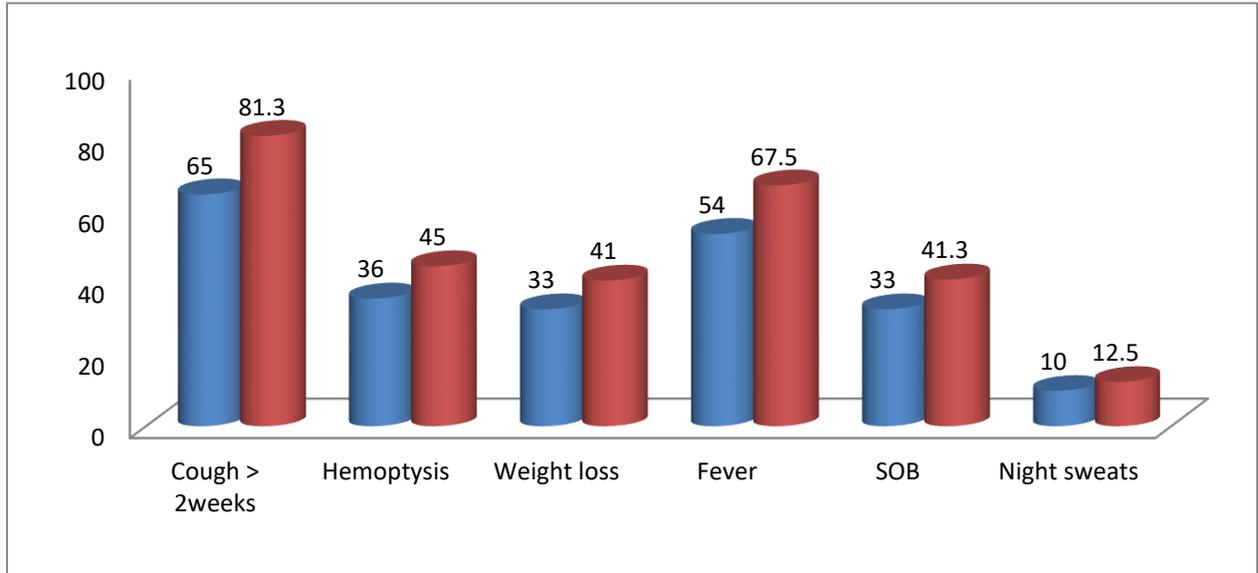


Figure 2: Symptoms observed in the patients included in this study

Table 2: Radiological features in the patients included in study

Features	Number	Percentage (%)
Consolidation	47	58.8
Effusion	51	63.7
Upper lobe infiltration	31	38.8
Cavity	10	12.5
Normal	3	3.8

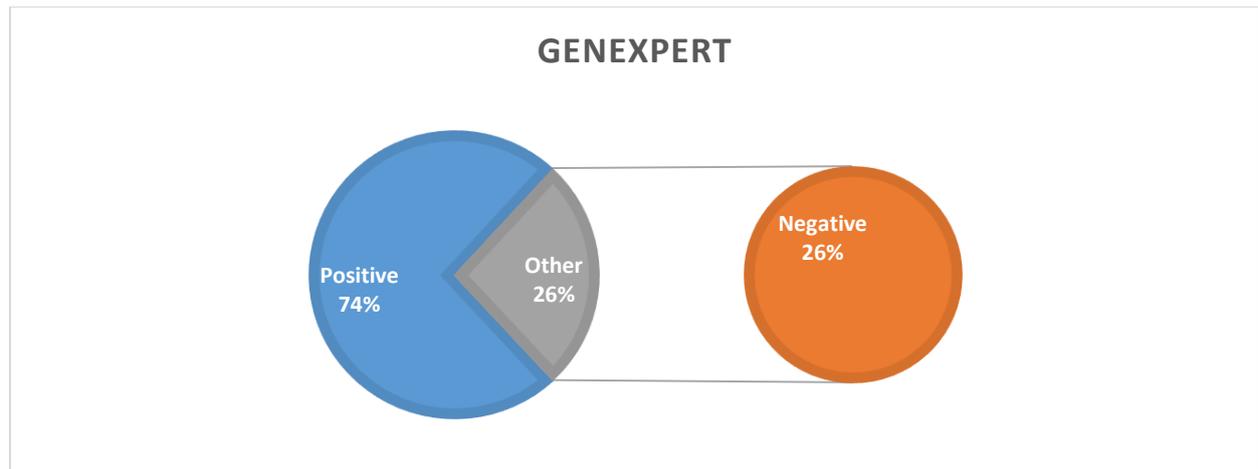


Figure 3: GeneXpert result on AFB negative patients

Table 3: Age wise distribution of Gene Xpert positive and negative cases

Age (years)	GeneXpert positive	GeneXpert negative	Total
16-30	6(7.5%)	3(3.7%)	9(11.2%)
31-45	23(28.7%)	6(7.5%)	29(36.2%)
46-60	18(22.5%)	4(5.0%)	22(27.5%)
61-75	11(13.7%)	8(10.0%)	19(23.7%)
>75	1(1.2%)	0	1(1.2%)
Total	59(73.6%)	21(26.2%)	80(100%)

Table 4: Sex wise distribution of GeneXpert Positive and negative cases

Sex	GeneXpert positive	GeneXpert negative	Total
Male	31(38.7%)	8(10.0%)	39(48.75%)
Female	28(35.0%)	13(16.2%)	41(51.25%)
Total	59	21	80(100%)

Table 5: Symptom wise distribution of GeneXpert positive and negative cases

Symptom	Total	GeneXpert positive	GeneXpert negative
Cough > 2weeks	65	44	21
Hemoptysis	36	23	13
Weight loss	33	24	9
Fever	54	43	11
SOB	33	19	14
Night sweat	10	6	4

Table 6: Radiological features in GeneXpert positive and negative cases

Features	GeneXpert positive	GeneXpert negative	Total
Consolidation	34	13	47
Effusion	40	11	51
Upper lobe infiltrate	20	11	31
Cavity	8	2	10
Normal	2	1	3

Table 7: Age wise distribution of symptoms in GeneXpert positive cases

Age /Features	16-30	31-45	46-60	61-75	>75
Cough > 2 weeks	4(6.7%)	20(33.8%)	13(22.0%)	7(11.8%)	0(0.0%)
hemoptysis	3(5.0%)	9(15.2%)	7(11.8%)	4(6.7%)	0(0.0%)
Weight loss	0 (0.0%)	9(15.2%)	7(11.8%)	7(11.8%)	1(1.6%)
Fever	3(5.0%)	15(25.4%)	16(27.1%)	9(15.2%)	0(0.0%)
SOB	2(3.3%)	3(5.0%)	9(15.2%)	5(8.4%)	0(0.0%)
Night sweat	0(0.0%)	2(3.3%)	2(3.3%)	2(3.3%)	0(0.0%)

5. Recommendation

This is to certify that the thesis entitled " **GeneXpert positivity in sputum negative cases with Clinico-radiologically suggestive of pulmonary tuberculosis infection in tertiary center** " is a genuinely original research work by **Dr. Raju Mourya** written under my supervision and guidance. The present research work submitted as thesis for Doctor of Medicine in Internal Medicine, is prepared in accordance with the rules and regulations of the Tribhuvan University.

6. Discussion

This study was conducted on the 80 patients presented in the national medical college in the one year duration with clinical or radiological findings suggesting pulmonary tuberculosis but with the AFB negative. Early diagnosis of active smear-negative pulmonary TB (PTB) is important for optimal treatment. According to the 2019 European Center for Disease Prevention (ECDC) report, from all laboratory confirmed TB cases, 82.4% met only culture positive criterion for TB[10]. Studies show that, smear negative PTB is responsible for 13-17% of transmission[11, 12]. According to the World Health organization, GeneXpert test is the most rapid sensitive test for TB diagnosis in respiratory samples[13]. Study conducted by Mohamed Sedky and his colleagues in 2017 included 30 patients suspected to be have TB, comprising 24 (80%) males and six (20%) females. Their age ranged from 18 to 70 years, with a mean age of 45.5±17.7 years. All patients have clinical and radiological signs consistent with TB, positive tuberculin test results, and three negative Ziehl–Neelsen sputum smears. They

found that GeneXpert was positive in 11 (36.7%) patients and negative in 19 (63.3%) patients. We found in our study GeneXpert positive cases were 59 cases (73.7%) and negative 21 cases (26.2%)[14]. In the study of N O Ndubuisi and his colleagues in 1500 patients found only 389 (25.9%) GeneXpert positive as compared to the negative 1111 (74.1%) cases with the most common age group 25-34 years with male predominance[15]. In a study conducted by Rai and his colleagues among 106 smear negative suspects who underwent GeneXpert testing, 37 (34.9%) patients were Xpert positive. In the same study, most of the cases were between the age 15-30[16]. Study conducted by the N O Ndubuisi and his colleagues in 1500 patients found that the most common age group was 25-34 and 35-44 years with male predominance with 66.1% positive cases [15]. This study shows most common age group was 31-45 years (36.3%) with the mean age is 48.6 years. Followed by the age group 46-60 years (18 cases). Lowest age group was >75 years only one case. In our study female predominance with 51.2% positive cases were noted. In this study six symptoms were included in which cough for more than two weeks in 81.3% cases was the most common presentation of pulmonary tuberculosis followed by fever in 67.3% cases and weight loss in 30.0% cases. In the study conducted by B Rajbhandari and his colleagues found the commonest symptoms were cough more than 2 weeks (94.4%) and fever (72.2%) and weight loss (61.1%)[17]. Rai and his colleagues found clinical symptoms cough and anorexia were more significantly associated with positive result in GeneXpert[16]. Among the 80 patients of pulmonary tuberculosis included in this study most common presentation was pleural effusion in 63.7% cases followed by consolidation in 58.8%. The most common CXR findings in B. Rajbhandari study were consolidation (77.8%), infiltration (72.2%) and fibrocavity (72.2%)[17]. In a study conducted by Cleef and his colleagues generalized reticulo-nodular infiltration (55%); cavity (30%) and pleural effusion (15%) were more frequent in smear negative than smear positive cases[18]. In the study conducted by Manoj Mathur and his colleagues found that the most common radiological finding was nodular opacities in 90% followed by the consolidation in 73.3% and in 60% cavitary lesion[19].

7. Conclusion

Tuberculosis is a major public health problem worldwide with 8 million cases and 1.3 million deaths each year. Sputum smear and chest X-rays are the most routinely applied test for TB diagnosis. GeneXpert has very high sensitivity in diagnosis of smear negative pulmonary tuberculosis and it has more role especially in developing country. GeneXpert is mainly indicated for early diagnosis and treatment of the pulmonary tuberculosis to prevent the TB related mortality and morbidity. Our study shows that GeneXpert testing increases the detection of pulmonary tuberculosis cases and it is also use full to diagnose and confirm the pulmonary tuberculosis in smear negative cases.

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