Journal of Nobel Medical College

Original Article

Diagnostic Yield of Bronchoscopic Alveolar Lavage Gene Xpert MTB/Rif in Smear Negative Clinico-Radiologically Suspected Case of Pulmonary Tuberculosis

Bidesh Bista*[1], Niraj Karmacharya[1], Ram Hari Ghimire[2], Pradeep Shrestha[1], Dipak Poudel[1], Janer kurumbang[1], Manoj Mahato[1], Deebya Raj Mishra[3]

[1]Department of Medicine, Civil Service Hospital, Kathmandu, Nepal, [2]Department of Medicine, Nobel Medical College Teaching Hospital, Biratnagar, Nepal, [3]Department of Medicine, B.P. Koirala Institute of Health Sciences, Dharan, Nepal

Abstract

Background
Early diagnosis of pulmonary tuberculosis is difficult but dreaded complications like cavitations, abscess, disseminations and fibrosis of lung parenchyma can be avoided. Sputum microscopy is still the most available test for diagnosis of pulmonary tuberculosis but sustainable number of active cases remains undiagnosed via this method alone. In strong clinico-radiological pulmonary tuberculosis patients who are sputum scarce or sputum microscopy and sputum Xpert MTB/Rif negative broncho-alveolar lavage may provide superior sample for Gene Xpert MTB/Rif in diagnosis of Pulmonary Tuberculosis.

Materials and Methods
Over 2 years period, patients with strong clinico-radiological suspicion of pulmonary tuberculosis who had sputum microscopy and sputum Xpert MTB/Rif negative were included in the study. Fibro-optic bronchoscopy was done for BAL Xpert MTB/Rif test. Base line demographic, clinical and radiological data were systematically analysedby SPSS software version 17.

Results
64 patients were included in the study with mean age 41 ± 10.52 years. The most common symptoms were cough, sputum production and weight loss with frequency of 58 (90.6%), 31 (48.4%) and 21 (32.11%) patients respectively. The most common CT scan findings were consolidation, cavitation and tree in bud pattern. BAL Xpert MTB/Rif was positive in 11 (17.18%) patients. According to the CT findings BAL Xpert MTB/Rif was most commonly present in patients presenting with cavitary lung disease.

Conclusion
Eleven patients had BAL gene Xpert/Rif positive out of 64 patients who were sputum scarce or had both microscopy and sputum gene Xpert/Rif negative. Bronchoscopy BAL Xpert/Rif could provide an additional diagnostic test in these groups of patients.

Keywords: *Bronchoalveolar lavage, Bronchoscopy, Tuberculosis*

*Corresponding Author:
Dr. Bidesh Bista
Registrar
Email: bideshbista@gmail.com
ORCID: https://orcid.org/0000-0003-4232-3871

Introduction

In Nepal, every year estimated 68000 new cases of tuberculosis occur with 17000 deaths per year. i.e., 189 new cases every day with 47 deaths per day. Almost one third to half of the population is infected with tubercular bacilli in Nepal [1]. Prompt diagnosis of active tuberculosis is very important to reduce overall transmission, mortality and morbidity in patients. Early diagnosis of tuberculosis is difficult but easy to treat; late diagnosis is easy but difficult to treat with severe complications like cavitation, abscess, and dissemination to other organs and fibrosis of lung causing long term morbidity [2]. Sputum microscopy is the most available test for detection of active pulmonary tuberculosis. The sensitivity of sputum microscopy ranges from 34 to 80 percent [3]. There require a minimal of 5000 to 10,000 bacilli per ml of sputum for sputum microscopy to be reliably positive [4]. The results also depend upon sputum quality, technical preparation of slides and expertise of laboratory personnel examining the smears. Therefore, substantial numbers of active pulmonary tuberculosis remain under diagnosed by conventional sputum microscopy only [5].

With the advent of Gene Xpert MTB/Rif (Xpert MTB/Rif), there has been much better accuracy and reliability in diagnosis of tuberculosis than sputum microscopy [6]. This assay is a novel integrated assay that performs real time Polymerase chain reaction (PCR) analysis and rapid detection of Rifampicin resistance via amplication of 81 bp fragment of the rpoB gene of tubercular bacilli. The detection of mutation in that region is associated with rifampicin resistance and the whole assay completes within 2 hours [7,8]. XpertMTB/Rif assay have shown overall sensitivity and specificity of 95.7 % and 99.3% respectively. In smear negative, culture positive cases sensitivity of Xpert MTB/Rif was found to be 77.7% [6]. In patients with sputum scarce, defined by sputum volume less than 1 ml, or smear negative pulmonary tuberculosis, Broncho-alveolar Lavage (BAL) specimen have shown to be an additional and superior tool in diagnosis of pulmonary tuberculosis in many clinical studies [9,10,11,12,13]. In this study, we intended to look at the additional value of utilizing Xpert MTB/Rif in BAL samples in patients with high clinico-radiologic suspicion of tuberculosis, who weresputum smear and sputum Xpert MTB/Rif negative or were sputum scarce.

Materials and Methods

The study was conducted as a prospective observational study in Civil Service Hospital, Nepal over the period of 2 years from July 2019 to June 2021. Adults above 18 years presenting with clinico-radiological features of pulmonary tuberculosis with sputum smear for acid fast bacilli and sputum for gene Xpert MRB/Rif negative were eligible for the study. The patients who had already received antitubercular therapy on clinical circumstances and who did not consent or were not fit for bronchoscopy due to general condition were also excluded from the study. Ethical approval was obtained from the institutional review board of Civil Service Hospital.

Pleural Effusion without parenchymal involvement, considered as Extra pulmonary tuberculosis (EPTB) was not included in our study but predominately parenchymal involvement with pleural effusion were included. Radiological features suggestive of malignancy or bronchoscopic evidence of malignancy were also excluded from our study. BAL was taken from a single or multiple Bronchopulmonary segments based of radiological picture and sent for Xpert MTB/Rif.

Baseline demographic, clinical and radiological information were systematically recorded in structured proforma. Data analysis was done through SPSS software version 17.

Results

In our study, 64 patients over 2 years were included. The mean age of our patients was 41 ± 10.52 years. 45 (70.3%) of the patients were male. The age range in our study was from 20 to 71 years. The most common age group was from 40 to 49 years which compromised of 26 (40.6%) patients followed by 30 to 39 years age group-comprising 23 (35.9%) patients (Table 1). The most common symptoms were cough, sputum production and weight loss which was present in 58 (90.6%), 31 (48.4%) and 21 (32.11%) patients respectively (Table 2). In our patients, CT scan was done in all cases and most common finding was consolidation followed by cavity and tree in bud pattern in 43 (67.18%), 16 (25%) and 14 (20.31%) patients respectively. Hilar lymphadenopathy was found in 11 (17.81%) patients. The most common combination pattern in CT chest was of consolidation and tree in bud pattern followed by consolidation and hilar lymphadenopathy in 12 (18.75%) and 9 (14.06%) patients respectively.

Out of the 64 patients, BAL Xpert MTB/Rif was positive in 11 (17.18%) patients. According to the CT findings BAL Xpert MTB/Rif was most commonly present in patients presenting with cavitary lung disease followed by consolidation and tree in bud appearance. (Table 3)

Nepal Journals Online: www.nepjol.info
Official website: www.jonmc.info
Journal of Nobel Medical College
Vol. 11, No. 1, Issue 20, January-June 2022
39

Table 1: Age Distribution of the Patients

Age Group	n (%)
20 -29	8 (12.5%)
30 – 39	23 (35.9%)
40 -49	26 (40.6%)
50 – 59	5 (7.8%)
≥60	2 (3.12%)

Table 2: Clinical symptoms of the patients.

Symptoms	n (%)
Cough	58 (90.6%)
Sputum	31 (48.4%)
Haemoptysis	4 (6.25%)
Chest pain	3 (4.68%)
Weight loss	21 (32.81%)
Fever	5 (7.8%)
Dyspnoea	7 (10.93%)
Asymptomatic	6 (9.37%)

Table 3: CT scan characteristic of the patients.

CT Findings	n (%)	BAL positive (%)
Consolidation	43 (67%)	5 (11.62%)
Cavity	16 (25%)	6 (37.50%)
Tree in bud pattern	14 (20.31%)	5 (35.71%)
Bronchiectasis	6 (9.37%)	3 (50%)
Hilar Lymphadenopathy	11 (17.18%)	2 (18.18%)
Pleural Effusion	2 (3.12%)	1 (50%)
Miliary Shadow	2 (3.12%)	0
Nodular Infiltrates	4 (6.25%)	1 (25%)

Discussion

Ever since the endorsement of Xpert MTB/Rif in the diagnosis of Pulmonary tuberculosis by WHO in 2010, it has served as a boon to the treating physicians and patients in high burden TB countries [13]. In Nepal, as TB burden is very high, patients with radiological evidence are usually seen to have sputum Xpert MTB/Rif positive due to its high sensitivity rate. Sensitivity of Xpert MTB/RIF is suboptimal in smear scarce and sputum negative culture positive cases as discussed [6]. In these cases, we wanted to look at the performance of Xpert MTB/Rif on the BAL samples with the presumption that the sensitivity would be enhanced due to better quality of samples.

The most common age group in our study was 40 to 49 years which compromised 26 (40.6%) patients followed by 30 to 39 years age group. Studies have shown tuberculosis in adults tend to occur in productive age groups. World Health Organization stated 20 to 50 years as the common age for tuberculosis in developing countries [14]. Large study carried out in India in 2019 showed productive age group below sixty years as the most common age group for tuberculosis [15]. This is probably due to the fact that this age group comes in frequent contact with tubercular patients in their daily work and business. In our study most common symptoms was cough (90.6%). In any respiratory disease cough is the most common symptoms that brings patient to the hospital. Fever was present in only 5 (7.8%) cases which was less in comparison to other studies like Gowda et al, SC. Kiaru et al, Khalil K.F et al, Bashir et al, Khan F.Y et al. in which percentage of fever in patients were 78.3%, 82%, 33.3%, 54.28% and 100% respectively [16,17, 18,19,20]. The reason we had less symptoms of fever patients than other studies was probably because we had mostly ambulatory type of chronic patients.

Significant number of patients had weight loss (32.81%) in our study. Some of the patients came to us with complaints of weight loss only. Weight loss was higher in studies like Chakradhar P et al, Gowda et al and khan F. Y et al with 70.3, 78.3% and 70.4 % respectively than in our study [5, 16, 20]. One important interesting group of patients we had were asymptomatic type. These patients had their chest radiograph abnormal when radiographs were taken for some different purpose. Most of these patients were going to the foreign countries as labours where chest radiographs was a part of medical examination. This group of patients were generally in their twenties and 4 out of 6 patients had BAL Xpert MTB/Rif positive in this group.

CT chest was done in all patients before bronchoscopy. Most common CT chest finding in our study was consolidation followed by cavitation and tree in bud appearance with frequencies of 67%, 25% and 20.3% respectively consistent with other similar studies [5, 16, 18, 21]. In our study BAL was most frequently positive for Xpert MTB/Rif in patients who had cavitation in CT scan. It is clear that cavity harbours abundant tubercular bacilli and right amount of lavage from that specific bronchopulmonary segment can provide us with quality specimen containing large number of bacilli. We had two patients presenting with pleural effusion.Both patients had consolidation in upper lobes in addition to effusion. Xpert MTB/Rif came positive in one patient containing pleural effusion. We had 2 patients with typical miliary shadowing in CT chest. In both patients BAL Xpert MTB/Rif along with other pulmonary samples like Transbronchial Lung Biopsies

Nepal Journals Online: www.nepjol.info
Official website: www.jonmc.info
Journal of Nobel Medical College
Vol. 11, No. 1, Issue 20, January-June 2022
40

(TBLB), Bronchial Brushing and Bronchial Biopsies were negative for tuberculosis. However, both patients were started on Antitubercular Treatment on clinical basis.

We found, out of 64 patients who underwent bronchoscopy BAL, Xpert MTB/Rif came out to be positive in 11 patients which comprises about 17.18 %. Thus, bronchoscopy helped 17.18% of our study group to have a bacteriologically confirmed case of pulmonary tuberculosis who were already sputum for Xpert MTB/Rif negative but had strong suspicious for tuberculosis through their clinico-radiological profile. The results of our study provide evidence that in high burden country like Nepal, if bronchoscopy facility is present, BAL samples provide additional sensitivity to that provided by sputum samples while doing Xpert MTB/Rif testing.

Limitation of our study was we could not include large sample in our study as we included patients only with sputum Xpert MTB/Rif negative cases. Another limitation was we couldn't send BAL sample for culture sensitivity of MTB as cultures for tuberculosis is done only in very few centres and mostly for suspected MDR tuberculosis only.

Conclusion

In patients with sputum scarce or sputum smear negative for Xpert MTB/Rif, BAL Xpert MTB/Rif can be a useful additional diagnostic tool in centres where bronchoscopy facility is present. BAL Xpert MTB/Rif has superior diagnostic yield with quality specimen which is cost effective, technically easy and less risky which also provide information regarding Rifampicin resistance within 2 hours.

Acknowledgement

We are thankful to study participants to allow us to conduct the study.

Conflict of interest: None

References

[1]   Government of Nepal, Ministry of Health and Population, Nepal Tuberculosis Control Center. Tuberculosis profile FY 2076/77. Global TB report. (2020). World Health Organization. https://nepalntp.gov.np/wp-content/uploads/2021/04/Factsheets_Final.pdf (accessed on 03.02.2022)

[2]   Keeler E, Perkins MD, Small P, Hanson C, Cummingham J et al, Reducing the global burden of tuberculosis: the contribution of improved diagnostic. Nature. 444 Suppl 1: (2006) 49-57. PMID: 17159894 DOI: 10.1038/nature05446

[3]   Brodie D, Schluger NW, The diagnosis of tuberculosis, Clinical chest medicine. 26: 2 (2005) 247 - 71. PMID: 15837109 DOI: 10.1016/j.ccm.2005.02.012

[4]   Rasool G, Khan AM, Mohy-Ud-Din R, Riaz M, Detection of Mycobacterium tuberculosis and AFB smear-negative sputum specimens through MTB culture and GeneXpert MTB/RIF assay, International journal of Immunopathology and Pharmacology. 33 (2019) 1-6. https://doi.org/10.1177/20587384198-27174

[5]   Chakradhar P, Bharath G, Veerasekharaiah M, Role of Fibroptic Bronchoscopy and Gene Xpert in evaluating sputum smear negative pulmonary tuberculosis suspects. Journal of evidence based medicine and healthcare. 6:9 (2019) 663-7. DOI:10.18410/jebmh/2019/138.

[6]   Sharma SK, Kohli M, Yadav RN, Chaubey J, Evaluating the diagnostic accuracy of Xpert MTB/RIF assay in pulmonary tuberculosis, PLoSone . 10:10 (2015) e0141011. DOI: https://doi.org/10.1371/journal.pone.0141011

[7]   Blakemore R, Story E, Helb D, Kop J, et al, Evaluation of the analytical performance of the Xpert MTB/RIF assay, Journal of clinical Microbiology. 48 (2010) 2495-01 DOI: 10.1128/JCM.00128-10.

[8]   Patil S, Narwade S, Mirza M, Bronchial wash Gene Xpert MTB/RIF in lower lung field tuberculosis: Sensitive, superior, and rapid in comparison with conventional diagnostic techniques, Journal of Translational Internal Medicine. 5:3 (2017) 174-81. DOI: 10.1515/jtim-2017-0030

[9]   Khalil KF, Butt T, Diagnostic Yield of Bronchoalveolar Lavage Gene Xpert in Smear-Negative and Sputum-Scarce Pulmonary Tuberculosis, Journal of the college or physicians and surgeon Pakistan. 25:2 (2015) 115-8. PMID: 25703755.

[10] Shin, J. A., Chang Y.S, Kim T.H, Fibrooptic bronchoscopy for the rapid diagnosis of smear-negative pulmonary tuberculosis, BMC Infected Disease. 12 (2012) 141-3. DOI: 10.1186/1471-2334-12-141.

[11] Lee H Y, Seong M, W. Park, S S Hwang, J Lee et al, Diagnostic accuracy of Xpert ® MTB/RIF on bronchoscopy specimens in patients with suspected pulmonary tuberculosis, International Journal of Tuberculosis Lung Disease. 17:1 (2013) 917-21. DOI:10.5588/ijtld.12.0885.

[12] Charoenratanakul S, Dejsomritrutai W, Chaiprasert A, Diagnostic role of fibroptic bronchoscopy in suspected smear negative pulmonary tuberculosis, Respiratory Medicine. 89:1 (1995) 621- 23. DOI 10.1016/0954-6111 (95) 90231-7.

[13] Albert H, Ruvandhi R, Nathavitharana, Isaacs C, Pai M et. al., Development, roll-out and impact of Xpert MTB/RIF for tuberculosis: what lessons have we learnt and how can we do better? Eur Respir J. 48 (2016) 516-25 | DOI: 10.1183/13993003.00543-2016.

[14] World Health Organization: WHO report 2010: Global tuberculosis control. Geneva, Switzerland: WHO (2010). https://apps.who.int/iris.bitstream/handle/10665/44425/9789241564069_eng.pdf?sequence=1 (accessed on 05.03.2022)

[15] Sharma P, Madhur V, Bhilwar M, Shekhar H, Roy N, Epidemiological profile of tuberculosis patients in Delhi, India: A retrospective data analysis from the directly observed treatment short?course (DOTS) center, Journal of Family Medicine and Primary Care. 8:10 (2019) 3388-92. DOI: 10.4103/jfmpc.jfmpc_409_19

Nepal Journals Online: www.nepjol.info
Official website: www.jonmc.info
Journal of Nobel Medical College
Vol. 11, No. 1, Issue 20, January-June 2022
41

[16] Gowda N.C, Ray A, Soneja M, Khanna A, Sinha S, Evaluation of Xpert Mycobacterium tuberculosis/rifampin in sputum - smear negative and sputum - scarce patients with pulmonary tuberculosis using bronchoalveolar lavage fluid, Lung India. 35:4 (2018) 295-300. DOI: 10.4103/lungindia.lungindia_412_17

[17] Kilaru S.C, Chenimilla N.P, Syed U. et. al., Role of Xpert MTB/RIF in Bronchoalveolar lavage fluid of sputum-scarce, suspected Pulmonary TB patients, Journal Clinical Tuberculosis other Mycobacteria Disease. 14 (2019) 7-11. PMID: 31720410. DOI: 10.1016/j.jctube.2018.11.003

[18] Khalil K.F, Butt T, Diagnostic Yeild of Brochoalveolar Lavage Gene Xpert in Smear - Negative and Sputum - Scarce Pulmonary Tuberculosis, Journal of the College of Physician and Surgeon Pakistan. 25:2 (2015) 115-18. PMID: 25703755

[19] Bashir Y. U, Nahvi Nahid N, Khan S, Jaostihan T, Diagnostic utility of Bronchoalveolar Lavage Xpert MTB/RIF assay in suspected Case of Pulmonary Tuberculosis. International Journal of contemporary medical Research. 6:6 (2019) F8 - F11. DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.6.29

[20] Khan F. Y, Aladab A. H, Role of Fiberoptic Bronchoscopy in the Rapid Diagnostic of sputum Smear-negative Disseminted Tuberculosis with Pulmonary Miliary Infilrates, Oman Medical Journal. 35:1 (2020) e87-e91 PMID: 31993225 DOI: 10.5001/omj.2020.05

[21] Shin J.A, Chang Y.S, Kim T.H, Ahn H.J, Byun M.K., Fibrooptic bronchoscopy for the rapid diagnosis of smear- negative pulmonary tuberculosis, BMC Infectious Diseases. 12 (2012) 141-2. DOI: 10.1186/1471-2334-12-141.

[22] Sanchez-Cabral O, Santillan-Diaz C, Flores-Bello A.P, Herrera-Ortega M. I, et al., Genexpert MTB/RIF assay with transbronchial lung cryobiopsy for Mycobacterium tuberculosis diagnosis, Annals of Translational Medicine. 8:6 (2020) 351 PMID: 32355795. DOI: 10.21037/atm.2020.02.100

[23] Horne DJ, Kohli M, Schiller JS, Dendukuri I, Tollefson N et al, Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampaicin resistance in adults, Cochrane Database System Review. 6 (2020) CD009593. DOI:10.1002/14651858. CD009593.pub4.

[24] Steingart KR, Sohn H, Schiller I, er al, Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults, Cochrane Database System Review. 1 (2013) 1-131. DOI: http://doi.wiley.com/ 10.1002/14651858.CD009593.pu b2

[25] Rajagopal T.V. Barney I, Davasahayam J C, Balamugesh T et al., The yield of bronchoscopy in sputum Xpert MTB/Rif negative tuberculosis in the Xpert era, European Respiratory Journal. 56: (2020) 534-5. DOI: 10.1183/13993003.congress-2020.534

[26] Mohan A, Sharma SK, Fibreoptic bronchoscopy in the diagnosis of sputum smear-negative pulmonary tuberculosis: Current status, Indian Journal Chest Disease and Allied Science. 50:1 (2008) 67-78 PMID: 18610691

[27] Theron G, Peter J, Meldeu R, Khalfey H, Gina P, et al. Accuracy and impact of Xpert MTB/RIF for the diagnosis of smear-negative or sputum scarce tuberculosis using bronchoalveolar lavage fluid. Thorax. 68:1 (2013) 1043-51. PMID: 23811536. DOI: 10.1136/thoraxjnl-2013-203485.

Nepal Journals Online: www.nepjol.info
Official website: www.jonmc.info
Journal of Nobel Medical College
Vol. 11, No. 1, Issue 20, January-June 2022
42