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Study of role of gene expert in diagnosis of Tuberculous Pleural Effusion

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Abstract

Background: Pleural effusion is accumulation of excess amount of fluid in the pleural space. Pleural effusion is often a secondary effect of another disease process eg. Congestive heart failure, hepatic cirrhosis, nephrotic syndrome, myxoedema, connective tissue disorders. The second most common form of extra pulmonary tuberculosis is Pleural Tuberculosis. It is caused by the immune system response to the presence of mycobacterial antigens in the pleural space, generating inflammation and causing fluid to accumulate. **Methodology-** The study was conducted at the Department of Pulmonary Medicine, tertiary care centre on the patients with pleural effusion. Duration of the study was from August 2016 to January 2018. 200 patients fulfilling the inclusion criteria were included in the study. A detailed clinical history and general physical examination was done on all the patients. Pleural fluid analysis was done by appropriate distribution of fluid sample. Patients were divided into 3 groups i.e. Group A, Group B and Group C. Genexpert test was done for nucleic acid amplification, and detection of the target sequences from the received samples. **Result-** Mean age of the study subjects were 37.04±16.87 years with more than 55% of patients were present in age group of 21-40 years**.** Cough was the most common symptom of presentation observed in 60% of patients, followed by fever (50.5%) chest pain (52%), breathlessness (50.5%), weight loss (22.5%), expectoration (11%) and haemoptysis (6.5%). **Conclusion-** Tuberculosis was the most common cause of pleural effusion followed by malignancy. The Genexpert assay had low sensitivity but high specificity.

Keywords: Tuberculosis, pleural effusion, gene, pleural, fluid.

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Introduction

Pleural effusion is accumulation of excess amount of fluid in the pleural space. Normally, the pleural space contains a small amount of fluid (about 0.26 ± 0.1 ml/kg body weight) which allows the lungs to expand and deflate with minimal friction during respiratory movements. Pleural fluid normally originates in the capillaries of the parietal pleura, filtrates into the pleural space, and is then absorbed by the parietal pleural lymphatics. Effusions accumulate whenever the rate of pleural fluid formation exceeds that of its reabsorption, usually the result of simultaneous malfunction of both processes rather than just one alone.[1] Pleural effusion is,

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often a secondary effect of another disease process eg. Congestive heart failure, hepatic cirrhosis, nephrotic syndrome, myxoedema etc. In India Tuberculosis is the most common aetiology leading to pleural effusion, followed by malignant pleural effusion. Pleural Tuberculosis is caused by the immune system response to the presence of mycobacterial antigens in the pleural space, generating inflammation and causing fluid to accumulate. The gold standard for the diagnosis of tuberculous pleuritis is pleural fluid culture but it takes 2 to 6 weeks to obtain the result and the yield of test varies from 10-70% due to paucibacillary nature of the disease.[2-3] The GENEXPERT MTB/RIF is cartridge-based nucleic acid amplification test. It is an automated diagnostic test that can identify Mycobacterium tuberculosis (MTB) DNA and resistance to rifampicin (RIF). In India Revised National Tuberculosis Control Programme have adopted the nucleic acid amplification test in its diagnostic approach for detection of Tuberculosis and rifampicin resistance. It is a rapid diagnostic method as it takes around 1 hour 55 minutes to complete the test and reporting.[4]
Presence of pleural effusion can be warning of underlying potentially life threatening condition hence study of case history, clinical examination and application of appropriate diagnostic tests is must to arrive at an etiological diagnosis of pleural effusion. The confirmatory diagnosis of tuberculous pleural effusion by conventional tests like pleural biopsy and Culture for mycobacterium tuberculosis is difficult to make in resource limited setting. As the conventional confirmatory methods of diagnosis are time consuming, with modest sensitivity, needs technical expertise and had associated biosafety concerns. There is need for a simple, rapid and more accurate test to diagnose pleural tuberculosis and hence, this study was conducted to study of role of gene expert in diagnosis of Tuberculous Pleural Effusion.

Materials And Methods

Study design- This study utilized observational cross sectional design.

Study Place- The study was conducted on the patients with pleural effusion attending Department of Pulmonary Medicine at a tertiary care centre from August 2016 to January 2018.

Inclusion criteria- All the patients with pleural effusion, age more than 13 years and those who are willing to give written consent for participation in the study were included.

Exclusion criteria- Patients who had no pleural effusion, age less than 13 years, with contraindications for thoracocentesis like bleeding diathesis, mechanical ventilatory support and those who are not willing to participate in the study or for thoracocentesis were excluded.

Sample size- Sample size calculated by formula [5]

$$N=\frac{(Z1-\frac{\alpha}{2})^2 pq}{d^2}$$

From previous year hospital data and the previous study literature, the prevalence of pleural tuberculosis ranges from 60-66%.[6,7,8] To obtain maximum sample size the prevalence was taken as 66%.

N = required sample size
Z (1-α/2) = 1.96(at 5% type 1 error)
p = Expected proportion in population based on previous or pilot study i.e. 66
q = (1-p) i.e. 34
d= absolute error or precision to be decided by researcher
i.e. here 10% of the prevalence i.e. 6.6
Hence, N =(3.84x66x34) / (6.6x6.6) = 198 (rounded to 200)
Total participant of the study were 200.

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Data analysis- Data analysis is done with the help of appropriate SPSS Software version 20. Quantitative data is presented with the help of Mean, Standard Deviation. Qualitative data is presented with Frequency and Percentage tables. Chi square / Fischer exact tests were applied for the association between study parameters.

Ethical considerations- All ethical considerations and necessary approvals were taken from Institutional Ethical Committee and after the permission, the same was sent to Maharashtra University of Health Sciences (MUHS) for the approval.

A detailed clinical history and general physical examination was done on all the patients. Various investigations were done including sputum examination, radiological examination (chest x- ray PA view), pleural fluid analysis. Patients were categorised and grouped on the basis of the etiology of effusion. Patients were grouped as follows-

Group A- Tuberculous Pleural Effusion

Group B-Malignant Pleural Effusion

Group C-Other etiologies which includes all non-tuberculous and non-malignant effusions.

Genexpert test [Xpert MTB/RIF Assay] was performed in all pleural fluid samples. The primers in the Xpert MTB/RIF assay amplify a portion of the rpoB gene containing the 81 base pair "core" region. The probes are able to differentiate between the conserved wild-type sequence and mutations in the core region that are associated with rifampicin resistance.[11,74] GeneXpert MTB/RIF assay simultaneously detects DNA of Mycobacterium tuberculosis (i.e. mutation of the rpoB gene) in 1Hr 45 minutes. Further, interpretation of the results was done. These results depend on the Ct value (cycle threshold value) of the MTB target present in the sample.

Results

TABLE 1: Etiological distribution of study population

Group	Etiology	Number of patients	Percentages
A	Tuberculous	135	67.5%
B	Malignant	29	14.5%
C	Other	36	18%
	TOTAL	**200**	**100%**

Classification of study subjects as per etiology of the effusion

Amongst total 200 patients

Group A- tuberculous effusion was noted in 135 (67.5%) patients,

Group B- malignant effusion was present in 29(14.5%) patients;

Whereas, Group C - 36(18%) patients with etiology other than tuberculosis and malignancy which includes transudative effusion of 21(10.5%of all the patients studied) patients, 6(3%) patients with synpneumonic effusion, empyema in 4(2%), pancreatitis and rheumatoid arthritis as main etiology of effusion in 4(2%), 1(0.5%) patients respectively.

TABLE 2: Age Group Distribution

Age in years		**13-20**	**21-30**	**31-40**	**41-50**	**51-60**	**≥61**	**Total**
Group								
A. Tuberculous	NO.	27	48	43	11	4	2	135
	%	20%	35.56%	31.85%	8.15%	2.96%	1.48%	100%
B. Malignant	NO.	0	0	2	8	6	13	29
	%	0%	0%	6.9%	27.59%	20.69%	44.82%	100%
C. Other	NO.	2	6	11	5	6	6	36
	%	5.55%	16.67%	30.55%	13.89%	16.67%	16.67%	100%

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Total	NO.	29	54	56	24	16	21	200
	%	14.5%	27%	28%	12%	8%	10.5%	100%

Mean age of the study subjects was 37.04±16.87 years (Mean± SD). More than 55% patients were in between 21-40 years. There were 18% of patients having age ≥51 years of which 10.5% were having age more than 60 years. The mean age of patients with Tuberculous pleurisy (Group A) was 30 ±10.5years. 67.41%of the patients in with tuberculous effusion were present in age group of 21 to 40 years. Majority (44.8%) of patients from Malignant effusion (Group B) present in age group of ≥60 years with 61±14yrs as mean age of presentation. There was varied age group distribution for group C patients which peaked in 31 to 40 years of age.

TABLE 3: Significance of age

Table indicating characteristics of age of presentation amongst Tuberculous n1=135) and malignant (n2=29) pleural effusion patients –

	Age in years		
	≤40	>40	
Tuberculous	118(87.40%)	17(12.60%)	135(100%)
Malignant	2 (6.90%)	27(93.10%)	29(100%)
P-value	< 0.00001		164(100%)
Chi-square Test			

87.40% of patients with tuberculous effusion (n1=135) had age ≤ 40 years and 93.10% of patients with malignant effusion (n2=29) were from age group of > 40 yrs. In present study, patients with Tuberculous effusion present significantly amongst the younger age groups (≤40 years) and the malignant effusion patients were significantly present in age group of more than 40 years (P< 0.00001).

TABLE 4: **Presenting symptoms in the study subject**

The symptomatology of study subjects noted as following

Symptoms / **Group**		Breathlessness	Fever	Cough	Expectoration	Chest Pain	Haemoptysis	Wt. Loss
A. Tuberculous	NO	47	95	88	19	70	2	37
(n1=135)	%	34.81%	70.37%	65.18%	14%	51.85 %	1.5%	27.4 %
B. Malignant	NO	25	6	11	0	20	9	7
(n2=29)	%	86.20%	20.68%	37.93%	0%	69%	31%	24.1 %
C. Other	NO	29	14	21	3	14	2	1
(n3=36)	%	80.55%	53.84%	58.33%	8.33%	38.89 %	5.55%	2.78 %
Total	**NO.**	**101**	**115**	**120**	**22**	**104**	**13**	**45**
	%	50.5%	57.5%	60%	11%	52%	6.5%	22.5 %

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Most common symptom of presentation amongst all study subjects (N=200) was cough present in 120 (60%) patients, fever was present in 115(50.5%) patients, 104 (52%) patients had chest pain, breathlessness was noted in101 (50.5%) patients, 45(22.5%) patients had weight loss, 22(11%) patients had expectoration, haemoptysis was present in 13(6.5%) patients.

In Group A Tuberculous effusion (n1=135) fever was most common presenting symptom noted in 95(70.37%) patients followed by cough in 88(65.18%) patients and chest pain in 70(51.85%) patients. In Group B Malignant effusion (n2=29) breathlessness was most common presentation noted in 25(86.20%) patients, 20(69%) patients had chest pain. In Group C patients of pleural effusion with etiology other than malignancy and tuberculosis (n3=36) present with breathlessness in 29 (88.55%) followed by cough in 21 (58.33%) and fever in 14 (53.84%) patients.

TABLE 8: Radiologically assessed severity of pleural effusion

Radiologically assessed severity of pleural effusion tabulated as following-

Severity		**Mild**	**Moderate**	**Massive**	**Total**
Group					
A. Tuberculous	NO	62	69	4	135
(n1=135)	%	45.93%	51.11%	2.96%	100%
B. Malignant	NO	1	12	16	29
(n2=29)	%	3.45%	41.38%	55.17%	100%
C. Other	NO	24	8	4	36
(n3=36)	%	66.67%	22.22%	11.11%	100%
Total (N=200)	NO.	87	89	24	200
	%	43.5%	44.5%	12%	100%

Amongst all 200 patients 89(44.5%) had moderate effusion, 87(43.5%) patients had mild effusion whereas massive effusion was noted in 24(12%) patients. In Group A patients (n1=135) – 69(51.11%) patients had effusion with moderate severity; mild effusion was present in 62(45.93%) patients, 4(2.96%) had massive effusion. In Group B (n2=29) - common presentation was massive effusion noted in 16(55.17%) patients, followed by moderate effusion in 12(41.38%) patients and mild collection only in 1(3.45%) patient. For Group C (n3=36) – 24(66.67%) patients had effusion of mild severity, moderate effusion noted in 8(22.22%) patients and massive effusion was present in 4 (11.11%) patients.

Pleural fluid analysis

Table 5: Appearance of Pleural Fluid

Appearance of fluid		**Clear**	**Straw**	**Haemorrhagic**	**Purulent**	**Total**
Group						
A. Tuberculous	NO	0	131	0	4	135
(n1=135)	%	0%	97%	0%	3%	100%
B. Malignant	NO	0	5	24	0	29
(n2=29)	%	0%	17.24%	82.76%	0%	100%

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C. Other	NO	4	24	4	4	36
(n3=36)	%					

Overall 160(80%) pleural fluid samples were straw in colour, 28(14%) were haemorrhagic, 8(4%) were purulent and 4(2%) were clear in appearance. In Group A, most of tuberculous effusion were straw in colour noted in 131(97%) patients and remaining 4 (3%) patients had purulent fluid. For Group B Haemorrhagic effusion present in 24(82.76%) patients with malignant effusion and remaining 5 (17.24%) patients had straw coloured pleural fluid. In Group C, Straw coloured pleural fluid was present in 24(66.67%) patients. Clear, Haemorrhagic and Purulent fluid noted in 4 (11.11%) patients each.

TABLE 6: Genexpert assay

In view of evaluation of Genexpert assay in the diagnosis of Tuberculous pleural effusion, we re-categories the study population as following - the Study Group B and C were combined and referred as Non tuberculous Group.

The newly formed Non tuberculous group then compared with Group A i.e. Group of Tuberculous effusion for the further assessment.

a) Table for Detection of Tuberculous Pleural Effusion by GENEXPERT Test

Disease	**Tuberculous**	**Non Tuberculous**	**Total**
Gene Xpert			
MTB Result			
Positive	49	0	49
Negative	86	65	151
Total	135(67.5%)	65(32.5%)	200(100%)

Among all 135 cases of Tuberculous pleural effusion GeneXpert assay was positive for MTB in 49 patients and 86 patients had Negative GeneXpert assay result. All patients with nontuberculous effusion group noted that had negative result for GeneXpert assay

Sensitivity=49/135*100=36.30%

Specificity=65/65*100=100%

b) Table for prevalence of RIF Resistant tuberculous pleural effusion.

Genexpert Result		**MTB Detected**	**MTB Not Detected**
1	Rif sensitive	47(34.81%)	
2	Rif Resistant	2(1.49%)	
	Total(n1 =135)	49(36.30%)	86(63.70%)

Amongst Tuberculous pleural effusion patients 1.49% of patients had RIF Resistant tuberculous effusion or Multidrug resistant tuberculous effusion whereas 34.81% of patients were diagnosed with Rif sensitive tuberculous effusion 63.70% patients with Tuberculous effusion had Negative GENEXPERT Test report.

Discussion

The most common etiology of effusion in this study was tuberculosis noted in 67.5%of study population followed by malignant effusion in14.5% and transudative effusion in 10.5% This is similar to the observation in another study from India by **Parikh P et al (2016)** [8] where they showed that the tubercular effusions constitute 62% of the effusions, malignancy 18%, and para pneumonic effusion 10%, transudative effusion 6%. This is consistent with the fact that in India tuberculosis is the most common cause of pleural effusion. This observation is

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different from that of the study from the Western world where the incidence of malignant effusion and para pneumonic effusion are much higher compared to that of tuberculous effusion; as showed in a study by **Santiago Romero et al (1993)[9]** Malignant effusion constitute 44.5% of effusion followed by Synpneumonic effusion in 16.5% Transudative effusion in 14.5% and Tuberculous effusion in 14.5% of study population. **Group A** which included patients with tuberculous pleural effusion which were 67.5% of total study population **Group B** had all the patients with malignant pleural effusion and it was 14.5% of total study population. **Group C** had patients with etiology other than tuberculosis and malignancy i.e. all non-tuberculous non-malignant pleural effusions and they constitute 18% of total study population.

The present study population had mean age similar to the studies of **Parikh P et al [8]** and **John K. Lusiba.[10]** Whereas studies of **F.Y. Khan[11]** and **Romero et al**[9] had mean age much higher than the present study. In the present study patients with tuberculous pleurisy were younger than patients with nontuberculous aetiology. 87.4% of patient with tuberculous pleurisy were <40 years of age, whereas 93.1% of patients with malignant effusion were from the age group of >40 years. Hence, the present study revealed that the prevalence of tuberculous pleurisy was significantly higher in younger study population and the prevalence of malignant effusion was significantly high amongst study population older than 40yrs of age (p-value is <0 .00001). The mean age of patients with Tuberculous pleurisy was 30yrs±10.5yrs. This finding was consistent with **Sharma S K (2001)[12]** mean age 33 ±14.4 years, **Arif Rahim et al (2002)[13]** mean age of 28.7± 9.73 yrs. Group B-Malignant effusions in this study were seen in older age group with mean age 61±14yrs. This finding similar with study findings by **Dr. Vasireddy Aruna (2018)[14]** where 64 years as mean age of patients with malignant pleural effusion was noted along with conclusion that patients with tubercular effusion were much younger than those with malignant effusions (mean age 36.54±12.91 Vs 52.43±13.49) which correlate with the present study. Group C of patients with effusion of benign, non-infectious and infectious (except tuberculosis) etiology were more common in age group 31-40yrs and >61 years in the present study. Similarly, **Luis Valde´s (1996)[15]** suggest that the proportion of effusion secondary to congestive heart failure rose steadily in the 0- to 30-year-old age group to a peak among 60- to 70-year-olds.

Group A with Tuberculous pleural effusion presented with fever in 70.3% of patients, cough in 65.1% of patients with weight loss in 27.4% of patients. Similar presentation of symptoms was seen in study by **A. Dambal (1998)[16]** with 97% tuberculous pleurisy patients present with cough followed by Fever in 91%, dyspnoea in 91%. In Group B- malignant effusion were present with complaint of breathlessness in 86.2% followed by chest pain in 69%. In Group C - pleural effusion with etiology other than malignancy and tuberculosis most common presenting symptom was breathlessness noted in 88.55% followed by cough present in 58.33% of patients.

43.5% of the patients in present study had mild pleural collection, 44.5% of the patients had moderate pleural effusion and 12% of patients had massive effusion. In group of tuberculous etiology 45.93% patient had mild effusion and 51.11% of patients had moderate effusion.

Group of malignant pleural effusion had moderate collection in 41.38%of patients and massive collection in 55.17% of patients. In Group of pleural effusions other than tuberculosis and malignancy- 66.67% of patients had mild pleural effusion. **Bhavsar Kaushal M et al (2016)[7]** reported that 50% patients had moderate pleural effusion and 30% had mild while 20% had large pleural effusion. Majority of the tuberculous (63.3%) patients presented with moderate effusion while in malignant effusion (55.6%) had large effusion.

In present study 80% of pleural fluids were straw in colour followed by haemorrhagic fluid which noted in 14% of samples. These findings were similar with study done by **Victoria**

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Villena (2004)[17] for Clinical Implications of Appearance of Pleural Fluid at Thoracentesis where they noted that 80% of fluid fitted in to category of serous and blood tinged fluids. **Bhavsar Kaushal M (*2016)***[7] observed 68% of patients had turbid appearance of pleural fluid, 16% had clear appearance and 16% had haemorrhagic appearance. Turbidity was present in 84.85% patients of tuberculous effusion. Similarly, in present study maximum number of patients (97%) with tuberculous pleural effusion had straw coloured appearance.

In group of malignant pleural effusion 82.76% of patients had haemorrhagic fluid and remaining 17.24% patients had straw coloured pleural fluid. **Bulent Ozcakar (2010)**[18] studied fluid appearance measurements in pleural effusions of patients with cancers and noted that 43.6% of patients had haemorrhagic and 56.4% non-haemorrhagic pleural fluid samples. For present study group C of non-tuberculous non-malignant effusion 66.67% of pleural fluids were of straw colour and remaining were, clear, haemorrhagic and purulent in 11.11% patients each.

Genexpert report and Genexpert assay was negative for 86 patients out of 135 cases of tuberculous pleural effusion and all cases (65) from group of non-tuberculous pleural effusion. The multidrug resistant tuberculous pleural effusion noted in 1.49% of patients. The sensitivity and specificity of Genexpert assay for present study obtained as 36.30% and 100% respectively. When compared with previous studies such as **Reechaipichitkul et al. (2000)**[19] observed sensitivity and specificity of 50% and 61%for PCR testing in diagnosis of tuberculous pleural effusion and had PCR positive in 100% of culture positive TB effusion and only in 30-60% of culture negative pleural fluid. **Chakravarthy et al. (2005)**[20] studied diagnosis of extra-pulmonary tuberculosis, and amongst tuberculous pleural effusion patients 75.47% were PCR positive cases (40/53), with a sensitivity of 75.5% and specificity of 93.8%, PPV of 97.6% and NPV of 53.6% for PCR test. **Kuan-Ting Liu (2006)**[21] out of 163 patients enrolled, PCR was positive in 43.4% of patients with TB pleurisy and 4.5% of patients with non-TB pleurisy and noted sensitivity and specificity of 43.4% and 95.5%, respectively. **Rhoda Lynn et al. (2008)**[22] observed 50.70% PCR positive cases (36 PCR positive in 71 patients) with sensitivity and specificity of 61% and 75% respectively.

Conclusion

From the above study we can conclude that Tuberculosis was the most common cause of pleural effusion followed by malignancy and these findings coincide with the findings from other studies which performed in areas of high tuberculosis prevalence. The Genexpert assay had low sensitivity but high specificity. The high specificity denotes potential role of assay in confirming diagnosis of tuberculous effusion rather than ruling out the tuberculosis. The assay had important role in rapid detection of rifampicin resistance in patients from high tuberculosis prevalence settings. Hence, along with diagnostic utility, Genexpert had key role in timely initiation of appropriate anti-tubercular therapy.

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