

Adenosine Deaminase and Interferon Gamma in Diagnosis of Tubercular Pleural Effusion in Chronic Kidney Disease (CKD) Patients

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ABSTRACT

Background: One of the major causes of pleural effusion is Tuberculosis (TB) which has lymphocytic and exudative characteristics. Approximately 20% of all cases of pleural effusion go undiagnosed. Traditional diagnostic methods have a low yield. New techniques used are chemical markers such as interferon-gamma and adenosine deaminase (ADA) that are produced during the inflammatory process. Pleural effusion is a common diagnostic dilemma as it may arise from CKD. The current study was undertaken to study the efficacy of ADA, Interferon gamma and Lymphocyte count individually and in their combination in CKD patients in diagnosing tubercular pleural effusion. ADA in combination with interferon –gamma.

Methodology: This observation, cross-sectional study was conducted over a period of 18 months, subjects were recruited based on the primary diagnosis of CKD (Stage 3-5) with pleural effusion. A total of 50 patients were included divided into two groups those with tubercular pleural effusion and patients with non-tubercular effusion. The single specimen of pleural fluid (50-100ml) was aspirated for cell count, ADA level and Interferon- gamma levels.

Results: Majority of patients in both the groups were diagnosed with stage 5 chronic kidney disease and were in the age group of 41-60 years, with 37 males and 13 females. Mean values of ADA, lymphocyte count, Interferon gamma in tubercular pleural effusion cases were significantly higher as compared to other group. The combination of ADA and Interferon gamma was found to have highest sensitivity and

most specific was the combination of ADA, Interferon gamma and lymphocyte/ neutrophil ratio and ADA was found to be the most sensitive test and Interferon gamma being more specific.

Conclusion: Thus, in our study there was a significant association of Interferon gamma levels in differentiating tubercular pleural effusion and Interferon gamma was more sensitive than ADA and ADA being more specific but the combination of ADA and interferon gamma increased the sensitivity in comparison to individual methods.

Key words: Tuberculosis; Pleural Effusion, Adenosine Deaminase, Interferon - Gamma.

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INTRODUCTION

Pleural effusion is the abnormal accumulation of fluid in the pleural space and indicates the presence of an underlying disease.¹ Pleural fluid accumulates when formation exceeds pleural fluid absorption² and is categorized as a transudative (result from systemic diseases) or exudative (result from local or systemic diseases that directly injure the pleural surface).

One of the major causes of pleural effusion accounting for 30-60% is Tuberculosis (TB) which has lymphocytic and exudative characteristics. One of the most common extra pulmonary manifestations of tuberculosis in U. S is tuberculous pleural

effusion (TPE) accounting for 2 to 5% of all pleural effusions which is approximately 1000 cases per year.³ Thereby it is prudent to consider the possibility of tuberculous pleuritis in all patients with an undiagnosed pleural effusion.⁴ Approximately 20% of all cases of pleural effusion go undiagnosed and treatment in such cases is adopted solely based on clinical criteria. In countries where there is high incidence of TB, the clinical profile of pleural TB has a high positive predictive value but where the prevalence of TB is lower, there always stand a higher risk of incorrect long-term use of potentially toxic pharmaceuticals.⁵

Traditional diagnostic methods are helpful for the diagnosis of pulmonary TB but have a low yield when applied to pleural fluid, detection of acid-fast bacilli (AFB) by the Ziehl-Neelsen or similar method is positive in less than 5% of cases and the culture on Löwenstein-Jensen medium does not surpass a 40% positivity rate.⁶

Due to difficulty in diagnosing pleural TB there has been an extensive search for methods that would optimize the workup of pleural effusion patients with suspected TB. Some such new techniques used are chemical markers such as interferon-gamma and adenosine deaminase (ADA) that are produced during the inflammatory process triggered by the *M. tuberculosis*. ADA is a group of enzymes of different molecular weights that have similar chemical functions in the purine metabolism that is to catalyze the conversion of adenosine and deoxyadenosine into inosine and deoxyinosine.⁷

At this moment a universal ADA cutoff value for pleural fluid which may be adopted as reference, has yet to be established as results vary widely from country to country and even among different health facilities within a given region. So the establishment of an ADA cutoff value for the diagnostic test of pleural TB should be regionalized due to different prevalence of TB and other diseases yet to be elucidated among pleural effusion patients. As such the recommended cut-off value of ADA is 40 units per liter (U/L).⁸

Another chemical marker for diagnosis is Interferon-gamma (IFN- γ) which is an important immune regulator that exhibits both antiviral and cytotoxic activities. It is produced by T lymphocytes in response to stimulation with specific antigens or non-specific antigens and is capable of modifying the response of other cells to the immune system.⁹ It is regarded as immunoregulatory cytokine and found to have clinical application as an immune-stimulator in chronic granulomatous diseases. A delayed hypersensitivity type of response to mycobacterial antigens in pleural space leads to localization of activated T lymphocytes in pleural space and production of large amounts of IFN- γ .¹⁰ Interferon gamma plays a fundamental role in the immune response to tuberculosis and high level in tuberculous pleural effusion have recently been attributed to in situ stimulation of T4 lymphocytes by tuberculous antigen.¹⁰

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal renal function and a progressive decline in glomerular filtration rate (GFR). Pleural effusion in such patients is a common diagnostic dilemma as it may arise from CKD itself (fluid overload, nephrotic syndrome, uraemic pleurisy), concomitant infections (especially tuberculosis (TB) in our country), pulmonary embolisms or diseases causing pleuro-renal syndromes like systemic lupus erythematosus.¹¹ Uraemic pleurisy is a diagnosis of exclusion that persists or recurs despite aggressive haemodialysis.¹²

Management of TB raises issues of drug dosing and interactions, especially in renal transplant recipients. Most studies looking into the incidence of pleural effusion in patients with CKD are retrospective studies of hospitalized patients on long-term dialysis.¹³

The current study is being undertaken to test the hypothesis that pleural effusion in CKD patients can be tubercular and to study the efficacy of ADA, Interferon gamma and Lymphocyte count individually and in their combination in such patients in diagnosing tubercular pleural effusion.

AIMS

The aim of the present study was to evaluate the use of Adenosine Deaminase (ADA), interferon gamma and lymphocyte count in diagnosing tubercular pleural effusion in patients with chronic kidney disease.

METHODOLOGY

The observation, cross-sectional study was conducted in the Department of Pulmonary Medicine and Nephrology Department, Himalayan Institute of Medical Science (HIMS), Swami Ram Nagar, Dehradun. The duration of study was 18 months, and over a period of 12 months, subjects were recruited based on the primary diagnosis of CKD (Stage 3-5) with pleural effusion. Prior to recruitment of the patients, the study was approved by the Institutional Ethics Committee. Only those patients were recruited in the study who were willing to give written informed consent. The study comprised of 50 patients of CKD with pleural effusion who satisfied the inclusion criteria.

All patients more than 18 years of ages of either sex diagnosed with chronic kidney disease (Stage 3-5) with exudative pleural effusion were included in the study. Patients with transudative pleural effusion, turbid or frank pus in pleural effusion and suffering from chronic kidney disease (stage 1 or 2) were excluded from the study.

A total of 50 patients were included in our study. 25 patients were those diagnosed to have CKD with tubercular pleural effusion forming group I and equal number i.e. 25 patients of CKD with non-tubercular effusion forming group II over a period of one year. The 18 month period for the entire study was used for further patient evaluation, data analysis, interpretation and thesis writing. All the patients attending Nephrology / Pulmonary Medicine outpatient department or admitted in the medical wards, diagnosed as a case of CKD with pleural effusion were taken up. CKD staging was done as per Glomerular Filtration Rate (GFR) estimated by MDRD equation:

$GFR (ml/min/1.73m^2) = 175 \times (\text{Serum Creatinine})^{-1.154} \times (\text{Age})^{-0.203}$
(The above equation was multiplied by 0.74 in case of females)

Table 1: Staging for Chronic Kidney Disease

CKD Stage	GFR Level (ml/min/1.73m ²)
Stage 1	>90
Stage 2	60-89
Stage 3	30-59
Stage 4	15-29
Stage 5	<15

Pleural fluid of these patients was aspirated with pleural tapping done either by needle aspiration under local anesthesia or intercostal drainage tube as per clinical condition. The aspirated fluid was subjected to cell count, sugar, protein and LDH examination to distinguish between transudative and exudative pleural effusion. Patients with transudative pleural fluids and purulent effusions were further excluded from the study after routine pleural fluid analysis (gross examination and Light's criteria). The remaining patients found to have exudative pleural effusion underwent further evaluation and investigation to find out the etiology of pleural effusion.

Demographic and anthropometric indices were recorded in subject proforma, relevant medical history was taken involving present

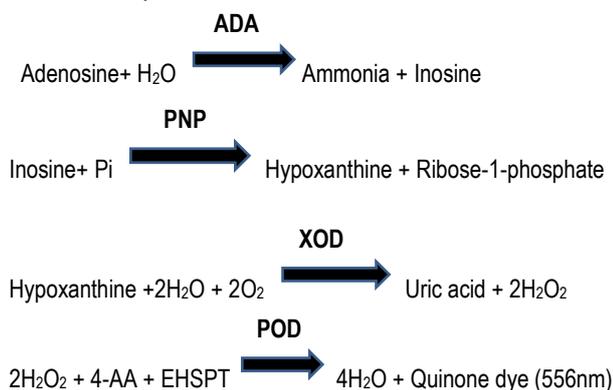
illness, past illness, personal and family history with clinical examination was done. The aspirated pleural fluid was subjected to AFB examination and sputum examination for AFB was also performed.

Patients in group I were those with etiologic diagnosis of exudative pleural effusion due to tuberculosis; whereas patient in group II had pleural effusion of etiology other than tuberculosis. The single specimen of pleural fluid (50-100ml) was aspirated for cell count, ADA level and Interferon- gamma levels.

ADA activity

Diazyme’s ADA assay is based on the enzymatic deamination of adenosine to inosine which is converted to hypoxanthine by purine nucleoside phosphorylase (PNP). Hypoxanthine is then converted to uric acid and hydrogen peroxide (H₂O₂) by xanthine oxidase (XOD). H₂O₂ is further reacted with N-Ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline (EHSPT) and 4-aminoantipyrine (4-AA) in the presence of peroxidase (POD) to generate Quinone dye which is monitored in a kinetic manner. The absorbance was read against water at 556 nm using chemistry analyzers.

The entire enzymatic reaction scheme is:



One unit of ADA is defined as the amount of ADA that generates one micromole of inosine from adenosine per min at 37°C.

Reagent: Working Solutions

Reagent 1	
Tris HCl, pH 8.0	50mM
4- AA	2mM
PNP	0.1 U/ml
XOD	0.2 U/ml
Peroxidase	0.6 U/ml
Stabilizers	
Reagent 2	
Tris HCl, pH 4.0	50mM
Adenosine	10mM
EHSPT	2mM

Interferon-gamma was detected by ELISA kit – It’s a solid phase sandwich ELISA for in-vitro qualitative and quantitative determination of Interferon gamma in supernatants, buffered solution or serum and plasma samples and other body fluids. This assay recognizes both natural and recombinant human Interferon gamma.

Statistical Analysis

The data was analyzed using SPSS software version 22.0 and Medical Interpretation and analysis of obtained results were carried out using descriptive statistics. Qualitative data was expressed in terms of frequency. Quantitative data was expressed

in term of mean ± SD. Student ‘t’ test was used to compare means of ADA, Interferon-gamma, lymphocyte count between groups. A p value of <0.05 was considered statistically significant.

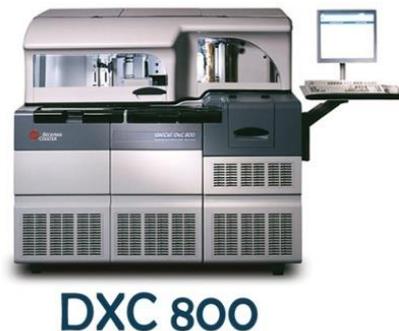


Figure 1: ELISA reader by BIORAD

RESULTS

A total of 50 patients completed the study out of which 37 were males and 13 females. Patients in Group I had tubercular pleural effusion, while patients in Group II had exudative pleural effusion due to malignancy (n=4), uremia (n=5), para pneumonic effusion (n=9) and cardiac failure (n=7). Majority of patients in both the groups were diagnosed with stage 5 chronic kidney disease: 23 in Group I and 24 in Group II, all the other patients suffering from stage 4 chronic kidney disease i.e. 2 in Group I and 1 in Group II.

The distribution of patient as per age in both groups is shown in Figure 2, majority of the patients in both groups were in the category of 41-60 years (11 in Group I and 13 in Group II)

Out of 25 patients with tubercular pleural effusion, 20 were males and 5 were females, and in pleural effusion due to other causes out of 25 included 8 females and 17 males.

Mean values of ADA, lymphocyte count, Interferon gamma in tubercular pleural effusion cases was 59.48, 73.60 and 349.32 respectively and in pleural effusion due to other causes was 26.86, 68.80 and 53.17 respectively.

It was also found that intergroup difference of Interferon gamma most statistically significant among all parameters (p < 0.0001) as shown in Table 2.

Sensitivity, Specificity, positive predictive value (PPV), negative predictive value (NPV) of ADA, Interferon gamma and lymphocyte/neutrophil ratio (using a cut off for all these three biomarkers)

In our present study we used a cut off of 40.4 IU/L for ADA, 110 pg/ml for Interferon gamma, 1.5 for lymphocyte/neutrophil ratio according to the ROC curve and the sensitivity, specificity, PPV and NPV were calculated. For ADA the sensitivity, specificity, PPV, and NPV were 100%, 76%, 80.65%, and 100% respectively, for Interferon gamma the values were 92%, 92%, 92%, and 92% respectively and for lymphocyte/neutrophil ratio it was 68%, 56%, 60.71%, and 63.64% respectively.

Sensitivity, Specificity, PPV, NPV of Three Biomarkers in Various combinations is shown in Table 3. The combination of ADA and Interferon gamma was found to have highest sensitivity to detect pleural effusion due to tuberculosis and most specific was found to be the combination of ADA, Interferon gamma and lymphocyte/neutrophil ratio and ADA was found to be the most sensitive test and Interferon gamma being more specific.

FLOW DIAGRAM FOR PATIENTS

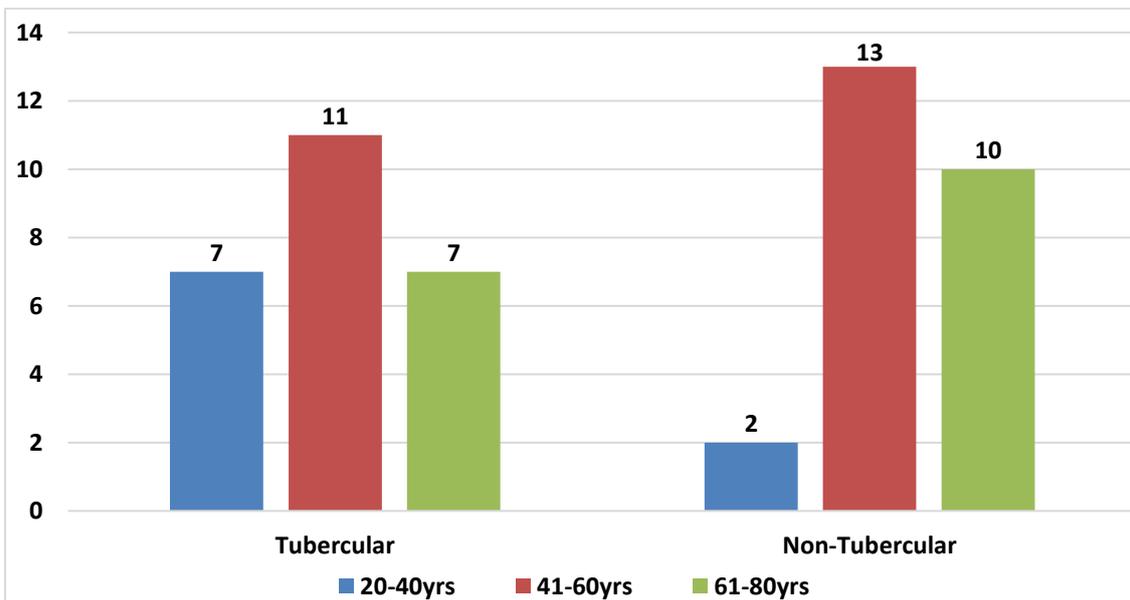
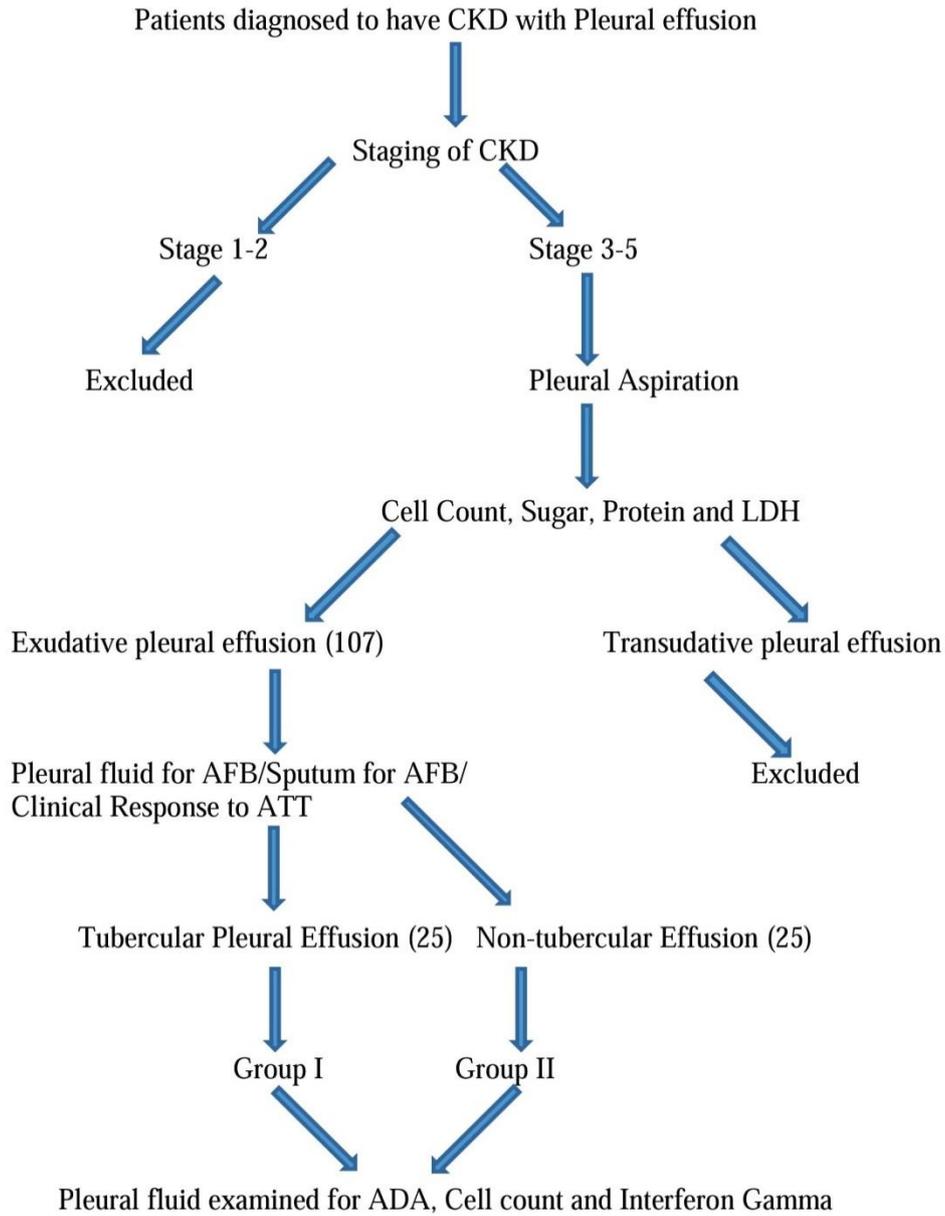


Figure 2: Age-wise Distribution of Cases between Two Groups

Table 2: Mean values of ADA, Lymphocyte count and Interferon-gamma in group-I and group-II (n= 50)

Mean values of ADA, lymphocyte count and interferon-gamma in group-I and group-II				
	Group	Mean \pm SD	Std. Error	P- value
ADA (IU/L)	I	59.48 \pm 16.31	3.26	0.001
	II	26.86 \pm 16.17	3.23	
Lymphocyte Count (%)	I	73.60 \pm 21.39	4.277	0.448
	II	68.80 \pm 22.97	4.594	
Interferon Gamma (pg/ml)	I	349.32 \pm 107.56	21.51	0.001
	II	53.17	19.94	

Table 3: Sensitivity, Specificity, PPV, NPV of various combinations along with Comparison to individual parameters (n=50)

	Sensitivity	Specificity	PPV	NPV
ADA & IFN- γ	100%	68%	75.76%	100%
ADA & L/N Ratio	100%	44%	64.10	100%
IFN- γ &L/N Ratio	100%	20%	55.56%	100%
ADA, IFN- γ &L/N Ratio	100%	16%	54.35%	100%
ADA	100%	76%	80.65%	100%
IFN- γ	92%	92%	92%	92%
L/N Ratio	68%	56%	60.71%	63.64%

DISCUSSION

Pleural effusion is one of most common extrapulmonary manifestations of tuberculosis. Patients with CKD have immune dysfunction manifested by depressed CMI. This impairment of CMI makes infection with Mycobacterium tuberculosis more difficult to detect and more likely to progress to TB disease than in immune competent individuals. The conventional laboratory methods that include direct examination of pleural fluid and Z-N staining which requires bacillary concentrations of 10,000/ml and, therefore, has a low sensitivity (0 to 1%).¹⁴ Although a culture is more sensitive (11 to 50%)¹⁵, it requires 2 to 6 weeks to grow Mycobacterium tuberculosis and a minimum of 10 to 100 viable bacilli. The sensitivity of pleural biopsy specimens is reportedly higher whether by culture (39 to 79%) or histological evaluation (71 to 80%). However, this procedure requires greater expertise, is more invasive, and is subject to sampling error.¹⁶

In our study of 50 patients with pleural effusion, the mean \pm SD of ADA was 59.48 \pm 16.31 in patients with tubercular pleural effusion while in other group (pleural effusion due to other causes) mean \pm SD was 26.86 \pm 16.17 respectively in comparison to study done by Haque et al.¹⁷ and Souvik et al.¹⁸ In our study there was a statistically significant association (p value <0.001) of ADA levels in differentiating tubercular pleural effusion from pleural effusion due to other causes.

We determined the sensitivity and specificity of ADA in patients of tuberculosis with CKD. Using a cut off of 40.4U/L we got sensitivity, specificity, PPV and NPV as 100 %, 76%, 80.65%, and 100% respectively. Levels of ADA above 40 U/L indicate pleural tuberculosis with sensitivity 81 to 100% and specificity 83 to 100%¹⁸⁻²⁰ in few studies done in patients with tuberculous pleural effusion. A study done by Kumar et al.²¹ showed the sensitivity and specificity of ADA for the diagnosis of tuberculosis as 66.7 and 90 per cent respectively, and Krenke R et al.²² calculated sensitivity 100% and specificity 93.9% respectively.

In our study the mean \pm SD of Interferon gamma, lymphocyte count was 349.32 \pm 107.5, 73.60 \pm 21.39 in patients with tubercular pleural effusion and in other group (pleural effusion due

to other causes) mean \pm SD was 53.17, 68.80 \pm 22.22 respectively, in comparison to the study done by Krenke R et al.²³ the calculated mean \pm SD in tuberculous pleural effusion was 614.1 \pm 324.5 and in non tuberculous pleural effusion was 15.1 \pm 36.0. Using a cut off 110 pg/ml in our study for interferon gamma the sensitivity, specificity, PPV, NPV were 92%, 92%, 92%, 92% respectively comparable with the study of Wongtim S et al.²⁴ and Krenke R. et al.²²

Very few studies have been done on combination of ADA and lymphocyte/neutrophil ratio we have explored this combination and calculated the sensitivity, specificity, PPV, NPV which were comparable with the data of study done by Lesley J. Burgess et al.²⁵ In our study the calculated sensitivity, specificity, PPV, NPV of this combination by using lymphocyte/neutrophil ratio of 1.5 as per ROC curve was 100%, 44%, 64.10%, 100% respectively and in comparison to study done by Lesley J. Burgess et al. using cut off lymphocyte/neutrophil ratio of 0.75 or greater in 303 patients the sensitivity, specificity, PPV, NPV was 88%, 95%, 95%, 88% respectively.

A study done by Villegas MV et al.¹⁴ they evaluated Polymerase Chain Reaction, ADA, and Interferon-gamma in Pleural Fluid for the differential diagnosis of pleural tuberculosis and found that combination of two methods, with a positive result by either two of the methods considered to be indicative of a positive diagnosis of pleural tuberculosis, increased the diagnostic sensitivity over all individual methods. Interferon-gamma levels in combination with ADA activity the sensitivity, specificity, PPV, NPV was 90.5%, 73.8%,77.6%, 93.4% respectively and in our study it was 100%, 68%, 75.76%, 100% respectively.

Thus, in our study there was a statistical significant association (p value <0.0001) of Interferon gamma levels in differentiating tubercular pleural effusion from pleural effusion due to other causes. On comparison of individual and combination test in our study, it is found that Interferon gamma more sensitive than ADA and ADA being more specific but the combination of ADA and interferon gamma increased the sensitivity in comparison to individual methods.

Therefore, the challenge of diagnostic efficiency in different circumstances of prevalence may be addressed using combinations of these rapid methods on pleural fluid. ADA and Interferon gamma measurement are simple, we believe that the results of this study demonstrate that individually and in combination, these methods can offer a means of obtaining diagnostic efficiency.

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