

ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN IN THE DIAGNOSIS OF TUBERCULOUS PLEURAL EFFUSION

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INTRODUCTION

Pleural Tuberculosis(TB) is a common cause of pleural effusion in India[1]. The diagnosis of Tuberculous pleural effusion (TBPE) is usually made by demonstrating Mycobacterium tuberculosis in pleural fluid or sputum. Histopathological demonstration of granulomas in the pleural biopsy specimen can also be used[2]. Mycobacterial smears and cultures of pleural fluid are frequently negative, so various biochemical parameters are used in the early diagnosis of TBPE[3].

The diagnostic value of pleural fluid ADA(Adenosine Deaminase) in TBPE was evaluated by many studies and it is widely accepted as a diagnostic marker for TBPE[4,5]. But specific equipments required for ADA measurement is not available in developing countries and making this test to perform under high cost. This makes the need for another biochemical marker for diagnosing TBPE, which should be available widely and inexpensive.

The usefulness of pleural fluid C-Reactive Protein in differentiating TBPE from other causes of effusion was evaluated in various studies[6]. It was found that pleural fluid CRP is elevated in inflammatory effusions than in non inflammatory effusions[7]. Some studies have also proved that CRP levels are higher in tuberculous pleural effusion than in other causes of effusion[8].

This study was conducted to determine the role of pleural fluid CRP in comparison with that of pleural fluid ADA values in the diagnosis of patients with TBPE.

MATERIALS & METHODS

This study “ROLE OF PLEURAL FLUID C-REACTIVE PROTEIN IN THE DIAGNOSIS OF TUBERCULOUS PLEURAL EFFUSION” was conducted in Department of Respiratory Medicine, in a Tertiary care Hospital, after obtaining approval from Institutional Ethical Committee.

Study design: Observational study

Study duration: One year

Study population: Patients with pleural effusion from outpatient and inpatient Departments of Tirunelveli Medical College Hospital, presented to Department of Respiratory Medicine.

Inclusion criteria:

Patients with pleural effusion who are giving informed written consent

Exclusion criteria:

- 1) Patients who are not willing for informed consent/thoracentesis
- 2) Patients with undiagnosed etiology of pleural effusion
- 3) Patients with minimal pleural effusion

After obtaining informed written consent, patient details, history, radiological findings and relevant investigations were recorded. Routine Blood and Sputum investigations were done. Diagnostic thoracentesis was performed with a 16-gauge needle after local anaesthesia. About 50 ml of pleural fluid was aspirated and sent for biochemistry (including ADA, CRP), cytology, gram stain, culture & sensitivity, AFB(acid Fast Bacilli) and NAAT (Nucleic Acid Amplification Test). Pleural fluid ADA levels were measured by BIOSYSTEM A15 AUTOANALYZER by enzymatic method. ADA levels were reported in U/L. Pleural fluid CRP levels were measured by BIOSYSTEM A15 AUTOANALYZER by utilizing immunoturbidimetric method. CRP values were expressed in mg/L.

Patients were classified into Tuberculous pleural effusion and Non tuberculous pleural effusion as follows:

1.Tuberculous pleural effusion:

Patients were diagnosed as tuberculous pleural effusion by one and/or more of the following criteria:

- (i)Sputum AFB smear positive
- (ii)Sputum for CBNAAT showing the result of Mycobacterium tuberculosis detected
- (iii)Pleural fluid AFB smear positive
- (iv)Pleural fluid CBNAAT showing the result of Mycobacterium tuberculosis detected
- (v)Pleural fluid ADA levels more than 70 U/L
- (vi)Pleural fluid ADA levels between 40 – 70 U/L and lymphocytic effusion
- (vii)ADA levels > 40 U/L, strong clinical suspicion, no other alternative diagnosis was made on follow up, and response to ATT.

2.Non Tuberculous pleural effusion:

Patients with Parapneumonic pleural effusion, Malignant effusion and Transudative effusion were included as Non Tuberculous pleural effusion.

Stastical analysis:

Patient characteristics , pleural fluid parameters, pleural fluid ADA and CRP levels were compared between the Tuberculous and Non Tuberculous pleural effusion and analyzed by SPSS software system.

RESULTS

93 patients were presented with pleural effusion during the study period, 15 patients were excluded from the study with exclusion criteria. Among the 78 patients included in the study, 57 were males and 21 were females. Final diagnosis of the study population is illustrated in (Figure 1).

Basic characteristics and radiological findings of the study population are given in Table 1. No significant difference was observed among tuberculous and non tuberculous pleural effusion groups except age and smoking history.

Pleural fluid ADA and CRP levels in four diagnostic groups:

Pleural fluid CRP and ADA levels in four diagnostic groups were illustrated in Figure 2. It was found that mean pleural fluid CRP levels were highest in parapneumonic effusion, followed by tuberculous, malignant and transudative effusion. Whereas Pleural fluid ADA levels were observed to be highest in tuberculous effusion followed by parapneumonic, malignant and transudative effusion.

Pleural fluid ADA and CRP in Tuberculous pleural effusion:

Pleural fluid ADA and CRP levels were higher in tuberculous effusion with statistically significant p values of <0.0001 and 0.033 respectively (Table -2). Pleural fluid CRP levels were compared with pleural fluid ADA levels in patients with TBPE, and it was found to be no significant correlation was observed between the two mentioned values (Figure 3).

For the diagnosis of TBPE, when the pleural fluid ADA cut off value of 40 U/L was used, the sensitivity and specificity was 80.77% and 84.62% respectively. Whereas if pleural fluid CRP cut off value of 30 mg/L was used, the sensitivity and specificity was 67.31% and 61.54% respectively.

Pleural fluid CRP levels in TBPE had significant difference with malignant and transudative effusion, no significant difference was noted in patients with parapneumonic effusion. Pleural fluid ADA levels in TBPE had significant difference with that of parapneumonic effusion, malignant effusion and transudative effusion (Table 3).

Pleural fluid CRP values in Parapneumonic effusion:

Pleural CRP levels were higher in parapneumonic effusion than in other types of effusion including tuberculosis (54.39 vs 35.58) and it was statistically significant with p value of 0.004 (Table 4).

Pleural fluid CRP values in Malignant and Transudative effusion:

Pleural fluid CRP levels were lower in malignant effusion and transudative effusion than in other types of effusion and it was found to be statistically significant with p values of 0.036 and < 0.0001 respectively. (Table 4).

DISCUSSION

Demonstration of an elevated pleural fluid ADA level is useful in establishing the diagnosis of tuberculous pleural effusion [4]. The role of pleural fluid C-Reactive protein has been evaluated in many studies and it was found that it can be useful to differentiate inflammatory and non-inflammatory effusions [7,9], tuberculous and malignant pleural effusions [3,10,11].

In our study, patients with TBPE had higher pleural fluid ADA levels with mean value of 53.36 ± 14.99 U/L than non TBPE (31 ± 11.36 U/L) and it was statistically significant ($p < 0.0001$). Thus it confirmed the diagnostic usefulness of pleural fluid ADA in TBPE. So ADA measurements in pleural fluid is useful to differentiate tuberculosis from other causes of pleural effusion, similar results were obtained in various studies [4,7,12-15].

Mean pleural fluid CRP value in TBPE was 40.90 ± 17.12 mg/L. The same finding was observed in various studies with mean pleural fluid CRP values ranging from 20 – 66 mg/L [7,8,10,16, 17-20]. It was found that mean pleural fluid CRP levels were highest in parapneumonic effusion, followed by tuberculous, malignant and transudative effusion. Similar findings were observed by Aliya *et al.* and Perlat *et al.* who reported that CRP levels were highest in parapneumonic effusions and high CRP levels were seen in tuberculous pleural effusion than malignant and transudative effusions [7,8].

No significant correlation was observed between pleural fluid CRP levels with pleural fluid ADA levels in TBPE. This is in contrast to Vihari *et al.* who showed that pleural fluid ADA and CRP levels had a statistically significant positive correlation[16].

Kim *et al.*[12] and Aliya *et al.*[7] showed that with the cut off value of ADA >40 U/L, the sensitivity and specificity was about 85% & 85% and 91.6% & 89.3% respectively. Bhoumik *et al.* concluded in their study that the sensitivity and specificity of ADA test was 94% and 88% , with the cut off value of 40 U/L[14]. In our study when the cut off value of 40 U/L was used, the sensitivity was 80.77% and specificity was 84.62%.

Various studies suggest different cut-off values of CRP for the diagnosis of TBPE. Daniil *et al.*[18] showed that TBPE had ADA levels of >45 U/L and CRP levels <40 mg/L in pleural fluid. Moallem *et al.*[10] and Gabhale *et al.*[6] reported that with cut-off value of pleural fluid CRP of 21 mg/L and 51.5 mg/L ,for diagnosing tuberculous pleurisy the sensitivity and specificity was 65.1% & 73.3% and 97.5% & 71.7% respectively. In our study with the cut off value of 30 mg/L, CRP had the sensitivity of 67.31% and specificity 61.54% which was lower than that observed for ADA.

Patients with parapneumonic effusion had a higher mean pleural fluid CRP values(54.38mg/L) than observed in tuberculous effusion(40.9mg/L), malignant effusion(24.75mg/L) and transudative effusion(14.48mg/L). Studies done by Garcia pachon *et al.*, Tatjana *et al.*, Aliya *et al.*, Perlat *et al.*, and Gabhale *et al.* reported the pleural fluid CRP values of 74.0 ,65.40, 73.2, 125.0 and 134.0 mg/L respectively in parapneumonic effusion.[6,7,9,20,21]. Whereas Moallem *et al.* and Ahmed *et al.* reported the mean pleural fluid CRP values of 12 and 20 mg/L in parapneumonic effusion respectively[10,22].

In our study we found that we cannot differentiate parapneumonic and tuberculous effusion by only pleural fluid CRP levels. But it can differentiate parapneumonic from malignant and transudative effusion. It was also found that ADA levels were significantly higher in tuberculous pleural effusion than in parapneumonic effusion(p value 0.030). So combination of the pleural fluid CRP and ADA levels can be used to differentiate tuberculous and parapneumonic effusion from other types of effusion.

OTHER OBSERVATIONS FROM OUR STUDY

When comparing the tuberculous and malignant effusion by CRP values, significant difference(40.90mg/L vs 24.75mg/L, p value <0.05) was noted in our study with lower values found in malignant effusion. Similar results were obtained by Kim *et al.*, Turay *et al.*, Garcia pachon *et al.*, and Chierakul *et al.*, they reported that CRP levels were significantly higher in tuberculous effusion[12,17,19,20] than malignant effusion. Usually malignant effusion and tuberculous effusion present with predominant lymphocytes in cytology. So CRP levels can be used to differentiate malignant pleural effusion from TBPE.

When comparing the CRP levels between transudative and exudative (tuberculous, parapneumonic, and malignant) effusion it was found that, significant difference was noted(14.49mg/L vs 40.79mg/L, p value <0.0001). Similar results were obtained by Ahmed *et al.*[22] and they concluded that CRP levels can be used to differentiate transudative and exudative effusion. Perlat *et al.*[9] showed that pleural fluid CRP levels were less than 15 mg/L in transudate and more than 20 mg/L in an exudate.

Study limitations:

1. Pleural biopsy was not done in patients with TBPE
2. As the study population is limited to patients presenting to Respiratory medicine department, patients with non tuberculous effusion sample size is less which may have introduced some selection bias in our study

In future, further studies with large numbers are needed to assess the diagnostic usefulness of pleural fluid CRP in the evaluation of pleural effusion.

CONCLUSION

Pleural fluid C - Reactive Protein alone does not have a definite role in the diagnosis of tuberculous pleural effusion, but it can be used along with pleural fluid ADA levels to differentiate tuberculous pleural effusion from non tuberculous pleural effusion. In the diagnosis of TBPE, pleural fluid CRP has low sensitivity and specificity than pleural fluid ADA levels. Pleural fluid CRP levels can be used to differentiate malignant pleural effusion from tuberculous effusion, and to differentiate transudative effusion from exudative effusions.

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TABLES:

Table 1 : Basic characteristics of Study population

CHARACTERISTICS	Tuberculous pleural effusion (N=52)	Non Tuberculous pleural effusion (N=26)	p- value
1)Gender - i.Males ii.Females	41(78.8%) 11(21.2%)	16(61.5%) 10(38.5%)	0.559
2)Mean age	37.7 years	51 years	0.000
3)Smoking- i.Smokers ii.Non smokers	17(32.69%) 35(67.31%)	12(46.15%) 14(53.83%)	0.041
4)Alcoholism - i.Alcoholic ii.Non alcoholic	21(40.3%) 31(59.7%)	12(46.15%) 14(53.83%)	0.971
5)Diabetes - i.Present ii.Absent	7(13.5%) 45(86.5%)	8(31%) 18(69%)	0.081
6)HIV Status - i.Positive ii.Negative	3(5.76%) 49(94.24%)	1(3.9%) 25(96.1%)	0.230
7)Radiological findings Side of effusion- i.Right ii.Left iii.Bilateral Quantity of effusion: i.Minimal ii.Moderate iii.Massive	26(50%) 25(48%) 1(2%) 10(19.2%) 38(73.1%) 4(7.7%)	15(57.7%) 11(42.3%) - 5(19.2%) 15(57.6%) 6(23.2%)	0.431 0.172

Table 2: Pleural fluid ADA and CRP in Study population

PLEURAL FLUID PARAMETERS	Mean \pm Std. Deviation		STATISTICAL SIGNIFICANCE
	Tuberculous pleural effusion	Non Tuberculous pleural effusion	
CRP (mg/L)	40.90 \pm17.12	31.45 \pm 20.11	0.033
ADA(U/L)	53.36 \pm 14.99	30.99 \pm 11.35	<0.0001

Table 3: Pleural fluid CRP and ADA in Tuberculous effusion in comparison to other effusions

PARAMETERS IN VARIOUS EFFUSIONS			MEAN DIFFERENCE	p VALUE
CRP	Tuberculous effusion	Parapneumonic effusion	-13.49	0.103
		Malignant effusion	16.15	0.042
		Transudative effusion	26.41	0.000
ADA	Tuberculous effusion	Parapneumonic effusion	14.16	0.030
		Malignant effusion	23.52	0.000
		Transudative effusion	29.53	0.000

Table 4 : Pleural fluid CRP levels comparison in other diagnostic groups

PLEURAL FLUID CRP VALUES	Diagnostic group	Number	Mean value (mg/dL)	p Value
1.	Parapneumonic effusion	9	54.39	0.004
	Others	69	35.58	
2.	Malignant effusion	8	24.75	0.036
	Others	70	39.24	
3.	Transudative effusion	9	14.49	<0.0001
	Others(Exudative)	69	40.79	

FIGURE LEGENDS:

Figure 1 : FINAL DIAGNOSIS OF STUDY POPULATION

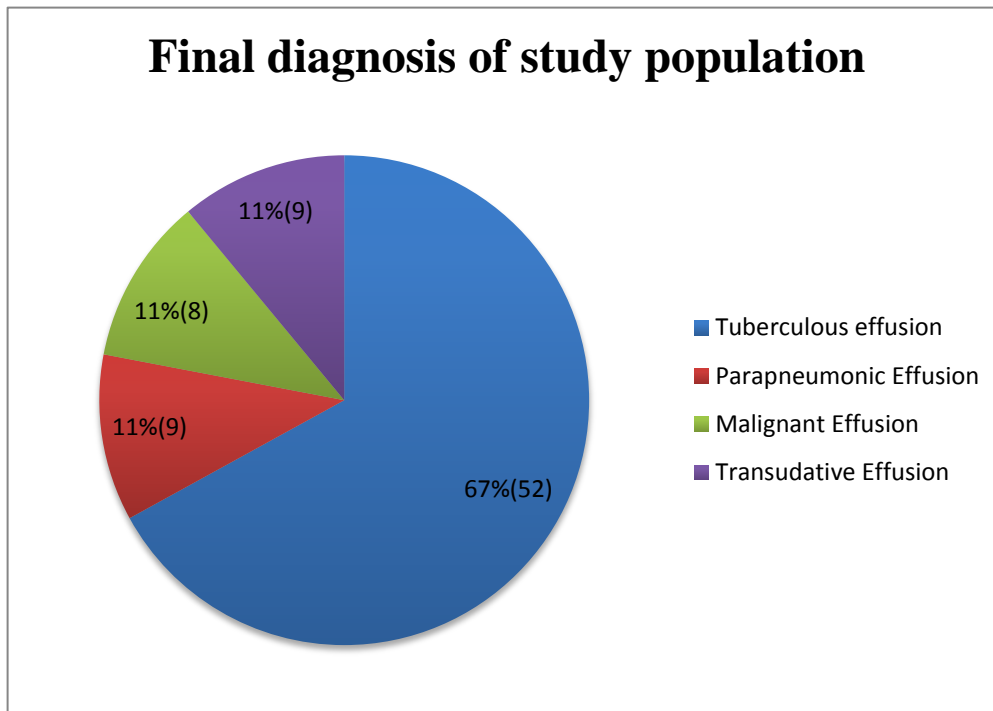


Figure 2: MEAN PLEURAL FLUID ADA & CRP VALUES IN FOUR DIAGNOSTIC GROUPS

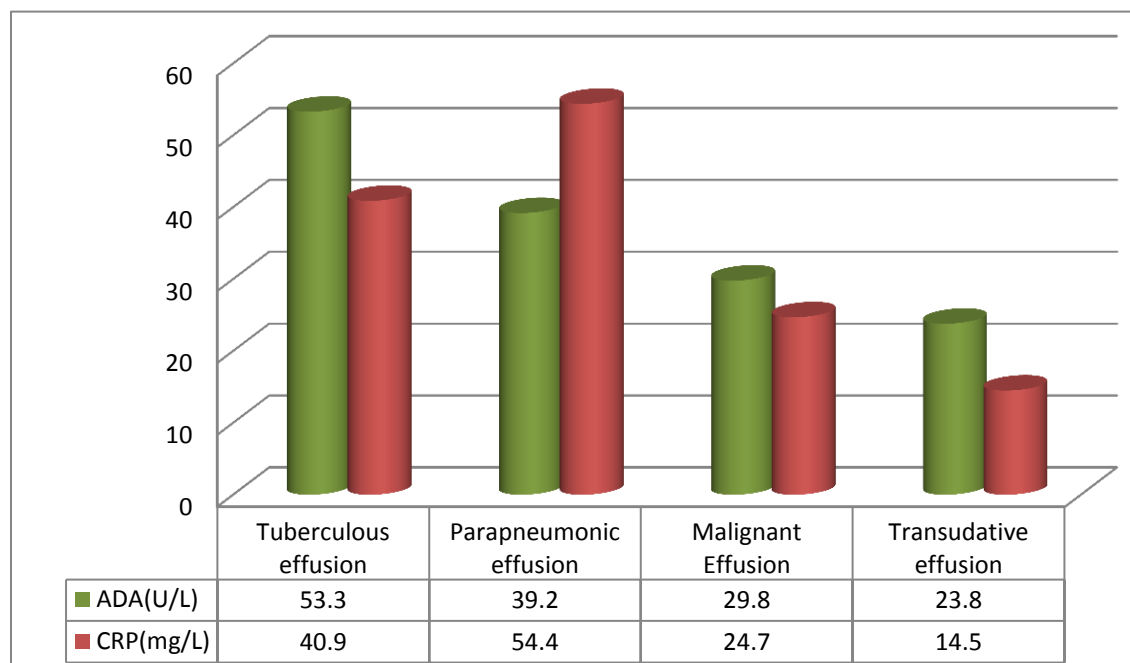


Figure 3: CORRELATION OF PLEURAL FLUID ADA AND CRP LEVELS IN TBPE

