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Utility of Pleural fluid ADA: Serum CRP ratio in diagnosing

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Abstract
Aim: *To estimate the utility of Pleural fluid ADA: Serum CRP ratio in differentiating Tuberculous and Malignant Pleural effusions*
Materials and Methods: *A hospital based prospective observational study was conducted at GHCCD, Visakhapatnam. A total of 43 patients were recruited in the study using inclusion and exclusion criteria. Pleural fluid analysis was done in all patients for protein, glucose, total and differential count, ADA levels along with Serum CRP levels. Subsequent statistical analysis was done using Microsoft Excel and SPSS software.*
Results: *Out of 43 patients, 19 were diagnosed with Malignant pleural effusion and 24 with Tuberculous pleural effusion. Mean ADA level in Malignant pleural effusions was 69±43 U/l with mean Serum CRP level of 85.56±61.56 mg/l. Mean ADA level in Tuberculous pleural effusion was 93±62 U/l with mean serum CRP level of 30.17±38.45 mg/l. Mean pleural fluid ADA: Serum CRP ratio in MPE and TPE was calculated as 1.36±1.28 and 6.96±7.32 (p=0.0006) respectively. ROC analysis showed thata cut off pleural fluid ADA: serum CRP ratio of ≤1.2 showed a sensitivity of 78.95% and a specificity of 83.33% (AUC=0.789;p=0.0001)*
Conclusion: *Pleural fluid ADA: Serum CRP ratio can be a useful add-on diagnostic test in predicting the probability of Malignant vs Tubercular pleural effusion.*
Key Words: *Pleural fluid , ADA, CRP*

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I. IIntroduction

- An abnormal or excessive accumulation of fluid in the pleural cavity is known as Pleural Effusion. An accurate etiological diagnosis is very important to treat the patients. However in about 15-20% of cases the diagnosis remain undiagnosed [1]
- Pleural effusions accompany a wide variety of disorders of lung ,pleura and systemic disorders.
- So diagnosis and management of the pleural effusions remain a challenge .
- The etiology of pleural effusions depends on the age , their geographical location and the treatment of the underlying etiology.
- Pleural effusions are classified into transudative, exudative pleural effusions based on Lights criteria.
- Pleural effusions which are exudative can be diagnosed mostly based on their clinical scenario[2]. Exudative effusions need to separated into non infectious , infectious , and malignant effusions depending on the underlying etiology .
- Parapneumonic effusion, malignant pleural effusion, tuberculous pleural effusion are most common etiologies of exudative pleural effusion of which tuberculous and malignant pleural effusions are lymphocytic rich effusions.
- Tubercular effusion is the most common cause of exudative pleural effusions in India followed by Malignant effusion [3]
- Whereas in the west parapneumonic effusions and malignant effusions are more common[4]
- Tuberculous pleural effusion accounts the 2 nd most common cause of extra pulmonary tuberculosis[5] after tubercular lymphadenitis.

- it is difficult to establish the etiology of pleural effusion even after subjecting the pleural fluid for biochemical ,microbiologcal and cytological tests sometimes[6]. Pleural biopsy is helpful to confirm an etiological diagnosis of exudative pleural effusion, particularly when malignancy is suspected in such cases [7] .
- Malignant pleural effusion and tuberculous pleural effusion are difficult to distinguish between them as they have similar biochemical profiles[8,9] . In both of these exudative effusions , there is general predominance of lymphocytes which are particularly CD4 positive T cells.[10]
- Although cytological examination of pleural fluid is an easy way to diagnose a pleural malignancy , a false negative rate of about 40% has been reported
- A combination of biopsy method and cytological method will increase the diagnosis eate to 73% [7]
- So there is an increasing demand for the markers that may help in the differentiation.
- C Reactive Protein (CRP) was discovered in 1930 and widely used as a sensitive marker but a non specific marker of systemic inflammation.
- Increase in the serum CRP levels are seen in many pulmonary diseases such as pneumonia , malignancies , pulmonary thrombo-embolism.
- ADA levels tend to be higher in tuberculous pleural effusion compare dto other exudative pleural effusion[(11-15)]. Higher the level more likely suggestive of tuberculosis.
- Higher pleural fluid ADA levels is also reported in small percent of neoplasms[16]
- Various biomarkers performanace such as lymphoctyes, eosinophills , nucleated cells , eosinophills , cholesterol , lactate dehydrogenase , proteins , adenosine deaminase , interleukin 6 ,are reported to differentiate between malignant and tuberculous pleural effusion[17-19]. But many studies are based on individual marker separately , and interpreted along with the clinical findings and other tests [18-19].
- So combination of biomarkers may increase the accuracy of the diagnosis.
- In this study tuberculous and malignant pleural effusion are differentiated based on the routine biomarkers .

AIMS AND OBJECTIVES

To estimate the utility of Pleural fluid ADA: Serum CRP ratio in differentiating Tuberculous and Malignant Pleural effusions.

II. Materials And Methods:

Study design: Hospital based prospective study.

Study setting: Department of pulmonary medicine , Andhra Medical College/ Government hospital for chest and communicable diseases , Visakhapatnam ,Andhra Pradesh.

Sample size: A Total of 43 consecutive cases were enrolled into the study according to inclusion and exclusion criteria.

Inclusion Criteria:

- Patients willing to participate in the study
- Age > 18 years.
- Only diagnosed tubercular and malignant effusions by the pleural biopsy positive and malignant cytology positive respectively.

Exclusion Criteria:

- Patients not willing to participate in the study
- Age< 18 years
- Immuno compromised patients.
- Other pleural effusions.

Methodology:

The following data was recorded.

- A detailed history of every case was obtained including age , sex , socioeconomic status.
- Past medical history
- General examination and physical examination.
- Investigations were carried out and recorded in all cases including:
- normal blood investigations ,
- serum CRP levels,
- sputum for Acid fast bacilli
- sputum for CBNAAT
- chest radiography posterior anterior view and lateral view.

- pleural fluid analysis such as pleural fluid total count , differential count , ADA, protein , sugar ,malignant cytology , cell block,CBNAAT .
- ultrasound chest
- ultrasound guided pleural biopsy

Study Procedure:

After taking informed consent , all 43 patients were subjected to diagnostic thoracocentesis. Once the site for the thoracocentesis is identified, the skin surrounding the site is cleaned thoroughly with an antiseptic solution. Then local anaesthesia is given with 2% xylocaine to skin, subcutaneous tissue, muscles and parietal pleura. Then 20 cc syringe with 22 G needle is introduced through the intercostal space at the upper border of lower rib and 10-20 cc of pleural fluid is aspirated.

Then for every patient light's criteria is applied to differentiate whether the pleural fluid sample is a transudate or an exudate.

PLEURAL BIOPSY:

The patient is positioned and the site for thoracentesis is selected by ultrasound. Skin is cleaned and local anesthetic is administered . when pleural fluid has been obtained with lidocaine syringe and needle , pleural biopsy can be performed with Abram s or Cope s needle.[20]

LIGHT S CRITERIA:

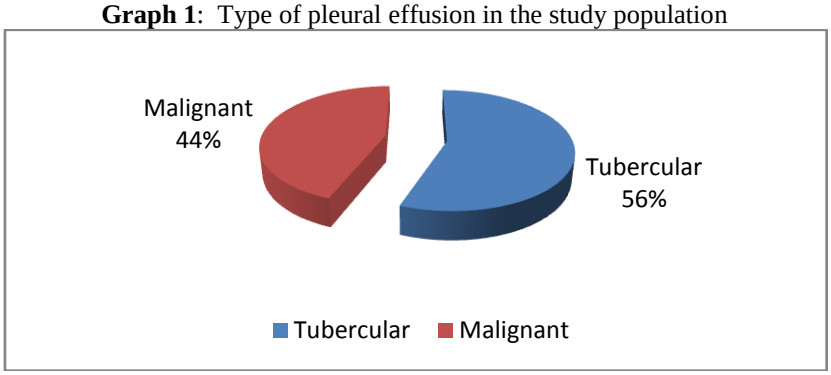
According to the traditional **Light's criteria** rule if atleast one of the following three criteria (i.e., component tests of the rule) is fulfilled, the fluid is defined as an exudate

1. Pleural fluid protein to serum protein ratio greater than 0.5
2. Pleural fluid LDH to serum LDH ratio greater than 0.6
3. Pleural fluid LDH greater than two thirds of the upper limit of normal for the serum LDH[21]

III. Results

In the given study among the 43 patients , 44% of patients are diagnosed to have malignant pleural effusions and 56% of patients are diagnosed to have tubercular pleural effusions.

Graph 1: Type of pleural effusion in the study population



Age Distribution:

In the present study most of the patients are in the age group 25-50 years in both malignant and tubercular pleural effusion groups which are 57.8% and 62.5% respectively. The mean age in malignant effusion patients is about 43.47±13.6 and mean age in tubercular effusion patients is about 43.04±11.09. Only 1 , 2 patients are present in malignant and tuberculous effusion groups.

Table no 1: Age distribution in the study population

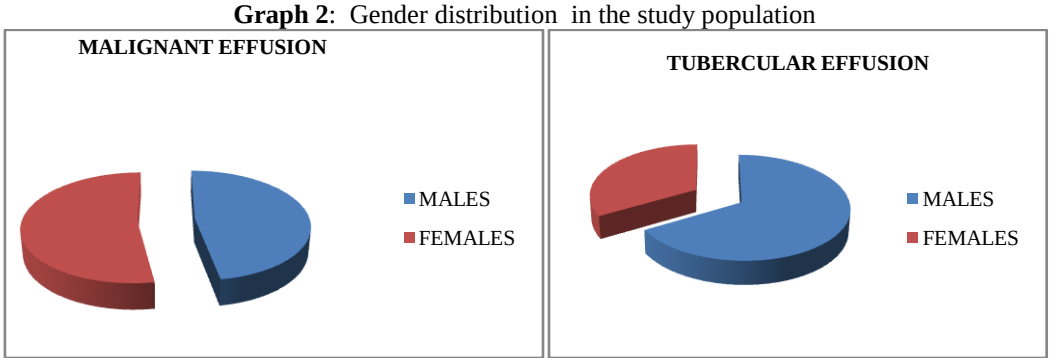
Age	Malignant pleural effusion	Tubercular pleural effusion
< 25 years	5.2%	8.33%
25-50 years	57.8%	62.5%
>50 years	37%	29.17%
Mean	43.47±13.6	43.04±11.09.

Gender Distribution:
Male predominance is observed in the study . Out of the 43 patients presented with pleural effusion 25 were males and 18 were females.

Table no 2: Gender distribution in the study population

Gender	Malignant pleural effusion	Tubercular pleural effusion
Males	9	16
Females	10	8

Graph 2: Gender distribution in the study population



Pleural fluid parameters:

In the given study both the effusions are exudative , so the mean of pleural fluid protein is about 4.09 mg/dl and 4.34 mg/dl in malignant and tubercular pleural effusion respectively. Both the effusions are lymphocytic rich , but compared to malignant effusion , lymphocytes are predominant in tubercular effusion (89.2 % compared to 76.18% in malignant effusions).

Table no 3: Pleural fluid parameters in the study population

	Malignant pleural effusion	Tubercular pleural effusion
Pleural fluid protein	4.09 mg/dl	4.34 mg/dl
Sugar	67.75 mg/dl	78.85mg/dl
Total Count	1675.38	1507.69
Lymphocytes	76.18%	89.2%
Polymorphs	23.82%	10.73%

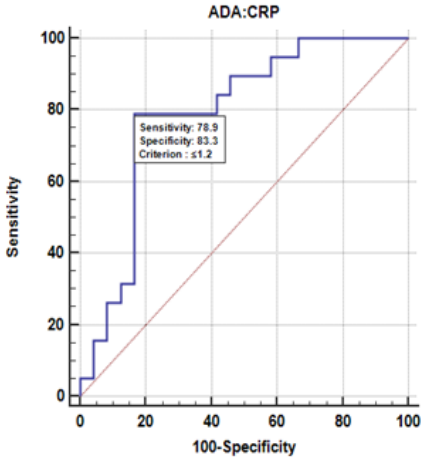
The mean pleural fluid ADA in malignant pleural effusion is 69±43 U/l and in tubercular pleural effusion is 93±62 U/l , which is not significant with a p value 0.1590. In this study the mean serum CRP in tuberculous pleural effusion is 30.17±38.45 and in malignant pleural effusion is 85.56±61.56 which is significant with p value 0.0008. The mean pleural fluid ADA: Serum CRP ratio in malignant pleural effusion and tuberculous pleural effusion is measured and the value is significant with p value 0.0006

Table no 4: Comparing Pleural fluid ADA and seum CRP in the study population

	Mean pleural fluid ADA	Mean serum CRP	Mean pleural fluid ADA : Serum CRP ratio
Malignant effusion	69 ± 43U/l	85.56 ± 61.56	1.36±1.28
Tubercular effusion	93 ± 62U/l	30.17 ± 38.45	6.96±7.32
P value	0.1590	0.0008	0.0006

Through the ROC curve analysis of mean pleural fluid ADA and Serum CRP ,a sensitivity of 78.95 and specificity of 83.33 was obtained for the cut off of ≤1.2, with a p value of 0.0001, which is significant.

Table no 5: ROC curve analysis of mean pleural fluid ADA and Serum CRP in the study population



AUC	0.789
P value	0.0001
Associated criterion	≤1.2
Sensitivity	78.95
Specificity	83.33

IV. Discussion

- The diagnosis of pleural effusion is a difficult challenge because the catalog of the diseases they cause is as big as it is diverse.
- In the present study the mean age in malignant effusion patients is about 43.47±13.6 and mean age in tubercular effusion patients is about 43.04±11, which is not significant. In study conducted by Nariman A. Helmy et al[22] ; the mean age in malignant effusion patients is about 55.2± 11.9 and mean age in tubercular effusion patients is about 29.2± 12.2 , which is significant with p value <0.001. In the study conducted by Sherif A.A. Mohamed et al [23]; the mean age in malignant effusion patients is about 57.65±10.03 and mean age in tubercular effusion patients is about 34.68±14.72 , which is highly significant. In the study conducted by Reza Darooei et al [24] , the mean age is significant with p value , <0.0001. This may be due to low study population in our study.
- In the present study Out of the 43 patients presented with pleural effusion 25 were males and 18 were females, with male predominance ,which is similar to Sherif A.A. Mohamed et al [23];Reza Darooei et al[24] ; studies.
- Circulating value of CRP reflects ongoing inflammation or tissue damage much more accurately than other parameters of the acute phase response.The serum CRP concentration is a very useful non specific biomarker of inflammation which is relatively simple, rapid and cheap marker in differentiating tuberculous pleural effusion and malignant pleural effusion.The plasma half life of CRP is about 19 hours .Intensity of the pathologic process stimulates the CRP production[25.]
- Plasma CRP is produced only by hepatocytes, predominantly under transcriptional control by the cytokine interleukin-6, although other sites of local CRP synthesis and possibly secretion have beensuggested[26] .
- In this study the mean serum CRP in tuberculous pleural effusion is 30.17±38.45 and in malignant pleural effusion is 85.56±61.56 which is significant with p value 0.0008. In the study conducted by Sherif A.A. Mohamed et al [23]; the mean serum CRP in tuberculous pleural effusion is 28.34±14.41 and in malignant pleural effusion is 27.87±13.21, which is not significant.

- The reasons for CRP elevation in malignant effusion are not completely understood ,one of the explanation may be due to cytokine production by tumour tissue which indicates high tumour burden.[27]. Scott et al.[28]reported a catabolic effect of acute-phase proteins such as CRP on metabolism, and this is associated with an increase in resting energy expenditure and loss of lean tissue in patients with lung cancer, key factors in determining cancer survival.
- The mean pleural fluid ADA in malignant pleural effusion is 69±43 U/l and in tubercular pleural effusion is 93±62 U/l , which is not significant with a p value 0.1590.In study conducted by Nariman A. Helmy et al[22] ; the mean pleural fluid ADA in malignant pleural effusion is 28.7 ±23.6 U/l and in tubercular pleural effusion is 83.5 ±50.3 ,which is significant with p value 0.002. In Reza Darooei et al [24] study there is significant difference with p value < 0.0001.
- ADA is an enzyme catalyzing the conversion of the adenosine and deoxyadenosine to the inosine and deoxyinosine in the purine degradation pathway. Its quantity increases in the immature and non-differentiated T-lymphocytes following mitogenic and antigenic stimulation[29]. While the increase of ADA activity in the MPE has been associated with the predominance of CD8, prominent rise observed in TPE has been tried to be explained with the presence of gradually increasing CD4 blastogenesis after the mycobacterial antigenic stimulus [30].

- The mean pleural fluid ADA: Serum CRP ratio in malignant pleural effusion and tuberculous pleural effusion is measured and the value is significant with p value 0.0006 and through ROC curve a cutoff of ≤1.2 can be taken as malignant pleural effusion and >1.2 can be taken as tuberculous pleural effusion .
- This study cannot be used as a stand alone diagnostic test for the diagnosis of malignant pleural effusions.
- It adds to the diagnostic probability of the malignant effusion before invasive testings can be done.

LIMITATIONS

- Small number of patients are only studied ,so definitive criteria cant be established on this sample size.
- The diagnostic accuracy of pleural fluid CRP is superior to serum CRP but due to cost and availability of pleural fluid CRP ,only serum CRP is studied.
- Other pleural effusions are not studied.

V. Conclusion

Pleural fluid ADA: Serum CRP ratio can be a useful add-on diagnostic test in predicting the probability of Malignant vs Tubercular pleural effusion especially in Lymphocyte rich high ADA exudative effusion.

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