

Pleural Fluid C-Reactive Protein in the Differential Diagnosis of Infectious and Malignant Pleural Effusion at Baghdad Teaching Hospital (Single Center Study).

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ABSTRACT:

BACKGROUND:

C-reactive protein (CRP) is an acute phase reactant produced primarily by hepatocytes; its production is stimulated by systemic inflammation of either infectious or noninfectious origin. The cytokines that are released during the inflammation are the main stimulants of the acute phase reactants. Interleukin-6 is the main stimulant cytokine of the synthesis of most acute-phase reactants.

OBJECTIVE:

To differentiate between infectious and malignant pleural effusions by measuring pleural fluid CRP titer.

MATERIALS AND METHODS:

This was a hospital-based cross-sectional study at Baghdad teaching hospital medical wards conducted from the 1st of November 2014 up to the 31th of August 2015.

Fifty patients with pleural effusion proved by the history, examination, Chest imaging and pleural tapping included in this study, all proved to have An exudative pleural effusion by the light criteria.

RESULTS:

Showing statistically significant differences in CRP titer between:-

1-Parapneumonic pleural effusion (PPE) and malignant pleural effusion (MPE)

2-TB pleural effusion (TBPE) and malignant pleural effusion (MPE).

CONCLUSION:

Pleural fluid C-reactive protein titer can be used as an aid in the differentiation between some infectious causes of pleural effusion and malignant pleural effusion as there is a statistically significant difference between the Pleural fluid C-reactive protein titer of the infectious pleural effusion and the malignant pleural effusion.

KEYWORDS: c-reactive protein (crp), para pneumonic pleural effusion (ppe), malignant pleural effusion (mpe).

INTRODUCTION:

Pleural effusion is abnormal collection of fluid within the layers of the pleura that results from disturbance of the equilibrium forces affecting the flow into and out of the area. The collection of Pleural fluid is related to different medical illnesses like

Heart failure, pneumonia and malignant neoplasms.⁽¹⁻³⁾

Pleural effusion is diagnosed by taking the patient's history and performing physical examination, chest imaging and pleural fluid analysis.⁽⁴⁾ The normal range of the pleural fluid is (8.4±4.3 mL).

Fluid that accumulate in the pleural space can arise from pleural capillaries, the

Interstitial spaces of the lung, the intrathoracic lymphatic, and the intrathoracic blood vessels or the peritoneal cavity.⁽⁵⁾

To diagnose the cause of pleural effusion we need to know whether the patient has transudate or exudate.⁽⁶⁾ Transudates are caused by raised hydrostatic pressure, reduced oncotic pressure, increased negative intrapleural pressure, or the movement of ascetic fluid through the diaphragmatic orifices, while exudates are caused by the exaggerated capillary permeability and/or impaired lymphatic drainage as a result of a proliferative or inflammatory process.⁽⁷⁾

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Differentiation of transudate and exudate:

A-Appearance of pleural fluid:

The appearance of pleural aspirate may provide a useful diagnostic benefit. A red pleural aspirate denotes that a blood is present (malignancy, trauma, or Pulmonary emboli), and a brown stain denotes that the blood is present for a long time. Turbid aspirate can occur with pyothorax, chylothorax or pseudochylothorax. The smell of the aspirate is also worthy in identifying the cause. A feculent smell points to the presence of anaerobic bacterial infection⁽⁸⁾

Light's criteria is used to discriminate transudates from exudates by assessing the concentrations of protein and lactate dehydrogenase in the pleural aspirate and serum, exudative aspirate has one or more of the followings:

- Pleural fluid protein divided by serum protein > 0.5
- Pleural fluid lactate dehydrogenase (LDH) divided by serum LDH > 0.6
- Pleural fluid LDH > 2/3 (67%) the upper normal limit for serum LDH⁽⁹⁾

B-Thoracentesis:

The removal of pleural fluid using a needle or syringe is used for either diagnostic or therapeutic indications. It should be coupled with a sample of blood (within 30 minutes from taking the pleural aspirate) needed for further aspirate analysis⁽¹⁰⁾ major contraindication of pleural fluid aspiration is bleeding tendency⁽¹¹⁾ most common complication of this procedure is pneumothorax⁽¹²⁾

Evaluation of the exudate:

The next step is to diagnose the cause of the exudate by considering clinical situation, exudate requires further tests. This consists of total and differential cell counts, smears and cultures to diagnose infection, biochemical tests, cytological study and tests for markers of TB pleurisy^(13, 14)

The use of diuretics in patients with heart failure results in elevating levels of different pleural fluid constituents. Misclassifying transudates as exudates^(15, 16)

Cytological analysis of pleural fluid:

The diagnostic yield of cytology is dependent on the type of tumor, tumor cells load in the pleural fluid and the cytologist experience⁽¹⁷⁾ Nodularity, pleural and diaphragmatic thickening are strongly suggestive of malignant pleural disease with a positive predictive value of 100%. these findings are not always present thus pleural fluid cytology has an important role in the diagnosis of malignancy⁽¹⁸⁾

If cytology is also negative and malignant pleural effusion is still a possibility,

Pleural biopsy will be indicated. This will enable histological study of the sample⁽¹⁹⁾

Microbiologic analysis of pleural fluid:

If pleural effusions are suspected to be caused by bacterial infection, the gram stain and culture of the pleural aspirate must be done⁽²⁰⁾

Predisposing factors are very important in expecting the possible organism. Pneumonia is the most frequent predisposing factor in development of empyema

In healthy adults with pneumonia, the most common bacteria causing empyema are staphylococcus aureus, streptococcus pneumoniae or streptococcus pyogenes⁽¹⁵⁾

Most cases of S.aureus empyema is seen in elderly hospitalized patients with underlying medical illnesses. S.aureus is a rare etiology of pneumonia in healthy people except during influenza outbreaks^(15,16) conditions that put the patient at a risk of aspiration, such as impaired mental state and alcohol consumption are common in patients with anaerobic infection of the pleura⁽¹⁶⁾

Pleural tuberculosis shows significant pleural fluid characteristics that participate in the diagnosis. Microscope study of Ziehl-Neelson stained pleural aspirate identifies acid-fast bacilli in less than 5% of cases⁽¹⁶⁾ Use of Lowenstein-Jensen media culture improves this positivity to nearly 35%. Nucleic acid amplification has specificity up to 97% and sensitivity of 60%⁽²⁷⁾

Biochemical analysis

Pleural fluid white blood cell differential counts are of limited diagnostic yield but can identify the stage of the inflammation and restrict the diagnostic probabilities. Predominant neutrophils denote an acute inflammation involving the pleura such as in the case of Para pneumonia, pulmonary embolism, viral infections, gastrointestinal diseases and TB pleurisy.

Predominant mononuclear cells denote a chronic inflammation.

Lymphocytic predominance may denote malignancy or TB pleuritis^(16, 17)

Pleural fluid pH level may be reduced in (complicated Para pneumonic effusion, empyema, esophageal rupture, malignancy, TB, and chronic rheumatoid pleurisy).⁽⁷⁾

Pleural fluid glucose, Low pleural glucose level (30-50 mg/dL) suggests

Malignant effusion, tuberculous pleuritis, esophageal rupture, or lupus pleuritis,

Lower pleural glucose level (< 30 mg/dL) suggests rheumatoid pleurisy or Empyema⁽¹⁶⁾

In cases with pleural infection, the pleural fluid parameters that are strongly suggest

complications and the need for chest tube drainage are pH level less than 7.20 and glucose concentration less than 60 mg/dL.⁽¹⁶⁾

Pleural fluid adenosine deaminase is an enzyme involved in purine catabolism and is thought to reflect the activity of immune cells.⁽¹⁷⁾ It is produced by activated lymphocytes, macrophages and neutrophils, and is considered a nonspecific marker of inflammation.⁽¹⁷⁾

Its increased activity in PF is a sensitive and specific indicator to identify tuberculous pleuritis, especially in high prevalence regions, with a sensitivity of 92% and specificity of 90% and a cutoff Point of 40 U/L. If pleural aspirate ADA level is very elevated (>250 U/L), Then empyema or lymphoma are more probable than TB.⁽¹⁸⁾

Amylase assays in different pleural aspirates was elevated like in pancreatitis and in esophageal rupture related effusions.⁽¹⁸⁾

C-reactive protein:

CRP is an acute-phase reactant produced primarily by hepatocytes; its production is stimulated by systemic inflammation of either Infectious or noninfectious origin.⁽¹⁸⁾

CRP is widely used as an indicator of Inflammation and tissue injury.⁽¹⁸⁾

In 1930 CRP was discovered and so named as it reacted with the pneumococcal C-polysaccharide in the plasma of patient during the acute phase of pneumococcal pneumonia.⁽¹⁹⁾

The acute-phase reactant was defined as one whose plasma level raises (positive acute-phase reactants) or reduces (negative acute-phase reactants) by at least 25% during inflammatory conditions.⁽¹⁹⁾

The cytokines that are released during the inflammation are the main stimulants of the acute-phase reactants.⁽¹⁹⁾ Interleukin-6 is the main stimulant cytokine of the synthesis of most acute-phase reactants.⁽²⁰⁾

Cytokine synthesis and the acute-phase reaction are different in variant inflammatory disorders. Cytokines synthesized by different cell types, but mainly by the macrophages and monocytes at the inflammation site.⁽²⁰⁾ The interleukin-6 acts on the hepatocyte inducing transcriptional stimulation of a group of acute-phase reactants causing a reprioritization of hepatic proteins production with elevated synthesis of the acute phase proteins and simultaneous reduction of normal export proteins. The acute phase reactants was noticed to take a main role in the suppression of extracellular proteases, blood coagulation, fibrinolysis, modulation of immunity, and the neutralization and clearance of harmful particles

from the circulation.⁽²⁰⁾ The stimulation of CRP in certain models needs both interleukin-6 plus either interleukin-1 or tumor necrosis factor.

Glucocorticoids increase the actions of cytokines on the synthesis of acute-phase reactants.⁽²⁰⁾ While insulin reduces their actions on the synthesis of some acute-phase reactants.⁽²¹⁾ CRP is a part of the innate immune system, its cardinal action is the ability to bind phosphocholine and recognizing some foreign pathogens as well as phospholipids of destroyed cells. It can stimulate the complement system when attached to any of its ligands and can also bind to phagocytes, as well as it can start the eradication of targeted cells by its interaction with both humoral and cellular effector systems of inflammation.⁽²²⁾ Normal plasma CRP range is (2-10 mg/liter). Patients with plasma CRP levels higher than 100 mg/liter, 80 to 85 % have bacterial infections.

AIM OF THE STUDY:

To differentiate infectious and malignant causes of pleural effusion using pleural fluid CRP titer as an aid in the diagnosis.

MATERIALS AND METHODS:

Study design, setting and timing:

This was a hospital-based cross-sectional study at Baghdad teaching hospital

Medical wards conducted from the 1st of November 2014 to the 31th of August 2015.

Patients and sample collection:

Fifty patients with pleural effusion, a history, examination, chest imaging and pleural tapping included in our study, all proved to have exudative pleural effusion by Light's criteria, samples of pleural fluid were collected immediately after admission along with blood samples within 30 minutes for further pleural fluid analysis {white cells count and differential, biochemical (sugar, protein, LDH), bacteriological (gram stain, culture and sensitivity, AFB, culture and sensitivity for AFB), cytological studies, nucleic acid amplification test and polymerase chain reaction}. Sputum samples and bronchoalveolar lavage samples also were sent for same parameters as pleural fluid. Biopsies (pleural, lymph node and lung biopsy) were also involved to evaluate the cause of exudate by histopathological study. In patients who were diagnosed to have (malignant, Para pneumonic and TB) effusions, CRP titer of pleural fluid were measured.

Exclusion criteria:

- 1- Transudative effusions.

2- Patients with possibility of more than one cause for the effusion.

3- Patients with heart failure, liver cirrhosis and Nephrotic syndrome on diuretics.

METHODS:

The semi-quantitative method was used as follow:

1-pleural fluid sample was centrifuged and the supernatant was separated and 50 microliters taken.

2-Serial two folds dilution with saline solution 9g/L was made using pippetes 50 Microliters.

3-One drop of each positive and negative control was placed on separate circles on the slide test.

4-CRP-latex reagent was mixed vigorously with wood stick spreading them over the entire surface of the circle with different sticks.

5- The slide placed on rotator-shaker at 80-100 r/min for two minutes

6-The used kit is (SPINREACT, S.A./S.A.U Ctra. Santa Coloma, 7E-17176 SANT ESTEVE DE BAS (GI) SPAIN.

7-The presence or absence of visible agglutination was examined macroscopically Immediately after removing the slide from the rotator-shaker, the titer in the semi quantitative method is defined as the highest dilution showing a positive result.

8-CRP normal value considered in the semi-quantitative method is 6mg/L.

Statistical analysis:

By using the statistical package for social sciences (SPSS) software for windows, version 22, IBM, USA, 50 patients with exudative pleural effusion were involved in a cross sectional study.

Descriptive statistics were presented as mean ± standard deviation for continuous variables {Age and CRP titer}.Categorical variables were presented as frequencies and proportions {gender and the type of pleural effusion}

Student's t-test was used to compare and assess the significance of differences between continuous variables.

Chi square test {cross tabulation} was used to assess the significance of association between categorical variables.

ANOVA test was used to compare 3-level categorical variables (CRP titer) with the mean values of continuous variables, with further analysis by LSD (Least significant Difference) for the significant results. Pearson's correlation and linear regression tests were used to calculate the association coefficient (*r*) to assess the strength, direction and significance of association {positive signed (*r*) indicated direct (positive association) and the negative signed (*r*) indicated inversed association}, the value of (*r*) ranged from 0 (no association) and 1 (perfect association), the higher (*r*) value, the stronger the association. Level of significance of ≤ 0.05 was considered significant difference or association.

RESULTS:

Description of demographic data in the study:

The study included 50 patients with exudative pleural effusion with 26 males and 24 females with a mean age of 55.04 years. Number of patients with (Para pneumonic effusion) PPE is 22 (44%) included 9 males and 13 females with mean age is 52.36 while patients with (TB pleural effusion) TBPE are 15 (30%) included 9 males and 6 females with mean age 53.06.patients with (Malignant pleural effusion) MPE are 13 (26%) included 8 males and 5 females with mean age is 61.84.this demographic data distribution was illustrated in the table (1)and figure (1).

Table 1: Description of demographic data in the study.

Diagnosis	Number of patients	Gender Distribution		Age Distribution (years)			
		Male	Female	Mean	Standard Deviation	Minimum	Maximum
Para pneumonic Effusion	22	9	13	52.36	11.83	30	72
TB Effusion	15	9	6	53.06	15.01	27	82
Malignant Effusion	13	8	5	61.84	5.29	52	70
Total	50	26	24	55.04	12.16	27	82

According to the percentages of variable groups contributed in the study as following

1- PPE represented in (44%).

2-TBPE represented in (30%).

3-MPE represented in (26%).

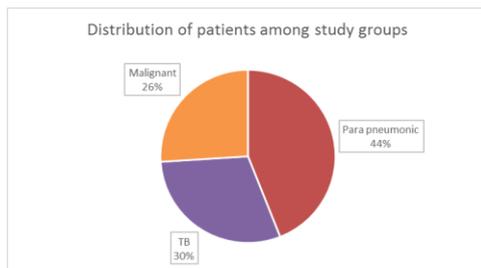


Figure 1: Showing distribution of patients among study groups.

The table (2) shows the type of exudative effusion and other study parameters including CRP titer, age and gender illustrating that there is statistically significant association between exudative effusion and CRP titer that colored red In the table (P value is 0.0001) while there is no statistically significant correlation

Between type of exudative Effusion with the age and gender.

- CRP titer { mean \pm std. Deviation } :for
- 1) Para pneumonic effusion is (305 \pm 110.34).
 - 2) TB pleural effusion is (274.8 \pm 130.47).
 - 3) Malignant pleural effusion is (52.92 \pm 30.25).

Table 2 :The Association between the type of exudative effusion and other study parameters.

Parameter	Para pneumonic Effusion (N=22)	TB Effusion (N=15)	Malignant Effusion (N=13)	P value	Pearson's Correlation (R)
CRP titer { mean \pm std. Deviation }	305 \pm 110.34	274.8 \pm 130.47	52.92 \pm 30.25	0.0001	0.662
Age (years) { mean \pm std. Deviation }	52.36 \pm 11.83	53.06 \pm 15.01	61.84 \pm 5.29	0.06	0.299
Gender	Male	9	9	0.379	0.18
	Female	13	6		

The table (3) compares the study groups with each other showing significant differences in CRP titer between:-
1-PPE and MPE

2-TBPE and MPE
3- Both PPE, TBPE and MPE
While there is **NO** statistically significant difference between PPE and TBPE.

Table 3: Shows the relations between the study group with each other .

Between		P value {between the 2 groups }	P value {Among all groups }
Para pneumonic Effusion	TB Effusion	0.571	0.00001
Para pneumonic Effusion	Malignant Effusion	0.00001	
TB Effusion	Malignant Effusion	0.00001	

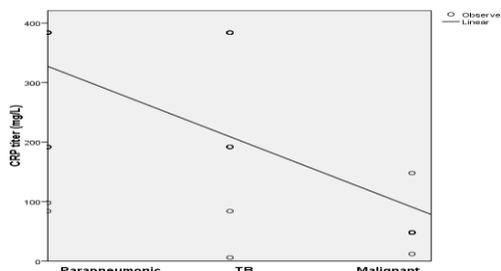


Figure 2 :The Association between The type of Effusion and the CRP titer .

DISCUSSION:

Once a pleural effusion is characterized as an exudate, the next challenge is to identify its etiology.⁽¹⁵⁾ So this study tried to make benefit from pleural fluid CRP titer to aid in the differentiation between some infectious causes of PF and malignant PF.

The following studies involved the use of pleural fluid CRP titer to differentiate infectious and malignant causes of PF and they found:

Kapisyzi Perlat et al.⁽²³⁾ a study in Albania concluded that CRP levels < 30 mg/L in an exudative pleural effusion strongly suggest a malignant or chronic TB effusion. Alternatively, pleural fluid CRP levels > 30 mg/L are suggestive of inflammatory etiology and almost exclude malignant origin of pleural effusion. So there is disagreement with our study in being classified MPE and chronic TBPE as to have same CRP range.

Theodoros S. Kiroopoulos et al.⁽²⁴⁾ a study in Greece and Qiaoying JI et al.⁽²⁵⁾ study in China showed that there is: a Statistically significant higher CRP titer in (PPE as compared to TBPE and MPE) and in (TBPE as compared to MPE) and these results agree with our study, but in our study there is no statistically significant difference between PPE and TBPE CRP titer.

Wafaa S. El-Shimy et al.⁽²⁶⁾ a study in Egypt showed that pleural fluid CRP level was statistically significant higher in patients with TBPE as compared with PPE and MPE. Pleural fluid CRP level was statistically significant higher in PPE and TBPE as compared to patients with MPE. This study agrees with our study in being CRP titer is higher in patient with PPE and TBPE than in MPE but differs in being showed a statistically significant higher CRP titer in TBPE than in PPE.

Alvin Tung et al.⁽²⁷⁾ a study conducted in Australia, Sang et al.⁽²⁸⁾ and Do-Sim Park et al.⁽²⁹⁾ are studies conducted in Korea, Daniil et al.⁽³⁰⁾ a study in Greece, they found that the pleural fluid CRP levels in the benign and inflammatory effusion were statistically significant higher than those in the malignant effusion and this agree with our results.

Wang et al.⁽²⁸⁾ in the USA, Chierakul et al.⁽²⁹⁾ in Thailand and Sedky et al.⁽³⁰⁾ in Egypt studied the value of CRP measurement to discriminate tuberculous from malignant PE especially in lymphocytic PE. Pleural fluid CRP levels were statistically significant higher in the TBPE group than in the MPE group. This was compatible with our study.

CONCLUSION:

Pleural fluid C-reactive protein titer can be used as an aid in the differentiation between some infectious causes of pleural effusion and malignant pleural effusion as there is a statistically significant difference between the Pleural fluid C-reactive protein titer of the infectious pleural effusion and the malignant pleural effusion.

Recommendations

My advice is to use pleural fluid CRP titer in the differentiation between the causes of exudative pleural effusion as it is simple, rapid, available, accurate and not costly test.

Also we need to study a larger sample to give a more accurate statistical value.

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Recommendations:

My advice is to use pleural fluid CRP titer in the differentiation between the causes of exudative pleural effusion as it is simple, rapid, available, accurate and not costly test also we need to study a larger sample to give a more accurate statistical value.