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Research Paper

The Use of Pleural Fluid C- Reactive Protein Level as a Diagnostic Marker for Pleural Effusions

Medical Science

KEYWORDS : pleural effusion, C-reactive protein, malignancy, transudative, exudative

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ABSTRACT

Background: Our objective was to determine the usefulness of pleural effusion C reactive protein levels in the diagnosis of pleural effusions.

Patients and Methods: A comparison of serum and pleural fluid C-reactive protein (CRP) levels in different subgroups of 286 patients with pleural effusion was made. We assessed prospectively the sensitivity, specificity, positive and negative predictive values, accuracy, Youden index, likelihood ratio and ROC curve of the test, for a period from February 2008 to November 2011.

Results: Among 286 patients with pleural effusion, 67 patients were included in the transudate group, 219 patients were included in the exudate group. In transudates the cut-off value of pleural fluid CRP ≤15 mg/L had a Youden index of 0.678 and the area under curve = 0.86 comparing with exudative pleural effusions. In malignant pleural effusions, the cut-off value of pleural fluid CRP ≤20mg/L had a Youden index of 0.728 and the area under curve = 0.89 comparing with tuberculous effusions. In tuberculous effusions, the cut-off value of pleural fluid CRP >20mg/L had a Youden index of 0.45 and the area under curve=0.96 comparing with malignant effusions. The values of pleural fluid/blood CRP ratios had a very small Youden index and the area under curve in all subgroups of patients with pleural effusion.

Conclusions: Levels of CRP in exudative pleural effusions less than 20 mg/L are strongly suggestive of malignant effusion and chronic tuberculous effusion.A CRP pleural fluid level > 20mg/L almost excludes transudative pleural effusion while the levels of CRP above 30mg/L are suggestive of an inflammatory etiology and almost exclude malignant pleural effusion.

INTRODUCTION

Correct diagnosis of pleural effusion remains a major challenge to clinicians. In recent years, various laboratory tests have been proposed to differentiate transudative from exudative pleural effusions and to elucidate the causes of exudative effusions. The exudative pleural effusion remains the greatest diagnostic challenge. C-reactive protein (CRP), which is synthesized by hepatocytes, is an acute-phase protein widely used as a marker of inflammation and tissue injury. Previous studies on CRP in pleural fluid have concluded that this measurement may differentiate transudates from exudates, but not as well as classical tests [1]. In other studies, it has been reported that CRP levels were significantly higher in parapneumonic and tuberculous effusions than in malignant effusions [2], while a CRP level <20 mg/L in an exudate suggested a malignant origin [3, 4, 5].

The present study was designed to assess whether C-reactive protein (CRP) in pleural fluid is a sensitive marker for discriminating between transudative and exudative pleural effusions and to evaluate whether it can be used to distinguish inflammatory pleural effusions from other types of effusion and specifically from malignant ones. Another aim was to determine the place of this marker in algorithm for the diagnosis of pleural effusions.

We hypothesized that levels of CRP in exudative pleural effusions less than 20 mg/L are related to malignant effusion and chronic tuberculous effusion, while the levels of CRP above 30mg/L are associated with an inflammatory etiology excluding malignant pleural effusion.

MATERIALS AND METHODS

We studied a population of 286 patients with pleural effusion for the period from February 2008 to November 2011. The diagnoses were established through clinical features, laboratory tests and pleural biopsy. Pleural effusions were considered as transudative when they did not fulfil any of Light's criteria (6). Transudative effusions due to heart failure were based on history, physical examination, chest X-rays, electrocardiogram and/or transthoracic echocardiographic findings, and response to diuretic therapy. We used cholesterol criteria (liquid cholesterol < 60 mg/dl; liquid/plasma cholesterol ratio < 0.3) and protein gradient (plasma protein-liquid protein >3.1) when patients with pleural effusion caused by heart failure fulfilled Light's criteria for an exudative effusion and had been under treatment with diuretics. When protein gradient and cholesterol criteria were in contradiction we took into consideration Pro BNP blood level.

Light's criteria were used in order to obtain a diagnosis of exudative pleural effusion. According to these criteria a pleural effusion is likely exudative if at least one of the following exists: A ratio of pleural fluid protein to serum protein greater than 0.5, a ratio of pleural fluid LDH to serum LDH greater than 0.6, or a pleural fluid LDH level greater than two thirds of the upper limit of normal value of serum LDH (upper limit of normal blood value of LDH is 400 IU/L).

A pleural fluid was considered to be lymphocytic when the differential nucleated cell count revealed more than 50% lymphocytes. Tuberculous pleurisy was diagnosed if an exudative lymphocytic

effusion had positive Ziehl–Neelsen stains or Löwenstein-Jensen cultures of pleural fluid, positive sputum or pleural biopsy tissue samples, showed granuloma, or response to antituberculous therapy. In these studies, we considered as being chronic the tuberculous pleurisy cases not in the acute phase (with long history of disease; symptoms onset over three months).

Exudative effusions were determined as malignant effusions when a positive pleural fluid cytology and/or positive pleural biopsy were evidenced.

Almost all pleural effusions in patients with lung cancer were exudative and only one case with lymphangitic spread of carcinoma was transudative effusion.

Exudative neutrophilic effusions secondary to pneumonia were diagnosed as parapneumonic effusions. Diagnosis of pneumonia was made according to the clinical and radiological findings. Diagnosis of empyema was established when frank pus or cloudy fluid was aspirated from the pleural space and manifested leukocitosis, low pH (< 7.20), low glucose (< 60 mg/dl), a high LDH (lactatae dehidrogenase), elevated protein and might contain infectious organisms.

We used the COBAS INTEGRA 400, Roche Diagnostic (GmbH Mannheim Germany) to measure the CRP. The Internal Review Board of Faculty of Medicine approved the study and the patients gave their informed consent.

The quality of CRP was evaluated using receiver operating characteristic (ROC) curve. ROC curve, Youden index, and likelihood ratio, were calculated to evaluate cut-off points and distinguish between populations. Youden index is defined as: sensitivity+specificity-1, where sensitivity and specificity are calculated as proportions. It is the single statistic that captures the performance of the test and enables the selection of an optimal cut-off value of biomarker. A comparison of serum and pleural effusion CRP levels in different subgroups of patients with pleural effusion was also made. We assessed sensitivity, specificity, positive and negative predictive value and accuracy of the test. The statistical analysis performed by Mann Whitney test used to analyze the difference between groups. The level of significance was considered to be <0.05. We used Student's paired t-Test with a two-tailed distribution to evaluate the significance between means and chi square to evaluate significance between comparisons of categorical independent groups ($p < 0.05$).

To compare the value of CRP of exudative pleural effusion between more than two groups we used One-Way ANOVA.

RESULTS

A total of 286 patients were included in our study. The demographic and biochemical baseline characteristics of patients are presented in Table 1. The patients included 181 men (63.2%) and 105 women (36.8%), with average age 60 ±18 years. The patients with transudative pleural effusion were significantly older than patients with exudative pleural effusions ($p<0.00016$).

According to the criteria used, 67 (23 %) patients were included in the transudative effusion group and 219 (77 %) had exudative pleural effusion. In transudative pleural effusions the CRP levels in the pleural fluid and blood were significantly lower than the CRP levels in patients with exudates ($p< 0.00032$; 0.00011, respectively). The pleural effusion/blood CRP ratio in the transudative group was lower than in the exudative group ($p<0.0125$).

The diagnostic accuracy, sensitivity, specificity, positive and negative predictive value, Youden index and likelihood ratio of CRP in pleural fluid for diagnosing transudates calculated at different cut-off points (≤ 5mg/L, ≤ 10mg/L, ≤ 15mg/L, ≤ 20mg/L, ≤25 mg/L are presented in Table 2.

In general, the lower the CRP, the more likely it was for the patient to have a transudative effusion. At a CRP level ≤ 5 mg/L, the test was very specific for transudates, but was not very sensitive. At this level the Youden index (0.41) was lower than at other values of CRP because of the low sensitivity.

When the pleural fluid CRP level was ≤ 15 mg/L, the sensitivity was 95.5%, specificity 72.3%, accuracy 78 %, negative predictive value 98.2% and Youden index 0.678 in separating transudates from exudates. The possibility that a pleural effusion with a CRP level > 15mg/L was transudative is low (negative likelihood ratio 0.06). Patients with pleural fluid CRP values ≤ 5mg/L were four times more likely to have a transudative effusion than patients with higher CRP values. For patients with pleural effusion CRP values ≤ 15 mg/L the possibility of a transudative effusion was 3.4 times higher than patients with higher values. The possibility that pleural effusion was a transudate in patients with pleural effusion CRP level > 20 mg/L was almost zero.

We measured the sensitivity, specificity, positive predictive, negative predictive, accuracy, Youden index, positive and negative likelihood ratio for transudate effusions according toeffusion/blood CRP ratio for different cut-off values. The value of pleural fluid/blood CRP ratio ≤0.30 had highest specificity, positive likelihood ratio and accuracy (85.1%, 2.84, and 75.50% respectively) compared with other cut off values (0.32, 0.36, and 0.40) but the lowest sensitivity, negative predictive value and Youden index. The value of pleural fluid/blood CRP ratio ≤ 0.32 had the highest Youden index (0.366), but the value ≤ 0.40 had the lowest negative likelihood ratio (0.516), highest negative predictive value (86.9%) with an accuracy of 73.5%.

The utility of CRP, serum cholesterol and Lights criteria in separating transudates and exudates are compared in Table 3. We found that CRP level ≤ 15 mg/L had a higher sensitivity than effusion/serum cholesterol ratio ≤ 0.3 (95.5% and 68.8% respectively), but lower specificity (72.3% and 95%, respectively). Light's criteria were better than both of them (94.7% sensitivity and 100% specificity).

The demographic and biochemical characteristics of the subgroups with exudates are presented in table 4. According to multiple comparisons (ANOVA), the differences in CRP values in exudative pleural effusions between the malignant, tuberculous and parapneumonic effusion are significant.

In malignant effusions subgroup, mean CRP level (10.4 ±9.9 mg/L) was significantly lower than that in all the other exudative subgroups (parapneumonic effusion, tuberculous effusion and chronic non-specific effusion $p < 0.002$, 0.003 and 0.001 respectively). The fluid/serum CRP ratio was equal in the malignant effusion (0.55 ±0.28 mg/L) and in parapneumonic pleural effusion (0.55 ±0.22) [$p= 0.986$]. No significant differences were seen in fluid/serum CRP ratios between malignant and tuberculous effusions (0.55 ±0.28 mg/L and 0.58±0.24 respectively) [$p= 0.514$].

The sensitivity, specificity, positive and negative predictive value, accuracy, Youden index, positive and negative likelihood ratio for malignant effusions, according to CRP level, is presented in Table 5.

CRP level ≤30 mg/L in pleural malignant effusion had a high sensitivity (94.1%), lower specificity (73%) and negative likelihood ratio 0.08 among other cut-off points for separating malignant from other types of exudative effusions. Pleural fluid CRP levels ≤20 mg/L had a higher Youden index (0.728), sensitivity of 88.2%, specificity 84.6% and a positive likelihood ratio of 5.73. A CRP fluid level ≤20mg/L in exudates is highly suggestive of malignancy. The cut-off value of fluid/blood CRP ratio ≤0.45 had

the highest Youden index (0.41) and negative predictive value (82%). Meanwhile, the cut-off value ≤0.30 had the highest specificity (89%) and positive likelihood ratio (2.47).

In malignant pleural effusions, the cut-off value of pleural fluid CRP ≤20mg/L had a Youden index of 0.728 and the area under curve = 0.89, as compared with tuberculous effusions. In tuberculous effusions, the cut-off value of pleural fluid CRP >20mg/L had a Youden index of 0.45 and the area under curve=0.96, as compared with malignant effusions (picture 1&2).

Sensitivity, specificity, positive and negative predictive value, accuracy, Youden index, positive and negative likelihood ratio for tubercular effusions according to CRP level is presented in Tables 6. In tuberculous effusion, the CRP cut-off value > 20mg/L had the highest Youden index (0.447). Meanwhile, the CRP cut-off value > 15mg/L had the highest sensitivity (86.2), negative predictive value (81.8) and the lowest negative likelihood ratio (0.25).The cut-off value of effusion/blood CRP ratio > 0.55 had the highest Youden index (0.223), negative predictive value (84.2) and the lowest negative likelihood ratio (0.39). The value of effusion/blood CRP ratio > 0.50 had the highest sensitivity (90.4%) and positive likelihood ratio (1.69). The biochemical characteristics of tuberculous effusion according to CRP cut-off are presented in table 6.

In 18 patients with tuberculuos effusion the pleural fluid CRP was less than 20mg/L. In table 7 we have presented the characteristic of tuberculous and malignant effusion according to CRP cut-off level < 20 mg/L. Significant difference were seen only in fluid CRP level between tuberculous and malignant effusions (14.05±3.99mg/L and 7.55±6.3mg/L, respectively) [p< 0.0001]

There is a good correlation between CRP level in pleural effusions and blood (table 8), but the sensitivity of CRP level in blood is very low.

Sensitivity, specificity, positive and negative predictive value, accuracy, Youden index, positive and negative likelihood ratio for parapneumonic effusions according to CRP values are presented in Table 9.

In parapneumonic effusion, the cut-off value of fluid CRP >60 mg/L had the highest Youden index (0.833), positive likelihood ratio (8.63), and very low negative likelihood ratio (0.06).The CRP value more than 40 mg/L had the highest sensitivity (100%), negative predictive value(100%) and the lowest negative likelihood ratio.

Discussion

The most frequent dilemma in diagnosis of exudative pleural effusions is related to differentiating the malignant pleural effusions from inflammatory non malignant ones. A dilemma not less challenging is to determine whether the pleural effusions with inflammatory origin are infectious or not.

In etiologic diagnosis of pleural effusions of inflammatory origin, an important step is to find out if the inflammation is acute, sub acute or chronic. This will help not only in the diagnostic, but also in the treatment approach.

In settling the former dilemma, the biomarkers have an important and indispensable role to play. The number of biomarkers of inflammation with infectious origin is equally large and diverse. This diversity bewilders us in deciding to choose the biomarker type and quantity. The smartest approach in selecting the biomarkers would be to identify the one which would immediately provide us as much information as possible. Is any biomarker which could shows us that the pleural effusion is of inflammation origin or not, that the inflammation is acute, sub acute or chronic, or could almost exclude malignant origin of effusion?

It would be wisely questioned: what is the difference between acute and chronic inflammation? It is known that acute inflammation normally begins immediately and lasts for hours or several days. Patients, who are presented with exudative pleural effusion, have a medical history of the diseases, lasting, in many cases, over a week or month. The diagnosis of parapneumonic effusion or empyema is decided in most of the cases without the need of using new biomarkers. The combination of past medical history, the presence of polymorphonuclear preponderance, the reduced levels of glucose and pH, the high levels of lactate dehydrogenase (LDH) in pleural effusion and leukocytosis and increased presence in the blood of the bends form of white blood cell, are fully enough to accurately diagnose the presence of an acute inflammation of infectious origin. Consequently, the most difficult diagnosis would be the distinction between sub acute and chronic inflammation. The presence of lymphocytes excludes the acute nature of inflammation and is characteristic of sub acute and chronic inflammation. The presence of neutrophils over 50% provides sufficient data in the diagnosis of pleural effusions due to acute inflammation. Therefore, the use of biomarkers of acute inflammation is essential not only in differentiating the activity of inflammation, sub acute or chronic, but also in excluding the non inflammatory aetiology of pleural effusion.

Inflammation is the root of many diseases, such as respiratory, cardiovascular, immunologic, diabetic, arthritis, neurologic, cancer and etc. The inflammation is triggered by many stimuli such as infections (bacterial, viral, parasitic) and microbial toxins, trauma (blunt and penetrating), physical and chemical agents (thermal injury, e.g., burns or frostbite, irradiation, some environmental chemicals), tissue necrosis (from any cause), foreign bodies (splinters, dirt, sutures), immune reactions (hypersensitivity or autoimmunity). Considering the big number of causes of acute inflammation, it is not reasonable to spend so much energy with new biomarkers of acute inflammation. There are traditional biomarkers and data of acute inflammation, such as values of glucose, pH and lactate dehydrogenase and the presence or absence of neutrophils in pleural effusions [1]. We would like to point out that in etiologic diagnosis of pleural effusion, as a result of acute inflammation, it is more difficult to find out the cause of infection than to differentiate if it is of infectious or non-infectious origin.

The first step in diagnosing pleural effusion is to find out if it is with inflammatory origin or not. After that it is important to differentiate if the inflammation is acute or chronic. The more frequent causes of acute inflammation in pleural effusion are parapneumonic effusions, pulmonary infarction, post cardiac injury syndrome (PCIS), lupus pleuritis, acute pancreatitis, sub diaphragmatic abscesses, liver, hepatic and splenic abscesses, splenic infarction.

Pleural fluid analysis, associated with the clinical presentation, should enable a definitive or confident presumptive diagnosis in close to 95% of patients. [2] The predominant cell population is determined by the type of pleural injury and the timing of thoracentesis in relation to the acute pleural injury. The acute response to any pleural injury, whether infectious, immunologic, or malignant, is the attraction of neutrophils to the pleural space, initiated by the chemotaxin interleukin-8. [3, 4]

Within 72 hours following the cessation of acute pleural injury, mononuclear cells enter the pleural space from the peripheral blood and become the predominant cells. [5]

This macrophage predominance is subsequently replaced by lymphocytes in effusions that persist for more than 2 weeks. Therefore, a neutrophil-predominant exudate is the rule when the patient presents shortly after the onset of symptoms, i.e., acute bacterial pneumonia, acute pulmonary embolism with infarction, and acute pancreatitis. In contrast to the insidious onset of disease, as with malignancy and tuberculosis, a lymphocyte-predominant exudate is found. [2]

However, the most difficult and frequent dilemma in diagnosis of pleural effusion is to differentiate the sub acute inflammation from the chronic one, whether it is triggered by an infection, or not. According to [8,9] elevated pleural fluid levels of CRP, soluble triggering receptor expressed on myeloid cells (sTREM-1), and lipopolysaccharide-binding protein (LBP), identify patients with infectious effusions, particularly those with CPPE. However, none of the new biomarkers achieved better performance characteristics than pH, glucose or lactate dehydrogenase in labelling CPPE. [8,9]

C-reactive protein (CRP) is considered to be the biomarker of choice to detect an inflammatory state, whether it is triggered by an infection, or not. Therefore, it is very important to know which differences of its values are encountered in inflammatory states of infectious and non-infectious origin, especially between sub acute and chronic infections. In all the studies concerning the diagnostic value of C-reactive protein in exudates, the authors have pointed out the fact that high CRP levels (higher than 45mg/l) are very suggestive of infectious and inflammatory pleuritis and low values suggest a malignant origin (1, 2, 3, 4, 5, 8, 9)

Porcel et al. [9] and Alvin Tung et al. [10] showed that a pleural fluid CRP level >80 mg/L argues for the presence of a parapneumonic (PPE) (LR+7.4), whereas CRP levels <20 mg/L are a strong indicator against an infectious pleural effusion, whether of bacterial or mycobacterial nature. In our study of 286 cases with pleural effusions the CRP has been less than 20mg/L in 18 cases of 67 with tuberculous effusion. These results show us that the values of CRP in pleural effusion can help to know if the inflammatory state is sub acute or chronic. In these cases, the low levels of pleural fluid and serum CRP suggest that TB infection is not in its acute phase corresponding to the long history of disease with lower levels of LDH and proteins in pleural effusions and more squeal. Meanwhile, the levels higher than 20 mg/L signify that infection is more or less in its acute phase. Therefore, the CRP values in pleural effusions less than 20 are characteristic of chronic inflammation and do not exclude the diagnosis of tuberculosis or other chronic infection. These findings are the same as in the study of Castaño Vidriales lJL et al [11] wherein they found out that two exudates with tuberculosis origin had a C-reactive protein value lower than 10 mg/L.

In our study, pleural fluid CRP levels have been found significantly lower in transudates group (5.91±5.3 mg/L.) This finding is the same as the result of Wilma Turay U et al. [6] In another study, Botana-Rial M et al. have pointed out that CRP levels in the pleural fluid and plasma were higher in patients with benign pleural effusions (BPE), particularly infectious pleural effusion. However, the measurement of CRP and PCT is not a useful parameter for discriminating between BPE and malignant pleural effusion (MPE) and does not provide useful information in the clinical practice [7].

A number of studies, highlighting the use of CRP as a diagnostic aid in tuberculous pleuritis, low pleural CRP levels (<30 mg/L), make this diagnosis unlikely, while being more indicative of a malignancy in patients with exudates [9, 10, 12, 13, 14]

The data of our study provide support for the use of CRP as a diagnostic aid in differential diagnosis between tuberculous and malignant effusions not for its value < 30mg/L, but for values >30mg/L, which almost exclude the malignancy as the cause of pleural effusions. The same result is presented in the study of Garcia-Pachon E et al [15], where a level above 45 mg/l virtually rules out this possibility.

We would like to point out the overuse of CRP in the daily practice, especially in patients with acute presentation of the disease where the utility of using CRP values in blood or fluid is smaller than in patients with sub acute or chronic diseases. The reason is simple, in front of acute inflammation, whatever the cause might be, infectious or not, the CRP values will be high. We do not think that CRP is superior to pH, glucose, in the diagnosis of complicated parapneumonic effusions. Do we really need in patients with neutrophilic pleural effusions, acute symptoms and findings of pH, glucose, LDH, the new acute inflammation biomarkers to make the diagnosis of acute inflammation or to decide our approach? Considering the results of many studies [1, 8, 9, and 10] and our daily practice we do not need new biomarkers of acute inflammation in the diagnostic step of acute pleural effusions. The biomarkers of acute inflammation, such as CRP, help in the diagnosis of pleural effusion almost excluding malignancy (CRP>30mg/L) and narrowing diagnostic options of lymphocytic exudative effusions.

The pleural fluid CRP >than 20 mg/l virtually exclude transudative nature of pleural effusion [16, 17].

The algorithm for the initial evaluation of pleural effusion modified from Light RW on 2002 was as follow (algorithm 1):

Considering the CRP levels in pleural effusion, especially higher than 30mg/L, we propose for the first time that measuring the CRP in pleural effusion could be the diagnostic step in analyzing the exudative pleural effusion. It is through this marker that we immediately receive the information whether the fluid could be malignant or non-malignant. The algorithm for the initial evaluation of pleural effusion modified from us is as follow (algorithm 2):

C-reactive protein (CRP), which is synthesized by hepatocytes, is an acute-phase protein widely used as a marker of inflammation and tissue injury. According to this fact, it is reasonable to mention that measuring the CRP levels in blood could be enough to be used in diagnosing pleural effusions. However, this is not true because the sensibilities and specificities of CRP levels in blood are lower than those in pleural effusions. In the case of discrimination of transudative from exudative effusions for a CRP cut-off level <20 mg / L in liquid and blood, sensitivity and specificity resulted to be 95.5% and 72.3% versus 59.3% and 74.7% respectively. In malignant effusion for a CRP cut-off level <20 mg / L in liquid and blood sensitivity and specificity resulted to be 88.2% and 84.6% versus 48.5% and 86% respectively. In tuberculous pleurisy for a CRP cut-off level >20 mg / L in liquid and blood sensitivity and specificity resulted to be 72.4% and 72.3% versus 85.1% and 38 respectively. We may explain this by the fact that CRP levels in pleural effusions are not so much influenced by other causes influencing the CRP levels of the blood.

Levels of CRP in exudative pleural effusion less than 30 mg/L do raise the question: malignant or TB pleural effusion? Measurement of the pleural fluid ADA would probably be a good option in this situation. Meanwhile, the levels of CRP in exudative pleural effusions higher than 30mg/l almost exclude the malignant aetiology of pleural effusion.

CONCLUSION:

CRP levels below 30 mg/L in an exudative pleural effusion strongly suggest a malignant or chronic TB effusion. Alternatively, pleural fluid CRP levels above 30 mg/L are suggestive of inflammatory etiology and almost exclude malignant origin of pleural effusion.

A pleural fluid CRP level lower than < 15 mg/L is a strong indicator of transudative effusion if other clinical and biochemical data are suggestive of transudative pleural effusion. In contrast, a CRP pleural fluid level > 20mg/L almost excludes transudative pleural effusion. In the differential diagnosis of pleural effusions, higher CRP-levels may help in differentiating parapneumonic effusions from other exudates types.

With relevance to the the data of our study, the pleural CRP-levels may be a helpful, practical, accurate and rapid method for differ-

ential diagnosis between malignant and non- malignant exudative pleural effusion. We would propose that CRP be included in modified algorithm (11) of diagnosis for the exudative pleural effusion.

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Author contributions: Dr. Kapisyzi planned the study, reviewed the data, analysis and contributed in writing the manuscript. Dr. Argjiri planned the study, participated in data gathering, performed the analysis, and contributed in writing the manuscript. Dr. Mitre performed the measuring of CRP in blood and effusion. Dr. Burazeri performed the statistical data analysis. Dr. Nuredini, Tashi participated in data gathering. Dr. Hasa performed the measuring of biochemical values of pleural effusions. Dr.Tabaku planned the study and contributed in writing the manuscript. Dr. Light planned the study, reviewed the data and contributed in writing the manuscript.

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Table 1: Demographic and biochemical baseline characteristics

	Total cases	Transudative effusion	Exudative effusion	P-value
Number (%)	286 (100%)	67 (23 %)	219 (77%)	<0.001
Gender M/F (number)	181/105	49/18	132/87	0.9
Age (mean ±SD)	60.3±18	72.8±7.1	56.6±18.5	0.00016
CRP in effusion ±SD mg/L	37.1±48	5.91±5.3	46±51.7	0.00032
CRP in blood ±SD mg/L	76.3±99.8	17.4±17	93.1±107	0.00011
Effusion /blood CRP ratio ± SD	0.57±0.38	0.36±19	0.64±0.49	0.0125
Total protein in fluid ±SD gm/dl	4.5±1.4	2.76±1.0	4.99±1.04	0.00079
Total protein in blood ±SD gm/dl	6.7±0.56	6.7±0.6	6.7±0.67	0.09
Protein effusion / blood±SD	0.6±0.17	0.41±0.16	0.74±0.14	0.00092
LDH in fluid ±SD IU/L	634±572	188±67	756±594	0.0001
LDH in blood ±SD IU/L	463±238	361.4±106	492±254	0.0691
LDH fluid /blood ±SD IU/L	1.38±0.95	0.54±0.18	1.59±0.94	0.00058
Cholesterol in fluid ±SD mg/dl	73.8±39	38±20.1	80±30	0.00047
Cholesterol in blood ±SD mg/dl	161.3±37.4	156±32	165±37	0.39
Cholesterol fluid/blood ratio	0.48±0.37	0.24±0.12	0.48±0.15	0.00003
Fibrinogen in blood ±SD mg/dl	565±257	411±67	609±262	0.0003

M: male, F: female, SD: Standard Deviation, CRP: C - reactive protein, LDH: Lactate dehydrogenase,

Table 2: Sensitivity, specificity, positive predictive, negative predictive, accuracy and Youden index,positive and negative likelihood ratio for transudative effusions according to CRP level.

	CRP<5mg/L	CRP<10mg/L	CRP<15mg/L	CRP<20mg/L	CRP < 25 mg/L
sensitivity	55%	84.40%	95.5%	95.5%	100%
Specificity	85.80%	78.70%	72.3%	72.3%	55.4%
PPV	53.10%	53.2%	50%	50%	39.4%
NPV	86.90%	94.5%	98.2%	98.2%	100%
Accuracy	79%	80%	77.5%	77.5%	65.5%
Lahr+	3.91	3.96	3.45	3.45	2.24
Lahr-	0.51	0.19	0.061	0.061	0
YOUDEN index	0.413	0.631	0.678	0.678	0.554

CRP: C - reactive protein, PPV: Positive Predictive Value, NPV: Negative Predictive Value, Lahr+:

Positive likelihood ratio, Lahr-: Negative likelihood ratio

Table 3: Statistical analysis of the parameters used to classify transudates (%)

	Fluid CRP	Fluid : serum cholesterol	Light's criteria
Cut- off level	≤ 15 mg/ L	≤ 0.3	at least one of parameter
Sensitivity	95.5	68.8	94.7%
Specificity	72.3	94.8	100%
P P V	50	79.4	98.2%
N P V	98.2	91.8	100%
Accuracy	77.5	89	98.6%

CRP: C - reactive protein, PPV: Positive Predictive Value, NPV: Negative Predictive Value

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Table 4: Demographic and biochemical characteristics of exudates subgroups

	Exudative effusions	Malignant effusions	Parapneumonic effusion	Tuberculous effusions	Others	P-value	
Total cases, N (%)	219(100%)	72(33%)	48(22%)	67(30%)	32(14%)	<0.0001	
Gender	Male	132(60%)	45(62.5%)	30(62.5%)	39(59%)	18 (57%)	0.6667
	Female	87 (40 %)	27(37.5%)	18 (37.5%)	28(41%)	14 (43%)	0.3954
Age (mean ±SD)	56.6±18.5	64.6±8.8	53±18	50.0±22.4	63.6±14	< 0.0001	
CRP in effusion mg/L, Mean± SD	46±51.7	10.4±9.9	125±67.9	34.6±19.3	38.3±19.2	<0.0001	
CRP in blood mg/L, Mean ± SD	93.1±107	27.4±34	248±124	70.3±50.7	64±49	<0.0001	
CRP effusion/blood ratio, Mean ± SD	0.64±0.49	0.55±0.28	0.55±0.22	0.58±0.24	0.67±0.2	0.1396	
Total protein in effusion, gr/dl ±SD	4.99±1.04	4.93±1.2	5.02±1.03	5.07±0.88	4.8±1.17	0.3384	
Total protein in blood, g/dl, ±SD	6.7±0.67	6.7±0.66	6.86±0.67	6.9±0.8	6.52±0.78	0.1135	
Protein effusion /blood ratio, ±SD	0.74±0.14	0.74±0.17	0.75±0.15	0.74±0.14	0.73±0.12	0.7962	
LDH in effusion, mg/dl, ± SD U/L	756±594	544±435	1242±790	815±558	458±315	0.0009	
LDH in blood, mg/dl, ±SD U/L	492±254	412±193	745±247	529±251	406±261	0.0001	
LDH effusion /blood ratio, ±SD	1.59±0.94	1.4±1	1.7±0.75	1.57±0.66	1.25±0.92	0.0877	
Cholesterol in effusion mg/dl ,±SD	80±36	78.4±36.2	85.3±43.7	82.6±29	96.7±51	0.1317	
Cholesterol in blood mg/dl, ±SD	162±39	171.4±46	160.9±38.5	156±34.6	160.4±20	0.0553	
Cholesterol fluid/blood ratio ±SD	0.55±0.36	0.47±0.26	0.66±0.68	0.53±0.16	0.63±0.44	0.0753	
Fibrinogen in blood mg/dl, ±SD	609±262	490±193	818±336	607±204	578±245	<0.0001	

SD: Standard Deviation, CRP: C - reactive protein, LDH: Lactate dehydrogenase,

Table 5: Sensitivity, specificity, positive and negative predictive value, accuracy and Youden index,
positive and negative likelihood ratio for malignant effusions according to CRP level versus all other exudates

	CRP≤10mg/L	CRP ≤ 15mg/L	CRP≤20mg/L	CRP≤25mg/L	CRP≤30mg/L
Sensitivity	62.9	68.7	88.2	90	94.1
Specificity	98	92.3	84.6	78.8	73
PPV	94.1	81.4	73.7	67.6	63.1
NPV	77.8	78.6	93.6	94.2	96.2
Accuracy	86.4	84.5	85.8	82.5	80
Lahr+	0.608	0.609	0.728	0.690	0.671
Lahr-	32.6	8.92	5.73	4.26	3.57
YOUDEN index	0.37	0.33	0.13	0.12	0.08

CRP: C - reactive protein, PPV: Positive Predictive Value, NPV: Negative Predictive Value, Lahr+:

Positive likelihood ratio, Lahr-: Negative likelihood ratio

Table 6: Sensitivity, specificity, positive and negative predictive value, accuracy, Youden index, positive and negative likelihood rtio for tubercular effusions according to CRP level versus all other exudates.

	CRP>15mg/L	CRP>20mg/L	CRP>25mg/L	CRP>30mg/L	CRP> 40mg/L
Sensitivity	86.2	72.4	62	51	29.3
Specificity	55.3	72.3	75.3	83	92.3
PPV	60	56	69.2	68	77.2
NPV	81.8	74.6	69	66	59.4
Accuracy	70	72.3	69.1	68.3	62.6
Lahr+	1.93	2.6	2.5	3.05	3.81
Lahr-	0.25	0.38	0.5	0.58	0.76
YOUDEN index	0.415	0.447	0.374	0.348	0.216

CRP: C - reactive protein, PPV: Positive Predictive Value, NPV: Negative Predictive Value, Lahr+:

Positive likelihood ratio, Lahr-: Negative likelihood ratio

Table 7. LDH, total protein, glucose and cholesterol in pleural fluid (means) according CRP cut-off < 20 mg/L (TB pleurisy vs. malignant effusion)

	TB pleurisy	malignant effusion	p-value
cases (nr)	18	64	
CRP in effusion, ±SD	14.05±3.99	7.55±6.3	<0.0001
CRP in blood, ±SD	31.4±16	19.7±23.7	0.0727
CRP in blood/ CRP in effusion,±SD	0.53±0.2	0.55±0.2	0.8

CRP: C - reactive protein, SD: Standard Deviation,

Table 8. Correlations between CRP level in effusion and blood

	Correlation
In total cases	0.847631
In transudative effusions	0.635741
In total exudative effusions	0.834478
In malignant effusions	0.797229
In TB pleurisy	0.743774
In parapneumonic effusions	0.542796
In "other "exudative effusions	0.864335

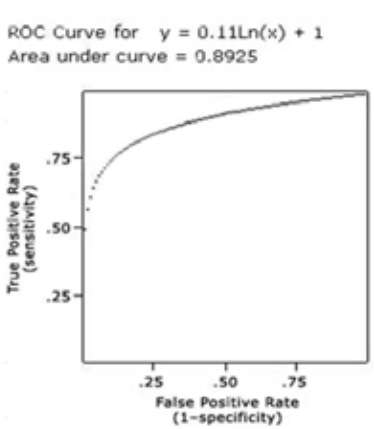
Table 9: Sensitivity, specificity, positive and negative predictive value, accuracy, Youden index,
positive and negative likelihood ratio for parapneumonic (empiema) effusions according to CRP

values versus all other exudates.

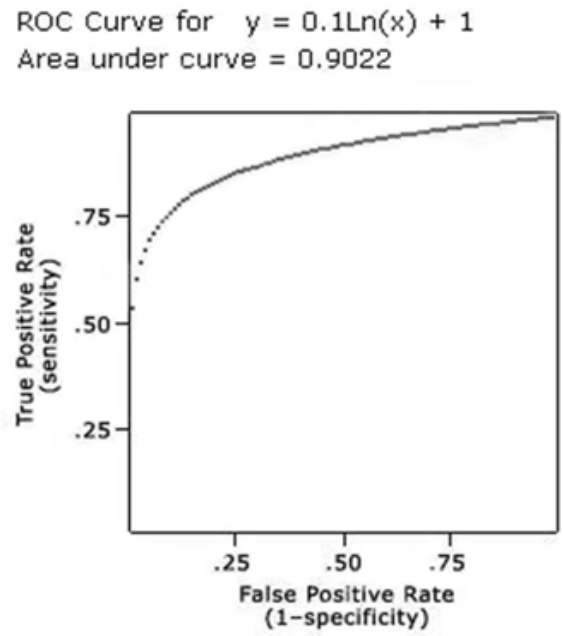
	CRP>40mg/L	CRP>50mg/L	CRP>60mg/L	CRP>70mg/L
Sensitivity	100	94.1	94.1	82.3
Specificity	76.9	84.6	89.2	95.3
PPV	53.1	61.5	69.5	82.3
NPV	100	98.2	98.3	95.3
Accuracy	81.7	87	90.2	92.7
Lahr+	4.32	6.11	8.63	17.5
Lahr-	0	0.069	0.066	0.18
YOUDEN index	0.769	0.786	0.833	0.776

CRP: C - reactive protein, PPV: Positive Predictive Value, NPV: Negative Predictive Value, Lahr+: Positive likelihood ratio, Lahr-: Negative likelihood ratio

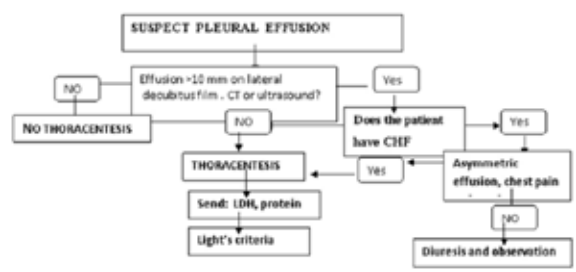
Receiver Operating Characteristic (ROC) Curve



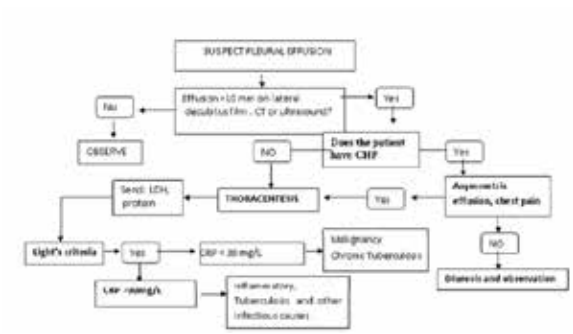
1. Malignant vs. TB pleural effusions.



2. Malignant vs. other non TB exsudative effusions.



Algorithm 1: The algorithm for the initial evaluation of pleural effusion modified from Light



Algorithm 2: Considering the CRP levels in pleural effusion, especially higher than 30mg/L in exudative pleural effusion

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REFERENCE

1. Parapneumonic Effusions and Empyema. Richard W. Light Proc Am Thorac Soc Vol 3. Pp 75–80, 2006. | 2. Steven A. Sahn, Evaluation of the Patient with a Pleural Effusion: PCCSU Article 01.15.08 | 3. Light RW, Erozan YS, Ball WC. Cells in pleural fluid: their value in differential diagnosis. Arch Intern Med 1973; 132:854-8604. | 4. Pettersson T, Riska H. Diagnostic value of total and differential leukocyte counts in pleural effusions. Acta Med Scand 1981; 210:129-135 | 5. Antony VB, Sahn SA, Antony AC, et al. Bacillus calmette-guerin stimulated neutrophils | release chemotaxins for monocytes in rabbit pleural spaces and in vitro. J Clin Invest 1985; 76:1514-1521) | 6. Yilmaz Turay U; Yildirim Z; Türköz Y; Biber C; Erdogan Y; Keyf A I; Ugurman F; Ayaz A; Ergün P; Harputluoglu M Use of pleural fluid C-reactive protein in diagnosis of pleural effusions. Respiratory medicine 2000; 94(5):432-438 | 7. Botana-Rial M, Casado-Rey P, Leiro-Fernández V, Andrade-Olivié M, Represas-Represas C, Fernández-Villar A. Validity of procalcitonin and C-Reactive protein measurement when differentiating between benign and malignant pleural effusion. Clin lab. 2011; 57 (5-6):373-8 | 8. S. C. Chen Æ W. Chen Æ W. H. Hsu Æ Y. H. Yu Æ C. M. S: Role of Pleural Fluid C- | Reactive Protein Concentration in Discriminating Uncomplicated Parapneumonic Pleural Effusions from Complicated Parapneumonic Effusion and Empyema Lung (2006) 184:141–45; | 9. J. M. Porcel , M. Vives , G. Cao , S. Bielsa , A. Ruiz-González , A. Martínez-Iribarren and A. Esquerda.Biomarkers of infection in pleural fluid for the differential diagnosis of pleural effusions, Eur Respir J, 2009;34:1383–9. | 10. Alvin Tung, Semra Bilaceroglu, Jose M Porcel, Jenette Creaney, YC Gary Lee Biomarkers in Pleural Diseases US Respiratory Disease, 2011;7(1):26-31 | 11. Castaño Vidriales JL, Amores Antequera C.Use of pleural fluid C-reactive protein in laboratory diagnosis of pleural effusions.Eur J Med. 1992 Jul-Aug;1(4):201-7.) | 12. Chierakul N, Kanitsap A, Chaiprasert A, et al. A simple C-reactive protein measurement for the differentiation between tuberculous and malignant pleural effusion. Respirology 2004;9:66–69. | 13. Garcia-Pachon E, Soler MJ, Padilla-Navas I, et al. C-reactive protein in lymphocytic pleural effusions: a diagnostic aid in tuberculous pleuritis. Respiration 2005;72:486–489. | 14. Daniil ZD, Zintzaras E, Kiropoulos T, et al. Discrimination of exudative pleural effusions based on multiple biological parameters. Eur Respir J 2007;30:957–964.) | 15. Garcia-Pachon E, Llorca I.Diagnostic value of C-reactive protein in exudative pleural effusions. Eur J Intern Med. 2002 Jun;13(4):246-249 | 16. Yilmaz Turay U, Yildirim Z, Türköz Y, Biber C, Erdoğan Y, Keyf AI, Uğurman F, Ayaz A, Ergün P, Harputluoğlu M.Use of pleural fluid C-reactive protein in diagnosis of pleural effusions. Respir Med. 2000 May;94(5):432-5. | 17. Kapisyzi P, Argjiri Dh,Byrazeri G, Mitre A, Beli J et al.Use of pleural fluid C reactive proteins level as diagnostic marker for pleural effusions.Chest;2009;136:30-36 |