

Value of C-reactive protein in differentiation between tuberculous and malignant pleural effusion

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Background Few studies had reported the value of C-reactive protein (CRP) in differentiating between tuberculous pleural effusion (TBPE) and malignant pleural effusion (MPE).

Aim The aim of this study was to investigate the diagnostic value of CRP in differentiating between TBPE and MPE.

Settings and design This prospective study was conducted in a University Hospital.

Patients and methods During a period of 18 months, a prospective study included 59 adult patients with pleural effusion. The study included two groups: group I, which included 29 patients with TBPE, and group II, which included 30 patients with MPE. Serum C-reactive protein (s-CRP) and pleural fluid C-reactive protein (p-CRP) were measured and compared in both groups, using enzyme-linked immunosorbent assay.

Results The mean values of s-CRP were 28.34 ± 14.41 and 27.87 ± 13.21 mg/dl in TBPE and MPE, respectively, with no significant difference. The mean values of p-CRP were 36.51 ± 3.91 and 26.39 ± 7.57 mg/dl in TBPE and MPE, respectively, with a highly significant difference ($P=0.001$). There were significantly positive correlations between s-CRP and p-CRP in both TBPE and MPE ($r=0.685$ and $P=0.001$; $r=0.594$ and $P=0.006$, respectively). With the use of cutoff values of 31.6

and 43.3 mg/l for p-CRP and s-CRP, sensitivity and specificity were 89.47 and 80.00% for p-CRP, and 15.79 and 100.00%, respectively, for s-CRP. The area under the receiver operating characteristic curve of p-CRP was 0.888, superior to that of s-CRP (0.525).

Conclusion Measurement of CRP levels in the pleural fluid has a good utility in the diagnostic workup of patients with pleural effusion. p-CRP can be a useful adjunctive test, as a potential differentiator between TBPE and MPE.

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Introduction

Diagnosis and management of pleural effusions remain a challenge because the catalog of the diseases they cause is as big as it is diverse. The dilemma is in differentiating transudative from exudative effusions. However, the more important dilemma in the diagnosis of exudative effusions is to differentiate benign from malignant effusions, which is very important as they have different outcome and management [1]. Although cytological examination of the pleural fluid is an easy way to diagnose a pleural malignancy, a false-negative rate of about 40% has been reported [2]; therefore, there is an increasing demand for markers that may help in this differentiation.

C-reactive protein (CRP) was discovered in 1930 and is widely used as a sensitive, but nonspecific, marker of systemic inflammation [3]. The induction of CRP synthesis is triggered by a number of cytokines, which are released in the inflammatory region, chiefly the pyrogenic cytokine, interleukin-6, which is released mainly from macrophages and monocytes [4]. Increased serum C-reactive protein (s-CRP) levels have been reported in many pulmonary disorders, including pneumonia, malignancies, and pulmonary

thromboembolism [5]. Some studies had investigated the value of CRP in the diagnosis of pleural effusion [6–8]. However, few studies had reported the value of CRP in the differentiation between tuberculous pleural effusion (TBPE) and malignant pleural effusion (MPE) [9,10]. The aim of the current study was to investigate the diagnostic value of CRP in the differentiation between TBPE and MPE.

Patients and methods

Study population

This study was conducted prospectively at the Department of Chest Diseases and Tuberculosis, Assiut University Hospital, from April 2013 to October 2014. The study protocol was approved by the Ethics Committee, Faculty of Medicine, Assiut University. It included adult patients who were admitted with the preliminary diagnosis of exudative pleural effusion. Thereafter, the patients were

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classified according to their final diagnosis into two groups: group I included patients with TBPE, and group II included patients with MPE.

All patients were subjected to the following:

- (1) Full medical history and clinical examination.
- (2) Routine laboratory investigations (e.g. blood urea and serum creatinine, liver functions, especially albumin, and collagen profile, as needed).
- (3) Radiological examination: Plain chest radiograph posteroanterior and lateral views, and chest ultrasonography. Whenever needed, computed tomography scan of the chest, abdominal ultrasonography, and echocardiography were performed.
- (4) Tuberculin skin testing, in cases of suspected tuberculous pleurisy.
- (5) Sputum examination for acid fast, alcohol fast bacilli with Ziehl–Neelsen stain on 3 successive days.
- (6) Sputum cytology was studied for the detection of malignant cells.
- (7) Diagnostic thoracocentesis: collection and processing of the pleural fluid samples (about 300–500 ml) were carried out and subjected to the following examinations:
 - (a) Physical examination.
 - (b) Chemical examination, including protein level, lactate dehydrogenase (LDH) level, total and differential cell count, and adenosine deaminase level when tuberculous effusion is suspected.
 - (c) Bacteriological examination.
 - (d) Cytological examination for malignant cells.
 - (e) Quantitative measurement of pleural fluid C-reactive protein (p-CRP).
- (8) Pleural biopsy: sonographic-guided closed pleural biopsy using either Cope's or Abram's needle pleural biopsy.
- (9) Collection of 3 ml of venous blood for quantitative measurement of s-CRP.

There were no reported major complications during the period of research, and all patients provided informed written consent.

Diagnostic criteria for pleural effusions

An exudative pleural effusion was defined, according to Light's criteria [11], by one or more of following: (a) ratio of LDH in the pleural fluid to that in the serum of more than 0.6; (b) ratio of total protein in the pleural fluid to that in the serum of more than 0.5; and (c) pleural effusion LDH level greater than two-thirds the upper limit of the laboratory's reference range of serum LDH.

The diagnosis of tuberculous pleurisy was suggested upon high tuberculin positivity, lymphocytic pleural fluid, few mesothelial cells, and elevated adenosine deaminase level in pleural fluid, and was confirmed with the presence of positive stain for *Mycobacterium tuberculosis* in the pleural fluid, sputum, or pleural biopsy, or the presence of caseating granuloma in the pleural biopsy.

MPE was defined as malignant cells detected on cytological examination of the effusion or pleural biopsy.

Exclusion criteria

- (1) Transudative pleural effusion.
- (2) Being under chemotherapy or radiotherapy.
- (3) Empyema.
- (4) Immunocompromised patients.
- (5) Contraindication for thoracocentesis (e.g. patient is confused or in a bad general condition).
- (6) Inadequate amount of effusion drained for diagnostic procedures.

Ultrasound-guided closed pleural biopsy

A real-time ultrasound scanner (Aloka Prosound SSD 3500SV, ALOKA Co., Ltd., Mitaka-shi, Tokyo, Japan) was used. Cope's closed pleural biopsy needle was used, which contains an outer needle 11 G with an adjustable needle stop, and an inner 13 G biopsy trocar (hook-shaped) for pleural biopsy sample collection. All biopsies were placed in 10% formalin and sent to the pathologist for histopathological examination.

Measurement of C-reactive protein

s-CRP and p-CRP concentrations were determined using enzyme-linked immunosorbent assay kit supplied by Chemux Bio Science (San Francisco, California, USA).

Statistical analysis

All statistical analyses of differences between TBPE and MPE were performed using the Mann–Whitney *U*-test. Spearman's correlations were used to determine the relationships between p-CRP and s-CRP. The diagnostic accuracies of p-CRP and s-CRP in discriminating between TBPE and MPE were compared by constructing receiver operating characteristic (ROC) curves. The optimum cutoff point from the ROC analysis was established by selecting the value that provides the greatest sum of sensitivity and specificity. Data were analyzed using the statistical package for the social sciences (SPSS) software (version 16; SPSS Inc., Chicago, Illinois, USA). Statistical significance was defined as *P* less than 0.05.

Results

Demographic data

During the study period, 59 adult patients with exudative pleural effusion were enrolled. These patients were classified according to their final diagnosis into two groups. Group I included 29 patients with TBPE, of whom 19 (66%) were male and 10 (34%) were female. Their ages ranged from 17 to 62 years, with the mean age of 34 years. Group II included 30 patients with MPE, of whom 18 (60%) were male and 12 (40%) were female. Their ages ranged from 35 to 70 years with the mean age of 57 years. This group comprised 10 female patients with metastatic breast cancer, 12 secondary to bronchogenic carcinoma (were diagnosed by means of bronchoscopic biopsy), three male patients with malignant mesothelioma, and five patients with metastatic carcinoma (renal, colon, gastric, and ovarian). Table 1 shows the demographic data, sonographic findings, and cytological findings of the studied groups.

Serum C-reactive protein and pleural C-reactive protein levels

Levels of s-CRP and p-CRP in the two studied groups are shown in Table 2. s-CRP levels ranged from 2.3 to 45.3 mg/dl, with a mean value of 28.34 ± 14.41 mg/dl in TBPE, whereas it ranged from 3.8 to 43.3 mg/dl, with a mean of 27.87 ± 13.21 mg/dl in MPE. No significant difference was found in the s-CRP levels between the two patient groups ($P=0.916$). p-CRP levels ranged from 30.2 to 43.5 mg/dl, with a mean value of 36.51 ± 3.91 mg/dl in TBPE, whereas it ranged from 13.8 to 44.0 mg/dl, with a mean of 26.39 ± 7.57 mg/dl in MPE. A highly significant difference ($P=0.001$) was

Table 1 Demographic data, sonographic findings, and cytological findings of the studied groups

	Tuberculous effusion (n=29) [n (%)]	Malignant effusion (n=30) [n (%)]	P-value
Age (years)			
Mean \pm SD	34.68 \pm 14.72	57.65 \pm 10.03	0.000*
Range	17.0–62.0	35.0–70.0	
Sex			
Male	19 (66)	18 (60)	0.389
Female	10 (34)	12 (40)	
Sonographic findings			
Simple effusion	19 (66)	16 (54)	0.240
Complex septated effusion	10 (34)	4 (13)	0.077
Pleural nodules	0 (0)	10 (33)	0.000*
Cytology			
Lymphocytes	26 (90)	10 (33)	0.000*
Malignant cells	0 (0)	11 (37)	0.001*
Mesothelial cells	3 (10)	9 (30)	0.098

*Highly significant difference.

found in the p-CRP levels between the two patient groups. Table 2 shows these data.

Correlation between serum C-reactive protein and pleural C-reactive protein

Figures 1 and 2 demonstrate the correlation between s-CRP and p-CRP in the two studied groups. There were significantly positive correlations between s-CRP and p-CRP levels in both patients with TBPE (Spearman's coefficient of correlation; $r=0.685$ and $P=0.001$) and patients with MPE (Spearman's coefficient of correlation; $r=0.594$ and $P=0.006$) (Figs 1 and 2).

Diagnostic values of C-reactive protein

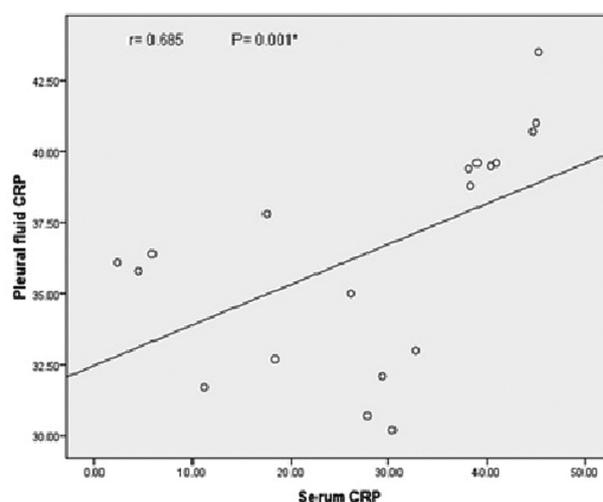
To evaluate whether p-CRP and s-CRP levels could discriminate between TBPE and MPE, cutoff values were determined by the maximum sum of sensitivity and specificity. We used cutoff values of 31.6 and 43.3 mg/l for p-CRP and s-CRP, respectively, yielding sensitivity and specificity values of 89.47 and 80.00% for p-CRP, and 15.79 and 100.00% for

Table 2 Serum and pleural fluid C-reactive protein levels among studied groups

	TB effusion (n=29)	Malignant effusion (n=30)	P-value
Serum CRP (mg/dl)			
Mean \pm SD	28.34 \pm 14.41	27.87 \pm 13.21	0.916
Range	2.3–45.3	3.8–43.3	
Pleural fluid CRP (mg/dl)			
Mean \pm SD	36.51 \pm 3.91	26.93 \pm 7.57	0.001*
Range	30.2–43.5	13.8–44.0	

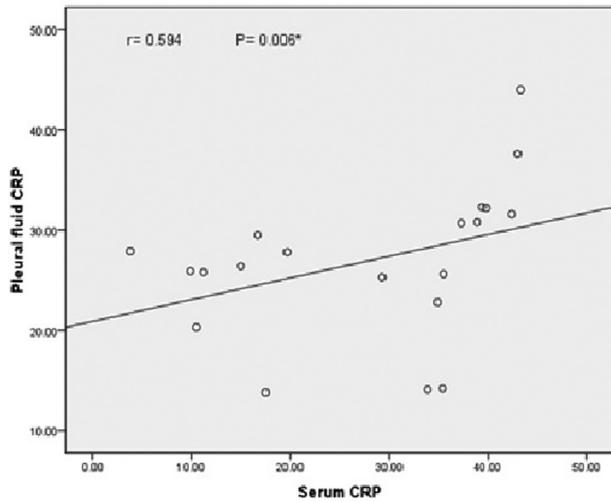
CRP, C-reactive protein; TB, tuberculosis. *Highly significant difference.

Figure 1



Correlation between serum and pleural C-reactive protein (CRP) levels in tuberculous pleural effusion. *Highly significant.

Figure 2



Correlation between serum and pleural C-reactive protein (CRP) levels in malignant pleural effusion. *Highly significant.

s-CRP, respectively. The ROC curves of p-CRP and s-CRP for distinguishing TBPE from MPE are shown in Figs 3 and 4. We found that the area under the ROC curve of ROC curves (diagnostic accuracy) of p-CRP (0.888) was superior to that of s-CRP (0.525).

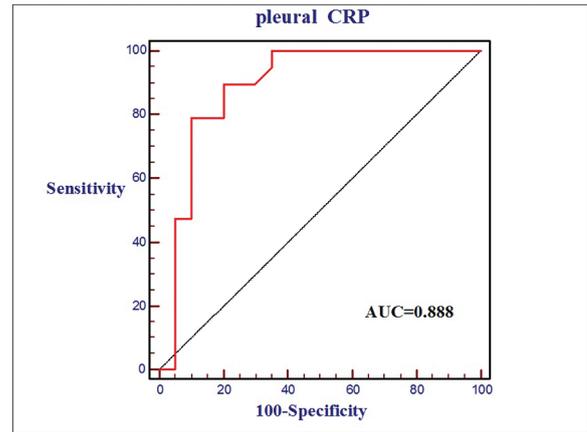
Discussion

The diagnosis of pleural effusion is a difficult challenge because the catalog of the diseases they cause is as big as it is diverse, and in most cases of pleural effusions data are not pathognomonic. The more frequent dilemma in the diagnosis of exudative pleural effusions is differentiating MPEs from inflammatory nonmalignant one [1]. Moreover, the conventional cytological examination of pleural fluids for differentiating benign from MPE is of limited diagnostic accuracy [1,2].

In a living organism, a biochemical, physiological, and immunological reaction cascade is produced as a response to chemical, physical, and immunological stimuli, infectious agents, and malignancies. This reaction is known as the acute-phase response [12].

CRP was discovered in 1930 and is widely used as a sensitive, but nonspecific, marker of systemic inflammation [3]. 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 been suggested [13]. The plasma half-life of CRP is about 19 h and is constant under all conditions of health and disease, and hence the sole determinant of circulating CRP concentration is the synthesis rate, which thus directly reflects the intensity of the

Figure 3

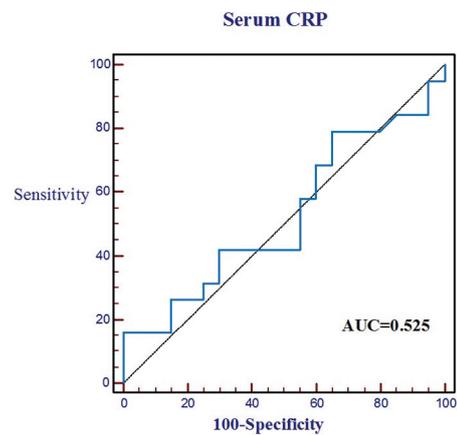


*AUC, area under the ROC curve

Cut-off	Sensitivity	Specificity	+PV	-PV	AUC
> 31.6	89.47	80.00	81.0	88.9	0.888

Diagnostic accuracy of pleural C-reactive protein (CRP) in differentiation between tuberculous and malignant pleural effusion.

Figure 4



*AUC, area under the ROC curve

Cut-off	Sensitivity	Specificity	+PV	-PV	AUC
> 43.3	15.79	100.00	100.0	55.6	0.525

Diagnostic accuracy of serum C-reactive protein (CRP) in differentiation between tuberculous and malignant pleural effusion.

pathological process(es) stimulating CRP production [14].

In most diseases, the circulating value of CRP reflects ongoing inflammation and/or tissue damage much more accurately than do other laboratory parameters of the acute-phase response, such as plasma viscosity and the erythrocyte sedimentation rate. Importantly, acute-phase CRP values show no diurnal variation. Hepatic failure impairs CRP production, and very few drugs reduce CRP

values unless they also affect the underlying pathology providing the acute-phase stimulus. Thus, the CRP concentration is a very useful nonspecific biochemical marker of inflammation [13,14]. Increased s-CRP levels have been reported in many pulmonary disorders, including pneumonia, malignancies, and pulmonary thromboembolism [5].

The current study was conducted prospectively to investigate the value of CRP in differentiating between TBPE and MPE.

Our results revealed that the mean value of s-CRP in MPE is lower than that in TBPE, but this difference did not reach a statistical significance. However, p-CRP values were significantly lower in MPE in comparison with TBPE. These findings are in agreement with previous reports [7–10].

Chierakul *et al.* [9] in their study of 161 patients with pleural effusion found that p-CRP and s-CRP levels were significantly higher in patients with tuberculous effusion in comparison with those with malignant effusion. They concluded that, in patients presenting with lymphocytic exudative pleural effusion, a simple marker of elevated p-CRP level may be helpful in discriminating between TBPE and MPE [9]. Garcia-Pachon *et al.* [15], in their evaluation of 144 patients with lymphocytic pleural effusion, observed that p-CRP level was higher in tuberculous pleurisy than in lymphocytic effusion of other origins. The authors concluded that CRP pleural fluid determination is useful in the diagnostic workup of lymphocytic pleural effusions. High CRP levels are very suggestive of tuberculous pleuritis and low CRP levels make this diagnosis unlikely [15].

We reported a significant difference between the mean values of p-CRP of 36.51 ± 3.91 and 26.39 ± 7.57 mg/dl in TBPE and MPE, respectively. Sedky *et al.* [10] found a highly significant difference in p-CRP between tuberculous (29.07 ± 9.32 mg/dl) and malignant (19.30 ± 4.35 mg/dl) effusions. They concluded that CRP is a useful and cheap marker for differentiating between TBPE and MPE.

Our data demonstrated significant correlations between serum and pleural fluid levels of CRP in both patients with tuberculous and those with malignant effusion.

This finding is in agreement with that of Park *et al.* [16], who studied the CRP levels in 80 patients with MPE and 68 patients with benign effusions and found

that p-CRP levels correlated with s-CRP levels ($r=0.82$ and $P<0.0001$).

In our data, more significant correlation was encountered in patients with TBPE than in those with MPE ($P=0.001$ vs. 0.006 , respectively). This could be attributed to higher p-CRP values in nonmalignant effusions that reflect a higher local production of p-CRP in response to a higher degree of inflammation, granuloma formation, and increased vascular permeability of the pleura in patients with tuberculous pleurisy [1,17].

In contrast, the reasons for CRP elevation in cancer patients are not completely understood. One possible explanation is as follows: due to cytokine production by tumor tissue, elevated CRP values may indicate a higher tumor burden [18]. Scott *et al.* [19] 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.

In the current work, we used cutoff values of 31.6 and 43.3 mg/l for p-CRP and s-CRP, respectively, which yielded sensitivity and specificity values of 89.47 and 80.00% for p-CRP, and 15.79 and 100.00% for s-CRP, respectively. The diagnostic accuracy of p-CRP was 0.888, and was superior to that of s-CRP (0.525). These findings are in accordance with those of previous reports [16,20,21].

Park *et al.* [16] observed that the diagnostic accuracy of p-CRP for distinguishing lung cancer with MPE from benign pleural effusion was 0.86, and superior to that of s-CRP (0.77). Botana-Rial *et al.* [20] reported that the diagnostic accuracies of p-CRP and s-CRP for differentiating MPE from benign pleural effusion were 0.752 and 0.667, respectively.

In a study on 97 patients with pleural effusion, Turay *et al.* [21] compared CRP levels between transudates and exudates, and between inflammatory effusions and other types. They found that p-CRP levels greater than 30 mg/l had a sensitivity of 93.7% and a specificity of 76.5% for inflammatory pleural effusions.

In an Egyptian experience, El-Shimy *et al.* [8] studied the value of CRP levels among 54 patients with pleural effusions of different etiologies (eight transudative, 14 parapneumonic, 14 tuberculous, and 18 malignant effusion). p-CRP levels ranged from 2.1 to 16 mg/dl

(mean: 6.992 ± 3.727 mg/dl) in tuberculous effusion and ranged from 1.01 to 6.8 mg/dl (mean: 2.491 ± 1.69 mg/dl) in malignant effusion. s-CRP level was significantly higher in patients with tuberculous effusion (14.110 ± 3.62 mg/dl) than in those with malignant effusion (6.450 ± 2.240 mg/dl) ($P < 0.001$). p-CRP level was significantly lower in patients with malignant effusion (2.491 ± 1.69 mg/dl) than in patients with tuberculous effusion (6.992 ± 3.727 mg/dl) ($P = 0.002$). Interestingly, the used cutoff values for CRP were different among different studies. Samaha *et al.* (7) studied CRP levels in both infectious and MPEs and showed that, at a cutoff value of $96.15 \mu\text{g/ml}$ for CRP, diagnostic sensitivity was 61% and specificity was 45%. Porcel [2] differentiated TBPE from MPE when CRP levels in pleural fluid were greater than 20 mg/l. Ji *et al.* [22] could differentiate between TBPE from MPE with p-CRP levels of 30 versus 18 mg/l, respectively, whereas Kapisyzi *et al.* [1] showed that p-CRP levels less than 20 mg/l are a strong indicator against an infectious pleural effusion, whether of bacterial or mycobacterial nature. These differences among studies could be attributed to different population demographics, numbers, laboratory assessment, and statistical analysis.

To summarize, our data are in agreement with previous studies reporting the importance of CRP in the diagnostic workup of pleural effusion, and, particularly, in differentiating tuberculous from malignant exudative pleural effusions. CRP is a relatively simple, rapid, and inexpensive test in the hands of the clinician, especially in the setting of developing countries.

In the view of our daily clinical practice, Kapisyzi *et al.* [1], in their review of the literature, concluded that CRP is very useful as a diagnostic aid in tuberculous pleuritis, wherein low p-CRP levels (< 30 mg/l) make this diagnosis unlikely. Considering these results, measuring CRP in pleural effusion has to be a routine examination of pleural effusions because it gives a broad information to following dilemma: inflammatory origin or non-inflammatory one, subacute or chronic inflammation [1].

The current study has a possible limitation – that is, the relatively low number of enrolled patients. Further studies with more enrolled participants are warranted.

Conclusion

Measurement of CRP levels in the pleural fluid has a good utility in the diagnostic workup of patients with pleural effusion. p-CRP can be a useful adjunctive test, as a potential differentiator between TBPE and MPE.

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Conflicts of interest

There are no conflicts of interest.

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