

# Role of CRP as a marker for discrimination of exudative and transudative pleural effusion

Omid Rismantab<sup>1</sup>, Seyed Ali Javad Moosavi<sup>2</sup>, Mohammad Reza Farahnak<sup>3</sup>, Maryam Dastoorpoor<sup>4</sup>, Hanieh Raji<sup>1</sup>

<sup>1</sup>Department of Internal Medicine, Air Pollution and Respiratory Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz; <sup>2</sup>Air Pollution Research Center, Iran University of Medical Sciences, Tehran, <sup>3</sup>Thoracic Surgery Department, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz; <sup>4</sup>Department of Biostatistics and Epidemiology, Air Pollution and Respiratory Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

## Abstract

Differentiation between exudative and transudative pleural effusion is sometime problematic. This study aimed to evaluate the diagnostic value of C-reactive protein (CRP) in differentiation of

Correspondence: Hanieh Raji, Emam Khomeini Hospital, Azadegan Street, Ahvaz, Iran.  
E-mail: dr.raji.h@gmail.com

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exudative and transudative pleural effusion. This is an analytical epidemiologic cross-sectional study that evaluates the role of CRP in differentiating transudative and exudative pleural effusion. Patients were divided into two groups of exudates and transudates, based on Light's criteria. The pleural effusion CRP levels were compared between the two groups. SPSS software version 16 was used for statistical analysis. The significance level was considered at  $p < 0.05$ . A total of 169 patients with pleural effusion enrolled in the study. Based on Light's criteria, 108 patients (63.9%) had exudative pleural effusion and 61 (36.1%) had transudative pleural effusion. The level of CRP in the pleural fluid of patients in the exudative and transudative groups was  $13.3 \pm 37.1$  and  $3.5 \pm 4.3$  mg/dl, respectively ( $p = 0.008$ ). The 3.31 mg/dl cut-off point of CRP level of pleural effusion had the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 96.3%, 72.1%, 86% and 91.7%, respectively. The results obtained in our study shows that the level of CRP in the effusion fluid can be helpful in differentiating exudative from transudative pleural effusions.

## Introduction

Approximately 1.5 million people in the United States suffer from pleural effusions annually which imposes significant costs on the health system for diagnosis [1]. The most common causes of pleural effusion include cancers, heart failure, pneumonia, tuberculosis, pericardial disease, and cirrhosis [1]. The imbalance between secretion and absorption of pleural fluid leads to abnormal accumulation of fluid in the pleural space and development of the pleural effusion [2]. The first step in the diagnostic approach to pleural effusion is to determine the nature of effusion in terms of exudate and transudate, which determines the overall diagnostic-therapeutic strategy by Light's criteria [1-5] which has 97.5% sensitivity in diagnostic differentiation of exudates and transudates [3]. Meanwhile, 18 to 30% of patients with transudative effusion due to liver cirrhosis and heart failure meet at least one of Light's criteria which leads to diagnostic dilemma [3,6]. In such situation, the use of other biochemical markers can be helpful to make a sound diagnosis of the exudative and transudative nature of the pleural effusion [7,8]. C-reactive protein (CRP) is an inflammatory marker and acute phase protein [9,10]. As inflammatory responses are responsible for exudative pleural effusion, various studies have been conducted to evaluate the role of pleural fluid CRP in differentiating exudative and transudative pleural effusions. The results indicate

the probable diagnostic value of CRP. However, this has not been fully proved and is still under review [1,2,10]. Moreover, pleural fluid CRP levels can be used to distinguish parapneumonic effusions and other types of exudative effusions [11]. This study sought to evaluate the sensitivity and specificity of pleural CRP in distinguishing exudative effusions and transudative effusions.

## Methods

This is an analytical epidemiologic cross-sectional study that evaluates the role of CRP by the Enzyme-Linked Immunosorbent Assay (ELISA) method in differentiating transudative from exudative pleural effusion in patients referring to Ahwaz Jundishapur University of Medical Sciences. After obtaining the permission of the Ethics Committee (Ethics code: IR.AJUMS.REC), we evaluated 169 patients with pleural effusion. The exclusion criteria were: not having definitive diagnosis, the presence of several etiologies for pleural effusion in a same subject, patients unwilling or unable to provide informed consent and the ambiguity of Light's criteria classification. Patients were divided into two groups of exudates and transudates, based on Light's criteria [12], and CRP levels were compared between the two groups.

All statistical analyses were performed using SPSS ver.16 (SPSS Inc. Chicago, IL, USA). Statistical analyses were performed with the chi-square test for categorical variables and sample *t*-test for continuous variables. The Receiver Operating Curve (ROC) was used to determine the optimal cutoff point for CRP. Moreover, the accuracy of sensitivity, specificity, positive predictive value

(PPV), and negative predictive value (NPV) of CRP were determined in differentiating exudative from transudative pleural effusion. Significance level was considered at  $p < 0.05$ .

## Results

A hundred sixty-nine patients with pleural effusion were included. The mean age of the patients was  $63.7 \pm 17.5$  years. The level of CRP in pleural fluid of patients ranged from 0.1 to 369 mg/dl with a mean and SD of  $9.8 \pm 30.1$ . One hundred and two (60.4%) of the patients were male and 67 (39.6%) were female. Based on Light's criteria, 108 patients (63.9%) had exudative pleural effusion and 61 patients (36.1%) had transudative pleural effusion. The mean age ( $\pm$  SD) of the patients with exudative pleural effusion was  $61. \pm 17.4$  years. In patients with transudative pleural effusion, it was  $67.9 \pm 17.0$  years, and the difference was statistically significant ( $p = 0.017$ ). The frequency distribution pleural effusion causing diseases is shown in Table 1. The level of CRP in exudative pleural effusion was  $13.3 \pm 37.1$  mg/dl, and in the transudate group it was  $3.5 \pm 4.3$  mg/dl; the difference was statistically significant ( $p = 0.008$ ). No significant gender difference was observed among the two groups ( $p = 0.542$ ). The ROC curve was used to calculate the sensitivity and specificity of the pleural fluid CRP level for differentiation of exudative from transudative pleural effusion based on the results for Light's criteria. ROC analysis revealed an AUC of 0.85 (CI 95% = 0.78-0.90), indicating a good diagnostic accuracy ( $p < 0.001$ ) (Figure 1). The 3.31 mg/dl cut-off point for the CRP level of pleural effusion had the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of 96.3%, 72.1%, 86.0% and 91.7%, respectively. Frequency of distribution for exudative and transudative pleural effusions according to CRP is shown in Table 2.

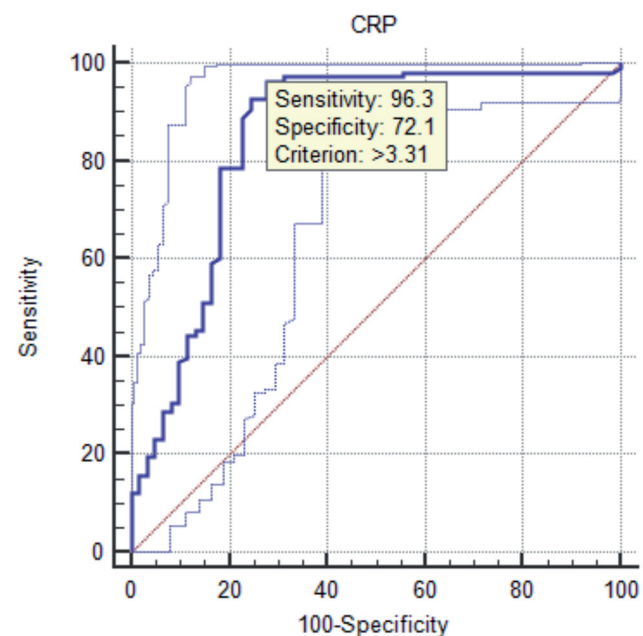
**Table 1. The distribution of frequency of transudative and exudative patients (n=169).**

Variable	n	%
Transudate effusion	61	36.1
Exudate effusion	108	63.9
Total	169	100.0
The kind of exudative effusion	N	%
Para malignant effusion	58	34.3
Para pneumonic effusion	15	8.8
Tuberculosis pleuritis	9	5.3
End stage renal diseases	7	4.1
Rheumatologic disorder	6	3.5
Pulmonary embolism	6	3.5
Post CABG	4	2.3
Pancreatitis	3	1.8
Total	108	63.9

CABG, coronary artery bypass graft.

**Table 2. The distribution of frequency of exudative and transudative pleural effusion according to C-reactive protein.**

C-reactive protein	Pleural effusion		p-value
	Exudative (%)	Transudative (%)	
Negative	4 (3.7)	44 (72.1)	
Positive	104 (96.3)	17 (27.9)	<0.001
Total	108 (100.0)	61 (100.0)	



**Figure 1. ROC curve CRP level for discrimination exudate and transudate effusion ( $p < 0.0001$ ). Blue line, CRP ROC area: 0.85; dotted blue line, 95% confidence interval for CRP ROC area: 0.78-0.90; dotted red line, reference.**

## Discussion

In this present study we have evaluated the diagnostic performance CRP in patients with transudative and exudative pleural effusions. The main observation of this study is that CRP marker can be helpful for the differentiation pleural effusions.

In our study the mean age of patients with exudative pleural effusion was lower than transudative form. The most common cause of transudative pleural effusion is congestive heart failure which may occur at older ages. Infectious causes of exudative effusion such as tuberculosis and para pneumonic effusion usually predominate among individuals younger than those affected by cancer.

Our results showed that CRP level in patients with exudative pleural effusion was higher than the transudative form. Cut-off point for the CRP level in pleural effusion was 3.3 mg/dl with high sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The results of this study are consistent with previous studies that showed that the levels of CRP of pleural fluid is higher in exudative effusions, with cut-off points ranging from 3 to 9 mg/dl [12-16]. It should be noted that the difference in the absolute amount of cut-off points can be due to various laboratory kits and methods to measure CRP levels. In addition, the different etiologies of pleural effusion can affect CRP levels. Kapisyzi *et al.* [15] observed that the sensitivity of pleural fluid CRP is higher than the serum CRP to differentiate exudative from transudative and malignant from benign pleural effusions.

Some studies show that CRP level in the pleural fluid has prognostic value for needing drainage in addition to the diagnostic value. Porcel *et al.* [13] found that CRP levels greater than 10 mg/dl is associated with complicated effusion and drainage intervention. Moreover, the combination of classical biomarkers (pH<7.2, LDH>1000IU/dl, and glucose<60mg/dl in pleural fluid) increases the accuracy of diagnosis [13,17].

According to a study by Kapisyzi *et al.* [15], among all 286 patients with pleural effusion, 67 patients (23%) were transudates and 219 (77%) were exudates, and CRP level was significantly lower in the transudative pleural effusion than the exudate group. The 1.5 mg/dl cut-off of pleural CRP had 78% accuracy, 95.5% sensitivity, 72.3% specificity, and 89.2% negative predictive value. Another study by Rezaeetalab *et al.* [2] on 79 patients with pleural effusion demonstrated that CRP level of pleural fluid was significantly higher in exudative pleural effusion (13.7±11.1) than the transudate group (2.9±1.3). Moreover, based on Light's criteria, 50 cases (63.3%) had exudative effusion and 29 cases (36.7%) had transudative effusion, which showed a sensitivity and specificity of 94% and 96.6% at the 5 mg/dl cut-off point of CRP for pleural effusion, respectively. A survey by Turay *et al.* [4] in 97 patients, CRP level in the pleural fluid was significantly higher in the exudative group (35.5±4.9 mg/dl) than the transudative group (14.9±4.9 mg/dl). Additionally, at the cut-off point of 3 mg/dl of CRP for differentiation of exudative and transudative pleural effusions had a sensitivity of 93.7%, specificity of 76.5%, and a positive predictive value of 98.4%.

Our limitation in this study is the lack of serum CRP level data which could serve for control and determination of gradient of CRP serum and pleural or the pleural-to-serum CRP ratio. However, strength of our study may be good sample size.

## Conclusions

Pleural fluid CRP levels may be helpful in differentiating exudative from transudative pleural effusions.

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