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The diagnostic value of pleural effusion pro-calcitonin level in different etiologies of exudative pleural effusion

Majid Malekmohammad, Parisa Adimi Naghan, Payam Tabarsi, Mihan Pourabdollah, Seyed Amir Mohajeri, Farzaneh Fotoohi and Seyed Mohammad Reza Hashemian*

Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Disease (NRITLD), Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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Pleural effusion etiologies are diagnosed based on serum and plural fluid characteristics. However, diagnosis of different etiologies such as Tuberculosis (TB) or malignancy is still a challenge. Pro-Calcitonin (PCT) may have diagnostic value in exudative pleural effusion. The aim of this study was to assess PCT level in plural fluid and to find an appropriate cut off point for different etiologies of plural effusion. This study was conducted on 49 patients with exudative plural effusion and measured plural PCT. There was no significant difference between different etiologies in plural fluid characteristics except for plural PCT. The mean Plural PCT was significantly higher in metastatic pleural effusion (1.08 ± 1.1 ng/mL) than in TB (0.24 ± 0.04 ng/mL). Area under curve for metastatic pleurisy was 0.78 with 95% CI of 0.61-0.94, and specificity and sensitivity were 0.44 and 0.90 at the 0.3 ng/mL cut-off values. Findings of present study showed that plural PCT level could be of diagnostic value in metastatic pleurisy but not TB with appropriate sensitivity and specificity.

Key words: Tuberculosis, pleurisy, plural effusion, procalcitonin, neoplastic.

INTRODUCTION

Pro-Calcitonin (PCT) is 116 amino acid with 13 kd molecular weight, secreted from neuroendocrine cells in thyroid but also from liver and lung in response to TNF- α and endotoxines (Nyamande and Laloo, 2006) in shock, metastatic cancers, and bacterial, fungal and viral infections (Karzai et al., 1997; Brunkhorst et al., 2000; Mandi et al., 2000; Rau et al., 2000). PCT has been typically defined as an acute phase reactant protein detected in many inflammatory process such as septic shocks and bacterial infections (Reinhart and Carlet, 2000). Serum PCT level has been used to diagnose sepsis, multiple organ failure (Nylen et al., 1992), differential diagnosis of bacterial and viral infections (Morgenthaler et al., 2002), and guideline to lower respiratory tract infections and response to treatment

(Polzin et al., 2003). Low serum PCT level accurately predicts the absence of bacteremia in adult patients with acute fever (Naderi et al., 2009), or high serum PCT has a direct correlation to severity of septic shock (Cheval et al., 2000). Interestingly, it is shown that serum PCT level in tuberculosis (TB) patients is higher than community-acquired pneumonia (Mofidi et al., 2009).

Pleura are involved by many bacterial or non-bacterial infections, malignancies, and TB. TB pleural effusion (PE) with or without lung TB component is about 5% of total tuberculosis cases. In fact, TB is the most common cause of treatable pleural exudates in many parts of the world. Mycobacterium Tuberculosis (MTB) could induce pleural effusions after sub-pleural caseous rupture into pleural space through a delayed type hypersensitivity reaction (Raviglion and O'brien, 2005). In addition, about 90% of patients have latent form of TB (WHO, 2004) which could silently produce pleural effusion (Kassim et al., 2000). On the other hand, malignancies and parapneumonic PE are among top causes of exudative

*Corresponding author. E-mail: smrhashemian@sbmu.ac.ir. Tel: 0098 912 111 9279.

Table 1. Comparison of clinical symptoms between TB and cancer group (including metastasis, malignancies, mesothelioma, and lymphoma). P-value was calculated by Fisher's Exact test ($P < 0.05$).

N	TB (%)	Cancer group (%)	P value
Dyspnea	5 (83)	28 (76)	0.571
Weight loss	4 (67)	10 (27)	0.077
cough	2 (33)	16 (43)	0.503
Hemoptysis	1 (17)	5 (14)	0.619
Fever	2 (33)	4 (11)	0.190
Chest pain	0(0)	4 (11)	0.535

PE. Differential diagnosis of exudative PE particularly in young patients has many technical difficulties and diagnostic evaluations are generally non-specific. Although the most specific diagnostic test for TB induced PE is smear and culture of PE, but the sensitivity of tests is low as 10,000 bacteria are needed to be positive. Culture could be positive in 1/3 of cases but takes 2-6 weeks and needs at least 10,000 bacteria (Reichler et al., 2002). Besides, other invasive diagnostic tools like blind biopsy and thoracoscopy has technical difficulties, low sensitivity, and are time consuming. Since the differential diagnosis of TB from malignant exudates is not simple (Corbett et al., 2003), finding specific biomarkers for MBT such as DNA-PCR, or adenosine deaminase (ADA) could be helpful, but each has some restrictions to limit their routine application. So the quest to find new biomarkers in differentiating malignant exudates, tuberculosis and para-pneumonic PE is ongoing.

Due to lack of definite criteria, PCT in pleural fluid has been rarely studied to diagnose different etiologies of exudative pleural effusions (PE) particularly malignant and TB exudates. In this study we embarked on diagnostic value of pleural fluid PCT level as an indicator for diagnosing different etiologies of exudative pleural effusion.

METHODS

This was a prospective study in our referral hospital center between Jan. 2010 until Jan. 2011. The study was reviewed and approved by the hospital ethics committee and been performed in accordance with the ethical standards laid down in an appropriate version of the 2000 Declaration of Helsinki (<http://www.wma.net/e/policy/b3.htm>). All patients gave their informed consents prior to their inclusion in the study according to University Hospital Ethical Board Committee.

All demographic information and clinical symptoms were recorded. A sample of PE was obtained and sent for biological and cytological studies to department of laboratory and pathology. In all patients whom diagnosis of exudates based on Light criteria (including: Protein pleura/serum > 0.5 g/l, LDH pleura/serum > 0.6 IU/ml, and pleural LDH $> 2/3$ serum LDH) were confirmed, a sample of PE were reserved and sent for Pro-Calcitonin measurements. Any patient with hemothorax, transudative PE, and acute feverish diseases were excluded from study.

Diagnostic criteria

The diagnostic criteria for tuberculous pleuritis was set as the following: (a) Mycobacterium tuberculosis was detected by culture from pleural fluid or pleural biopsy specimen; (b) caseating granuloma was present on biopsy specimen, with or without positive staining for acid-fast bacilli (AFB); (c) positive sputum culture for M. tuberculosis with no alternative explanation for exudative pleural effusion was obtained. Malignant pleural effusion was diagnosed when malignant tissue in the pleural cavity was shown by pleural biopsy or cytopathology, and type of the cancer was revealed after final diagnosis based on pathologic diagnosis of the specimen.

Statistics

Differences between the two groups were tested using the nonparametric Mann-Whitney U-test for continuous variables. Fisher's exact test was used for categorical variables. Optimal cutoffs for predicting pulmonary TB or cancer were investigated using receiver-operating characteristics (ROC) analysis, and the diagnostic accuracy was assessed from the area under the ROC curves (AUCs). To test the assumption of difference of different variables in pleural fluid we used multi-factor ANOVA. A $p < 0.05$ was regarded as statistically significant, and analyses were performed using SPSS 16.

RESULTS

Demographic and clinical characteristics of patients

From 49 patients with exudative PE, 30 patients (70%) were men. Patient age range and mean (\pm SD) were 18-84 and 55 ± 19 years. Only 6 patients ultimately were diagnosed with TB through detecting mycobacterium tuberculosis in smear or culture of pleural effusion or biopsy from pleura, and 27 patients diagnosed with cancers. Different ultimate diagnosis of patients is included in Table 2. There were no significant differences between age and gender between TB and cancer group of patients. In total, there were 33 patients (77%) with dyspnea, 14 patients (33%) with weight loss, 18 (42%) with cough, 6(14%) with hemoptysis, 6 patients (14%) with fever, and 4 patients (9%) with chest patients (Table 1).

Table 2. Comparison of pleural effusion characteristics between different etiologies of Pleural effusion value are mean \pm standard deviation. The significance was calculated by ANOVA. P value significance level <0.05 .

Disease	n	P-Glucose	*P-WBC	P-LDH	**S-LDH	P-Protein	S-Protein
Lymphoma	5	71.60 \pm 38.5	3566 \pm 3027	1643 \pm 2326	1407 \pm 1741	4.42 \pm 1.8	6.25 \pm 0.5
Malignancy	12	99.40 \pm 55	1550 \pm 700	998 \pm 2055	489 \pm 316	4.27 \pm 1.3	6.96 \pm 0.2
Mesothelioma	5	103 \pm 108	1100 \pm 655	471 \pm 281	330 \pm 74	3.58 \pm 2	7.29 \pm 0.3
Metastasis	10	130 \pm 57	1935 \pm 905	865 \pm 633	595 \pm 333	3.91 \pm 0.9	6.92 \pm 1.3
TB	6	208 \pm 340	1278 \pm 1252	983 \pm 1264	590 \pm 342	5.25 \pm 0.4	7.70 \pm 0.8
PPPEs	3	133 \pm 72	2400 \pm 2262	1944 \pm 1470	311 \pm 34	4.7 \pm 0.5	6.25 \pm 0.7
Transudate	10	137 \pm 43	1401 \pm 1888	211 \pm 346	409 \pm 119	2.2 \pm 1.5	6.8 \pm 1
P value	-	0.77	0.32	0.71	0.14	0.4	0.36

N: number of patients; *P: pleural fluid; **S: serum; PPPE: para pneumonic pleural effusion.

Table 3. Comparison between pro-calcitonin level (mean \pm SD) of pleural effusion (PE) in different etiologies of pleural effusion in patients. P-value was calculated by ANOVA test. P value significance level <0.05 .

Etiologies	Pleural Pro-calcitonin	P value
Lymphoma	0.20 \pm 0.03	0.11
Malignancy	0.51 \pm 0.12	0.085
Mesothelioma	0.28 \pm 0.14	0.549
Metastasis	1.08 \pm 1.1	0.017
TB	0.24 \pm 0.04	0.984
PPPEs	0.6 \pm 0.2	0.077
Transudate	0.25 \pm 0.1	0.685

Pleural effusion characteristics

The glucose mean and range and mean \pm SD in total patients were 10-900 mg/dl and 134 \pm 144 mg/dl; The WBC range was from 50-6800 and mean was 1584 \pm 1508; LDH range and mean was 74-7170 and 1095 \pm 1544 IU/ml; Protein level range and mean in PE of total patient was 1.7-6.1 and 4.2 \pm 1.2 respectively. Protein level in TB was significantly higher than cancer group but the other components were not statistically different in two groups (Table 2). Comparison between Pro-Calcitonin levels (mean \pm SD) of pleural effusion (PE) in different etiologies of pleural effusion in patients by using multi factor ANOVA showed only PCT in metastatic pleurisy is significantly different among all etiologies (Table 3).

Pro-Calcitonin level in pleural effusion of TB and cancer group patients

The AUC for PCT in PE of TB patients were 0.27 with 95 % CI of 0.11-0.42, and Specificity and sensitivity values for pleural fluid PCT are 0.46 and 0.50 at the 0.3 ng/mL cut-off values, respectively (Figure 1a). The median and inter-quartile range (IQR) was 0.3 and 0.2-0.5 ng/dl.

There was no significant difference between TB and other patients in Pro-Calcitonin level of pleural effusion.

Specificity and sensitivity of Pro-Calcitonin in malignant pleural effusions

This study compared the Pro-Calcitonin level in PE of TB and all different malignant PE pleurisy and found that the procalcitonin level did not perform more accurately in TB compared to cancer group PE diagnosis. To explore the specificity of Pro-Calcitonin in diagnosing TB and non TB pleuresia by using a cutoff point of 0.3 ng/ml by using a ROC curve and area under the curve (AUC) it appears that only in metastasis we have a statistical significant AUC. The areas under the curve values for PCT level in malignancies other than metastasis, mesothelioma and lymphoma was 0.75 with 95% confidence interval of 0.64-0.89 and Specificity and sensitivity values for pleural fluid PCT are 0.47 and 1.00 at the 0.3 ng/mL cut-off values, respectively (Figure 1b). These values were 0.05 and 1.00 at the 0.1 ng/ml cut-off values, respectively.

The AUC for PCT in metastatic pleurisy were 0.78 with 95% CI of 0.61-0.94, and Specificity and sensitivity values for pleural fluid PCT are 0.44 and 0.90 at the 0.3 ng/mL cut-off values, respectively (Figure 1c). These values were 0.05 and 0.96 at the 0.1 ng/ml cut-off values, respectively. The area measures the ability of the Pro-Calcitonin to correctly classify the etiologies of pleural effusions. In fact, when we lowered the PE Pro-Calcitonin cut off value from 0.3 to 0.1 ng/dl, the false negative rate probability decreased but the false positive rate also increased. Similarly,

DISCUSSION

Pro-Calcitonin (PCT) has been investigated as a marker to diagnose various etiologies of pleural effusion (PE). In this study we evaluated exudative pleural fluid PCT level in patients to find out the sensitivity, specificity of PCT to discover different etiologies. Besides, in our

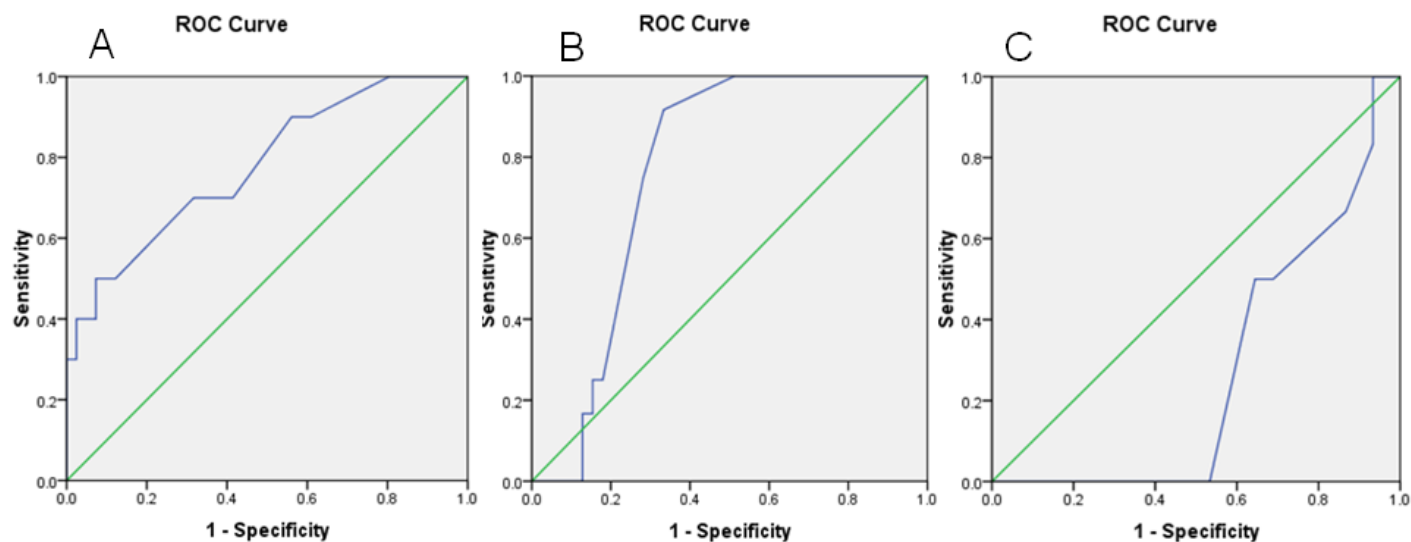


Figure 1. The AUC for pro-caltonin level of plural effusion in patients with metastatic pleurisy(A), malignancy pleurisy (B),and TB pleurisy (C) are depicted in this figure. Details are described in results section.

study diagnostic value of pleural fluid PCT was tested among different etiologies separately, although more cases may be needed to conclude such. Notably, PCT level in pleural fluid had diagnostic value only in metastasis but not in other malignancies or not in TB or pneumonia which was consistent to others studies (Lawn et al., 1998). The diagnostic and predictive value of calcitonin and its prohormone procalcitonin has been much debated in cancers and metastasis. The results of Walter et al. (2010) indicate a superior diagnostic accuracy of calcitonin and an independent predictive value of the procalcitonin: calcitonin ratio. Another study by Matzaraki et al. (2007) revealed that PCT levels are related to liver metastasis stage in cancer patients.

One of our intriguing findings in our study was that PCT levels in PE showed a good sensitivity for distinguishing invasive or metastatic cancers. As a matter of fact, pleural fluid PCT was more sensitive in metastasis than chest originated malignancies, lymphomas, or mesotheliomas. It seems that metastasis from remote sites could induce higher secretion of PCT in pleural fluid from unknown sources. In addition, PCT level cut off point is not a major factor in determining the diagnostic value of PCT in PE. In our study we characterized the sensitivity and specificity of PCT with 0.3 ng/ml in PE. Even though our cut of point was lowered compared to the similar study by Cakir et al. (2005) our result indicated that PCT concentration is not a useful parameter for the diagnosis of tuberculous pleurisy, but that improved sensitivity could be obtained after reducing the cut-off level. When we raised the cut off from 0.3 to 0.4 ng/dl, the false positive rate decreased, but the false negative rate increased. Besides, large confidence intervals in our study may reflect the limitation of our study to include few

cases in some etiologies such as TB patients. On the other hand, Kang et al. (2009) suggested that the high sensitivity and negative predictive value for differentiating pulmonary TB from bacterial CAP suggest a supplementary role of CRP and PCT in the diagnostic exclusion of pulmonary TB from bacterial CAP in areas with an intermediate prevalence of pulmonary TB.

One main feature of our study was to test the predictive value of different characteristics of PCT pleural fluid for different plural effusion etiologies. Our results demonstrated that PCT has no predictive value in TB or PPPEs PE, but PCT has a statistical significance as a predictive index for metastasis induced PE. Procalcitonin has been well established as an important marker of sepsis and systemic infection. Baylan et al. (2006) study mentioned a predictive value of serum PCT levels in adult patients with active TB. The dissimilarity in their results may be due to the source of PCT. Serum PCT is mostly secreted from liver in blood but do not reach the high concentration in pleural fluid. In Wang et al. (2011) study, PCT levels were found to be high in PPPE, empyema, and malignant PE, although they did not described the diagnostic value in different cancerous PE. Very interestingly, they mentioned PCT levels were low in TB pleurisy, malignant effusions, and transudative effusions which are similar to our study findings. Contrary to our study, Kandemir et al. (2003) showed that procalcitonin levels increased both in patients with pulmonary tuberculosis and in the staff, and could be a good indicator for TB chronic PE. Very interestingly, Schleicher studies in consistent with our study showed that PCT in TB have no diagnostic value (Schleicher et al., 2005). They showed that HIV-seropositive patients with pneumococcal community-acquired pneumonia had

significantly higher procalcitonin levels than those with pulmonary tuberculosis.

In conclusion, the findings of this study demonstrated that pleural fluid Pro-Calcitonin is not elevated in patients with pulmonary tuberculosis even at extreme circumstances such as disseminated TB. The significantly raised pleural fluid PCT levels in patients with metastatic pleurisy may indicate that pleural PCT levels are occasionally elevated in patients who are in severe situations with extensive metastasis that involved pleura or who have advanced malignancies and metastatic pleural exudates. The determination of pleural PCT levels appears clobbered in diagnosing TB exudative PE but still have value in detecting malignant PE particularly in metastatic pleurisy.

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