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Research Article

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Evaluation of the diagnostic values of pleural fluid procalcitonin in transudates and exudates pleural effusions

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ABSTRACT

Different etiologies of pleural effusion are diagnosed based on serum and plural fluid characteristics. Recently it has been found that the ProCalcitonin (PCT) might have the diagnostic value in exudative pleural effusion (PE). The aim of this study was to assess PCT level in plural fluid and serum to find the specificity and sensitivity of PCT for different etiologies of PE. This study was conducted on 80 patients with exudative PE (Parapneumonic; PE (20 cases), Tuberculosis; TB (20 cases), Malignant effusions (20 cases) and transudate PE (20 cases) to measure the serum and PE level of PCT. The mean Plural PCT was significantly higher in pleural PE of parapneumonic effusion (115.10 ±14.06 µg/mL). The cutoff point of value to explore PCT for diagnosing considered at 0.3 ng/mL and this cut-off calculated by using ROC method. It appears that only in parapneumonic pleurisity, a statistically significant area under curve was observed (P=0.001). The area under curve amount in blood PCT level for parapneumonic pleurisity versus non parapneumonic pleurisity was 0.44 with 95% confidence interval of 0.24-0.61 and specificity and sensitivity values for pleural fluid PCT were 0.42 and 0.42 (P=0.09). Present study showed that plural PCT level in parapneumonic pleurisy could have diagnostic value neither in TB nor in malignancies pleurisity patients. The pleural PCT has higher diagnostic accuracy comparing withserum PCT in differentiating parapneumonic pleurisy from non parapneumonic pleurisy. Both pleural fluid PCT and serum PCT were useful for assessing the severity of pneumonia with parapneumonic plural effusions.

Key words: Procalcitonin, parapneumonic, Plural effusion Tuberculosis, pleurisy, Malignancy

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INTRODUCTION

Procalcitonin (PCT) hormone with 13Kd molecular weight is a protein by 116 aminoacids with 32 identical to calcitonin prohormone. Calcitonin secretes from neuroendocrine C cells of thyroid gland under normalmetabolic conditions and cleavage after prohormone PCT. Also serum PCT (SPCT) is produced in liver and lung in response to TNFα and endotoxins [1] in shock, metastatic cancers and bacterial sepsis, fungal and viral infections [1-6]. The serum PCT level raises in multiple organ failure [7] and sepsis unlike pnenomoniasis of other respiratory infections and community acquired pneumoniasis [8-10]. Therefore SPCT seems a good diagnostic marker for bacterial infection [8,11-13]. Increased SPCT level, due to elevated levels of interleukin 6 and TNFα and depending on the

severity of the systemic inflammation, significantly is correlated with the severity of septic shock [14,15]. Also high SPCT level is showed in Tuberculosis (TB) patients [16]. Previous studies showed that pleural effusions (PE) develop by many bacterial or non bacterial infections, malignancies and TB [17]. In suspect to pleural infection, rapid and accurate diagnosis is still remained a major clinical challenge. This is due to the negative specimen culture in 40% of parapneumonic (PAR) PE cases [18]. On the other hand light differential criteria for diagnosis of exudates and transudate effusions like lactate dehydrogenase and glucose levels in pleural fluid have high specificity but low sensitivity and need chest wall drainage[19-20,21-23]. Besides, there are other invasive diagnostic tools including blind biopsy and thoracoscopy and measuring the specific biomarkers for mycobacterium tuberculosis (MBT), DNA PCR that the technical difficulties, low sensitivity and time consuming methods remained challenge. Recently the diagnostic role of PPCT in the different etiologics of exudative and transudative PE has been investigated [21-23]. However a few studies have underlined to compare the usefulness and diagnostic role of pleural PCT (PPCT) and SPCT as a differential diagnosis marker of PE. This study was embarked on the diagnostic value of PPCT in transudative and exudative PE with different etiologies.

EXPERIMENTAL SECTION

This was a prospective study in our hospital from April 2011 until April 2012. This study was approved by our Ethical Committee in accordance with the ethical standards of Helsinki declaration in Mashhad University of Medical Sciences (MUMS),Mashhad, Iran. We obtained informed consent form from all patients prior to assess their inclusion criteria for enrollment in this study. The patients with age more than 18 years old and measurable pleural effusions (>10 cc) were included in this study. Also chest guided thoracocentesis performed by pulmonary specialist for all included patients on the first day of enrollment of each subject. The patients with coagulation disorders (platelet count less than 10000cumm), lower than 10 cc of pleural effusions were excluded. All demographic information and clinical symptoms were recorded. Pleural fluid samples were obtained and cytological studies were performed in our Immunology department and pathology laboratory. Pleural fluid samples immediately were analyzed for glucose, lactate dehydrogenase (LDH), protein and cell count while the supernatants were frozen within 4 hours of collection for PCT analysis at the end of this study. The transudative and exudative PE diagnosis was based on Light criteria. These criteria for differentiation of exudative from transudative are including: ratio of fluid protein to serum protein more than 0.5, and ratio of fluid LDH to upper limit for serum more than 0.6 or two third of serum LDH. Pleural and serum level of PCT were measured by ELIZA technique (RayBio) according to the manufacturer instruction. In this study we included all patients admitted to our referral hospital, MUMS, Iran. Subsequently a total of 80 cases were analyzed and divided into four group; 1) Parapneumonic PE (20 cases), 2) Tuberculosis effusions (20 cases), 3) Malignant effusions (20 cases) and 4) Transudates (20 cases). Transudate PE was categorized to the following criteria; 1) heart failure (6 cases) approved by cardiac echocardiography as dysfunction of the left ventricle, 2) liver cirrhosis (3 cases) approved by abdominal ultrasonography as liver cirrhosis, 3) chronic renal failure (6 cases) if a renal ultrasonographic study showed small kidney.

Statistical analysis

The data were analyzed using SPSS 15 for windows version 11.05 (SPSS Inc., Chicago, IL, USA). All data were checked for normality by Kolmogorov–Smirnov test (K–S test). Descriptive statistics and compare means (one sample t test and paired sample t test) were also used. P-value less than 0.05 was considered significant. Numerical data are expressed as mean ± SD or as proportions of the sample size. One way ANOVA for analysis of different variables in pleural fluid of four studied groups were performed. Also Pearson correlation test performed to find the correlation of serum and pleural PCT in four studied groups.

RESULTS

Patient's clinical characteristics

Table 1 shows the demographic and descriptive analysis of studied pleural fluid biomarkers. Among 45 female (57%) and 34 male (43%)enrolled patients, 60 ones had exudative PE and 20 ones with transudative PE. From exudative cases 20 patients (32.20%), 20 (33.89%) and 20 (33.89%) were diagnosed with malignant, TB and parapeumonia respectively. Referred transudative PE patients with heart failure, liver cirrhosis and renal failure were showed in 6 (28.57%), 3 (14.28) and 6 (28.57%) respectively.

Patients were ranged between 22 to 86 years old with mean±SD equal to 57.59±18.14 years. Malignancies were confirmed by evaluation of pleural cytological and biopsy assay. This examinations allocated 13 (68.4%) cases in

malignant group and remained ones 6 case (31.6%) were negative. There were no significant difference between age and gender between four studied groups of the patients.

Table 1: Demographic and some pleural fluid biomarkers in patients

Variables	Transudates N=20	Malignant N=20	Tuberculosis N=20	Parapneumonic N=20
Age (years)	65 (59-71)	66 (61-71)	45 (36-54)	53 (44-63)
Gender (male)	10 (11)	11 (8)	11 (9)	13 (6)
P.CDL*, Cells/µl	1515 (980-2050)	1941 (1332-2550)	3575 (2456-4658)	3921 (2731-5110)
PMN, Cell/µl	43.57 (34-53.12)	17.10 (10.56-23.64)	36 (23.35-48.64)	33.5 (23.35-48.64)
LYMPH (…)	56.42 (46.87-65.98)	85.55 (81.94-89.16)	64 (51.35-76.64)	66.50(54.39-78.60)

Data presents as mean (95% confidence interval for mean; lower bound and upper bound)
**Pre calcitonin*

Table 2 shows the serum and pleural effusions characteristics. The pleural glucose range and mean ±standard deviation in total patients were 40 to 190 mg/dl and 95.57±30.63 mg/dl, respectively. Analysis of serum glucose range and mean ±SD in patients were 99-270 mg/dl and 171.16±36.84 mg/dl. According to Light criteria and as we expected, the statistical analysis showed that there was significant difference between glucose level of patients' pleural samples and transudate had significantly higher level of glucose (P<0.05). LDH ranged between 71 to 795 IU/ml with 163.60±18.29 IU/ml in pleural effusions and 210 to 840 IU/ml with 115±12.86 IU/ml in serum. There were significant difference between LDH level of serum and pleural effusions (P<0.001).

Table 2: Descriptive statistics for each parameter and pleural effusion in studied group
P-Value significant level considered <0.05.

Variable	Transudates	Malignant	Tuberculosis	Parapneumonic	P-Value
P.PRO (mg/dl)	1.74 (1.35-2.13)	4.04 (3.77-4.30)	4.62 (4.26-4.97)	4.35 (3.95-4.70)	<0.001
B.PRO (mg/dl)	6.11 (5.74-6.48)	5.90 (5.59-6.20)	5.95 (5.61-6.28)	5.93 (5.58-6.29)	0.77
P.LDH (mg/dl)	187.66 (105.96-169.36)	478.21 (441.71-514.70)	423.05 (372.89-473.20)	416.90 (363.37-470.42)	<0.001
B.LDH (mg/dl)	476.66 (422.41-530.91)	653.68 (616.68-690.74)	578.25 (534.08-622.4)	581.75 (537.90-625.54)	<0.001
P.GLU (mg/dl)	124.19 (108.05-140.32)	98.10 (88.82-107.38)	79.25 (71.97-86.52)	79.45 (68.77-90.12)	<0.001
B.GLU (mg/dl)	179.42 (163.27-195.58)	171.31 (155.19-187.43)	164.70 (143.73-185.66)	168.80 (153-0.8-184.51)	<0.001

Data presents as mean (95% confidence interval for mean; lower bound and upper bound). P; Pleural, B: Blood, PRO: Protein,

As malignant patients and transudate ones experienced the highest and the lowest levels of LDH, respectively. Protein ranged 0.70 to 6.40 with mean level of 3.6±1.37 in pleural effusions and ranged 4.5 to 7.50 with 5.97 ±0.72 in serum. Protein level in pleural effusions of transudate patients was significantly lower than cancer group (P<0.001). Comparison between PCT level of PE and serum in different etiologies is presented in Table 3.

Table 3: Comparison between procalcitonin level of pleural effusion and blood in different etiologies of pleural effusion in patients
Data presents as mean (95% confidence interval for mean; lower bound and upper bound). P-Value significant level considered <0.05.

Etiologies	Pleural Procalcitonin	Blood Procalcitonin	P-Value (r)
Transudates	48.42-185.28	116.86-150.3	0.45 (0.18)
Malignant	34.50-97.39	65.94 -6.52	0.31 (-0.23)
Tuberculosis	35.73-138.26	87-109.54	0.21 (0.35)
Parapneumonic	49.28-180.91	115.10-140.60	0.004 (0.61)

Specificity and sensitivity of serum and pleural PCT between different etiologies of pleural effusion

This study compared the PCT level in TB, malignant and parapneumonic with transudates in PE and blood. We found that the PCT level is more accurate in TB compared to transudate group PE diagnosis. The cut off point values to explore the specificity of PCT in diagnosing considered at 0.3 ng/mL by using a ROC method and area under the curve (AUC). The findings showed that only in parapneumonic group in PE (Figure 1a), a statistically significant AUC was observed (P=0.001). The AUC amount in blood PCT level for parapneumonic group versus non parapneumonic was 0.44 with 95% confidence interval of 0.24-0.61 and specificity and sensitivity values for pleural fluid PCT were 0.42 and 0.42 (P=0.09) (Figure 2a).

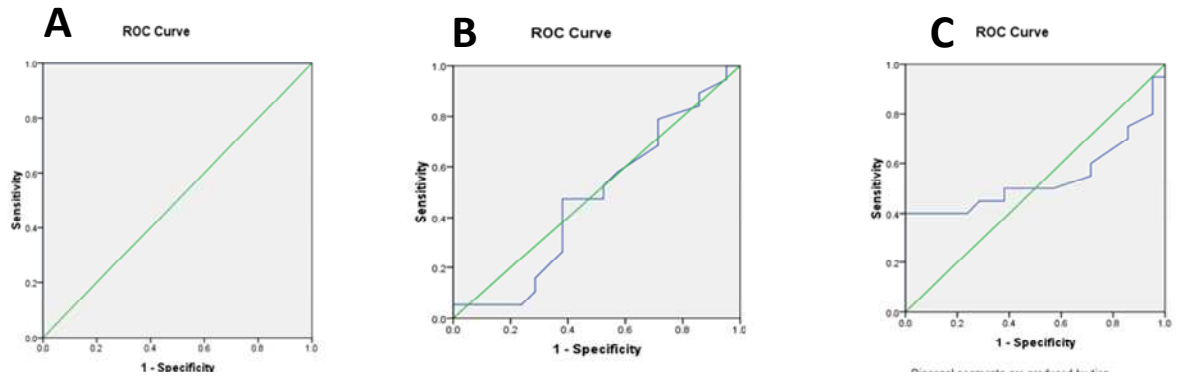

Figure 1: The area under curve (AUC) for procalcitonin level of pleural effusions in patients with parapneumonic pleurisy (A), malignancy pleurisy (B), and tuberculosis pleurisy (C). Details are described in results section

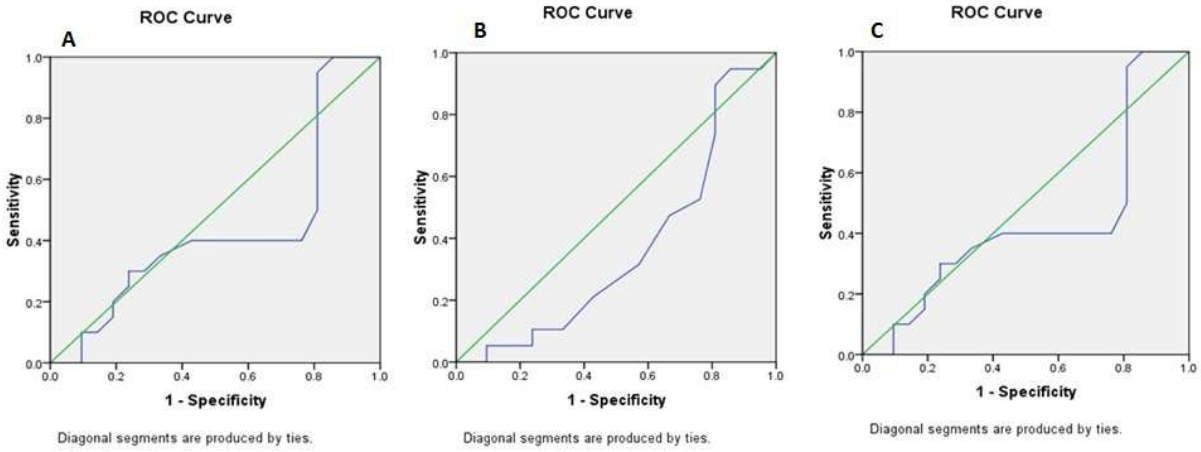

Figure 2: The area under curve (AUC) for procalcitonin level in serum of patients with parapneumonic pleurisy (A), malignancy pleurisy (B), and tuberculosis pleurisy (C). Details are described in results section

The areas under the curve values for PCT level in malignancies versusnon malignancy was 0.75 with 95% confidence interval of 0.29-0.65 and specificity and sensitivity values for pleural fluid PCT were 0.47 and 0.38 at the 0.3 ng/mL cut-off point, respectively (P=0.76) (Figure 1b). These values for blood PCT were 0.19 and 0.55 with AUC equal to 0.36 at the 0.3 ng/ml cut-off point, respectively (P=0.36) (Figure 2 b).The areas under the curve values for PCT level in TB versus non TB was 0.54 with 95% confidence interval of 0.34-0.73 and specificity and sensitivity values for pleural fluid PCT measured 0.38respectively (P=0.76) (Figure 1c). These values for blood PCT were 0.57 and 0.4 with AUC equal to 0.4 respectively (P=0.27) (Figure 2 c).

DISCUSSION

Procalcitonin (PCT) hormone as a protein by 116 amino acids and 32 identical ones to calcitonin prohormone has been investigated as a marker to diagnose various etiologies of PE. In this study we evaluated exudative and transudative pleural fluid and serum level of PCT in the enrolled patients to find out the sensitivity, specificity of PCT to discover different etiologies, with evaluating the diagnostic value of pleural fluid PCT among different etiologies, separately. The diagnostic and predictive value of calcitonin and procalcitonin has evaluated previously in other studies for cancers and metastatic malignancies.

Previous study by Lawn et al [24] found that 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.

Mean while Walter et al. (2010) Matzaraki et al. (2007) indicated that a superior diagnostic accuracy of calcitonin and the procalcitonin: calcitonin ratio are related to liver metastasis stage in the patients [25, 26]. Malekmohammadi et al [22] found that PCT levels in PE demonstrated a high sensitivity for distinguishing invasive malignancies and lymphomas. While we found that AUC for metastatic pleurisy effusions was 0.47 while AUC for parapneumonic was one and showed the highest amount of sensitivity in comparison to other pleural effusions. In previous study[22] like our study, the sensitivity and specificity of PCT were considered 0.3 ng/ml in PE, even though we considered lower cutoff point compared to the similar study by Cakir et al. [27].

Meanwhile like our study Malekmohammadi et al [22] found that PCT concentration is not a useful parameter for the diagnosis of TB pleurisy. Besides by increasing the cutoff point from 0.3 to 0.4 ng/dl, the false positive rate decreased, but the false negative rate increased.

Procalcitonin is recognized as an important marker of sepsis and systemic infection. Due to this hypothesis previous studies [28-29] suggested it due to the high sensitivity value for differentiating pulmonary TB from bacterial CAP for predicting the serum PCT levels in adult patients with active TB,, in our study we evaluated the serum level of PCT and observed that although serum PCT is mostly secreted from liver in blood, but do not reach a very high concentration in pleural fluid.

Like our, study San José et al [21] evaluated the PCT level in the pleural fluid and blood. But they found that it does not seem to provide a great value for the diagnosis of parapneumonic. However, due to increased values have a high specificity and predictive values of the total neutrophil count and the CRP; they concluded that it might be useful in the diagnosis of these effusions.

In Wang et al. [30] study like our result, PCT levels were found to be high in parapneumonic PE particularly in empyema, and malignant PE, although they did not describe the diagnostic value in different cancerous PE. But Lin et al [23] confirmed our study results as they revealed that PCT level had a higher sensitivity and specificity for diagnosis of parapneumonic patients. Moreover, they discovered that for differentiating the parapneumonic PE from non- parapneumonic PE, the serum level of PCT has a higher diagnostic accuracy than the pleural PCT level. However, both pleural and serum PCT are useful in the assessment of the severity of parapneumonic pleural effusions. Therefore in our study, finding of the present study revealed that plural PCT level could be of diagnostic value in parapneumonic pleurisy but not in TB and not in malignancies with appropriate sensitivity and specificity.

The findings of this study demonstrated that pleural fluid Pro-Calcitonin did not increased in TB and malignancies patients. The significantly raised pleural fluid PCT levels in the patients with parapneumonic pleurisy might indicate that pleural PCT levels are elevated in patients who are in severe health situations.

In conclusion we found that the pleural PCT has higher diagnostic accuracy than serum PCT in differentiating parapneumonic pleurisy from non parapneumonic pleurisy. Both pleural fluid PCT and serum PCT were useful for assessing the severity of pneumonia with parapneumonic plural effusions.

CONCLUSION

Present study showed that plural PCT level in parapneumonic pleurisy could have diagnostic value neither in TB nor in malignancies pleurisity patients. The pleural PCT has higher diagnostic accuracy comparing with serum PCT in differentiating parapneumonic pleurisy from non parapneumonic pleurisy. Both pleural fluid PCT and serum PCT were useful for assessing the severity of pneumonia with parapneumonic plural effusions.

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