Diagnostic value of procalcitonin in pleural effusion

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Background
A wide range of diseases can cause pleural effusion. Its diagnosis and management remain a clinical challenge, bearing a significant cost to both patients and health care system.
Objective
To assess the role of procalcitonin (PCT) level in discriminating transudative from exudative pleural effusion and in differentiation between some types of exudative effusion.
Patients and methods
A total of 45 patients having pleural effusion were enrolled in this study and were divided into two groups. Group I included 15 patients having transudative pleural effusion. Group II included 30 patients having exudative pleural effusion. This group was subdivided into group IIa, which included 10 patients having tuberculous effusion; group IIb, which included 10 patients having malignant effusion; and group IIc, which included 10 patients having parapneumonic effusion. Quantitative measurement of PCT in both serum and pleural fluid was done using enzyme-linked immunosorbent assay.
Results
Exudative effusion had significantly higher levels of serum and pleural PCT when compared with transudative one. Regarding serum and pleural PCT levels in different types of exudative effusion, highest level was in parapneumonic followed by malignant, and then tuberculous pleural effusion, and the difference between them was statistically significant.
Conclusion
Measurement of both serum and pleural PCT may be used to differentiate transudative from exudative type of pleural effusion and may be used also to discriminate parapneumonic from other causes of exudative pleural effusion.

Keywords:
exudative effusion, parapneumonic effusion, pleural effusion, procalcitonin

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Introduction

Pleural effusion is a fairly common clinical disorder that needs to be diagnosed [1]. Many technical difficulties face clinician in differentiation between different types of exudative pleural effusion, and diagnostic evaluations are generally also nonspecific [2]. Procalcitonin (PCT) is a potential indicator of systemic inflammation due to infection. PCT has the advantage of being stable in blood samples, so it can be used as an indicator of both disease severity and effect of antibiotics [3]. PCT has been investigated to recognize its role in diagnosis of different etiologies of exudative and transudative pleural effusion [4].

Aim

This study was done to assess the role of PCT level in discriminating transudative from exudative pleural effusion and in differentiation between some types of exudative effusion.

Patients and methods

This cross-sectional study included 45 patients having pleural effusion. They were selected and diagnosed in Chest Department of Benha University Hospitals and Tanta Chest Hospital during the period between February 2018 and February 2019. They were divided into two groups. Group I included 15 patients having transudative pleural effusion. From this group, six patients had hepatic hydrothorax, six patients were had heart failure, and three patients had chronic renal failure. Group II included 30 patients having exudative pleural effusion, who were subdivided into three groups: group IIa, which included 10 patients having tuberculous effusion; group IIb, which included 10 patients having malignant

effusion; and group IIc, which included 10 patients having parapneumonic effusion. Ethical approval of this study was obtained from the Ethical Committee of the Faculty of Medicine, Benha University. All patients signed a written informed consent before being enrolled in this study.

Diagnosis of transudative pleural effusion was done according to Light's criteria. Pleural effusion was referred to congestive heart failure according to examination together with ECG, chest radiograph, and echocardiography finding of enlarged heart, congested pulmonary veins, and peripheral edema. Patients with liver cell failure were diagnosed depending upon clinical and laboratory evidence of hypoalbuminemia and lever damage by ultrasonography, and the diagnosis of chronic renal failure was done depending upon clinical and laboratory evidence of lower limb edema, hypoalbuminemia, and impaired renal function [5]. Tuberculosis is suspected in pleural effusion when toxemic manifestations are present, positive tuberculin test result is seen, positive sputum culture for mycobacteria is seen, pleural biopsies were pathologically positive for caseating granulomas, and there was lymphocytic predominance in cytological examination of pleural aspirate. Malignant effusion was diagnosed when there was positive cytological examination for malignant cells, and patients with negative cytology result further underwent medical thoracoscopy for biopsy, and diagnosis of parapneumonic effusion was done when there was purulent phlegm, and pulmonary infiltrates associated with acute febrile disease with response to antibiotic therapy [6].

All patients underwent history taking, full clinical examination, complete blood count, liver and kidney functions, blood sugar, plain chest radiograph posteroanterior view, tuberculin skin test, sputum examination by Ziehl–Neelsen stain in suspected cases of tuberculosis, thoracocentesis for pleural fluid analysis, measurement of PCT in serum and pleural fluid using enzyme-linked immunosorbent assay (ELISA), and other investigations when needed (computed tomography chest, medical thoracoscopy, echocardiography). Patients were excluded when they were under chemotherapy or radiotherapy, had bleeding tendency, or had blood dyscrasias.

Estimation of serum and pleural procalcitonin

Human PCT ELISA kit is an *in vitro* double-antibody sandwich ELISA. The precoated antibody is human PCT monoclonal antibody and the detecting antibody is polyclonal biotin-labeled antibody. Samples and biotin-labeled antibody were added into ELISA plate wells and splashed out with phosphate buffer saline. Then avidin-peroxidase conjugates were added to wells. Tetramethylbenzidine was used as a color substrate for reactant and comprehensively cleaned by phosphate buffer saline. Tetramethylbenzidine changes into blue in peroxidase catalytic reaction and lastly turns yellow by the action of acid. The color intensity and the tested PCT in samples correlate positively. The development of color is then ended and color intensity is estimated using the ELISA device Infinite F50 ELIZA Reader (TECAN Company, Singapore, China). The developed color optical density was measured at 450 nm. The standard optical density was presented on the horizontal axis whereas the PCT concentration on the vertical axis, and the standard curve was drawn on the graph paper. The results were calculated by Magellan Tracker software (Tecan Trading AG, Männedorf, Switzerland). The detection range is 31.2–2000 pg/ml, and the kit sensitivity is 12 pg/ml [7].

Statistical analysis

The gathered information were arranged and examined by statistical package for social science (SPSS Inc., Chicago, Illinois, USA) and summed up regarding mean±SD and run for quantitative information, recurrence, and rate of subjective information. χ^2 test was used to compare between the studied groups. Fisher exact test was used to compare proportions as appropriate as possible, and one-way analysis of variance (F) test was used to identify distinction between parametric quantitative information. Significant analysis of variance was trailed by different post-hoc examinations utilizing least square difference test to distinguish the noteworthy sets, whereas the Mann–Whitney test was used to analyze nonparametric information. Receiver operating characteristic (ROC) curve was used for surveying estimation of pleural and serum PCT to distinguish transudative from exudative pleural effusion and in separation between parapneumonic from non-parapneumonic pleural effusion.

Results

A total of 45 patients with pleural effusion were enrolled in this study. They were classified into two groups: group I included 15 patients having transudative effusion, comprising 11 (73%) males and four (27%) females. Their ages were between 47 and 71 years, with a mean±SD of 58±6.8 years. Group II included 30 patients having exudative effusion,

Table 1 Statistical comparison between studied groups regarding demographic characteristics

Variables	Group I: transudative effusion (*N*=15)	Group IIa: tuberculous effusion (*N*=10)	Group IIb: malignant effusion (*N*=10)	Group IIc: parapneumonic effusion (*N*=10)	Test
Age (years)					
Range	47–71	44–62	48–71	43–65	ANOVA test$F$=2.54 P=0.07 (NS)
Mean±SD	58±6.8	53±6.5	60.6±7.2	54.5±6.9	
Sex [*n* (%)]					
Male	11 (73)	7 (70)	6 (60)	7 (70)	Fisher's exact testχ^2=0.7 P=0.96 (NS)
Female	4 (27)	3 (30)	4 (40)	3 (30)	

ANOVA, analysis of variance.

comprising 20 (67%) males and 10 (33%) females. Their ages were between 43 and 71 years. This group was subdivided into three groups: group IIa included 10 patients having tuberculous effusion, comprising seven (70%) males and three (30%) females. Their ages were between 44 and 62 years, with a mean±SD of 53±6.5 years. Group IIb included 10 patients having malignant effusion, comprising six (60%) males and four (40%) females. Their ages were between 48 and 71 years, with a mean±SD of 60.6±7.2 years. Group IIc included 10 patients having parapneumonic effusion, comprising seven (70%) males and three (30%) females. Their ages were between 43 and 65 years, with a mean±SD of 54.5 ±6.9 years (Table 1). In this study, there was a highly statistical significant difference among the included groups regarding the mean pleural and serum lactate dehydrogenase (LDH), which was highest in parapneumonic effusion (1928.3±450.6 and 3060.1 ±782 U/l), then tuberculous effusion (913.9±135.7 and 1473.3±213.3 U/l), then malignant effusion (496.9±29.52 and 776.8±62.3 U/l) and lastly transudative effusion (180.86±12.8 and 349.7 ±27.6 U/l). There was a highly statistically significant difference among the examined groups regarding the mean pleural and serum protein, which was highest in tuberculous effusion (4.54±0.533 and 7.05±0.59 g/dl, respectively) followed by parapneumonic effusion (4.29 ±0.50 and 6.81±0.36 g/dl, respectively), malignant effusion (4.07±0.34 and 6.71±0.40 g/dl, respectively), and transudative effusion (2.20±0.59 and 5.48±1.25 g/dl, respectively). There was also a highly statistically significant difference among the examined groups regarding pleural/serum LDH, which was highest in malignant group (0.64±0.035) followed by parapneumonic group (0.63±0.029), tuberculous group (0.62±0.016), and transudative group (0.51 ±0.038). There was also a highly statistically significant difference among the included groups regarding pleural/serum protein ratio which was highest in tuberculous group (0.645±0.076) followed by parapneumonic group (0.630±0.076), malignant group (0.607±0.054), and transudative group (0.405 ±0.06) (Table 2). Both serum and pleural PCT levels in exudative effusion (0.979±1.213 and 1.387±1.566, respectively) had significantly higher values when compared with those in transudative one (0.166 ±0.051 and 0.186±0.063, respectively); however, there was no statistically significant difference between the transudative and exudative groups regarding the pleural/serum PCT ratio (Table 3). There was a highly statistically significant difference among the different types of exudative pleural effusion regarding pleural and serum PCT levels. In parapneumonic effusion, both pleural and serum PCT levels were significantly higher (3.400±1.021 and 2.734±1.104 ng/ml, respectively) compared with malignant effusion (0.500±0.239 and 0.316±0.166 ng/ml, respectively). Pleural PCT levels of malignant effusion were higher when compared with tuberculous effusion (0.262±0.171 and 0.281 ±0.149 ng/ml, respectively). There was a statistically significant difference among the three subgroups regarding pleural/serum PCT ratio, which was highest in malignant pleural effusion (1.885 ±1.449 ng/ml) (Table 4). In this study, there was a highly statistically significant positive correlation between pleural and serum PCT between the examined groups (r=0.965 and P<0.0001; Table 5). Value of pleural and serum PCT levels in discrimination between transudative and exudative pleural effusion is shown in Tables 6 and 7. Value of pleural and serum PCT levels in discrimination between parapneumonic from non-parapneumonic pleural effusion is shown in Tables 8 and 9.

Discussion

Pleural effusion refers to unusual accumulation of fluid in the pleural sac. Management of patients with pleural

Table 2 Statistical comparison between studied groups regarding lactate dehydrogenase and protein levels in both serum and pleural fluid

Variables	Group I: transudative effusion (*N*=15)	Group IIa: tuberculous effusion (*N*=10)	Group IIb: malignant effusion (*N*=10)	Group IIc: parapneumonic effusion (*N*=10)	Test
Pleural LDH (U/l)					
Range	159–198	752–1153	446–543	980–2500	ANOVA test *F*=133.18 *P*<0.0001 (HS)
Mean±SD	180.86±12.8	913.9±135.7	496.9±29.52	1928.3±450.6	
Serum LDH (U/l)					
Range	305–408	1224–1890	655–838	1506–4166	ANOVA test *F*=109 *P*<0.0001 (HS)
Mean±SD	349.7±27.6	1473.3±213.3	776.8±62.3	3060.1±782	
Pleural/serum LDH ratio					
Range	*0.45–0.59*	0.6–0.65	0.59–0.70	0.60–0.68	ANOVA test *F*=42.4 *P*<0.0001(HS)
Mean±SD	abc0.51±0.038	0.62±0.016	0.64±0.035	0.63±0.029	
Pleural protein (g/dl)					
Range	*1.4–3.09*	3.8–5.3	3.4–4.5	3.7–5.2	ANOVA test *F*=56.7 *P*<0.0001(HS)
Mean±SD	abc2.20±0.59	4.54±0.533	4.07±0.34	4.29±0.50	
Serum protein (g/dl)					
Range	*3.6–7.2*	6–8	6.2–7.4	6.4–7.6	ANOVA test *F*=9.5 *P*<0.0001 (HS)
Mean±SD	abc5.48±1.25	7.05±0.59	6.71±0.40	6.81±0.36	
Pleural/serum protein ratio					
Range	0.303–0.490	0.532–0.779	0.515–0.672	0.526–0.758	ANOVA test *F*=36.5 *P*<0.0001 (HS)
Mean±SD	abc0.405±0.06	0.645±0.076	0.607±0.054	0.630±0.076	

a, Significant with tuberculous effusion group; b, significant with malignant pleural effusion group; c, significant with parapneumonic effusion group.ANOVA, analysis of variance; HS, highly significant; LDH, lactate dehydrogenase.

Table 3 Statistical comparison between transudative and exudative pleural effusion regarding serum procalcitonin, pleural procalcitonin, and procalcitonin plural/serum ratio

Variables	Group I: transudative (*N*=15)	Group II: exudative (*N*=30)	Test
Serum PCT (ng/ml)			
Range	0.086–0.254	0.088–4.286	Mann–Whitney*U* test*P*<0.0001 (HS)
Mean±SD	0.166±0.051	0.979±1.213	
Pleural PCT (ng/ml)			
Range	0.083–0.265	0.105–4.672	Mann–Whitney*U* test*P*<0.0001 (HS)
Mean±SD	0.186±0.063	1.387±1.566	
Pleural/serum PCT ratio			
Range	0.615–1.512	0.594–5.872	Mann–Whitney*U* test*P*=0.142 (NS)
Mean±SD	1.114±0.209	1.394±0.922	

HS, highly significant; PCT, procalcitonin.

effusion continues to be a medical problem. Though a large number of laboratory tests are available, some cases cannot be diagnosed. This is particularly true regarding the differentiation between different causes of exudative pleural effusion [8]. In the current work, there was no statistically significant difference between the examined groups regarding mean age and sex, which means that our groups are well matched in age and sex. In the present study, there was a highly statistically significant difference between the examined groups regarding mean pleural and serum LDH, which was highest in parapneumonic effusion followed by tuberculous effusion, then malignant effusion, and lastly, transudative effusion. There was a highly statistically significant difference between examined groups regarding mean pleural and serum protein, which was highest in tuberculous pleural effusion followed by parapneumonic, malignant, and then transudative one. These results agree with those of Wang *et al.* [3], who found that the mean LDH level was highest in parapneumonic effusion including empyema followed by tuberculous effusion then

Table 4 Statistical comparison between different types of exudative pleural effusion regarding serum procalcitonin, pleural procalcitonin, and pleural/serum procalcitonin ratio.

Variables	Group IIa: tuberculous effusion (*N*=10)	Group IIb: malignant effusion (*N*=10)	Group IIc: parapneumonic effusion (*N*=10)	Test
Serum PCT (ng/ml)				
Range	0.088–0.559	0.124–0.644	0.876–4.286	ANOVA test *F*=46.6 *P*<0.0001 (HS)
Mean±SD	0.281±0.149	0.316±0.166	2.734±1.104ab	
Pleural PCT (ng/ml)				
Range	0.105–0.720	0.192–0.916	1.275–4.672	ANOVA test *F*=80.9*P*<0.0001 (HS)
Mean±SD	0.262±0.171	0.500±0.239	3.400±1.021ab	
Pleural/serum PCT ratio				
Range	0.594–1.557	0.959–5.872	0.911–1.748	ANOVA test *F*=2.7 *P*=0.082 (SS)
Mean±SD	0.983±0.326	1.885±1.449a	1.315±0.263	

a, significant with tuberculous pleurisy group; b, significant with malignant pleural effusion group; c, significant with parapneumonic effusion group.ANOVA, analysis of variance; HS, highly significant; PCT, procalcitonin; SS, statistically significant.

Table 5 Correlation between pleural procalcitonin and serum procalcitonin among the studied groups

Pleural PCT variables	Pearson's correlation coefficient (*r*)	*P*
Serum PCT	0.965	<0.0001

PCT, procalcitonin.

Table 6 Value of pleural procalcitonin in the differentiation between transudative and exudative pleural effusion

	Pleural procalcitonin level
Cut off	0.19
Sensitivity (%)	86
Specificity (%)	54
PPV (%)	78
NPV (%)	66
Correctly classified (accuracy) (%)	75.5
AUC	0.87 (95% CI, 0.76–0.97)
P value	<0.001

AUC, area under curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

Table 7 Value of serum procalcitonin in the differentiation between transudative and exudative pleural effusion

	Serum procalcitonin level
Cutoff	0.20
Sensitivity (%)	76
Specificity (%)	74
PPV (%)	85
NPV (%)	61
Correctly classified (accuracy) (%)	75
AUC	0.85 (95% CI, 0.74–0.96)
P value	<0.001

AUC, area under curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

malignant one. In the same study, mean pleural total protein level was highest in tuberculous effusion followed by parapneumonic and then malignant pleural effusion.

Table 8 Value of pleural procalcitonin in the differentiation between parapneumonic from non-parapneumonic pleural effusion

	Pleural procalcitonin
Cutoff	0.25
Sensitivity (%)	88
Specificity (%)	67
PPV (%)	40
NPV (%)	95
Correctly classified (accuracy) (%)	69
AUC	0.92 (95% CI, 0.81–1.00)
P value	<0.001

AUC, area under curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

Table 9 Value of serum procalcitonin in the differentiation between parapneumonic from non-parapneumonic pleural effusion

	Serum procalcitonin
Cutoff	0.27
Sensitivity (%)	89
Specificity (%)	69
PPV (%)	53
NPV (%)	90
Correctly classified (accuracy) (%)	64
AUC	0.85 (95% CI, 0.73–0.98)
P value	0.001

AUC, area under curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

In the current study, both serum and pleural PCT levels in exudative effusion had significantly higher values when compared with those in transudative one. However, there was no statistically significant difference between the transudative and exudative groups regarding the pleural/serum PCT ratio. These results agree with those of Kim *et al.* [9], who found that pleural PCT level in exudative effusion had significantly higher values when compared with those

in transudative one (0.81±3.09 and 0.12±0.12 ng/ml, respectively), with *P* value of 0.007. They declared that PCT can be useful in discriminating exudative from transudative pleural effusion.

In the current study, there was a highly statistically significant difference between different types of exudative pleural effusion regarding pleural and serum PCT. In parapneumonic effusion, both pleural and serum PCT levels had significantly higher values when compared with malignant effusion, and those of malignant effusion were higher when compared with tuberculous effusion. There was a statistically significant difference between the exudative groups regarding pleural/serum PCT ratio, which was highest in malignant pleural effusion. These results were in concordance with those of Lin and colleagues; their study included 82 patients, comprising 45 cases of para pneumonic and 37 cases of non-parapneumonic pleural effusion. They found that both pleural and serum PCT had significantly higher levels in parapneumonic group when compared with the non-parapneumonic group (P=0.01 and 0.0003, respectively). They concluded that serum PCT is better than pleural fluid PCT in differentiating parapneumonic from non-parapneumonic pleural effusion [10]. The study by Hooper *et al.* [11] included 145 patients with different types of pleural effusion, and they found that serum and pleural fluid PCT could be helpful in differentiating parapneumonic from non-parapneumonic effusion, and thus, it can be useful to the clinician to decide a proper guided treatment. El-Shimy *et al.* [12] found significantly higher serum PCT level in patients having parapneumonic pleural effusion (2.171±0.341 ng/ml) than those with malignant one (0.965±0.164 ng/ml) (P<0.001), and its level in patients with malignant effusion was significantly higher than those with tuberculous effusion (0.265±0.152 ng/ml) (P<0.05). He and colleagues found that serum level of PCT was significantly higher in parapneumonic effusion (5.44 ± 9.82 ng/ml) than in malignant (0.15 ± 0.19 ng/ml), tuberculous (0.18 ± 0.16 ng/ml) and transudative pleural effusion (0.09 ± 0.03 ng/ml) ($P < 0.001$). They concluded that both serum and pleural PCT may aid in diagnosis of parapneumonic effusion [13].

The aforementioned results may be owing to the strong association of PCT with inflammatory and septic conditions compared with infection-free situations and several studies have confirmed the inflammatory nature of malignant pleural effusion [14].

In the present work, there was a highly statistically significant positive correlation between pleural and serum PCT. Lin and colleagues conducted a study on 45 patients with parapneumonic effusion and 37 with non-parapneumonic effusion and reported that serum and pleural PCT levels were correlated significantly ($r = 0.754$, P<0.0001). They explained this correlation by the possible origin of pleural PCT from systemic arteries through areas of high pleural and capillary vessels permeability [10]. Wang and colleagues also found that both pleural and serum PCT were positively correlated in patients having parapneumonic effusion (r^2=0.967, P<0.001). They speculated that levels of PCT in serum and body fluids are closely similar in patients having variable diseases and that the systemic expression of PCT occurs irrespective of the existence of systemic septic or local inflammatory conditions [3].

The current study showed that regarding pleural PCT, an optimal differentiation between transudative and exudative pleural effusion can be achieved at a cutoff value 0.19 ng/ml with area under the curve (AUC) of 0.87 (sensitivity: 86% and specificity: 54%); however, regarding serum PCT, differentiation can be achieved at a cutoff value of 0.20 ng/ml with AUC of 0.85 (sensitivity: 76% and specificity: 74%).

In the present study, an optimal discrimination between parapneumonic and non-parapneumonic pleural effusion regarding pleural and serum PCT can be accomplished at a cutoff value of 0.25 and 0.27 ng/ml, with AUC of 0.92 and 0.85, respectively. This agrees with Hooper and colleagues, who reported that distinguishing parapneumonic effusion from noninfective causes regarding pleural PCT can be established at a cutoff value of 0.1 ng/ml with AUC 0.809 [95% confidence interval (CI), 0.709–0.908] (sensitivity: 81% and specificity: 78%). The ROC curve of serum PCT gave an AUC of 0.779 (95% CI, 0.658–0.899) at a cutoff value 0.09 ng/ml (sensitivity: 73% and specificity: 81%). Therefore, they concluded that pleural PCT might be used in diagnoses of parapneumonic effusion [11]. In the study of Wang and colleagues, the ROC curve analysis for pleural PCT provided AUC of 0.776 at a cutoff value of 0.18 ng/ml for distinguishing empyema and parapneumonic plural effusion from non-parapneumonic one, and when they excluded malignant pleural effusion, it discriminated better at a cutoff value of 0.09 ng/ml, with an AUC of 0.820 (sensitivity: 87.9%, specificity: 68.7%) [3]. Lin and colleagues also reported that ROC curve analysis for

pleural PCT gave an AUC of 0.752 at a cutoff value of 0.18 ng/ml, with sensitivity of 66.7% and specificity of 77.4%. They concluded that PCT can be a helpful tool in distinguishing parapneumonic effusion from non-parapneumonic one [10]. However, Dixon and colleagues found that ROC curve analysis for PCT gave AUC of 0.77, for weight cell count gave AUC of 0.77, and for C-reactive protein gave AUC of 0.85; in their study, serum PCT more than 0.085 μg/l for the identification of pleural infection had a sensitivity of 0.69, specificity of 0.80, and negative predictive value and positive predictive value of 0.46 and 0.91, respectively. They concluded that serum PCT is not more beneficent than C-reactive protein or weight cell count in diagnosis of bacterial pleural infection [15]. This disparity in results between different studies may be owing to variation in severity of the infectious process between patients enrolled in these studies.

Conclusion

Measurement of both serum and pleural PCT may be used to differentiate transudative from exudative type of pleural effusion and may be used also to discriminate parapneumonic from other causes of exudative pleural effusion.

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Conflicts of interest

There are no conflicts of interest.

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