ORIGINAL ARTICLE

Procalcitonin: Is it a predictor of noninvasive positive pressure ventilation necessity in acute chronic obstructive pulmonary disease exacerbation?

Ahmet Cemal Pazarli, Handan Inonu Koseoglu, Sibel Doruk, Semsettin Sahin[1], Ilker Etikan[2], Serhat Celikel, Bahadir Berktas[3]

Departments of Pulmonary Diseases, [1]Biochemistry, [2]Biostatistics, Gaziosmanpasa University, Tokat, [3]Ataturk Chest Disease and Surgery Education and Research Center, Ankara, Turkey

Background: Acute exacerbations of chronic obstructive pulmonary disease (AeCOPD) are important causes of morbidity and mortality. In this study, we analyzed procalcitonin (PCT) levels in AeCOPD and stable period of COPD in order to evaluate usage of PCT in the prediction of the severity of AeCOPD, and its value on the planing of noninvasive positive pressure ventilation (NPPV). **Materials and Methods:** In this cross sectional study (2009-2010) 118 COPD patients were enrolled, 68 of them (58%) were in acute exacerbations (case group). The others had stabile COPD and they were defined as control group. **Results:** In case group the mean levels of PCT (0.19 ± 0.02) C-Reactive Protein (44.7 ± 5.92), erythrocyte sedimentation rate (28.4 ± 2.65), white blood cell (9.4 ± 0.43) and %neutrophils (69.9 ± 1.22) were significantly higher than controls (P = 0.0001). There was no difference between PCT levels based on stages of COPD. There were significiant differences in mean PCT levels according to type and severity of AeCOPD. Mean PCT level in hospitalized patients receiving NPPV was 0.36 ng/ml, while it was 0.15 ng/ml for those treated without NPPV (P = 0.0001). PCT cut-off value for NPPV indication was determined to be 0.10 ng/ml. **Conclusions:** PCT levels were found to be higher in AeCOPD patients than in stable COPD patients, as expected. Also mean PCT levels increased especially in cases with severe AeCOPD and those receiving NPPV among them. In the present study, we determined a cut off value of PCT as 0.10 ng/ml as a predictor of necessity of NPPV in AeCOPD.

Key words: Acute exacerbation, chronic obstructive pulmonary disease, procalcitonin, noninvasive positive pressure treatment

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by chronic airflow limitation associated with the inflammatory process of the lung.[1,2]

Acute exacerbations of COPD (AeCOPD) are characterized by dyspnea, increase in the production and purulence of sputum.[2] These AeCOPDs impair the health status of the patients, accelerate progression of the disease, and increase in healthcare costs also it may cause death if respiratory failure develops. Sometimes, AeCOPD is mild and can be treated at home. However some of them requires hospitalization even in intensive care unit.[3] The severity of the exacerbation should be determined when deciding on treatment.

A 50-60% of AeCOPD are because of infection. Approximately half of the exacerbations due to bacterial infection, 30% of them due to viral infection and 5-10% of them due to atypic bacterial infection.[4] Procalcitonin (PCT) as a good marker is frequently used to reveal the presence of a bacterial infection. It is a polypeptide composed of 116 amino acids with a molecular weight of 13 kDa.[5,6] Its serum level markedly increases especially in bacterial infections, it does not change in viral infections or autoimmune inflammations.[7,8] In comparison with C-reactive protein (CRP), as demonstrated in the literature, diagnostic accuracy of PCT in proving bacterial infection is relatively higher, while it is more sensitive, and specific in differentiation between bacterial infection, and non-infectious inflammation.[9] In AeCOPD cases, it is well known the possible role of PCT in addition to CRP, white blood cell (WBC), sputum cultures in the desicion of antimicrobial treatment.[2] PCT

Access this article online	
Quick Response Code:	Website: www.journals.mui.ac.ir/jrms
	DOI: ***

Address for correspondence: Dr. Sibel Doruk, Department of Pulmonary Medicine, Gaziosmanpasa University, 60100 Tokat, Turkey.
E-mail: sibeldoruk@yahoo.com
Received: 06-05-2012; **Revised:** 24-07-2012; **Accepted:** 16-08-2012

may provide clinically relevant information and it may be a guideline for antibiotic treatment.[10,11] We could not find any report which indicated the role of PCT in prediction of necessity of noninvasive positive pressure ventilation (NPPV) treatment.

In this study, we aimed to examine PCT levels during AeCOPD and stable period of COPD, to evaluate possible usage of PCT in the prediction and the severity of an acute exacerbation and its importance on the planing of NPPV treatment. We also investigated the correlation between PCT levels, and the stage of COPD, arterial blood gas (ABG) analysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), WBC, and neutrophil counts.

MATERIALS AND METHODS

In this cross sectional study (2009-2010) 118 consecutive COPD cases were enrolled, 68 of them (58%) were in acute exacerbations (case group), while 50 of them (42%) were stable COPD patients (control group). Diagnoses of COPD were based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[1] Acute exacerbation was defined with the presence of at least one of the following respiratory symptoms such as deterioration of stable state COPD, increase in the amount and purulency of sputum, gradually worsening dyspnea, and wheezing.[1,2] Patients without any symptoms of an acute exacerbation at least four weeks were considered cases with stable COPD. Individuals less than 18 years of age, pregnants, cases with pulmonary diseases other than COPD (asthma, bronchiectasia, pneumonia, tuberculosis), sepsis, pulmonary and extra pulmonary malignancies and any diseases which cause an increae in serum PCT levels. These subjects were excluded from the study. Also the cases who had received antibiotherapy before our evaluation were not included in our study. The study was approved by Ethics Committee of Gaziosmanpasa University Faculty of Medicine and supported by The Commission of Scientific Research Projects (2009/34). All patients participating in the study gave their written consents.

Postero anterior chest X-ray, hemogram, ESR, ABG (Medica Corp. Bedford, MA, USA), pulmonary function tests (PFTs)[12] (Jager, Master Screen Pneumo), serum CRP ve PCT levels were obtained. Quantitative assessment of PCT was performed using mini VIDAS® (Biomerieux Diagnostic, France) by Enzyme Linked Florescent Assay (ELFA) method and the results were evaluated in the same day. In healthy individuals reference value was determined as <0.05 ng/ml varying slightly with the analytical method used.

For the evaluation of the type of exacerbations, Anthonisen criteria were used.[2] Accordingly, the presence of all of the following criteria such as an increase in the severity of dyspnea, intensity of the purulency, and amount of the sputum were defined as Type 1 exacerbation, while Type 2 exacerbation requires the presence of two of these symptoms. The presence of one of the syptom described previously and upper respiratory tract infection, fever, and an increase in the severity of wheezing and cough, a 20% increase in the respiratory/heart rate within the previous 5 days was defined as Type 3 AeCOPD.

The severity of exacerbations was evaluated according to Turkish Thoracic Society, Guidelines for the Diagnosis and Management of COPD.[13] The cases were evaluated according to the presence of homecare facilities, the absence of cyanosis/impared consciousness/long term oxygen treatment/damaged daily activities and social conditions. If the patient says 'yes' ≥4 of these questions, he/she is determined as mild AeCOPD and they were treated on an ambulatory basis, while moderate/severe cases were hospitalized. Non Invasive Positive Pressure Ventilation (NPPV) therapy was administered for in- patients whose ABG analyses revealed moderate/severe acidosis (pH < 7.35), hypercapnia ($PaCO_2$ > 45 mmHg) or resistant hipoxemia inspite of nasal oxygen support.[14]

For statistical analysis SPSS (Statistical Package for Social Sciences) Release 18.0 software package program (SPSS, Inc. Chicago, IL) was used. For the comparison of qualitative data, chi-square test was used. Correlations among procedures with measurable outcomes were analysed using Pearson Correlation coefficient. In the comparison of means of measurable variable 'test for the sigificance of a differerence between two means' was used, in cases where data do not fit into normal distribution Mann Whitney U test which is a non-parametric counterpart of the latter test was employed. For the establishment of PCT cut-off value so as to make a distinction between cases treated with or without NPPV, ROC (Receiver Operating Characteristic) analysis was performed, and area under curve (AUC) was calculated. *P* values below 0.05 were considered statistically significant.

RESULTS

Totally 118 COPD patients cases were enrolled into the study. Sixty eight of them had AeCOPD (case group) and the others had a stable COPD (control group). The groups were comparable as for mean ages and gender distribution. Demographic, and clinical characteristics of the groups are seen in Table 1.

Fourthy five of 68 (66%) AeCOPD patients were hospitalized and 22 of them treated with NPPV. None of these hospitalized cases were intubated. Patients with mild exacerabiton (n = 23) were treated as out patient.

CRP, ESR, WBC, neutrophil (%), and PCT values were significantly higher in the case group [Table 2].

Mean PCT levels were significantly different in terms of type and severity of AeCOPD [Table 3].

PCT levels in 40 (59%) of 68 patients with AeCOPD were higher than normal value (0.05 ng/ml), in 15 cases (22%) PCT levels were higher than 5 folder of normal value (0.25 ng/ml).

PCT cut-off value was defined as 0.07 ng/ml for differentiation of mild and moderate/severe exacerbation, the sensitivity and the selectivity were 82% and 91%, respectively (area under ROC curve = 0.887, confidence interval [CI] 0.804- 0.970, $P = 0.0001$) [Figure 1]. In 3 of 23 hospitalized AeCOPD cases who were not perform NPPV, PCT levels were higher than 0.25 ng/ml. In 12 of the cases who were performed NPPV, PCT levels were higher than 0.25 ng/ml ($P = 0.003$).

In AeCOPD cases who had indications for hospitalization, mean (SD) PCT levels in those managed with or without NPPV therapy were respectively 0.36 (0.26) ng/ml, and 0.15 (0.16) ng/ml ($P = 0.0001$) [Figure 2]. ROC analysis was performed to determined the cut-off value of PCT for indication of NPPV treatment and PCT cut-off value was determined higher than 0.1 ng/ml (sensitivity, 95%; selectivity, 78%; area under ROC curve 0.894, CI 0.821-0.967, $P = 0.0001$) [Figure 3].

Any difference between PCT levels based on stages of COPD was not observed ($P = 0.128$)

We determined significiant negative correlation between PCT levels and pH and pO_2 also we detected significiant positive correlation between PCT levels and ESR, WBC, neutrophil and CRP in AeCOPD cases.

A strongly positive correlation was detected between the number of acute exacerbations during the previous year, and PCT values measured during acute exacerbations of COPD (r = 0.514, $P = 0.0001$).

Among in-patients, any association between duration of

Table 1: Demographic, and clinical characteristics of the study groups

Mean	Case group (*n*=68) (%)	Control group (*n*=50) (%)	*P* value
Age (yrs)[a]	65.9 (0.97)	64.1 (1.22)	0.245
Gender (male/female)	58 (85)/10(15)	46 (92)/4(8)	0.266
BMI (kg/m^2)[a]	26.6 (0.58)	26.9 (0.78)	0.752
Smoking history (Packet/year)[a]	46.1 (2.89)	45 (2.88)	0.785
Stage of COPD			
1	8 (12)	9 (18)	0.042
2	23 (34)	27 (54)	
3	29 (42)	11 (22)	
4	8 (12)	3 (6)	

BMI=Body mass index; COPD=Chronic obstructive pulmonary disease. [a]Data were presented as mean (standart error of mean)

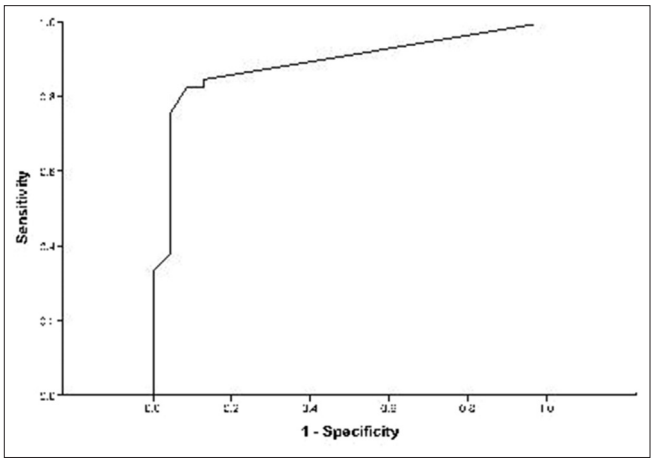

Figure 1: ROC curve, sensitivity, and specificity of PCT cut-off value in mild or moderate/severe exacerbations

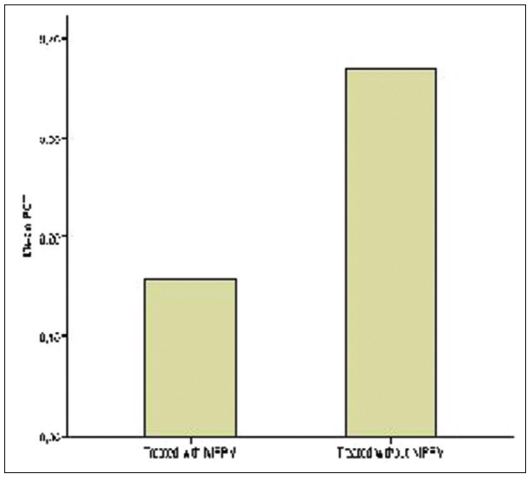

Figure 2: Mean PCT levels (ng/ml) in patients treated with or without NPPV

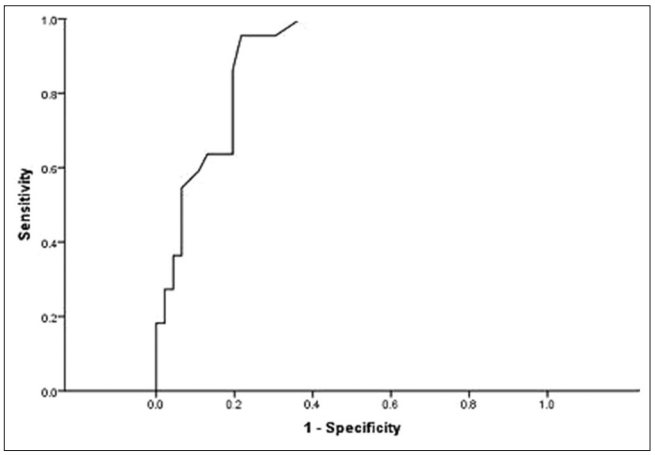

Figure 3: Mean PCT cut-off value predicting the indication for NPPV, and related ROC curve

Table 2: Comparison of the groups as for markers of inflammation, and infection

	Case group (*n*=68) Mean (SEM)	Control group (*n*=50) Mean (SEM)	*P* value
PCT (ng/ml)	0.19 (0.02)	0.05 (0.00)	0.0001
CRP (mg/l)	44.7 (5.92)	6.0 (0.90)	0.0001
ESR(mm/hr)	28.4 (2.65)	12.8 (1.38)	0.0001
WBC (mm^3)	9.4 (0.43)	7.0 (0.20)	0.0001
Neutrophil (%)	69.9 (1.22)	58.3 (1.16)	0.0001

PCT=Procalcitonin; CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; WBC=White blood cells; SEM=Standart error of mean

hospital stay, and levels of PCT (r = 0.254, *P* = 0.105) was not detected.

Table 3: PCT levels stratified based on type, and severity of exacerbations

	PCT level (ng/ml) Mean (SEM)	*P* value
Type of exacerbation		
Type 1 (*n*=31)	0.33 (0.04)	
Type 2 (*n*=23)	0.08 (0.02)	0.0001[a]
Type 3 (*n*=14)	0.05 (0.00)	
Severity of the exacerbation		
Mild (*n*=23)	0.06 (0.01)	0.0001
Moderate/severe (*n*=45)	0.26 (0.04)	

SEM=Standard error of mean; PCT=Procalcitonin. [a]Significant differences in mean PCT levels were noted between patients with type 1 and 2 (*P*=0.0001), type 1 and 3 (*P*=0.0001), type 2, and 3 (*P*=0.028), respectively

DISCUSSION

In this study the mean levels of PCT were found to be higher in AeCOPD patients than in stable COPD patients and in cases with severe AeCOPD than others. According to our results we can say that PCT levels may be used to predict the necessity of NPPV therapy in AeCOPD patients and value of PCT as 0.10 ng/ml may be a cut off as a predictor of necessity of NPPV treatment in these patients.

In Ece *et al*.'s study, it was reported that PCT levels were higher in AeCOPD patients, than controls who had noninfectious pulmonary diseases.[15] Similarly, in a study performed by Polzin *et al*., a difference was observed between AeCOPD patients and stable COPD patients according to PCT levels.[16] Tasci *et al*. reported same results, too.[17] Our results are compatible with these studies. In the same study a correlation was detected between PCT levels, and ESR, lenght of hospital stay and purulance of sputum while any association between WBC, and clinical symptoms was revealed.[17] We detected a significant positive correlation between PCT levels during an acute episode, and CRP, ESR, WBC and neutrophil counts. In compliance with our study Daniels *et al*. repoerted positive correlation between PCT and CRP.[18]

In another study evaluating 167 AeCOPD cases according to Anthonisen classification, higher levels of CRP were determined in type 1 accute attack than other types. It was also indicated that PCT levels were associated with lenght of hospital stay. In the same study PCT levels of patients requiring intensive care on admission were also found to relatively higher than others.[19] We determined statistically significiant difference according to PCT levels in all types of acute attacks and highest level was determined in type 1. PCT levels were higher in in-patients than out-patients, and among in-patients PCT levels were higher in cases who were underwent NPPV therapy than others. A significant positive correlation between PCT levels and pCO_2 was seen, and a negative one between pH, and pO_2 was observed. These findings suggested that PCT levels were associated with severity of respiratory failure in AeCOPD. In our study any correlation between duration of hospital stay, and levels of PCT was not found but Tasci et. al indicated a positive correlation between lenght of hospital stay and PCT levels.[17]

Among the studies where the association between the stage of COPD, and PCT has been evaluated, Stolz *et al*. found similar PCT levels in all stages of COPD, while Daubin *et al*. reported PCT levels of >0.25 µ/L in patients with very severe (FEV_1 < 30%) COPD.[19,20] In our study PCT levels in various stages of COPD did not differ. A positive correlation was detected between the number of acute exacerbations within last year, and levels of PCT. This finding indicated that levels of PCT might provide information about frequency of acute exacerbations, and inadequacy of treatment.

Rammaert *et al*. revealed that higher PCT levels in a severe AeCOPD cases were associated with necessity of mechanic ventilation and intensive care unit mortality. In the same study they reported high mortality rate in cases whose PCT livels higher than 0.24 ng/ml.[21] In another study, the levels of PCT higher than 0.25 µg/L in COPD cases who treated in intensive care unit were found to be related with mortality.[20] Unlike these studies Hurst *et al*. reports that systemic biomarkers were not helpful in predicting the severity of AeCOPD.[22] In our study, we could not make any prognostic evaluation because of none of the patients did not die during hospitalisation because of AeCOPD. We do not have any data about long term mortality of these cases out of hospital. In 55% of the cases managed with NPPV, PCT levels higher than 0.25 ng/ml were seen, which were significantly higher than others (13%). Besides, PCT cut-off value for indicating the necessity of NPPV was determines as 0.10 ng/ml. This result is important to predict the necessity of NPPV treatment in terms of the PCT level in the first evaluation of COPD patients.

CONCLUSION

We know that our study has the limitation of a relatively small number of patients, particularly when determining cutoff points for PCT levels but in literaure we could not find any report which investigated the importance of PCT on the planing of NPPV treatment in AeCOPD patients. We know the fact that the physicians should follow the universally accepted criteria for NPPV in AeCOPD patients and the clinical evaluation and the gas exchange are the main criterias. But PCT which is an important marker in the prediction of infectious episodes of COPD might be a predictor of NPPV treatment necessity. We think that the positive correlation between the levels of PCT and pCO_2 which is the main predictor in our clinic to start NPPV treatment shows the compliance of our results with the criterias defined previously for this therapy. Detection of PCT levels higher than 0.10 ng/ml in a AeCOPD patient could alert us to think the necessity of NPPV.

REFERENCES

1. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global startegy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2009. Available from: http://www.goldcopd.com. [Last Accessed on 2010 Mar 12].
2. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.
3. Voelkel NF, Tuder R. COPD exacerbation. Chest 2000;117:376S-9S.
4. Wedzicha JA. Exacerbations: Etiology and pathophysiologic mechanisms. Chest 2002;121:S136-41S.
5. Maruna, P, Nedelnikova K, Gurlich R. Physiology and genetics of procalcitonin. Physiol Res 2000;49:S57-61.
6. Oczenski W R, Fitzgerald D, Schwarz S. Procalcitonin: A new parameter for the diagnosis of bacterial infection in the peri-operative period. Eur J Anaesthesiol 1998;15:202-9.
7. Wrodycki W. Usefulness of plasma procalcitonin (PCT) estimation to diagnose patients in departments of infectious diseases. Przegl Epidemiol 2003;57:211-9.
8. Jimeno A. Assessment of procalcitonin as a diagnostic and prognostic marker in patients with solid tumors and febrile neutropenia. Cancer 2004;100:2462-9.
9. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60:925-31.
10. Koutsokera A, Stolz D, Loukides S, Kostikas K. Systemic biomarkers in exacerbations of COPD: The evolving clinical challenge. Chest 2012;141:396-405.
11. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, *et al.* Antibiotic treatment of exacerbations of COPD: A randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest 2007;3:9-19.
12. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, european community for steel and coal. Official statement of the European respiratory society. Eur Respir J 1993;16:5-40.
13. Ucan ES, Kocabas A. Turkish Thoracic Society. Guidelines for the diagnosis and management of chronic obstructive pulmonary disease; 2000. Available from: http://www.toraks.org.tr/book.aspx?list=149 and menu=140. [Last accessed on 2010 Mar 20].
14. Garpestad E, Brennan J, Hill NS. Noninvasive ventilation for critical care. Chest 2007;132:711-20.
15. Ece F, Kilickan L, Aytac J, Halim Issever H, Bayindir O. The effect of CRP and procalcitonin levels on the estimation of infection in the COPD patients admitted to ICU with respiratory failure. Turkiye Klinikleri Arch Lung 2009;10:13-21.
16. Polzin A, Pletz M, Erbes R, Raffenberg M, Mauch H, Wagner S, *et al.* Procalcitonin as a diagnostic tool in lower respiratory tract infections and tuberculosis. Eur Respir J 2003;21:939-43.
17. Tascı C, Balkan A, Karadurmus N, Inal S, Kilic S, Ozkan M, *et al.* The importance of serum procalcitonin levels in patients with chronic obstructive pulmonary disease exacerbations. Turk J Med Sci 2008;38:139-44.
18. Daniels JM, Schoorl M, Snijders D, Knol DL, Lutter R, Jansen HM, *et al*. Procalcitonin vs C-reactive protein as predictive markers of response to antibiotic therapy in acute exacerbations of COPD. Chest 2010;138:1108-15.
19. Stolz D, Christ-Crain M, Morgenthaler NG, Leuppi J, Miedinger D, Bingisser R, *et al*. Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. Chest 2007;131;1058-67.
20. Daubin C, Parienti JJ, Vabret A, Ramakers M, Fradin S, Terzi N, *et al*. Procalcitonin levels in acute exacerbation of COPD admitted in ICU: A prospective cohort study. BMC Infect Dis 2008;8:145.
21. Rammaert B, Verdier N, Cavestri B, Nseir S. Procalcitonin as a prognostic factor in severe acute exacerbation of chronic obstructive pulmonary disease. Respirology 2009;14:969-74.
22. Hurst JR, Donaldson GC, Perera WR, Wilkinson TM, Bilello JA, Hagan GW, *et al.* Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;15;174:867-74.

How to cite this article: Pazarli AC, Koseoglu HI, Doruk S, Sahin S, Etikan I, Celikel S, *et al.* Procalcitonin: Is it a predictor of noninvasive positive pressure ventilation necessity in acute chronic obstructive pulmonary disease exacerbation?. J Res Med Sci 2012;17:1047-51.

Source of Support: This study is funded by 'Comittee of Scientific Researh of Gaziosmanpasa University'. **Conflict of Interest:** None declared.