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Original Article

Measurement of Procalcitonin in acute exacerbation of COPD and its correlation to Spirometric Indices

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ABSTRACT:

Background: rational prescription of antibiotics in acute exacerbation of COPD (AECOPD) requires predictive markers. Acute phase reactants are capable of demonstrating the inflammation; however, they cannot be employed to make a difference between bacterial and non-bacterial causes of the inflammation. The bacterial infection plays an important role in the exacerbation of COPD patients. Recently, measurement of serum procalcitonin levels appears to be useful in order to minimize this problem. We aim to evaluate the prognostic and diagnostic. **Methods & methods:** 51 COPD patients with bacterial exacerbations, 47 patients without bacterial exacerbations, similar age and sex were included in the study. PCT levels in the serum samples were measured in all subjects. **Results:** Procalcitonin levels ranged from 0.01 to 12.03 ng/ml. Mean levels were 3.18±2.60 ng/ml in Group I and 0.23±0.39 ng/ml in Group II. Median values in Groups I and II were 2.98 and 0.09 ng/ml respectively. Statistically, there was a significant difference between two groups (p<0.001) with Group I showing a higher mean value as compared to Group II. A significant near strong correlation was observed between TLC levels and serum Proclacitonin levels (r=0.699; p<0.001). However, a weak negative and borderline significant correlation.

Conclusions: This study found increased PCT serum levels among AECOPD patients and suggests a role for PCT in the predicting of the bacterial exacerbations and their needs for ventilator support. We recommend other large studies to augment our findings.

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INTRODUCTION

COPD constitutes a major health problem [1]. COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. COPD is the fourth leading cause of the death worldwide [2]. According to World Health Organization estimates, 65 million people have moderate to severe COPD. More than 3 million people died of COPD in 2005 corresponding to 5% of all deaths globally and it is estimated to be the third leading cause of death by 2030 [3].

Crude estimates suggest there are 30 million COPD patients in India [4]. India contributes a significant and growing percentage of COPD mortality which is estimated to be amongst the highest in the world; i.e. more than 64.7 estimated age standardized death rate per 100,000 amongst both sexes. This would translate to about 556,000 in case of India (>20%) out of a world total of 2,748,000 annually [5]. Such mammoth volumes of disease have the potential to overwhelm health systems and state economies. Acute exacerbations of COPD (AECOPD) have considerable impact on morbidity, mortality and quality of life [6].

Although cigarette smoking is the best-studied COPD risk factor, there is consistent epidemiological evidence that nonsmokers may also develop chronic airflow limitation [7-10]. Across the world, cigarette smoking is the most commonly encountered risk factor for COPD. Cigarette smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual rate of decline in FEV1, and a greater COPD mortality rate than nonsmokers [11]. Other types of tobacco [e.g., pipe, cigar, water pipe [12] and marijuana [13] are also risk factors for COPD [14, 15]. Passive exposure to cigarette smoke (also known as environmental tobacco smoke) may also contribute to respiratory symptoms [16] and COPD [17] by increasing the lung's total burden of inhaled particles and gases [18, 19]. Serum procalcitonin levels are suggested to be one of the best biomarkers for predicting a bacterial infection [20]. Procalcitonin is a serum marker that rises in response to bacterial infections, but remains low in nonbacterial infections and other proinflammatory conditions. Procalcitonin (PCT) is a protein having a molecular weight of 13 kDa and it consists of 116 amino acid residues. The exact regions of its secretion are not yet clear [21]. Some literature suggests that PCT is secreted from neuroendocrine cells of the liver, small intestine and thyroid cells. In healthy humans, its normal serum level is 0.1 ng/mL. In a previous study, administration of bacterial endotoxin to healthy individuals resulted in an increase in PCT levels starting two hours after administration, with a peak value reached in 12 h [22].

Consequently, the serum level remains constant for another 12 h and decreases back to normal level in 20–24 h. PCT gives rapid response to bacterial infections [23]. Studies performed in patients with pneumonia revealed that serum PCT levels have high sensitivity and specificity in showing the inflammatory response caused by pneumonia [24]. It has also been suggested in some studies that serum PCT levels might have a relatively higher sensitivity and specificity in differentiating pneumonias of bacterial origin from those of viral origin [25]. The ubiquitous release of procalcitonin during infections is induced either directly by microbial toxins (eg. endotoxin) and/or indirectly by humoral factors or the cell-mediated host response. This induction is rather attenuated by cytokines released during viral infections [21]. Therefore, circulating levels of procalcitonin are markedly elevated in patients with bacterial infections compared to those with viral infections or other inflammatory conditions [26].

The aim of this study was to investigate whether the measurement of PCT can be used in the differentiation of bacterial and non-bacterial infection causes of COPD exacerbation, thus helping in planning the treatment.

MATERIALS AND METHODS

Study Design and Participants

The present study is cross-sectional and was conducted at a tertiary care teaching hospital of North India. Total 98 newly diagnosed patients from 30-80 years suffering from COPD attending the department of pulmonary medicine as per GOLD guidelines 2012 were included in the study.

The written informed consent was obtained fulfilling the inclusion and exclusion criteria of the study. The study was approved by the institutional ethics committee.

Inclusion Criteria

- Diagnosed case of Chronic Obstructive Pulmonary Disease
- Diagnosis was made by taking clinical histories of individuals i.e. cough breathlessness, expectoration, dyspnea, smoking status.
- Spirometry performed according to GOLD criteria (COPD was defined by a post bronchodilator FEV1/FVC ratio < 0.70. COPD severity was determined by the GOLD criteria. Subjects with a post bronchodilator FEV1/FVC ratio \geq 0.70 were considered not to have COPD) in the study.

Exclusion Criteria:

- Patients with acute respiratory distress syndrome.
- Serious systemic disorders incompatible with the study (either acute or chronic affecting any other target organ in the human body)
- Patients with history of poorly controlled associated diseases such as heart disease, thyroid disorders, coagulation disorders and hematologic problems etc were excluded from the study
- Patients were recruited from outdoor patient's department of respiratory medicine. They had undergone a detailed questionnaire and after that spirometry was performed of every individual and the patients were enrolled finally according to the GOLD criteria (In accordance with current GOLD guidelines (2012) COPD was defined by a post bronchodilator FEV1/FVC ratio < 0.70. COPD severity was determined by the GOLD criteria. Subjects with a post bronchodilator FEV1/FVC ratio \geq 0.70 were considered not to have COPD) in the study
- 98 diagnosed cases of COPD patients fulfilling the inclusion and exclusion criteria from outdoor patient's department by face to face conversation on demographics, smoking behaviors, physical measurements and medical history from the period March 2013 to January 2016 were recruited. The age criteria 30-60 years old were enrolled in the study. The study was approved by the corresponding institutional ethics committees and all participants gave written informed consent. The criteria for diagnosis & severity of COPD were taken as per GOLD guidelines 2012. In accordance with current GOLD guidelines (2012) COPD was defined by a post bronchodilator FEV1/FVC ratio < 0.70. COPD severity was determined by the GOLD criteria.

Subjects with a post bronchodilator FEV1/FVC ratio \geq 0.70 were considered not to have COPD. All the participants in this study were selected using convenience sampling. All participants gave written informed consent. The age criteria were 25-60 years old. All participants classified as COPD and healthy controls subjects were selected for Enzyme-Linked Immunosorbent Assay estimation in the serum samples.

Methods: Participants diagnosed as COPD were selected for the Complete medical history, General and local chest examination, Chest radiography, Spirometry was performed according to American Thoracic Society Guidelines, Routine blood tests (including CBC, ESR and CRP), Blood cultures, sputum culture, and Gram stain (Sputum was induced with hypertonic saline if subjects were unable to expectorate an adequate sputum sample spontaneously). Sputum specimens were considered adequate by standard criteria of >25 polymorphonuclear leukocytes and <10 epithelial cells per high power field. Blood samples were collected from all patients in order to perform complete blood count and routine

biochemistry, as well as to analyze acute phase reactants and serum PCT. The blood collected for serum PCT measurement was centrifuged and kept at -80°C until the time of the measurement. Any sample showing hemolysis was discarded. Procalcitonin were determined with a high sensitivity Enzyme-Linked Immunosorbent Assay using respective estimation kits recommended. The kits were obtained from BECTON, DICKINSON and COMPANY BD BIOSCIENCES. SAN JOSE, CA 95131 USA. Absorbance was measured at $\lambda=450$ nm on a microplate ELISA reader (BIO-RAD, i-MARK).

Statistical analysis: The analysis was carried out using SPSS 16.0 version (SPSS Inc., Chicago, Illinois, USA). The results are presented in mean SD and percentages. The Kolmogorov test was used to test the pattern for normal distribution. The test showed non-normal pattern of these parameters. Hence, Kruskal-Wallis test followed by Tukey's post hoc comparison tests were used to compare the levels of Procalcitonin. The P-value <0.05 was considered significant.

RESULTS

Table 1: Clinical Characteristics of COPD Patients with bacterial exacerbations and COPD Patients without bacterial exacerbation

Patients characteristics	COPD Patients with bacterial exacerbation (n=51)	COPD Patients without bacterial exacerbation (n=47)
Age	57.95 \pm 10.43	52.06 \pm 11.89
Sex (M/F)	135/15	89/11
Height in mtr (Mean \pm SD)	162.01 \pm 8.43	160.02 \pm 9.78
Weight in kgs (Mean \pm SD)	52.28 \pm 13.02	62.53 \pm 13.02
BMI in kg/mtr ² (Mean \pm SD)	19.79 \pm 4.09	24.35 \pm 0.95
Cigarette (pack years)	146.4 \pm 1.7	33.7 \pm 1.2
Smoker	118	45
Non- smoker	32	55
Smoking period	46.40 \pm 1.70	25.36 \pm 1.9
No. of pack years	299.0 \pm 66.7	35 \pm 1.2
Spirometry Parameters		
Pre FVC	1.84 \pm 0.63	2.86 \pm 0.73
Post FVC	2.08 \pm 0.67	2.96 \pm 0.70
Post FEV1/FVC	55.06 \pm 9.51	99.00 \pm 15.78
Pre FEV1	1.02 \pm 0.44	2.25 \pm 0.59
Post FEV1	1.13 \pm 0.46	2.43 \pm 0.58
Post FEV1% Predicted	44.72 \pm 18.79	89.77 \pm 7.22

Data were expressed in MEAN \pm SD

Table 2: comparison for Hematological parameters between COPD Patients with bacterial exacerbations and COPD Patients without bacterial exacerbation

S. No.	Characteristic	Group I (n=51)		Group II (n=47)		p-value	
		Mean	SD	Mean	SD	't'	'p'
1.	Hb (g%)	11.14	2.02	11.80	1.19	-1.945	0.055
2.	TLC ('000)	9.81	3.14	8.39	1.61	2.782	0.007

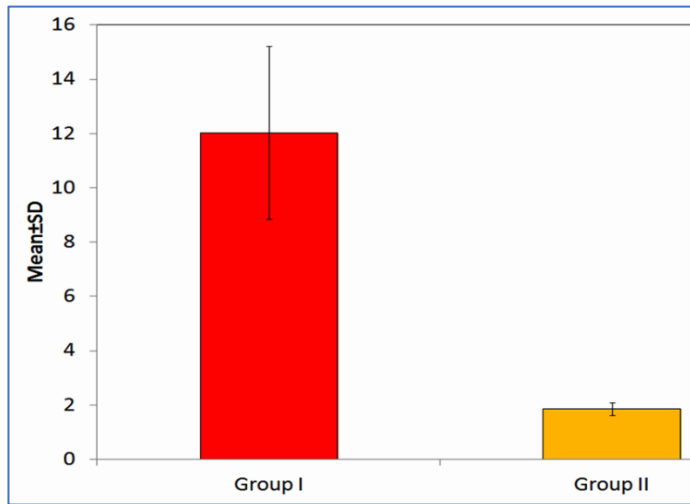


Figure 1: Comparison of Procalcitonin levels between COPD Patients with bacterial exacerbations (group I) and COPD Patients without bacterial exacerbation (group II)

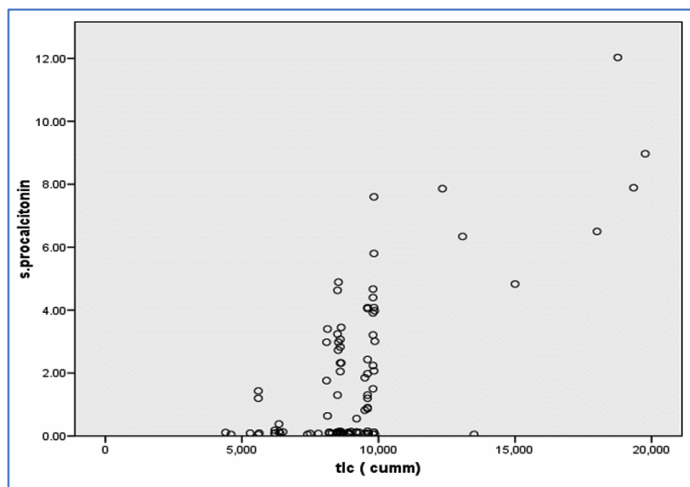


Figure 2: Correlation of Procalcitonin levels with TLC levels and Post-bronchodilator FEV₁/FVC ratio (Pearson correlation coefficient) (Overall)

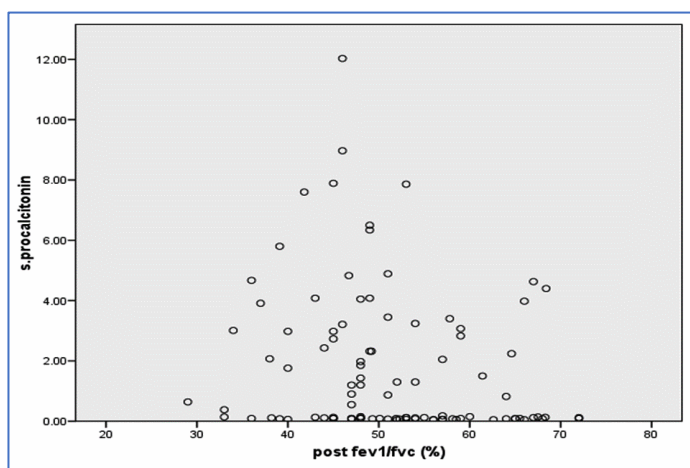


Figure 3: Correlation of Procalcitonin levels with TLC levels and Post-bronchodilator FEV₁/FVC ratio (Pearson correlation coefficient) (Group wise)

Table 1 shows a patient shows clinical characteristics of COPD patients, clinical characteristics of smoker and healthy control, clinical characteristics of non-smoker and healthy control. Table-2 shows Mean hemoglobin levels were 11.14 ± 2.02 g% in Group I and 11.80 ± 1.19 g% in Group II. Statistically, there was a significant difference among groups with respect to mean hemoglobin levels ($p=0.055$). TLC was 9.81 ± 3.14 thousands/cumm in Group I and 8.39 ± 1.61 thousands/cumm in Group II.

Statistically, this difference was significant ($p=0.007$). Figure 1 shows Procalcitonin levels ranged from 0.01 to 12.03 ng/ml. Mean levels were 3.18 ± 2.60 ng/ml in Group I and 0.23 ± 0.39 ng/ml in Group II. Median values in Groups I and II were 2.98 and 0.09 ng/ml respectively. Statistically, there was a significant difference between two groups ($p<0.001$) with Group I showing a higher mean value as compared to Group II. Figure 2 shows A significant near strong correlation was observed between TLC levels and serum Procalcitonin levels ($r=0.699$; $p<0.001$).

However, a weak negative and borderline significant correlation between FEV₁/FVC levels and serum procalcitonin levels was observed ($r=-0.199$; $p=0.050$). Figure 3 shows the correlation of Procalcitonin levels with TLC and FEV₁/FVC levels in independent groups, only significant correlation was observed in Group I where a strong positive correlation between TLC levels and Procalcitonin levels was observed ($r=0.772$; $p<0.001$). All the other correlations did not yield a significant association.

DISCUSSION

Infection is a major cause of morbidity and mortality among patients with COPD [27]. In COPD patients presenting to the hospital with dyspnea, our study demonstrates a wide variety of viral and bacterial pathogens, as well as a high incidence of pneumonia. Recently, use of procalcitonin to guide clinical decisions has been shown to reduce antibiotic use significantly in patients with respiratory illnesses without compromising composite patient outcomes in a number of randomized interventional trials [26, 28, 29]. Serum procalcitonin levels are suggested to be one of the biomarkers for predicting a bacterial infection. In this study, we have demonstrated that the levels of PCT for patients of group A with bacterial COPD exacerbation were significantly higher than group B with non-bacterial COPD exacerbation ($p<0.001$).

Chang *et al.*, [30] showed that patients admitted with COPD exacerbation and positive sputum cultures for bacterial pathogen had significantly higher PCT values. A similar result was found in our study. Also other studies have shown that the level of circulating procalcitonin is increased in severe bacterial infections, but remains fairly low in viral infection and nonspecific inflammatory diseases [21]. Our study, and consistent with the European literature, we found that a high procalcitonin level was relatively specific for invasive bacterial disease such as pneumonia [21, 31]. In addition, elevated procalcitonin values in the AECOPD group correlated with higher temperature, white blood cells, and more severe illness, suggesting the possibility of occult pneumonia.

Thus, high procalcitonin values may alert clinicians to the presence of bacterial pneumonia when the chest radiograph results are negative or ambiguous. It has been estimated that approximately 40%–50% of AECOPD cases are due to bacterial infections [32]. The precise contribution of bacterial infection is difficult to define because the airways of COPD patients may be chronically colonized [33, 34]. Acquisition of new strains of *Haemophilus influenzae* and *Moraxella catarrhalis*, rather than bacterial load, appears to be the most important factor in the pathogenesis of acute exacerbations [35]. This factor has not been accounted for in AECOPD antibiotic trials and might explain the modest beneficial effects of antimicrobial treatments observed. The sensitivity and specificity of PCT in bacterial infections were found to be 92.6% and 97.5%, respectively [36].

Serum PCT level above 0.5 ng/mL indicates bacterial infections, whereas levels above 2 ng/mL show sepsis [22]. When the threshold level of PCT indicative of bacterial infection was accepted as 0.5 ng/mL, the positive and negative predictive values were found to be 100% and 87%, respectively [37]. We found that PCT has a significant correlation with leucocytic count suggesting that when these parameters are used in combination with the PCT increases the predictive value in identifying bacterial infection. A significant correlation was found between the PCT level and FEV1 in COPD exacerbations of bacterial etiology in our study, indicating that high PCT may point to increasing severity of AECOPD. The level of circulating procalcitonin is increased in severe bacterial infections. Since the extent and severity of infection gradually increase in bacterial infections, serum PCT levels have also been shown to increase [21].

In previous study, a significant correlation was established between serum procalcitonin (PCT) levels and duration of hospital stay, ESR and sputum purulence ($P = 0.002$, $P = 0.007$, respectively). But there was no significant correlation between serum PCT levels and white blood cell count and. They concluded that serum PCT measurements would be effective in guiding the treatment in patients with acute exacerbations of COPD [38]. When they had returned to their stable state, the levels of PCT for patients of group A, were significantly lower than that in exacerbation. This agree with a recent study, included nineteen patients with acute exacerbation of COPD and 16 patients with stable COPD as the control group, the investigators found that the mean serum PCT levels in COPD patients with exacerbations was 1.8 ng/mL and in stable COPD patients was 0.2 ng/mL [38].

Our study adds to the growing body of literature which questions the utility of procalcitonin levels to discriminate viral-associated from bacterial-associated AECOPD. In a study by Daniels et al, procalcitonin levels were measured in outpatients enrolled in a trial of doxycycline for AECOPD [39]. A significant benefit of doxycycline was noted for patients with procalcitonin levels <0.1 ng/mL. In this study, as well as in two additional reports, no differences in procalcitonin levels were noted in patients with or without bacteria in sputum during exacerbation [39, 40]. Our study provides the most rigorous microbiologic analysis of moderate to severe illness requiring hospitalization to date, particularly for subjects who were

deemed negative for bacterial infection. Unlike prior studies, we did not consider patients to be free of bacterial infection unless adequate samples were taken in a timely fashion and without antibiotic use prior to hospitalization. Our findings suggest that, serum PCT levels have high sensitivity and specificity in displaying the inflammatory response in patients admitted with COPD exacerbation. In the stable COPD patients, serum PCT levels were found to be within normal limits. These findings agree with previous studies Lacoma *et al.*, [21] and Bafadhel *et al.*, [31].

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