Serum procalcitonin as a biological marker to distinguish between bacterial and non-bacterial exacerbation of COPD: A comparative cross-sectional study at a tertiary care centre in India

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Aims: The goal of this study was to determine the diagnostic importance and cut-off value of serum PCT as a vital biomarker in differentiating bacterial and non-bacterial causes of exacerbation of COPD

Study design: It was a comparative cross-sectionalstudy.

Place and Duration of Study: Study was conducted on 80 patients recruited from VMMC and Safdarjung Hospital, New- Delhi, India, for a period of 18 months. Forty patients has COPD and other 40 had acute exacerbation of COPD,

Methodology: Everyenrolledpatient received a thorough history, a clinical assessment, and records of tests such as a venous blood sample, spirometry, and a chest X-ray.We excluded from our study patients with various respiratory conditions such as hydrothorax, pneumothorax, CHF, pleural effusion, and those outside the respiratory system, as well as those who started antibiotic medication earlier than 48 hours after enrollment.Venous samples were obtained from each participant in order to measure procalcitonin levels and blood counts.SerumPCT levels were assessed by ELISA kit.Gram stain and culture was done of sputum sample collected from the exacerbated group.

Results: Patients with bacterial COPD exacerbations had significantly higher mean serum PCT levels compared to non-bacterial exacerbations (2.58±1.54 vs 0.45±0.51 ng/ml; P=0.0001) based on sputum culture results. PCT cutoff of 0.9 ng/ml differentiated bacterial exacerbations with 100% sensitivity and 76.9% specificity

Conclusion: The findings of the study indicate the serum PCT levels can be regarded as an appropriate biomarker to differentiate between the bacterial and non-bacterial cause of exacerbation in COPD.

Keywords: procalcitonin, COPD, AECOPD, Bacterial and non-bacterial exacerbation

1. INTRODUCTION

Chronic obstructive pulmonary disease ranks fifth globally in terms of disease burden in 2020, making it a serious health concern.[1] Acute exacerbations of chronic obstructive lung disease (AECOPD), a significant complication of COPD is associated with an increased risk of morbidity and mortality that is caused by a variety of bacterial and viral infectious agents[2,3]. The neuroendocrine cells of the stomach and lung, and the parafollicular cells (C cells) of the thyroid, secrete procalcitonin (PCT), a 116-amino acid peptide precursor of calcitonin. [4], under the regulation of the CALC-1 gene [5]. In

healthy individuals serum PCT levels stay below the detection limit of 0.01 microg/l [6]. It is a unique diagnostic marker of systemic inflammatory disorders because its levels do not rise or very slightly do so in cases of viral, non-infectious, or localized bacterial infection, however it increases significantly in case of bacterial infections [7]. Administering antibiotics for acute respiratory illnesses with bacterial causes strictly mandates early identification and appropriate treatment measure commencement. The application ofserum PCT-guided antibiotic therapy holds great potential to transform the results of appropriate antibiotic stewardship, improving patient outcomes and hospital environments alike. The goal of this study was to determine the diagnostic importance and cut-off value of serum PCT as a vital biomarker for separating COPD exacerbations caused by bacteria from those caused by non-bacteria.

2. MATERIAL AND METHODS

This 18-month prospective observational study involved both in- and out-patients with respiratory symptoms who presented to the medicine department at VMMC and Safdarjung Hospital. Subjects with acute change in patients baseline dyspnea, cough and /or sputum production that was normal than day to day variability and warranting change in medical therapy wre defined as COPD exacerbations according to American Thoracic society and the European Respiratory Society. The GOLD [8] criteria were used to classify the patients based on COPD and AECOPD. Subjects with worsening respiratory symptoms, such as coughing up sputum and shortness of breath, were clinically classified as AECOPD when their post-bronchodilator FEV1/FVC% was less than 0.7.Forty patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD), 40 with stable COPD were diagnosed and enrolled for the study after taking informed written consent.

Patients with other respiratory diseases like hydrothorax, pneumothorax, CHF, pleural effusion and those with infectionoutside the respiratory tract and with initiation of antibiotic therapy before 48 hours of enrolment were excluded from our study.

All patients underwent a detailed history, clinical evaluation and parameters like chest X-ray, spirometry, and venous blood sampling were recorded.All spirometries were done by the single operator.

According to the standard guidelines [9] the sputum was collected from the exacerbated patients before starting the antibiotic treatment.The patients were told to rinse their mouth twice with an antiseptic solution and to collect their sputum into a screw-capped, labelled, sterile, universal container. The sample was delivered in two hours to the microbiology lab, where it was inspected for quality in accordance with Bartlett criteria [10]. It was only approved for culture when ≥10 mucus-producing leucocytes but<25 squamous epithelial cells per LPF (low power field X100) were observed [11]. In addition, the CFU count and bacterial growth in the culture were examined. Using different biochemical tests, the growth of pathogenic organisms (CFU count ≥ 10^4/ml) was identified.

For the purpose of measuring procalcitonin levels and blood counts, venous samples were taken from each participant.

The adequate sample was plated on sheep blood agar, MacConkey and chocolate media and incubated at a temperature of 37 degree C for 18- 24 hours. Bacterial isolation and identification was performed with the use of standard techniques. The Kirby Bauer [12] disk diffusion susceptibility test was performed and the zone of inhibition was measured around each antibiotic disk and interpreted as per the CLSI guidelines. [13]

At the time of admission 5 ml of venous blood sample was collected from all the study subjects for biochemical markers and serum procalcitonin levels. SerumPCT levels were assessed by ELISA kit, Qayee-Bio manufacturers of Human-BAFF-R kit using Double- Antibody sandwich technique. The serum PCT was done once and repeated if the error was reported.Accuracy with standard linear regression coefficient R with the expected value of the concentration (R value greater than or equal to 0.99) with range and repeatability between 0-50ng/ml and the plate coefficient of variation less than 15%.

2.1 SAMPLE SIZE

The study by Gao D et al observed that serum PCT concentration was (2.07±5.57) in the exacerbated group of COPD patients and (0.21±0.17) in healthy group.[14] Taking these values as reference, the minimum required sample size with 80% power of study and 5% level of significance is 36 patients in each study group. To reduce margin error, total sample size taken was 80 (40 patients per group).

2.2STATISTICAL ANALYSIS:

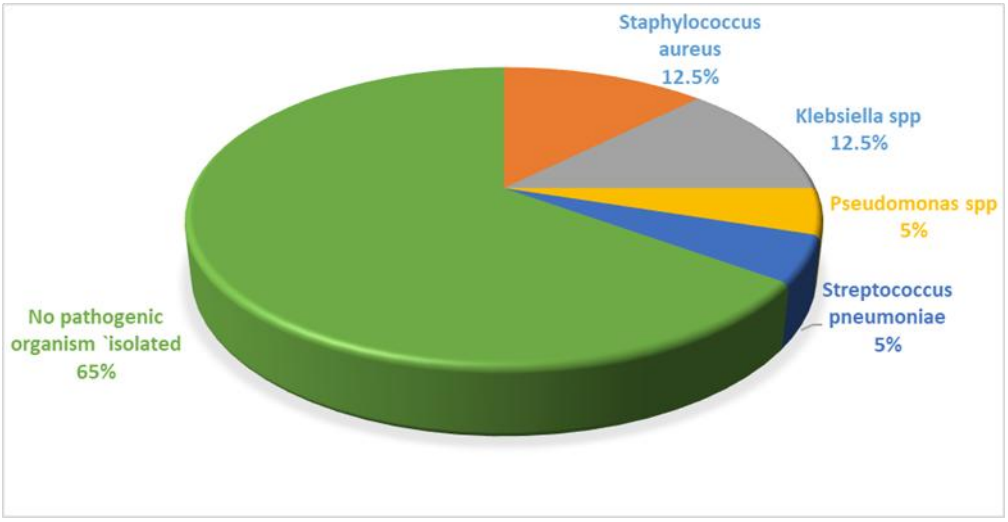
The results are presented in frequencies, percentages and mean ± SD. The categorical variables and continuous variables were compared were compared by using Chi-square and unpaired t-test/ Mann- Whitney U test. The receiving operating curve (ROC) analysis was performed. The area under curve (AUC) with its 95% confidence interval (CI) was calculated. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with their 95% CI was calculated. The *P*<.05 was considered significant. All the analysis was carried out on SPSS 16.0 version.

3. RESULTS AND DISCUSSION:

The mean age of patients with stable COPD and AECOPD was 60.52 ± 10.48 and 62.28 ± 10.65 respectively with male predominance 82.5%. Both the groups showed no significant difference in age and gender distribution (*P*=0.46). Biochemical parameters like Random Blood Sugar, Kidney Function Test, Liver function test, coagulation profile were comparable between both the groups (*P*=0.05). Total Leucocyte Count was significantly higher in AECOPD subjects. SPO2 was significantly higher (*P*=0.0001) among patients of stable COPD (96.52±1.88) compared to AE COPD (89.62±8.88). Spirometer parameters were significantly higher among patients of stable COPD compared to AE COPD (*P*=0.05).

Bacteria was detected in six patients (7.5%) of AECOPD on sputum Gram stain. Sputum culture was positive in 14 patients (35%) of AECOPD with *Staphylococcus aureus* and *Klebsiella pneumoniae* were isolated in 5 patients each and *Streptococcus pneumoniae* and *Pseudomonas spp.* were isolated in 2 patients each as seen in fig .1

Fig: 1 shows the spectrum of bacterial isolates from sputum culture



The mean serumPCT value in stable COPD (0.16±0.10) and in AECOPD (0.67 ±0.94) was calculated to be statistically significant (*P*=0.0001) as seen in Table 1.

Table 1: Comparative analysis of Serum PCT in both groups

Groups	Serum PCT (Mean±SD)

Stable COPD	**0.16 ± 0.10**
AECOPD	**0.67 ± 0.94**
***P* value**	**0.0001**

Based on Gram stain serum PCT levels were compared between bacterial and non- bacterial exacerbation of COPD. The mean serumPCT level in bacterial exacerbation was 2.58±1.54 and in non-bacterial exacerbation was 0.45±0.51. The difference was statistically significant (*P*=0.0001) as seen in Table 2.
Based on sputum culture serum PCT levels were compared between bacterial and non- bacterial exacerbation of COPD. The meanserum PCT level in bacterial exacerbation was 1.70±1.37 and in non- bacterial exacerbation was 0.27±0.15 and the difference was statistically significant (*P*=0.0001) as seen in Table 2.

Table 2: Comparison of serum PCT level among bacterial and non-bacterial exacerbation of COPD on sputum Gram Stain and culture

Groups	Serum PCT in Gram stain positive (Mean±SD)	Serum PCT in sputum culture positive (Mean±SD)
Bacterial exacerbation	**2.58 ± 1.54**	**1.70 ± 1.37**
Non-bacterial exacerbation	**0.45 ± 0.51**	**0.27 ± 0.15**
***P* value**	**0.0001**	**0.0001**

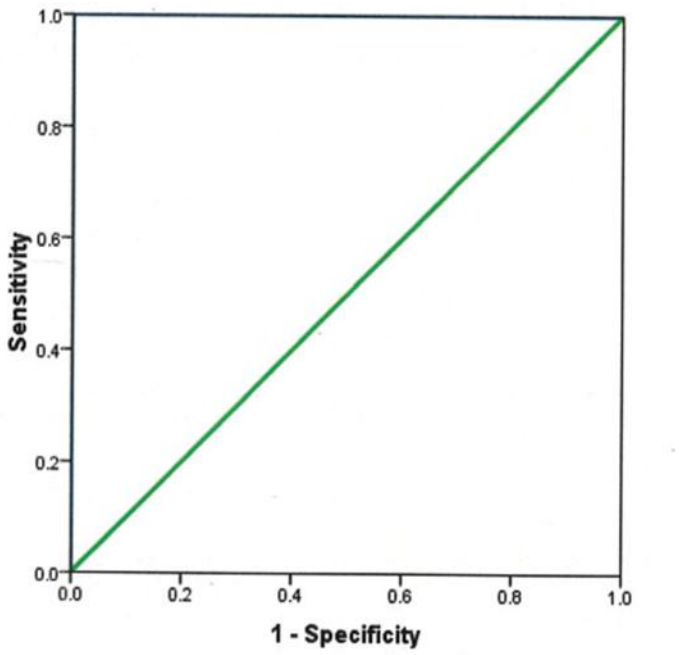
As per table 3 the Predictive value of serum PCT in differentiating bacterial from non- bacterial exacerbation according to sputum culture was calculated and a cut-off value of serum PCT 0.9 ng/ml correctly differentiated bacterial exacerbation from non- bacterial exacerbation on sputum gram stain in 35% patients with sensitivity 100%, specificity of 76.9% with PPV 70.0 and NPV 100 respectively.

Table.3 shows the predictive values of Serum PCT in differentiating bacterial exacerbation from non-bacterial exacerbation on sputum culture

Serum PCT	Bacterial exacerbation		Non-bacterial exacerbation		Total	
	No.	%	No.	%	No.	%
>0.90	14	35.0	6	15.0	20	50.0
≤0.90	0	0.0	20	50.0	20	50.0
Total	14	35.0	26	65.0	40	100.0
Predictive values, % (95%CI)						
AUC, p-value	1.00 (1.00-1.00), 0.0001*					
Sensitivity	100.0(100.0-100.0)					
Specificity	76.9 (60.7-93.1)					
PPV	70.0(49.9-90.1)					
NPV	100.0(100.0-100.0)					

In fig 2 the AUC is 1.00 because 35% of patients in AE of COPD group have bacterial growth on sputum culture and all 35% of patients have serum PCT values >0.90ng/ml. The sensitivity and specificity of serum PCT was found to be 100% and 76.9%

Fig: 2 ROC curve showing sensitivity and specificity of Serum PCT in differentiating bacterial exacerbation from non-bacterial exacerbation on sputum culture



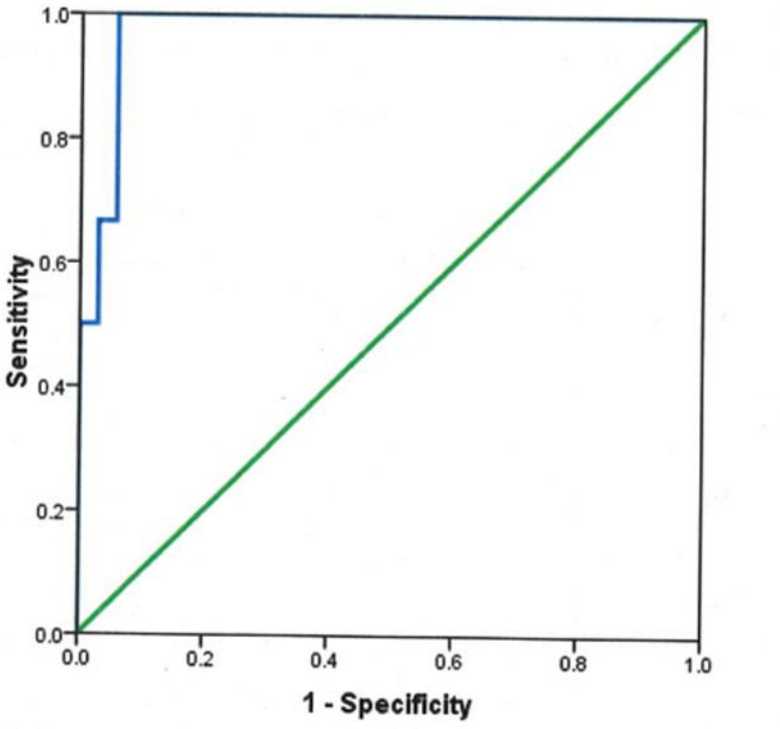
As per table 4 the Predictive value of serum PCT in differentiating bacterial from non- bacterial exacerbation according to sputum gram stain was calculated and a cut-off value of serumPCT 0.9 ng/ml correctly differentiated bacterial exacerbation from non- bacterial exacerbation on sputum Gram Stain in 12.5% patients with sensitivity of 83.3% specificity of 94.1% with PPV 71.4 % and NPV 97.0% respectively.

Table 4 shows the predictive values of Serum PCT in differentiating bacterial exacerbation from non-bacterial exacerbation on sputum Gram Stain

Serum PCT	Bacterial exacerbation		Non-bacterial exacerbation		Total	
	No.	%	No.	%	No.	%
>0.90	5	12.5	2	5.0	7	17.5
≤0.90	1	2.5	32	80.0	33	82.5
Total	6	15.0	34	85.0	40	100.0
Predictive values, % (95%CI)						
AUC, p-value	0.97(0.93-0.99), 0.0001*					
Sensitivity	83.3(53.5-98.9)					
Specificity	94.1(86.2-99.9)					
PPV	71.4(38.0-98.9)					
NPV	97.0(91.1 - 99.9)					

In fig 3 the AUC is 0.97. Serum PCT values >0.90ng/ml correctly differentiated bacterial exacerbation from non-bacterial exacerbation on sputum Gram Stain in 12.5% patients with sensitivity and specificity of 83.3% and 94.1% respectively.

Fig: 3 ROC curve showing sensitivity and specificity of Serum PCT in differentiating bacterial exacerbation from non-bacterial exacerbation on sputum Gram Stain



As per the World Health Organization, COPD, a chronic and debilitating disease, is predicted to become the fourth leading cause of death by 2030 [15]. Acute exacerbations of COPD are used to calculate the disease's morbidity, mortality, and associated medical expenses [16]. Previous studies have described exacerbations brought on by bacteria, viruses, or increased eosinophilic inflammation [17].

However, the lack of easy testing to distinguish between different forms of acute exacerbations has been a substantial challenge. As a result, oral steroids and antibiotics are used excessively in a substantial percentage of exacerbations, regardless of the cause, posing considerable and potential risks to individual patients and to society also, in the form of bacterial resistance and the adverse effects of the antimicrobial therapy [18].

PCT, a calcitonin prohormone is secreted in several tissues in response to bacterial infections, but not viral infections, or non-specific inflammation. As a result, serumPCT is a promising biomarker that is now being employed to diagnose bacterial infections in a variety of contexts [19] [20].

The present study was conducted in the department of Microbiology and General Medicine, VMMC & Safdarjung hospital, New – Delhi with the objective to evaluate serum PCT between stable COPD and AE COPD and its role in differentiating between bacterial and non-bacterial exacerbation. A total of 40 patients in each stable COPD and AECOPD were included in the study.

In this study, serum PCT was significantly (*P*=0.05) lower among patients of stable COPD (0.16±0.10) compared to AE OF COPD (0.67±0.94)

In the study by Lakshmi et al. 43 stable COPD patients and 43 AECOPD patients from Tamil Nadu population were recruited. Serum PCT level in the COPD group was 1.10 ± 0.18 ng/ml, while it was 44.39 ± 3.16 ng/ml in the AECOPD group, and their difference was statistically significant with P value < 0.001.[21]

In a comparable study, Rathore et al. found a highly significant difference in mean serumPCT value (*P*=0.003) between patients with AECOPD (1.34±2.53ng/ml) and stable COPD patients (0.07±0.05 mg/ml). [22] Pandey et al. also discovered that mean serum PCT levels in the AECOPD group (1.31± 0.79ng/ml) were substantially higher than in the stable COPD group (0.1±0.09ng/ml) (*P*=0.001) [23].

The serum PCT concentration in the AECOPD group was 2.07±5.57ng/ml in a study conducted by Gao et al., while it was 0.21±0.17 ng/ml in the healthy control group. The study found a significant difference in serum PCT values between the two groups with *P*=0.05 [14].

Furthermore, comparing patients with AECOPD (1.44±0.542 ng/ml) and stable COPD patients (0.05±0.012 ng/ml), Halim et al. found a very statistically significant difference (*P*=0.001) in mean PCT values [24].

Our study found that serum PCT was significantly (*P*=0.0001) higher among patients of bacterial exacerbation (2.58±1.54ng/ml) than non-bacterial exacerbation (0.45±0.51ng/ml) according to sputum Gram stain. Serum PCT was significantly (*P*=0.0001) higher among patients of bacterial exacerbation (1.70±1.37ng/ml) than non-bacterial exacerbation (0.27±0.15ng/ml) according to sputum culture also.

The results of this investigation were consistent with those of a study by Borsi et al., where 25 with AECOPD and 25 with stable COPD were compared. The PCT level was 0.272± 0.586 ng/ml in the exacerbated group and 0.066± 0.027 ng/ml in the non-exacerbated group showing a statistically significant difference of (*P*=0.001) [25].

Additionally, So-Ngern et al. discovered that patients with bacterial infections had a considerably higher median serumPCT level (1.90ng/ml vs. 0.16 ng/ml, *P*=0.001) than patients without bacterial infections. For the purpose of differentiating between bacterial and non-bacterial illnesses, the area under the ROC curve of serumPCT was 0.874 (95% confidence interval: 0.834, 0.914; *P*=0.001). The ideal PCT cut-off value for differentiating between fevers caused by bacterial infectious aetiology was 0.5ng/ml, with a sensitivity of 84.7%, specificity of 79.9%, positive predictive value of 81.1%, and negative predictive value of 83.7%. The authors report that serumPCT was demonstrated to be a reliable biomarker for the identification of bacterial infections in patients admitted to medical and surgical intensive care units. 0.5ng/ml was the ideal serumPCT cut-off for the detection of bacterial infections [26].

In our study we considered a higher serumPCT cut off value of 0.9ng/ml which correctly differentiated bacterial exacerbation from non-bacterial exacerbation on sputum Gram Stain in 12.5% patients with sensitivity and specificity of 83.3% and 94.1% and also correctly differentiated bacterial exacerbation from non-bacterial exacerbation on sputum culture in 35% patients with sensitivity and specificity of 100% and 76.9% respectively.

5. CONCLUSION

This study was conducted to evaluate the role of serum PCT as a potential marker to distinguish between bacterial and nonbacterial cause of acute exacerbation of COPD.

In comparison to other studies a higherserum PCT cut off value (0.9 ng/ ml) was used which increased the specificity, sensitivity and PPV of serum PCT as a marker to diagnose bacterial exacerbations. To conclude we suggest that serum PCT levels (with a cut off level of 0.9 ng/ ml) should be used in the initial evaluation of acute exacerbation of COPD for appropriate antibiotic usage and reduction of resistant pathogens.

6. COMPETING INTERESTS

Authors have declared that no competing interests exist.

7. AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript

8. CONSENTAND ETHICAL APPROVAL

The study was approved by the Institutional ethical committee of VMMC and Safdarjung Hospital, New-Delhi.The Committee reviewed the study protocol and found it to be suitably drawn and based on sound scientific and ethical foundation.Before being enrolled in this study, all eligible individuals were asked to complete an informed consent form to give their consent.The information provided by the participants was kept private and utilized exclusively for this study.

9. LIMITATIONS OF THE STUDY

One of the limitations of this study was the small sample size. The studies with larger sample size are required to have more robust findings and results.
Autoimmune inflammatory disorders which can lead to rise in serum PCT levels were excluded from the study on the basis of history and no investigation was done for such disorders.
This study was a single centric study, not a multicentre study, however multicentre would have been more beneficial for the better correlation of serum PCT levels with bacterial COPD exacerbation.
Viral cultures and viral RTPCR tests were not performed on the sputum samples, so the viral etiology of COPD exacerbation was not confirmed.
Influence of vaccination (for example- influenzae, pneumococcal vaccination) was not evaluated in terms of COPD exacerbation and also not considered in this study.

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ABBREVIATIONS

COPD- Chronic Obstructive Pulmonary Disease
GOLD- Global Initiative for Chronic Obstructive Lung Disease