Original Article

DOI: 10.7860/JCDR/2021/52498.15756

Evaluation and Correlation of Serum C-Reactive Protein and Procalcitonin Levels in Acute Exacerbation and Stable Phase of Chronic Obstructive Pulmonary Disease Patients: An Observational Study

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ABSTRACT

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is characterised by limitation of airflow that is not fully reversible. Acute exacerbations lead to worsening of respiratory symptoms which results in increased hospitalisation incurring high socio-economic costs. Timely diagnosis and early treatment of exacerbation can avoid unnecessary hospitalisation and mortality. Biomarkers which may function as diagnostic and prognostication aids are of great help in resource constrained countries like India. Indian literature on the role of biomarkers in such context are scarce.

Aim: To evaluate serum levels of C-Reactive Protein (CRP) and Procalcitonin (PCT) in COPD patients admitted in respiratory ward with acute exacerbation and assess their correlation with course of disease.

Materials and Methods: The present study was an observational study in which a total of 103 COPD patients, diagnosed as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines admitted with acute exacerbation, were included in the study. All patients were subjected to routine investigations at admission. The serum CRP and PCT levels were assessed at the time of admission, discharge and at four weeks after discharge as well. Normality of quantitative data was checked by measures of Kolmogorov-Smirnov tests of normality. For normally distributed data means were compared using unpaired t-test. For skewed data or scores Mann-Whitney Test was applied. For categorical variables, numbers and percentages were calculated. The data observed at various points of time was compared using Wilcoxon Signed-Rank test or paired t-test whichever was applicable depending on its normality. Correlation analysis was performed using Spearman's Rank Test. All calculations were two-sided and were performed using Statistical Package for the Social Sciences (SPSS) trial version 17.0 (SPSS, Chicago, IL). A p-value of <0.05 was considered to indicate statistical significance.

Results: Serum levels of CRP and PCT measured were as follows; 10.80±21.1 mg/L, 7.40±8.9 mg/L and 3.50±6.20 mg/L (mean±standard deviation) and 0.08±0.11 mg/L, 0.05±0.70 mg/L, and 0.01±0.04 mg/L (mean±standard deviation) at admission, discharge and follow-up, respectively. The CRP and PCT levels were significantly higher at the time of admission than at discharge and follow-up (p-value ≤ 0.001, p-value ≤ 0.001) which correlated with severity of breathlessness as per Modified Medical Research Council (mMRC) dyspnoea scale. A significant correlation between CRP and PCT values was found at the time of admission ($r=0.423$, p-value ≤ 0.001) and at discharge ($r=0.310$, p-value ≤ 0.001) but not at follow-up ($r=0.049$, p-value=0.622).

Conclusion: The serum levels of CRP and PCT dropped significantly from admission to discharge and then follow-up after one month. The change in these parameters correlated well with exacerbation and stable phases of COPD. Further research is required to validate their role as biomarkers of acute exacerbation of COPD.

Keywords: Biomarkers, Breathlessness, Modified medical research council dyspnoea scale

INTRODUCTION

COPD is estimated to be ranked 3rd amongst global burden of diseases by 2020 [1]. In India, the prevalence of COPD is 4.1%, with a male-to-female ratio of 1.56:1 in the population of above 35 years of age [2]. The GOLD defines COPD as "a common preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and is associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles and gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients. Acute exacerbation of COPD (AECOPD) is defined as "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication" [1]. It is characterised by increased breathlessness, often accompanied by wheezing, increased cough and sputum, change in colour of sputum or tenacity of sputum and fever. Commonly, exacerbations are triggered by secondary infection and air pollution. Acute exacerbations are a cause of severe respiratory failure in COPD patients that warrant hospitalisation and constitute significant socio-economic burden.

According to GOLD guidelines [1], antibiotics are recommended for moderate to severe exacerbations. However, only in approximately 50% of patients with severe AECOPD, bacteria have been isolated in respiratory tract [1,3]. Review of literature showed virus detection rates of 22-64% in AECOPD patients in 24 studies conducted from 2001-2015 [4,5]. Also, around 20-30% of exacerbations are triggered by non infectious causes including air pollutants, non adherence to standard treatment and sub-optimal management of co-morbidities [6]. Any person seeking medical attention for dyspnoea is not necessarily a true COPD exacerbation. The AECOPD can be mimicked by other medical conditions like congestive heart failure, pneumonia and pulmonary embolism [7]. In view of non availability of well defined criteria for diagnosis of AECOPD, the role for more objective criteria like biomarkers becomes more relevant.

The CRP belongs to a class of acute-phase reactants, as its levels rise dramatically during inflammation, infection, trauma and tissue necrosis, malignancies and autoimmune disorders. An elevated CRP level does not diagnose a specific disease, however, it is a sensitive and accurate reflection of acute phase response [8-11]. The PCT is a peptide precursor of the hormone calcitonin, which is involved with calcium homeostasis. In severe infection, the blood levels of PCT may rise to 100 ng/mL. Measurement of PCT can be used as a marker of severe sepsis and generally correlates well with the degree of sepsis [11-13]. Nikolakopoulou S et al., found that serum levels of CRP and angiopoietin-2 in COPD patients hospitalised with exacerbation were significantly higher at day 1 than at day 7 of hospitalisation [11]. The CRP alone was neither sensitive nor specific in determining clinical severity or outcome of COPD exacerbations. It was speculated that utilising combinations of biomarkers may prove more useful. Similarly, Lacoma A et al., assessed serum levels of PCT, CRP and neopterin in acute exacerbations of COPD and showed that higher biomarker levels correlated well with short-term prognosis. Other studies also supported that CRP and PCT can be promising markers for diagnosis of AECOPD, guiding therapy and monitoring response to therapy and evaluation of prognosis [14-16].

However, data on the role of these two biomarkers in combination in Indian scenario is lacking. The present study was planned to evaluate serum levels of CRP and PCT in acute exacerbation and stable phases of COPD and find their correlation with course of disease if any.

MATERIALS AND METHODS

The observational and longitudinal study was conducted in the Department of Pulmonary Medicine in Government Medical College and Hospital Chandigarh, India, from November 2014 to May 2016. The Institutional Ethics Committee (IEC) (letter no.6519) approved the study.

Inclusion criteria: Total 103 COPD patients diagnosed as per GOLD guidelines [1], admitted consecutively with acute exacerbation, from either gender belonging to all socio-economic strata were included.

Exclusion criteria: Patients having concurrent tuberculosis, other major respiratory co-morbidities like pneumonia, interstitial lung disease, malignancy, pulmonary embolism, and critically sick and haemodynamically unstable patients were excluded.

An informed consent was obtained from all patients. Each patient was subjected to detailed medical history, general physical and systemic examination and severity of breathlessness was assessed as per mMRC dyspnoea scale [17]. Routine investigations such as Chest X-ray, serum electrolytes, liver function tests, blood sugar levels, Total Leucocyte Count (TLC), sputum for Ziehl-Neelsen staining, Cartridge Based Nucleic Acid Amplification Test (CBNAAT), Gram staining and culture, urine routine and microscopy and estimation of serum levels of CRP and PCT at the time of admission were done. Five millilitre (mL) blood was drawn for evaluation of PCT and CRP. The sample was stored at -20°C temperature till analysis. Serum CRP and PCT levels were measured in patients at the time of discharge and 4-5 weeks after discharge as well.

Particle-enhanced immune-turbidimetric assay was employed for in-vitro quantitative determination of CRP on Roche Modular P-800 Automated Analyser. The functional sensitivity of assay was 0.6 mg/L. In normal subjects, range of CRP concentration was considered as 0-5 mg/L. The PCT was done by chemiluminescence (ADVIA Centaur BRAHMS PCT assay). The amount of relative light units detected by the system was proportional to the amount of PCT. The functional sensitivity of the assay was <0.05 ng/mL. In normal subjects, PCT concentration is <0.1 ng/mL.

STATISTICAL ANALYSIS

Quantitative data was presented as mean±SD or median and inter-quartile range, as appropriate. Normality of quantitative data was checked by measures of Kolmogorov-Smirnov tests of normality. For normally distributed data, means were compared using unpaired t-test. For skewed data or scores Mann-Whitney test was applied. For categorical variables, numbers and percentages were calculated. The data observed at various points of time was compared using Wilcoxon Signed-Rank test or paired t-test whichever was applicable depending on its normality. Correlation analysis was performed using Spearman's Rank Test. All calculations were two-sided and were performed using SPSS trial version 17.0 (Chicago, IL). A p-value of <0.05 was considered to indicate statistical significance.

RESULTS

A total of 118 patients were screened. However, 15 patients dropped out (five refused to participate in the study, six did not come for follow-up and four were ineligible on the basis of exclusion criteria). Out of 103 patients left, 93 were males and 10 were females. The mean age of males and females was 60.24±9.63 years and 59.00±9.92 years, respectively. The subjects were well matched with regards to age distribution (p-value=0.071). Overall, 87 (84.5 %) had been exposed to smoke due to tobacco and majority of patients had smoking index more than 300 [Table/Fig-1]. The measured median and Standard Deviation (SD) serum CRP levels were 10.80± 21.1 at admission, 7.40±8.9 at discharge and 3.50±6.20 at follow-up (in mg/L± interquartile range), while median PCT levels were 0.08±0.11, 0.05±0.70, and 0.01±0.04, respectively (in mg/L±SD) [Table/Fig-2]. Serum levels of CRP and PCT dropped significantly from the time of admission to discharge and follow-up after one month (p-value ≤0.001 for all three pairwise comparisons) [Table/Fig-2].

Parameters	N (%)
Gender	
Males	93 (90.3)
Females	10 (9.7)
Mean Age±SD (years)	
Overall	60.12±9.62
Males	60.24±9.63
Females	59.00±9.92
Mean BMI (kg/m^2)	22.82±4.46
Co-morbidities	
HTN	22 (21.3)
DM	9 (8.7)
Old treated TB	8 (7.7)
Exposure to smoke	
Non smokers	16 (15.5)
Smokers	87 (84.5)

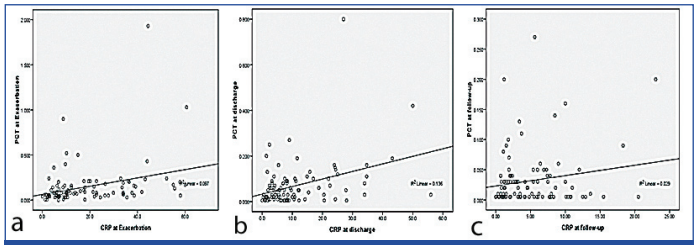
[Table/Fig-1]: Demographic details.
BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; SD: Standard deviation, TB: Tuberculosis

Variables	Exacerbation	Discharge	Follow-up
CRP (mg/L) (mean±SD)	10.80±21.1	7.40±8.9	3.50±6.20
PCT (ng/mL) (mean±SD)	0.08±0.11	0.05±0.70	0.01±0.04
Pair wise comparisons	**At discharge-at exacerbation**	**At follow-up-at exacerbation**	**At follow-at discharge**
CRP Z value	-6.598	-7.784	-6.363
p-value	<0.001	<0.001	<0.001
PCT Z value	-6.598	-7.784	-6.363
p-value	<0.001	<0.001	<0.001

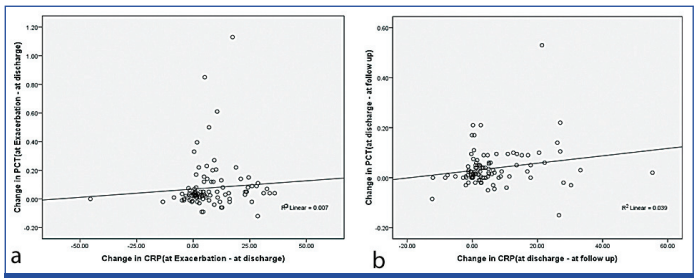
[Table/Fig-2]: Distribution of serum levels of CRP and PCT at different intervals and pair wise comparisons of serum CRP and PCT at different intervals.
CRP: C-reactive protein, PCT: Procalcitonin, SD: Standard Deviation

Serum CRP and PCT levels correlated well at the time of exacerbation of COPD and at discharge. However, no significant correlation was seen at the time of follow-up after four weeks though their levels

decreased independently [Table/Fig-3a-c]. Change in CRP at exacerbation versus discharge and then further at discharge versus follow-up was significantly correlated with change in PCT at given time intervals [Table/Fig-4a,b].



[Table/Fig-3]: a-c) Scatter plot showing correlation between serum levels of CRP and PCT at exacerbation (r value=0.423, p-value=<0.001), at the time of discharge (r=0.310, p-value=0.001) and follow-up (r=0.049, p-value=0.622) in patients of COPD.
TLC: Total leucocyte count, CRP: C-reactive protein, PCT: Procalcitonin, COPD: Chronic obstructive pulmonary disease



[Table/Fig-4]: Scatter plot showing correlation between change in levels of CRP and PCT in patients of COPD at exacerbation and discharge (r=0.240, p-value=0.015) and at discharge and follow-up (r=0.918, p-value=0.045).
TLC: Total leucocyte count, CRP: C-reactive protein, PCT: Procalcitonin, COPD: Chronic obstructive pulmonary disease

Similarly, shift of mMRC grades analysed using Wilcoxon Signed-Rank test showed significant decreement with respect to time (p-value ≤0.001). Distribution of serum levels of CRP and PCT with respect to mMRC grades at exacerbation, discharge and follow-up were analysed using Kruskal-Wallis test as shown in [Table/Fig-5].

mMRC Grade	Mean CRP (nmol/L)±SD			Mean PCT (ng/mL)±SD		
	At exacerbation	At discharge	At follow-up	At exacerbation	At discharge	At follow-up
I	----------	7.35±9.2	3.20±6.15	----------	0.02±0.05	0.010±0.02
II	10.2±15.3	6.40±7.7	5.60±6.15	0.08±0.12	0.05±0.06	0.03±0.04
III	12.7±26.5	24.00±21.7	14.55	0.08±0.09	0.16±0.15	0.10
IV	39.2±41.0	---------	--------	0.20±0.17	----------	---------
p-value* (Kruskal-Wallis test)	0.018	0.031	0.748	0.018	0.007	0.006

[Table/Fig-5]: Distribution of CRP and PCT with respect to mMRC grades at exacerbation, discharge and follow-up.
*A p-value <0.05 was considered to be statistically significant

There was significant association between grade of dyspnoea and CRP levels at exacerbation as well as at discharge. However, the association of serum PCT levels and grades of dyspnoea remained significant at all levels of assessment.

TLC in mMRC grade II, III and IV patients are shown in [Table/Fig-6]. On applying Mann-Whitney test, TLC had no statistically important difference in patients with mMRC grade II v/s III (p-value=0.07) and grade III v/s IV (p-value=0.379), however it was significant in grade II v/s IV (p-value =0.027) at exacerbation.

mMRC grade	Median TLC at Exacerbation±SD (counts/μL)	Grades	p-value* (Mann-Whitney test)
II	8900±3950	II v/s III	0.07
III	9800±3875	III v/s IV	0.379
IV	9800±6800	II v/s IV	0.027

[Table/Fig-6]: Distribution of TLC with respect to mMRC grades at exacerbation.
*A p-value <0.05 was considered to be statistically significant

Smokers had significantly higher levels of CRP as compared to non smokers (p-value ≤0.001). Smokers and non smokers were well matched with respect to age (p=0.070) and Body Mass Index (BMI) (p=0.183) as described in [Table/Fig-7].

Variable	Smoker	N	Mean±SD	p-value* (Student's t-test)
Age (years)	Yes	87	61.15±9.795	0.070
	No	16	54.50±6.261	
BMI (kg/m^2)	Yes	87	23.02±4.54	0.183
	No	16	21.45±3.87	
TLC (counts/μL)	Yes	87	10259.77±3741.02	0.098
	No	16	8650.00±2055.24	
CRP at exacerbation (nmol/L)	Yes	87	19.74±16.66	<0.001
	No	16	10.16±16.69	
PCT at exacerbation (ng/mL)	Yes	87	0.15±0.27	0.574
	No	16	0.12±0.13	

[Table/Fig-7]: Distribution of serum levels of CRP and PCT at exacerbation with respect to smoking status.
BMI: Body mass index, CRP: C-Reactive protein, PCT: Procalcitonin, SD: Standard deviation, TLC: Total leucocyte count; *A p-value <0.05 was considered to be statistically significant

Majority of patients (85.4%) reported normal flora in sputum culture reports. Only 15 patients showed growth of specific organism with frequency as follows: *Streptococcus pneumoniae* 5 (4.9%), *Haemophilus influenzae* 4 (3.9%), *Escherichia coli* 3 (2.9%), *Pseudomonas aeroginosa* 2 (1.9%), and *Acinetobacter* species 1 (1%). Patients with positive sputum culture had significantly higher TLC counts, serum levels of CRP at exacerbation (p-value ≤0.001) and serum levels of PCT at exacerbation. (p-value=0.001) [Table/Fig-8]. Serum levels of CRP at exacerbation significantly correlated with TLC (r value=0.229, p-value= 0.020) and PCT at exacerbation (r value=0.423, p-value=≤0.001). However, no such significant correlation was seen between PCT levels and TLC [Table/Fig-9].

Sputum culture		N	Mean±SD	p-value
TLC (counts/μL)	Positive	15	14993.33±4274.921	≤0.001
	Negative	88	9160.23±2648.076	
CRP at exacerbation (nmoL/L)	Positive	15	42.673±15.577	≤0.001
	Negative	88	14.085±11.708	
PCT at exacerbation (ng/mL)	Positive	15	0.348±0.501	0.001
	Negative	88	0.111±0.126	

[Table/Fig-8]: Distribution of TLC, CRP, PCT at exacerbation with respect to sputum culture status.
TLC: Total leucocyte count; CRP: C-reactive protein; PCT: Procalcitonin; SD: Standard deviation

Parameters		TLC	CRP at exacerbation	PCT at exacerbation
TLC	r value	1.00	0.229	0.153
	p-value		0.020	0.122
	N	103	103	103
CRP at exacerbation	r value	0.229	1.00	0.423
	p-value	0.020		≤0.001
	N	103	103	103
PCT at exacerbation	r value	0.153	0.423	1.00
	p-value	0.122	≤0.001	
	N	103	103	103

[Table/Fig-9]: Correlations of TLC, CRP and PCT at acute exacerbation.
TLC: Total leucocyte count; CRP: C-reactive protein; PCT: Procalcitonin; r value: correlation coefficient (Spearman's rho), p value: Sig.(2-tailed) value i.e. Significance probability; 2-tailed t-test

DISCUSSION

The AECOPD is one of the most common respiratory conditions in adults leading to frequent hospital visits. It is not only a huge socio-economic burden but a diagnostic challenge as well. A significant number of exacerbations are triggered by factors other than bacterial

infection like viruses, air pollutants and cardiac conditions. Literature review suggested that most of the research work on CRP and PCT has been in settings of severe bacterial infections especially in intensive care. Their role in exacerbation of COPD which can be managed as per standard protocol in non ICU settings is limited especially in Indian context. This study reflected that change in levels of CRP and PCT correlated well with exacerbation and stable phases of COPD.

The mean age of study population was 60.12±9.62 years. This study showed mean male to female ratio of 9:1 which was grossly in contrast to multicentric study on epidemiology of COPD by Jindal SK et al., which showed male to female ratio of 1.56:1 [2]. One of the factors for less number of females recruited in study could be that COPD is less prevalent in females and the present tertiary care centre caters to population from Chandigarh and adjoining areas where factors like smoking and indoor air pollution are less [18]. Other reasons could have been relatively small sample size and enrolment of patients in a consecutive manner.

The CRP is an acute phase reactant which exhibits raised levels in inflammatory disorders, cancer and infections. CRP levels rise in 6-8 hours and decline over 18-20 hours when stimulation ends [8,19]. It is being investigated in many countries for diagnosis of infectious diseases [11,14,15]. Similarly, studies have shown that PCT levels may rise to 100 ng/mL in severe infection especially of bacterial origin. Recently PCT is being investigated to guide antibiotics in sepsis [20-22]. Falsey AR et al., reported that high PCT values is an indicator of severe illness like pneumonia in AECOPD but low values did not rule out bacterial infection [13].

Present study has evaluated role of CRP and PCT as biomarkers of AECOPD among patients admitted in respiratory wards. It was found that CRP levels were higher during exacerbation of COPD and statistically significant decreasing trend was observed as patient headed towards recovery. Though there were no healthy subjects taken as controls in the study but serum levels of CRP and PCT were recorded at time of follow-up which was four weeks after discharge when episode of acute inflammation had subsided and patients were in stable condition which was counter-confirmed by clinical assessment and mMRC grades. Given the short half-life of above biomarkers (CRP: 18-20 hours and PCT: 25-30 hours), it can be safely presumed that these values at follow-up reflected the baselines levels in same patients. So it was concluded that CRP levels correlated well with exacerbation and stable phases of COPD. Lacoma A et al., also found statistically significant elevated CRP-values in acute exacerbation phase as compared to stable phase (after one month) in paired samples taken in 23 patients in AECOPD [14]. Nikolakopoulou S et al., revealed that serum angiopoetin-2 and CRP levels on day 1 were significantly higher compared to day 7 in their prospective study on patients with AECOPD [11]. Scheutz P et al., proposed that PCT was selectively raised in bacterial infections and so could be used as a promising marker to guide antibiotic treatment in patients with Acute Respiratory Infections (ARIs) [10]. Daubin C et al., stressed that PCT is sensitive marker for bacterial invasion in AECOPD [16]. But there are a number of studies including by Soler N et al., and Gao D et al., which concluded that PCT values do not show significant difference between bacterial and non bacterial AECOPD [23,24]. There is a strong possibility that utilising combinations of biomarkers may prove more useful.

In present study too, serum CRP and PCT levels individually correlated well at admission and discharge. However, the change in CRP at exacerbation versus discharge and then further at discharge versus follow-up significantly correlated with change in PCT at given time intervals suggesting that the simultaneous use of these biomarkers can have implications in short term prognosis.

Tobacco smoking is one of the major risk factors, so CRP levels were compared in smokers and non smokers. In present study, it was found that smokers had significantly higher levels of CRP as compared to non smokers (p-value <0.001). Present results were in agreement with a study conducted by Karadeniz G et al., [25]. However, a cross-sectional study conducted by Pinto-Plata V et al., revealed contradictory results [26]. There was no difference among the patients with COPD who were current smokers and those who were ex-smokers. The reasons cited were either absence of an inflammatory response in the smokers and or persistence of inflammation in COPD patients even after smoking cessation.

In present study, the correlation of CRP and PCT was studied with traditional markers like TLC and sputum culture also. It was found that patients with positive sputum culture had significantly higher serum CRP (p-value= ≤0.001), PCT levels (p-value= 0.001) and also TLC (p-value= ≤0.001). Becker K et al., also found that majority of COPD patients in acute exacerbation with bacterial pathology had elevated CRP levels but their PCT levels were low [12]. Daubin C et al., also found contradictory results [16]. Lacoma A et al., reported that PCT (p=0.620) and CRP (p=0.568) levels did not show any significant differences when culture result was normal flora or negative in comparison to isolation of predominant bacteria [14]. The reason for this could be that it is not possible to differentiate between infection and colonisation according to sputum culture report. So, a normal flora or a negative culture report does not rule out the presence of the microorganism responsible for exacerbation. Present study findings of higher CRP levels in patients with higher TLC were in aggreement with the results of Pinto-Plata V et al., [26]. The contradictory outcome of some of the results could be due to variation in ethnicity and heterogeneity of various factors.

Limitation(s)

The sample size was relatively small with fewer number of females so no gender based association could be studied. There were no controls, so data regarding sensitivity and specificity of markers with cut-off values could not be extrapolated. Review of literature suggested that CRP had a poor sensitivity and specificity when used alone for diagnosis of AECOPD. Hurst and colleagues reported sensitivity of CRP at 5 mg/L and specificity for confirmation of AECOPD as 74.4% and 57.5% respectively [27]. Also, its levels are subject to variability with respect to age, gender, BMI, menstrual cycles and hormone replacement therapy in females and immunosuppressive drugs like steroids. Some studies have highlighted significant heritable component also. The COPD is a chronic systemic inflammatory disorder which could affect baseline CRP levels [8,19,28].

CONCLUSION(S)

Newer modalities like biomarkers are under evaluation to diagnose infective AECOPD and mitigate irrational empiric usage of antibiotics especially at primary healthcare settings. This study reflected that change in levels of CRP and PCT correlated well with exacerbation and stable phases of COPD. The present can be presumed that CRP and PCT may have a potential diagnostic and prognostic utility in AECOPD. However, further research especially intervention trials with larger sample size are required to validate results and determine their role in guiding antibiotic usage in AECOPD especially in Indian context.

However, CRP test is low cost and widely available, so its use in combination with PCT and or traditional markers like TLC and sputum culture can increase its diagnostic accuracy and deserve merit for further research.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 22, 2021
- Manual Googling: Nov 19, 2021
- iThenticate Software: Nov 29, 2021 (16%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 21, 2021**
Date of Peer Review: **Oct 22, 2021**
Date of Acceptance: **Nov 30, 2021**
Date of Publishing: **Dec 01, 2021**