10.21761/jms.v2i02.5

ORIGINAL RESEARCH ARTICLE

A Comparative Study to Evaluate C-Reactive Protein and Procalcitonin as a Marker of Bacterial Infection in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Anshul Jain[1], Nipun Agrawal[2*], Lalit Singh[3], Abhishek Jain[4]

ABSTRACT

Introduction: Exacerbations of chronic obstructive pulmonary disease (COPD) can be precipitated by several factors. The most common causes appear to be respiratory tract infections. The overuse of antibiotics is common and accelerates the development of drug resistance and hospital-acquired infections. In some recent studies, both C-reactive proteins (CRP), as well as procalcitonin (PCT) levels, have been shown to be useful in differentiating bacterial etiology of exacerbations and thus helping in guiding the treatment as well as in prediction of outcome. This study aims to evaluate the sensitivity and specificity of CRP and procalcitonin as a marker of bacterial infection in patients with acute exacerbation of COPD.

Material and Methods: A total of 50 patients from patients of COPD with acute exacerbation attending/admitted to pulmonary OPD/IPD were included in the study, excluding those below 40 years old or presenting with acute breathlessness due to comorbid conditions. Demographic information, relevant clinical data, and lab investigations were recorded from all patients, including C-reactive protein and procalcitonin, on admission following which the patients have started antibiotics as per guidelines. Reassessment of S. procalcitonin and CRP was done on the 3rd and 7th day of hospitalization. Receiver-operating characteristic (ROC) curve was applied to compare sensitivity and specificity.

Results: Sputum culture was found positive in 27 (54%) patients. At all the three intervals, CRP levels had ROC area under curve (ROC AUC) values above 0.70. The area under curve value was maximum on day 3. For PCT, the area under curve values was >0.8 on day 1 and 3, but on day 7 this value was only 0.624. On evaluating the correlation between S. C-reactive protein and PCT levels, a mild positive and significant correlation was observed at day 1 and 7 intervals, whereas on day 3 a moderate positive and significant correlation was observed between the two markers.

Conclusion: The CRP is a good marker when tested early and late, while PCT is better when tested early.

[1]Junior Resident, [2,4]Assistant Professor, [3]Professor

[1,3,4]Department of Pulmonary Medicine, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India

[2]Department of Community Medicine, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India

Corresponding Author: Nipun Agrawal, Department of Pulmonary Medicine, Shri Ram Murti Smarak Institute of Medical Sciences, Bareilly, Uttar Pradesh, India, e-mail: dr.nipun.agrawal@gmail.com

Keywords: Acute exacerbation of COPD, C-Reactive Protein, Procalcitonin.

How to cite this article: Jain A, Agrawal N, Singh L, Jain A. A comparative study to evaluate C-reactive protein and procalcitonin as a marker of bacterial infection in patients with acute exacerbation of chronic obstructive pulmonary disease. SRMS Journal of Medical Sciences. 2017;2(2):84-90.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

According to the 2010 Global Burden of Disease study, COPD was responsible for about 5% of global disability-adjusted life years – DALYs (76.7 million), and 5% of total deaths (2.9 million).[1,2] Presently, COPD is projected as the fourth most common specific cause of death globally and it is predicted to reach at third place by the year 2030, in the absence of interventions that address the risks– especially tobacco smoking, exposures to combustion products of biomass fuels and environmental pollution.[3,4] Situation is much worse in India, with prevalence as high as 10% in a recent community-based study in the national capital, i.e., Delhi.[5]

COPD patients are sometimes at a high risk for worsening of symptoms. The periods of acute worsening of this disease are termed as exacerbations- which greatly affect the quality of life and health of patients with COPD[6] will therefore place a greater burden on the health services. Mortality is known to be increased in both the short and long-term period after an acute exacerbation.[7,8]

About half of COPD exacerbations are caused or triggered primarily by bacterial and viral infections.[9,10] Overuse of antibiotics is common and accelerates the development of drug resistance and hospital-acquired infections.[11] The consensus is not to provide antibiotics for every suspected infection because of emerging issues with bacterial resistance. Therefore, a marker specific for bacterial infection will be most helpful.

Among several markers of inflammation and sepsis, PCT and CRP markers are being studied to differentiate bacterial etiology of exacerbations and thus, helping in guiding the treatment as well as in prediction of outcome.[12-17]

Encouraged by aforesaid, the present study was carried out with an aim to evaluate sensitivity and specificity of PCT and CRP as a marker of acute exacerbation of different etiologies in COPD and to find out the role of these markers in defining use of antibiotic therapy in patients of bacterial etiologies of exacerbation of COPD.

MATERIAL AND METHODS

The present observational, longitudinal study was carried out at our institute. The study population included patients of COPD presenting with acute exacerbations from Oct 2015 to Mar 2017.

All the patients of COPD with acute exacerbation attending OPD/IPD were included in the study excluding those below 40 years of age, presenting with acute breathlessness due to comorbid condition like left ventricular failure, coronary artery disease, pulmonary embolism, cor pulmonale, or hospitalization primarily for a reason other than acute exacerbation of COPD (mimics), e.g. acute severe asthma, acute exacerbation of bronchiectasis, pulmonary embolism, congestive cardiac failure, acute myocardial infarction, and non-consenting patients.

The study was approved by the Institutional Ethical Committee. Informed consent was taken from all the patients. None of the investigators had any financial interest involved.

Demographic information was obtained from all the patients. Presenting complaints were noted along with the history of respiratory or systemic disease, family history of COPD, or any other respiratory illness, personal history regarding smoking, biomass fuel exposure, tobacco, and alcohol use. All the patients underwent a thorough general and systemic examination. Vitals, blood gas analysis, hematological and biochemical assessment, and sputum samples for culture sensitivity were taken. Blood samples were obtained from all the patients and were subjected to serum CRP measurement using an automated clinical analyzer (Abbott Architect Ci8200; Abbott Laboratories) which has a lower limit of detection of 5 mg/L and serum PCT assessment using a time-resolved amplified cryptate emission technology assay (Kryptorpct; brahmsag; Cambridge England) the lower limit of detection is 0.02 ng/mL.

After obtaining the results of serum PCT and serum CRP on admission (day-1), the patients will be started antibiotics as per guidelines. Reassessment of serum PCT and serum CRP was done on 3rd and 7th day of hospitalization as well. Results of culture sensitivity were correlated with different study variables and serum PCT and serum CRP levels.

All this data was obtained in a semi-structured predefined pretested questionnaire, recorded in MS-Excel 2013, and analyzed using IBM SPSS v21.0.0.

RESULTS

A total of 50 cases fulfilling the inclusion criteria and not falling in the exclusion criteria were enrolled in the study. Age of patients ranged from 47 to 87 years with the mean age being 68.5 ± 10.06 years, and most of them being above 60 years (39, 78%) of age. The majority of patients were males (38, 76%), and the male:female ratio was 1:0.32. Out of 50 patients, sputum culture was found to be sterile among 23 (46%), and bacterial infection was found in rest 27 (54%) patients.

At all the three intervals, CRP levels had ROC AUC values above 0.70. Area under curve value was maximum at day 3. Underbalanced considerations, for day 1, CRP ≥20.55 mg/dL had a projected sensitivity and specificity of 74.1 and 66.7%, respectively. At day 3, CRP value ≥11 mg/dL had a projected sensitivity and specificity of 74.1 and 72.2%, respectively, whereas on day 7, CRP value ≥4.1 had a sensitivity and specificity of 70.4 and 66.7%, respectively, for bacterial acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (Figure 1; Table 1).

For procalcitonin, the area under curve values were > 0.8 at day 1 and 3, but on day 7 this value was only 0.624. For day 1, under balanced consideration, procalcitonin level ≥ 0.695 ng/mL had a projected sensitivity and specificity of 77.8 and 77.8%. On day 3, procalcitonin level ≥ 0.285 ng/mL had a projected sensitivity and specificity of 74.1 and 72.2%. However, on day 7, no combination with both sensitivity and specificity > 75% could be deduced. Underbalanced consideration, Procalcitonin level ≥ 0.085 was projected to be 66.7% sensitive and 61.1% specific for the outcome of bacterial AECOPD (Figure 2; Table 2).

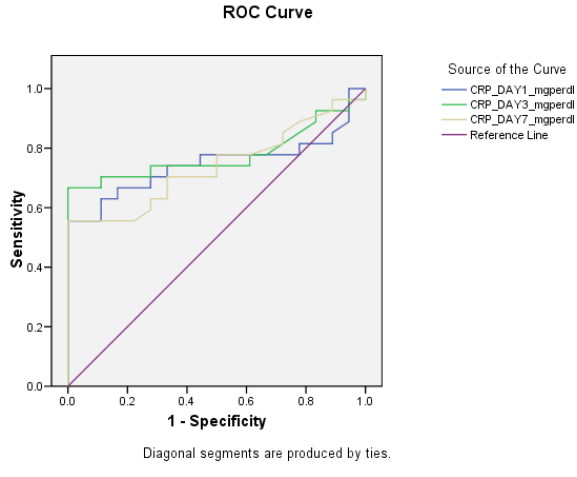

Figure 1: ROC curve of serum CRP levels on days 1, 3, and 7

Table 1: Assessment of discriminant role of serum C-reactive proteins levels on Day 1, 3 and 7 for differentiating bacterial from Non-bacterial acute exacerbation of chronic obstructive pulmonary disease

Day of estimation	*Area under curve (AUC)*	*Consideration*	*Cut-off value (mg/dL)*	*Projected sensitivity (%)*	*Projected specificity (%)*
		High sensitivity	≥9.40	92.6	10
Day 1	0.746	High specificity	≥33.35	55.6	94.4
		Balanced	≥20.55	74.1	66.7
		High sensitivity	≥4.85	92.6	16.7
Day 3	0.777	High specificity	≥19.15	66.7	100
		Balanced	≥11.00	74.1	72.2
		High sensitivity	≥2.35	92.6	11.1
Day 7	0.739	High specificity	≥7.2	55.6	100
		Balanced	≥4.10	70.4	66.7

Table 2: Assessment of discriminant role of Day 1, 3 and 7 procalcitonin levels for differentiating bacterial from non-bacterial acute exacerbation of chronic obstructive pulmonary disease

Day of estimation	*Area under curve (AUC)*	*Consideration*	*Cut-off value (ng/mL)*	*Projected sensitivity (%)*	*Projected specificity (%)*
Day 1	0.833	High sensitivity	≥0.365	92.6	27.8
		High specificity	≥0.845	51.9	94.4
		Balanced	≥0.695	77.8	77.8
Day 3	0.874	High sensitivity	≥0.215	92.6	61.1
		High specificity	≥0.435	59.3	100
		Balanced	≥0.285	74.1	72.2
Day 7	0.624	High sensitivity	≥0.005	92.6	11.1
		High specificity	≥0.270	14.8	94.4
		Balanced	≥0.085	66.7	61.1

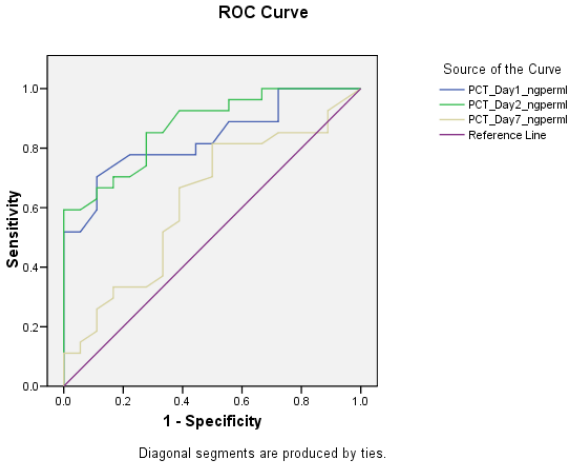

Figure 2: ROC curve of S. PCT levels on days 1, 3, and 7

On evaluating the correlation between serum CRP and PCT levels, a mild positive and significant correlation was observed at day 1 and day 7 intervals, whereas on day 3 a moderate positive and significant correlation was observed between the two markers (Table 3).

The difference in means of serum CRP levels and S. PCT levels on days 1, 3, and 7 were compared to assess the effect of antibiotic therapy in acute exacerbation due to bacterial etiology. On applying one way analysis of variance (ANOVA) to compare the differences in means, it was observed that steady fall observed in the serum levels of CRP and PCT in patients of COPD having acute exacerbation due to bacterial etiology was statistically highly significant (Table 4).

DISCUSSION

In the present study, we attempted to evaluate the role of PCT and CRP levels in cases of acute exacerbation of the COPD. For this purpose, a total of 50 cases with acute exacerbation of COPD were enrolled in the study and underwent a thorough history taking, clinical, general and systematic examination and laboratory investigations along with estimation of serum PCT and serum CRP levels on Day 1, 3, and 7 of admission to assess their role as diagnostic tool, predictor of outcome and indicator of clinical status.

The age of patients enrolled in the present study ranged from 47 to 87 years with a mean age of 68.5 + 10.06 years with the majority (32, 64%) patients being aged > 65 years. In various studies reviewed by us, the mean age of patients has been reported to be above 60 years. Similar to findings of the present study, Stolz *et al*. (2007)[18] in their study reported the mean age of patients with AECOPD

Table 3: Correlation between serum C-reactive proteins and S. procalcitonin levels at different time intervals

Time	*The correlation coefficient (r)*	*Level of correlation*	*Significance*
Day 1	0.311	Mild Positive	0.028 (S)
Day 3	0.585	Moderate positive	<0.001 (S)
Day 7	0.388	Mild positive	0.008 (S)

Table 4: Mean C-reactive proteins and procalcitonin at Day 1, 3 and 7

		Bacterial AECOPD mean ± SD	*Non-bacterial AECOPD mean ± SD*	*t-test*
CRP level (mg/dL)	Day 1	42.94 + 25.70	17.19 + 9.06	t = 4.465; p<0.001
	Day 3	30.66 + 24.75	8.12 + 4.85	t = 4.291; p<0.001
	Day 7	10.02 + 7.76	4.01 + 1.71	t = 3.220; p = 0.002
	ANOVA	F = 16.814 p < 0.0001		
PCT level (ng/dL)	Day 1	0.84 + 0.38	0.64 + 0.32	t =2.023; p = 0.049
	Day 3	0.64 + 0.47	0.28 + 0.17	t = 3.660; p = 0.001
	Day 7	0.19 + 0.20	0.09±0.09	t = 2.127; p = 0.039
	ANOVA	F = 22.15 p < 0.0001		

Table 5: Prevalence of bacterial etiology in different studies

S.No.	*Author (Year)*	*Bacterial AECOPD rate (%)*
1.	Abd-El Halim and Sayed (2015)[12]	100
2.	Peng *et al.* (2013)[14]	68.3
3.	Mohamed *et al.* (2012)[17]	40
4.	Bircan *et al.* (2008)[21]	38.6
5.	Falsey *et al.* (2012)[22]	65.8
6.	Present study (2017)	54

as 70 years. Bafadhel *et al*.[19]also reported the mean age of their patients as 69 years. In a more recent study from Iran, Ali *et al*. (2016)[16] reported the mean age of their patients to be much higher at 76.52 years. However, Abd Al Halim *et al*.,[12] in their study, said the mean age as 60.52 years. In general, all the studies report the mean age of AECOPD patients to be above 60 years, thus indicating that AECOPD episodes are primarily linked with aging and probably a long history of COPD.

The study sample in the present study was predominantly male with a male to female ratio of 3.17. This is probably a high risk of COPD among males owing to smoking being the major etiology. In various studies reviewed by us, a skewed gender ratio has been shown. Daniels *et al*.[20]and Ali *et al*. (2016)[16] in their study had a male-female ratio of 1.41, Pahuja *et al*.[13] had this ratio as 2.04 and Abd Al Halim *et al*.[12] reported this ratio as 2.33. The male-female ratio in the present study was close to that reported by Mohamed *et al*.,[17] who reported this ratio as Lopez AD *et al*. Although some workers like Bafadhel *et al*.[19] report an inverse male-female ratio (M:F = 0.59), however, in general, most of the studies report a higher prevalence of males over females, probably owing to the reason described above.

In the present study, sputum and culture-positive were seen in 27 (54%), thus, establishing the bacterial etiology in more than half the patients.

An overview of Table 5 above shows that the proportion of culture-positive patients in different case series varies substantially owing to the difference in study design, environmental conditions, and patient's susceptibility to bacterial infection.

In the present study, day 1 mean CRP levels were almost 2.7 times higher in AECOPD of bacterial origin as compared to AECOPD of non-bacterial origin. On day 3, bacterial AECOPD cases had 4.1 times higher CRP values as compared to non-bacterial AECOPD; however, at day 7, mean CRP levels were 2.7 times higher in bacterial AECOPD as compared to non-bacterial COPD cases. There was a declining trend of CRP levels with increasing time, thus showing that with stabilization of AECOPD, the CRP levels tended to decline. Thus, day 7 CRP levels were nearly 4.2 times higher at day 1 in both bacterial as well as non-bacterial AECOPD cases. These findings are similar to the observation made by Abd-El Halim and Sayed (2015)[12] who in their study compared to the CRP levels of AECOPD and stable COPD patients and found the CRP levels in AECOPD patients to be 10 times higher. Thus, findings of the present study suggest that the trend of change in CRP levels irrespective of bacterial or non-bacterial etiology could be taken as the indicators of the clinical status of the patients. As far as their association with etiology is concerned, many studies have shown raised CRP levels to be reflective of bacterial etiology of disease.[12,14,16,19,21]

The present study differed from these studies in the sense, that for the first time were made multiple assessments to evaluate the role of these parameters as status indicators of the AECOP patients in terms of their clinical progression and found that CRP levels had a useful role in differentiation of bacterial and non-bacterial pathology and change in CRP levels were reflective of clinical change. In the present study, we observed that CRP levels at all three estimations were significantly higher in bacterial AECOPD as compared to non-bacterial COPD. At the same time, the mean duration of hospital stay was also significantly higher in bacterial etiology as compared to non-bacterial etiology, thus showing that CRP levels were also predictive of a duration of hospital stay. On evaluating the role of CRP levels in the prediction of duration of hospital stay too, we found promising results with a significant difference in mean values at all

the three estimates. Similar to the present study, Helmy *et al*.[23] also found that CRP levels were significantly correlated with the duration of hospital stay. Daniels *et al*.,[20] in their study, also observed that CRP levels were significantly associated with a clinical success rate at different time intervals.

In the present study, for bacterial etiology, on drawing receiver operator characteristic (ROC) curve, the area under curve values for CRP were 0.746, 0.777, and 0.739, respectively, at day 1, day 3 and day 7 estimates. However, in their study Peng *et al*. (2013)[14] found an AUC value of 0.832 for differentiation of bacterial and non-bacterial AECOPD. However, Abd-El Halim and Sayed (2015)[12] in their study found a relatively lower AUC value of 0.52. Bafadhel *et al*.,[19] in their study found AUC value of CRP to be 0.96, thus showing a near-absolute discriminant role of CRP levels in distinguishing bacterial and non-bacterial exacerbations. In fact, most of the studies in past have not carried out ROC Analysis for the purpose of deriving a cut-off value for differentiating bacterial AECOPD from non-bacterial AECOPD. In the present study, though a moderate to a strong correlation between the duration of hospital stay and CRP levels at different time intervals was observed, however, it was strongest on day 3 of observation. On drawing receiver-operator characteristic curves to day 1 CRP levels had minimum area under curve (AUC 0.744) while day 3 CRP levels had a maximum area under curve (AUC 0.814). In their study, Daniels *et al*.[20] drew ROC curve for Day 1 CRP levels only and found area under curve values for 10 day and 30-day clinical success as 0.655 and 0.599. These findings suggest the role of serial assessments in achieving higher accuracy in outcome prediction as done in the present study.

For procalcitonin levels, day 1, 3, and 7 mean values were 1.8, 3, and 1.9 times higher in bacterial AECOPD cases as compared to non-bacterial AECOPD cases. Falsey *et al*. (2012)[22] in their study also found mean PCT levels to be higher in bacterial as compared to non-bacterial AECOPD patients. However, Mohamed *et al*.[17] found mean procalcitonin levels among bacterial AECOPD patients to be almost 38 times higher in bacterial etiology as compared to non-bacterial etiology cases. Abd-El Halim and Sayed (2015)[12] on the other hand found PCT levels to be 28.8 times higher when compared to bacterial AECOPD patients with stable COPD patients. Bafadhel *et al*.[19] have also shown a significant difference in mean PCT levels between bacterial and non-bacterial etiologies. The findings of the present study are close to observations of Ali *et al*.,[16] who observed PCT levels to be 3.2 times higher in pneumonia as compared to exacerbated COPD etiologies. One of the reasons for the variability in the extent of difference between bacterial and non-bacterial etiologies might be owing to the difference in selection criteria of patients in different studies. Unlike the present study, which followed a cross-sectional design, most of the other studies used purposive sampling and did not necessarily include AECOPD patients for comparison between bacterial and non-bacterial etiologies. One of the reasons for differences might be owing to a difference in the spectrum of bacterial pathogens. In a previous study, Abd-El Halim and Sayed (2015)[12]showed that type of pathogen also affects the PCT values. In their study, they found that AECOPD patients with *Pseudomonas aeruginosa (P. aeruginosa)* had significantly higher PCT levels as compared to other etiologies. Notwithstanding these differences in designs of study, it is established that bacterial AECOPD affects the PCT levels, and findings of the present study endorsed that.

On drawing ROC curve, day 1, 3, and 7 AUC values for PCT were 0.833, 0.874, and 0.624, respectively, for differentiation of bacterial and non-bacterial etiologies of AECOPD. In their study, Abd-El Halim and Sayed (2015)[12] found PCT AUC value to be 0.851 for differentiating *P. aeuroginosa* from other bacterial infections. In the present study, we did not make such an attempt but instead focused on the discriminant role for bacterial and non-bacterial pathologies. Bafadh el *et al*.,[19] however, found AUC value for PCT to be as high as 0.94 for differentiation between bacterial and non-bacterial pathologies. However, in the present study, we achieved a maximum of 0.874 for day 3 PCT levels.

In present study, PCT and CRP levels showed mild to moderate positive and significant correlation on different times of estimation with maximum correlation on day 3 ($r = 0.583$; $p < 0.001$). El Hakim and Sayed (2015)[24] too, in their study found a moderate positive and significant correlation between PCT and CRP. A similar observation was also made by BafadhelF *et al*. (2011)[19] in their study. Daniels *et al*. (2010)[20] also observed a mild positive correlation between two markers as observed on day 1 and 3 of estimation in the present study. Being systemic inflammatory markers, the correlation between two markers was on expected lines. However, as far as the extent of this correlation is concerned, it depends on the chronology of achieving peak value of two depending upon their nature for acute/chronic inflammation.

In the present study, it was observed that the mean values of serum levels of CRP and PCT in the patients of COPD with acute exacerbation due to bacterial infections was highest on day 1 (42.94 ± 25.7 and 0.84 ± 0.38, respectively). The mean values of serum levels of CRP and PCT in the patients of COPD with acute exacerbation not

due to bacterial infections was also highest on day 1 (17.9 ± 9.06 and 0.51 ± 0.21, respectively) which was significantly (p-value < 0.0001) lower than that for acute exacerbation due to bacterial etiology. After receiving CRP and PCT reports for day 1 and culture reports, patients whose culture was negative and CRP was 15 ± 7 mg/L, i.e., in the range of acute exacerbation due to non-bacterial causes as observed in studies done by Pahuja *et al*. (2016)[13] and Peng *et al*. (2013),[14] were withdrawn from antibiotic therapy. The mean values of serum levels of CRP and PCT in the patients of COPD with acute exacerbation due to bacterial infection slower on day 3 (30.66 ± 24.75 and 0.64 ± 0.47, respectively) when the patients were on antibiotic therapy which lowered further on day 7(10.02 ± 7.76 and 0.19 ± 0.2, respectively) with continuous use of antibiotics. This decrease in means of serum levels of CRP and PCT was found to statistically highly significant (p-value < 0.0001). A similar fall in serum levels of PCT and CRP was observed by Li Y *et al*. (2017)[25] in their study amongst patients of COPD having concomitant bacterial infections before and after treatment with antibiotics. Daniels *et al*. (2010)[20] also observed identical lowering in serum levels of PCT and CRP, thus, defining and justifying the use of antibiotic therapy in such patients.

CONCLUSION

The findings of the present study thus showed that study of inflammatory markers like serum CRP and PCT among AECOPD patients helps to distinguish between bacterial and non-bacterial etiologies. Among these two CRP was found to have a higher sensitivity as well as specificity at all the three time intervals with almost equivalent efficacy at all the three time intervals, however, PCT, being an acute phase marker showed decline to differentiate between bacterial and non-bacterial etiology with the passage of time. The declining trends of both the markers with passage of time were in accordance with the clinical course of disease. Considering the high potential of both the markers for their predictive and discriminant values, further studies are recommended to find out standardized cut-off values.

REFERENCES

1. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, *et al*. Disability–adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2197–2223.
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095–2128.
3. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, *et al*. Chronic obstructive pulmonary disease: current burden and future projections. EurRespir J. 2006;27:397-412.
4. Mathers CD. Uncertainty and data availability for the global burden ofdisease estimates 2000–2002. In: Evidence and Information for Policy Working Paper. Geneva, Switzerland: WHO, 2005.
5. Sinha B, Vibha, Singla R, Chowdhury R. An epidemiological profile ofchronic obstructive pulmonary disease: A community-based study in Delhi. Journal of Postgraduate Medicine. 2017;63(1):29-35.
6. Seemungal TAR, Donaldson GC, Paul EA, *et al*. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;157:1418-1422.
7. Connors AF Jr, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, *et al*. SUPPORT Investigators. Outcomes following acute exacerbation of severe chronic obstructive lung disease: Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. Am J Respir Crit Care Med 1996;154:959-967.
8. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortalityrelated factors after hospitalization for acute exacerbation of COPD. Chest 2003;124:459-467.
9. Wedzicha JA, Donaldson GC. Exacerbations of Chronic Obstructive Pulmonary Disease. Resp Care 2003; 48(12):1204-1215.
10. Pela R, Marchesani F, Agostinelli C, *et al*. Airways microbial flora in COPD patients in stable clinical conditions and during exacerbations: a bronchoscopic investigation. Monaldi Arch Chest Dis. 1998;53:262-267.
11. Bauer MP, van Dissel JT, Kuijper EJ. Clostridium difficile: controversies and approaches to management. Curr Opin Infect Dis. 2009;22(6):517-524.
12. Abd Al Halim A, Sayed M. The value of serum procalciton in among exacerbated COPD patients. Egyptian J Chest Dis Tub. 2016;64(4):821-827.
13. Pahuja S, Yadav P, Gautam AK, Kumar A, Kumar A, Chaudhri S. Study of serum C-reactive protein levels in acute exacerbations of chronic obstructive pulmonary disease patients. Int. J. Med. Sci. Pub. Health. 2016;5(4):694-699.
14. Peng C, Tian C, Zhang Y, Yang X, Feng Y, Fan H. C-Reactive protein levels predict bacterial exacerbation in patients with chronic obstructive pulmonary disease. Am. J. Med. Sc. 2013; 345(3):190-194.
15. Leuzzi G, Galeone C, Taverna F, Suatoni P, Morrelli D, Pastorino U. C-reactive protein level predicts mortality in COPD: a systematic review and meta-analysis. Eur. Resp. Rev. 2017;26:160070.
16. Ali T, Hassan S, Farzad R, Kavous SN, Hossein K. Comparison of Serum Levels of Procalcitonin and C-Reactive Protein in Patients with Community Acquired Pneumonia and COPD Exacerbation. Iran Red Crescent Med J. 2016 December; 18(12):e25811.
17. Mohamed KH, Abderabo MM, Ramadan ES, Hashim MM, Sharaf SM. Procalcitonin as a diagnostic marker in acute exacerbation of COPD. Egyptian J Chest Dis Tub. 2012;61(4):301-305.
18. 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 Apr;131(4):1058-1067.

19. Bafadhel M, Clark TW, Reid C, *et al*. Procalcitonin and C-reactive protein in hospitalized adult patients with community-acquired pneumonia or exacerbation of asthma or COPD. Chest. 2011;139(6):1410-1418.
20. Daniels JM, Schoorl M, Snijders D, Knol DL, Lutter R, Jansen HM, Boersma WG. Procalcitoninvs C-reactive protein as predictive markers of response to antibiotic therapy in acute exacerbations of COPD.Chest. 2010 Nov;138(5):1108-1115.
21. Bircan A, Gokirmak M, Kilic O, Ozturk O, Akkaya A. C-Reactive Protein Levels in Patients with Chronic Obstructive Pulmonary Disease: Role of Infection. Med PrincPract 2008;17:202-208.
22. Falsey AR, Becker KL, Swinburne AJ, *et al*. Utility of serum procalcitonin values in patients with acute exacerbations of chronic obstructive pulmonary disease: a cautionary note. International Journal of Chronic Obstructive Pulmonary Disease. 2012;7:127-135.
23. Helmy TA, Baess AI, Monsif DAA, Elnashrty AAA. Role of C-reactive protein and interleukin-6 in predicting the prognosis of ICU-admitted patients with acute exacerbation of COPD. Egyptian J. Chest Dis. Tub. 2014; 63(4): 829-835.
24. El Hakim AA, Sayed M. The value of serum procalcitonin among exacerbated COPD patients. Egyptian J Chest Dis Tub 2015; 64(4): 821-827.
25. Li Y, Xie L, Xin S, Li K. Values of procalcitonin and C-reactive protein in the diagnosis and treatment of chronic obstructive pulmonary disease having concomitant bacterial infection. Pak J Med Sci 2017; 33 (3):566-569.