International Journal of Research in Health and Allied Sciences

Journal home page: www.ijrhas.com

Official Publication of "Society for Scientific Research and Studies" [Regd.]

ISSN: 2455-7803

Original Research

To evaluate the role of CRP as a biomarker in COPD acute exacerbation

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ABSTRACT:

Aim: The aim of this study to evaluate the role of CRP as a biomarker in COPD acute exacerbation. **Methods:** This cross-sectional study was done in the Department of Pulmonary medicine. All the patients were instructed to collect deep coughed out sputum into a sterile wide mouth container with a screw cap after rinsing the mouth twice with plain water. The samples were brought to microbiology laboratory immediately and processed within 30 minutes of collection. Gram stain was done from sputum sample and reported according to Bartlett's grading system. A score of 1 and above was considered as suitable sample. The suitable sputum samples were inoculated into Mac Conkey's agar, chocolate agar and blood agar plates. The isolated organisms were identified by standard microbiological techniques specified by American society for microbiology. Sputum samples were culture showed pathogenic bacteria were classified as Bacterial exacerbations and samples were no pathogenic bacteria or oral commensals were isolated were classified as Non bacterial exacerbations. **Results:** Among the 100 cases, 68 cases bacterial growth was seen on culture and were classified as Bacterial exacerbation of COPD. The remaining 32 cases where the culture did not yield any bacterial growth/ oral commensals were isolated were classified as Non Bacterial COPD exacerbation. Majority of the patients in the study were ≥ 65years (58 cases (58%) with predominance of male sex (67 cases (67%)). Comorbidities like Diabetes was seen in 24 cases (24%) and hypertension was seen 33 cases (33%). Those with ≥5 years duration of COPD and those with current history of smoking had a significant risk of bacterial exacerbation. Using crude odds ratio, it was concluded that Odds of Bacterial Exacerbation for subjects with duration of COPD "≥5 years" is 2.77(95% CI: [1.16,6.78]) times higher than subjects with duration of COPD "<5 years". Also, the Odds of Bacterial exacerbation for smokers is 3.67(95% C:[1.40,10.18]) times higher than non-smokers. The ideal cut-off point of CRP for distinguishing Bacterial COPD patients with Bacterial Exacerbation from those Non-Bacterial Exacerbation is 8.62 mg/L in our study (sensitivity:97.67%; specificity:40.39%; PPV:75.36%; NPV:87.67%, AUC:0.74(95% CI: [0.62,0.87]). Among the organisms isolated klebsiella(25) and pseudomonas(11) were predominant. **Conclusion:** We concluded that the higher CRP levels are associated with patients showing Bacterial exacerbations of COPD than Non Bacterial COPD exacerbation. CRP levels could thus be used for predicting Bacterial exacerbations and as well as to guide the usage of antibiotic therapy.

Keywords: CRP, acute exacerbation, COPD

Received: 16 October, 2021 Accepted: 21 November, 2021

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This article may be cited as: Katoch J, Negi RS. To evaluate the role of CRP as a biomarker in COPD acute exacerbation. Int J Res Health Allied Sci 2021; 7(6):65-68.

INTRODUCTION

In the natural history of chronic obstructive pulmonary disease (COPD), exacerbations have a significant impact on mortality,[1] especially in those who require hospital admission. Indeed, exacerbations become more frequent and more severe as the severity of COPD increases.[2] Although exacerbations have multiple causes, an infectious etiology is by far the most frequent, with figures up to 78% for hospital-admitted COPD patients.[3] Bacterial infections account for one-half of the acute episodes, while respiratory viruses are identified in more than one-quarter, with rhinovirus (RV) and influenza being the most commonly detected viral pathogens. Microbiological studies have identified change in sputum color and purulence as good surrogate markers for bacterial infection,[4,5] while the detection of viruses in exacerbations is only marginally associated with the appearance of changes in the characteristics of sputum.[6,7] Both respiratory bacteria and viruses are able to produce major local and systemic inflammatory responses, and biomarkers such as C-reactive protein (CRP) have been extensively studied and used as an alternative test to diagnose bacterial

infections in both COPD and pneumonia.[8,9] Likewise, in stable COPD, CRP levels have been examined as a marker of bacterial colonization and/or subclinical infection10 but in studies of exacerbated COPD patients, including viral etiology, they have proven unable to distinguish virus-associated exacerbations from others.[7] In fact, a recent study by Clark et al demonstrated a higher level of CRP in exacerbations due to viruses than in those with positive cultures for bacteria.[11] Few studies have evaluated the usefulness of CRP as a predictor of the severity of acute episodes. Studies that have suggested that high CRP levels are a marker of exacerbation in COPD have not demonstrated its value for the identification of episodes severe enough to require admission.[12] In severe COPD outpatients, studies of CRP are scarce, and the relationship between microorganisms and the severity of exacerbations is not fully understood.

MATERIAL AND METHODS

This cross-sectional study was done in the Department of Pulmonary medicine, after taking the approval of the protocol review committee and institutional ethics committee. After taking informed consent detailed history was taken from the patient or relatives.

A total of 110 patients of COPD presenting as acute exacerbation to our hospital were included in this study. COPD was defined as FEV1 to FVC ratio of <70% without significant bronchodilator reversibility in FEV1 OR FVC (as per Global Initiative for Obstructive Lung Disease guidelines). Acute Exacerbation (AE) of COPD was considered in patients with background of COPD & worsening respiratory symptoms including shortness of breath, cough, wheeze and change in volume & colour of sputum. After a thorough history, clinical examination the patients were subjected for chest X-ray, ECG, complete blood count, CRP and sputum (mucoid, mucopurulent) for culture and sensitivity, CT chest was done in suspected cases of bronchiectasis. Ethical approval was obtained from institutional ethical committee. CRP levels in blood samples of patients were determined by nephelometric technology with the help of MISPA I2 specific protein analyzer.

MICROBIOLOGY

Patients were instructed to collect deep coughed out sputum into a sterile wide mouth container with a screw cap after rinsing the mouth twice with plain water. The samples were brought to microbiology laboratory immediately and processed within 30 minutes of collection. Gram stain was done from sputum sample and reported according to Bartlett's grading system. A score of 1 and above was considered as suitable sample.[13] The suitable sputum samples were inoculated into Mac Conkey's agar, chocolate agar and blood agar plates. The isolated organisms were identified by standard microbiological techniques specified by American society for microbiology.[14] Sputum samples were culture showed pathogenic bacteria were classified as Bacterial exacerbations and samples were no pathogenic bacteria or oral commensals were isolated were classified as Non bacterial exacerbations.

STATISTICAL ANALYSIS

Analyzing data collected from the study was done by descriptive statistic methods (frequency, percentage, mean ± standard deviation) and by SPSS statistical software version 25.0 using Chi-square test or Fisher's Exact test and Independence samples t-test. *P*-value less than 0.05 was considered as statistically significant.

RESULTS

Of the 100 patients hospitalized with COPD AE were studied. The remaining 10 were excluded because of coexisting illness like pneumonia, bronchiectasis, recent antibiotic usage, those not producing adequate quality sputum, IHD(Ischemic heart disease). Among the 100 cases, 68 cases bacterial growth was seen on culture and were classified as Bacterial exacerbation of COPD. The remaining 32 cases where the culture did not yield any bacterial growth/ oral commensals were isolated were classified as Non Bacterial COPD exacerbation. The distribution of subjects by age, sex, duration of COPD, current smoking history, those on regular inhaler therapy is shown in Table 1.

Table 1: Distribution of patients based on various factors

Profile			Bacterial COPD Exacerbation=68	Non-Bacterial COPD Exacerbation=32	Total	%	P-value
Age		<65years	27	15	42	42	0.94
		≥65years	41	17	58	58	
Sex		Male	40	17	67	67	0.16
		Female	18	15	33	33	
Duration of COPD		<5 years	46	22	58	58	0.03*
		≥5 years	32	10	42	42	
Comorbidity	DM	Yes	4	20	24	24	0.05
		No	64	12	76	76	
	HTN	Yes	20	13	33	33	0.64
		No	48	19	67	67	
H/o current Smoking		Yes	35	8	43	43	0.007*

	No	33	24	57	57	
On inhalers	Yes	52	22	74	74	0.21
	No	16	10	26	26	

Majority of the patients in the study were ≥ 65years (58 cases (58%)) with predominance of male sex (67 cases (67%)). Comorbidities like Diabetes was seen in 24 cases (24%) and hypertension was seen 33 cases (33%). Those with ≥5 years duration of COPD and those with current history of smoking had a significant risk of bacterial exacerbation.

Using crude odds ratio, it was concluded that Odds of Bacterial Exacerbation for subjects with duration of COPD "≥5 years" is 2.77(95% CI: [1.16,6.78]) times higher than subjects with duration of COPD "<5 years". Also, the Odds of Bacterial exacerbation for smokers is 3.67(95% C:[1.40,10.18]) times higher than non-smokers

Table 2: CRP levels in Bacterial COPD exacerbations and Non Bacterial COPD exacerbations

Factor	Overall	Bacterial COPD Exacerbation	Non-Bacterial COPD Exacerbation	P-value
CRPLevels(Mg/L)	47.6[13.58,61.63]	49.72[19.68,75.62]	34.28[4.70,57.51]	0.021*

Using Mann-Whitney U-test, it was concluded that median of C- reactive protein levels are significantly more for Bacterial Exacerbation than Non-Bacterial Exacerbation. Odd of COPD Bacterial Exacerbation for subjects with higher CRP level is 26.65(95% CI: [3.20,221.87]) times higher than subjects with normal CRP levels (Table 2). The ideal cut-off point of CRP for distinguishing Bacterial COPD patients with Bacterial Exacerbation from those Non-Bacterial Exacerbation is 8.62 mg/L in our study (sensitivity:97.67%; specificity:40.39%; PPV:75.36%; NPV:87.67%, AUC:0.74(95% CI: [0.62,0.87]).

Table 3: CRP level in COPD patients with Bacterial Exacerbation corresponding to the bacteria isolated.

Organism	Number of cases	AverageCRP	SD
Klebsiella	25	61.68	51.21
Acinetobacter	3	64.61	
Citrobacter	3	69.63	
Enterococcus species	4	64.91	
Enterobacter species	3	69.62	
Moraxella	5	68.7	64.96
Non-Fermenting GmNeg Bacilli	6	65.3	46.8
Pseudomonas	11	64.548.6	52.25
Staphylococcus	5	71.0	58.2
Streptococcus	3	66.6	48.3

Among the organisms isolated klebsiella(25) and pseudomonas(11) were predominant. Other organisms isolated are listed in Table 3. There were no statistically significant differences in median CRP levels among the different Bacterial pathogens.

DISCUSSION

CRP is an acute-phase protein, which, when elevated, provides good evidence of an active tissue-damaging process. Thus its measurement provides a simple screening test for active organic disease. Increased CRP production is a very early and sensitive response to most forms of bacterial infections. CRP, additionally, was a good predictor of the severity of the exacerbations; patients with CRP levels .100 mg/L presented a fourfold increase in hospitalization. CRP emerges as a good biological marker for the identification of severe exacerbations in COPD patients with advanced disease, mainly related to bacterial infections due to S. pneumoniae and H. influenza.

Acute exacerbations of COPD are responsible for the high morbidity and mortality associated with COPD. They can be caused by various factors, most predominant among these being bacterial or viral infections.[15,16] Early antibiotic therapy especially in Bacterial exacerbation of COPD would improve outcomes in such patients. Biomarkers play an important role in determining the cause of exacerbations at point of care and several studies to date have analyzed the role of biomarkers like CRP in predicting bacteria exacerbations in COPD patients.[17,18] Our findings also proved that CRP level cut off of 8.62 mg/L could help in the demarcation of these two groups (Bacterial and non-Bacterial COPD AE) with a sensitivity of97.67% and specificity of 40.39%.

Studies by Peng et al correlated CRP levels of patients with pathogens isolated from these patients and determined that *Pseudomonas* was responsible for exacerbations in 25% of the cases.[17] Our findings are similar to this study, in fact bacteria were isolated from patients with AE COPD, having a high level of CRP in serum. But contrary to the study by Peng et al[17] in our study *Klebsiella* was detected in 36.76% of the COPD patients with exacerbations. A recent study has also correlated an increase in CRP values and the presence of Bacterial pathogens (both alone and mixed with viral/atypical microbes.[19] We found out that among the various demographic factors, duration of COPD and smoking influence the development of exacerbations in patients, whereas other factors like age, sex, didn't have a statistically significant effect. Smoking has been established as a risk factor for the development of exacerbations in COPD patients.[20-22] The CRP cut off at point of care has been used to guide antibiotic prescription and showed a reduction in the use of antibiotics by 20% in primary care patients.[19] That could be a further objective of our study, that is, to use the cut off value of CRP obtained in our study to guide therapy in a controlled trial with patients exhibiting COPD exacerbations.

CONCLUSION

This study contributed in establishing that higher CRP levels are associated with patients showing Bacterial exacerbations of COPD than Non Bacterial COPD exacerbation. CRP levels could thus be used for predicting Bacterial exacerbations and as well as to guide the usage of antibiotic therapy.

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