Original Research Article

Significance of CRP as a Biomarker in COPD Acute Exacerbation

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) exacerbation is a cause of high mortality in COPD patients. C reactive protein (CRP) role in predicting exacerbation has been studied before, but it's value in Predicting etiology is not well established. In this study the role of CRP to determine the presence of bacterial exacerbations in Indian population was studied which could guide us in early initiation of therapy in these cases.**Methods:**In this study CRP levels were measured from patient's serum using nephelometric method. Sputum samples were obtained from COPD Acute exacerbations (AE) patients and evaluated microscopically and subjected to culture. 60 patients with Bacterial exacerbation were compared with 33 patients of Non-Bacterial exacerbation and the relationship between CRP and Bacterial exacerbation was assessed. **Results:**Using Mann-Whitney U-test, high CRP median values were seen in Bacterial COPD AE as compared to Non-Bacterial COPD AE. The ideal cut-off point in our study for distinguishing Bacterial COPD AE with Non-Bacterial COPD AE was 7.62 mg/l calculated using Youden criteria (sensitivity: 96.67%; specificity:39.39%; PPV:74.36%; NPV:86.67%, AUC:0.64(95% CI: [0.52,0.77])**Conclusion:**In patients exhibiting symptoms of COPD AE an elevated serum CRP level >7.62mg/l indicates Bacterial exacerbation which might be useful in early initiation of antibiotic therapy in these cases.**Abbreviations:** COPD:Chronic obstructive pulmonary disease, CRP:C reactive protein, AE:Acute exacerbations

Keywords: Chronic obstructive pulmonary disease, C reactive protein, Bacterial exacerbation, Non- Bacterial exacerbation

Introduction

Chronic obstructive pulmonary disease is the 4th leading cause of death in the world [1]. More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally. COPD is a major cause of chronic morbidity and mortality throughout the world; many people suffer from the disease for years and die prematurely from it or its complications. Globally the incidence of COPD is going to increase in the coming decades because of continued exposure to COPD risk factors and aging of the population [2]. 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 in a patient with underlying COPD [3].Exacerbations of COPD are important events in the management of COPD because they negatively impact health status, rates of hospitalization and readmission, and disease progression. COPD exacerbations are complex events usually associated with increased airway inflammation, increased mucus production and marked gas trapping. These changes contribute to increased dyspnoea which is a key symptom of exacerbation. Other symptoms include increased sputum purulence and volume, together with increased cough and wheeze [4].

A multitude of factors have been implicated in causing exacerbations in COPD which include environmental factors, pollution, smoking, bacterial and viral infections [5], out of which bacterial and viral infections account for a majority of the exacerbations [6].

Biomarkers are biological molecules that can be harnessed as indicators of biological and pathogenic processes and several of these have been studied in COPD AE [7]. The best-studied biomarkers in diagnosing acute exacerbations of COPD include C reactive protein (CRP), Interleukin 6(IL-6) and Tumour necrosis factor (TNF-α), of which CRP levels were consistently raised in cases with acute exacerbations of COPD [8].The role of CRP as a valuable biomarker in diagnosing exacerbations has also been indicated in a recent study,where levels of systemic inflammation markers like Procalcitonin and CRP were correlated with the presence of Bacterial infection and efficacy of antibiotic therapy [9]. A study in the UK has also proved the efficacy of CRP-guided prescription of

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antibiotics, which resulted in a reduction in the number of patients using antibiotics [10].The objective of the current study was to establish the role of CRP as a biomarker in determining the presence of Bacterial exacerbations in indian scenario which would, in turn, justify the prescription of early antibiotics for these patients.

Methods

This study was conducted at Department of Pulmonary Medicine, ShriDharmasthalaManjunatheshwara Medical College and Hospital Dharwad, India. It was a cross-sectional study conducted between Jan 2019 to Dec 2020. A total of 132 patients of COPD presenting as acute exacerbation to our hospital were recruited. 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 level Assessment

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 [11] . 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 [12]. 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

Data Analysis done using R i386 4.0.3.categorical data represented by frequency and percentage and Non normal continuous data represented using Median [1st quartile,3rd Quartile]. Between groups, comparison of continuous data is done using Mann-Whitney U-test test. Between groups, comparison of categorical data is done using chi-square test/fisher exact test. Crude Odds ratio is calculated to check the effect size. Ideal cut off point of CRP level for distinguishing Bacterial COPD exacerbation subjects from Non-Bacterial COPD exacerbation is calculated using Youden criteria. P<0.05 is considered as significant.

Results

Of the 132 patients hospitalized with COPD AE, 93 were selected for evaluation. The remaining 39 were excluded because of coexisting illness like pneumonia, bronchiectasis, recent antibiotic usage, those not producing adequate quality sputum, IHD(Ischemic heart disease). The exclusion criteria are depicted in Fig.1. Among the 93 cases, 60 cases bacterial growth was seen on culture and were classified as Bacterial exacerbation of COPD. The remaining 33 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

Factor		Sub- category	Overall	Bacterial COPD Exacerbation	Non-Bacterial COPD Exacerbation	P-value
Age		<65years	39 (41.94%)	25 (64.1%)	14 (35.9%)	0.943
		≥65years	54 (58.06%)	35 (64.81%)	19 (35.19%)	
Sex		Male	62 (66.67%)	43 (69.35%)	19 (30.65%)	0.167
		Female	31 (33.33%)	17 (54.84%)	14 (45.16%)	
Duration of COPD		<5 years	54 (58.06%)	30 (55.56%)	24 (44.44%)	0.033*
		≥5 years	39 (41.94%)	30 (76.92%)	9 (23.08%)	
Comorbidity	DM	Yes	22 (23.66%)	18 (81.82%)	4 (18.18%)	0.052
		No	71 (76.34%)	42 (59.15%)	29 (40.85%)	
	HTN	Yes	31 (33.33%)	19 (61.29%)	12 (38.71%)	0.645
		No	62 (66.67%)	41 (66.13%)	21 (33.87%)	
H/o current Smoking		Yes	40 (43.01%)	32 (80%)	8 (20%)	0.006*
		No	53 (56.99%)	28 (52.83%)	25 (47.17%)	
On inhalers		Yes	69 (74.19%)	47 (68.12%)	22 (31.88%)	0.218
		No	24 (25.81%)	13 (54.17%)	11 (45.83%)	

Majority of the patients in the study were ≥ 65years (54 cases (58.06%)) with predominance of male sex (62 cases (66.67%)). Comorbidities like Diabetes was seen in 22 cases (23.66%) and hypertension was seen 31 cases (33.33%). 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 2.67(95% CI: [1.06,6.68]) times higher than subjects with duration of COPD "<5 years". Also, the Odds of Bacterial exacerbation for smokers is 3.57(95% C:[1.39,9.18]) times higher than non-smokers.

Abbreviations: COPD: Chronic obstructive pulmonary disease, DM: Diabetes Mellitus,
HTN: Hypertension

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

Factor	Sub-category	Overall	Bacterial COPD Exacerbation	Non-Bacterial COPD Exacerbation	P-value
CRPLevels(Mg/L)		46.6[14.58,62.63]	48.72[20.68,76.62]	33.28[5.70,58.51]	0.026M*

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 25.65

(95% CI: [3.10,211.87]) times higher than subjects with normal CRP levels (Table 2, Figure 2).The ideal cut-off point of CRP for distinguishing Bacterial COPD patients with Bacterial Exacerbation from those Non-Bacterial Exacerbation is 7.62 mg/L in our study (sensitivity:96.67%; specificity:39.39%; PPV:74.36%; NPV:86.67%, AUC:0.64(95% CI: [0.52,0.77]) as shown in Figure 3.

Abbreviations: COPD: Chronic obstructive pulmonary disease, CRP: C Reactive Protein

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

Organism	Number of cases	AverageCRP	Median	SD	Range
Klebsiella	22	60.68	46.6	52.21	4.61-225
Acinetobacter	2	63.61			
Citrobacter	2	68.63			
Enterococcus species	3	63.91			
Enterobacter species	2	68.62			
Moraxella	5	67.7	44.9	65.96	6.12-236.2
Non-Fermenting GmNeg Bacilli	5	64.3	50.12	47.8	7.62- 183.9
Pseudomonas	10	63.548.6	48.65	53.25	4.61-225
Staphylococcus	5	70.0	48.78	59.2	6.12-236.28
Streptococcus	4	65.6	48.9	49.3	7.62-166.3

Among the organisms isolated klebsiella(22) and pseudomonas(10) 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.

Abbreviations: COPD: Chronic obstructive pulmonary disease, CRP: C Reactive Protein,
SD : Standard Deviation

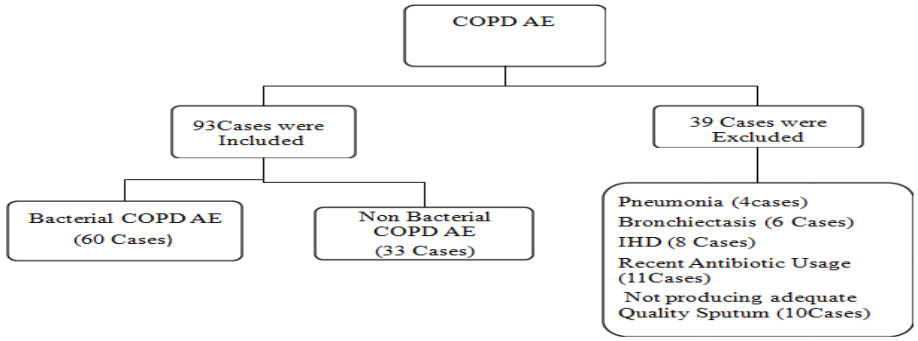

Fig1:Flow chart of selection criteria for patients

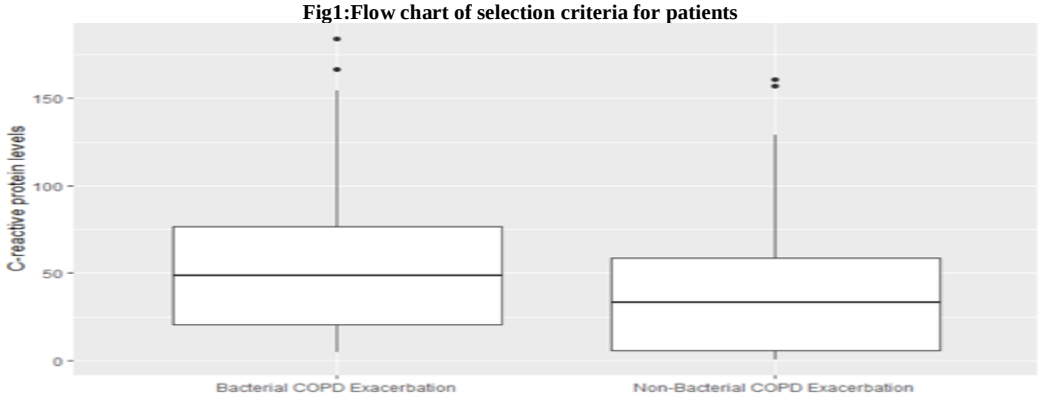

Fig 2:Visualization of CRP levels Over COPD Exacerbation

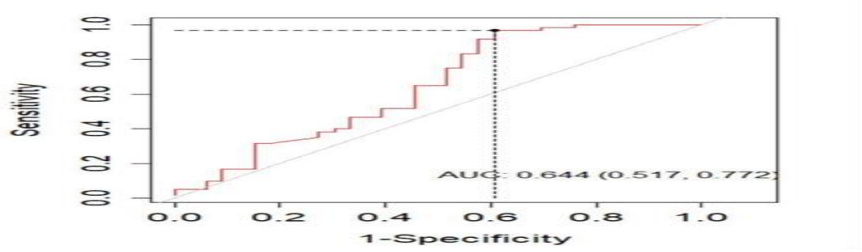

Fig 3: Area under the curve (AUCs) for C-reactive protein (CRP) in the diagnosis of COPD exacerbation.

*Criteria used: Youden index, Missing values are replaced by suitable measure of central tendency

Discussion

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 [5,13,14].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 [15,16]. Our findings also proved that CRP level cut off of 7.62 mg/L could help in the demarcation of these two groups (Bacterial and non-Bacterial COPD AE) with a sensitivity of96.67% and specificity of 39.39%.

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 [15]. 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 [15] in our study *Klebsiella*was detected in 40% 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) [17].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 [18-20]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 [17]. 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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References

1. World Health Organization. Chronic obstructive pulmonary disease (COPD) Fact sheet No 315.World Health Organization, 2011.
2. Salvi S, Agarwal A. India needs a national COPD prevention and Control program. JAssoc Physicians India. 2012; 60(Suppl):5–7
3. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA.Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 1987; 106:196–204.
4. Sethi S, Murphy TF. Current concepts: infection in the pathogenesis and course of chronic obstructive pulmonary disease. New Engl J Med. 2008; 359:2355-65.
5. Bafadhel M, McKenna S, Terry S et al. Acute exacerbations of COPD: identification of biological clusters and their biomarkers. Am J RespirCrit Care Med. 2011; 186:662–71.
6. Koutsokera A, Stolz D, Loukides S, Kostikas K. Systemic biomarkers in exacerbations of COPD: the evolving clinical challenge. Chest. 2012; 141(2):396-405.
7. Chen, Yu-Wei Roy et al. A Systematic Review of Diagnostic Biomarkers of COPD Exacerbation. PloS one. 2016; 11(7): e015 8843.
8. Daniels JMA, Schoorl M, Snijders D, Knol DL,Lutter R, Jansen HM, Boersma WG. Procalcitoninvs C-Reactive Protein as Predictive Markers in Response to Antibiotic Therapy in Acute Exacerbations of COPD. Chest, 2010, 138(5):2
9. Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E et al. C-ReactiveProtein testing to guide antibiotic prescribing for COPD exacerbations. N Engl J Med, 2019; 381(2):111–20.
10. Van derValk P,Monninkhof E, van der Palen J. Clinical predictors of bacterial involvement in exacerbations of chronic obstructive pulmonary disease.Clin Infect Dis. 2004; 39:980-986.
11. YoudenWJ. Cancer.Index for rating diagnostic tests, 1950, 32–35.
12. Stockley RA, Pye A, Hill SL. Relationship of sputum color to nature andoutpatient management of acute exacerbations of COPD. Chest. 2000,117:1638–1645.
13. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC.Antibiotics for exacerbations of chronic obstructive pulmonary disease. CochraneDatabase Syst Rev. 2006; 2:CD004403.
14. Peng C, Tian C, Zhang Y, Yang X, Feng Y, Fan HC. Reactive ProteinLevels Predict Bacterial Exacerbation in Patients With Chronic Obstructive Pulmonary Disease. The American Journal of the Medical Sciences. 2013; 345(3):190–194.
15. Bircan A, Gokirmak M, Kilic O, Ozturk O, Akkaya A. C-Reactive Protein Levels inPatients with Chronic Obstructive Pulmonary Disease: Role of Infection. Med PrincPract. 2008; 17:202-208.
16. Dev D, Wallace E, Sanrakan R, Cunniffe J, Govan JRW, Wathen CG, Emmanuel FXS.Value of C-reactive protein measurements of chronic obstructive pulmonary disease. Respir Med. 1998; 92:664 –667.
17. Weis N, Almdal T. C-reactive protein – can it be used as a marker of infection inpatients with exacerbation of chronic obstructive pulmonary disease. EurJIntern Med. 2006; 17:88–91.
18. Hurst JR,Wedzicha JA.Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease.Am J RespirCrit Care Med. 2006; 174:867–874.
19. Halpin DM, Miravitlles M, Metzdorf N, Celli B. Impact and prevention of severe exacerbations of COPD: a review of the evidence. Int J Chron Obstruct Pulmon Dis. 2017; 12:2891-2908.
20. Francis NA, Gillespie D, Wootton M, White P, Bates J, Richards J, Melbye H, Hood K, Butler CC. Clinical Features and C-Reactive Protein as Predictors of Bacterial Exacerbations of COPD. Int J Chron Obstruct Pulmon Dis. 2020; 15:3147-3158.

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