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Original Research Article

Correlation of Blood Markers Including CRP with Severity of COPD in Eastern Part of Rajasthan

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Abstract

Background: Previous studies& scientific knowledge have indicated that Systemic inflammation, which is multifactorial, in COPD plays a major role in disease pathogenesis, severity, manifestations& in causation of its comorbidities. CRP being a sensitive and easily available biomarker even in resource limited health facilities can help detect this ongoing occult inflammation which turns COPD into a multisystem disease with mammoth implications which can be timely & properly managed by optimum control of the COPD pathology.

Methods: 100 COPD patients aged >40 years visiting Chest department at RBM Hospital, GMC, Bharatpur were assessed clinically, by spirometry and laboratory tests. Patients were staged according to GOLD Criteria &according to MMRC scale.

Results: Strong association of disease severity was observed with positive inflammatory titres of CRP (P value <0.05). High inflammatory CRP also correlated strongly with low SPO_2, low BMI and dyspneic grades of MMRC, besides total smoking Pack years.

Conclusion: Raised inflammatory titres of CRP were significantly associated with the Severity of COPD reflecting the ongoing systemic inflammation which should be tested as a routine to address COPD inflammatory syndrome timely & properly so as to decrease disease morbidity & mortality.

Keywords: COPD, Systemic Inflammation, CRP, Morbidity, Severity.

Introduction

As per latest GOLD Guidelines on COPD 2022 “COPD is a common, preventable & treatable disease that is characterized by persistent respiratory symptoms & airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality” [1].

GOLD report 2022 has also expressed concern that COPD is grossly underrecognized & underreported in all nations & governments & people have not taken it seriously enough. The prevalence of chronic obstructive pulmonary disease (COPD) is ~10% in adults older than 40 years[2]. And now COPD is one of the top three causes of death worldwide and 90% of these deaths occur in low- & middle-income countries [3]

It is well established that COPD is a multifactorial disease composed of both modifiable (smoking, occupational exposures, pollution, etc.) and nonmodifiable (genetics, ageing, bronchial hyperreactivity, etc.) risk factors, with cigarette smoking being the most significant factor [4].

The inflammation which sets in the COPD patients is chiefly secondary to smoking, hypoxia, endothelial dysfunction, coagulation: fibrinolysis and vascular remodeling (which all takes origin in the small airways) this inflammation finally "spills over" and is not restricted to lung parenchyma [5].

Scientific Knowledge on C-reactive protein (CRP) has shown it to be a marker of inflammation in atherosclerosis [6,7] and also levels of CRP correlate with the degree of pulmonary inflammation. [8,9] CRP is the most valuable measurement in low grade fevers & inflammatory states being a cytokine driven acute phase reactant like fibrinogen & compliment components whose increased production occurs which is particularly helpful in detecting occult disease.[10]

CRP being a sensitive, & easily available biomarker to detect the occult inflammation which usually accompanies the COP syndrome. Thus, CRP could be one of the ideal biomarkers to follow in COPD as it is sensitive & easy to measure has a long half-life& has got a definite established role in pathogenesis.[11]

Methodology

100 patients of COPD who were willing and aged >40 years visiting Chest department at RBM Hospital, GMC, Bharatpur were assessed clinically, spirometricaly & by laboratory parameters from August 21 to December 21 after the May 2021 Covid-19peak wave subsided in the region. Firstly, patients were selected according to inclusion and exclusion criteria after that staged according to GOLD Criteria &according to MMRC scale.

Pt. having chronic cough (any pattern) with or without sputum for more than 3 months each year for last two year and Progressive, persistent dyspnea over time which increases with exercise were included in the study while patients with active or recent Covid/TB/HIV infection, Chronic lung disease other than COPD, malignancy and patient with other Systemic diseases which may have pulmonary and systemic manifestations (CVD), portal hypertension, HIV, drugs, toxins, pulmonary veno occlusive disease etc) were excluded from the study.

After a detailed clinical history and thorough physical examination, the patients underwent a battery of tests, comprising CBC, Liver function tests, Kidney function tests, Lipid profile, Serum Ca+2, C-reactive protein, Blood sugar, Skiagram chest both P.A and Rt. Lateral view, Sputum smear for AFB, Serum total proteins, albumin and globulin, SPO_2, Spirometry on RMS Medspiror system and Covid 19 RT PCR.

SPIROMETRY

Patient's categorization into GOLD stages 1, 2, 3 and 4 was done on the basis of spirometry done on RMS Medspiror instrument based on Recorder's system which was closer to the profile of Indian patients. Salbutamol 400 mcg through MDI was given to all patients for the post BDL

effect and recordings taken 20 mins after the inhalation.

Grade	FEV1/FVC ratio	FEV1	Disease level
I	<0.7	≥80%	Mild COPD
II	<0.7	50-80	Mod. COPD
III	<0.7	30-50	Severe COPD
IV	<0.7	≤30	Very Severe COPD

Statistical analysis

Statistical analysis was done mainly by Chi square test when comparing many variables whilst student t test was used to compare two variables

P value was considered significant if it was below 0.05 and highly significant in case <0.001

The COPD Assessment test ™ was administered which is an 8 itemuni-dimensional measure of health status impairment in COPD.The score ranges from 0-40, provides measures of the symptomatic impact of COPD but does not categorize patients into symptom severity groups for the purpose of treatment.

Results

Table 1: Patient distribution according to CRP (C-reactive protein); A marker of systemic inflammation

CRP (mg/l)	No. of Cases	Percentage
<10	45	45%
>10	55	55%
Total	50	100%

Above table shows 45 patients had CRP levels<10 mg/l while 55 had >10mg/l CRP levels.

Table 2: Blood Parameters along stage of COPD

Stage of COPD No. of Cases	CRP No. of cases		Total Cholesterol Mg/dl	Hemoglobin in mg%	Hematocrit
	<10mg/l	>10mg/l			
Mild (Grade I)15	13	2	190.19 ±13.28	14.05 ± 1.37	43.87 ±4.70
Mod. (Gr II) 31	12	19	197.65 ±23.07	12.6 ±1.62	39.90 ±5.39
Severe (Gr III) 40	16	24	194.58 ±20.72	12.52 ±1.51	40.27 ± 4.62
V. Severe (Gr IV) 14	4	10	192.20 ±19.73	13.25 ±1.66	39.64 ±4.83
Total (100)	45	55	194.14 ±20.67	12.9 ±1.721	40.06 ±5.14

Above table shows as disease severity increased CRP more patients had CRP levels >10mg/l

The raised inflammatory level of CRP is associated with severity of COPD. When we applied chi squire test for these patients, we found $X^2 = 7.48$, P value <0.01 which is significant. Other parameters of blood not found to have a strong association with staging of COPD

Table 3: Correlations of CRP with patient variables

CRP Titre	Resting SPO_2%	BMI (kg/m^2)	MMRC grade
<10mg/l (n=45)	91.09±3.14	22.04±2.72	I-6, II-18, III-15, IV-6, V-0
>10mg/l (n=55)	88.42±3.14	18.2±2.46	I-2, II-16, III-22, IV-10, V-5
Total	89.60±3.41	19.89±3.21	I-8, II-34, III-37, IV-16, V-5

With inflammatory titres of CRP (>10mg/l) the patient's SPO_2 and BMI tend to fall and the MMRC grade of dyspnea increases. On applying student t test between CRP/sPO_2- P value <0.001 -Highly significant, CRP/BMI – P value <0.001 – Highly significant, CRP/ MMRC grade of dyspnea – P value <0.05 significant

Systemic inflammation as assessed by the CRP titers incapacitates the patient gradually& it also further reflects in fall in SPO_2, BMI and in MMRC dyspnea scale.

Table 4: Correlation of CRP with patients GOLD stage and smoking pack years taken in this study

CRP titre	Spirometry grade	Smoking pack years
<10mg/l (n=45)	I-14, II-12, III-15, IV-4	I-2, II-14, III-19 IV-5, V-4, VI-1
>10mg/l (n=55)	I-2, II-19, III-24, IV-10	I-4, II-11, III-12, IV-12, V-14, VI-2

(Smoking pack years I=nonsmoker, II= 0-20 pack years, III=20-40 pack years, IV=40-60 pack years, V=60-80 pack years, VI=80-100 pack years)

CRP titres tend to increase with increasing spirometric grade of COPD and smoking pack years.

On applying Chi Square testCRP/Smoking pack years; X^2 =9.6, P value <0.05= significant

CRP/GOLD stage; X^2 =7.48, P value <0.05 = significant

Systemic inflammation as assessed by the CRP titres increases significantly with the Stage of COPD and Patients with increased titres of CRP have a more pack year history.

Discussion

Increasing evidence has now suggested that increased serum CRP levels are associated with lung inflammation in stable COPD both in smokers as well as nonsmokers [12]. It was also found to beassociated with other important clinical variables like the stage of COPD, BMI, FEV1, & their 6 MWD that help in predicting outcome of the patients (11), also independent of their smoking behavior and biomass exposure, hinting towards genetic and other factors [13]. CRP was further found to be significantly higher in AECOPD patients compared to patients with stable COPD.[14]**.** C-reactive protein (CRP), an acute-phase protein that can be measured accurately within minutes at the point of care, is a biomarker for assessing acute exacerbations of COPD. [15,16].

In this study we found higher CRP levels in severe disease. As severity increases CRP levels also increased and this increment was statistically significant(p<0.001). It signifies strong correlation of CRP with progression of disease. Similar study by Ahmad et al found CRP levels weresignificantly higher in COPD patients compared with controls. Another study by Karadag et al [17] and Garcia Rio et al [18]

also found higher CRP in COPD patients than in controls. More recently, Aksu et al [13] and other researchers [19] found higher CRP levels in COPD patients, On the other hand, Silva et al [20] could not demonstrate differences between patients with COPD and controls regarding CRP levels (P = 0.62).

In the lung, CRP has protective functions in innate immune responses against bacteria and apoptotic cells. CRP enters the lung from plasma and is primarily produced by hepatocytes in response to IL-6 stimulation which in turn is due to tissue damage, insult or inflammation. Activated epithelial cells and increased numbers of alveolar macrophages and other inflammatory cells in COPD may release IL-6 into the circulation.[21] This stimulates an acute-phase response and increases the level of plasma CRP, two other IL6–regulated acute-phase reactants (fibrinogen and 1-antitrypsin) were also associated with features of COPD [22,23].

Many previous studies have also concluded that Systemic inflammation leads to loss of body mass in general and lean body mass in particular, each of which are associated with increased mortality in COPD [24], whilst in one study by Breyer MK et al they found positive correlation of elevated CRP titres with Obesity [25] which is in contrast to our present study. Smoking (pack year) in our study showed a positive correlation with CRP in the patient, Abdelsadek et al[26] also found similar results as in our study.

CRP point-of-care testing in primary care have shown to reduce antibiotic prescribing for respiratory tract infections in general [27,28] A nonrandomized Spanish study showed that the rate of antibiotic overprescribing for acute exacerbations of COPD was lower among primary care clinicians who received training in CRP testing than among those who did not.[29]

Slightly increased serum CRP levels have also been shown to be associated with presence of inflammation in atherosclerosis and with increased risk of coronary heart disease and myocardial infarction[30].Higher cardiovascular mortality risk was reported in studies using a cut-off value of 3 mg/L and in those enrolling an Asiatic population.[31]

Further large studies are required to know the clinically important values of CRP leading to increased disease morbidity & mortality due to COPD itself or due to its comorbidities

Conclusion

It can be safely & definitely concluded that CRP Correlates not only with severity of COPD but also along other parameters of the patient like BMI, SPO_2, MMRC grades of dyspnea, and smoking pack years. Yet its desirable to know further which subsets of COPD are affected with systemic inflammation more who may be benefitted with CRP testing.

So, its suggested that CRP should be measured as a routine in assessment like spirometry of COPD patients so as to manage the COP Syndrome holistically and more effectively.

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