C-Reactive protein as prognostic biomarker -predictor in chronic obstructive pulmonary diseases [COPD]

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ABSTRACT The present study aimed to estimate & evaluate for circulating CRP level are a biomarker of systemic inflammation & predictor of future COPD outcome . During study, 232 patients with stable COPD & age & gender matched with healthy subjects with normal respiratory function were observed . Follow up of pts performed to evaluate the strength of associations between CRP levels & future outcome The present study showed that serum CRP levels were significantly higher in stable COPD pts than in control subjects [5.08=+0.73vs ,1.02 +-0.28mg/l respectively [p<0.05] .During the study it was observed that a serum CRP conc. >3 mg/l is poor prognostic variable of COPD compared to CRP conc. <3mg/l [.hazard ratio 2.81]. 95%confidence interval[CI] 1.06-6.88,p<0.05. The previous studies including 1750 COPD pts was performed & similar results were observed statistically [HR 1.54 ,95 of CI ,1.14-2.07 ,p<0.01] The present study showed, circulating CRP level are significantly higher in stable COPD pts & may be used as predictor of future outcomes [1]

INTRODUCTION

COPD is third leading cause of morbidity & mortality world wide by the yr 2020. The cigarette smoking is significant risk factor for COPD & as a consequence of local damage to small airways .[1,2,3]

Epidemiological studies have shown that serum markers of inflammation like circulating C-R.P are higher in pts with stable COPD than in healthy controls [2,3].

In many studies CRP has been reported as independent predictor of future outcome in pts with COPD [4] The airflow obstruction is the hallmark feature of COPD .but it is poorly predicted by FEV1 only [forced expiratory volume in first second]. [5,6]

The Circulating CRP level assay is inexpensive & convinent in stable COPD . serum estimation of CRP assay may be most valuable predictor of future outcome in stable COPD. however CRP assay usually estimated in an excerabation of COPD . however association between CRP levels & mortality in COPD Patient is conflicting on the basis of this background [10,13].

Present study is conducted, aimed to estimate circulating CRP levels in patients with stable COPD are significant predictor of prognosis & prognostic variable in COPD patients .

MATERIALS & METHODS

The present study is prospective cohort study includes total 232 patients & been diagnosed as COPD > = 6 mths [24wks] previously & under treatment for more than or equal to months . Diagnosis of COPD done by medical detailed history, present symptomatology, pulmonary function tests ,following Global initiative for COPD guidelines [13]. Patients with evidence of asthma ,h/o allergic rhinitis improvement in FEV1 >12% from the predicted values following inhalation of bronchodilators. Extensive pulmonary tuberculosis ,malignancy ,psychosis were excluded from study. no evidence of respiratory infection for at least a 4 week period preceding the study. Approval for this study was obtained from institutional board SKN Medical college GH Pune & informed consent was obtained from all participating subjects. All patients with COPD were clinically stable .

Estimation of CRP

Fasting blood samples were obtained from the pts at rest ,& prior to any other test being done . serum CRP level were measured by high sensitivity immunoturbidimetry. [Beckman coulter ,inc Fl, USA].

The results were given in units of mg/l &the analytical sensitivity of this analysis was 0.1mg/l. The cut off point for the CRP concentration was 3mg/l as in previous studies [9,10 14]

Follow up of patients

The present study was conducted between march 2012 to Feb 2014 with follow up of 1yr or until patient mortality. The followup was carried out by telephoning the pt & requesting them to attend Chest OPD & checking hospital records . The critically ill pts were recorded by the physician incharge of the follow up . Patient who were located at follow up & were not known to have succumbed of their illness were considered os censored at the end of study period .

STATISTICAL ANALYSIS

The continuous variables are presented as mean +_ SD .The categorical variables are presented as absolute numbers & percentages . Cox Regression analysis is used to examine time to COPD mortality using hazard ratio [HR] & 95% confidence interval . Risk measures were adjusted for age ,gender ,FEV1 % predicted, smoking & presence of disease . Kaplan - Meier mortality curves was created to show differences in mortality by selected risk factors .

Quantitative synthesis of all relevant studies are performed & methods used have been described in detail in previous studies [15, 16,].

The HRs of time to event Data were directly extracted or were read off survival curves to estimate the log HR & its variance as suggested by Parmar et al [17].

The stastical analysis are using SPSS,inc. USA version 13.0 . & review manager 5.0 .17 [Coch. software oxford U.K]

Two tailed - p <0.05 was considered to indicates a statistical significant difference .

RESULTS

A total 232 COPD patients [including 150 males] were registered for the study 70 healthy subjects [including 36 males]aged over 50 yrs,with no evidence of COPD .The healthy individuals are randomly selected from a population sample of subjects residing in the same area as the patients .The baseline parameters of COPD pts are given in Table A .

The majority of pts were a mean age of 70 yrs [range 48-90] and more than 50% were male [65%] . Some pts had co-morbidity associated with Diabetes mellitus ,hypertension, IHD, Gastritis ,APD, Cataract.

The controls [healthy] were compared with COPD pts in relation to age, gender ,body mass index,[BMI] ,Smoking status,,no significant differences were observed in parameters between healthy controls and COPD pts The present study showed serum CRP levels were significantly high in stable COPD pts as compared to healthy controls [5.01+_82vs 1.02+_0.27respectively p<0.05.

Table A, At the end of followup 42 pts had succumbed [18%]. The information concerning the etiology of mortality of 8 pts were not available because of change in contact no   and uncooperativeness from pts families .

The CRP values CRP <_3mg/l used as reference index and value >3mg/l were associated with high mortality [HR 2.81,95% CI ,1.07- 7.00, p<0.05] .

Kaplan –meier survival curves for mortality in COPD pts according to CRP categories .

The clinical partameters were compared between survivors and non survivors .

It is observed that non survivors had high degree airflow obstruction as compared to survivors .[FEV1% predicted ,41.6+_18.1VS 55.5 +_ 18.1respectively . p <0.05].

CRP levels [8.45,18.0 vs 3.50+_6.57 mg/l respectively <0.05]. However no significant difference in age,gender ,and BMI were observed in two groups .

The quantitative synthesis of four studies and published studies were performed [9,10 ,14]. Among these studies the median duration of the follow ups ranged between 3-10 yrs The clinical parameters were adjusted for age, gender, FEV1% predicted and smoking .

The HR mortality in pts with CRP >3mg/Lwas 1.54[95% ci ,1.14_2.07]
Compared to those with CRP <_3mg/ Fig 1.

DISCUSSION

The present study was performed for the   evolution of circulating CRP levels are prognostic biomarkers and predictor of future COPD outcomes .The CRP is a biomarker of systemic inflammation ..

The current study showed that serum CRP ,levels were found significantly higher in stable COPD pts than in healthy control subjects .The results found were consistent with previous studies indicating the presence of systemic inflammation in stable COPD pts [1, 2,3].

A number of independent predictors of future COPD outcomes have been studied previously including smoking status [22].,exercise capacity, [18] BMI[[20 ,21,22].

Severity of dyspnoea [23] biomarkers of systemic inflammation FEV1 [4,5]and PaO2.[22]

The present study ,we use serum CRP levels which is best studied and most convinent to evaluate .

The present study showed that increased serum CRPlevels are strong predictor of COPD mortality .

In the study by Liu etal showed that serum CRP level more than 3mg/l was poor prognostic biomarker of COPD. Compared with CRP ;levels less than or equal to 3mg/l .11 .

Dhal et al the HR of mortality due to COPD was 2.2 fold higher in pts with a high CRP level than in those with low CRP level .

The observations in the present study are in favour with these studies .

However de Torres et al reported that CRP levels are not associated with survival status   considering the inconsistent results of previous studies   a quantitative synthesis of the evidence using rigorous methods were performed .

Meta analysis was conducted on 4 studies with 1750 subjects to evaluate the association between CRP level & mortality in COPD patients.

This meta analysis showed the high level of serum CRP level is associated with increased risk of mortality .

High sensitivity CRP assays are inexpensive & convinent . It is important for clinicians to use CRP values in stable copd patients. The present study also found that high CRP levels is associated with an increased risk of mortality in copd patients.These results indicate that selection of serum CRP concentration as a prognostic biomarker in stable copd patients may be useful for clinicians.

However limitations to the present study where patients were clinically stable, serum CRP concentration fluctuation over time may affect the validity of CRP level as a predictor biomarker .

To various drugs & treatments among patients may have an unpredictable effect on serum CRP concentration .

Table 1 Clinical parameters & features of study participants

SN	PARAMETERS	COPD PTS n=232	Controls n=70	P value
1	Male	150	36	0.15
2	Female	82	34	
3	Age in yrs	70 .0 +_ 8.0	67.9+_5.1	0.08
4	BMIkg/m2	25.5+_ 3.1	26.1+_5.4	0.13
5	Smoking status			0.14
6	Present smoking	92	28	
7	Ex- smoker	68	10	
8	Non smoker	72	32	
9	FEV1 % predicted	44.1+_11.9	90.1+_6.5	<0.001
10	Steroids inhaled %	60.9		
11	Beta 2 agonist %	60.9		
12	Ipratropium bromide %	53.0		
13	Theophylline %	35.9		

Co –morbid diseases, n

0	72
1	104
2	30
3	20
4	6

CRPmg/l   4.45 +_ 0.80, 1.01+_0.25   0.025

Data are presented as mean +_ SD , n or %

TABLE 2

sr	Study group	Log Hazard Ratio	SE	WEIGHT	HR IV Random,95%CI
1	Dahl etal 2007	0.3365	0.1256	38.5%	1.40[1.09,1.79]
2	Torres etal 2008	0.2503	0.0689	47.1%	1.28[1.12,1.47]
3	Liu etal 2011	1.639	0.5883	6.0%	5.15[1.63,16.31]
4	Zai-chundeng 2013	0.9982	0.483	8.4%	2.71[1.05,6.99]
5	Present study2014	0.9990	0.487	8.3%	2.81[1.07,7.0]

CONCLUSION

THE present study showed that serum CRP concentrations are higher in stable COPD patients than in healthy subjects.

CRP levels are significant long term predictor of future COPD outcomes in individuals with airways obstruction.

These results highlight the significance of high sensitivity CRP assay in stable COPD patients .

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