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Association of Serum C-Reactive Protein (CRP) with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

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Abstract **Original Research Article**

Background: Chronic obstructive pulmonary disease consists of Chronic Bronchitis & Emphysema. It is persistent airflow limitation, usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung. The cause is tobacco smoking, occupational dusts, indoor and outdoor air pollutions. ***Objective:*** To find out association between serum C - reactive protein with acute exacerbation of Chronic Obstructive Pulmonary Disease. ***Methods:*** A Cross-sectional comparative study was carried out at Outpatient and inpatient department of Medicine and Respiratory unit of Z.H. Sikder womens Medical College & hospital, Dhaka, Bangladesh from 1 year (July-2020 to june-2021). A total number of 100 subjects of both sexes age range of 40-75 years who fulfilling inclusion and exclusion criteria & attending outpatient and inpatient departments of the Medicine and Respiratory unit of Z.H. Sikder womens Medical College & Hospital, Dhaka within the time frame. The study subjects were then divided into three groups Group I (AECOPD), Group II (SCOPD), and Group III (Control group). ***Results:*** A total number of 100 subjects of both sexes were included in this study in the age range of 40-75 years. Most of the subjects belong to 51-60- & 61-70-years age groups. The mean ages of group 1 were 59.4±9.0; group 2 was 59.4±6.7 and group 3 was 59.5±10.8 and the of total subjects' mean age was 59.5±8.4. Men had a higher prevalence of chronic obstructive pulmonary disease than women. In this study 85.4% of the patients of acute exacerbation of COPD were male and 14.6% were female. The ratio was 5.83:1. The common symptoms during exacerbation are increased dyspnoea (78%), increase cough (73%), increased sputum production (68%), change in sputum color (66%). The mean FEV1/FVC ratio in percentage was 45.5±9.7% in AECOPD; 68.5± 9.7% in stable COPD. The mean value of serum CRP was 16.9±4.4 in AECOPD (group-1); 10.9±3 in stable COPD (group-2) and 5.1±1.7 in case of a normal person (group-3). In this study shows the Association between FEV1/FVC ratio and CRP. Among the study patients FEV1/FVC ratio is decreasing as well as CRP level is increasing with a significantly negative correlation. This study showed that COPD with risk factors that demonstrate that smoking and elevated CRP were strongly associated to acute exacerbation of COPD. ***Conclusion:*** C-reactive protein (CRP) levels are useful in determining COPD exacerbation. There is a statistically significant rise of CRP levels in acute exacerbation of COPD. Thus, CRP may be considered as a useful biomarker in distinguishing acute exacerbation of COPD from stable COPD and in guiding management of the disease.

Keywords: Serum C- Reactive Protein (CRP), With Acute Exacerbation, Chronic Obstructive Pulmonary Disease (COPD).

INTRODUCTION

Chronic obstructive pulmonary disease consists of Chronic Bronchitis & Emphysema. It is persistent airflow limitation, usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung. The cause is tobacco smoking, occupational dusts, indoor and outdoor air pollutions. Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide and economic and social burden that is both substantial and increasing. The global prevalence of COPD is 11.7% and In Bangladesh

prevalence of COPD is 13.5% [1,2]. According to WHO, almost 90% of COPD death occur in low- and middle-income countries. Spirometric tests are difficult to perform during an exacerbation and measurements are not accurate enough. In some recent trials in abroad it is found that plasma CRP is significantly high in exacerbation of COPD [3-5]. An acute exacerbation is characterized by worsening of patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication. The average frequency is one to two exacerbations annually, it increases as the disease progresses. pneumonia, pulmonary embolism, congestive heart failure, cardiac arrhythmia, pneumothorax pleural effusion should be ruled out [6]. Categorizing COPD is difficult in clinical practice. Plasma CRP is able to reliably differentiate exacerbation of COPD from day-to-day symptom variation. Demographic profile, climate, nutritional condition, incidence and prevalence of COPD are different in Bangladesh than developed countries [7]. That is why this study was designed to find out association between Serum CRP and acute exacerbation of COPD and whether it can be used as a biomarker for early detection of COPD exacerbation.

General Objective

To find out association between serum C - reactive protein with acute exacerbation of Chronic Obstructive Pulmonary Disease.

Specific objective

1. To measure Serum CRP levels in acute exacerbation of COPD, stable COPD and healthy subjects.
2. To compare serum CRP level among 3 groups of study subjects.
3. To assess relationship between serum C-reactive protein with status of COPD.

MATERIAL & METHODS

Study Design- Cross sectional comparative study.

Study period – 1 year (July-2020 to june-2021).

Study place- Outpatient and inpatient department of Medicine and Respiratory unit of Z.H. Sikder womens Medical College & hospital, Dhaka.

Study population- Adults (40-75 years) male and female person fulfilling inclusion and exclusion criteria & attending outpatient and inpatient department of Medicine and Respiratory unit of Z.H. Sikder womens Medical College & hospital, Dhaka within the time frame.

Inclusion criteria

Group-1 (AECOPD) - This group includes the patients who fulfill the ANTHONISEN & COLLEGUE clinical criteria for acute exacerbation of Chronic obstructive pulmonary disease.

Group-2(Stable COPD) - this group includes the patients who fulfill the GOLD criteria (clinical and spirometry) for Chronic obstructive pulmonary disease patient without a history of exacerbation for previous 6 months.

Control group-Asymptomatic non smokers who are age and sex matched with the patients (healthy subjects).

Exclusion criteria

Patient with diseases which can raise serum CRP like- Type-1 DM, CKD, CLD, Active Inflammatory Arthritis (RA), SLE, Scleroderma, Cardiovascular disease (IHD) etc. Patient who do not fulfill criteria of COPD by GOLD criteria (clinical & Spirometry)

Sample size

The sample size was calculated by using the formula for difference between two means-

$N= (Z_{\alpha/2}+Z_{\beta})^2 \times 2\sigma^2/ d^2$. Where n =n1 = n2 & N =n1 + n2.

$N= (1.96+0.84)^2 \times 2 \times (11)^2/ (7.3)^2 = 1897.28/53.29 = 35.60$

So sample size for each group is 35 and total 105.

Sampling method

Patients was selected by purposive consecutive method from the inpatient and outpatient department who fulfill the inclusion criteria of the study.

Data collection instrument

A structured questionnaire were developed in English. The questionnaire was developed using the selected variables according to the specific objective. A check list was also developed.

Data collection technique

After selecting a patient, I collected data through face-to-face interview. The interview was conducted individually as far as possible and a data collection sheet which consists of structured questionnaire were filled up.

Data analysis

After collection all the data was checked and edited. Then data were entered into computer with the help of software SPSS (Statistical package for social science) for the windows programmed version 22. Data were expressed in percentage, frequencies, and means and standard deviation. Continuous variables was compared through the Student's t-test and for the categorical variables the chi-square test. P value of less than .05 was considered as significant.

Ethical consideration

Data were collected after getting the research proposal from the honorable faculty members of ethical committee. Written consent was received from each individual prior to inclusion in the study. They were informed of their right to withdraw from the study at any stage of study period. Assurance was given that the data

shall be collected individually and the confidentiality concerning their information will be maintained strictly. The research was conducted in full accord with ethical principles.

Operational Definition

COPD: A common preventable and treatable disease is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.

Spirometry is required to make a clinical diagnosis of COPD; the presence of a post bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation and thus of COPD.

Acute exacerbations of COPD (AECB): Anthonisen and colleagues proposed three clinical criteria to define AECOPD: a) Increased sputum volume, b) increased sputum purulence, c) Increased dyspnoea over baseline.

Serum CRP:

- CRP is an annular, pentameric protein found in blood plasma, whose levels rise in response to inflammation. It is an acute phase protein of hepatic origin.
- In this study, measurement of serum CRP will be done from venous blood which base on latex agglutination method then semi quantitative test which will be done by NEPHELOMETRY.
- Normal range of Serum CRP is 0-6mg/l
- Spirometry is a simple test to measure the amount of air a person can breathe out, and the amount of time taken to do so.
- A spirometer is a device used to measure how effectively, and how quickly, the lungs can be emptied.
- A spirogram is a volume-time curve.

RESULTS AND OBSERVATIONS

A total number of 100 subjects of both sexes were included in this study by fulfilling inclusion and exclusion criteria in the age range of 40-75 years. The study subjects were then divided into three groups as Group I (AECOPD), Group II (SCOPD) and Group III (Control group). The findings obtained by data analysis are presented below.

Table I: Age distribution of the study patients

Age in years	Group I (n= 41)		Group II (n=30)		Group III (n=29)		Total (n=100)		p value
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
40 – 50	7	(17.1)	4	(13.3)	6	(20.7)	17	(17)	
51 – 60	17	(41.5)	13	(43.3)	11	(37.9)	41	(41)	
61 – 70	12	(29.3)	11	(36.7)	6	(20.7)	29	(29)	
>70	5	(12.2)	2	(6.7)	6	(20.7)	13	(13)	
Mean ± SD (Range)	59.4±9.0 (44-81)		59.4±6.7 (46-71)		59.9±10.8 (44-81)		59.5±8.4 (44-81)		0.96_{ns}

Results were expressed as mean±SD. P value reached from one way analysis of variance (ANOVA test). Ns = Not significant (p>0.05)

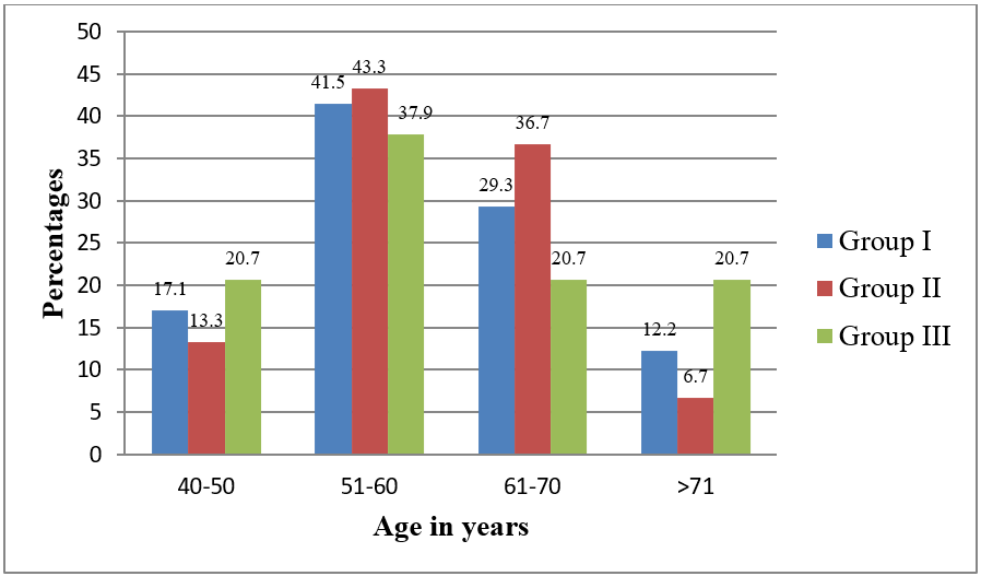

Table 2: Sex distribution of the study patients

Gender	Group I (n= 41)		Group II (n=30)		Group III (n=29)		Total (n=100)		p value
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Male	35	(85.4)	27	(90.0)	22	(75.9)	84	(84)	0.32^{ns}
Female	6	(14.6)	3	(10.0)	7	(24.1)	16	(16)	0.32^{ns}

Results were expressed as number and percentage. P value reached from Chi Square test (2X3 contingency table). Ns = Not significant (p>0.05).

Table 3: Socio demographic profile of the study patients

Occupation	Number	(%)
Business	6	(6.0)
Day labor	45	(45.0)
House wife	9	(9.0)
Shop keeper	37	(37.0)
Retired	3	(3.0)
Monthly income		
Less than 10,0000 (Tk.)	76	(76.0)
10,000 – 20,000 (Tk.)	24	(24.0)
Residence		
Urban	7	(7.0)
Semi-urban	25	(25.0)
Slum	68	(68.0)

Table 4: Risk factor profile of the study subjects

Smoking	Number	(%)
Smoker	75	(75.0)
Non-Smoker	25	(25.0)
Smoking duration in pack year		
≤10	6	(6.0)
11-20	45	(45.0)
>20	24	(24.0)
Mean ± SD (Range)	17.0 ± 4.4	(6-23)
Family history of COPD		
Present	61	(61.0)
Absent	39	(39.0)

Table 5: Distribution of the study patients according to risk factors

Risk factors	Study groups			P value
	Group I (n=41)	Group II (n=30)	Group III (n=29)	
Age (Mean±SD) years	59.4±9.0	59.4±6.7	59.9±10.8	0.96^{ns}
Range	44 - 81	46 - 71	44 – 81	
Smoking history (Mean±SD) (Pack – years)	18.2±3.8	16.8±4.4	10.5±2.9	<0.001^{s}
Range	16.94 – 19.36	15.16 – 18.50	7.48 – 13.52	

Results were expressed as mean±SD. P value reached from one way analysis of variance (ANOVA test.) S= Significant (p<0.05), ns =Not significant (p>0.05)

Table 6: Distribution of study groups according to Cough & Dyspnoea

Variables	Study groups					
	Group I (n=41)		Group II (n=30)		Group III (n=29)	
	No	(%)	No	(%)	No	(%)
Cough						
Persistent	15	(36.6)	2	(6.7)	0	(0.0)
Productive	41	(100)	20	(66.7)	0	(0. 0)
Dyspnoea						
Grade-1	00	(00)	7	(23.3)	0	(0.0)
Grade-2	7	(17.1)	15	(50.0)	0	(0.0)
Grade-3	19	(46.3)	6	(20.0)	0	(0.0)
Grade-4	13	(31.7)	6	(20.0)	0	(0.0)
Grade-5	0	(0.0)	0	(0.0)	0	(0.0)

Table 7: Distribution of study groups according to Sputum characteristic

Variables		Study groups					
		Group I (n=41)		Group II (n=30)		Group III (n=29)	
		No	(%)	No	(%)	No	(%)
Sputum volume							
	Increased	37	(90.2)	5	(16.7)	0	(0.0)
Sputum purulence							
	Increased	40	(97.6)	15	(50.0)	0	(0.0)

Table-8: Distribution of study groups according to no of hospital admission & exacerbation.

Variables		Study groups					
		Group I (n=41)		Group II (n=30)		Group III (n=29)	
		No	(%)	No	(%)	No	(%)
No. of exacerbation /year							
	1	11	(28.9)	6	(20.0)	0	(0.0)
	2	20	(52.6)	3	(10.0)	0	(0.0)
	3	6	(15.8)	0	(0.0)	0	(0.0)
Hospital admission times							
	1	11	(26.8)	6	(20.0)	0	(0.0)
	2	25	(61.0)	3	(10.0)	0	(0.0)
	3	2	(4.9)	0	(0.0)	0	(0.0)

Table 9: Distribution of study groups according to co-morbidities

Co-morbidities	Study groups					
	Group I (n=41)		Group II (n=30)		Group III (n=29)	
	No	(%)	No	(%)	No	(%)
Hypertension (HT)	11	(26.8)	9	(30)	6	(20.7)
Diabetes mellitus (DM)	0	(0.0)	1	(3.3)	0	(0.0)
IHD	1	(2.4)	0	(0.0)	1	(3.4)
PUD	35	(85.3)	14	(46)	17	(58.6)
Migraine	0	(0.0)	0	(0.0)	1	(3.4)

Table 10: Distribution of study groups according to FEV1/FVC ratio

FEV1/FVC ratio in %	Study groups						P value
	Group I (n=41)		Group II (n=30		Group III (n=29)		
	No	%	No	%	No	%	
<70%	41	(100)	14	(47)	0	(0.0)	
>70%	0	(0.0)	16	(53)	29	(100.0)	
Mean±SD	45.5±9.7		68.5±9.7		81.1±1.1		<0.001s

Results were expressed as number and percentage. P value reached from one way analysis of variance (ANOVA test. S= Significant ($p<0.05$)

Table 11 –Distribution of study groups according to CRP level

CRP mg/l	Study groups					
	Group I (n=41)		Group II (n=30)		Group III (n=29)	
	No	%	No	%	No	%
Very high CRP (>13mg/l)	35	(85)	6	(20.0)	0	(0.0)
High CRP (>6-<13mg/l)	5	(12)	22	(73.3)	7	(24.1)
Normal (0 -<6mg/l)	1	(3)	2	(6.7)	22	(75.9)

Table12 -Severity of exacerbation of COPD with CRP level

CRP mg/l	Study groups			P value
	Group I (n=41)	Group II (n=30)	Group III (n=29)	
Mean±SD	16.9±4.4	10.9±3.0	5.1±1.7	<0.01s

Results were expressed as mean±SD. P value reached from one way analysis of variance (ANOVA test). S= Significant (p<0.05)

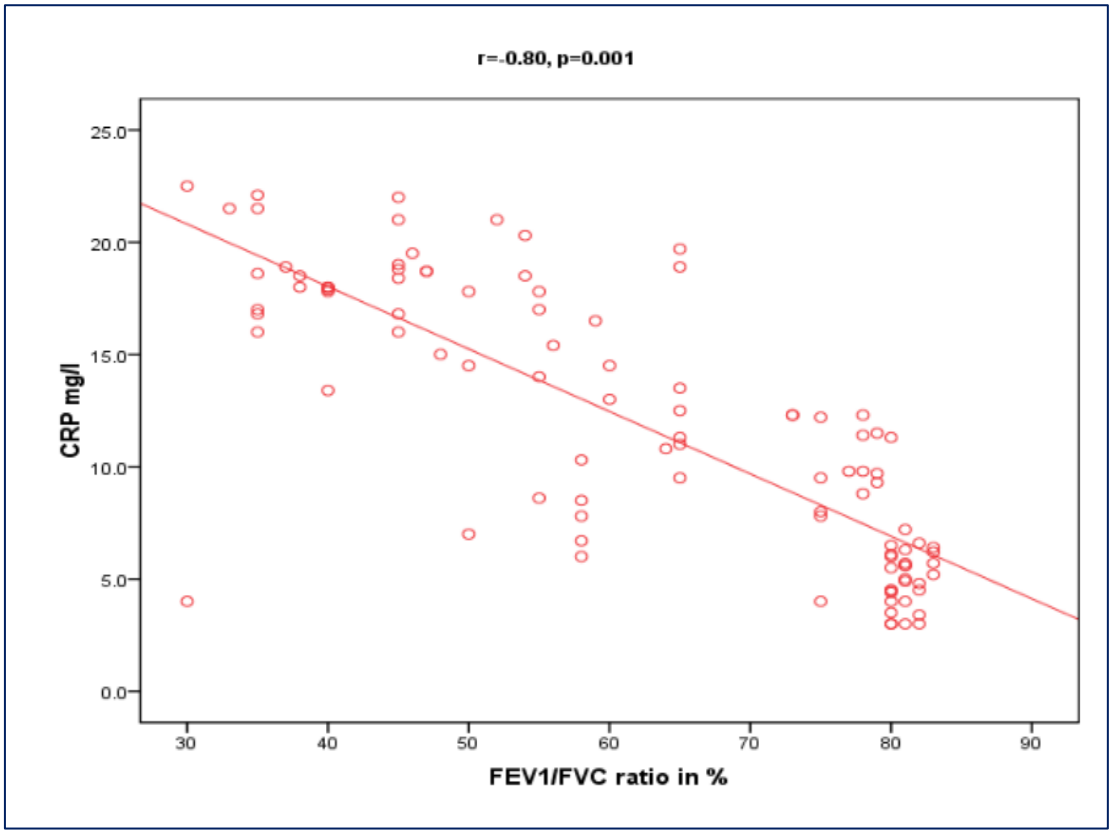

Figure- Scatter plot diagram showing correlation between FEV1/FVC ratio and CRP among the study patients

The above figure exhibits that FEV1/FVC ratio is decreasing as well as CRP level is increasing with significantly negative correlation (r=-0.88, p=0.001).

Table-13: Binary logistic regression analysis of acute exacerbation COPD with risk factors

Variables of interest	Standardized coefficient (β)	Odds Ratio (OR)	95% CI OR	p value
Advance age>50 yrs	0.211	1.20	0.312 – 3.120	0.31ns
Smoking	0.242	1.14	1.019 - 1.278	0.02s
Elevated CRP	1.942	9.50	7.374– 20.699	<0.001S
Occupation (Day labor)	0.329	1.21	0.112 – 4.409	0.42ns
Residence (Slum)	0.354	1.32	0.300 - 5.401	0.41ns
Family H/O of COPD	0.178	0.92	0.377 – 3.714	0.44ns

The above table demonstrates the binary logistic regression analysis of Odds Ratio for characteristics of the subjects likely to cause of AECOPD. s= Significant; Ns= Not significant

DISCUSSION

Most of subjects belong to 51-60- & 61-70-years age group. Mean ages of group-1 was 59.4±9.0; group-2 was 59.4±6.7 and group-3 was 59.5±10.8 and that of total subjects mean age was 59.5±8.4. Peng *et al.*, [8] showed that in asian people the mean age of exacerbation of COPD is 62.05±5.76 which is similar with this study. Man had a higher prevalence of chronic obstructive pulmonary disease than woman. In this study 85.4% of the patients of acute exacerbation of COPD were male and 14.6% were female. The ratio was 5.83:1. Chunhong Peng *et al.*, [8] in their study showed 84.20% male & 15.80% female and the ratio was 5.33:1. That is nearly similar to the present study. Distribution of population on the basis of occupation were day laborer (45%), shop keeper (37%), housewife (9%), business (6%), retired (3%). Most of the study subject was from low socioeconomic condition with low-income source. Majority of the study patients (68%) lived in slum followed by 25% in semi-urban and 7% in urban area. That is different from the western country because of our socioeconomic status of the people and most of the poor people of Dhaka city live in slum area According to "Bangladesh development series paper no-17"- secure shelter is a major challenge for Dhaka's urban poor.

Among the study subjects 75% were smoker, other risk factors include traffic and other outdoor pollution, secondhand smoke, biomass smoke, and dietary factors are associated with COPD. Nicholas A. *et al.,* [9] in their study showed smoking as a cause of COPD ranged from 9.7 to 97.9%. The mean pack use was 17.0 ± 4.4 packets with ranging from 6 to 23. Riverry l. *et al.,* [10] state that in USA cigarette smoking is higher in rich people, that is different in our country. The common symptoms during exacerbation are increased dyspnea (78%), increase cough (73%), increased sputum production (68%), change in sputum color (66%). These observations are very much similar with the study of Parker C.M. *et al.,* [11]. It is shown that increasing level of severity of the condition of the patient, there is increase chance of being admitted in the hospital. From the study of Stogent l. *et al.,* [12] it is assumed that total admission in USA for COPD were less than that of Bangladesh. It is due to improved home care system of patient in abroad. The mean FEV1/FVC ratio in percentage was 45.5±9.7% in AECOPD; 68.5± 9.7% in stable COPD, which had similarity with the study of Hurst *et al.,* [13], which states that most of the patient of COPD has FEV1/FVC was < 0.70 and as increases the severity of COPD there are further deterioration of the ratio between 45-65%. 85% of AECOPD had very high CRP while 20 % of SCOPD had very high CRP; none of the cases of control group had very high CRP. According to Smith j. *et al.,* [14] In UK, CRP in case of stable patient of COPD is 6 to 10 mg/l and in case of exacerbation it is 8 to 15 mg/l that is little bit lower in comparison to our country. In India there is similar result like our country. According to Snciri N. *et al.,* [15] in India the CRP is high up to 25 mg/l in acute exacerbation of COPD. Smith D. *et al.,* [16] states that the average CRP value in Africa due to exacerbation of COPD is 12-30 mg/l and that is of stable COPD is 8-18 mg/l. The CRP values of COPD patient in the western countries are different. According to Russell p. and Sanchita D, [17] the average CRP values of a COPD patient in stable condition are 5-9mg/l and that is of exacerbation of COPD 8-14mg/l that is bit lower than our study. The mean value of serum CRP was 16.9±4.4 in AECOPD (group-1); 10.9±3 in stable COPD (group-2) and 5.1±1.7 in case of normal person (group-3). the study results of Chunhong Peng, *et al.,* [8] states that in South East Asia mean CRP value of COPD exacerbation is 17.2±5.3 and that of normal person is 4.8±2.6. Scatter plot diagram between FEV1/FVC ratio and CRP among the study patients showed that FEV1/FVC ratio is decreasing as well as CRP level is increasing with significantly negative correlation. In this study we use 'Binary logistic regression analyses' of acute exacerbation COPD with risk factors which demonstrates that smoking and elevated CRP was strongly associated to acute exacerbation of COPD. According to Kartik J. and Shaha D [18]. In South East Asia active and passive smoking & bacterial infection are the main cause of exacerbation of COPD.

CONCLUSION

C-reactive protein (CRP) levels are useful in determining COPD exacerbation. There is a statistically significant rise of CRP level in acute exacerbation of COPD. Thus, CRP may be considered as a useful biomarker in distinguishing acute exacerbation of COPD from stable COPD and in guiding management of the disease.

LIMITATION & RECOMMENDATION

In this small study, only 100 cases were studied. This may not reflect the exact situation of the disease in the community. Some patients were at their extreme age so it was difficult to perform spirometry perfectly. There were limitation of time and financial constrain. But its proximity to the reality cannot be underestimated. So a large scale study can be performed to evaluate the finding more precisely.

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