

Original article:

Study of plasma fibrinogen levels and its correlation with severity of disease in patients with chronic obstructive pulmonary disease

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Abstract :

Background: COPD has been accepted as component of systemic inflammatory syndrome. The widely used marker of disease severity and progression in COPD is Expiratory volume in first second (FEV1). However it poorly correlates with symptoms and difficulty to perform in elderly patients⁴. Thus there is a need of other markers which are superior and easy to administer in sick and elder patients. The plasma fibrinogen could be used as a disease severity marker **Aims:** To estimate plasma fibrinogen level in patients with chronic obstructive pulmonary disease. And Correlation of plasma fibrinogen level with severity of chronic obstructive pulmonary disease using GOLD staging and BODE index staging methods and study design :In this cross sectional study 100 COPD patients were evaluated by measuring plasma fibrinogen and this was correlated with the severity of disease using GOLD Staging, BODE Index and 6 minutes walk test. **Results:** Plasma fibrinogen present in all COPD patients. Significant correlation of Plasma fibrinogen with bode Index ($r=0.66$, $p<0.001$), Gold staging ($r=0.942$, $p<0.001$), 6MWT ($r=0.39$, $p<0.001$) were observed. **Interpretation and conclusion :** Plasma fibrinogen levels were significantly elevated in COPD and can be used as a marker in COPD which correlates with disease severity.

Keywords: COPD; Plasma fibrinogen; GOLD stage ;BODE Index

Introduction:

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and / or alveolar abnormalities usually caused by significant exposure to noxious stimuli that is not fully reversible¹. Chronic obstructive pulmonary disease is fourth leading cause of death in the World² but projected to be the third leading cause of death by 2020. More than 3 millions people died of COPD in 2012 accounting for 6% of all deaths globally. Globally, the COPD burden is projected to increase incoming decades because of continued exposure to COPD risk factors and aging of the population.³

The widely used marker of disease severity and progression in COPD is Expiratory volume in first second (FEV1). However it poorly correlates with symptoms and difficulty to perform in elderly patients⁴. Thus there is a need of other markers which are superior and easy to administer in sick and elder patients. Fibrinogen, which is an acute phase plasma protein, is formed primarily in liver⁵. This is later converted into fibrin by thrombin during blood coagulation. In COPD there is pulmonary inflammation, which is associated with increased levels of acute phase reactants⁵. Thus we hypothesized that plasma fibrinogen could be used as indicator of the severity and exacerbation of disease in COPD patients. There had been only few studies in the past in this regard. Thus the need for simple laboratory parameter such as plasma fibrinogen could be considered to evaluate the severity

and exacerbation of COPD with chronic systemic inflammation as the common link between plasma fibrinogen in COPD patients.

Aims and Objectives of the study :

Primary objective :To estimate plasma fibrinogen level in patients with chronic obstructive pulmonary disease.

Secondary objective:Correlation of plasma fibrinogen level with severity of chronic obstructive pulmonary disease using GOLD staging and BODE index.

Materials and Methods:

Source of data:

The study will be conducted on 110 patients with Chronic obstructive pulmonary disease admitted in Department of medicine,

study design: Cross sectional study.

period of study: November 2017 to May 2019.

sample size:

110 patients with COPD who give consent for study and satisfying the inclusion criteria.

Based on previous study by Sumathy D et al⁶, Plasma fibrinogen level was 315.37mg/dl. Sample size calculation is $n=z^2 \sigma^2/d^2$

$$D=\text{precision}= 15 \quad n=(1.96)^2 \times (80.3)^2/(15)^2= 99$$

inclusion criteria :

- Age group: >18 years.
- Diagnosed case of COPD using GOLD criteria 2017
- Patients willing to give written informed consent

exclusion criteria:

- Age <18years
- Patients not willing to give written informed consent\
- Spirometry proved bronchial asthma.
- Inability to perform spirometry and six minute walk test.
- Active infections.
- Chronic kidney disease and Acute kidney injury.
- Congestive cardiac failure and Myocardial infarction.
- Patients on oral steroids.
- Sputum positive Tuberculosis

After obtaining institutional ethical committee clearance and written informed consent , 100 patients diagnosed with COPD according to GOLDS criteria 2017 and fulfilling inclusion and exclusion criteria were included in study. Demography data was collected by semi structured questionnaire, clinical examination and investigations .Data was collected and analyzed of all the patients satisfying the inclusion and exclusion criteria.

Statistical analysis used: Statistical analysis will be performed using SPPSS software. Correlation of plasma fibrinogen levels between various stages of patients with COPD will be performed using pearson correlation test and ANOVA test,.

P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers Y, USA) was used to analyze

Observation and Results:

Age distribution

Table 1: Age and sex distribution of the subjects

	N	Minimum	Maximum	Mean	Std. Deviation
Age	100	30	85	59.35	10.597

Out of 100(100%) subjects, more than half of the subjects were males- 85(85%) whereas 15(15%) were females in the present study.

GOLD STAGE and subjects

Table 2: Distribution of the subjects based on gold staging (using fev1)

GOLD STAGE	Frequency	Percent
I (MILD FEV1 > 80)	14	14.0
II (MODERATE 50% < FEV1 < 80%)	35	35.0
III (SEVERE 30% < FEV1 < 50%)	32	32.0
IV (VERY SEVERE FEV1 < 30%)	19	19.0
Total	100	100.0

Out of 100 subjects, majority (35%) were in gold staging I, followed by 32% in stage II, 19% in stage III and 14% in stage IV

Plasma fibrinogen and subjects

Table 3: Distribution of the subjects based on plasma fibrinogen

	Frequency	Percent
350 to 375	37	37.0
375.1 to 390	42	42.0
390.1 to 400	16	16.0
Above 400	5	5.0

Total	100	100.0
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Plasma fibrinogen and gold stage

Table 4: cross-tabulation of plasma fibrinogen and gold staging

		Gold Staging				Total
		I	II	III	IV	
350 to 375	Count	14	23	0	0	37
	Percent	100.0%	65.7%	0.0%	0.0%	37.0%
375.1 to 390	Count	0	12	29	1	42
	Percent	0.0%	34.3%	90.6%	5.3%	42.0%
390.1 to 400	Count	0	0	3	13	16
	Percent	0.0%	0.0%	9.4%	68.4%	16.0%
Above 400	Count	0	0	0	5	5
	Percent	0.0%	0.0%	0.0%	26.3%	5.0%
Total	Count	14	35	32	19	100
	Percent	100.0%	100.0%	100.0%	100.0%	100.0%
Chi-square value- 134.84						
P value- 0.00*						

*significant

Table 5: correlation between mean plasma fibrinogen and gold staging using pearson correlation (2 tailed)

Gold staging	N	Minimum	Maximum	Mean	Std. Deviation	R-value	P value
I	14	350	360	354.64	3.551	0.942	0.01*
II	35	358	378	371.85	5.171		
III	32	376	399	384.65	5.101		
IV	19	384	405	398.66	4.410		

*significant

In our study it was found that, as GOLD stage increased, Mean fibrinogen levels also increased and this was statistically significant with a p value of 0.01. R value of this correlation was 0.942.

Table 6: pearson’s correlation between bode index with plasma fibrinogen

Bode Index	N	Minimum	Maximum	Mean	Std. Deviation
1	19	351	378	360.43	9.223
2	35	358	389	374.62	7.119
3	26	370	401	386.63	9.234
4	20	350	405	392.54	12.353

Table 7:Correlation between PLASMA FIBRINOGEN and various factors in the study

PLASMA FIBRINOGEN	TOTAL SUBJECTS	PEARSON CORRELATION(r)	P value
GOLD STAGE BASED FEV1	100	0.942	<0.001
BODE INDEX	100	0.66	<0.001
BMI	100	-0.081	0.422
Fev1	100	-0.87	<0.001
6 min walk test	100	-0.39	<0.001

Discussion:

This is a cross sectional study which aims to assess plasma fibrinogen in COPD patients and correlate values with severity of COPD using GOLD staging and BODE index and also assess relationship with other parameters like age, BMI, FEV1, 6MWT. 100 patients were included in our analysis.

Age distribution :Out of the 100 patients in our study, maximum number of patients in our study were more than 60 years of age (44%) with mean age of 59.35 years (SD 10.597). The lowest age encountered was 30 years whereas the oldest patient was 85 years in our present study series. The mean age group in our study can be comparable to the study of Chopra R K et al⁷ (2018) 63.16 (SD ±10.4) conducting a similar study design. It was also comparable to Raheem Hussain et al⁸(2017) study on the Indian population in hyderabad (52.58±11.25).

Sex distribution : In the present study 15(15%) patients of the study population were females and 85(85%) were males. The female to male F: M ratio is 1:5.6 with no sex related variability which was comparable to Raheem

Hussain et al (2017) which had F:M ratio of 1:9. A similar distribution was also seen in Chopra R K et al (2018) which also had F : M ratio of 1:2.57. There was no significant sex related variability in our study.

In the present study , Out of 100 subjects, majority (35%) were in gold staging I , followed by 32.5% in stage II, 19% in stage III and 14% in stage IV. This is comparable to study by Chopra.R.K etal 2018, which had 6% in stage I, 34% in stage II, 40% in stage III and 20% in stage IV.

Distribution of the subjects based on bode index:

In present study ,out of 100 subjects 35% were under category 2 of Bode index followed by 26% in category 3, 20% in category 4 and 19% in category 1. BODE index has not been taken for comparision in most studies.

Distribution of the subjects based on plasma fibrinogen:

In our study ,most of them (42%) of had plasma fibrinogr in the range of 375.1 to 390, whereas 37% had in the range of 350 to 375, 16% of them in the range of 390.1 to 400 and only 5% had above 400.

Mean distribution of plasma fibrinogen classified by gold staging:

The mean plasma fibrinogen was highest in gold staging iv (398.66 \square 4.410) followed by stage iii (384.65 \square 5.101), stage ii (371.85 \square 5.171) and stage i (354.64 \square 3.551) in our study.

It is similar to study by sumathy etal 2016 in madras medical college, where the mean plasma fibrinogen was about 460.25(\pm 27.60) in severe copd ;345.33(\pm 27.73) in moderate copd ;246(\pm 24.81) in mild copd.

Correlation between plasma fibrinogen levels and gold staging :

In our study it was found that, as gold stage increased, mean fibrinogen levels also increased and this was statistically significant with a p value of 0.001. R value of this correlation was 0.942.

It is similar to study by sumathy etal 2016 in madras medical college,as gold stage increased, mean fibrinogen levels also increased and this was statistically significant with a p value of <0.001.

Also a study by chopra r k etal showed similar positive correlation between plasma fibrinogen and GOLD stage (p<0.0001)

Thomas etal showed similar positive correlation between plasma fibrinogen and GOLD stage(p<0.001) .

David M et al ¹¹ conducted study , which showed increased levels of fibrinogen associated with severity and increased mortality of disease ,which is similar to this study

Correlation between plasma fibrinogen levels and bode staging :

There is positive and strong correlation between bode index with plasma fibrinogen (r=0.66, p=0.00) which is highly statistically significant

In our study it was found that, as BODE INDEX stage increased, Mean fibrinogen levels also increased and this was statistically significant with a p value of 0.001. R value of this correlation was 0.66.

Kashifa Ehsan et al⁸ conducted study showed that plasma fibrinogen found to be pontential marker in determining the severity of disease in COPD using GOLD and BODE index ,which is similar to thi study

Duvoix A, et al⁹ concluded that fibrinogen is a useful biomarker in COPD, particularly in defining those more likely to exacerbate, linking to important clinical endpoints and in acting as a surrogate marker of treatment success, which is similar this our study.

In another small cohort of 96 Japanese individuals with milder COPD (median FEV1 70% predicted), Higashimoto and colleagues found that those with higher blood levels of fibrinogen had a non-significant trend towards faster decline in lung function (p=0.054) over a median 2-year follow-up¹⁰. Conversely fibrinogen was

associated with baseline FEV1 but not longitudinal decline in FEV1, in a larger multinational cohort of 1793 individuals from the ECLIPSE study⁴. Which is similar to this study

Limitation:

Lack of a control group with similar demographics was not compared in this study. Smoking was also found to be a confounding variable .,Small sample size

Conclusion

1. Plasma fibrinogen levels are significantly elevated in COPD patients.
2. Plasma fibrinogen values correlated well with,FEV1,GOLD Staging, BODE Index and6mwt significantly.
3. Do not correlate with age, gender and BMI.
4. Plasma fibrinogen can be used as biomarker in predicting the severity of COPD and

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For any images presented appropriate consent has been obtained from the subjects: NA

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