**Original article:**

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

**Dr Shashidhar Ramappa , Dr Aishhwarrya Umeshchandara G , Dr Aishwarya R,**

**Dr Madhumathi R**

Name of Institute: Department of Medicine , Bangalore Medical College and Research Institute

Corresponding Author : Dr shashidhar Ramappa

**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 stagingmethods 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 withbode 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 3millions 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=z2 σ2/d2

 D=precision= 15 n=(1.96)2 x( 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 distributionof 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 325 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 |

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 corelation 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 fibrinogrn in COPD patients and correlate values with severity of COPD using GOLD sstaging 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 fibrinogrn 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 fibrinogrn classified by gold staging:

The mean plasma fibrinogen was highest in gold staging iv (398.66 4.410) followed by stage iii (384.65 5.101), stage ii (371.85 5.171) and stage i (354.64 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(±27.60) in severe copd ;345.33(±27.73) in moderate copd ;246(±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

**References:**

1. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL.Harrisons manual of medicine. Mcgraw-Hill Medical publishingdivision; 2016 May 22. John J Reilly, Edwin K Silverman, Steven dshapiro. Chronic Obstructive Pulmonary Disease, Part 11, Sec 314, Pg1700.
2. Global Initiative for Chronic Obstructive Lung Disease, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (Updated 20118)
3. Mathers C, Loncar D. Projections of Global Mortality and Burden of Disease from 2002 to2030.plos Medicine. 2006:3(11):e442.
4. Vestbo J, Rennard S. Chronic Obstructive Pulmonary Disease Biomarker(s) for Disease Activity Needed—Urgently. American Journal of Respiratory and Critical Care Medicine. 2010;182(7):863-864.
5. Nordestgaard B. Markers of early disease and prognosis COPD. International Journal of Chronic Obstructive Pulmonary Disease. 2009;:157
6. S A, A., 2018. Serum Fibrinogen Level in COPD Patients- A Comparative Study. *Journal of Medical Science And clinical Research*, 6(6).
7. Mohd. Raheem Hussain et al Association of CRP and Fibrinogen in Patient with COPD – an Observation Study ICV: 77.
8. Ehsan, K., Zulfiqar, S., Hassan, A. And Waseem, H., 2021. Plasma Fibrinogen as a Biomarker of Stable and Exacerbated Chronic Obstructive Pulmonary Disease. *The Open Biomarkers Journal*, 11(1), pp.48-53.
9. Duvoix A, et al. Thorax 2013;68:670–676. Doi:10.1136/thoraxjnl-2012-201871
10. Higashimoto Y, Iwata T, Okada M, et al. Serum biomarkers as predictors of lung function decline in chronic obstructive pulmonary disease. Respir Med 2009;103:1231–8.
11. Mannino DM, Tal-Singer R, Lomas DA, et al. Plasma fibrinogen as a biomarker for mortality and hospitalized exacerbations in people with COPD. J COPD F. 2015; 2(1): 23-34. Doi: http://dx.doi.org/10.15326/jcopdf.2.1.2014.0138

 Date of Publication: 25 June 2021

Author Declaration: Source of support: Nil, Conflict of interest: Nil

Was informed consent obtained from the subjects involved in the study?  YES

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

Plagiarism Checked: Urkund Software

Author work published under a Creative Commons Attribution 4.0 International License

DOI: 10.36848/IJBAMR/2020/29215.55835