

Plasma Fibrinogen Level in Chronic Obstructive Pulmonary Disease and Its Correlation with GOLD Severity Staging

Achyut Gyawali¹, Niraj Bam², Pankaj Pant², Santa K Das²

Author(s) affiliation

¹Department of Internal Medicine, Bheri Hospital, Nepalgunj, Banke

²Department of Pulmonary and Critical Care Medicine, Maharajgunj Medical Campus, Tribhuvan University Teaching Hospital, Maharajgunj

Corresponding author

Santa K Das, MBBS, MD
drsantadas@hotmail.com

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ABSTRACT

Introduction

Chronic obstructive pulmonary disease (COPD) has great implications on global health accounting for significant morbidity and mortality. It is a state of chronic inflammation of airways. The aim of this study was to measure the plasma fibrinogen level in patient with COPD and find the relationship between plasma fibrinogen levels and severity of airflow obstruction.

Methods

This observational study was conducted from September 2017 to October 2018, where 80 eligible patients with the diagnosis of acute exacerbation of COPD (AECOPD) were included in the study and their plasma fibrinogen level was measured at the time of discharge. Clinical information was obtained and pulmonary function test (PFT) was done.

Results

A total of 80 patients were enrolled. The mean age of the patient was 67.87 ± 11.60 years. Plasma fibrinogen level was 159 ± 12.72 mg/dl in mild COPD, 273.52 ± 62.34 mg/dl in moderate COPD, 312.30 ± 103.67 mg/dl in severe COPD, and 487 ± 102.76 mg/dl in very severe COPD. The comparison between groups showed significant difference in plasma fibrinogen level ($p < 0.001$). There was significant negative correlation between plasma fibrinogen level and forced expiratory volume in one second ($FEV_1\%$) predicted ($r = -0.71$, $p = 0.01$).

Conclusion

High plasma fibrinogen level on discharge was found in COPD patients with severe airflow obstruction, frequent exacerbations and severe level of dyspnoea during AECOPD.

Keywords

Acute exacerbation, AECOPD, COPD, GOLD, plasma fibrinogen

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has great implications on global health accounting for significant morbidity and mortality and is one of the most common preventable respiratory diseases in clinical practice.¹ COPD is currently the fourth leading cause of death in the world and according to World Health Organization (WHO) by year 2030 COPD would become the third leading cause of death worldwide.²

Diagnosis of COPD should be suspected in any patient over age of 40 years presenting with chronic cough, chronic sputum production, dyspnea at rest or exertion or history of inhalational exposure to tobacco smoke, occupational dust, or occupational chemicals.³ Clinical diagnosis needs to be confirmed by standardized spirometric test in the presence of not-fully reversible airflow limitation.⁴

COPD being a chronic inflammatory state plasma fibrinogen level are usually elevated. The plasma fibrinogen levels is higher in patients with COPD exacerbations than in those with stable COPD and plasma fibrinogen level could thus serve as a useful biomarkers for the evaluation of exacerbated COPD.⁵

This study makes an effort to establish correlation of spirometric parameters with plasma fibrinogen level and its relation with severity of airflow obstruction.

METHODS

In this observational study, plasma fibrinogen level was measured in 80 eligible patients above 40 years of age of both sexes at the time of discharge under Department of Pulmonology and Critical Care Medicine of Tribhuvan University Teaching Hospital (TUTH) from September 2017 to October 2018. Ethical approval for the study was obtained from Institutional Review Committee (IRC) of Institute of Medicine (IOM). Patients above 40 years of age were only included because COPD is a chronic and progressive disease that usually takes longer to manifest and is usually seen only after 40 years. Participants were included after carefully applying the inclusion and exclusion criteria; and after obtaining signed informed consent.

Inclusion criteria were patients meeting criteria of case definition, subjects with previous diagnosis of COPD by a respiratory physician and age > 40 yrs. Exclusion criteria were inability or unwillingness to cooperate with investigator, patient with comorbidities that significantly influence fibrinogen level like chronic kidney disease (CKD), severe liver dysfunction, malignancies, history of chronic respiratory disorder other than COPD like pulmonary tuberculosis, bronchial asthma, bronchiectasis.

Diagnosis of COPD was considered on the basis of history, clinical examination and radiological

findings and confirmed by pulmonary function test (spirometry) and in case of cases under domiciliary oxygen it was solely clinical diagnosis with exclusion of other causes and presence of typical features and risk factors.

Subjects with prior diagnosis of COPD by a respiratory physician (with typical presentation, risk factors and exclusion of other lung pathology like pulmonary tuberculosis, Post TB fibrosis/ bronchiectasis, interstitial lung disease, bronchogenic carcinoma) under domiciliary oxygen are also taken as COPD cases.

Spirometry was done in laboratory of TUTH, after resolution of acute exacerbation episode near the time of discharge. The test was done with Spirolab III and care was taken to involve same technician for the test as much as possible and suspected reports were repeated using same technician for confirmation. Plasma fibrinogen level was measured in TUTH central laboratory at the time of discharge. All confounding variables were considered. As this study is done in stable COPD patient after the infective exacerbation has been resolved to exclude the confounding variables especially during exacerbation, patients at the time of discharge were included as the participants.

All the data regarding the patients were recorded in a structured manner that include patients' demographic, clinical and laboratory data. In clinical evaluation, detailed information regarding the history of cough, sputum production and dyspnea was obtained. Physical examination including vital signs, general physical examination and chest findings was also obtained. Risk factor in the form of smoking was included and cases were grouped according to severity of COPD based on spirometric findings and divided into mild, moderate, severe and very severe COPD. Prescribed medication/standard therapy (oxygen, corticosteroids IV/Oral and inhaled corticosteroids/ inhaled beta-2 agonist/inhaled muscarinic antagonists along with antibiotics and diuretics) was written on the pro forma. Patients were evaluated at the time of discharge (including vital signs, general physical examination and chest findings) ongoing prescribed medications/standard therapy and duration of stay in hospital.

IBM SPSS Statistics version 25 was used for data entry and statistical analysis. Both descriptive and inferential statistics were used for analysis. In descriptive statistics; frequencies, mean and standard deviation were computed. In inferential statistics, independent sample t-test and one way ANOVA were performed to establish the level of significance between the variables and Pearson correlation test was applied to test the association between variables. All statistical analysis was 2 tailed and p-value of <0.05 was considered to be statistically significant.

Table 1. Sample distribution and plasma fibrinogen level according to GOLD severity

GOLD staging	Number of patients	Plasma fibrinogen level (mg/dl)			p-value
		Mean	Min	Max	
Mild	2	159	150	168	<0.001
Moderate	29	273.52	120	390	
Severe	20	312.30	52	432	
Very severe	29	487	159	598	

RESULTS

Out of total 80 cases, 43.8% were female (n=35) and 56.3% were male (n=45) and most of the patients were of the age group 71-80 years i.e. 27. There were five participants in age group 41-50, 18 in age group 51-60, 18 in age group 61-70 and 12 participants in age group 81-90.

The mean age of the patient included in the study was 67±11.60 years, ranging from minimum of 45 years to maximum of 90 years. Among the participants, 4 (5%) of them had never smoked while 76 (95%) had smoked cigarettes. Among the smokers, 30 participants (39.5%) were current smokers and 46 (60.5%) were ex-smokers. Likewise, 36 (45%) participants had no history of household smoke exposure while 44 (55%) had household smoke exposure in the form of biomass fuel, kerosene etc.

Mild COPD was seen in 2(2.5%), Moderate COPD was seen in 29(36.3%) cases, Severe COPD in 20(25%) cases and Very Severe COPD in 29 (36.3%) cases. Plasma fibrinogen level was 159±12.72 mg/dl in Mild COPD, 273.52±62.34 mg/dl in Moderate COPD, 312.30±103.67 mg/dl in Severe COPD, and 487±102.76 mg/dl in Very Severe COPD. In between group comparison showed significant difference in Plasma fibrinogen level (p<0.001) while using ANOVA test.

Out of 80 cases, 36 (45%) had less than two exacerbations in the past one year (non-frequent exacerbation) and 44 (55%) had more than or equal to 2 exacerbations (frequent exacerbation). Mean plasma fibrinogen level was 243.11±68.94 mg/dl in Non-frequent exacerbation group and 451.52±195.60 mg/dl in the frequent exacerbation group. The in between group analysis for difference in plasma fibrinogen level showed statistically significant difference (p=0.01) with cases having less than two exacerbations in past one year having significantly low plasma fibrinogen level than those having more exacerbations by using independent sample t-test.

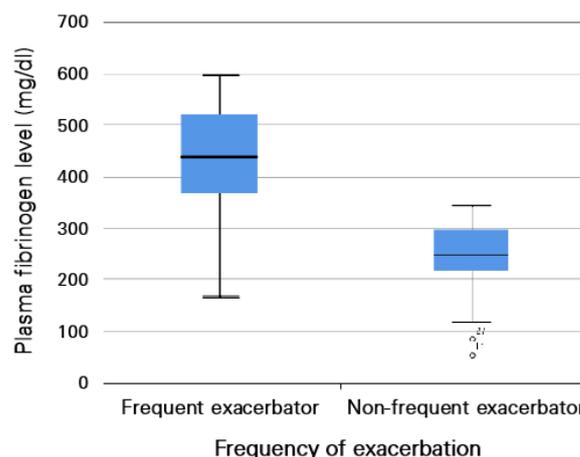


Fig 1. Boxplot of plasma fibrinogen levels in study patients according to exacerbation frequency

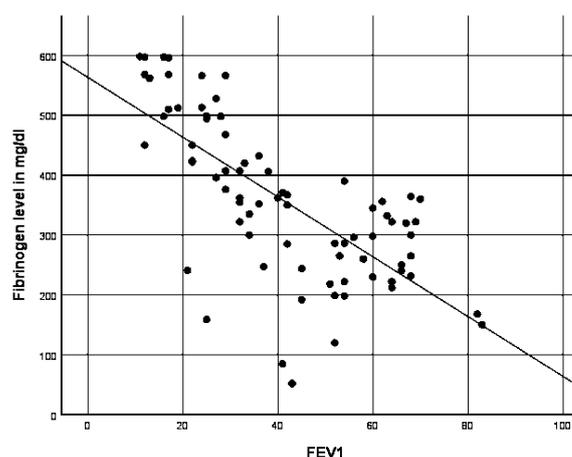


Fig 2. Scatter diagram of correlation between plasma fibrinogen levels and FEV₁% predicted in study population

There was significant negative correlation between plasma fibrinogen level and FEV₁% predicted (r=-0.712, p=0.01) which is significant at <0.05 (2-tailed) while using Pearson correlation coefficient. It signifies that plasma fibrinogen level increases with increasing severity of airway obstruction in COPD.

DISCUSSION

In this study, COPD was more common in people who smoked and this correlates with other studies where cigarette smoking was the most common cause of COPD as shown in the study done by Burrows et al.⁶

According to the GOLD spirometry classification, 36.3% (n=29) of total patients had Stage IV: Very Severe COPD, 25% (n=20) had Stage III: Severe COPD, then 36.3% (n=29) had Stage II: Moderate COPD, and 2.5% (n=2) had stage I: Mild COPD. In

a study done by Bednarek et al, mild COPD was present in 30.6%, moderate COPD in 51.4%, severe in 15.3.% and very severe in 2.7%.⁷ In a PREPOCOL study, COPD prevalence by GOLD classification of severity was distributed as follows: mild, 68.9%; moderate, 26.3%; severe, 3.4%; and very severe, 0.5%.⁸

Plasma fibrinogen level was 159±12.72 mg/dl in Mild COPD, 273.52±62.34 mg/dl in Moderate COPD, 312.30±103.67 mg/dl in Severe COPD, and 487±102.76 mg/dl in Very Severe COPD. The in between group comparison showed significant difference in Plasma fibrinogen level ($p < 0.001$). This is similar to the result of ARIC⁹ study conducted at USA where the subjects with stage 3 or 4 COPD were most likely to have a fibrinogen level more than 393.0 mg/dl with mean fibrinogen level at 307.6 mg/dl .

There was significant negative correlation between mean plasma fibrinogen levels and Number of Exacerbations in the past one year. When exacerbation was grouped as increased frequency (≥ 2 exacerbation per year according to GOLD Guidelines) vs low frequency (< 2 exacerbation per year) there was significant high fibrinogen level in those with increased frequency exacerbation compared to low frequency exacerbation ($p = 0.045$). Recent data from the large ECLIPSE cohort suggest that the frequent-exacerbation phenotype is more common in more severe disease¹⁰ and this may, in part, explain the associations between high fibrinogen levels with disease severity and exacerbation frequency.

There was significant negative correlation between plasma fibrinogen level and FEV₁% predicted ($r = -0.712$) which is significant at the 0.01 level (2-tailed). A large population based spirometry study in japan observed significant associations between plasma fibrinogen levels and spirometry values in general population and found an inverse relationship between spirometric measures (percent predicted forced vital capacity [%FVC] and forced expiratory volume in 1s [%FEV₁], and FEV₁/FVC) and plasma fibrinogen levels .

So this study shows that plasma fibrinogen level increases with increasing severity of airflow obstruction as per GOLD criteria and it correlates with various parameters of severity of COPD. This is a small observational study which recommends that a separate large prospective trial should be performed to study the levels of fibrinogen in COPD patients who get admitted in hospital with acute exacerbation to see the relationship of fibrinogen with severity of airflow obstruction.

CONCLUSION

High plasma fibrinogen level on discharge was associated with more severe airflow obstruction. Frequent exacerbation in the past was associated with higher plasma fibrinogen level on discharge as compared to nonfrequent exacerbation. Also higher fibrinogen level was associated with more severe level of dyspnoea in patients with AECOPD. Plasma fibrinogen level was increased with decreasing value of FEV₁ showing significant negative correlation between plasma fibrinogen level and FEV₁% predicted. This suggests that high plasma fibrinogen level could be a diagnosis of severity of COPD and a poor prognostic factor. The results of the present study, combined with the fact that plasma fibrinogen is a widely and rapidly available, easy to interpret, low-cost biomarker, suggest a possible role for plasma fibrinogen in the identification of COPD patients at an increased risk of adverse outcomes who may need early intensive management.

CONFLICT OF INTEREST

None declared.

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