" ROLE OF SERUM FIBRINOGEN LEVELS IN DETERMINING THE SEVERITY AND PROGNOSIS OF ACUTE EXACERBATION OF COPD PATIENTS – AN OBSERVATIONAL STUDY "

BY

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LIST OF ABBREVIATIONS

AECOPD	Acute exacerbation of Chronic Obstructive Pulmonary Disease
CT	Computed tomography
BMI	Body Mass Index
ABG	Arterial blood gas
CHF	Congestive Heart Failure
VAS	Visual analogue scale
COPD	Chronic Obstructive Pulmonary Disease
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HSCRP	Highly sensitive c-reactive protein
CRP	C-reactive protein
IMV	Invasive Mechanical Ventilation
LMWH	Low molecular weight heparin
MNA	Mini nutritional assessment
NIV	Non-Invasive Ventilation
DVT	Deep vein thrombosis
SABA	Short Acting Beta2 Agonist
MMP-9	Matrix metalloproteinase-9
NE	Neutrophil elastase
12-OXO-ETE	12-oxo-eicosatetraenoic acid
5-OXO-ETE	5-oxo- eicosatetraenoic acid
PTE	Pulmonary thromboembolism
NPPV	Non-invasive positive pressure ventilation
CAT	Copd assessment test

CCIS	Charlson’s comorbidity index score
SAA	Serum amyloid -A
TNF-A	Tumor necrosis factor -alpha
IL-8	Interleukin-8
IL-6	Interleukin -6
BODE	Body mass index ,Obstruction,Dyspnea and Exercise
ADO	Age,Dyspnea and airflow Obstruction
DOSE	Dyspnea ,Obstruction,Smoking exacerbation
FDA	Food and drug administration
CKD	Chronic kidney disease
6MWT	6 Minute walk distance
RA	Room air
PCT	Procalcitonin
CVD	Cerebro vascular disease
PTCA	Percutaneous transluminal Coronary angioplasty
CABG	Coronary artery byepass graft
IHD	Ischemic heart diesease

ABSTRACT

BACKGROUND AND OBJECTIVE: Chronic obstructive pulmonary disease (COPD) is a progressive condition characterized by declining respiratory function, exercise capacity, and health status. COPD exacerbations are a significant cause of morbidity and mortality, particularly in India, where frequent hospitalizations due to acute exacerbations (AECOPD) are reported.

This study aims to assess the role of serum fibrinogen levels in determining the severity and prognosis of AECOPD patients, as fibrinogen is a promising biomarker for inflammation and COPD severity.

METHODS: This observational study was conducted after ethical approval at KLE's Dr. Prabhakar Kore Charitable Hospital and Medical Research Center, Belagavi. Eligible AECOPD patients were recruited, and informed consent was obtained.

Demographic data, clinical history, and baseline investigations including Pulmonary Function Tests, Chest X-ray, and 6-Minute Walk Test (6MWT) were recorded. Serum fibrinogen levels were measured using turbidimetric immunoassay, and the Modified Borg Scale was used to assess respiratory symptoms. Statistical analysis was performed using SPSS version 26.0.

RESULTS: The study included 105 patients. The mean serum fibrinogen level was 408.248±114.264 mg/dl, with 63.8% of patients showing elevated levels. Significant correlations were found between serum fibrinogen levels and the 6MWT and the need for non-invasive ventilation (NIV). The 6MWT served as a predictor for serum fibrinogen levels, with a cut-off value of 433.5 mg/dl showing 75.8% sensitivity and 29.2% false positivity.

Additionally, FEV1 (Forced Expiratory Volume in 1 second) was assessed, with lower FEV1 values correlating with higher serum fibrinogen levels, indicating more severe airway obstruction. The duration of hospital stay averaged 7.33±3.32 days.

CONCLUSION: Serum fibrinogen is a valuable biomarker for assessing the severity and prognosis of AECOPD.

Elevated fibrinogen levels correlate significantly with the severity of disease, lower FEV1 values, and the need for NIV, highlighting its potential utility in clinical practice for managing AECOPD patients.

KEYWORDS: COPD, AECOPD, serum fibrinogen, biomarkers, prognosis, Mortality.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease which is characterized by an inexorable decline in respiratory function, exercise capacity, and health status [1]

This disease is common worldwide with significant morbidity and mortality [2,3] which is characterized by "persistent respiratory symptoms, such as dyspnea, productive cough, history of recurrent lower respiratory tract infections, and airflow limitation". Chronic obstructive pulmonary disease is the 4th leading cause of death by 2040. [4] Men over 40 were predicted to have an airflow blockage prevalence ranging from "5.7% (Pune, India) to 23.0% (Cape Town, South Africa) and women over 40 to 20.7% "(Uppsala, Sweden) respectively. Much more variation was shown in the prevalence of spirometric restriction, which ranged from "8.4% in males (Bergen, Norway) to 67.7% in Mumbai, India, and from 6.7% in women (Bergen, Norway) to 70.5% in women" (Srinagar, India). [5]

The economic and social burden of chronic obstructive pulmonary disease (COPD) is significant and growing. Long-term exposure to toxic chemicals and particles, in addition to a confluence of variables such as hereditary, airway hyper reactiveness, and improper lung development in childhood, all contribute to the development of COPD. As the world's population ages and risk factors continue to be present, COPD is expected to become more common and to have a greater impact. More people will suffer from the long-term effects of exposure to COPD risk factors as life expectancy increases. [6]

Long-term exposure to toxic chemicals and particles causes COPD. Other contributing factors include genetics, hyperresponsive airways, and inadequate lung development in childhood. Future projections indicate that the aging global population and ongoing exposure to risk factors will increase the prevalence and impact of COPD. More people will suffer the long-term consequences of exposure to COPD risk factors as life expectancy increases. [7]

Even in India COPD is a frequently encountered clinical problem with AECOPD as a common cause for hospitalization. Recently, in a study done by the Burden of Lung Disease investigators a high prevalence was reported in Northern India, [5,8] indicating high frequency of hospitalizations because of AECOPD with considerable morbidity and mortality. A study from South India recently recorded 12% in-hospital mortality among AECOPD. These exacerbations can vary from mild, self-limited diseases to episodes of severe respiratory failure that require mechanical ventilation. On average, a patient with COPD experiences two of these episodes per year, and they result in significant use of healthcare resources. While mild events of AECOPD can usually be reversed, High death rates and protracted disability periods for survivors are associated with more severe instances of respiratory failure.

The triggering factors of AECOPD include infectious and noninfectious precipitants, however up to 30% of AECOPD is of unknown etiology. [1,3] The most widely used measure for determining the severity and progression of a disease is the forced expiratory volume in one second (FEV1). However, FEV1 is not an accurate measure for disease activity because it is a poor indication of other disease progression metrics as well as symptoms [9]. Proteins and other substances have therefore been the focus of a massive hunt for biomarkers.

They can be found in breath condensate ,BAL,sputum,urine and blood,that have been implicated in pathogenesis of COPD[9]

BIOMARKERS IN COPD EXACERBATIONS

Fibrinogen is one of the most promising biomarkers in COPD and approved by the "US Food and Drug Administration" [9] A key modulator of inflammation and fibrosis development, as well as tissue injury, therefore used as COPD biomarker for severity assessment. Higher baseline fibrinogen is

associated with increasing incidence of COPD, COPD hospitalization, and all-cause mortality and related to severity of COPD. [10]

During blood coagulation, thrombin transforms fibrinogen a soluble plasma protein mostly generated in the liver during the acute phase into fibrin. In blood normal levels of fibrinogen are considered between 1.5 and 3.5 g/litre. This increases by three times in acute phase due to increased production of IL-6 due to stimulation [9] One study found that fibrinogen levels were higher during AECOPD and then returned to baseline 40 days after exacerbation. [11] It is increasingly being studied as an inflammatory biomarker in chronic obstructive pulmonary disease (COPD), but there are limited data on the role of fibrinogen in assessing the severity of AECOPD.

In this study, we have primarily aimed to assess the severity and prognosis of AECOPD using Serum Fibrinogen levels as S. Fibrinogen levels are now proved to be a promising biomarker.

AIMS AND OBJECTIVES

To assess the role of serum fibrinogen levels in determining the severity and prognosis in **AECOPD** patients

REVIEW OF LITERATURE

Burden of AECOPD

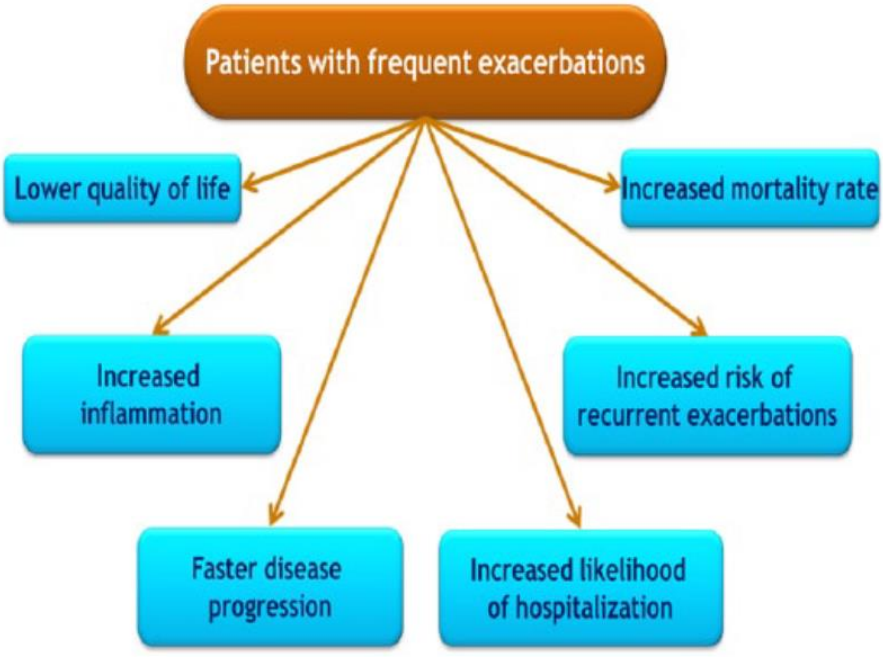
In a review published in 2016, Ko et al. [3] discovered that COPD significantly affects health and the economy in the Asia-Pacific area as well as globally. 6.2% was the estimated prevalence of COPD in another population-based study that was carried out in nine Asia-Pacific territories. Of COPD patients, 19% of patients needed to be hospitalized, and 46% had at least one exacerbation in the year prior. [12] Exacerbations ranged in frequency from 0.06 to 0.78 incidents per person per year, according to a Hokkaido, Japan research. During the follow-up period, patients who experienced exacerbations during the first year of the research reported lower quality of life (QOL) and a greater incidence of AECOPD. [13] Globally, COPD is among the leading causes of mortality, and a significant contributing factor to this is acute exacerbations.

In 2002, COPD ranked as the fifth most common cause of death; by 2030, it is expected to rise to the third spot. [4] COPD was reported to be the third most prevalent cause of respiratory mortality in Hong Kong, after lung infections and malignancy. Japanese research on 177,207 patients hospitalized with COPD as the major disease or comorbidity found that patients with lower body mass index (BMI), male gender, older age, more severe dyspnea, lower level of awareness, and worse quality of life had a higher death risk. [14] In similar fashion, New Zealand research including hospitalized patients with AECOPD discovered a high correlation between an elevated 30-day death rate (2.0%, 6.7%, and 21.3%, respectively)

and the CURB65 score (0 to 1, 2, and 3 to 5). [15] Furthermore, a significant economical loss and health expense result from COPD patients' physical disabilities that limit their capacity to work or force them to retire early.

2008 research on 8217 COPD patients in rural Xuzhou, China (48 percent men) found that a sizable portion of patients (36%) required hospitalization due to respiratory symptoms. An estimated 4,327,050 yuan ($US 678,000) in total indirect economic damage resulted from this. The increased prevalence of exacerbations may also be partially explained by the fact that these people were found to know very little about COPD and to have gotten care that did not match international standards during both stable and acute attack stages. [16] Moreover, a lower quality of life, a higher chance of mortality, and a decrease in physical activity are all linked to recurrent exacerbations. [6]

Fig1: Impact of chronic obstructive pulmonary disease exacerbations [6]



Definition of AECOPD

Chronic obstructive pulmonary disease (COPD) has been classified as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases" [(17)].

"An acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an acute worsening of dyspnea, cough, and/or sputum production/change in the quality that is beyond normal day-to-day variation and sufficient to warrant a change of medications". [(8)]

An acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is diagnosed when a patient with COPD experiences a sustained (>24-48 hours) increase in cough, sputum production, and/or shortness of breath. On average, patients with COPD have two AECOPD episodes per year, and 10% of these cases require hospitalization, leading to significant use of healthcare resources. [(7)]

Recurrent exacerbations are linked to a faster decline in lung function, a key characteristic of COPD. In one study, individuals experiencing frequent exacerbations experienced a decline in forced expiratory volume in 1 second (FEV1) of 40.1 ml/year [95% confidence interval (CI) 38–42], compared to 32.1 ml/year (95% CI 31–33) in patients with either nil or less exacerbations ($p < 0.05$). In a more recent 3-year longitudinal cohort study, it was found that exacerbations during the study were connected to a greater decline in lung function (FEV1) with an average loss of 2 ml per year per exacerbation ($p < 0.001$). [(6)]

Staging of AECOPD

Different staging approaches can be used to classify the severity of AECOPD without respiratory failure. Based on a double-blind, placebo-controlled experiment evaluating the use of antibiotics in COPD patients having acute exacerbations, the Winnipeg criteria are the foundation of the traditional approach. [18]

The WINNIPEG Criteria

Three main symptoms serve as the foundation for this three-stage system:

1. An increase in the amount of sputum
2. A rise in purulent sputum, and
3. An increase in dyspnea

Type of Exacerbations	**Criteria**
1	All three symptoms increase
2	Any two of the symptoms increase
3	Any one of the symptoms increase plus At least one of the following present: • Upper respiratory tract infection lasting 5 days, • Fever; • Increase in wheezes, • Increase in cough, • Increase in heart rate ⩾ 20%

There is a strong correlation between the efficacy of antibiotic treatment and a staging system for AECOPD. Antibiotics lower the chance of treatment failure in type 1 exacerbations, but they have almost little effect in type 3 exacerbations.

Based on a five-stage severity classification, the Canadian Medical Association recently released guidelines for the management of AECOPD. [19] Using the standard Winnipeg criteria plus factors such age over 65, severe co-occurring diseases, FEV1 < 50% of anticipated, and frequency of exacerbations per year that are known to correlate with poorer response to medication, this approach yields a severity score. The dosage of antibiotics is modified according on how severe the exacerbation is. Furthermore, a three-level staging scheme that takes into account comorbidities, illness history, and symptom criteria has been proposed for AECOPD. [20]

Causes of AECOPD

Almost 70–80% of COPD exacerbations are due to by viral or bacterial respiratory infections. The rest 20–30% are because of environmental pollution exposure or have an unknown cause. [1] COPD exacerbations may be mistaken for other medical conditions. Pathogens that cause flare-ups of chronic obstructive pulmonary disease. [6]

"Bacteria"

- 20–30% of bacteria are Haemophilus influenzae.
- Pneumonia due to streptococcus: 10–15%
- 10–15% is Moraxella catarrhalis

- 5–10% is Psuedomonas aeruginosa.
- Undefined Enterobacteriaceae
- Not specified for H. hemolyticus and H. parainfluenza
- Undefined for Staphylococcus aureus

"Viruses"

- 10–25% of cases are rhinovirus.
- 5–10% is the parainfluenza virus
- Viral influenza: 5–10%
- 5–10% of cases are respiratory syncytial virus.
- 3-5 percent adenovirus
- 3% to 5% coronavirus
- 3-5% is the human metapneumovirus.
- 3–5% of cases are Chlamydophilia pneumoniae.
- 1-2% is Mycoplasma pneumoniae.
- Undefined Pneumocystis jeroveci

Risk factors for chronic obstructive pulmonary disease (COPD) exacerbations. [6]

- Age
- Previous use of COPD drugs
- Severity of airway obstruction

- Bacterial colonization
- Chronic bronchial mucus secretion
- Comorbid conditions
- Chronic COPD
- Poor quality of life with respect to health
- Productive cough and wheezing
- Prior history of exacerbations
- Antibiotic or systemic steroid use

Diagnosis of AECOPD:

An acute episode of chronic obstructive pulmonary disease (COPD) is defined as a rapid deterioration that lasts for less than 14 days and is characterized by increasing dyspnea and/or intense coughing up mucus. This deterioration may manifest alongside rapid breathing and/or elevated heart rate and is frequently linked to heightened inflammation in both the affected area and throughout the body, triggered by factors like infection, environmental pollution, or other irritants affecting the airways.

These exacerbations typically involve increased airway inflammation, heightened mucus production, and significant gas retention, leading to worsened dyspnea as the primary symptom. Additional symptoms include increased cough, sputum purulence, and wheezing.

Individuals diagnosed with COPD are also more susceptible to other acute illnesses such as pneumonia, pulmonary embolism, and heart failure, which can mimic or exacerbate exacerbations of the disease. Therefore, accurately diagnosing exacerbations requires careful consideration of symptoms to differentiate them from these other potential contributors.

Diagnosis of COPD once confirmed by spirometry, the COPD assessment is done to guide therapy by identifying the four main factors listed below:

- Airflow limitation severity
- Current symptoms nature and intensity
- History of moderate and severe exacerbations in the past
- Type and presence of additional diseases (multimorbidity)

IMAGING:

Imaging techniques play a crucial role in the diagnosis and management of COPD, with chest radiography and computed tomography (CT) being the most commonly utilized modalities. While both imaging methods serve to assess lung pathology and aid in differential diagnosis, CT imaging offers superior sensitivity and specificity compared to chest radiography.

Chest radiography is often the initial imaging modality used in patients with suspected COPD. Common findings on chest X-ray suggestive of COPD include radiolucency, indicating hyperinflation and air trapping, as well as flattening of the diaphragm.

However, chest CT is considered the gold standard for the detection and quantification of COPD-related lung changes providing detailed visualization of pulmonary structures and abnormalities, making it indispensable for preoperative assessment in lung volume reduction surgeries. Expiratory CT scans can reveal bronchial thickening and small airway disease, showing air trapping, which is characteristic of COPD.

These scans are also vital for ruling out other respiratory conditions that may resemble COPD. Due to the heightened risk of lung cancer in COPD patients, screening guidelines recommend CT scans for individuals aged 55 to 74 with a substantial smoking history (30 pack-years) or recent quitters within 15 years. This screening aims to catch lung cancer early, especially in high-risk groups with COPD, for better treatment outcomes.

GOLD grades and severity:

GOLD staging	**Severity**	**FEV1**
1	Mild	≥ 80% predicted
2	Moderate	≤ 50% FEV1 to < 80% predicted
3	Severe	≤ 30% FEV1 to < 50% predicted
4	Very Severe	< 30% predicted

Role of Biomarkers in AECOPD

Systemic inflammation is a critical aspect of COPD and serves as a diagnostic tool through circulating inflammatory biomarkers. Among these biomarkers, fibrinogen is extensively studied for its role in inflammation, fibrosis development, and tissue injury modulation. Furthermore, as COPD worsens, there is evidence that adiponectin, C-reactive protein (CRP), leukocyte count, IL-6, IL-8, TNF-α, and chitinase-3-like protein 1 (YKL-40) rise. Adiponectin, specifically, influences inflammation regulation, with elevated serum levels and increased expression of adiponectin receptors observed in COPD lung tissue, suggesting its potential as a biomarker for emphysema progression [(21)].

Increased amounts of neutrophil elastase (NE), IL-8, and matrix metalloproteinase-9 (MMP-9) are correlated with a worsening of respiratory function in sputum samples from COPD patients. Prostaglandin D2, 12-oxo-eicosatetraenoic acid (12-Oxo-ETE), and 5-oxo-eicosatetraenoic acid (5-Oxo-ETE) are also shown to be higher in sputum during exacerbations. [(21)].

Sun et al. (10) conducted a retrospective observational study on 4,535 patients with acute AECOPD diagnosed between January 2016 and June 2021. According to their results, individuals with fibrinogen levels >4 g/L had higher incidence of deep vein thrombosis (DVT), pulmonary thromboembolism (PTE), pneumonia, emphysema, and atherosclerosis, as well as higher inflammatory responses. NPPV (non-invasive positive pressure ventilation) failure is also linked to higher fibrinogen levels, especially in individuals with emphysema, a history of pneumonia, long-term oxygen treatment, and increased CRP and leukocyte counts.

Based on the study, fibrinogen levels >3.55 g/L independently predict the severity of AECOPD in patients under NPPV management, suggesting that fibrinogen can be a reliable predictor of NPPV failure. [21].

A prospective study was conducted by Mohan et al. [22] to assess Fibrinogen as a feasible biomarker in identifying the severity of AECOPD using 105 participants. And the study concluded that plasma fibrinogen level was significantly higher in COPD groups compared to control group. Individuals with acute exacerbations of COPD (AECOPD) had greater plasma fibrinogen levels than individuals with stable COPD. Additionally, these levels showed a positive correlation with key functional indices and prognostic markers such as BODE, ADO and DOSE indices, and a negative correlation with lung function. Plasma fibrinogen levels were significantly elevated in COPD groups compared to a control group. The odds of predicting an acute COPD exacerbation, were notably high for patients with FEV1 of 50%, with corresponding area under the curve (AUC) values of 0.791 (sensitivity = 57.7%, specificity = 92.5%) and 0.825 (sensitivity = 90.4%, specificity = 62.79%). Because plasma fibrinogen relates to both the severity of the illness and the level of AECOPD, the study concluded that plasma fibrinogen could serve as a key biomarker in the management of disease and its exacerbations.

Crapo et al. [23] conducted the FOOTPRINTS clinical trial, a prospective longitudinal study spanning three years. They investigated the association between biomarkers of inflammation and lung tissue destruction and the severity and progression of COPD in ex-smokers with mild to severe COPD.

The study included ex-smokers classified by "Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 1–3", ex-smokers with COPD and alpha-1-antitrypsin deficiency (A1ATD), and a control group of ex-smokers without airflow limitation (EwAL). Data collected at study entry encompassed demographics, disease characteristics, comorbidities, COPD exacerbation history, symptoms, lung function, exercise capacity, soluble biomarkers, and computed tomography findings.

Baseline data analysis revealed descriptive statistical comparisons for soluble biomarkers in individual GOLD and A1ATD groups compared to the EwAL group. Biomarkers, including fibrinogen, were evaluated in various biological fluids up to 13 months, showing increased mean expression levels or concentrations correlating with disease severity across all GOLD groups (GOLD 1–3). Specifically, levels of white blood cells (WBC), fibrinogen, high-sensitivity C-reactive protein (hs-CRP), and plasma surfactant protein-D (SP-D) showed a linear increase with disease severity. Notably, in all GOLD groups, these biomarkers were numerically higher compared to the EwAL group.

A meta-analysis by Duvoix et al. [(9)] assessed the data relating fibrinogen levels to the severity, progression, and mortality of obstructive illness as well as its correlation with COPD comorbidities and anti-inflammatory treatment response using words such as exacerbation, mortality, FEV1, peripheral vascular disease, COPD, chronic bronchitis, and cardiovascular disease, they methodically searched PubMed for papers during a one-year period.

The study examined the cross-sectional and longitudinal associations between fibrinogen and COPD using cohorts from the general population. In one cohort of 8,955 randomly selected individuals from Copenhagen, they found an inverse correlation between baseline fibrinogen levels and % predicted FEV1. The yearly drop in FEV1 was higher in individuals with the highest tertile of fibrinogen than in those with the lowest tertile. Additionally, during the course of the six-year study, hospitalization rates for COPD exacerbations were greater in those with higher baseline fibrinogen, rates in the highest and lowest fibrinogen tertiles are 52 and 93 per 10,000 person-years, respectively.

Although plasma fibrinogen levels remained constant in patients in stable conditions, they rose during exacerbations, as would be predicted for an acute phase protein, and then fell over the course of the next four to six weeks. Small-scale studies indicated a more pronounced rise in fibrinogen levels during exacerbations linked with symptoms suggestive of an infectious cause, particularly in cases where a viral pathogen was identified.

The potential utility of fibrinogen in guiding the use of antimicrobial agents during exacerbation treatment was also noted, pending validation through larger studies that can replicate these findings and establish clinically relevant parameters for individualized use. Larger-scale investigations are needed to further elucidate fibrinogen's role in assessing recovery from COPD exacerbations.

A Retrospective cross-sectional study conducted by Kim et al. [25] among 140 individuals with COPD, and the study concluded that in Korean patients with COPD, plasma fibrinogen was level associated with CAT (copd assessment test) score and history of exacerbation. The COPD severity indexes positively correlated with plasma fibrinogen level. 48 (34.3%) of the 140 patients were found to be in the high-level fibrinogen category. The high-level group had a higher history of exacerbations than the low-level group. Lung functions such as FEV1, FVC, and 6MWT distance were considerably lowered in the high-level group.

Multivariate regression analysis in a high fibrinogen level was linked to a poor CAT score ($P<0.001$) and an exacerbation experience ($P=0.033$), according to a Korean research. severity indices including DOSE ($\rho=0.185$, $P<0.05$), BODE ($\rho=0.195$, $P<0.05$), and ADO ($\rho=0.175$, $P<0.05$) demonstrated a favorable relationship between the study's fibrinogen level and found that severe clinical characteristics and frequent exacerbations may be identified by high fibrinogen levels. [25]

Dahl et al. [26] measured plasma fibrinogen and forced expiratory volume in one second (FEV1) in a prospective epidemiological study involving patients enrolled in the Copenhagen City Heart Study. The study's goal was to determine whether elevated concentrations of the acute-phase reactant fibrinogen correlate with pulmonary function and the rate of hospitalization for COPD. 8,955 people from the Danish general population who had previously been hospitalized for COPD were prospectively examined.

In comparison to smokers with fibrinogen in the lower tertile (2.7 g/L), those with plasma fibrinogen in the upper and middle tertiles (3.3 and 2.7–3.3 g/L) had a 7% and 2% poorer percentage predicted FEV1. Comparably, nonsmokers had declines of 6% (4–7%) and 0% (1-2%), respectively. Hospitalization rates for COPD were 52 per 10,000 person-years for those in the lower tertile, whereas hospitalization rates for those with plasma fibrinogen levels in the upper and middle tertiles were 93 and 60 per 10,000 person-years, respectively. Individuals with fibrinogen levels in the upper and middle tertiles had 1.7 times greater relative chances of hospitalization for COPD than those in the lower tertile, even after adjusting for age, body mass index, sex, pack-years of smoking, and recent respiratory illnesses. According to the study's findings, higher levels of plasma fibrinogen were linked to lower FEV1 and a higher chance of COPD exacerbations. Moreover, a number of additional studies showed a connection between the development of COPD and increased levels of these inflammatory biomarkers.

Additional research has also shown a connection between the progression of COPD and increased levels of inflammatory biomarkers. The advancement of COPD has been associated with increased levels of CRP, fibrinogen, leukocyte count, IL-6, interleukin-8 (IL-8), TNF-α, and chitinase-3-like protein 1 (YKL-40). One important regulator of the inflammatory process is adiponectin. People with COPD have shown elevated blood levels and enhanced expression of its receptors in the lung parenchyma. [21,27]

Prospective research was carried out by Koutsokera et al. [11] to assess the alterations in clinical, functional, and biochemical indicators in a cohort of hospitalized patients with type-I ECOPD who are all identical to each other. The alterations that coincide with exacerbation recovery and are correlated with functional and clinical indicators, or biomarkers, were also covered in this study. Participants in the study who were over 50 years old and had smoked for at least 20 pack-years were those who showed these biomarkers. Following a 72-hour evaluation at the commencement of symptomatic deterioration, each patient was admitted to the hospital based on the GOLD criteria. Following hospitalization, patients were assessed on days 0, 3, 10, and 40. Clinical observations, medication usage, medical history, Charlson's Comorbidity Index Score (CCIS), and Mini Nutritional Assessment (MNA) were all documented at the time of admission. Patients were then asked how severe their dyspnea was when it returned to its pre-exacerbation state. The following blood tests were performed: C-reactive protein (CRP), plasma fibrinogen, interleukin-6 (IL-6), serum amyloid-A (SAA), and tumor necrosis factor-alpha (TNF-a). They observed that the mean duration of hospital stay was 6 days. Biomarkers such as CRP, IL-6, and SAA showed more rapid improvement in their study. By day 40, there had been a substantial decline in both fibrinogen and white blood cell counts. During the first day of the follow-up, they saw rather steady levels of fibrinogen. Almost a month after the first deterioration, there was a little drop.

MATERIALS AND METHODS

Study design : An Observational Study

Place of Study : KLES DR. PRABHAKAR. KORE HOSPITAL
M.R.C NEHRU NAGAR, BELAGAVI

Duration of study : 1 YEAR

Sample size :

Prevalence of COPD in India as per literature review was 7.4% and taking a precision of 5% allowable error the sample size was estimated to be 105.

Formula = $\mathbf{Z^2 \times (p) \times (q) / d^2}$

= $1.96 \times 1.96 \times 7.4 \times 92.6 / 5^2$

= $2632 / 25$

Total sample size = 105

Sampling method : Consecutive Sampling Method

Conflict of interest : Nil

Hazards of study : Nil

Inclusion Criteria:

- All Patients presenting with Acute Exacerbation of COPD to Respiratory Medicine OPD at KLEs Dr. Prabhakar Kore Hospital will be included.

Exclusion Criteria:

- Patients not willing to participate in the study
- Presence of other severe lung abnormalities (bronchiectasis, pulmonary TB and bronchial asthma)
- Presence of end stage chronic diseases (CKD, CHF, Malignancy) with less than 1year expected survival.
- Patients requiring intubation before admission.

Study methodology:

After the approval of the Institutional Ethics Committee the study was commenced. Cases at KLE'S Dr. Prabhakar Kore Charitable Hospital and Medical Research Center Belagavi were screened and those who fulfilled the inclusion and exclusion criteria were recruited for the study. Informed consent was taken from all the participants enrolled for the study by the principal investigator after explaining about the study. Patients presenting with AECOPD were recruited in the study.

The demographic details such as age, gender, body mass index (BMI) was recorded. Clinical history of COPD exacerbation, clinical examination of the patient was done as per routine protocol. The baseline Investigations, Pulmonary Function Tests, Chest X ray and 6 Minute Walk Test were done.

The 6MWT was conducted on the AECOPD patients on the day of discharge while in stable condition. The blood sample was collected to measure the Serum Fibrinogen levels to assess the severity and prognosis. Serum fibrinogen levels were assessed by turbid metric immunoassay according to the standard protocols. The normal assay range for serum fibrinogen is 180 – 360 mg/dl. The modified BORG Scale was used to assess the respiratory symptoms on the day of admission. The Modified Borg Scale is a subjective rating scale that is commonly used to measure a person's perceived exertion during physical activity. The scale consists of a range of numbers from 0 to 10, where 0 represents no exertion at all, and 10 represents the maximum exertion a person can tolerate. Participants are asked to rate their perceived level of exertion on the scale during or immediately after physical activity.

Table 1: Modified BORG Dyspnea Scale [28]

Score	Dyspnea
0	No dyspnea
1	Very slight
2	Slight
3	Moderate
4	Somewhat Severe
5	Severe
6	
7	Very Severe
8	
9	Very, very Severe
10	Maximal

Once the patients were stable, before discharge the 6MWT was also performed to study functional, therapeutic response, and prognosis in the care of patients with AECOPD. The principal investigator trained the staff to perform the test. The following steps were followed to perform the test [29]:

- The patient should rest for approximately 10 minutes before starting the test.

- The baseline heart rate and oxygen saturation were measured and continuously monitored to identify the lowest oxygen saturation.
- The patient's baseline dyspnea was then rated using the Borg scale.
- The lap counter and timer were set.
- The patient was explained in detail about how to proceed during the test.
- The patient was then positioned at the starting line and allowed to walk unassisted once the test begins.
- As each minute passes, the patient should be informed of the time left to complete the test and encouraged to continue.

Statistical analysis:

The data obtained was entered in excel sheet and tabulated. Statistical analysis was done using SPSS software version 26.0 which was used for computing and analysing the data. The categorical data was described using frequency and percentages. The continuous data was represented as mean and standard deviation. To test for significant association, Chi square test was applied for Categorical variables. All tests were two tailed. P values of less than 0.05 were considered significant at 95% confidence interval.

RESULTS

In the present study 105 eligible patients were enrolled.

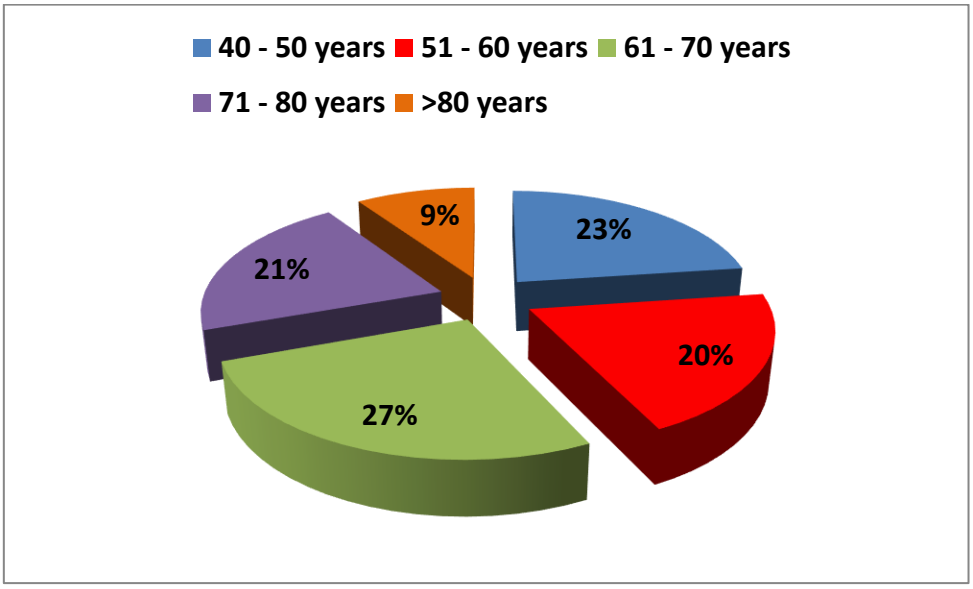
AGE

The mean age of the study group was 62.94 years with a standard deviation of 12.59 years. The youngest patient was 40 years old and the oldest was 90 years old. The age group between 61 to 70 years comprised 26.7% (n=28) followed by 22.9% (n=24) of 40 – 50 years patients. The least prevalence was in patient of 80 years and above at 9.5% (n=10).

Table 2: Frequency distribution of Age in the study participants (n=105)

AGE (YEARS)	Frequency (n)	Percent (%)
40 – 50	24	22.9
51 – 60	21	20
61 – 70	28	26.7
71 – 80	22	21
>81	10	9.5
Total	105	100

Fig 1: Graph depicting the age frequency distribution



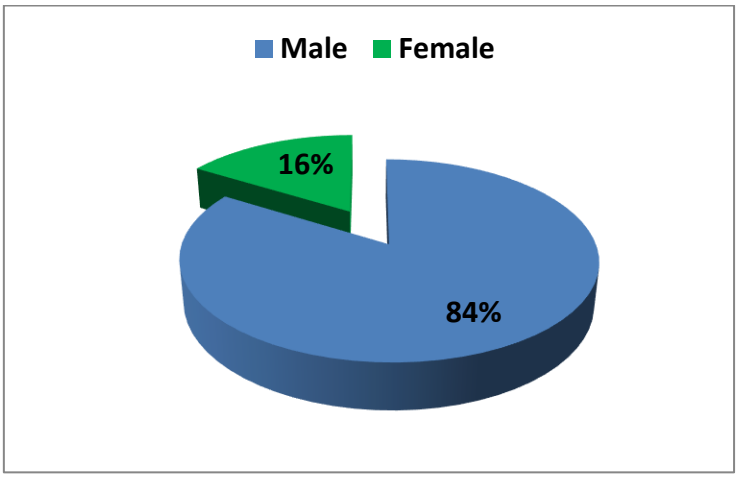
GENDER

The males outnumbered the females at 83.8% (n=88). Females were only 16.2% (n=17) in the present study group.

Table 3: Frequency distribution of Sex in the study participants (n=105)

SEX	Frequency (n)	Percent (%)
Male	88	83.8
Female	17	16.2
Total	105	100

Fig 2: Graph depicting the gender frequency distribution

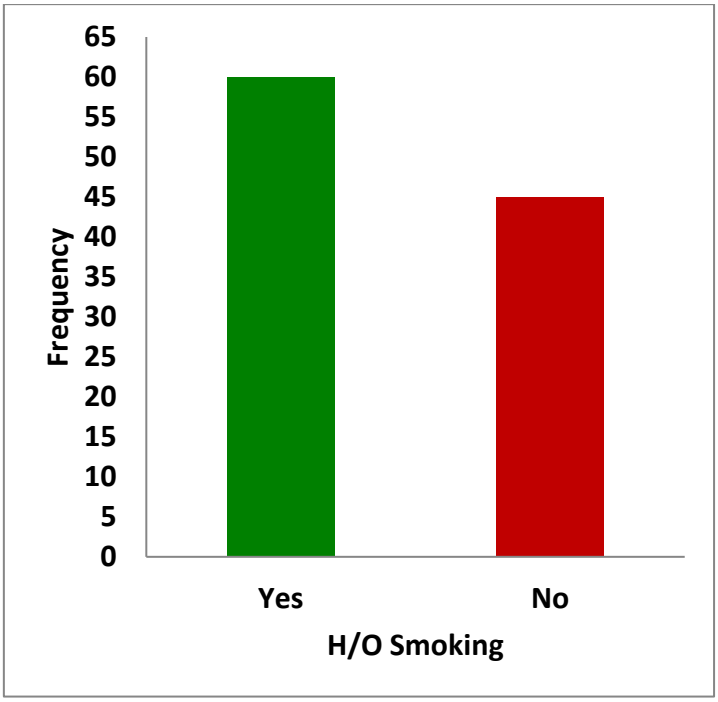


In more than half (n=60, 57.2%) of the study population the history of smoking habit was positive.

Table 4: Frequency distribution of Smoking in the study participants (n=105)

SMOKING	Frequency (n)	Percent (%)
Yes	60	57.2
No	45	42.9
Total	105	100

Fig 3: Graph depicting the H/O smoking frequency distribution



BASELINE CHARACTERISTICS

All patients were examined to establish the baseline statistics of the vitals. The range, mean and standard deviation of the variables are as shown in the table below.

Table 5: Baseline Characteristics of Study Patients

BASELINE CHARACTERISTICS	MINIMUM	MAXIMUM	MEAN	STD. DEVIATION
HEART RATE (PER MINUTE)	66.0	114.0	84.314	±10.699
RESPIRATORY RATE (PER MINUTE)	16.0	40.0	25.829	±6.276
RA SATURATION (%)	64.0	98.0	84.533	±9.248
PH	6.30	7.60	7.222	±0.229
INITIAL PaO2 (MM HG)	40.7	98.0	66.128	±16.213
PCO2 (MM HG)	18.0	94.2	56.904	±11.316
FEV1 (%)	30.0	87.0	56.581	±14.076
MODIFIED BORG SCALE	3.0	10.0	5.981	±2.2531

Fig 4: Graph depicting the Heart rate frequency distribution

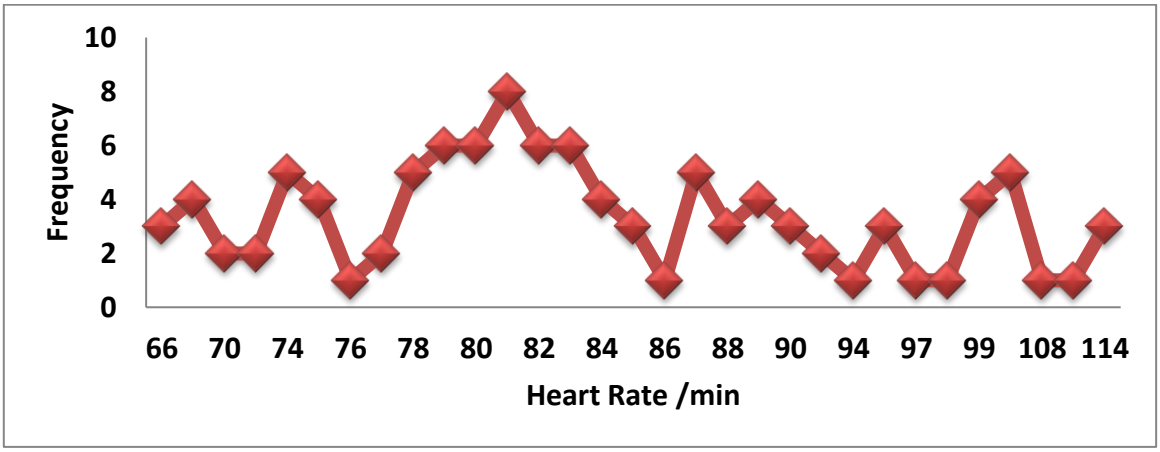


Fig 5: Graph depicting the Respiratory rate frequency distribution

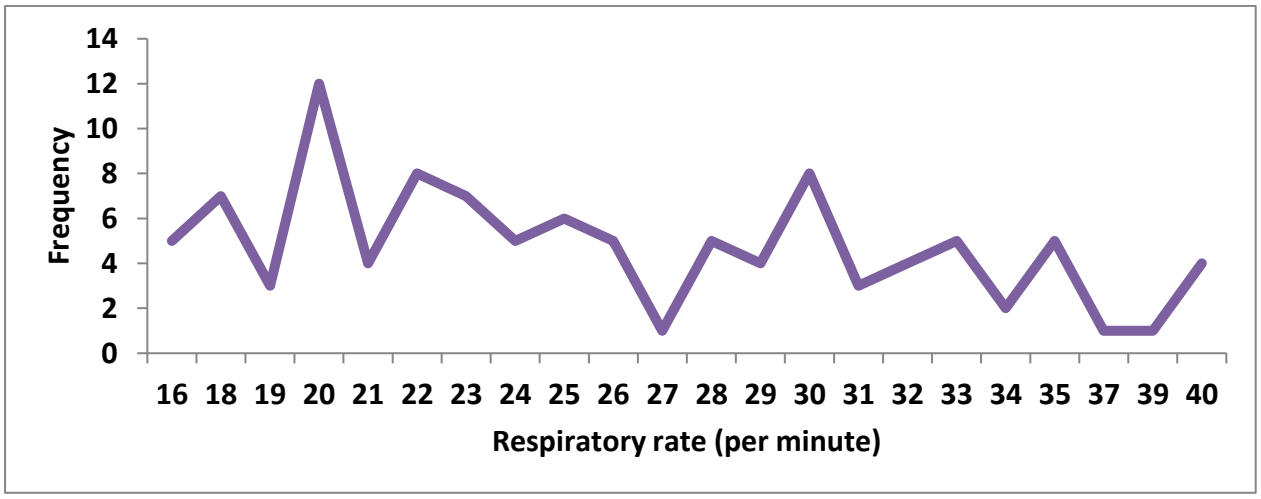


Fig 6: Graph depicting the Blood pressure frequency distribution

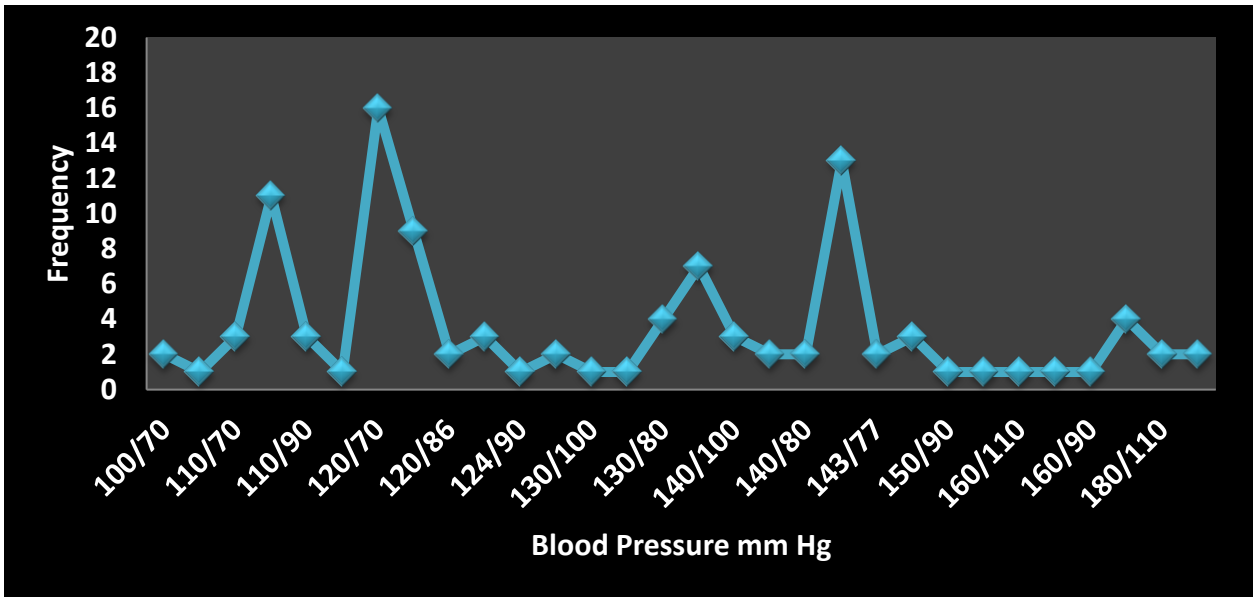


Fig 7: Graph depicting the RA saturation frequency distribution

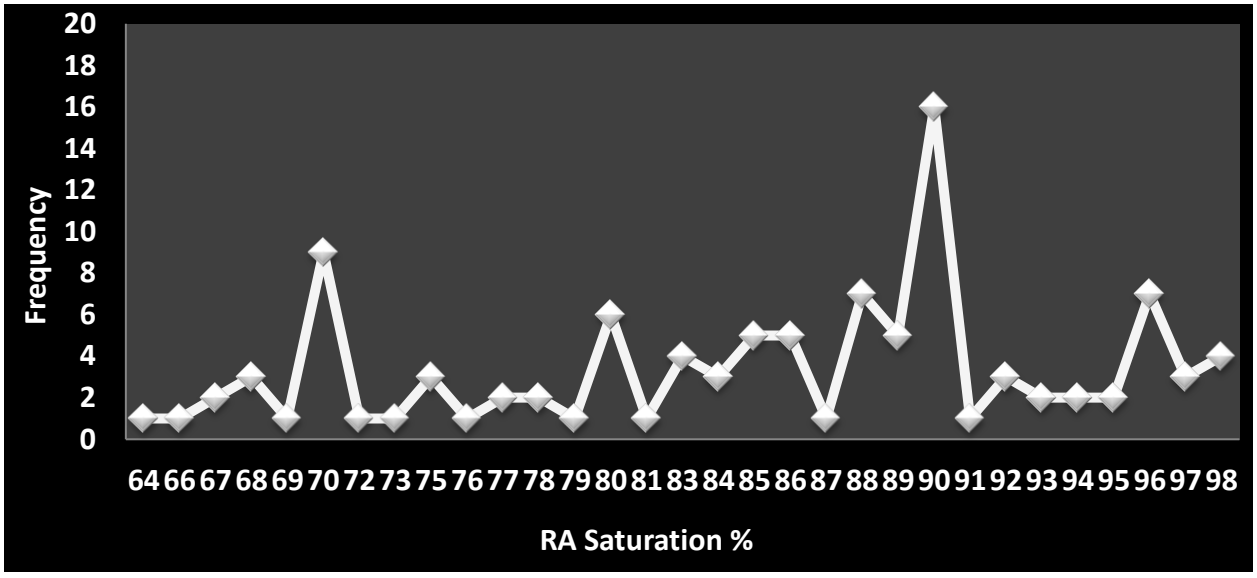


Fig 8: Graph depicting the arterial blood pH frequency distribution

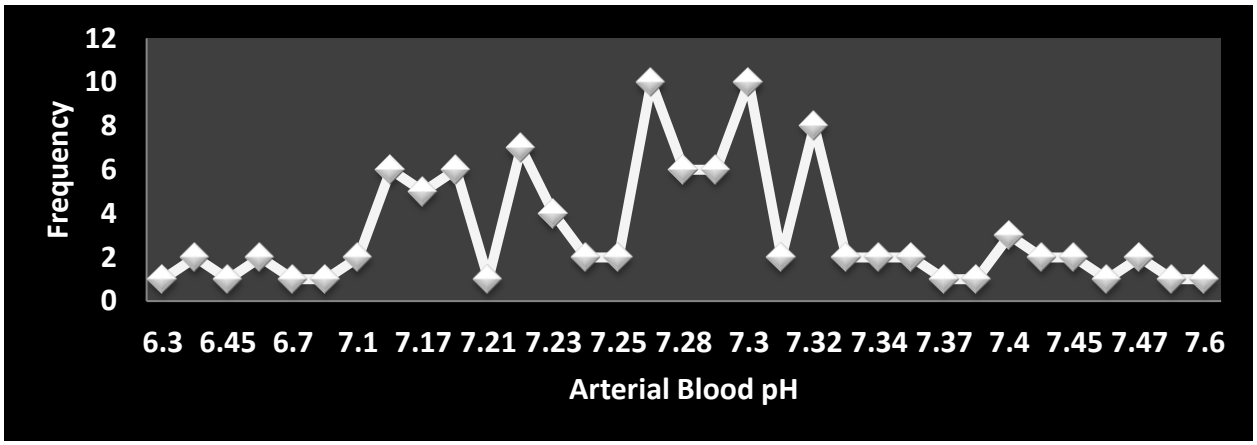


Fig 9: Graph depicting the PaO_2 frequency distribution

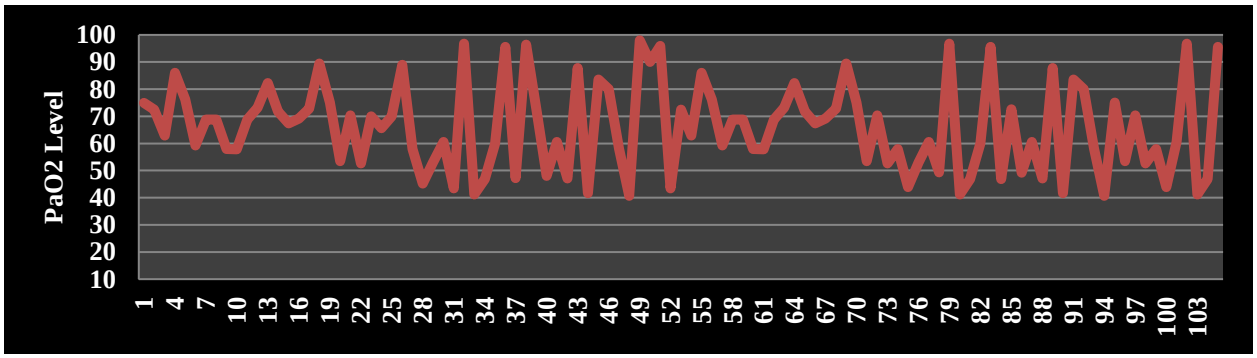


Fig 10: Graph depicting the $PaCO_2$ frequency distribution

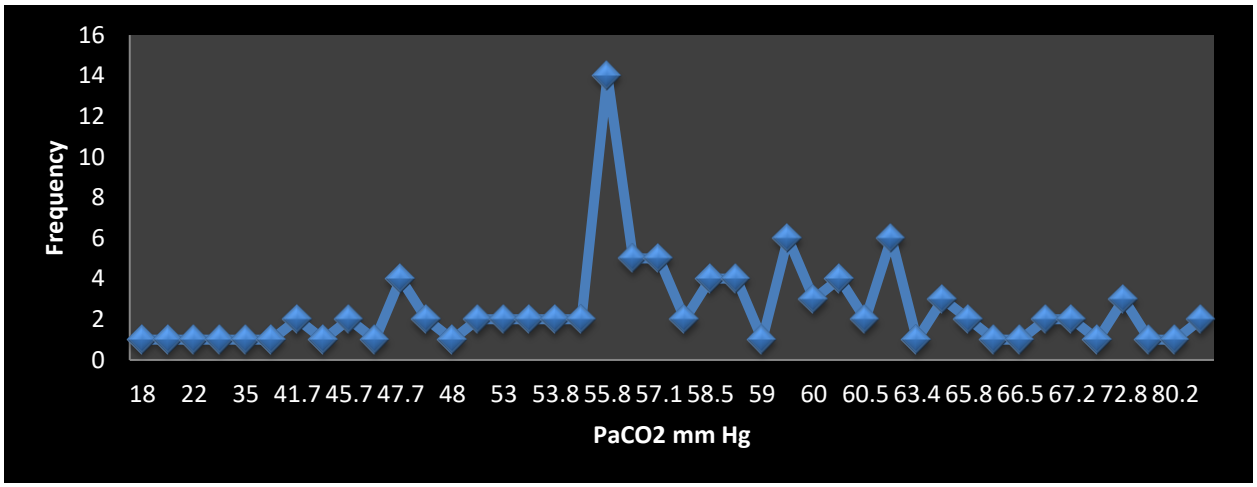


Fig 11: Graph depicting the FEV1 frequency distribution

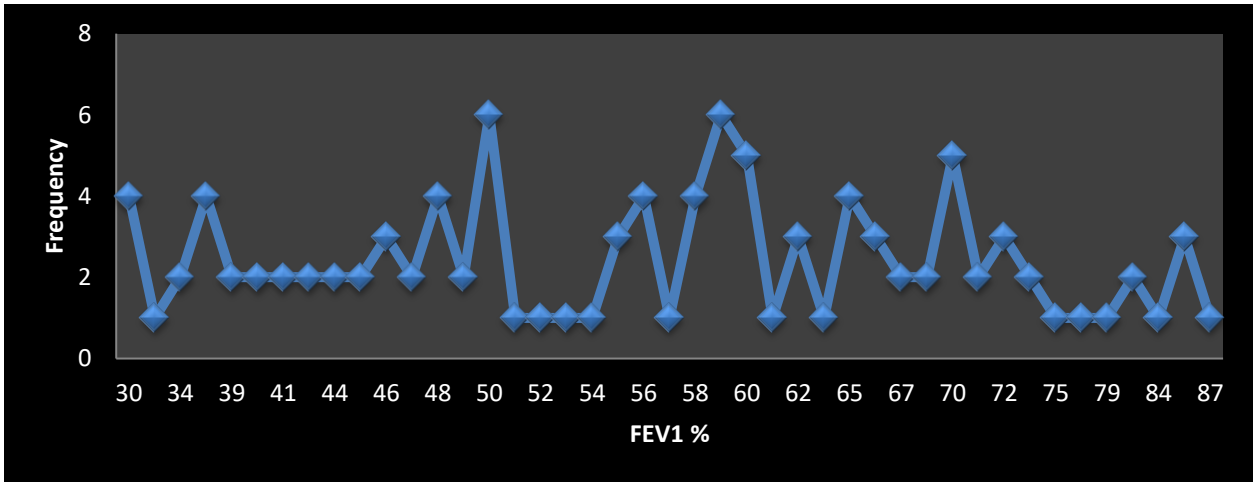


Fig 12: Graph depicting the Modified BORG Scale frequency distribution

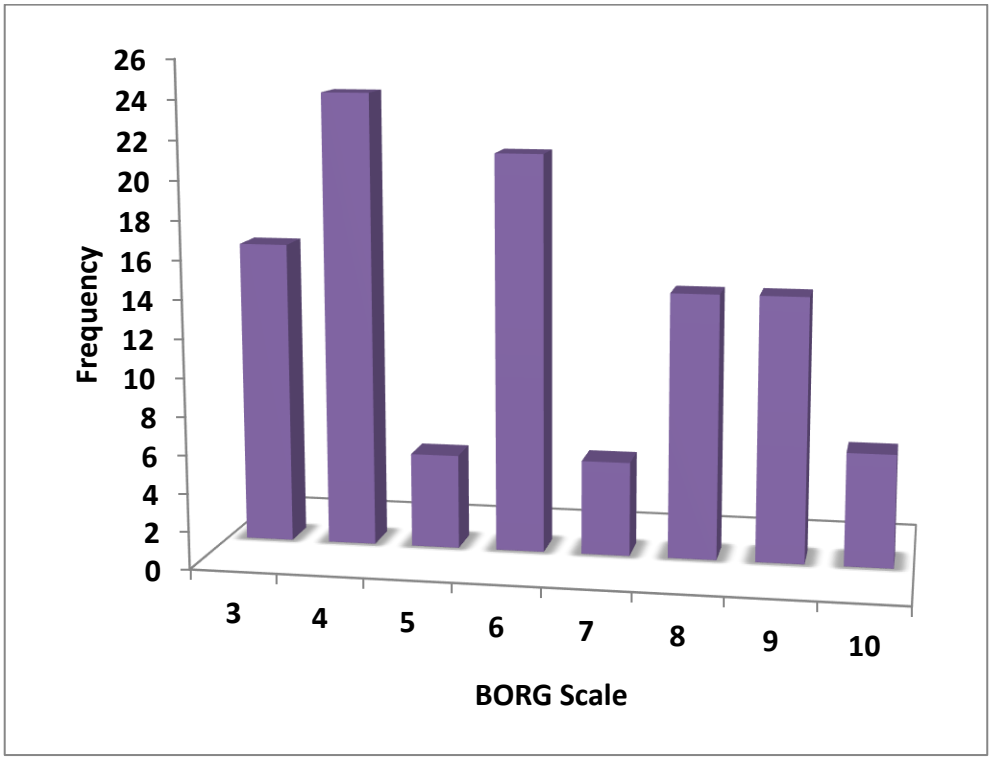


Table 6: Frequency distribution of Modified BORG Scale in the study participants (n=105)

MODIFIED BORG Scale	Frequency (n)	Percent (%)
Up to 5	45	42.9
6 – 10	60	57.1
Total	**105**	**100**

COMORBIDITIES

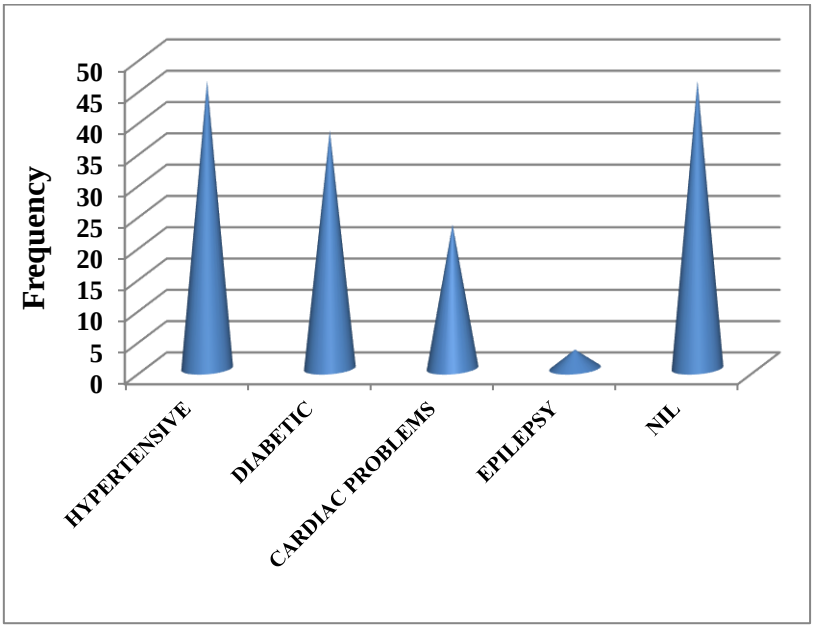
Among the patients enrolled for the study 59 (56.2%) had comorbidities. Out of these 59, 46 (43.81%) patients had hypertension, 38 (36.19%) had diabetes and 23 (21.9%) had cardiac problems such as IHD, CVA, PTCA and CABG. Diabetes and hypertension coexisted in 13 (12.4%) patients. 6 (5.7%) patients had only diabetes, 3 (2.9%) had S/P PTCA (2.9%), epilepsy in 2 (1.9%) patients, old CVA history in 1 (1.0%) patients and S/P pacemaker was seen in 2 (1.9%) patients. Patients with only hypertension were 14 (13.3%) and an equal number suffered with hypertension, diabetes and IHD along.

Table 7: Frequency distribution of comorbidities in the study participants (n=105)

COMORBIDITIES*	Frequency (n)	Percent (%)
HYPERTENSIVE	46	43.81
DIABETIC	38	36.19
CARDIAC PROBLEMS	23	21.9
EPILEPSY	3	2.86
NIL	46	43.81

*Multiple response

Fig 13: Graph depicting the comorbidities frequency distribution



INVESTIGATIONS

At the time of admission, the patients were investigated for the serum fibrinogen, serum PCT, HS-CRP. The observations recorded are shown in the below table.

Table 8: Serum biomarkers of Study Patients

SERUM BIOMARKERS	MINIMUM	MAXIMUM	MEAN	STD. DEVIATION
SERUM FIBRINOGEN (MG/DL)	195	672	408.25	±114.264
SERUM PCT	0.01	14.9	1.9566	±3.269
D DIMER	127	5000	673.11	±706.2127
HS-CRP	0.2	517	30.732	±90.18205
TOTAL COUNT	4.1	26.1	9.9482	±4.48896
NEUTROPHILS	24	98	73.029	±18.3997
LYMPHOCYTES	2	68	19.124	±18.5901

SERUM FIBRINOGEN

The mean serum fibrinogen in the study group was 408.248±114.264 mg/dl. The minimum reading was 195 mg/dl and maximum was 672 mg/dl.

Fig 14: Graph depicting the serum Fibrinogen frequency distribution

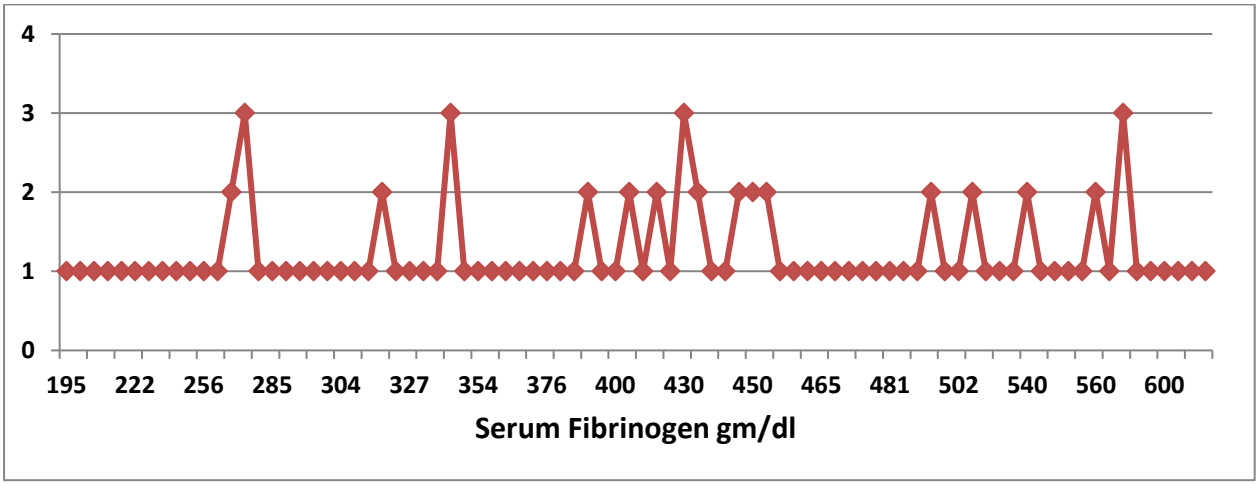


Table 9: Frequency distribution of Serum Fibrinogen in the study participants (n=105)

SERUM FIBRINOGEN	Frequency (n)	Percent (%)
Normal (180 – 360 mg/dl	38	36.2
Increased (>360 mg/dl)	67	63.8
Total	**105**	**100**

The research population's mean blood fibrinogen, measured at 360 g/dl, was shown to be statistically significant ($p<0.05$) at a 95% confidence interval, according to one sample t test analysis.

Table 10: One sample t test analysis for Serum fibrinogen

Test Value = 360 mg/dl					
t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
				Lower	Upper
4.327	104	**0.000**	48.2476	26.135	70.361

SERUM PROCALCITONIN (PCT)

The mean serum PCT in the study group was 1.9566 ± 3.269 ng/ml. The minimum reading was 0.01 ng/ml and maximum was 14.9 ng/ml.

Fig 15: Graph depicting the serum PCT frequency distribution

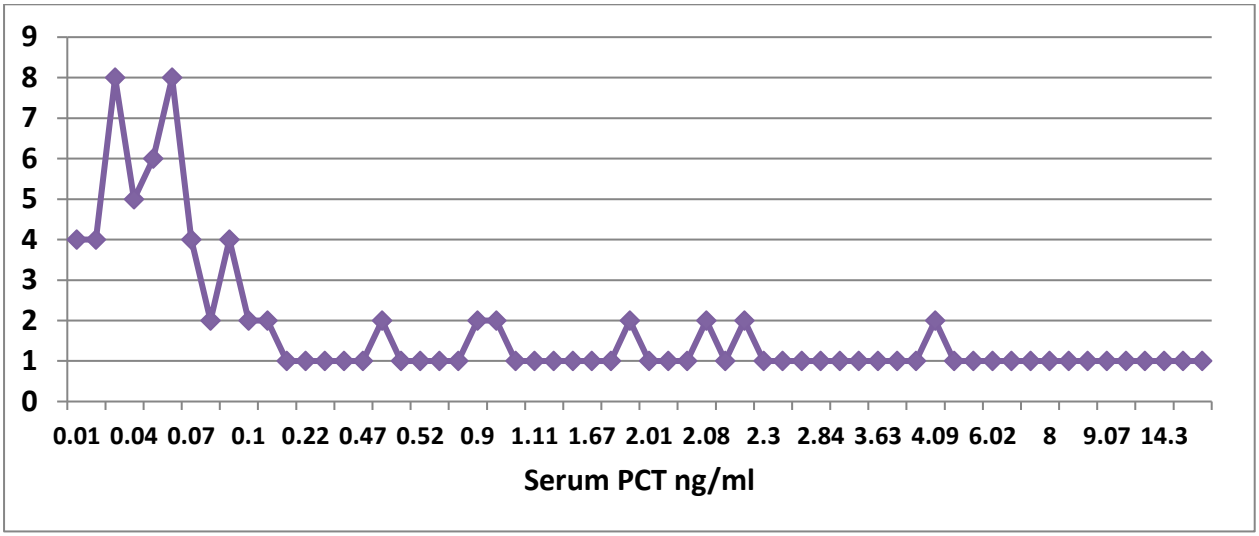


Table 11: Frequency distribution of Serum PCT in the study participants (n=105)

Serum PCT	Frequency (n)	Percent (%)
Normal (0.5 ng/ml)	57	54.3
Increased (>0.5 ng/ml)	48	45.7
Total	**105**	**100.0**

With a test result of 0.5 ng/ml, the mean serum PCT of the study population was statistically significant ($p<0.05$) at 95% confidence interval, according to one sample t test analysis.

Table 12: One sample t test analysis for Serum PCT

Test Value = 0.5 ng/ml					
t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
				Lower	Upper
4.565	104	**0.000**	1.45657	0.8238	2.0893

HIGH SENSITIVE – C- REACTIVE PROTEIN (HS-CRP)

The mean serum HS-CRP in the study group was 30.7315 ± 90.182 mg/L. The minimum reading was 0.2 mg/L and maximum was 517 mg/L.

Fig 16: Graph depicting the HS CRP frequency distribution

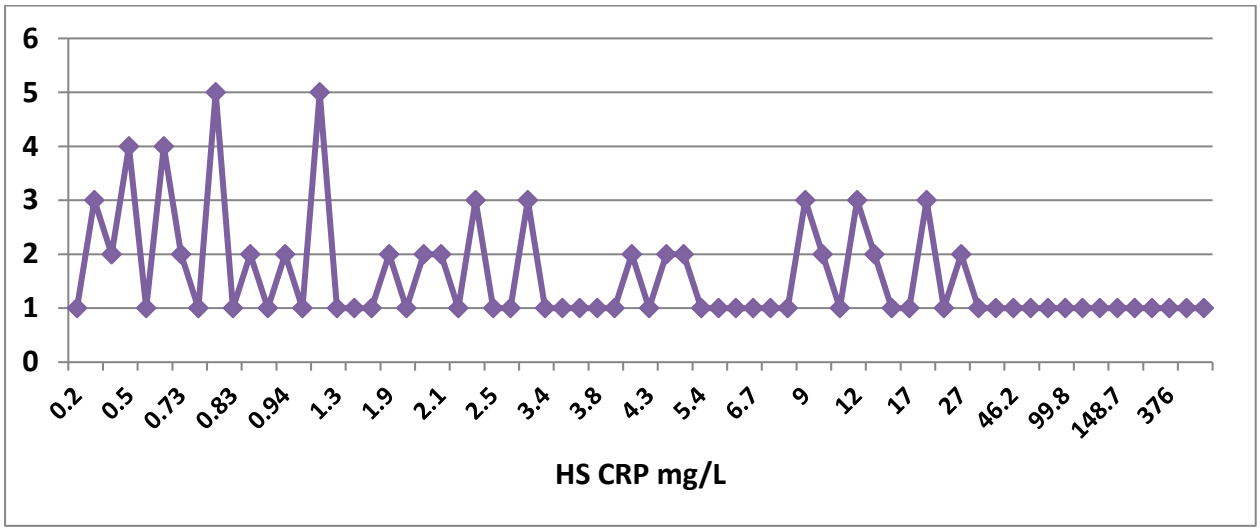


Table 13: Frequency distribution of HS-CRP in the study participants (n=105)

HS-CRP	Frequency (n)	Percent (%)
1.0	66	62.9
2.0	39	37.1
Total	**105**	**100.0**

With a test value of 5 mg/L, the mean HS-CRP of the study population was shown to be statistically significant ($p<0.05$) at a 95% confidence interval, according to one sample t test analysis.

Table 14: One sample t test analysis for HS –CRP

Test Value = 5 mg/L					
t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
				Lower	Upper
2.924	104	**0.004**	25.73152	8.2791	43.1840

MANAGEMENT AND OUTCOME

Patients were managed according to GOLD 2023 guidelines like:

- Administration of supplemental oxygen therapy, pulse oximetry measurements and obtaining serial ABG analysis.
- Bronchodilators:
    - Increasing the dose and frequency of SABA as and when required
    - Combining SABA and anticholinergics
- Administration of oral corticosteroids
- Administration of antibiotics
- At all times
    - Fluid balance
    - Subcutaneous heparin or LMWH for thromboembolism prophylaxis

And outcome was measured in terms of non-invasive ventilation, invasive ventilation, hospital stay, 6-minute walk test (6MWT) and mortality

NON – INVASIVE VENTILATION (NIV)

Majority of the of patients in the study required NIV support that is, 58 (55.2%). The remaining 47 (44.8%) did not required NIV support.

Table 15: Frequency distribution of NIV in the study participants (n=105)

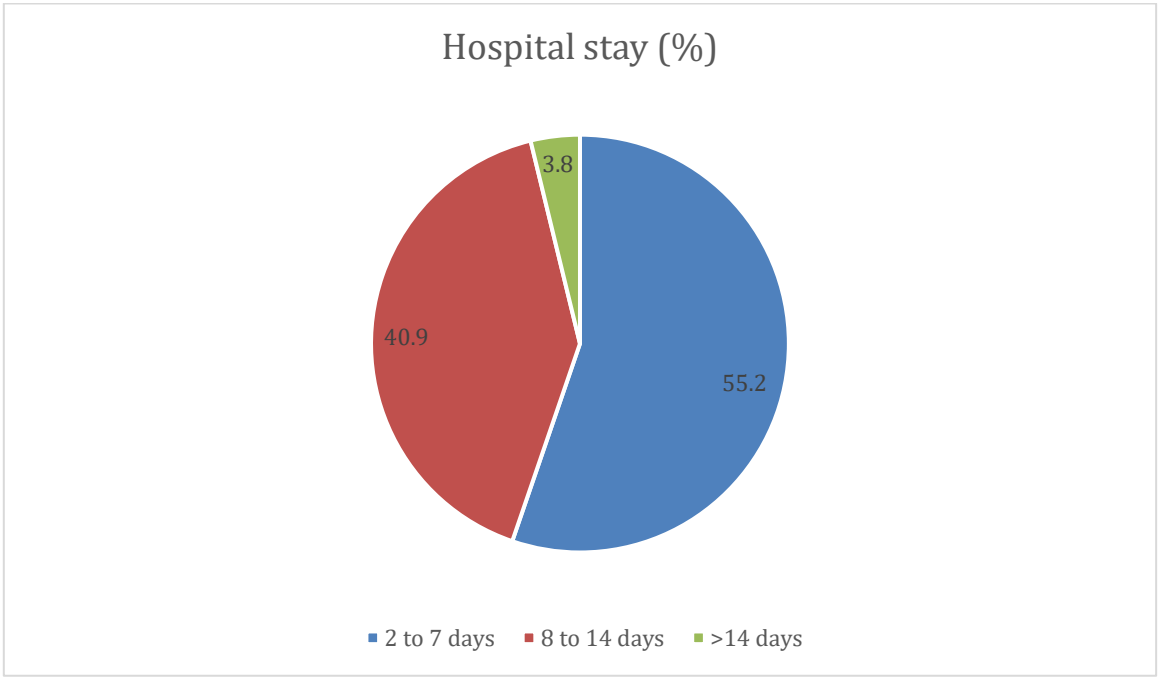
NIV	Frequency (n)	Percent (%)
Yes	58	55.2
No	47	44.8
Total	**105**	**100.0**

The minimum days of hospital stay recorded in our study was 2 days which was seen in 3 (2.9%) patients. The maximum length of stay was 17 days seen in one (1.0%) patient. Majority (n=15, 14.3%) of patients were admitted for 5 days. The mean duration was 7.33 ± 3.32 days in the study group.

Table 16: Frequency distribution of Hospital Stay in the study participants (n=105)

Hospital stays	Frequency	Percentage
2 to 7 days	58	55.2
8 to 14 days	43	40.9
>14 days	4	3.8
Total	**105**	**100.0**

Fig 17: Graph depicting the hospital stay frequency distribution



Before discharge when patient is stable patient was exposed to 6-minute walk test. In the study subjects the mean of the 6MWT was 479.476 ±144.91 meters, with a range of 200 to 700 meters. Almost 68.6% (n=72) had normal 6MWT covering a distance of 400 meters or more. The remaining 31.4% (n=33) had decreased distance during 6MWT.

Table 17: Outcome of Study Patients at discharge

VARIABLES AT DISCHARGE	MINIMUM	MAXIMUM	MEAN	STD. DEVIATION
6 MINUTE WALK TEST (MTS)	200.0	700.0	479.476	±144.9103

Fig 18: Graph depicting the 6MWT frequency distribution

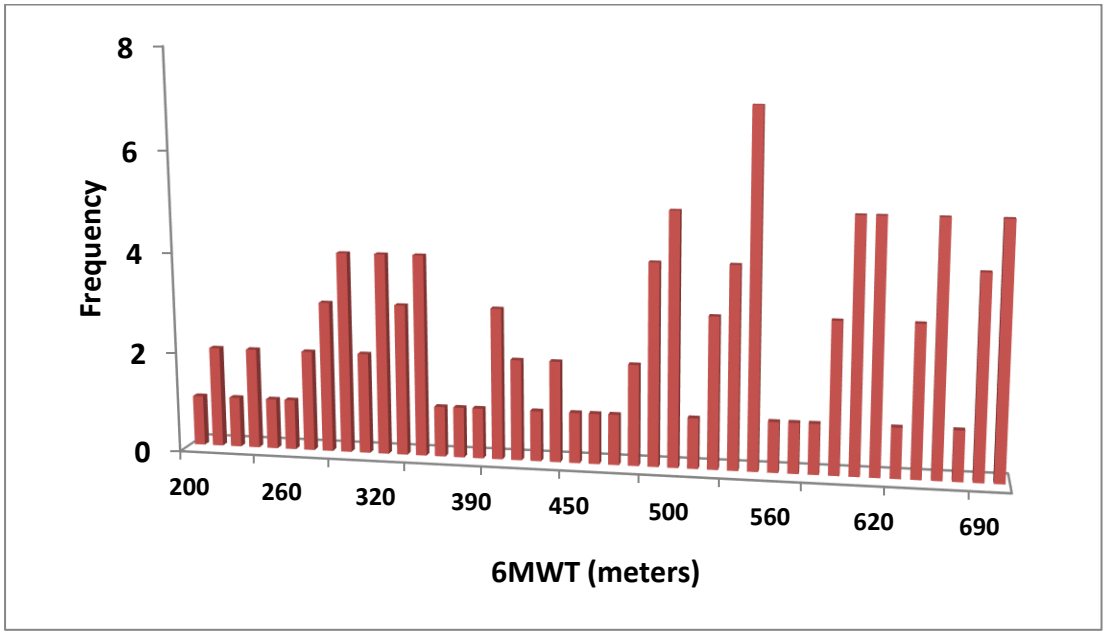


Table 18: Frequency distribution of 6 Minute Walk Test in the study participants (n=105)

6 MINUTE WALK TEST	Frequency (n)	Percent (%)
Decreased (<400 meters)	33	31.4
Normal (≥400 meters)	72	68.6
Total	**105**	**100.0**

The serum fibrinogen and the 6MWT were correlated using the Pearson's chi-square. The correlation between the two variables was statistically significant (Chi-square = 15.304, p = 0.000). Additionally, the 95% confidence interval showed that the differences in the variable means were statistically significant ($p<0.05$).

The association between the serum fibrinogen and the different variable was evaluated using the Pearson's correlation. The age, gender and BORG scale was not significantly correlated with serum fibrinogen increase in the study group. The other variables had more than 20% empty cells in more than 5 cells in the contingency table thus making the chi-square value invalid. The variables that were significantly correlated with the serum fibrinogen were NIV and the 6MWT.

Table 19: Correlation between the Serum Fibrinogen and other variables

Variables		Serum Fibrinogen		Total	Chi-square	p-value
		Normal (<360mg/dl)	Abnormal (>360 mg/dl)			
AGE	40 – 50 years	3 (12.5%)	21 (87.5%)	24		
	51 – 60 years	7 (33.3%)	14 (66.7%)	21		
	61 – 70 years	14 (50.0%)	14 (50.0%)	28	9.257	0.055
	71 – 80 years	9 (40.9%)	13 (59.1%)	22		
	>80 years	5 (50.0%)	5 (50.0%))	10		
SEX	Male	29 (33.0%)	59 (67.0%)	88		
	Female	9 (52.9%)	8 (47.1%)	17	2.465	0.116
SMOKING	Yes	22 (36.7%)	38 (63.3%)	60		
	No	16 (35.6%)	29 (64.4%)	45	0.014	0.907
HEART RATE (PER MIN)	60 – 70	1 (11.1%)	8 (88.9%)	9		
	71 – 80	14 (45.2%)	17 (54.8%)	31		
	81 – 90	15 (34.9%)	28 (65.1%)	43	3.601	0.463
	91 – 100	6 (35.3%)	11 (64.7%)	17		
	>100	2 (40.0%)	3 (60.0%)	5		
RESPIRA-TORY RATE (PER MIN)	<20	4 (17.4%)	19 (82.6%)	23		
	21 – 30	21 (39.6%)	32 (60.4%)	53	4.727	0.094
	31 – 40	13 (44.8%)	16 (55.2%)	29		

BLOOD PRESSURE (MM HG)	Normal Increased	18 (41.9%) 20 (32.3%)	25 (58.1%) 42 (67.7%)	43 62	1.014	0.314
RA SATURATION (%)	<80 81 – 90 91 – 100	8 (34.8%) 12 (28.6%) 18 (45.0%)	15 (65.2%) 30 (71.4%) 22 (55.0%)	40 42 40	2.420	0.298
PH	Normal Increased	29 (32.6%) 9 (56.3%)	60 (67.4%) 7 (43.8%)	89 16	3.289	0.07
PaO2	40 – 80 81 – 90 91 – 100	27 (%) 8 (%) 3 (%)	57 (%) 4 (%) 6 (%)	84 12 9	5.454	0.065
PaCO2	<30 31 – 44 45 – 65 >65	4 (80.0%) -- 28 (35.0%) 6 (37.5%)	1 (20.0%) 4 (100%) 52 (65.0%) 10 (62.5%)	5 4 80 16	6.485	0.09
FEV1	≤80 >80	31 (40.8%) 7 (24.1%)	45 (59.2%) 22 (75.9%)	76 29	2.520	0.112
S. PCT	Normal Increased	23 (40.4%) 15 (31.3%)	34 (59.6%) 33 (68.8%)	57 48	0.935	0.334
HS-CRP	Normal Increased	24 (36.4%) 14 (35.9%)	42 (63.6%) 25 (64.1%)	66 39	0.002	0.962
NIV	Yes No	15 (25.9%) 23 (48.9%)	43 (74.1%) 24 (51.1%)	58 47	5.986	**0.014**
6MWT	Decreased Normal	3 (9.1%) 35 (48.6%)	30 (90.9%) 37 (51.4%)	33 72	15.304	**0.000**

MOD BORG SCALE	3	2 (12.5%)	14 (87.5%)	16		
	4	9 (37.5%)	15 (62.5%)	24		
	5	3 (60.0%)	2 (40%)	5		
	6	8 (38.1%)	13 (61.9%)	21	11.573	0.115
	7	--	5 (100%)	5		
	8	5 (35.7%)	9 (64.3%)	14		
	9	7 (50%)	7 (50%)	14		
	10	4 (66.7%)	2 (33.3%)	6		
Hospital stays	2-7 days	26	32	58	4.186	0.123
	8-14 days	11	32	43		
	>14 days	1	3	4		

Table 20: Association between Fibrinogen levels and FEV1 values among the study participants.

Variable	**Fibrinogen**			**odds ratio (95% confidence interval)**	**Upper limit**	**Lower limit**	x^2	**p value**
	Normal (n)	**Abnormal (n)**	**Total (n)**					
FEV 1								
Mild	2	5	7					
Moderate	30	34	64	3.83	1.41	10.39	8.522*	0.014*
Severe	6	28	34					

* Fisher-exact test is applied when cell value is less than 5.

In the present study, statistically significant association has been found between fibrinogen levels and FEV1 values, with p value of 0.01.

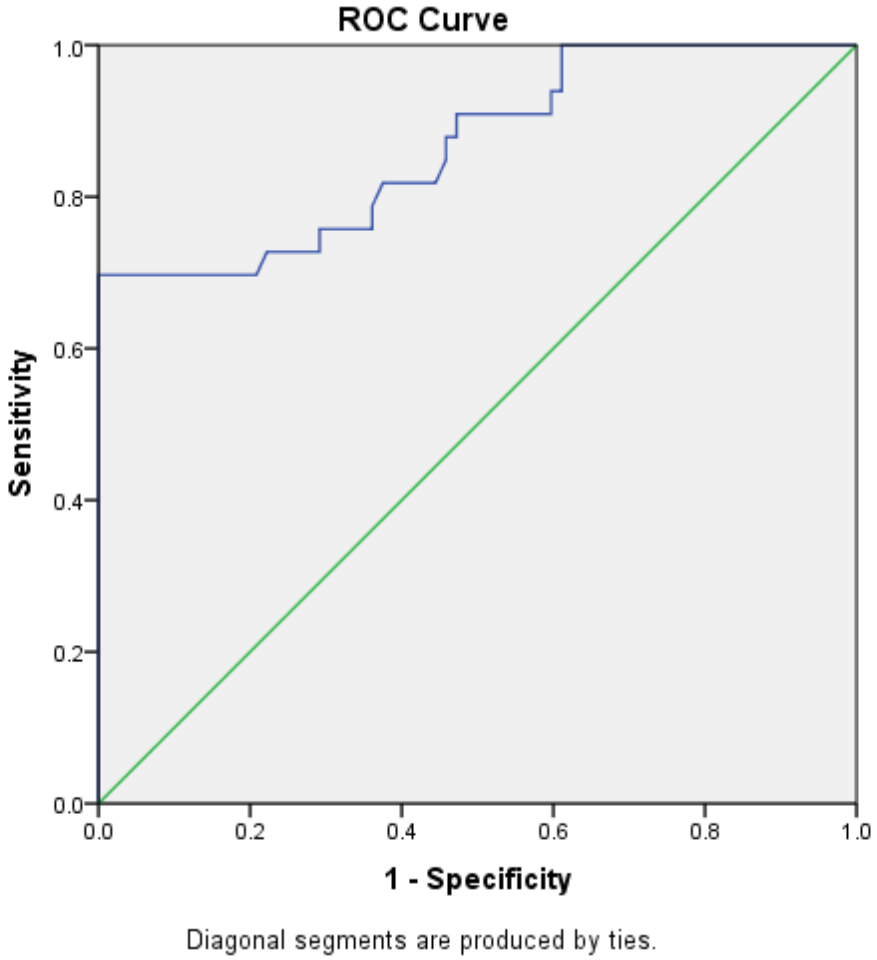
Table 21: Association between Serum fibrinogen and use of invasive mechanical ventilation and between serum fibrinogen and mortality.

Variable	Fibrinogen			Chi-square	p value
	Normal (≤360 mg/dl)	Abnormal (>360 mg/dl)	Total		
Invasive mechanical ventilation					
Yes	10	12	22	1.03	0.31
No	28	55	83		
Mortality					
Yes	5	14	19	0.98	0.32
No	33	53	86		

ROC Curve

Case Processing Summary

6MWT cat	Valid N (listwise)
Positive	33
Negative	72



Diagonal segments are produced by ties.

Area Under the Curve

Test Result Variable(s): SERUM FIBRINOGEN

Area
.866

Using the ROC curve the cut off value for serum fibrinogen was determined using the 6MWT. The area under the curve was 0.866, that is the serum fibrinogen is a good diagnostic tool to estimate the 6MWT outcome. At serum fibrinogen 360 mg/dl, sensitivity was 90.9% but false positive was 51.4%. the serum fibrinogen value of 433.5 mg/dl had sensitivity of 75.8% and false positivity 29.2%. As the fibrinogen value increased the false positivity decreased at the cost of sensitivity.

Regression Analysis of variables serum fibrinogen (independent variable) and 6MWT (dependent variable)

The model summary:

Model	**R**	**R^2**	**Adjusted R Square**	**Std. Error of the Estimate**	**Sig.**
1	0.554[a]	0.307	0.301	121.1882	0.000

The linear regression model of 6MWT and serum fibrinogen at F(1,103) = 45.7, p= 0.000.

The linear equation derived is:

Y = 766.499 + (-0.554) X [Y= c (intercept)+ bX]

With t= 17.391 for constant and t = (-6.76) for serum fibrinogen. This is statistically significant ($p<0.05$).

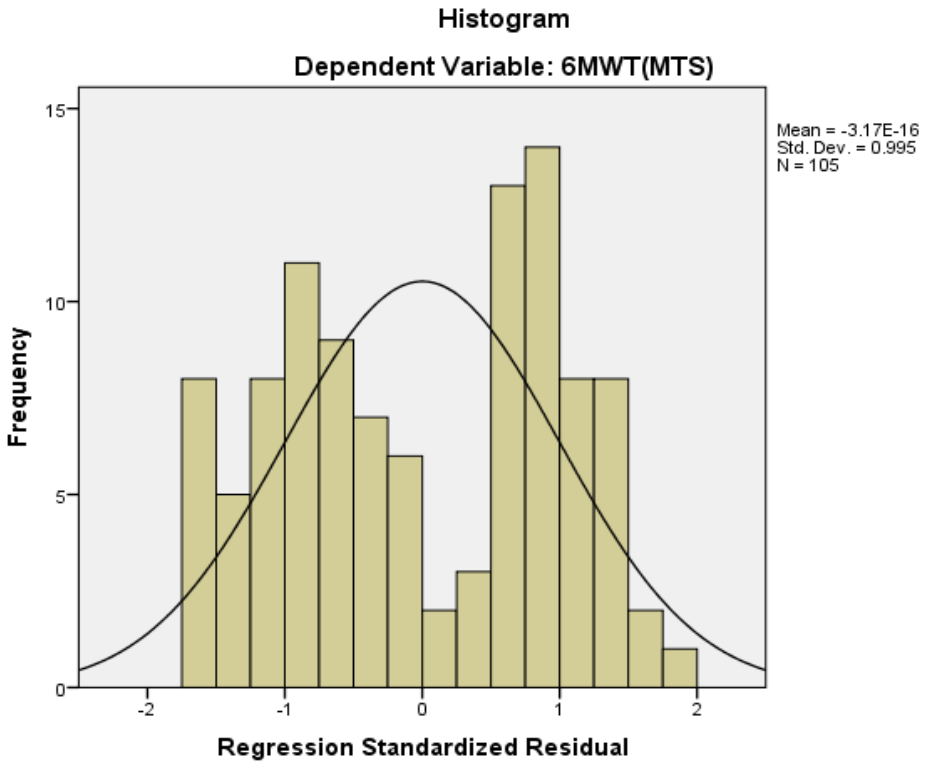
Thus, showing an inverse relation between the two variables.

Coefficients[a]

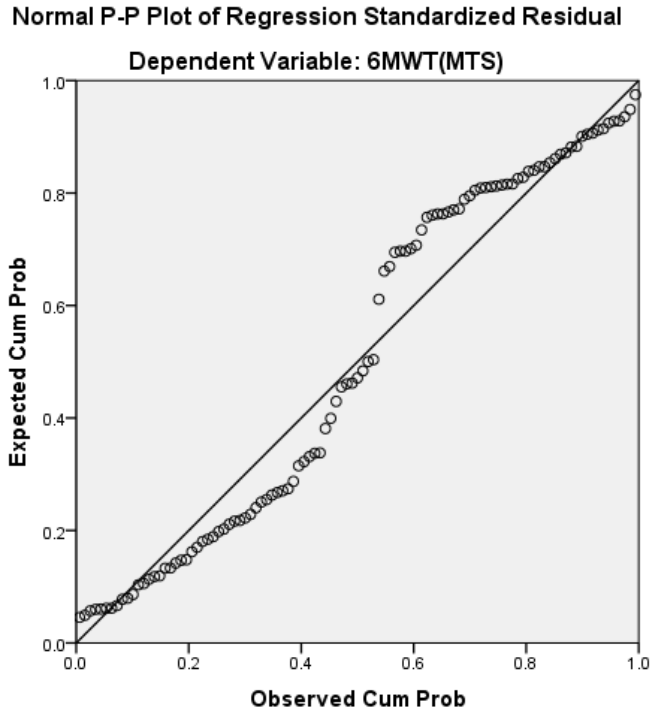
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	766.499	44.074		17.391	.000
	Serum Fibrinogen	-.703	.104	-.554	-6.760	.000

Coefficients[a]

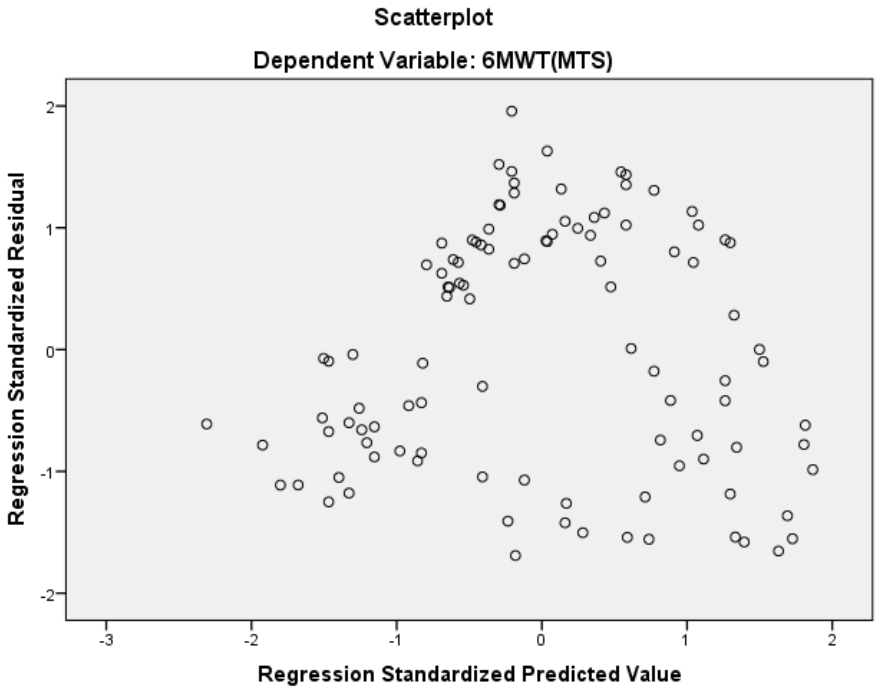
Model		95.0% Confidence Interval for B	
		Lower Bound	Upper Bound
1	(Constant)	679.088	853.910
	SERUM FIBRINOGEN	-.909	-.497



This is a histogram showing normal frequency distribution of dependent variable (6MWT) and independent variable (serum fibrinogen).



This is a P-P plot showing inverse relationship between dependent (6MWT) and independent variable (serum fibrinogen)



This is a scatter plot showing inverse relationship between dependent (6MWT) and independent variable (serum fibrinogen)

Regression Analysis of variables serum fibrinogen (independent variable) and BORG Scale (dependent variable)

The model summary:

Model	R	R^2	Adjusted R Square	Std. Error of the Estimate	Sig.
1	0.262[a]	0.069	0.060	2.1847	0.007

The linear regression model of BORG Scale and serum fibrinogen at F(1,103) = 7.614, p= 0.007.

Model Summary[b]

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics		
					R Square Change	F Change	df1
1	.262[a]	.069	.060	2.1847	.069	7.614	1

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	8.093	.795		10.186	0.000
	Serum Fibrinogen	-.005	.002	-.262	-2.759	0.007

Coefficients[a]

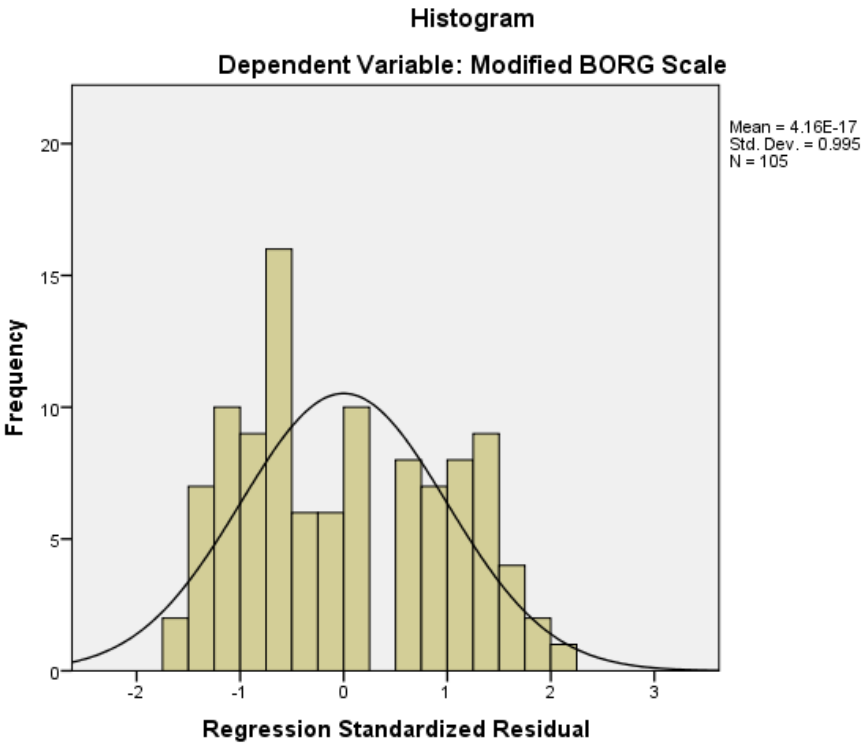
Model		95.0% Confidence Interval for B	
		Lower Bound	Upper Bound
1	(Constant)	6.517	9.669
	SERUM FIBRINOGEN	-.009	-.001

The linear equation derived is:

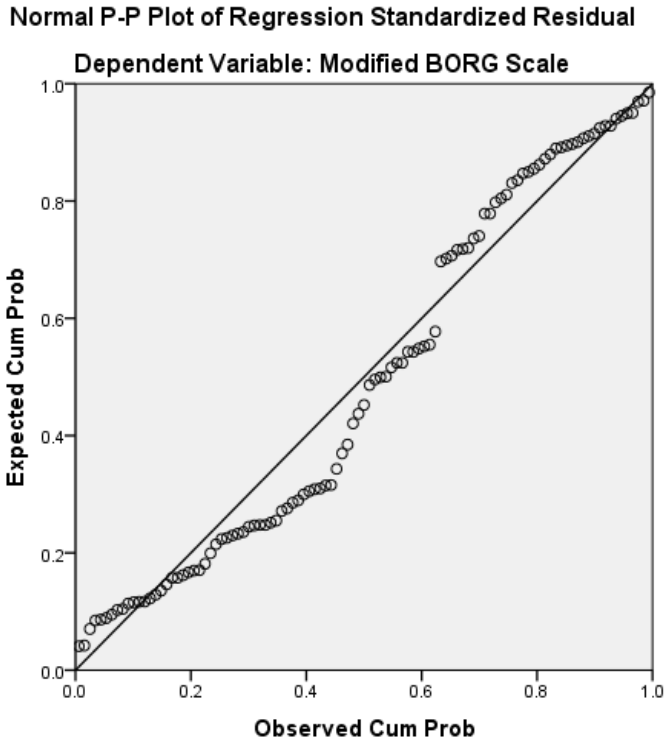
Y = 8.093 + (-0.262) X [Y= c (intercept)+ bX]

With t= 10.186 for constant and t = (-2.759) for serum fibrinogen. This is statistically significant ($p<0.05$).

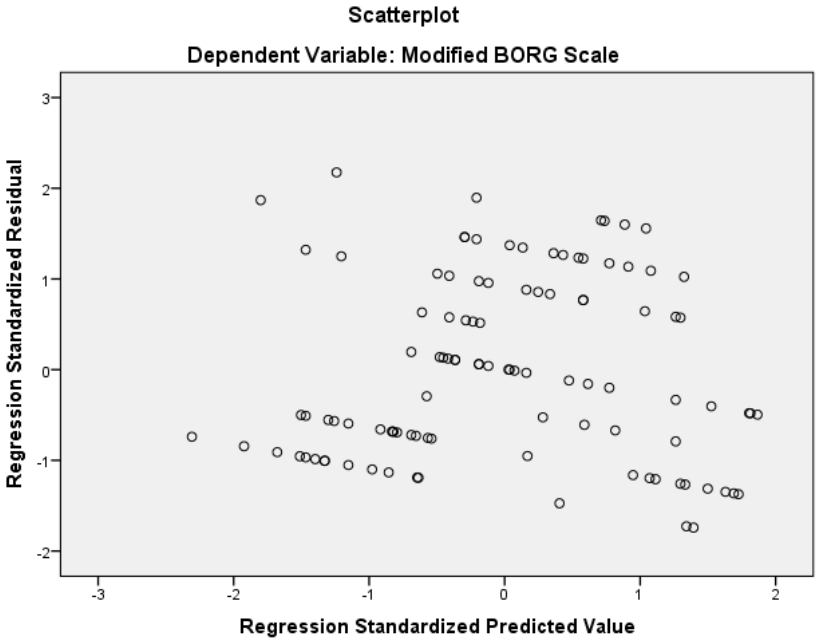
Thus, showing an inverse relation between the two variables.



This is a histogram showing normal frequency distribution of dependent (Modified BORG scale) and independent variable (serum fibrinogen)



This is a P-P plot showing inverse relationship between dependent (Modified BORG scale) and independent variable (serum fibrinogen)



This is a scatter plot showing inverse relationship between dependent (Modified BORG scale) and independent variable (serum fibrinogen)

DISCUSSION

The common lung illness known as chronic obstructive pulmonary disease (COPD) is marked by limited airflow and respiratory problems, which can cause tiredness, wheezing, coughing, and dyspnea. It is the third most common cause of death worldwide, accounting for 3.23 million fatalities in 2019.The two main causes of COPD are smoking and air pollution; in low- and middle-income countries, tobacco use alone accounts for 30–40% of cases. People with COPD are more vulnerable to lung infections like pneumonia, as well as heart problems, depression, anxiety, and lung cancer.

Symptoms of COPD typically emerge in mid-life and worsen over time, making daily activities progressively challenging due to breathlessness. This can lead to substantial economic burden due to reduced productivity at work and home, alongside healthcare costs.

One of the extensively studied inflammatory markers in COPD is fibrinogen, which plays a critical role in inflammation, fibrosis development, and tissue damage. Fibrinogen synthesis rises in response to inflammation, a characteristic feature of COPD, and is a prominent acute-phase reactant. The US Food and Drug Administration has approved plasma fibrinogen as a biomarker for determining the severity of COPD (FDA) [30]

The mean age of the COPD patients in study group was 62.94±12.59 which is similar to Mohan et al. [22] and Singh et al. study [31]. COPD was more common in the older patients which is comparable with the Mohan et al. study [22] (The mean age of patients with stable COPD and AECOPD was 60.7 ± 9.87 and 63.7 ± 9.28 years, respectively, whereas the mean age of controls was 59.5 ± 13.1).

COPD was more common in males than in females as seen in the Mohan et al. study [22] (95.2%) and in Singh et al. study [31]. In a study done by Valvi et al. more females suffered with COPD contradictory to our findings [32]

Smoking itself may cause systemic inflammation, resulting in increased total leukocyte count, but in COPD patients the degree of systemic inflammation is greater. [33] Like many other research, more than half of the participants in our study had a history of smoking. [22,30,32] which reported higher prevalence of smoking in COPD patients. Other studies show that the fibrinogen has a strong relation with the smoking habit and that it induces the interleukin (IL)-8, tumour necrosis factor-a (TNF-a), hydrogen peroxide, and isoprostanes in COPD patients. But the association with fibrinogen level was not significant in our study unlike the other studies. This can be due to the small size of the study and that it was only and observational study. Also like the other studies we did not consider the other details of smoking history.

Heart rate and respiratory rate when correlated with the fibrinogen was significant in Sun et al. [10] study but in our study this correlation was not statistically significant. In terms of laboratory results, we saw no differences between individuals with high or low fibrinogen, which is consistent with the findings of Kim et al.'s study. [25], where they found “no difference in the number of leukocytes (P=0.167), neutrophils (P=0.082), lymphocytes (P=0.134), and eosinophils (P=0.389). Although in their study the CRP level was elevated in the high fibrinogen level group (P<0.001)”.

In the present study 56.2% had comorbidities such as hypertension (43.81%), diabetes (36.19%) and cardiac problems (21.9%). Additionally, prior research shows that individuals with COPD often also have additional medical diseases such osteoporosis, DM, lung cancer, and ischemic heart disease. Even though some of these disorders may have similar origins, certain COPD comorbidities may be related to a person's systemic inflammatory response. Consequently, increased fibrinogen levels should encourage more research since they may indicate the existence of these comorbidities in COPD patients.

Both people with COPD and people with cardiovascular disease have higher amounts of fibrinogen in otherwise healthy people, circulating fibrinogen has been found to be an independent risk factor for the development of heart disease. [(9)]

The mean serum fibrinogen in our study group was 408.248±114.264 mg/dl. The minimum reading was 195 mg/dl and maximum was 672 mg/dl. The control group in Mohan et al.'s research [(22)] had the lowest plasma fibrinogen level at 267 ± 37.2 mg/dL, followed by groups with stable COPD (353 ± 32.2 mg/dL) and AECOPD (405 ± 71.6 mg/dL). This trend of increase in the fibrinogen with increase severity was noted in our study too.

The percentage of patients with fibrinogen >4 g/L in Sun et al.'s [(10)] research was 16.1% (n=86), which is lower than what we found in our study variations in the average numbers and percentages of patients with elevated fibrinogen levels between our study and other studies might be explained by changes in methodology.

The current study focused exclusively on individuals experiencing acute exacerbations of COPD (AECOPD). Valvi et al. [32] on the other hand included patients with stable COPD, patients with respiratory symptoms but no abnormalities in lung function, and healthy controls in addition to AECOPD patients. Zhou et al. [6] conducted a meta-analysis which revealed that patients with acute exacerbations of COPD had circulating fibrinogen levels that were three times greater than those of controls. (weighted mean difference: 182.59 mg/dl, 95% CI: 115.93–249.25, P<0.001). Furthermore, in comparison to the equivalent control groups, the meta-analysis demonstrated a gradual rise in circulating fibrinogen levels related to the severity of COPD. With a test result of 360 gm/dl, the mean serum fibrinogen of the study population was found to be statistically significant ($p<0.05$) at a 95% confidence interval, according to one sample t test analysis.

The relationship between circulating fibrinogen levels and the risk of COPD has been the subject of several studies, with varying and contradictory results. For example, whereas some people have discovered that circulating fibrinogen levels in COPD patients are much higher than in healthy controls, other researchers have found that levels in the two groups are equivalent or even higher in the controls. [30]

In the study group, the average serum PCT was 1.9566 ± 3.269 ng/ml. was 95% confidence interval statistically significant ($p<0.05$). This biomarker needs to be studied further I future to understand its role in AECOPD patients more clearly.

The mean serum HS-CRP in the study group was 30.7315 ± 90.182 mg/L. A measurement of 0.2 mg/L is the minimum and 517 mg/L is the highest. In Kim et al study [25] the mean CRP levels in the low and high fibrinogen groups were 0.2±0.3 mg/dl and 1.4±1.4 mg/dl respectively. The mean HS-CRP of the study population at a test value of 5 mg/L was shown to be statistically significant ($p<0.05$) at a 95% confidence interval, according to one sample t test analysis. Because of the different evaluation methods used in Kim et al.'s study [25] there was a positive association between the fibrinogen level and CRP level that was not observed in our study. In particular, the high-level group had a higher CRP level that substantially linked with fibrinogen.

The mean duration of hospitalisation was 7.33 ± 3.32 days in the study group. Additionally, the fibrinogen readings were greater in the individuals who stayed longer. Hospitalization rates have been shown to be impacted by increased fibrinogen, according to Mannino et al. [34] The correlation between longer hospital stays and increased fibrinogen levels suggests that fibrinogen may be a useful biomarker of COPD disease activity and a possible target for treatment approaches.

In the Mohan et al. [22] study, two groups of patients were made based on cut-off of fibrinogen as 350 mg/dL. Age-adjusted CCI analysis revealed no discernible difference between the two groups ($p = 0.939$). Contrary to our findings, compared to the low fibrinogen group, the high fibrinogen group experienced a significantly greater loss in lung function as shown by FEV1 ($p = 0.017$).

The low and high fibrinogen groups in Kim et al.'s study [25] were 64.7% and 34.3%, respectively. A mean of 327.2 (±94.7) mg/dL was found for fibrinogen. Similar to our study, they also found no significant differences in the two groups' age (P=0.654), sex (P=0.994), BMI (P=0.562), smoking status (P=0.861), and length of smoking (P=0.867).

Contrary to our findings, Mannino et al. [34] showed that in their cohort, fibrinogen levels were statistically significantly correlated with age, sex, race/ethnicity, current smoking status, overweight and obesity, and the presence of chronic diseases like COPD, diabetes mellitus, and CVD.

The patients with AECOPD in the Koutsokera et al. [11] trial had mean fibrinogen values of 545.1 mg/dl, 564.6 mg/dl, 476.4 mg/dl, and 455.4 mg/dl on days 0, 3, 10, and 40, respectively. This study shows that with recovery of the acute stage the serum fibrinogen level decreases. Though such follow up of serum fibrinogen was not done in our study the trend of fibrinogen elevation in patients is similar in the present study too.

In the present study, 55.2% were on NIV, among them 41% had abnormal fibrinogen levels and 14.2% had normal fibrinogen levels with statistical significance (p=0.01) indicating that patients with abnormal fibrinogen levels needed NIV support. Among the 63.8% participants who had high fibrinogen levels,11.4% participants received invasive ventilation. while, out of 36.2% patients with normal fibrinogen levels, 9.5% received invasive ventilation, indicating that no association between serum fibrinogen levels and need for invasive ventilation. In a study done by Sun et al, highlighted that higher fibrinogen levels were seen in NPPV failure patients necessitating the need for invasive ventilation [10].

In our study, serum fibrinogen and BORG scale values were not significantly associated which is evident by the p value of 0.115. Although, inverse relationship had been observed between the two variables. In the study subjects the mean of the 6MWT was 479.476 ±144.91 meters. In Kim et al study [25] 6MWT mean was 399.3±112.9 and 348.0±106.3 meters in low and high fibrinogen level groups respectively and there was a positive correlation as seen in our study. In Koul et al study the at-discharge 6MWD ranged from 82 to 498 meters and a mean of 241.2 ± 97.1 m [8]. This is very low when compared to our study findings.

The correlation between serum fibrinogen and 6MWT were statistically significant (Chi-square = 15.304, p = 0.000). The comparison between the means of the variables was also significant in our study. This is consistent with the results of the Mohan et al study [22] which showed that the low fibrinogen group outperformed the high fibrinogen group on the six-minute walk test by a substantial margin (p = 0.016).

The fibrinogen cut-off for all COPD patients in the Mohan et al. study was 358 mg/dL, with a sensitivity of 80% and a specificity of 68.57%. and AUC = 0.820. [22]. This is comparable to our study with serum fibrinogen 360 mg/dl, sensitivity was 90.9% but false positive was 51.4%.

The fibrinogen AUC (0.899, 95% CI 0.846–0.952) in the research by Sun et al. [10] was greater than the AUCs for" leukocytes (0.724, 95% CI 0.637–0.812), neutrophils (0.795, 95% CI 0.724–0.867), lymphocytes" (0.792, 95% CI 0.707–0.876), and CRP (0.71, 95% CI 0.625–0.795).

In Manon-Jensen et al. study the corresponding AUC of fibrinogen was 0.67 (95% CI 0.64:0.70). Subjects with high plasma fibrinogen levels (>350 mg/dl) had a significantly increased mortality risk within the two years of follow up [(35)].

In the current study, FEV 1 was mild among 6.7% participants, moderate among 60.7% participants, whereas 32.4% had severe FEV 1 value. This study reveals a statistically significant association between FEV1 and fibrinogen showing a strong association with a p value of 0.01 indicating that a severe FEV1 is directly proportional to abnormal fibrinogen levels. On comparing with FEV1 <50% and fibrinogen levels, we found statistically significant association with p = 0.006. Thus, a decline in FEV1 is proportional to rising fibrinogen levels.

In a systematic review done by Duvoix A et al., they have reported that fibrinogen as an emerging biomarker in COPD as per FDA in the field of drug development. Also, they found that a higher fibrinogen levels in individuals had an association with faster decline in FEV1[(9)]

Our results are in line with those of Dahl et al. [(26)] and Mannino et al. [(34)], who demonstrated that elevated plasma fibrinogen levels were linked, regardless of smoking status, to worse lung function and an increased risk of COPD.

Since baseline fibrinogen levels were the only ones tested, we are unable to determine whether high fibrinogen induced COPD or elevated fibrinogen caused COPD. Additionally, we were unable to assess differences in fibrinogen levels between AECOPD and stable COPD.

Because our research focused only the acute exacerbation (AE) phase and excluded data from before hospitalization.Consequently, the findings of this research should only be used in the AECOPD population. Future studies should include serial measurements to confirm the changes in fibrinogen during the acute phase of COPD.

Furthermore, nationally representative NHANES III data indicate a relationship between decreased lung function and fibrinogen concentration, and that a high fibrinogen concentration raises the risk of death in both the general population and COPD sufferers. For this reason, it seems sense to view circulating "fibrinogen as a potential clinical biomarker for estimating the severity and risk of COPD".

LIMITATIONS

Analysis was only done with using baseline fibrinogen levels, as follow up fibrinogen levels were not done. Because it is an observational study with a limited sample size and is conducted at only one center, this limitation should be taken into consideration when interpreting our results. The investigator's bias may be there but that is tried to overcome by keeping the lab technicians unaware of the lung function test of the patient or disease status of subject.

CONCLUSION

AECOPD was linked to elevated plasma fibrinogen in terms of predicting lengthier hospital stays and worse lung function.

Blood biomarkers such as plasma fibrinogen can be used to estimate the degree of systemic inflammation. These values are currently used in clinical diagnostic practice and are easily quantified. Furthermore, patients can have their blood biomarkers tested without invasive procedures.

This offers a method to classify individuals in clinical trials or a choice for therapies for patients exhibiting signs of systemic inflammation. It will need more studies to determine whether a targeted decrease in plasma fibrinogen levels would result in better COPD outcomes.

SUMMARY

- The mean age of 105 eligible patients was 62.94 ±12.59 years. Almost 27% belonged to 61 to 70 years age group.
- Males outnumbered the females at 83.8% .
- More than half of them (57.2%) had history of smoking.
- The mean heart rate was 84.314±10.699 per minute.
- The mean respiratory rate was 25.829±6.276 per minute.
- The mean RA saturation was 84.533±9.248%.
- The mean pH was 7.222±0.229.
- The mean PaO2 and PCO2 was 66.128±16.213 and 56.904±11.316 mm Hg respectively.
- The pulmonary function assessed by FEV1 showed mean of 56.581±14.076%.
- The Modified BORG scale used to assess the severity of shortness of breath had a mean of 5.981±2.2531,which indicates moderate SOB in the study group.
- In the study 56.2% had comorbidities. Out of these 43.81% patients had hypertension, 36.19% had diabetes and 21.9% had cardiac problems.

- The mean serum D DIMER in study group was 673.105±706.2127.
- The mean total count was 9.9482±4.48896, neutrophils count was 73.029±18.3997 and lymphocytes was 19.124±18.5901.
- The normal range of serum fibrinogen was taken as 180 – 360 mg/dl in our study. The mean serum fibrinogen was 408.248±114.264 mg/dl. The minimum reading was 195 mg/dl and maximum was 672 mg/dl. 36.2% of the patients with AECOPD had normal readings while 63.8% had increased levels. One sample t test analysis for mean serum fibrinogen was statistically significant ($p<0.05$).
- The serum levels upto 0.5 ng/ml were taken a normal for PCT which was seen in 54.3%. The mean was 1.9566 ± 3.269 ng/ml with minimum reading of 0.01 ng/ml and maximum 14.9 ng/ml. One sample t test analysis for serum PCT was statistically significant ($p<0.05$).
- The mean serum HS-CRP in the study group was 30.7315 ± 90.182 mg/L. The minimum was 0.2 mg/L and maximum was 517 mg/L. Normal reading was seen in 62.9%. One sample t test analysis for mean HS – CRP was also statistically significant ($p<0.05$).
- 55.2% patients needed NIV.
- The mean duration of hospital stay was 7.33 ± 3.32 days with minimum 2 days of stay and maximum 17 days. Majority (14.3%) of patients were admitted for 5 days.

- In the study subjects the mean of the 6MWT was 479.476 ±144.91 meters, with a range of 200 to 700 meters. Almost 68.6% (n=72) had normal 6MWT.
- The correlation between serum fibrinogen and the 6MWT was statistically significant.
- The association between the serum fibrinogen and age, gender and BORG scale was not significantly.
- There was a significant correlation between serum fibrinogen and use of NIV in AECOPD and 6MWT.
- Taking 6MWT as a predictor in ROC curve for serum fibrinogen 360 mg/dl had sensitivity of 90.9% and false positivity 51.4%. With a serum fibrinogen value of 433.5 mg/dl sensitivity was 75.8% and false positivity was 29.2%. The area under the curve was 0.866.
- The linear regression model of 6MWT and serum fibrinogen at $F(1,103) = 45.7$, $p= 0.000$.
- The linear equation derived is: $Y = 766.499 + (-0.554) X$ [Y= c (intercept)+ bX]
- With t= 17.391 for constant and t = (-6.76) for serum fibrinogen. This is statistically significant ($p<0.05$). Thus showing an inverse relation between the two variables.
- Similarly, the linear regression model of BORG Scale and serum fibrinogen at $F(1,103) = 7.614$, $p= 0.007$.

- The linear equation derived is: Y = 8.093 + (-0.262) X [Y= c (intercept)+ bX]
- With t= 10.186 for constant and t = (-2.759) for serum fibrinogen. This is statistically significant ($p<0.05$). Thus showing an inverse relation between the two variables.

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ANNEXURE I – CONSENT FORM

ROLE OF SERUM FIBRINOGEN LEVELS IN DETERMINING THE SEVERITY AND PROGNOSIS OF ACUTE EXACERBATION OF COPD PATIENTS – AN OBSERVATIONAL STUDY

Name of Student/Principal Investigator: REG NO: BR0121003

Name of Guide/ Co Investigators:

PURPOSE OF THE STUDY: In this study, we have primarily aimed to assess the severity and prognosis of AECOPD using Serum Fibrinogen levels as S. Fibrinogen levels are now proved to be a promising biomarker in patients coming to KLE's Dr.Prabhkar Kore Hospital and MRC.

PROCEDURES INVOLVED: If you agree to enroll yourself in my study, you will be subjected to clinical examination which will involve assessment of your vitals, general physical examination and focussed systemic examination. You will then be subjected to Lung function test, 6-minute walk test, Chest X-ray, Serum Fibrinogen Levels.

RISKS AND BENEFITS: There are no potential risks involved in this study.

BENEFITS OF TAKING PART IN THIS RESEARCH: By taking part in this study to evaluate the severity and prognosis of Acute Exacerbation of COPD patients by Serum Fibrinogen Level.

VOLUNTARY PARTICIPATION / WITHDRAWAL FROM THE STUDY: Taking part in the study is voluntary. You may choose not to enroll yourself in this study and may choose to leave the study anytime in between.

ALTERNATIVES: Your decision regarding participation in study will not change present or future health care services offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. You would simply be excluded from the study if you wish to, and all your details shall be kept confidential and you will get the routine line of management.

PRIVACY AND CONFIDENTIALITY: All data collected or disclosed by you during the course of participation of study, will be kept fully confidential. If, however during the course it becomes necessary for the progress of the course to disclose the identity, it would be done so only after your informed & written consent. The only people to know that you are a research subject are members of the research team. No information about you will be disclosed to other without your written permission except:

In emergency to protect your rights AND welfare.

If required by law.

AUTHORIZATION TO PUBLISH RESULT: The results of the study may be used to publish an article. When the results of research are published or discussed in a conference, no information will be displayed that would disclose your identity. Any information obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION: No additional costs shall be incurred upon you for the purpose of this study. It is purely being done with the idea of research and all the cost of study will be borne by the investigator.

COMPENSATION: In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, or you will be given information about where to receive medical care. However, no reimbursement, compensation or free medical care will be given.

QUESTIONS/CONTACT DETAILS: You shall be free to contact the below mentioned name & addresses anytime during the study period for any clarification or help as you may desire for.

If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Annexure - I

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "***ROLE OF SERUM FIBRINOGEN LEVELS IN DETERMINING THE SEVERITY AND PROGNOSIS OF ACUTE EXACERBATION OF COPD PATIENTS – AN OBSERVATIONAL STUDY***". My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb
Impression of the participant:

Name of the witness:

Signature or left thumb
Impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE II – PROFORMA

ROLE OF SERUM FIBRINOGEN LEVELS IN DETERMINING THE SEVERITY AND PROGNOSIS OF ACUTE EXACERBATION OF COPD PATIENTS – AN OBSERVATIONAL STUDY

CASE NO	
NAME	
IP NO	
AGE	**YEARS**
SEX	**MALE FEMALE**
ADDRESS	
OCCUPATION	

Complaints and History	
Past history	
Family history	
Personal history ● **ALCOHOLISM** ● **SMOKING** ● **CO-ORBIDITIES**	
Treatment history	

VITALS:

Temperature	
Pulse	
Respiratory rate	
Blood pressure	

SPIROMETRY:

	VALUE	**PERCENTAGE**
FEV1		

BLOOD INVESTIGATIONS:

Serum fibrinogen :

D-dimer :

Hscrp :

S.Pct :

Total counts :

Neutrophils :

Lymphocytes :

ABG:

MODIFIED BORG SCALE:

Score	Dyspnea
0	No dyspnea
1	Very slight
2	Slight
3	Moderate
4	Somewhat Severe
5	Severe
6	
7	Very Severe
8	
9	Very, very Severe
10	Maximal

6MWT (IN MTRS)

OUTCOME:

NIV :

IV :

Mortality :

Length of hospital stay :

ANNEXURE III – MASTER CHART

AGE	SEX	COMPLAINTS	COMORBIDITIES	SMOKING	HR	RR	BP	RA SATURATION	PH	PaO2	PCO2	FEV1	SERUM FIBRINOGEN	S.PCT	D DIMER	HS-CRP	NIV	IV	Mortality	HOSPITAL STAY	TOTAL COUNT	NEUTROPHILS	LYMPHOCYTES	6MWT	Modified BORG Scale
61	M	Breathlessness,cough with expectoration,fever	Nil	yes	94	34	140/90	89	7.3	75	36	59	435	0.04	307	45.3	yes			3	10	95	4	290	7
59	M	breathlessess,fever,chest pain	hypertensive,diabetic,old CVA	yes	82	18	130/80	88	7.17	72.5	66.5	44	455	0.06	560	1.7	yes			5	7.7	56	51	320	8
48	M	Breathlessness,fever,cough,chest pain	Nil	yes	87	18	110/70	90	7.32	62.9	63.4	84	341	0.05	547	0.5	no		yes	7	9.5	43	23	340	5
73	M	Breathlessness,cough,wheeze,fever	Nil	yes	80	20	140/90	95	7.22	86	80	35	429	0.08	413	42.7	no			5	21.5	85	57	260	7
83	F	Breathlessness on exertion,cough,fever,wheeze	Diabetic,hypertensive	no	93	22	110/90	88	7.13	76.2	68.6	30	614	0.47	1049	376	yes	yes		5	10.25	79	26	200	9
75	F	Breathlessness on exertion,cough,fever,wheeze	Diabetic,hypertensive,IHD	no	95	24	110/80	93	7.27	59.2	47.8	72	215	0.07	202	0.8	no			6	12.6	84	46	450	4
79	M	fever ,chest pain,cough	Nil	yes	93	24	128/90	97	7.29	68.8	67.2	58	376	0.06	4376	46.2	no			5	17.3	57	54	320	5
61	M	chest pain,breathlessness,cough	S/P PTCA	yes	100	20	140/110	98	7.4	68.8	66.8	44	546	8.8	1361	3	yes		yes	8	11.4	80	26	290	8
85	M	Breathlessness,cough with expectoration,fever	hypertensive	no	114	33	120/80	75	7.47	58	94.2	50	315	1.53	875	14	yes	yes		4	4.1	94	47	455	5
76	M	Generalized weakness,cough,breathlessness	diabetic	yes	99	32	130/90	81	7.2	57.9	60.6	40	422	0.12	492	7.9	yes			13	6.1	92	20	340	8
85	F	cough ,breathlessness	hypertensive	no	113	18	140/100	88	7.3	68.8	18	74	390	0.22	425	0.6	no		yes	10	7.9	77	11	320	6
58	M	fever ,chest pain,cough,Pedal edema	Diabetic,hypertensive	yes	67	18	120/90	90	7.35	73.2	46.5	34	455	0.37	312	4.9	yes			8	5.6	88	66	410	7

75	M	Breathlessness,cough,wheeze,fever	Nil	yes	66	32	170/110	85	7.47	82.3	48	30	576	0.86	1103	148.7	yes			3	8.4	90	19	210	8
57	M	Breathlessness,cough with expectoration,fever ,Wheezing	Nil	no	80	35	140/90	70	7.32	71.8	41.7	70	389	0.03	432	0.74	yes			10	6.25	49	12	340	4
71	M	chest pain,breathlessness,cough	Nil	no	90	30	200/110	94	7.22	67.4	45.7	60	442	0.06	560	15.8	yes			10	5.9	82	51	600	9
75	M	cough ,breathlessness	hypertensive	no	100	20	120/70	86	7.13	69.2	53	45	550	0.12	1154	306.2	no			6	13.8	83	32	300	10
46	M	loss of appetite,weight loss,fever	Nil	no	84	20	120/70	68	7.27	72.8	53.1	55	465	1.02	251	1.3	yes			2	7.85	47	6	490	8
55	F	Breathlessness,cough with expectoration,fever	hypertensive	no	99	29	130/80	86	7.3	89.5	58.5	59	237	0.07	335	4.1	no		yes	7	9.8	94	68	600	4
75	M	Breathlessness,cough with expectoration,fever	hypertensive	no	88	27	120/80	94	7.3	75.1	64.8	59	362	0.17	3706	322	no	yes		5	5.1	85	68	600	3
63	M	Breathlessness,fever,cough,chest pain	hypertensive,diabetic,old CVA	yes	67	22	120/86	90	7.27	53.5	60.2	39	430	0.04	456	57	no			8	13.1	90	52	620	6
44	M	breathlessess,fever,chest pain	Nil	yes	66	33	140/90	68	7.25	70.4	60	62	474	1.11	324	1.2	yes	yes		3	9.92	65	9	520	5
58	F	breathlessness,cough,fever,weight loss	hypertensive	no	80	24	100/70	80	7.25	52.6	59.7	67	390	0.1	206	3.5	no			10	11.7	88	7	620	8
69	F	Breathlessness,cough with expectoration,fever	Nil	no	90	25	143/77	84	7.2	70	55.8	72	442	0.05	531	99.8	yes		yes	5	11.3	66	24	640	9
70	F	breathlessness,dry cough,loss of apetite	Nil	no	78	28	180/110	70	7.27	65.6	58.8	50	320	0.03	439	4.2	yes			8	8.6	80	15	700	9
76	M	Breathlessness,chest pain,cough	Nil	yes	99	20	140/90	86	7.37	70	58.5	60	405	0.5	530	0.6	no			5	7.6	54	25	590	6
72	M	chest pain,breathlessness,cough	Diabetic,hypertensive,IHD	yes	100	16	110/70	96	7.35	89	64.8	65	342	0.03	680	0.5	yes			6	5.6	67	25	690	8
49	M	vomiting,fever,breathlessness	Diabetic,hypertensive	yes	84	28	170/110	73	6.4	58	60.2	87	450	2.03	259	0.73	yes	yes	yes	3	9.8	50	3	550	6
75	M	Wheeze,cough with expectoration	hypertensive	yes	80	16	110/80	92	7.45	45.2	56.8	50	255	0.03	325	5.4	no			16	5.1	64	22	490	3
68	M	Breathlessness,wheeze	diabetic	yes	74	20	120/80	98	7.4	53	72.8	58	304	0.5	127	3.7	yes			14	14.3	65	30	650	9
82	M	cough ,breathlessness,vomiting and nausea	hypertensive	yes	83	16	100/80	90	7.3	60.5	60.5	56	441	2.84	560	4.3	yes			10	9.7	70	18	600	7
74	M	chest pain,cough	old CVA	yes	89	26	150/100	96	7.4	43.5	48.7	46	338	0.5	234	0.6	yes	yes		6	20.8	88	12	530	6

77	M	cough with expectoration,wheeze,fever,loss of apetite	Nil	yes	108	30	150/100	96	7.39	96.8	58.8	34	506	0.52	842	4.7	yes			6	10	91	5	300	3
43	M	abdominal pain,wheeze,fever,vomiting	Nil	yes	114	37	160/110	75	6.8	41.2	57.7	41	456	2.14	367	2.2	no		yes	6	8.5	41	5	550	6
67	M	Breathlessness on exertion ,cough,fever,wheeze	Nil	yes	89	31	150/100	85	6.5	46.9	57.1	30	503	0.04	202	3.2	yes			4	12.3	72	18	310	4
84	M	breathlessness,cough with expectoration,wheze	S/P PTCA	yes	98	21	120/80	84	7.56	60	20	45	307	0.05	172	0.3	yes	yes		7	7.3	80	10	500	10
62	M	Breathlessness,cough with expectoration,fever	Nil	no	97	30	130/100	97	7.46	95.6	35	59	260	0.9	345	2.1	no			10	15.9	59	26	690	8
58	M	Breathlessness,cough with expectoration,fever ,Wheezing	Nil	no	67	31	128/90	88	6.7	47.2	59.7	63	568	2.08	861	3.8	no			4	4.3	56	7	240	3
56	M	cough with expectoration,wheeze,fever.	S/P CABG,diabetic	yes	66	26	140/110	90	7.41	96.4	55.8	46	359	1	243	4.2	yes		yes	5	18.1	81	12	650	9
69	M	cough with expectoration,fever,breathlessness ,wheeze	Nil	yes	80	30	120/80	90	7.34	72.6	60.6	48	513	1.57	652	112	yes			9	26.1	79	12	350	4
66	F	breathlessness,fever,chest pain	Nil	no	90	24	130/90	96	7.45	48.1	55.8	48	499	2	213	0.4	no			7	7.4	84	8	500	4
41	M	Breathlessness,chest pain,cough	Nil	no	78	26	140/100	92	6.4	60.6	55.8	85	257	3.12	421	0.3	no			5	5.8	52	10	620	9
55	F	Breathlessness,cough with expectoration,fever	Nil	no	99	29	120/90	80	7.2	47.1	47.7	49	450	0.05	699	0.8	no			6	10	95	7	570	6
65	M	Breathlessness on exertion ,cough,fever,wheeze	Diabetic,hypertensive	yes	89	23	170/110	88	7.23	87.8	57.1	70	260	1	670	12	no		yes	4	12	90	8	440	4
62	M	loss of appetite,weight loss,fever	Diabetic,hypertensive,IHD	no	87	22	140/90	66	6.5	41.7	59.7	54	473	0.09	264	4.7	yes			11	5.6	29	23	500	4
65	M	fever,breathlessness	hypertensive	no	83	40	200/110	87	7.6	83.5	55.8	79	342	0.07	980	19	yes			8	7	87	5	650	8
61	F	Wheeze,cough with expectoration	diabetic	no	81	35	160/70	90	7.1	80	60.6	72	201	0.05	456	12	no	yes	yes	4	8.3	90	4	550	6
56	M	Breathlessness,fever,cough,chest pain	Nil	no	74	22	110/80	75	7.23	58.2	55.8	66	249	0.05	298	0.73	no			6	7.9	49	16	400	3
70	F	Wheeze,cough with expectoration	Nil	no	83	29	120/70	95	7.31	40.7	55.8	50	264	4.09	675	0.8	no			3	9.3	70	6	530	5
78	M	chest pain,breathlessness,cough	hypertensive,diabetic,S/P pacemaker	yes	75	30	120/70	89	7.27	98	47.7	40	432	0.06	1032	12	yes			7	21.5	87	8	640	10
70	M	breathlessess,fever,chest pain	Nil	yes	77	40	110/80	88	7.27	90	57.1	55	346	8	790	6	no	yes		8	10.2	90	11	700	9

80	M	Wheeze,cough with expectoration	Nil	yes	81	35	130/90	70	7.28	96	47.8	65	211	2.3	845	19	no			3	12.6	92	6	430	4
67	M	fever,breathlessness	epilepsy	yes	79	20	130/60	79	7.22	43.5	67.2	30	576	0.08	980	17	yes			9	17.3	84	15	350	4
46	M	abdominal pain,wheeze,fever,vomiting	Nil	no	87	23	110/80	85	7.28	72.5	66.8	67	560	6.07	273	0.92	no		yes	7	11.2	54	8	230	3
60	F	vomiting,fever,breathlessness	Diabetic,hypertensive	no	85	23	120/70	90	7.33	62.9	94.2	58	285	0.02	230	0.2	no	yes		5	4.1	95	8	690	9
64	M	fever,breathlessness	Nil	yes	81	22	120/70	96	7.28	86	60.6	57	342	2.09	389	0.6	yes			6	6.1	87	7	700	9
53	M	vomiting,fever,breathlessness	Nil	yes	100	25	120/70	86	7.3	76.2	55.8	62	576	5.04	351	2	yes	yes	yes	6	7.3	77	21	280	3
69	M	Generalized weakness,cough,breathlessness	Diabetic,hypertensive,IHD	yes	82	33	120/70	77	7.32	59.2	55.8	48	264	0.01	1024	3.2	no	yes		4	5.6	93	8	550	6
90	M	Wheeze,cough with expectoration	Diabetic,hypertensive	yes	79	28	120/70	67	7.28	68.8	47.7	56	256	0.06	672	4.9	no			3	8.4	90	9	400	4
61	F	chest pain,ausea,abdominal pain	hypertensive	no	87	25	110/80	90	7.29	68.8	57.1	59	354	0.09	928	1.2	yes			8	6.3	92	4	580	6
49	M	chest pain,cough	Nil	yes	83	22	110/80	64	7.17	58	56.8	74	552	2.08	398	2	yes			7	5.9	79	17	320	4
67	M	Wheeze,cough with expectoration	Diabetic,hypertensive,IHD	yes	81	29	120/70	97	7.32	57.9	72.8	39	503	1.78	670	11	yes	yes		10	13.8	90	8	360	4
70	M	fever,breathlessness,abdominal pain	Nil	yes	74	30	120/70	90	7.22	68.8	66.4	65	222	14.9	200	1.2	no			7	7.8	76	8	410	4
55	M	Wheeze,cough with expectoration	Diabetic,hypertensive	yes	83	31	110/80	96	7.13	73.2	80.2	43	430	0.03	189	9	yes			9	9.8	95	5	630	8
73	M	breathlessness,wheeze,chest pain	Diabetic,hypertensive,IHD	yes	75	23	130/90	70	7.27	82.3	56.8	52	320	0.04	923	3.4	yes			8	5.1	36	3	520	6
54	M	Wheeze,cough with expectoration	epilepsy,htn	yes	77	33	110/90	89	7.29	71.8	53.8	43	234	3.89	1123	6.8	yes	yes		4	15.7	82	6	590	6
82	M	vomiting,fever,breathlessness	Diabetic,hypertensive	yes	81	22	120/90	90	7.23	67.4	65.8	60	289	4.09	387	19	no			3	9.9	98	4	650	10
44	M	loss of appetite,weight loss,fever	diabetic	yes	79	18	130/90	69	7.34	69.2	54.1	50	290	0.09	299	0.5	yes			8	8.1	56	55	700	8
60	F	Wheeze,cough with expectoration	Nil	no	87	32	120/70	89	7.21	72.8	59	66	202	0.03	763	100	no			8	15.3	88	8	530	6
68	M	fever,loss of appetite,generalized weakness	Nil	no	85	33	120/70	76	7.32	89.5	60	46	460	0.06	239	22	yes		yes	9	9.4	78	10	550	6

68	M	Wheeze,cough with expectoration	Diabetic,hypertensive,IHD	yes	81	39	110/80	90	7.22	75.1	45	32	502	0.01	678	27	yes			10	5	90	21	400	4
81	M	breathlessess,fever,chest pain	Diabetic,hypertensive,IHD	no	100	40	130/90	67	7.32	53.5	34	59	286	2.04	1094	9	no			4	6.9	84	2	480	4
62	M	Wheeze,cough with expectoration	hypertensive	yes	82	40	160/90	93	7.24	70.4	22	60	195	0.03	672	0.4	no			7	8.7	89	5	510	6
50	M	Breathlessness,chest pain,cough	Nil	no	79	21	120/70	77	7.23	52.6	41.7	51	404	0.01	718	1.94	yes			8	7.9	66	37	680	9
49	M	Breathlessness,cough with expectoration,fever ,Wheezing	Nil	no	86	24	120/70	83	7.24	58	45.7	70	367	0.07	245	0.94	no	yes	yes	12	9.3	48	65	640	9
75	F	breathlessness,cough with expectoration,pedal edema,giddiness	Diabetic,hypertensive	no	79	23	130/80	90	7.2	43.9	53	35	327	0.1	550	11.9	yes			5	21.5	73	19	390	10
42	M	abdominal pain,wheeze,fever,vomiting	Diabetic,hypertensive,IHD	no	89	19	120/80	68	7.33	53	53.1	71	432	0.02	315	2.3	yes			8	10.9	60	14	700	9
48	M	Breathlessness,cough with expectoration,fever ,Wheezing	Nil	yes	95	26	120/86	70	7.27	60.5	58.5	80	557	14.3	236	2.1	yes	yes		9	12.6	55	9	370	4
75	M	loss of appetite,weight loss,fever	hypertensive	yes	75	19	140/90	86	7.28	49.3	64.8	35	487	0.01	678	14	yes			10	17.3	78	9	500	4
43	M	vomiting,fever,breathlessness	diabetic	yes	95	18	100/70	84	7.3	96.8	60.2	48	560	11.7	361	0.8	no		yes	10	11	66	13	300	3
57	M	Breathlessness,chest pain,cough	Diabetic,hypertensive,IHD	no	75	23	143/77	91	7.13	41.2	60	70	370	9.07	502	0.54	no			11	4.1	48	11	620	8
83	F	Breathlessness,fever	Nil	no	80	28	180/110	98	7.28	46.9	59.7	49	540	2	299	0.9	yes			8	6.1	93	4	310	4
47	M	Breathlessness,fever,cough,chest pain	Nil	yes	70	22	140/90	85	7.29	60	55.8	47	393	6.02	618	0.9	no	yes		9	7.9	50	5	650	9
42	M	abdominal pain,wheeze,fever,vomiting	Nil	no	70	18	110/70	72	7.17	95.6	58.8	85	481	7.5	602	0.83	no		yes	12	5.6	70	3	490	3
85	M	breathlessness,wheeze,chest pain	Nil	yes	79	20	170/110	98	7.31	46.9	58.5	50	478	9.3	863	6.7	yes			9	8.4	83	5	520	7
46	M	Breathlessness,cough with expectoration,fever ,Wheezing	Diabetic,hypertensive,IHD	no	78	20	120/80	88	7.3	72.6	60.2	66	520	2.14	983	1	yes			5	5.9	49	4	300	3
54	M	Breathlessness,cough,chest pain	Nil	yes	76	30	140/80	80	7.29	49.2	56.8	35	422	3.63	226	96.4	yes	yes		5	13.8	87	8	560	6
40	M	chest pain,cough	Nil	no	67	21	130/80	70	7.17	60.6	72.8	56	470	3.69	842	0.8	yes			13	7.8	56	3	500	4
43	M	vomiting,fever,breathlessness	Nil	yes	82	16	140/80	92	7.32	47.1	60.5	69	580	5.14	295	1.9	no		yes	4	9.8	54	6	350	4

63	M	cough ,breathlessness	hypertensive,diabetic,S/P pacemaker	yes	84	30	120/60	70	7.22	87.8	48.7	47	581	14.35	1395	517	yes			8	5.1	90	5	290	3
71	M	Breathlessness on exertion ,cough,fever,wheeze	Diabetic,hypertensive	no	78	25	140/90	89	7.13	41.7	58.8	69	281	0.02	5000	5.6	no			10	15.7	86	8	460	4
55	M	Breathlessness,chest pain,cough	Diabetic,hypertensive,IHD	yes	74	19	120/80	83	7.27	83.5	57.7	75	300	8.12	834	0.3	no	yes		14	9.9	42	44	440	4
53	F	Wheeze,cough with expectoration	S/P PTCA	no	82	35	140/100	80	7.3	80	57.1	53	430	0.9	540	9	yes			7	9	88	4	550	6
47	M	Breathlessness,chest pain,cough	Nil	yes	72	20	120/80	90	7.3	58.2	56.8	62	540	0.09	465	0.94	no			7	7.88	50	37	280	3
49	M	Breathlessness,cough with expectoration,fever ,Wheezing	diabetic	yes	84	20	110/90	90	7.17	40.7	53.8	77	380	0.04	863	0.5	no			16	9.24	43	51	620	8
70	M	abdominal pain,wheeze,fever,vomiting	Diabetic,hypertensive,IHD	yes	88	21	140/90	78	7.32	75.1	65.8	56	324	2.01	256	27	yes	yes		2	22.5	90	7	350	10
55	M	abdominal pain,wheeze,fever,vomiting	hypertensive	no	72	23	140/90	83	7.22	53.5	54.1	61	487	0.03	564	1.9	no			14	10.2	56	48	530	6
58	M	Breathlessness,cough with expectoration,fever ,Wheezing	Nil	no	74	25	124/90	85	7.13	70.4	59.7	41	600	0.02	712	2.3	no			3	12.6	49	63	210	3
66	M	breathlessess,fever,chest pain	Diabetic,hypertensive	yes	81	35	140/90	83	7.27	52.6	55.8	58	628	0.51	318	11	yes	yes		5	13.9	80	15	230	3
47	M	Breathlessness,fever,cough,chest pain	epilepsy	yes	82	16	110/80	96	7.29	58	60.6	80	400	0.06	988	1.4	yes			17	11.3	48	49	600	6
74	M	cough ,breathlessness	Diabetic,hypertensive,IHD	no	81	25	120/70	90	7.2	43.9	55.8	60	483	0.06	378	2.5	yes		yes	5	4.3	96	3	480	4
47	M	Breathlessness,cough with expectoration,fever ,Wheezing	Nil	yes	83	20	110/80	78	6.3	60.5	47.7	85	463	3.5	1004	1.2	no			11	7.9	85	5	550	6
48	M	chest pain,cough	Diabetic,hypertensive	yes	85	32	150/90	70	7.1	96.8	59.7	71	482	2.6	564	2.3	yes			15	8.4	36	66	490	3
72	M	breathlessness,cough with expectoration	Diabetic,hypertensive	yes	114	34	140/90	70	6.45	41.2	55.8	65	264	0.29	460	3.2	no			6	6.79	85	10	690	8
57	M	breathlessess,fever,chest pain	hypertensive	no	78	26	130/90	80	7.2	46.9	60.6	70	404	2.8	366	1.2	yes	yes	yes	2	5.9	24	4	590	6
73	M	Breathlessness,cough with expectoration,fever ,Wheezing	Nil	no	88	28	160/100	80	7.41	95.6	55.8	55	672	1.67	996	510	yes			9	7.64	90	6	220	3