A CLINICAL STUDY OF SERUM CYSTATIN C LEVELS IN CASES OF COPD AND ITS CORRELATION WITH SPIROMETRY AND IMPACT ON THEIR QUALITY OF LIFE

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LIST OF ABBREVIATIONS

COPD	:	Chronic obstructive pulmonary disease
%	:	Percentage
ELISA	:	Enzyme linked immunoassay
ROC	:	Receiver operator characteristic curve
FEV_1	:	Forced expiratory volume in 1^{st} second
MMRC	:	Modified medical research council
CAT	:	COPD Assessment test
SGRQ -C	:	St.George respiratory questionnaire for COPD
CCQ	:	Clinical COPD questionnaire
CD 8+	:	Cluster differentiated cells
EELV	:	End expiratory lung volume
MMP 12	:	Matrix metalloproteinases 12
FVC	:	Forced vital capacity
ROS	:	Reactive oxygen species
CKD	:	Chronic kidney disease
AKI	:	Acute kidney injury
GFR	:	Glomerular filtration rate
CCR	:	Creatinine clearance ratio
PETIA	:	Particle enhanced turbidimetric immunoassay

PENIA	:	Particle enhanced nephlometric immunoassay
BAL	:	Broncho alveolar lavage
US	:	United States
GOLD	:	Global initiative for obstructive lung diseases
AECOPD	:	Acute exacerbation of chronic obstructive pulmonary disease
MMEF	:	Maximum mid expiratory flow
MVV	:	Maximal voluntary ventilation
RV	:	Residual volume
TLC	:	Total lung capacity
DLCO	:	Diffusing capacity of the lungs for carbon monoxide
S COPD	:	Stable chronic obstructive pulmonary disease
$PaCO_2$	:	Partial pressure of carbon di oxide
PaO_2	:	Partial pressure of oxygen
HsCRP	:	Highly sensitive C-Reactive protein
CRP	:	C-Reactive protein
Cr	:	Creatinine
SI	:	Sarcopenic index
HRQOL	:	Health related quality of life
6MWT	:	6 minute walk test
BMI	:	Body mass index

ABSTRACT

BACKGROUND:

Chronic obstructive pulmonary disease (COPD), which is now the fourth leading cause of mortality worldwide but is anticipated to become the third most common reason by 2020, is a significant public health issue that is both curable and preventable. In 2012, COPD claimed the lives of more than 3 million individuals, or 6% of all fatalities worldwide. A significant public health issue that is both preventable and curable is COPD.

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease with high mortality and morbidity. Serum Cystatin C is a sensitive indicator for various chronic inflammatory diseases. The imbalance between protease and anti-protease is a component of the pathophysiology.

This study is undertaken to see whether Cystatin C levels have any correlation with the clinical severity of COPD and know its association with lung function in those patients. This study also aims to assess the impact on the quality of life of COPD patients.

AIMS AND OBJECTIVES:

The aim of the study is to correlate serum Cystatin C level with spirometry and also to evaluate its impact on the quality of life in chronic obstructive pulmonary disease patient.

To determine serum Cystatin C levels in chronic obstructive pulmonary disease patients. To perform pulmonary function tests in chronic obstructive pulmonary disease patients.

MATERIALS AND METHODS:

Patients with COPD diagnosed according to gold guidelines 2020 attending the out-patient and in-patient department of Respiratory Medicine in Shri B. M. Patil Hospital, Vijayapura, will be enrolled in the study and are subjected to routine blood investigations, pulmonary function tests, and also an examination of serum Cystatin C levels by ELISA method.

RESULTS:

Among 42 patients enrolled in this study, most of the patients belonged to the age group more than 55 years, with male predominance with Ideal body weight, Mean serum Cystatin C level was 560.1± 285.5ng/ml which is less when compared to other studies, so ROC analysis was performed to find out the cut-off, that is 532.1ng/ml with the highest sensitivity of 100% and specificity of 79.3% with area under the curve being 0.942. According to spirometry-based classification, 45.2%patients had serum Cystatin C levels above 532.1ng/ml and 54.7% patients had serum Cystatin C levels less than or equal to 532.1ng/ml, association between them is statistically significant. Mean serum Cystatin C was notably increased as airflow limitation (% FEV_1 Predicted) decreases and the association between them was significant statistically ($P<0.001$). It was also increased with increasing disease severity (ABCD Tool) and was also associated with an increased number of exacerbations and the association between them was statistically significant ($p<0.05$). Duration of disease of more than 4 years have odds of 6.5 times chance of increased serum Cystatin C levels that was found to be statistically significant ($P<0.05$).

There is a positive association between the six-minute walk and serum Cystatin C levels and patients with a 6-minute walk test less than 250m have odds of 13 times chance of increased serum Cystatin C levels it was found to be statistically significant ($P<0.05$). Serum CRP levels

increased with increased serum Cystatin C levels and are correlated Positively and statistically significant. There was a positive association between SGRQ total score and serum Cystatin C ng/ml and patients with St George total score more than 50 have odds of 4.8 times chance of increased levels of serum Cystatin C levels and were found to be statistically significant. ($P<0.05$). There is a positive association between the clinical COPD questionnaire and serum Cystatin C levels and patients with Clinical COPD questionnaire scores more than or equal to 3 have odds of 4.7 times chance of increased serum Cystatin C levels and found it was statistically significant ($p<0.05$). There was a positive association between cat score and serum Cystatin C levels and patients with CAT score more than 20 have odds of 4.5 times chance of increased serum Cystatin C levels and found to be statistically significant ($p <0.05$).

CONCLUSION: The mean serum Cystatin C level is 560.1± 285.5ng/ml in our study which is far less than controls in our study. So standardized values from our lab of serum Cystatin C has been taken with help of ROC analysis that is 532ng/ml. There was a negative correlation between FEV_1, six-minute walk test, and Cystatin C levels in a positive correlation between Cystatin C and CRP levels, duration of disease, CCQ score, mMRC, CAT score, and St. George questionnaire.

KEY WORDS: Spirometry, serum Cystatin C, COPD

INTRODUCTION

A serious public health problem that can be prevented and treated is chronic obstructive pulmonary disease (COPD), which is currently the fourth major cause of death worldwide but is predicted to be the third leading cause by 2020. [1]

COPD is defined by enduring respiratory symptoms and airflow restrictions that are brought on by anomalies in the airways and/or alveoli, which are typically brought on by prolonged exposure to noxious particles or gases. Not only can acute exacerbations of COPD enhance airway inflammation, but also systemic inflammation. The imbalance between protease and anti-protease is a component of the pathophysiology. [2]

Inflammatory cells may be recruited into the lungs of COPD patients with persistent inflammation, which also raises protease activity. Because chronic cigarette smoking in the lungs inhibits the enzyme cathepsin L, there may be a drop in serum Cystatin C levels in those who smoke.[3]

In contrast, bronchoalveolar lavage and serum Cystatin C levels were increased in patients with emphysema, smokers, and in inflammatory lung disease [3]. Additionally, smokers' macrophages had higher amounts of Cystatin C in their culture media than nonsmokers' macrophages did.[3]

It was believed that the rise of Cystatin C was a result of the inflammatory processes occurring in the lung since several studies shown a substantial relationship between inflammatory markers including interleukin-6, tumour necrosis factor, and CRP and Cystatin C. [3,2]. Patients with COPD had elevated levels of serum Cystatin C, which may be a sign of systemic inflammation as the disease progresses [4,5,6]. Hence the measurement of serum Cystatin C levels might help in assessing the severity of disease

The purpose of this study is to determine whether Cystatin C levels have any correlation with the clinical severity of COPD and determine its association with lung function in those patients. This study also aims to assess the impact on the quality of life of COPD patients.

AIM AND OBJECTIVES OF THE STUDY

AIM:

The aim of the study is to correlate serum Cystatin C level with spirometry and also to evaluate its impact on the quality of life in chronic obstructive pulmonary disease patients.

OBJECTIVES:

1. To determine levels of serum Cystatin C in COPD patients.
2. To perform pulmonary function tests in chronic obstructive pulmonary disease patients.
3. To assess the impact of quality of life using MMRC grading, CAT scoring, SGRQ-C, CCQ, 6 Minute walk test and Refined ABCD assessment tool as per Gold 2020 Report.
4. To correlate the quality of life with Cystatin C levels.

REVIEW OF LITERATURE

HISTORY

Since the period of Laennec, chronic obstructive pulmonary disease has been extensively investigated. The relationship between the Disease and smoking was not made until the beginning of the first half of the 20th century.(7)

By OPIE, et al. in 1905, the concept of an enzyme imbalance and the presence of antienzymes as a potential cause of emphysema was first documented. (8)

There were also other more emphysema research studies. Emphysema most frequently impacted the heart, according to a study done in 1934 by Kountz and Alexander.

A vascular atrophy model of the illness was also put up by Liebow et al. in the 1950s.

Proteinase and anti-proteinase hypothesis in emphysema was developed in 1960 as a result of Gross and his co-workers' discovery that patients with emphysema had a 1 antitrypsin deficit.

In its publication, the Medical Research Council introduced the phrase "chronic bronchitis" for the first time in 1956 to describe an illness characterised by a persistent cough and expectoration when other causes, such as pulmonary tuberculosis and bronchiectasis, were ruled out. (9)

In the year, Higgins discovered a connection between smoking and persistent coughing and sputum production in 1959. (10)

Owen and Campell discovered the pathological abnormalities brought on by smoking in 18 airways in the late 1960.(11)

Dr. William Briscoe is thought to be the first person to use the term “chronic obstructive pulmonary disorder” at the 9thAspen Emphysema Conference in June of 1965.

In 1971, 108 people with chronic obstructive pulmonary disease were investigated by Boushy SF et al. The pulmonary function test and hemodynamic data were linked with the ECG. [12]

A series of publications on chronic obstructive pulmonary disease prognostic factors were published in 1973 by Bougly and colleagues mainly includes Lung function test prognostic values in Chronic Obstructive Pulmonary Diseases and pulmonary disease.

Due to the long-term nature of this disease's course, it puts a significant strain on the resources of the healthcare system. Since COPD is a condition that may be prevented, it is extremely important for public health.

PREVALANCE:

Chronic obstructive pulmonary disease (COPD), which is now the fourth leading cause of mortality worldwide but is anticipated to become the third most common reason by 2020 [(1)], is a significant public health issue that is both curable and preventable.

In 2012, COPD claimed the lives of more than 3 million individuals [(1)], or 6% of all fatalities worldwide. A significant public health issue that is both preventable and curable is COPD.

It affects middle-aged and older people, and people under the age of 35 are less likely to contract it.

Due to their higher smoking prevalence than women, men are the most frequently impacted.

Due to an increase in environmental trigger factors throughout the winter, COPD exacerbations are more common.

Previous research from other regions of the country claimed that among people over 40, the prevalence of chronic bronchitis was as high as 16% in North India[(13)] than in South India because of the climatic fluctuations there.

Another study by Bhattacharya et al. [14] revealed that 57 per 1000 people in a rural population had chronic bronchitis by the age of 30 or older. The incidence of the disease increased in direct proportion to age and the number of pack-years of smoking.

PREVALENCE IN WESTERN COUNTRIES:

Around 16 million people in the USA are thought to have COPD, of which 14 million have chronic bronchitis and another 2 million have emphysema. The male-to-female ratio varies between 4 and 6% and 1 and 3%. With almost 1 lakh deaths each year, it is the third most common cause of mortality in the US.

Prospective research conducted in the UK including 40,000 medical professionals revealed that chronic bronchitis was higher in smokers and proportional to pack years.

Chronic Obstructive Pulmonary Disease (COPD)

COPD is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

Nearly all patients have both the air space destruction associated with emphysema as well as the pathologic airway changes that are consistent with chronic bronchitis. However, subsets of the COPD population can differ in terms of natural history and response to therapeutic intervention. Daily cough and sputum for 3 months for two or more years is the qualifying definition for chronic bronchitis.

Common, preventable, and treatable pulmonary disease generally caused by significant long-term cumulative exposure to noxious particles or gases (such as cigarette smoking) combined with other factors including hyperresponsiveness of airway, genetics and abnormal

development of lung, ultimately resulting in airflow limitations due to chronic airway inflammation and/or parenchymal destruction (emphysema)[15]

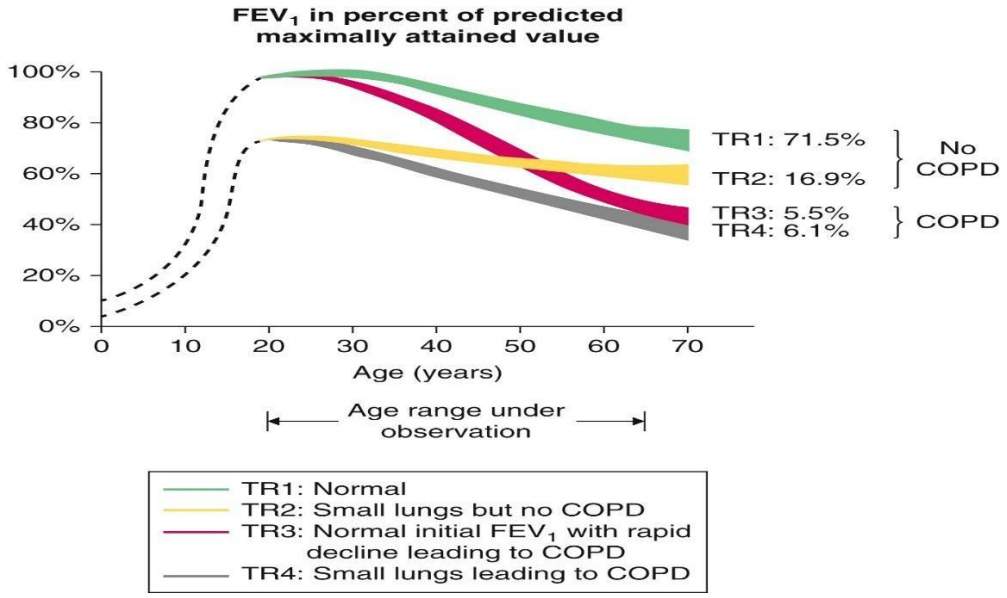
Terms "emphysema" and "chronic bronchitis" not included in Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of COPD

i. Chronic bronchitis - cough and excess sputum production for ≥ 3 months per year in each of 2 consecutive years
ii. Emphysema - pathological term describing destruction of gas exchanging surfaces of lung (alveoli)

COPD exacerbation defined as acute worsening of respiratory symptoms requiring additional therapy [15]

Epidemiology[15]

90% of COPD deaths reported to occur in low- and middle-income countriesprevalence increases with age, but unclear if healthy ageing leads to COPD or if age reflects sum of cumulative exposures throughout life.



Graph 1:Decline in lung function with age[1]

An estimated 175 million adults worldwide are thought to have COPD, an adult disease that typically manifests in the sixth or later decade of life. COPD is the third most common cause of death in the world, with an estimated 3.2 million deaths each year. [16] Given the time lag between starting to smoke and the manifestation of clinical illness, the frequency of cigarette smoking worldwide and the average population age predict that the number of cases will continue to climb. The projected yearly cost of COPD in the United States is $50 billion, of which $30 billion is spent on direct medical expenses and $20 billion on indirect expenses.

The idea that smoking cigarette is the main risk factor for the onset of COPD is supported by epidemiologic data. The "dose" of smoking, expressed in pack-years is inversely correlated with FEV 1 at the population level.

Lower peak lung function in adulthood is caused by factors that prevent full lung development, such as childhood respiratory illnesses; subsequent decrease, whether or not it is accelerated, can lead to the development of COPD.

The primary cause of COPD is unquestionably cigarette smoking, but other exposures are also linked, particularly when biomass fuels are burned in poorly ventilated areas where they are used for heating and cooking. Less is known about the function of environmental air pollution. People who are exposed to workplace dust in mines, grain-handling facilities, and cotton mills may also have coughing, sputum, and a permanent loss of lung function. Research showing that higher pollution levels are temporally related to higher mortality in individuals with existing COPD. It is unknown if previous respiratory infections have any lasting consequences on adult lung function.

Risk factors

- Factors associated with COPD development and progression
    i. Tobacco smoke (active smoking or passive environmental exposure)

ii. other particle exposures such as
    a) outdoor air pollution such as from urban environments
    b) Indoor air pollution such as animal dung, crop residues, burning wood, or coal
    c) occupational exposures including organic and inorganic dusts, chemical agents, and fumes
iii. genetic factors and family history of COPD
iv. demographic factors
    a) older age
    b) male sex
    c) low socioeconomic status
v. Respiratory features including
    a) suboptimal lung development during gestation or childhood (including leading to reduced maximal attained lung function)
    b) asthma and airway hyperreactivity
    c) infections such as
        a. history of severe childhood respiratory infection
        b. Pseudomonas aeruginosa infection
        c. Tuberculosis
    d) chronic bronchitis
vi. HIV

Associated Conditions[15]

- COPD frequently co-occurs with comorbidities (due to causal or exacerbating relationship and/or shared risk factors) which may affect prognosis and management strategies
    i. shared symptoms and/or signs between COPD and multiple frequent comorbidities necessitate careful evaluation and consideration
    ii. COPD may occur as part of multi-morbidity (≥ 2 chronic conditions)
- significant comorbidities include[15]
    i. cardiovascular diseases, including
    ii. hypertension
    iii. coronary artery disease (CAD)
    iv. atrial fibrillation
    v. peripheral vascular disease
    vi. heart failure with reduced ejection fraction or heart failure with preserved ejection fraction
    vii. increased subclinical cardiovascular disease assessed by surrogate markers (carotid intima-media thickness and arterial stiffness measured by pulse wave velocity)
- lung cancer[15]
    i. risk factors for lung cancer in patients with COPD include
        a) age > 55 years
        b) smoking history > 30 pack years
        c) emphysema on computed tomography scan
        d) airflow limitation on forced expiratory volume in 1 second/forced vital capacity < 0.7

e) body mass index < 25 kg/m2

f) family history of lung cancer

Etiology and pathogenesis:

Causes:-[15]

• persistent airway inflammation and/or parenchymal destruction brought on by prolonged cumulative exposure to noxious particles or gases (such as cigarette smoking) and other factors like heredity and faulty lung development (emphysema)

• People who never smoked can also get COPD, while it is uncertain what causes the inflammatory response in these circumstances.

Pathogenesis[15]:-

According to data, the pulmonary vasculature, lung parenchyma, and airways all play significant roles in COPD patients. The relative relevance of these processes differs between patients, which affects how the disease manifests and how it responds to treatment.

The protease-antiprotease theory is the most widely recognized idea for how emphysema develops. According to this idea, emphysema happens when there is an excess of elastolytic protease activity compared to antiprotease levels. This theory's foundation is the finding that those who are lacking in 1 -antiprotease have a higher likelihood of acquiring emphysema. 1 -Antiprotease is a significant inhibitor of neutrophil elastase and a member of the serpin (serine protease inhibitor) superfamily. Emphysema can result from the degradation of elastin by proteases. Emphysema can also be brought on by macrophage elastases in addition to neutrophil elastase.

Smoking cigarettes cause an influx of inflammatory cells, such as neutrophils and macrophages, into the lung. In terms of quantity, macrophages make up the majority of this

reaction. The theories that vascular processes and apoptosis may play a role in the emergence of emphysema are also supported by experimental findings. Smokers frequently experience small airway irritation and the presence of pigmented macrophages.

Neutrophils and CD8+ lymphocytes are also crucial elements of the inflammatory response. Eosinophils are a very minor part of the inflammatory response in COPD, in contrast to many asthma patients, but a subset of COPD patients exhibit sputum and peripheral eosinophilia. Reactive oxygen species and oxidative stress may play a role in the signalling that supports this inflammatory response.

The inflammatory response in the lung is still present in COPD patients even after they stop smoking. This finding offers a plausible explanation for the clinical observation of the disease's ongoing development despite smoking cessation, along with data on microbiome changes and evidence of autoimmunity in people with COPD.

Smoking results in intimal thickening, smooth muscle proliferation, a reduction in vascular endothelial growth factor (VEGF) production, and endothelial cell death in septal arteries in emphysema patients' pulmonary vasculature. Emphysema can be created by manipulating VEGF expression in animal models, which implies that pulmonary vascular alterations may be the main cause of COPD in some people. Chronic hypoxemia also causes pulmonary vascular constriction, which eventually results in pulmonary hypertension.

In chronic bronchitis, symptoms of cough and excessive sputum production are all correlated with hypertrophied bronchial mucous glands, an increased epithelial goblet cell population, and increased airway mucin concentration, but not with airflow restriction.

PATHOPHYSIOLOGY: -

COPD is indicated by obstruction of the expiratory airflow. Anatomically, this flow limitation is located in the small airways (less than 2 mm). A few of the mechanisms that can cause

obstruction include constriction of the smooth muscles of the airways, inflammation of the small airways, wall thickening and scarring, loss of the small airways due to parenchymal destruction, and dynamic airway collapse due to the loss of parenchymal tethering secondary to the parenchymal destruction that is typical of emphysema.

In the context of parenchymal injury, a contemporaneous alteration might be a reduced driving power as a result of a loss of elastic rebound. The extended expiratory duration brought on by this airflow limitation may be seen as a definite "coving" of the flow rates with time on a spirogram the part of the flow volume loop that is expiratory. When the expiratory time is shortened prior to the beginning of the succeeding inspiration due to an elevated respiratory rate, only a portion of the previous tidal volume is expelled. In a situation known as dynamic hyperinflation, the end-expiratory lung volume (EELV) increases to the point where the expiratory flow rates are high enough to completely expel the preceding tidal volume.

Independent of hypoxemia, an increase in EELV might cause a feeling of dyspnea. Emphysema, in its purest form, causes dynamic expiratory airway collapse as a result of the loss of tethering, the destruction of parenchymal tissue, the loss of tiny airways, and the loss of the alveolar gas exchange surface.

In contrast, chronic bronchitis is characterized by mucous gland enlargement and hypersecretion, increased airway responsiveness with subsequent dynamic smooth muscle constriction, and airway inflammation. Airflow obstruction and a persistent, productive cough that produces sputum are the results of this.

GENETICS:

Alpha One-antitrypsin deficiency is the most prevalent monogenic characteristic linked to COPD. The serine protease inhibitor that the liver produces and secretes, 4 alpha b-1-antitrypsin, is encoded by the SERPINA1 gene. A functional protein cannot be secreted as a

result of the most frequent mutations linked to deficiency, which cause polymerization of 1 -antitrypsin in the liver.

Approximately 15% of normal circulating levels of alpha 1-antitrypsin are related with an increased risk of emphysema, bronchiectasis, and liver illness in some people.

The likelihood that these mutations induce clinically significant organ damage is probably influenced by other variables, particularly smoking, as fewer people than predicted are identified with COPD and 1 -antitrypsin deficiency. It is debatable if people who are heterozygous for a mutant allele have a higher chance of developing lung disease. Emphysema or airflow restriction are two other hereditary disorders.

Cutis laxa (elastin, fibulin 4 and fibulin 5), Ehlers-Danlos syndrome, and Marfan syndrome are among the conditions caused by these genes. The finding that a minority of smokers acquire COPD and that there is family clustering of COPD cases have given rise to the theory that genetic variables account for the varied responses to cigarette smoke. MMP-12 and Serpin E2 are two of the genes that have been linked, however these results have been contradictory. Current longitudinal research might perhaps offer greater proof of genetic influences on COPD.

CLINICAL FEATURES: -

Persistent and Progressive Breathlessness is the sign of COPD [(1)]. Maximum effort is frequently not constrained by ventilatory capacity; therefore, people might have substantial COPD before experiencing symptoms. Patients frequently experience symptoms for months or years before a COPD diagnosis is obtained due to the illness's sluggish course and the fact that other conditions including heart disease, obesity, and deconditioning can also cause dyspnea when exerted,

When a patient experiences an exacerbation, which is marked by increased dyspnea, coughing, and sputum production and may or may not be accompanied by fever and other constitutional

symptoms suggestive of infection, the condition is commonly diagnosed as COPD. When these symptoms first appear, the patient may decide to consult a doctor, at which point the history may reveal exposures that increase the risk of COPD and prior exercise-induced dyspnea (usually persistent cigarette smoking). In a minority of persons, recurrent exacerbations play a crucial role in the course of COPD.

COPD with chronic bronchitis, by definition, has a persistent cough and phlegm. Patients with chronic bronchitis may experience hemoptysis, especially during an exacerbation. Clubbing is not a sign of COPD, therefore if you have it, you should get checked out for other diseases, such lung cancer or pulmonary fibrosis.

Hypoxemia or hypercarbia may occur in patients with more severe illness. Cyanosis can result from hypoxemia, which is often detected by pulse oximetry. An arterial blood gas test is necessary to confirm hypercarbia, which may be indicated by a raised serum bicarbonate level.

Systemic symptoms of COPD might potentially include arrhythmias like atrial fibrillation. Emphysema patients lose body mass and may become sarcopenic. An important restriction in activity may cause pulmonary hypertension to develop. COPD and depression frequently co-occur.

The diagnosis may be affected by a history of smoking, other inhalational exposures, preterm delivery or repeated lung infections in infancy, a cough (chronicity, frequency), and sputum production. The degree to which dyspnea restricts activity should be emphasised in particular since patients may gradually reduce activity over time to avoid the painful sensation of being out of breath and may not report having dyspnea when engaging in normal daily activities. Patients should be questioned about coexisting conditions and any lung disease in their families.

A large anteroposterior thoracic dimension (barrel chest), the use of the arms to stabilise the shoulder girdle to enable the use of accessory muscles of respiration (tripod position), a history of less dyspnea when pushing a cart than when walking, and, in severe cases, retraction of the lower rib cage with inspiration due to the altered biomechanics of flattened diaphragms are all possible effects of chronic hyperinflation associated (Hoover sign). Abdominal wall motion that contradicts itself with inspiration is a sign of fatigued respiratory muscles. Chest percussion may demonstrate elevated resonance. In patients with emphysema as their primary diagnosis, auscultation may indicate diminished breath sounds; asymmetry increases the risk of pneumothorax. When pushed to exhale, patients with airway illness may wheeze and have rhonchi.

The shape of the chest wall and the right heart's function are primarily implicated in cardiac abnormalities in COPD. A decrease in heart sounds might result from increased retrosternal airspace. Elevated jugular venous pressure, a louder-than-normal pulmonic valve closure sound (P2), a right ventricular heave, hepatic congestion, and peripheral edema all enhance the risk of pulmonary hypertension (cor pulmonale). Given that smoking is a risk factor for lung cancer and that persons with COPD have an approximately 2-fold greater risk of acquiring lung cancer than smokers without COPD, hemoptysis should prompt a check to see whether the patient has lung cancer. Patients with emphysema as their predominant COPD symptom may have weight loss and sarcopenia, as revealed by a physical exam.

Assess severity of symptoms; useful tools include [15]

- modified Medical Research Council (mMRC) questionnaire evaluates breathlessness based on the scale of 0 (breathless with strenuous exercise) to 4 (too breathless to leave the house or breathless when dressing or undressing)

- COPD Assessment Test (CAT) is an 8-item questionnaire that may aid in determining the disease-specific, health-related quality of life
- The impact of COPD on a specific patient is determined by combining their symptom evaluation with their spirometric classification and/or exacerbation risk. Because it incorporated patient-reported outcomes and emphasised the significance of exacerbation prevention in the management of COPD, the "ABCD" assessment tool of the 2011 GOLD update represented a significant improvement over the straightforward spirometric grading system of earlier versions of GOLD.
- To start, the ABCD evaluation method did not outperform spirometric grades in predicting death or other crucial health outcomes in COPD1. Additionally, results for group "D" were influenced by either exacerbation history or lung function, which led to misunderstanding. A modification of the ABCD evaluation instrument is suggested that isolates spirometric grades from the "ABCD" categories in order to solve these and other issues (while retaining consistency and simplicity for the practical clinician). The ABCD categories for certain therapy suggestions are generated only from the symptoms and exacerbation history of the patient. Spirometry continues to be essential for the diagnosis, prognosis, and evaluation of other significant treatment options. It should be used in conjunction with patient symptoms and a history of mild and severe exacerbations. This novel method of assessment is demonstrated in the figure 1.
- Number provides information regarding severity of airflow limitation (spirometric grade 1 to 4) while the letter (groups A to D) provides information regarding symptom burden and risk of exacerbation which can be used to guide therapy. FEV1 is a very important parameter at the population-level in the prediction of important clinical outcomes such as mortality and hospitalizations or prompting consideration for non-pharmacological therapies such as lung volume reduction or lung transplantation.

However, it is important to note that at the individual patient level, FEV1 loses precision and thus cannot be used alone to determine all therapeutic options. Furthermore, in some circumstances, such as during hospitalization or urgent presentation to the clinic or emergency room, the ability to assess patients based on symptoms and exacerbation history, independent of the spirometric value, allows clinicians to initiate a treatment plan based on the revised ABCD scheme alone. This assessment approach acknowledges the limitations of FEV1 in making treatment decisions for individualized patient care and highlights the importance of patient symptoms and exacerbation risks in guiding therapies in COPD. The separation of airflow limitation from clinical parameters makes it clearer what is being evaluated and ranked. This facilitates more precise treatment recommendations based on parameters that are driving the patient's symptoms at any given time.

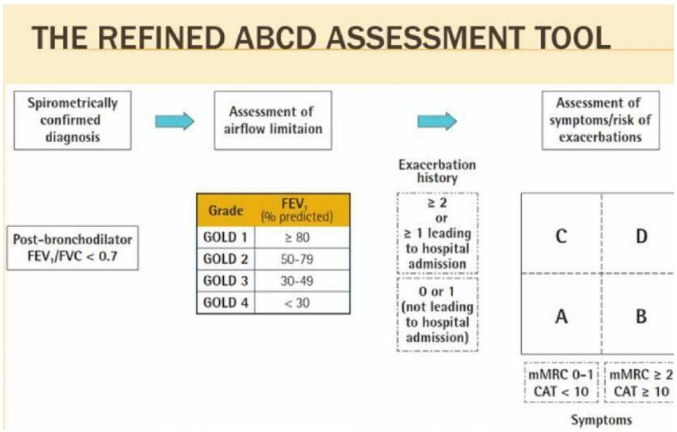


Fig:1 REFINED ABCD ASSESSMENT TOOL[(1)]

ACUTE EXACERBATION OF COPD:-

An increase in dyspnea beyond the patient's typical level, a coughing fit, or an increase and modification in the nature of mucus production are all considered signs of an acute exacerbation of COPD. Roughly 60% of the direct medical expenses associated with COPD

are attributable to acute exacerbations, which have an independent negative impact on quality of life and have a short-term death rate of about 10%.

The most prevalent mechanism for an exacerbation, regardless of the initial stimulus, is an inflammatory response that comprises airway inflammation, mucus hypersecretion, and airway smooth muscle constriction, which combined produce in the classic triad of dyspnea, cough, and sputum. It is possible to find viral or bacterial infections in 75–80% of COPD acute exacerbations.

Rhinovirus, influenza, parainfluenza, respiratory syncytial virus, coronaviruses, and adenovirus are the viruses that are most commonly implicated. The bacterial species that have been linked to exacerbations in a number of individuals with chronic bronchitis include Streptococcus pneumoniae, Haemophilus influenza, Moraxella catarrhalis, and, to a lesser extent, Pseudomonas aeruginosa.

Other environmental exposures most certainly have a role as well, especially in the 20 to 25 percent of cases when no pathogen or viral exposure was found. For instance, people with COPD who visit the emergency room more frequently for respiratory symptoms do so when ambient air pollution is higher.

Clinical Manifestations and Diagnosis:

The symptoms of acute exacerbations of COPD are typically comparable to those of acute bronchitis because they are frequently accompanied by fever or happen after contact with ill people. Questions concerning the patient's recent history of exacerbations, concomitant conditions including heart disease, previous viral exposures, baseline functional state, past treatment responses (if any), and the presence of somnolence or disorientation that might indicate hypercarbia should be asked. In addition to acute COPD exacerbations, decompensated heart failure, pneumonia, pulmonary embolism, and pneumothorax should also

be taken into account as potential causes. A big airway tumour is less probable. The signs and symptoms of acute exacerbations of COPD are typically comparable to those of other illnesses since they frequently come with fever or happen after contact with sick people.

Vital signs evaluation and detection of respiratory distress symptoms should be part of the physical examination. symptoms of left or right heart failure should all be looked for during the cardiac examination to determine whether there is tachycardia, irregular rhythm, or any of these conditions. Unusual mental state should prompt worries about hypercarbia.

An arterial blood gas should be performed on individuals who are experiencing respiratory distress or who have other causes to suspect hypercarbia as part of the laboratory examination. Measuring the circulating amount of brain natriuretic peptide in patients may assist identify those with substantial left heart failure since tachycardia, increased jugular venous pressure, and peripheral edema can occur in both left and right heart failure. Antibiotic prescriptions can be decreased with no evidence of damage by using point-of-care C-reactive protein testing to direct dosing.

Only around 5% of patients will likely have their medication changed as a result of a chest radiograph, which shows abnormalities in roughly 15% of individuals. Any patient with chest discomfort, leukocytosis, a history of heart disease, or another aggravating condition should always have a chest radiograph taken. A sputum culture is often unlikely to have an impact on treatment.

Imaging Studies

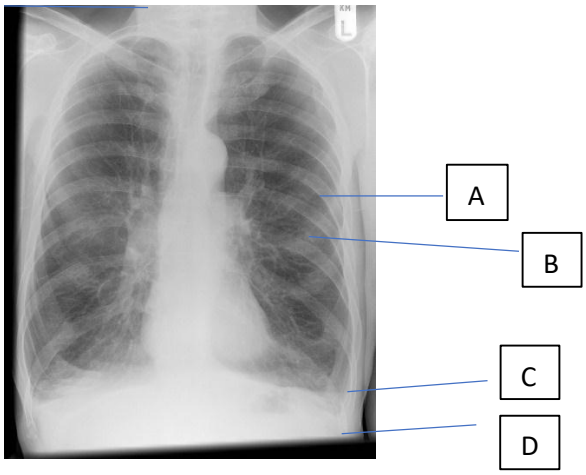


Fig:2 chest-xray[17]

Signs of hyperinflation such as[(18)]

A Hyperlucency of the lungs

B Increased rib space

C. Obtuse costophrenic angle

D. Low diaphragm (considered low if the border of the right hemidiaphragm in the midclavicular line lies at or below anterior end thethe of seventh rib)

- Diaphragmatic flattening
    a) Seen best on lateral films
    b) Perpendicular height < 1.5 cm indicates flattening

Other findings include:

- Saber-sheath trachea (trachea normal to level of thoracic inlet, then narrows in coronal plane)
- Increased retrosternal airspace (> 2.5 cm between sternum and ascending aorta)
- Increased length of lung (> 30 cm)

- Prominent vessels (large central pulmonary arteries if pulmonary hypertension has developed)
- vascular markings get tapered rapidly

Computed Tomography (CT) Scan:-

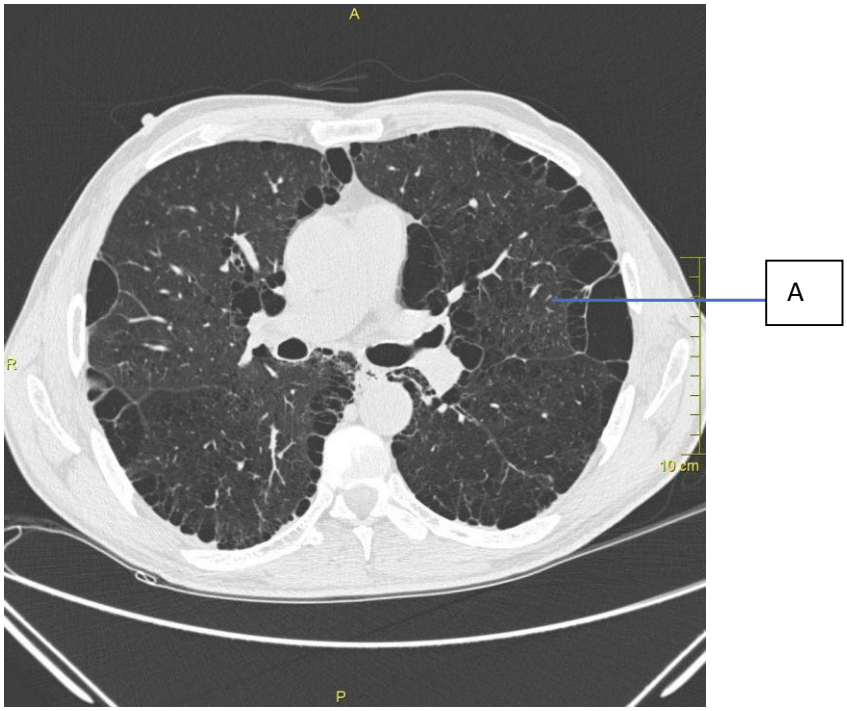


Fig:3 computed Tomography[17]

A. Emphysematous lesions in the parenchyma adjacent to the pleural surfaces

- Paraseptal emphysema

Other uses:-

i. Planned surgical procedure such as lung volume reduction or transplant, or prior to bronchoscopic lung volume reduction
ii. For detecting comorbidities or differential diagnoses

Diagnostic Testing:

The diagnosis is established by spirometry showing airflow obstruction When the FEV 1 / FVC ratio drops to less than 0.7, obstruction is present. Lower ratios, which are typically stated as a percentage of expected determined from reference data gathered for a normal population, indicate severe blockage (standardised by age, sex, height, and ethnic background). The lung volumes may show residual volume (RV) and total lung capacity.(TLC). Emphysema or pulmonary hypertension patients may have lower DLCOs, depending on how many pulmonary capillary vessels involved in gas exchange have been lost.

Pulmonary Function Tests

Pulmonary function test (PFTs) are diagnostic tests to evaluate lung function

clinical role of PFTs includes

- Aiding in the diagnosis of lung diseases by determining presence and severity of lung function defects
- Monitoring of lung function in patients with known lung disease

PFT measurements include

- Capacities
    i. total lung capacity (TLC) - volume of air in the lungs at maximum inhalation
    ii. vital capacity (VC) - volume of air from maximal inspiratory effort to maximal expiratory effort
    iii. inspiratory capacity (IC) - volume of air from resting expiratory level to maximal inspiratory effort
    iv. functional residual capacity (FRC) - volume of air in the lungs after unforced tidal volume expiration

v. maximal voluntary ventilation (MVV) - maximal inspiration and expiration over 12-15 seconds

- volumes
    i. tidal volume (Vt) - volume of air from nonforced expiratory level to normal nonforced inspiratory level
    ii. expiratory reserve volume (ERV) - volume of air that can be exhaled after resting expiration
    iii. inspiratory reserve volume (IRV) - volume of air that can be inhaled after normal inspiration
    iv. residual volume (RV) - volume of air left in the lungs after maximal expiratory effort
    v. forced expiratory volume in 1 second (FEV1) - maximal amount of air exhaled during forceful expiration in first second from a point of maximal inspiration
- Ratios
    i. FEV1/FVC ratio - ratio of the volume of air expelled during the first second of forced expiration from maximal inspiration to the total volume of forced expiration from maximal inspiration
    ii. FEV1/VC ratio - similar to FEV1/FVC ratio, but the largest VC determination is used which can be obtained by slow inspiration, forced inspiration, slow expiration, or forced expiration
- Flow rates and flow-volume loops
    i. peak expiratory flow (PEF) - maximum flow rate of air during forced expiration from maximal inspiration
    ii. forced expiratory flow25%-75% (FEF25-75) - flow rate in the middle half of forced expiration from maximal inspiration

iii. (flow-volume curve) - graphic display of the flow of air during forced expiration and forced inspiration

i. bronchoprovocation testing is a method that measures bronchial hyper-responsiveness to a stimulant

Table :1Common patterns of disease on PFTs [(1)]

Measurement	DISEASE CATEGORY	
	Obstructive	Restrictive
FVC	Normal/decreased	Decreased
FEV_1	Decreased	Decreased
FEV/FVC	Decreased	Normal

- obstructive pattern common in
  - i. asthma (reversible)
  - ii. COPD
  - iii. bronchiolitis obliterans
  - iv. constrictive bronchiolitis obliterans
  - v. sarcoidosis
  - vi. bronchiectasis
  - vii. cystic fibrosis (CF)
  - viii. alpha-1 antitrypsin deficiency
  - i. sarcoidosis
- increased DLCO common in
  - i. obesity
  - ii. pulmonary alveolar hemorrhage

iii. asthma

iv. polycythemia

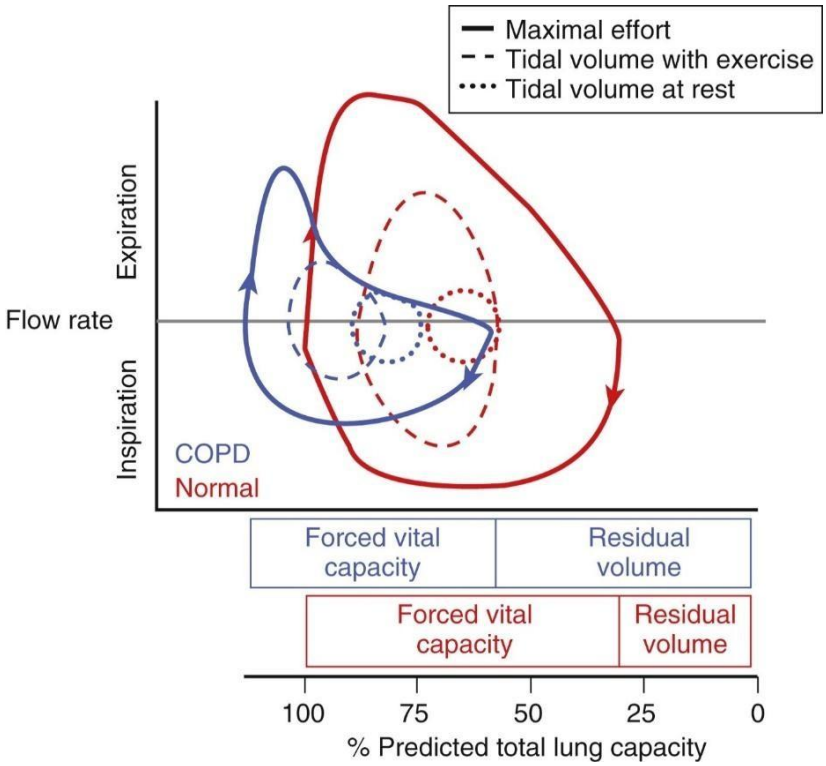


Fig :4 [15] Representative flow-volume loops in normal subjects (red) and COPD (blue).

Spirometry

- Spirometry reported to be most reproducible, objective, noninvasive, and readily available measurement of airflow obstruction
- Use spirometry to diagnose airflow obstruction in patients with respiratory symptoms but not to screen for airflow obstruction in patients without respiratory symptoms
- Spirometry demonstrating forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio < 0.7 confirms diagnosis

- In addition to diagnosis of COPD, spirometry also useful for COPD severity assessment and follow-up evaluations to inform therapeutic decisions and to identify worsening conditions.

Table 2: Classification of Airflow limitation Severity in COPD [(1)]

STAGE AND SEVERITY	DEFINITION
I: Mild	$FEV_1/FVC < 0.70$, $FEV_1 \geq 80\%$ of predicted
II: Moderate	$FEV_1/FVC < 0.70$, $50\% \leq FEV_1 < 80\%$ of predicted
III: Severe	$FEV_1/FVC < 0.70$, $30\% \leq FEV_1 < 50\%$ of predicted
IV: Very severe	$FEV_1/FVC < 0.70$, $FEV_1 < 30\%$ of predicted or $FEV_1 < 50\%$ of predicted plus chronic respiratory failure

Mechanisms of Oxidant Injury and Antioxidants

Oxidant stress and injury resulting from reactive oxygen species (ROS) is the ultimate trigger for the three major pathologic changes (mucus abnormalities, emphysema, and pulmonary microvascular changes) culminating in distinct COPD clinical phenotypes.

The principal ROS are superoxide anion, hydrogen peroxide, and the hydroxyl radical, the most damaging ROS.ROS arise either exogenously, from air pollution, or endogenously. Mainstream CS contains high concentrations of oxidants (1014 molecules/puff) and 3000 ppm nitric oxide/puff, and over 4700 chemical compounds.[(19)]

ROS in CS range from short-lived oxidants, such as the superoxide radical and nitric oxide, to long-lived organic radicals, such as semiquinones.

Aerosols from vaping and heat-not-burn tobacco products have much lower free radical levels than CS but do emit volatile carbonyls, furans, and toxic metals, including chromium, lead, and nickel. Inhalational exposure to e-cigarette vapor causes adverse respiratory outcomes in animal models.[21-22]

One study of e-cigarette users showed elevated lung concentrations of neutrophil elastase (NE) and the matrix metalloproteinases (MMPs)-2 and -9 with no change in antiprotease concentrations. [23] Insights have come from the public use data files for the Population Assessment of Tobacco and Health, which collected nationally representative, population-based, longitudinal data[24] three times from 2013 to 2016. Results imply that use of e-cigarettes is a risk factor for respiratory disease, independent of combustible tobacco smoking, and that dual use, the most common pattern, is riskier than using either alone. These devices were also recently associated with a syndrome of acute lung injury in humans.

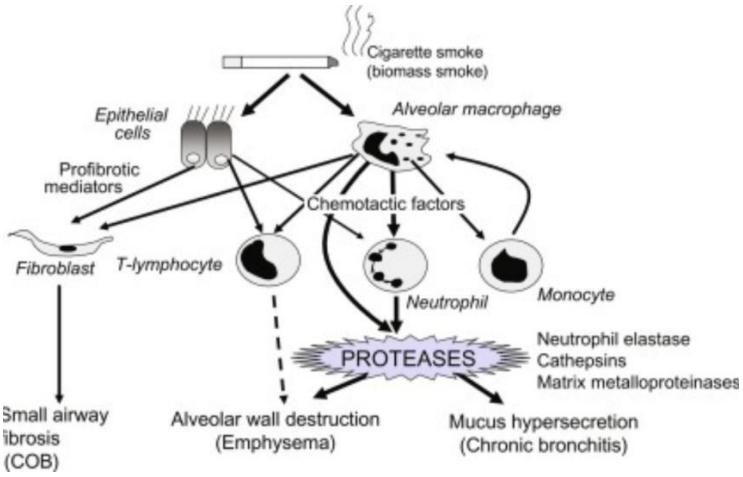


Fig:5 [24]smoking induces endogenous ROS production and destruction of lung

Smoking and other oxidative inhalational stressors induce endogenous ROS production by lung epithelial cells, alveolar macrophages (AMø), and other phagocytes. Reduced nicotinamide adenine dinucleotide phosphate oxidase is the principal intracellular ROS source, but mitochondrial respiration and the xanthine/xanthine oxidase system also participate. The

impact of oxidant stress is amplified in smokers due to the increased levels of iron in their lungs, which, by redox cycling of Fe ++ and Fe +++ (via the Fenton and Haber-Weiss reactions), can produce the highly toxic hydroxyl radical. Phagocytes also produce two very damaging oxidants, hypochlorous acid and hypo bromous acid, via cell-type specific enzymes that include myeloperoxidase and eosinophil peroxidase. During severe AE-COPD, oxidant stress in the lungs increases markedly in parallel with neutrophil recruitment. Oxidative stress can be measured by a host of biomarkers.

Excessive ROS damage cells in multiple ways. Lipid peroxidation of polyunsaturated fatty acids causes them to reorient out of the membrane plane, making them targets for scavenger receptors.Because the reaction of a radical with a nonradical always produces another free radical, lipid peroxidation can proceed as a chain reaction. One stable product of lipid peroxidation, 8-isoprostane, potently stimulates airway smooth muscle contraction via the thromboxane A 2 receptor.

ROS produce diffusible reactive aldehydes, including acrolein, that create protein adducts by targeting cysteine, histidine, and lysine residues. Such adducts impair the function of matrix components and of enzymes crucial to regulating gene expression, such as histone deacetylase 2, which is important for inactivation of proinflammatory genes. The reaction of ROS with nitric oxide forms peroxynitrite, which causes tyrosine nitration, particularly of histone deacetylase 2, perpetuating inflammatory mediator production. Carbonylation describes two distinct kinds of damaging results of oxidants, both the direct non-enzymatic, irreversible oxidation of amino acid side chains, and non-oxidative covalent adduction of reactive carbonyl species generated by the oxidation of lipids or carbohydrates.

Multiple pathways lead to reactive carbonyl species, particularly by metal-catalyzed oxidation of lysine, arginine, proline, and threonine residues. Carbonylation may be important in late

stages of COPD because it renders proteins potentially antigenic. Finally, ROS can damage DNA directly, particularly at guanine residues.

Cystatin C

In place of or in addition to creatinine, the endogenous filtration marker Cystatin C has been proposed. Cystatin C has a long history dating back to 1961. Cystatin C was initially discovered in CSF and urine in individuals with renal insufficiency in 1961 as a trace protein (gamma trace). Grubb and initially detailed the Cystatin C amino acid sequence.

Lofberg. It was initially shown to be higher in patients with renal failure. Grubb and colleagues originally proved its use in the assessment of GFR in 1985. [25] Following this, there has been substantial research on the involvement of Cystatin C in CKD and AKI.

structure and function:

A single polypeptide chain containing 120 amino acid residues makes up the 13,343-dalton protein known as Cystatin C.[26]

Cystatin C controls cysteine proteases' actions to stop unchecked proteolysis and tissue injury. [27,28]

Plasma levels:

The 0.52 to 0.98 mg/L reference range for serum Cystatin C is given. The precise "normal level," however, is unknown since, like other filtration indicators, it relies on the GFR level. The third National Health and Nutrition Examination Survey (NHANES III), a sample of the non-institutionalized US population, found that among young adults aged 20 to 39 without hypertension or diabetes, 0.85 mg/L was the median plasma Cystatin C level. and the upper 99th percentile was 1.12 mg/L. [29]

It was calculated that the median blood level was 8% lower in women than in men, that it rose dramatically with ageing, and that it was greater in non-Hispanic whites. Age, sex, and ethnicity all had a correlation with Cystatin C levels.

The prevalence of increased blood Cystatin C levels (>1.12 mg/L) was 1%, 41%, and greater than 50%, respectively, in those under the ages of 20, 60, and 80. Higher serum Cystatin C levels are associated with older age, non-Hispanic white ethnicity, hypertension, current smoking, lower levels of education, lower levels of high-density lipoprotein, higher levels of body mass index, C-reactive protein, and triglyceride values, as well as all of the previously mentioned risk factors. [30]

Generation

it is believed that all human nucleated cells consistently produce Cystatin C. Contrary to creatinine and urea, Cystatin C is not removed in the urine, hence studies of its synthesis in humans have evaluated the link between varied plasma levels and demographic and clinical characteristics after accounting for the quantity of observed Ccr or GFR. These results show that Cystatin C has a weaker association with age and sex than creatinine and is less dependent on muscle mass and diet. As a result, it is not racially linked. Higher BMI, increased levels of C-reactive protein, and smoking are the most dependable indicators of higher levels of Cystatin C. [31–34].

Renal Handling:-

Because Cystatin C is completely filtered at the glomerulus, taken up by the proximal tubular cells, and then catabolized, it is anticipated that very small amounts of Cystatin C are lost in the urine under normal circumstances.

• Filtration inside the glomus. Cystatin C's molecular size (3 nm) implies that the glomerulus may readily filter it.

• Tubular secretion and reabsorption. Following its passage through the glomerular membrane, Cystatin C is broken down by proximal tubular cells. [35] Cystatin C is lost in the urine more often in renal illness because tubular damage prevents it from being reabsorbed. [36,37] No evidence exists for tubular secretion.

Extrarenal Elimination :

In nephrectomized rats, extrarenal Cystatin C elimination was seen to occur in the spleen, diaphragm, heart, liver, and lungs, with a 15% removal of Cystatin C overall, according to estimates. [38,39]

Assay:

Particle-enhanced turbidimetric immunoassay (PETIA) and particle-enhanced nephelometric immunoassay (PENIA) are the two methods used most frequently by commercially available auto analyzers to assess Cystatin C [40,41].

Commonly seen interfering variables including bilirubin, rheumatoid factor, hemoglobin, and triglycerides do not cause any interference when using the PENIA technique. However, bilirubin concentrations of 150 to 300 mol/L (8.8 to 17.5 mg/dL) only slightly increase Cystatin C levels by less than 10%, according to the PETIA technique.[40]

Even though the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on Standardization of Cystatin C has developed and characterised both a primary and a secondary reference preparation for Cystatin C, there are still substantial variances around the globe. [41,42].

After evaluation by BioVendor, an easy-to-use ELISA method has been developed and is commercially available for human use.

serum Cystatin C measurement showed an excellent correlation across a wide assay range by the three methods. There was, however, a significant lack of parallelism between the measured levels from the three methods. A normalization factor of 0.66 multiplied by ELISA-derived Cystatin C level improved the accuracy of the ELISA method to predict Cystatin C measured by both nephelometric and turbidimetric methods [42]

ROLE OF SERUM CYSTATIN C IN COPD :-

An inflammatory condition called COPD causes rapid lung function decline. The migration of inflammatory cells and an increase in protease activity in the lungs are both possible effects of ongoing inflammation in COPD.

Chronic cigarette smoking may lower the lungs' levels of Cystatin C, an inhibitor of cathepsin L, which may result in emphysematous alterations [44]. In contrast, elevated levels of Cystatin C in BAL and serum were seen in emphysema patients, particularly in smokers and people with inflammatory lung disease [45,46,47]. Additionally, it has been demonstrated that smokers' alveolar macrophages have greater levels of Cystatin C in their culture media than non-smokers [48]. Emphysema and serum Cystatin C were significantly correlated in a different investigation in a sizable representative US sample.

In comparison to the healthy controls, the emphysema group's mean Cystatin C levels were considerably greater. The authors came to the conclusion that exposure to either active or passive smoking might raise blood Cystatin C levels [47].

it was previously believed that the rise of Cystatin C was a result of the inflammatory processes in the lung since inflammatory markers including interleukin-6, resistin, tumour necrosis factor, and CRP were discovered to have a strong relationship with Cystatin C. [47, 49].

Factors that affect serum Cystatin C levels :

In a sample of the general population, variables linked to the synthesis and/or catabolism of serum Cystatin C may have a greater impact on serum Cystatin C levels than GFR.

Thus, it is crucial to remember that advanced age, male gender, larger weight, and height In comparison to the healthy controls, the emphysema group's mean CysC levels were considerably greater.

AGE:

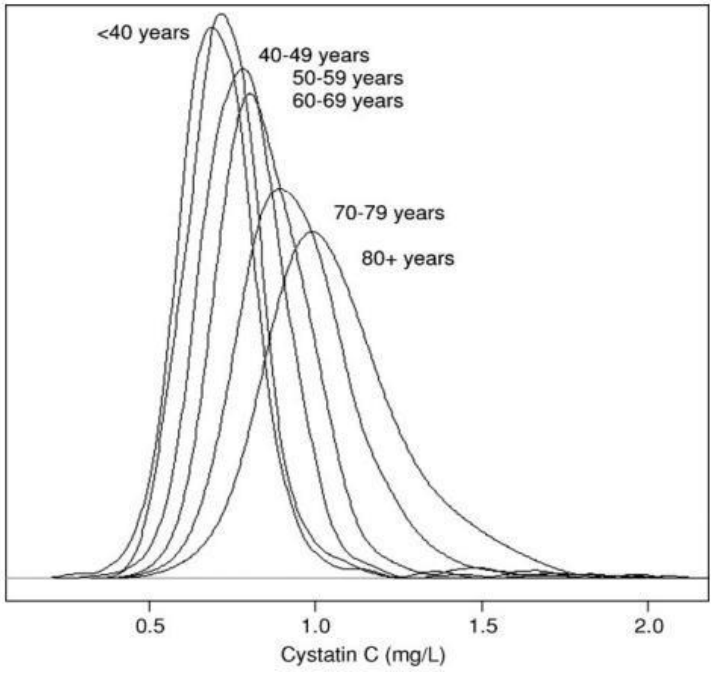


FIG :6[(50)] The graphic shows how participants without kidney disease risk factors distributed their Cystatin C concentrations by decade of age. With each additional decade of age, the mean and variance increase.

When those without any clinical risk factors for renal disease had a range of Cystatin C values, we saw a substantial correlation between age and Cystatin C. (Figure 4). With an almost normal distribution, the mean Cystatin C concentration and the variation increased with each decade of higher age.

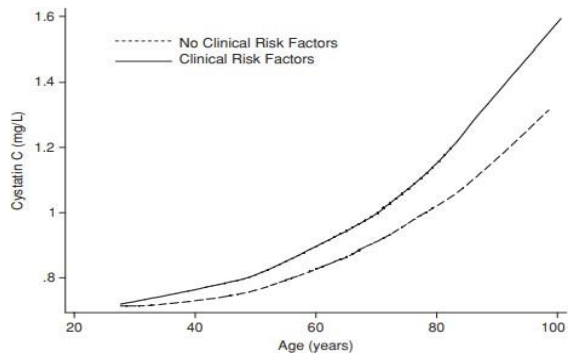


Fig:7[50] Age and Cystatin C over the age range for participants with and without clinical risk factors for kidney disease, shown in a smoothed manner. Clinical risk factors included coronary heart disease, cerebrovascular disease, peripheral arterial disease, diabetes, hypertension, obesity, smoking, and heart failure. We found that participants with and without clinical risk factors for renal disease had a substantial, non-linear relationship between age and Cystatin C concentrations across the age spectrum those without risk elements

It was found that participants with and without clinical risk factors for renal disease had a substantial, non-linear relationship between age and Cystatin C concentrations across the age spectrum (Figure 5). When compared to people without risk factors, the rate of rise in Cystatin C concentrations appeared to accelerate with age, especially in people who had clinical risk indicators for renal disease.[50]

Sex:-

According to several research, the demographics, obesity, thyroid function, and inflammation all had an impact on Cystatin C levels [51-53].

Male gender was independently related to greater blood Cystatin C levels, according to Eric L. Knight et al.[53]

BODY MASS INDEX:-

Males and females in the overweight and obese groups have substantially higher blood Cystatin C levels than those in the control group, indicating a possible influence of BMI.

Since all nucleated cells, including adipocytes, are known to generate Cystatin C, overweight and obese people are likely to have greater blood Cystatin C levels.

Serum Cystatin C levels [54] do seem to be affected by a number of variables, including higher weight and height.

Serum Cystatin C and BMI have also been found to significantly correlate in other studies.[55,56].

PATHOPHYSIOLOGY:-

The imbalance between protease and anti-protease is a component of the pathophysiology. [2]

Based on their chemical makeup, proteases are divided into four groups: Serine, Metallo, Cysteine, and Aspartic. The major function of the cathepsin family of papain-like cysteine proteases is to degrade of protein and peptides in the lysosomes. Lung extracellular matrix, particularly lung elastin, is broken down by extracellular cathepsins released by neutrophils and macrophages in the alveoli. The breakdown products of elastin fibres exert chemotactic effects on monocytes, which encourage their infiltration and worsen the lung's inflammatory response. When lung elastic tissue is more severely damaged due to COPD, transforming growth factor beta-1 is released from proteoglycan storage sites, which increases Cystatin C synthesis.[2]

Inflammatory cells secrete Cystatin C, one of the main human extracellular cathepsins inhibitors, into the bloodstream.[3] Protein released from alkali having a 133kda molecular weight.[4] Cyc regulates protease production or leakage from lysosomes of sick cells by forming

complexes with cathepsins.[5] The activity of cathepsin may be indirectly reflected in Cystatin C levels. [6]

Studies on COPD and its association with Cystatin C

In 2012, Nowinski et al.[57] conducted a study to see the relationships regarding COPD severity and serum Cystatin C levels in prospective study. Study reported that COPD patients with more severe GOLD stages have higher serum Cystatin C levels but not creatinine or calculated creatinine clearence levels.

In 2014, Zhang Y et al.[58] conducted a study on the possible biomarker of serum Cystatin C for the assessment of COPD. Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (n = 93), stable COPD (n = 299), and healthy controls (n = 151) were the three groups in the research that had their serum Cystatin C levels measured. Further research was conducted on the effects of smoking on serum Cystatin C levels and the relationship between Cystatin C and lung function metrics. Patients with COPD had considerably higher serum Cystatin C levels than healthy controls. Smoking raised the blood level of Cystatin C in SCOPD patients but not in AECOPD or control patients. In the SCOPD group, serum Cystatin C levels were inversely connected with FEV1% predicted, FEV1%FVC, MMEF75/25% predicted, and MVV% predicted, and favourably correlated with RV%TLC. DLco% forecasted, etc. FEV1% predicted and age were revealed to be independent predictors of serum Cystatin C levels in multiple line analysis, but not smoking status, sex, or BMI. Serum Cystatin C levels were greater in COPD, but smoking merely elevated Cystatin C levels in SCOPD. The predicted FEV1% was inversely linked with serum Cystatin C levels. These findings imply that Cystatin C may serve as a potential biomarker for the severity of COPD and the destruction of lung tissue.

In 2016, Nakajima et al.[59] performed a study to investigate the potential role of plasma levels of cathepsin S or Cystatin C as COPD biomarkers. According to the study, the plasma levels of cathepsin S and Cystatin C were noticeably greater in the COPD and AT Risk (AR) groups than in the NS and HS groups. Plasma cathepsin S levels and cathepsin S/Cystatin C ratios were adversely correlated with severe airflow restriction (% FEV1 predicted 50%) and severe emphysema as measured by low attenuation area (LAA) score on chest CT scans in COPD patients and AR subjects, but not with Cystatin C levels (LAA 8.0).

In 2016, Hu G et al. [6] carried out research to look at Cystatin C predictive value for in-hospital mortality in patients with a COPD exacerbation. Measurements were made on 477 participants in the study who had COPD exacerbations. Additionally, clinical traits were noted. The Cystatin C concentration that distinguished survivors from those who did not survive was determined using a receiver operating characteristic curve analysis. The risk variables for in-hospital death were found using both univariate and multiple logistic regression models. Subgroup analyses were carried out based on the comorbidities, such as heart failure, renal dysfunction, pH, PaCO2, and PaO2 levels, in order to lessen the impact of confounders. According to the study, 418 participants had a full recovery whereas 59 subjects passed away while they were hospitalised . Lower pH (7.27 0.17 vs. 7.38 0.06, P .001), greater Cystatin C (2.21 1.05 mg/L vs. 1.39 0.54 mg/L, P .001), higher PaCO2 (77 39 mm Hg vs. 48 14 mm Hg, P .001), and lower PaO2 (74 32 mm Hg vs. The Cystatin C prediction of mortality has an area under the receiver operating characteristic curve of 0.77 (95% CI: 0.70-0.84). A substantially increased in-hospital death rate was linked to Cystatin C levels below 1.59 mg/L (relative risk = 5.49, 95% CI 3.24-9.32, P .001). In-hospital mortality was independently predicted by pH 7.20, Cystatin C 1.59 mg/L, and heart failure, according to multiple logistic regression analysis. The subgroup analysis revealed that the findings that Cystatin C was a mortality risk factor for those with COPD exacerbations were unaffected by the coexisting conditions of renal

dysfunction, congestive heart failure, and values of pH, PaCO2, and PaO2. exacerbation was unaffected by the values of pH, PaCO2, and PaO2.

In 2016, Zhang et al.[(2)] conducted a research on patients with exacerbation and recovery from COPD using serum Cystatin C as an indicator of inflammation. According to the study, serum Cystatin C was inversely connected with predicted FEV1% and FEV1/FVC in convalescent COPD patients and positively correlated with hsCRP in both the exacerbation and convalescence phases of COPD. In conclusion, serum Cystatin C in COPD patients is a positive acute-phase reactant and may signify systemic inflammation during the development of COPD.

In 2018, Telo S et al.[(3)] conducted a study on the possible diagnostic significance of serum Cystatin C levels and respiratory functioning in COPD. Study results 50 healthy participants and 126 people with COPD participated in the research (68 in stable times and 58 during exacerbation periods). The study discovered that serum Cystatin C levels were considerably higher in both COPD groups than the control group despite the fact that there was no statistically significant difference between the COPD groups ($p>0.05$) (p0.001 for both). Cystatin C levels showed a negative link with forced expiratory volume in one second (FEV1) and a positive correlation with C-reactive protein (CRP) levels in people with stable COPD. Blood Cystatin C levels and serum urea, creatinine, and CRP levels were significantly correlated in individuals with COPD exacerbation ($r=0.333$, $p=0.011$; $r=0.260$, $p=0.049$). When stable COPD and control groups were evaluated, serum Cystatin C showed an area under the curve (AUC) in the receiver operating characteristic (ROC) curve of 0.951 (0.909-0.994).

In 2019, Diago et al[(60)]conducted a study on Glomerular filtration rate estimated using serum creatinine and Cystatin C, and Creatinine Cleareance measured in COPD patients. Study reported that 44 COPD patients 65+/-6 years, FEV1 55,2 +/-17% Exacerbations during

previous year: 1 (0-2), mMRC dyspnea score 1 (0-2) CAT score 14,3+/-8,7, Charlson 1,39+/-0,6. Cystatin C 97,18+/-17 mL/min, and both creatinine an Cystatin C 91,94+/-11,5 mL/min.

In 2020, Chai Limin et al.[4] comprehensive meta-analysis of the research on the association between Cystatin C and COPD. This study's meta-analysis included 5949 controls, 4079 COPD patients, and a total of 15 studies. The results showed that blood Cys C levels were significantly greater in AECOPD patients than in SCOPD patients and statistically different from controls in COPD patients The relationship between serum Cystatin C levels FEV1%pre and FEV1/FVC were below normal values (Z = 0.45, 95%CI = -0.58--0.32, P = 0.011 and 0.006, respectively), while FEV1%pre was also below normal. Ethnicity, study methodology, or test technique had no impact on the serum Cystatin C levels. FEV1/FVC (Z = 0.32, 95%CI = 0.50, P = 0.006). The serum Cystatin C levels were unaffected by test technique, research design, or ethnicity.

In 2021, Nishiki et al.[61] conducted a research to see if the blood Cr level adjusted for serum Cystatin C may be used to predict lung function and disease severity in COPD patients. Serum Cr and Cystatin C levels were evaluated in 201 individuals with COPD and 99 patients without COPD who had smoked more than 10 pack-years before to enrollment. Low attenuation area (LAA%) (960 Hounsfield units (HU).According to the study, there is a substantial association between the Cr/CysC ratio and the ESMCSA. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) values were substantially correlated with the Cr/CysC ratio, notably in ex-smokers.

In 2021, Hirai et al.[62] conducted a study on Serum creatinine/Cystatin C ratio as a surrogate marker for sarcopenia in patients with chronic obstructive pulmonary disease. Study included 234 male outpatients with COPD. Serum Cr/Cystatin C was shown to substantially correlate with both muscle mass and handgrip strength (r = 0.44, P 0.01) in the study. Serum Cr/Cystatin

C ratio had a considerably greater area under the sarcopenia curve than the other biomarkers (Cr/Cystatin C: 0.87, Cystatin C: 0.63, Cr: 0.61, albumin: 0.57). The incidence of acute exacerbations between patients in the low- and high-Cr/Cystatin C group, as determined by the cutoff value of 0.71, did not differ substantially according to multivariate analysis, although the frequency of severe acute exacerbations was considerably greater in the low-Cr/Cystatin C group. According to the study's findings, the serum Cr/Cystatin C ratio may be utilised to assess sarcopenia in male COPD patients with reasonable cost and ease.

In 2021, Amado et al.[(63)] conducted a study on the Ratio Serum Creatinine/Serum Cystatin C (a Surrogate Marker of Muscle Mass) as a Predictor of Hospitalization in Chronic Obstructive Pulmonary Disease Outpatients. The study comprised 65 stable COPD outpatients and 18 healthy control participants with stable COPD. After enrolling in the trial, patients were prospectively observed for a period of one year. According to a study, COPD patients had less muscle mass and a lower SI than controls. Furthermore, compared to patients without these features, patients with a high risk of exacerbation, patients with a COPD Assessment Test score of 10, and patients with a modified Medical Research Council dyspnea score of 2 had lower levels of SI. SI had a significant inverse relationship with FEV1 (r = 0.491, p 0.001), the 6-minute walking test (r = 0.560, p 0.001), and the fat-free mass index (r = 0.431, p = 0.017). A low SI is an independent predictor of, as demonstrated by univariate and multivariate Cox proportional risk analysis, healthy control participants with stable COPD. Hospitalization of COPD outpatients was monitored for a year after (HR 5.16, p = 0.025).

An essential factor to consider when assessing the effects of chronic illnesses is quality of life (QOL). Measuring HRQOL makes it easier to assess the success of medical therapies and identify populations at risk for psychological or behavioural issues. [64]

Patients with COPD may delay seeking medical attention or present with little or no symptoms in the early stages, which might cause them to be overlooked in hospital settings and result in a worse QOL overall.

St. George's Respiratory Questionnaire (SGRQ)

SGRQ is a standardised, self-administered questionnaire used to assess HRQOL perception and diminished health in patients with airways illness. The St. George's Respiratory Questionnaire (SGRQ) was developed into the SGRQ-C, a condensed form, after extensive data analysis from significant research on COPD. [65]

In place of the initial 50 items, it now has 40 items with 76 weighted responses that span three domains: symptoms, activities, and effect. [66] It also calculates a total score in addition to the domain scores. There is an empirical weight assigned to each item. SGRQ-C scores range from 0 to 100, with 0 being the highest HRQOL. Among COPD patients, this tool has been shown to be valid, reliable, and responsive. [66]

Included studies Assessment of patient-reported outcome measures, such as the health-related quality of life (HRQL), is critical for determining how chronic illnesses affect patients. The St. George's Respiratory Questionnaire (SGRQ) is a respiratory-specific instrument that was initially developed to evaluate patients with COPD's health-related quality of life. However, the SGRQ has grown to be one of the most widely used instruments for evaluating patients with other chronic lung diseases, such as lymphangioleiomyomatosis (LAM), and interstitial lung disease linked to connective tissue disease (CTD-ILD). These studies shown that the SGRQ total score was a very significant predictor of mortality and that the SGRQ scores were related to the outcomes of the pulmonary function test (PFT). [65] stable control patients and 18 healthy.

Clinical COPD questionnaire:

The Clinical COPD Questionnaire (CCQ) has three categories and ten items with scores ranging from 0 to 6. (symptoms, functional, mental). [67] Adding together the individual item scores and dividing them by ten yields the total score, which ranges from 0 to 6, with higher scores denoting lower HRQoL.

The adoption of a quicker health status questionnaire could result in more effective service delivery and subsequent cost savings, according to several recent studies that have proposed the CAT as a simpler, more practical alternative HRQoL measure to time-consuming questionnaires like the CRQ and SGRQ [68,69,70]. Compared to more well-known surveys, the CCQ takes far less time and staff involvement to complete[71] , but it could possibly give more information due to the inclusion of domain and overall scores. Recent studies also seem to indicate that there is a modest preference for the CCQ over the CAT at the patient and clinician level. [71,72,73]

COPD ASSESSMENT TEST:

Eight items make up the CAT, which concentrates on respiratory symptoms like cough, sputum production, tightness in the chest, and dyspnea as well as non-respiratory symptoms like fatigue or sleep disturbances and additional indicators like difficulty performing tasks at home or lack of confidence leaving the house [74]

According to Jones and colleagues, the item "breathlessness" has the most power of discrimination for milder patients, whereas the item "confidence leaving home" discriminates more well for more severe patients [74]

CAT total score determines the GOLD classification of patients with COPD (classifying patients into low (A/C) and high (B/D) symptom groups) and, in turn, the recommended respiratory pharmacological treatment strategy [1]

It's critical to comprehend how the CAT score is calculated and how each individual item contributes. Overall, there were strong connections between item and overall scores. Only 44.7% of patients with a CAT total score of fewer than 10 points, however, reported having more severe symptoms (>3 points) on 3 or 4 of the respiratory categories, including "cough," "phlegm," "chest tightness," and "breathlessness."

Six minute walk test:

A straightforward cardiopulmonary functional assessment method is the six-minute walk test. Its simplicity enables an integrative, non-specific evaluation of the several systems engaged during physical exercise. In particular, its findings may help determine the level of functional impairment and might influence how various cardiovascular and pulmonary disorders are treated.

The primary physiological phenomena pertinent to the test are the exchanges between the heart and lungs during exercise. Generally speaking, deoxygenated blood returns to the right heart through the veins pushed into the pulmonary circulation by the right ventricle. Gas exchange takes place when the blood travels through the lung capillaries, with oxygen enter the bloodstream and carbon dioxide being discharged into the alveoli.

The left ventricle of the left heart then pumps oxygenated blood into the systemic circulation, which finally transports it to the organs to support aerobic metabolism. This process also involves the neurological or musculoskeletal systems, particularly when it comes to the process of adjusting minute breathing to cardiac function in response to changing exercise levels of intensity. This happens as a result of reflex actions that modify pulmonary and cardiac activity to match the amounts of oxygen consumption required by the level of effort.

The Total distance walked is the main test result (6MWD). [75] The typical 6MWD in healthy people ranges from 400 to 700 meters.

While 6MWD is closely correlated with worse life quality indices, respiratory and impaired functioning, and survival, it has been proven as a relevant index of symptom severity for COPD patients.

The primary test outcome is the final distance walked (6MWD).(75) Among healthy individuals, the average 6MWD is between 400 and 700 meters.

6MWD has been established as a significant marker of disease severity for COPD patients since it directly correlates with lower quality of life indices, respiratory and functional impairment, and survival.

- modified Medical Research Council (mMRC) questionnaire, which evaluates breathlessness based on scale of 0-4
    i. grade 0: patient breathless with strenuous exercise
    ii. grade 1: patient short of breath when hurrying on level ground or walking up slight hill
    iii. grade 2: patient walks slower than same-age peers due to breathlessness, or has to stop for breath when walking at own pace on level ground
    iv. grade 3: patient stops to catch breath after walking about 100 meters or after a few minutes on level ground
    v. grade 4: patient too breathless to leave the house or breathless when dressing or undressing

BODE INDEX:-

The BODE index, for Body-mass index, airflow Obstruction, Dyspnea, and Exercise, is a multidimensional scoring system and capacity index used to test patients who have been diagnosed with chronic obstructive pulmonary disease (COPD) and to predict long-term outcomes for them. The index uses the four factors to predict the risk of death from the disease.

The BODE index will result in a score of zero to ten dependent upon FEV1 or "forced expiratory volume in one second", Body-mass index, the distance walked in six minutes, and the modified MRC dyspnea scale.

MATERIALS AND METHODS

SOURCE OF DATA: This study will be carried out in the Department of respiratory medicine, B.L.D.E. (Deemed to be university) Shri B. M. Patil Medical College, Hospital and Research Centre, Vijayapur.

METHOD OF COLLECTION OF DATA:

Study Design: Cross sectional study.

Study Period: Two years.

Sample Size: 42 patients.

With Anticipated correlation between Cys C and FEV1 r= -0.475^2, at 95% confidence level and 80 power in the study, the sample size worked out is 42.

Formula used is

N= The standard normal deviate for $\alpha = Z\ \alpha = 1.9600$

The standard normal deviate for $\beta = Z\ \beta = 1.6449$

C=0.5*ln=0.5165

N=42

INCLUSION CRITERIA:

- Patients diagnosed as chronic pulmonary obstructive disease
- Patients aged between 20-60 years.
- Patients of either sex.
- Smokers and nonsmokers
- Patients exposed to biomass and other inhalational injury
- Patient with history of occupational exposure and dust fumes.

EXCLUSION CRITERIA:

- Patient unwilling to take part in the study or to give written consent for the study.
- Patients with other system diseases such as chronic kidney disease, coronary artery disease, cancer, bronchial asthma, thyroid dysfunction.

METHODOLOGY:

Patients with copd diagnosed according to gold guide lines 2020 attending the out-patient and in-patient department of Respiratory Medicine in Shri B. M. Patil Hospital, Vijayapura, from November 2020 to December 2022, will be enrolled in the study and are subjected to routine blood investigations, pulmonary function test and also blood examination of serum Cystatin C levels.

Pulmonary function test procedure: -

The baseline spirometry performed in subjects with sitting position and highest value of forced expiratory volume in 1 sec and forced vital capacity are obtained. Three acceptable values are obtained in each subject. Then salbutamol nebulization was given. Spirometry was repeated 20min after administration of salbutamol. Reversibility was calculated in COPD patient groups and categorized as below-

GOLD 1	Mild	FEV_1> 80%
GOLD2	Moderate	FEV_1 50-80%
GOLD3	Severe	FEV_1 30-50%
GOLD 4	Very severe	FEV_1<30 %

Table :3 **SEVERITY OF AIRFLOW LIMITATION ACCORDING TO GOLD CRITERIA** [(1)]

Peripheral blood examination serum Cystatin C levels: -

Venous blood will be drawn into collected in to tubes. All samples are processed by centrifugation at a speed of 3500 rpm over a duration of 10minutes to separate serum from the plasma. The serum floats over the plasma as a supernatant, which is pipetted into Eppendorf tubes and stored at –20c till further analysis by ELISA KIT

Patients are assessed for quality of life according to quality questionnaire as admitted in proforma

STATISTICAL ANALYSIS

The data obtained will be entered in a Microsoft Excel sheet, and statistical analysis will be performed using statistical package for the social sciences (Version 20). Results will be presented as Mean (Median)±SD, counts and percentages and diagrams. For normally distributed continuous variables between two groups will be compared using. Independent t test for not normally distributed variables Mann Whitney U test will be used. Paired data will be compared using paired t test/Wilcoxon signed rank test. Categorical variables between two groups will be compared using Chi square test. Correlation coefficient will be used to find the correlation between quantitate variables. ROC Curve analysis will be performed to find the sensitivity and specificity. $P<0.05$ will be considered statistically significant. All statistical tests will perform two tailed.

RESULTS

AGE DISTRIBUTION:

The distribution of patients according to different age groups is depicted in Graph 2. The mean age was 57.95±3.66 years.

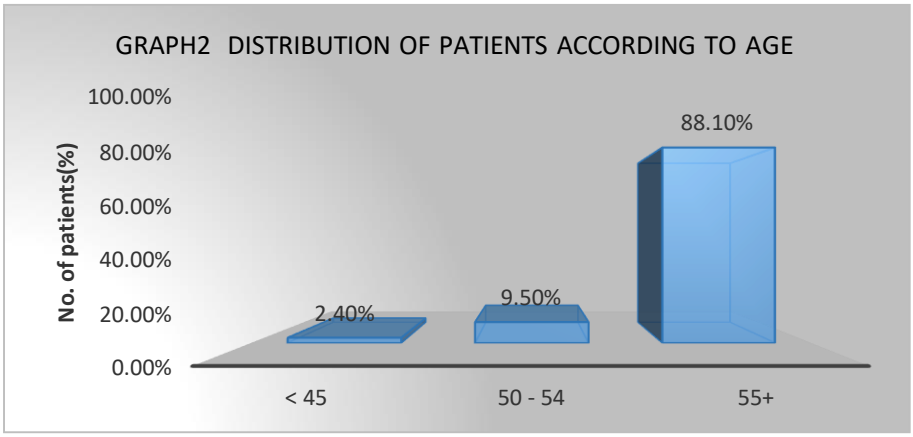


TABLE 4: DISTRIBUTION OF SERUM CYSTATIN C (ng/ml) ACCORDING TO AGE

There is a positive association between age and serum Cystatin C where the levels of serum Cystatin C increased with increasing age and it is statistically significant is represented in table 4.

Serum Cystatin C level ng/ml	<45-49 years	50-54 years	>55years	Mean±SD age in years	MANN Whitney test	p-value
≤532.3ng/ml	1	4	18	56.8±4	150	**0.004**
>532.3ng/ml	0	0	19	59±1		

GENDER DISTRIBUTION

It was observed that the gender inclination was towards Males with 64.3% of patients (27 in number) while 35.7% of patients were Females (15 in number) (Graph 3).

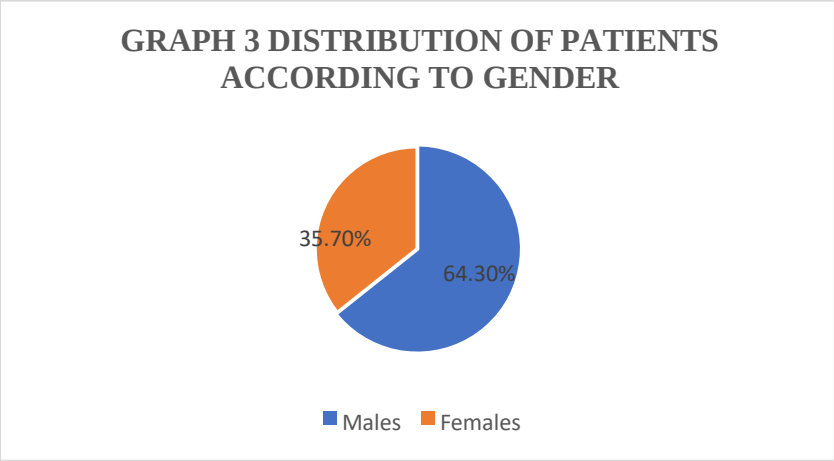


TABLE:5 DISTRIBUTION OF SERUM CYSTATIN C ng/ml LEVELS ACCORDING TO SEX

There is a positive association between sex and serum Cystatin C where the levels of serum Cystatin C increased in males and it is statistically significant (table 5)

Gender	N	Mean±SD	p value
Females	15	444.49±237.57	**0.04**
Males	27	624.48± 293.3	

BMI DISTRIBUTION -

Of the 42 patients, 21 were of Ideal body weight, whereas 6 were overweight, 15 were Underweight. The distribution of cases is shown in Graph 4.

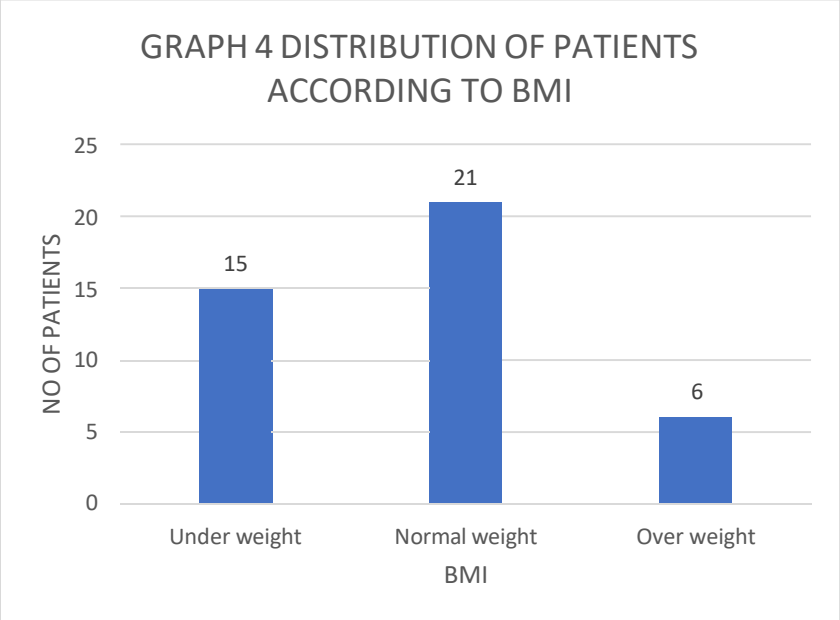


TABLE:6 DISTRIBUTION OF PATIENTS ACCORDING TO BMI IN RESPECT TO SERUM CYSTATIN C NG/ML

There is a No association between BMI and serum Cystatin C levels and it is statistically not significant (table 6)

Serum Cystatin C level ng/ml	Over weight	Normal weight	Under weight	Mean BMI	Chi square test	P value
≤532.3ng/ml	3	12	8	20.49	0.1153	0.94
>532.3ng/ml	3	9	7	20.47		

TABLE :7 DISTRIBUTION OF PATIENTS ACCORDING TO BMI DOMAIN OF BODE INDEX IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There is a No association between BMI Domain of BODE index and serum Cystatin C levels and it is statistically not significant (table 7).

BMI Domain of BODE index	No of patients with mean serum Cystatin C level >532ng/ml	No of patients with mean serum Cystatin C level ≤532ng/ml	CHI-SQUARE VALUE	P value	ODDS RATIO
≤21	11	15	0.237	0.31	0.733 C.I (0.2099-2.563)
>21	8	8			
TOTAl	23	19			

TABLE NO:8 DISTRIBUTION OF PATIENTS ACCORDING TO PACK YEARS OF SMOKING

Of the 27male patients, maximum no of patients have pack years of smoking more than 10 years The distribution of cases is shown in Table 8

Pack years	No of patients
≤ 10 years	7
>10 years	20

TABLE:9 DISTRIBUTION OF PATIENTS ACCORDING TO PACK-YEARS OF SMOKING WITH RESPECT TO SERUM CYSTATIN C NG/ML

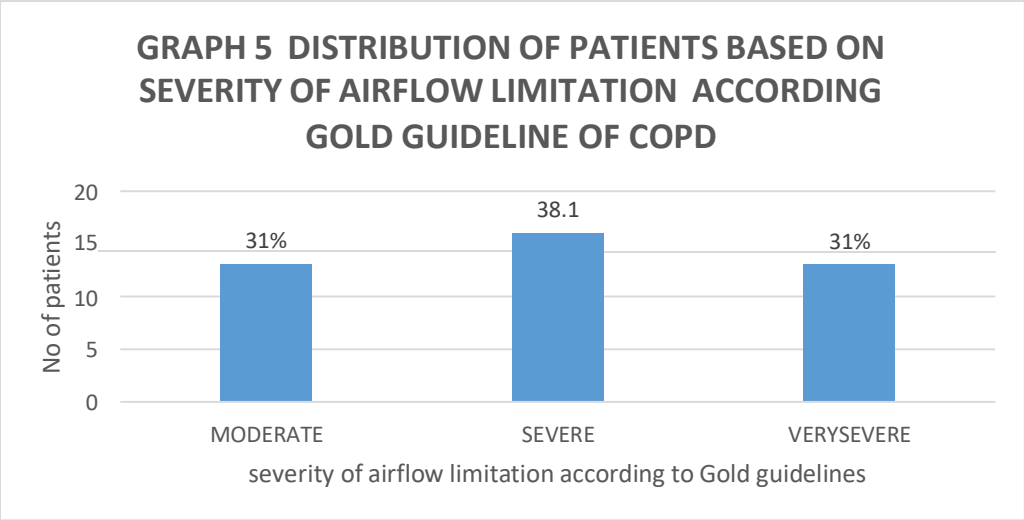
There is a positive association between pack-years and serum Cystatin C. patients with more than 10 pack years have odds of 5.8 times higher chance of increased serum Cystatin C ng/ml levels and was statistically significant (table 9).

Pack years	Serum Cystatin C level ≤532ng/ml	Serum Cystatin C level 532ng/ml	Odds ratio	P value
>10 years	6	14	5	**0.03**
≤ 10years	5	2	.833 (CI 0.74-38.9)	

TEST USED – MID P EXACT TEST

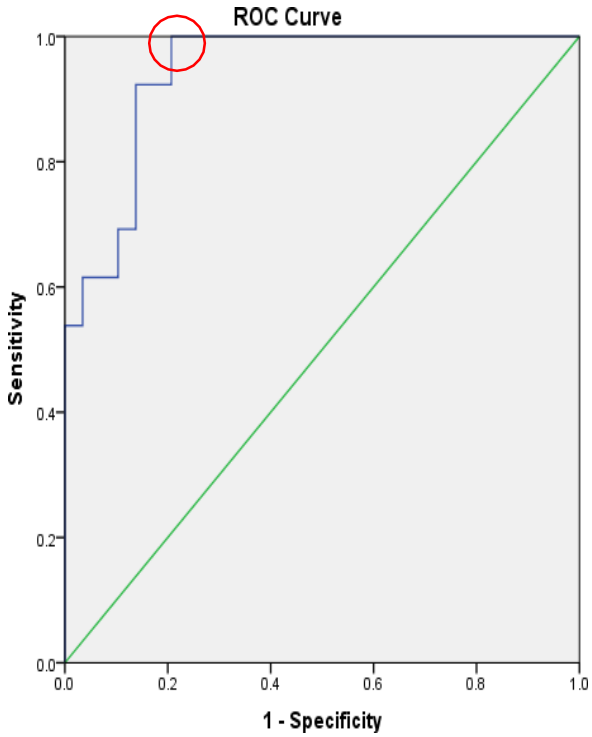
GRAPH 5: DISTRIBUTION OF CASES BASED ON THE SEVERITY OF AIRFLOW LIMITATION ACCORDING TO GOLD GUIDELINES OF COPD

Out of 42 patients, 31% had moderate airflow limitation whereas 38.1% were with severe air limitation and 31% were with very severe airflow limitation



GRAPH :6 RECEIVER OPERATING CURVE INDICATING SENSITIVITY AND SPECIFICITY OF SERUM CYSTATIN C TO DIAGNOSE COPD

This point represents serum Cystatin C value of 532.3ng/ml. Has highest sensitivity of 100% and specificity of 79.3%



Area Under the Curve is 0.942

Serum Cystatin C had an area under the curve in the receiver operating characteristic curve of 0.942. A Cystatin C level of 532.3 ng/ml was accepted as the cut-off value. Cystatin C has a highest sensitivity of 100% and specificity of 79.3%

TABLE10: DISTRIBUTION OF PATIENTS ACCORDING TO SERUM CYSTATIN C LEVELS ng/ml

Of 42 patients, 54.7% had a serum Cystatin C level equal to less than 532ng/ml whereas 45.3% had a serum Cystatin C level ng/ml more than 532ng/ml. (table 10)

SERUM CYSTATIN C LEVEL (ng/ml)	NO OF PATIENTS	PERCENT
≤532.3ng/ml	23	54.7
>532.3ng/ml	19	45.3
TOTAL	42	100

TABLE 11: DISTRIBUTION OF CASES BASED ON THE SEVERITY OF SPIROMETRY BASED ON POST BRONCHODILATOR FEV_1% PREDICTED IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

The association between the severity of spirometry and serum Cystatin C levels(ng/ml) was found to be statistically significant. (table 11). Odd ratio cant be done as values are missing

SEVERITY OF SPIROMETRY BASED ON POSTBRONCHODILATOR FEV_1% PREDICTED ACCORDING COPD GOLD GUIDELINES	SERUM CYSTATIN C LEVEL (≤532.3ng/ml)	SERUM CYSTATIN C LEVEL (>532.3ng/ml)	CHI – SQUARE TEST	P VALUE
≥80FEV_1%PREDICTED	0	0	26.8	**0.0001**
50%≤FEV_1 <80% PREDICTED	13	0		
50%≤FEV_1≥30% PREDICTED	10	6		
FEV_1 <30% PREDICTED	0	13		
TOTAL	23	19		

GRAPH:7 DISTRIBUTION OF MEANS OF SERUM CYSTATIN C WITH RESPECT TO STAGES OF SPIROMETRY ACCORDING TO GOLD GUIDELINES OF COPD.

Mean serum Cystatin C levels ng/ml in moderate, severe, and very severe stages were 250.02ng/ml, 567.6ng/ml and 861.2ng/ml respectively**.**

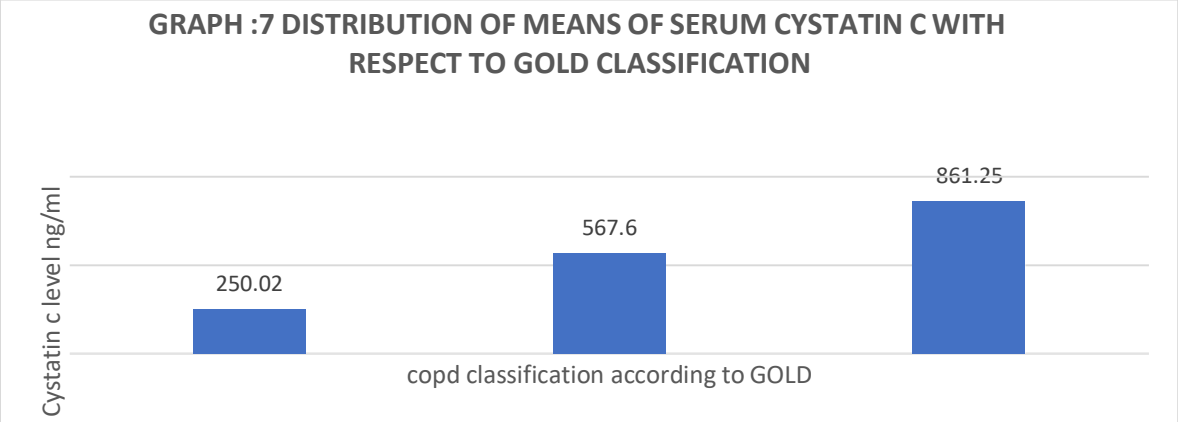


TABLE:12 COMPARISON OF MEANS OF SERUM CYSTATIN C WITH RESPECT TO STAGES OF SPIROMETRY ACCORDING TO GOLD GUIDELINES OF COPD.

Mean serum Cystatin C levels increases as airflow limitation increases and were found to be statistically signification as in table 12

SEVERITY OF SPIROMETRYBASED ON POSTBRONCHODILATOR FEV_1% PREDICTED ACCORDING COPD GOLD GUIDELINES	**Mean±SD**	**ANOVA**	**P VALUE**
≥80%FEV_1PREDICTED	0	51.5	**0.001**
50%≤FEV_1<80% PREDICTED	250.02±57.25		
50%≤FEV_1≥30% PREDICTED	567.61±163.67		
FEV_1 <30% PREDICTED	861.25±199.56		

TABLE:13 DISTRIBUTION OF PATIENTS ACCORDING TO FEV $_1$ DOMAIN OF BODE INDEX IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There is an association between FEV $_1$ Domain of BODE index and serum Cystatin C levels and it is statistically significant (table 13)

FEV1 (% PREDICTED) OF BODE INDEX	No of patients with mean serum Cystatin C level ≤532ng/ml	No of Patients with mean serum Cystatin C level >532ng/ml	CHI-SQUARE	P value
≥65	5	0	19.11	**0.0001**
50-64	8	0		
36-49	7	0		
≤35	3	13		
TOTAL	23	19		

TABLE 14: DISTRIBUTION OF PATIENTS ACCORDING TO REDEFINED ABCD TOOL

Out of 42 patients 3 belongs to a group, 5 belong to B group and 34 belong to D group as represented in the table 14

ABCD Tool	NO of patients
A	3
B	5
C	0
D	34

TABLE 15: DISTRIBUTION OF CASES BASED ON ABCD TOOL IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

The association between the severity of disease and serum Cystatin C levels(ng/ml) was found to be statistically significant. (table 15). Odds ratio cant be done as values are missing

REDEFINED ABCD TOOL	SERUM CYSTATIN C LEVEL <532.3ng/ml	SERUM CYSTATIN C LEVEL >532.3ng/ml	CHI-SQUARE VALUE	P VALUE
A	3	O	8.164	**0.017**
B	5	0		
C	0	0		
D	15	19		
TOTAL	23	19		

GRAPH :8 DISTRIBUTION OF PATIENTS ACCORDING TO DURATION OF DISEASE

Out of 42 patients, maximum no of patients were with duration of disease less than equal to 4 years of duration as depicted in (GRAPH 8).

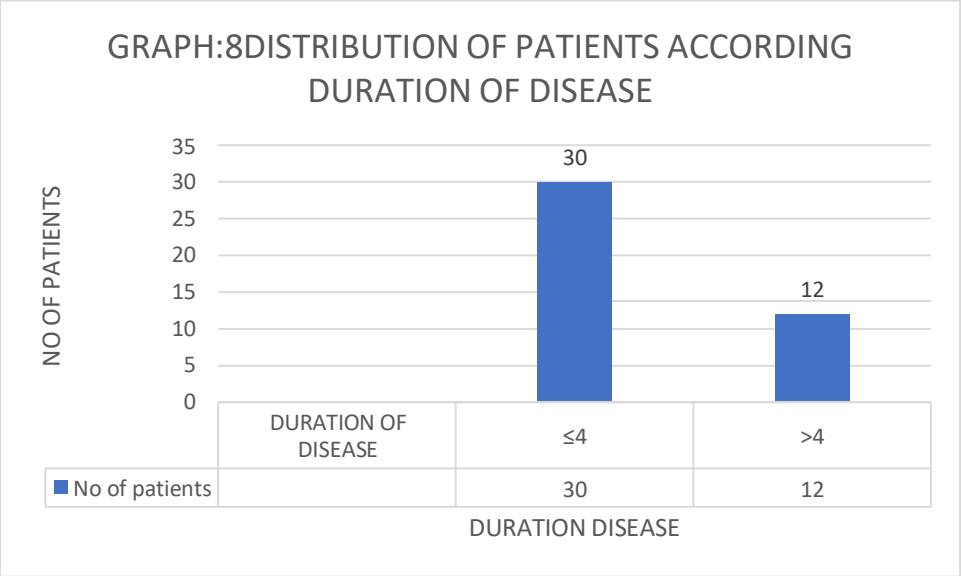


TABLE 16: DISTRIBUTION OF CASES BASED ON DURATION OF DISEASE IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There is a positive association between serum Cystatin C ng/ml and Duration of disease and patients with a duration of disease more than 4 years have odds of 6.5 times chance of increased serum Cystatin C levels found to be statistically significant as mentioned the table 16.

DURATION OF DISEASE	SERUM CYSTATIN C LEVEL ≤532.3ng/ml	SERUM CYSTATIN C LEVEL >532.3ng/ml	OddS ratio	P VALUE
≤4YEARS	13	17	6.53 CI(1.21-35.1)	**0.01**
>4YEARS	10	2		

TEST USED- MID P EXACT TEST

TABLE 17: DISTRIBUTION OF PATIENTS ACCORDING TO mMRC SCALE

Out of 42 patients, a maximum no of patients had mMRC scale 3 as mentioned in table 17

mMRC SCALE	No of patients
0	**0**
1	2
2	5
3	34
4	1

TABLE: 18 DISTRIBUTION OF PATIENTS ACCORDING TO mMRC SCALE IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There is an association between mMRC scale and serum Cystatin C levels and it is statistically significant (table 18**)**

mMRC Scale	No of patients with mean serum Cystatin C level ≤532ng/ml	No of patients with mean serum Cystatin C level >532ng/ml	CHI-Square	P value
0	0	0	16	**0.001**
1	2	0		
2	5	0		
3	16	18		
4	0	1		

GRAPH9: DISTRIBUTION OF PATIENTS ACCORDING TO 6-MINUTE WALK TEST

Out of 42 patients, the maximum no of patients belongs to Grade 1(240-349m) as shown inGraph 9

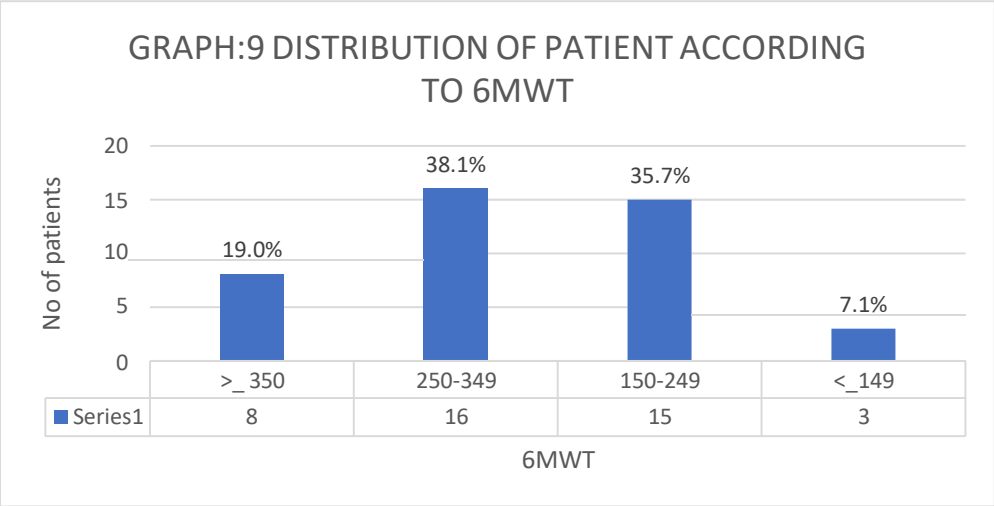


TABLE :19DISTRIBUTION OF PATIENTS ACCORDING TO SIX MINUTE WALK DOMAIN OF BODE INDEX IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There is a positive association between six minute walk and serum Cystatin C levels and patient with 6 minute walk test <250 have odds of 13 times chance of increased serum Cystatin C levels it was found to be statistically significant (table 19).

SIX MINUTE WALK TEST	No of patients with mean serum Cystatin C level ≤532ng/ml	No of patients with mean serum Cystatin C level >532ng/ml	CHI-SQUARE VALUE	P value	ODDS RATIO
<250	4	14	13.1	**0.0001**	13.3 CI (3.01-58.7)
≥250	19	5			

TABLE :20DISTRIBUTION OF PATIENTS ACCORDING TO BODE INDEX IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There is a positive association between BODE index and serum Cystatin C levels and patients with bode index more than 6 have odds of 14 times chance of increased serum Cystatin C levels and it was statistically significant (table 20)

BODE INDEX	No of patients with mean serum Cystatin C level ≤532ng/ml	No of patients with mean serum Cystatin C level >532ng/ml	CHI-SQUARE	P value	ODDSRATIO
>6	3	13	17.023	**0.01**	14.4 CI(3.06-68.1)
≤6	20	6			

TEST USED : MID P EXACT TEST

GRAPH10: DISTRIBUTION OF PATIENTS ACCORDING TO CLINICAL COPD QUESTIONAIRE SCORE

Out of 42 patients, maximum no of patients has CCQ score <3 as shown in Graph 10

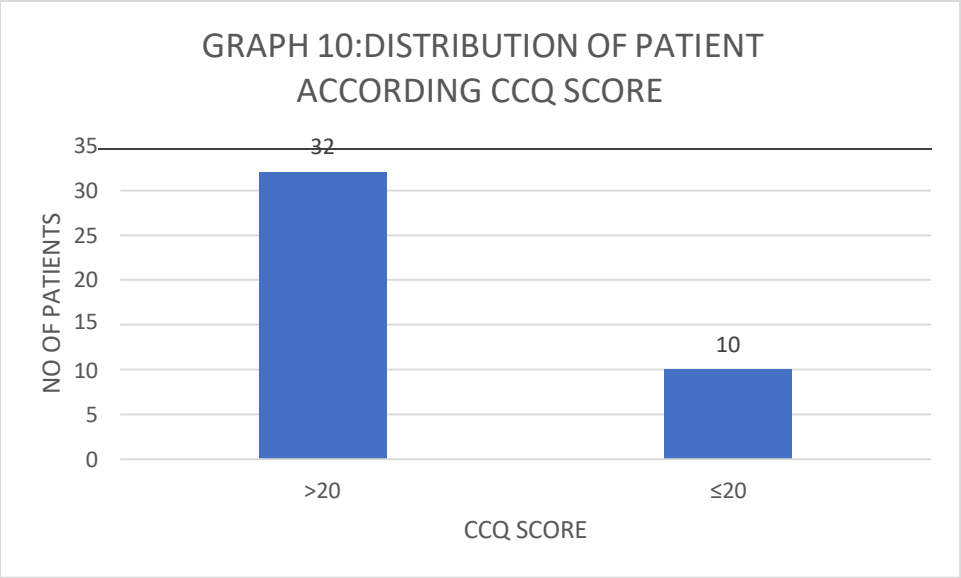


TABLE:21 DISTRIBUTION OF PATIENTS ACCORDING TO CCQ SCORES IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There is an association between clinical COPD questionnaire and serum Cystatin C levels and patients with ccq score more than equal 3 have odds of 4.7 times chance of increased serum Cystatin C levels and found it was statistically significant (table 21).

CCQ	No of patients with mean serum Cystatin C level ≤532ng/ml	No of patients with mean serum Cystatin C level >532ng/ml	CHI-SQUARE	P value	ODDS RATIO
≥3	3	12	4.92	**0.004**	4.7 CI 1.13-19.4
<3	20	7			

GRAPH11: DISTRIBUTION OF PATIENTS ACCORDING TO CAT SCORES

Out of 42 patients, maximum no of patients were with High CAT scores as shown in Graph 11

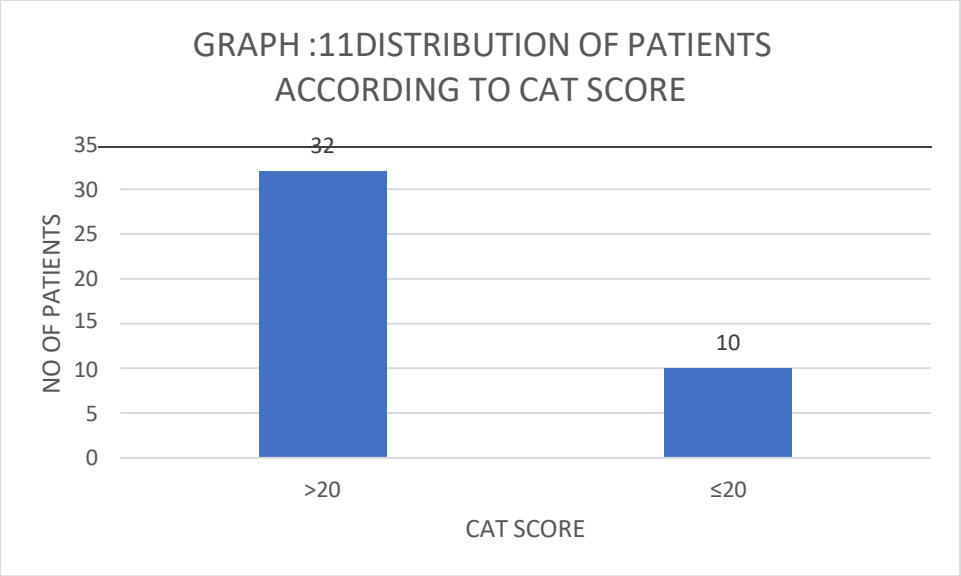


TABLE:22 DISTRIBUTION OF PATIENTS ACCORDING TO CAT SCORES IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There is a positive association between cat score and serum Cystatin C levels and patients with CAT score more than 20 have odds of 4.5 times chance of increased serum Cystatin C levels and found it was statistically significant (table 22)

CAT SCORE	No of patients with mean serum Cystatin C level ≤532ng/ml	No of patients with mean serum Cystatin C level >532ng/ml	ODDS RATIO	P value
>20	15	17	4.5 CI(0.83-24.7)	**0.03**
≤20	8	2		

TEST USED-MID P EXACT TEST

TABLE:23 DISTRIBUTION OF PATIENTS ACCORDING TO SGRQ SCORES IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There was a positive association between sgrq total score and serum Cystatin C ng/ml and patient with St George total score more than 50 have odds of 4.8 times chance of increased levels of serum Cystatin C levels and found to be statistically significant shown in the (table 23)

STGEORGE TOTAL SCORE	No of patients with mean serum Cystatin C level ≤532ng/ml	No of patients with mean serum Cystatin C level >532ng/ml	CHI-SQUARE	P value	ODDS RATIO
>50	10	15	5.304	**0.001**	4.87 CI 1.23-19.3
≤50	13	4			

TABLE:24 DISTRIBUTION OF PATIENTS ACCORDING TO SYMPTOMS DOMAIN OF SGRQ IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There was a positive association between sgrq symptom score and serum Cystatin C ng/ml and patient with St George symptom score more than 50 have odds of 9 times chance of increased levels of serum Cystatin C levels and found to be statistically significant shown in the (table 24)

STGEORGE SYMPTOM SCORE	No of patients with mean serum Cystatin C level ≤532ng/ml	No of patients with mean serum Cystatin C level >532ng/ml	P value	ODDS RATIO
>50	11	17	**0.001**	9.27 CI 1.73-49.6
≤50	12	2		

TEST USED- MID P EXACT TEST

TABLE:25 DISTRIBUTION OF PATIENTS ACCORDING TO IMPACT DOMAIN OF SGRQ IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There was a positive association between sgrq impact score and serum Cystatin C ng/ml and patient with St George total score more than 50 have odds of 7.03 times chance of increased levels of serum Cystatin C levels and found to be statistically significant shown in the

(table 25)

STGEORGE IMPACT SCORE	No of patients with mean serum Cystatin C level ≤532ng/ml	No of patients with mean serum Cystatin C level >532ng/ml	P value	ODDS RATIO
>50	8	15	**0.002**	7.03 CI(1.73-28.4)
≤50	15	4		

TEST USED- MID P EXACT TEST

TABLE :26 DISTRIBUTION OF PATIENTS ACCORDING TO ACTIVITY DOMAIN OF SGRQ IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There was a positive and statistically significant association between Activity domain of sgrq and serum Cystatin C ng/ml as shown in the (table 26). Odd ratio can't be calculated as one value is missing

STGEORGE ACTIVITY SCORE	No of patients with mean serum Cystatin C level ≤532ng/ml	No of patients with mean serum Cystatin C level >532ng/ml	CHI-SQUARE	P value
>50	15	19	7.969	**0.002**
≤50	8	0		

TABLE :27 DISTRIBUTION OF PATIENTS ACCORDING TO C-REACTIVE PROTEIN LEVELS

Out of 42 patients, maximum no of patients (38) had C – Reactive protein more than 10

CRP (mg/dl)	No of patients
<10	4
>10	38
Total	42

TABLE :28 DISTRIBUTION OF PATIENTS ACCORDING TO C-REACTIVE PROTEIN IN RESPECT TO SERUM CYSTATIN C LEVEL ng/ml

There is a positive association between C -Reactive protein and serum Cystatin C level

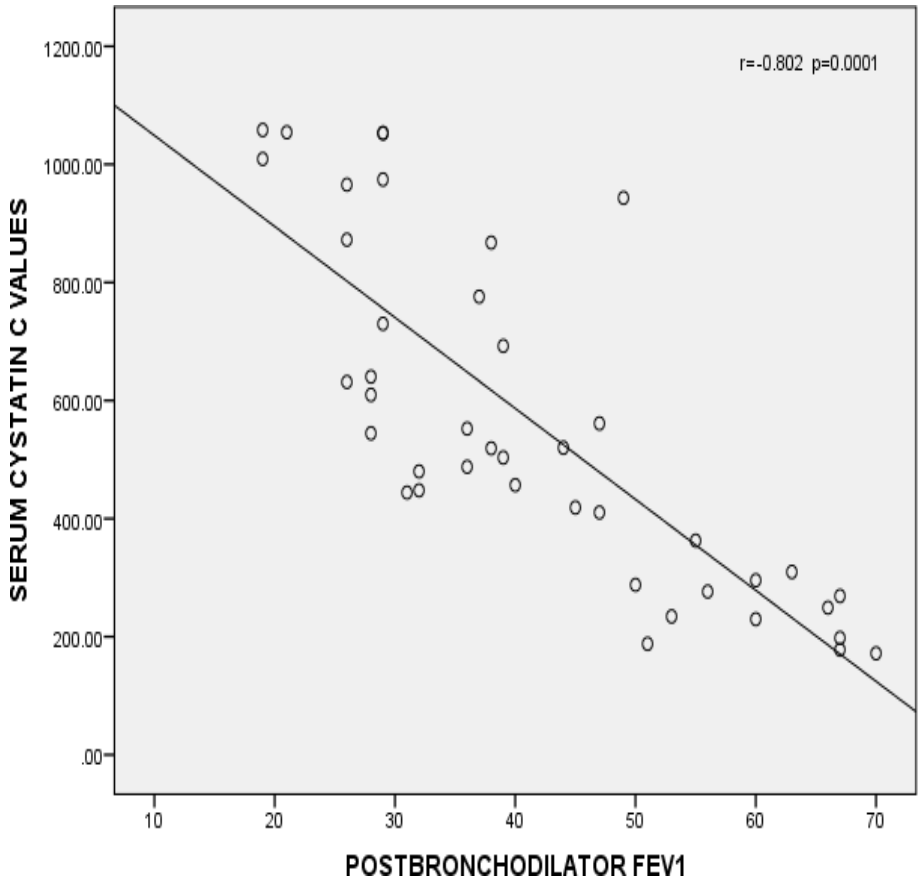
CRP	No of patients with mean serum Cystatin C level ≤532ng/ml	No of patients with mean serum Cystatin C level >532ng/ml	CHI-SQUARE	P value

<10	4	0	5.62	**0.04**
>10	19	19		
TOTAl	23	19		

GRAPH :12 CORRELATION BETWEEN POST BRONCHODILATOR FEV_1 % AND SERUM CYSTATIN C (ng/ml)

There is a negative correlation between serum Cystatin C level (ng/ml)and post bronchodilator FEV_1% and it is statistically significant

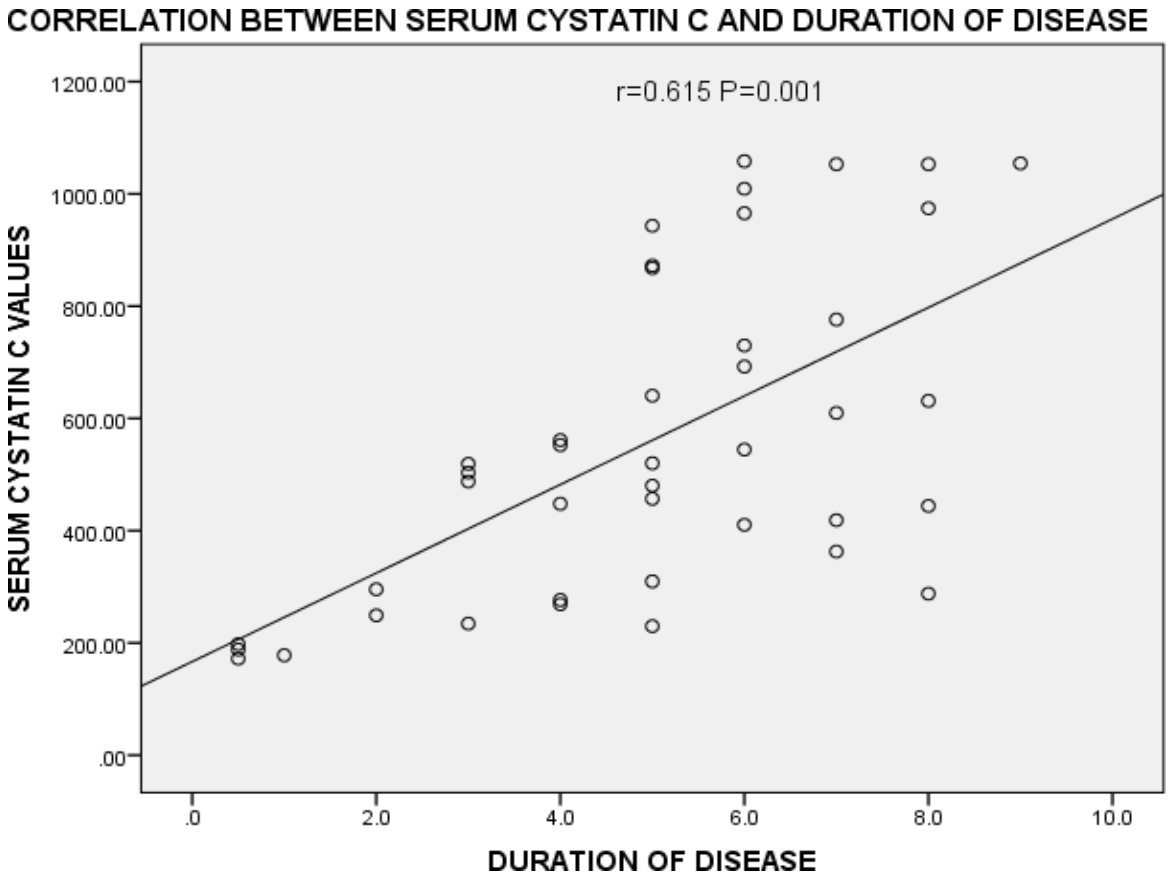
CORRELATION BETWEEN POSTBRONCHODILATOR FEV1 % AND SERUM CYSTATIN C (ng/ml)



POSTBRONCHODILATOR FEV1 %	SERUM CYSTATIN C VALUES
r co-efficient	-.802
P value	**0.0001**

GRAPH :13 CORRELATION BETWEEN DURATION OF DISEASE AND SERUM CYSTATIN C (ng/ml)

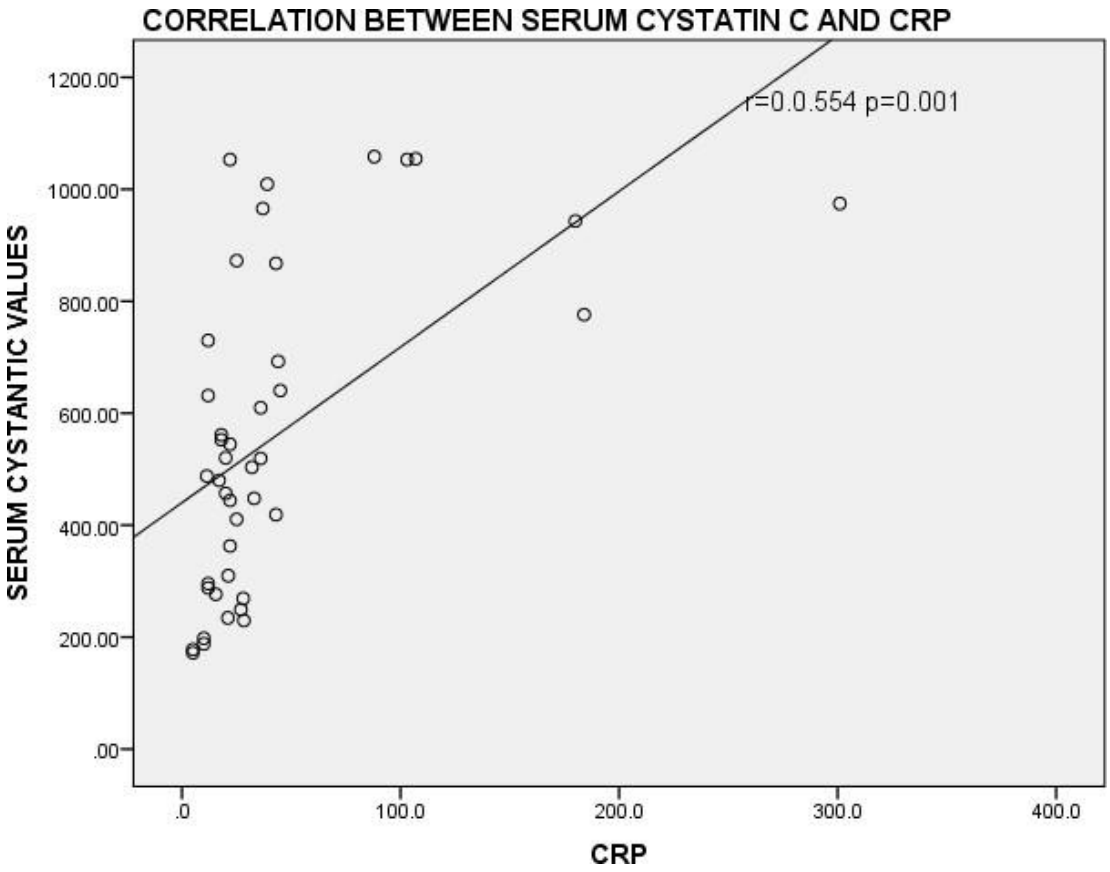
There is a positive correlation between serum Cystatin C level (ng/ml)and Duration of disease and it is statistically significant.



DURATION OF DISEASE	SERUM CYSTATIN C VALUES
r co-efficient	0.615
P value	**0.001**

GRAPH :14 CORRELATION BETWEEN CRP AND SERUM CYSTATIN C (ng/ml)

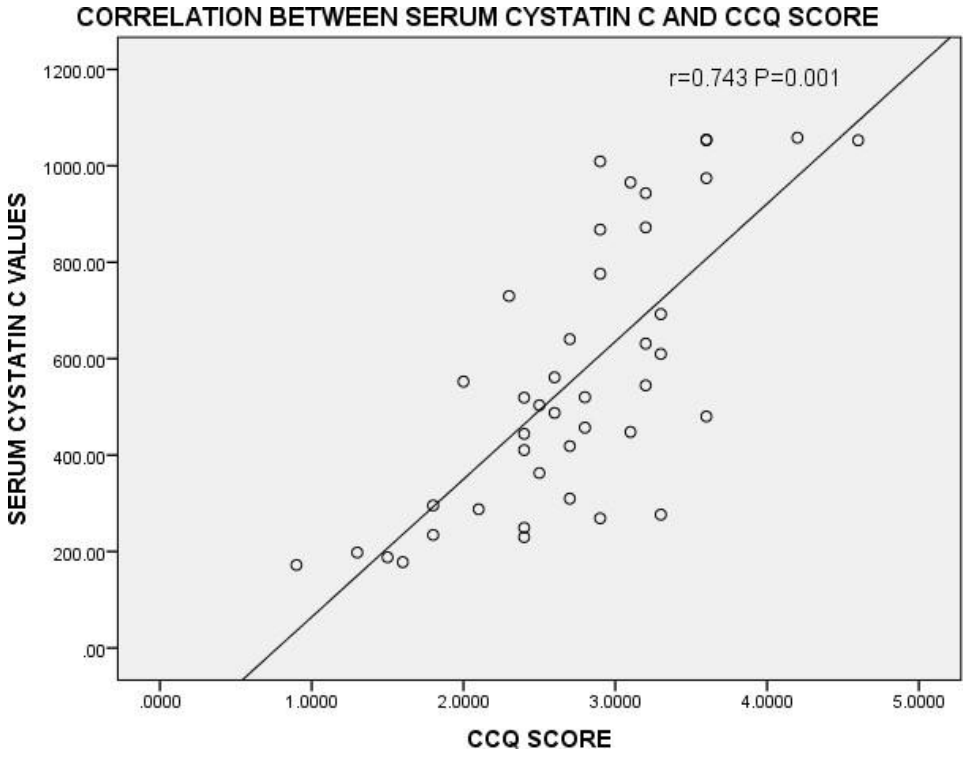
There is a positive correlation between serum Cystatin C level (ng/ml)and C- reactive protein and it is statistically significant.



CRP	SERUM CYSTATIN C VALUES
r co-efficient	0.0554
P value	**0.0001**

GRAPH :15 CORRELATION BETWEEN CCQ SCORE AND SERUM CYSTATIN C (ng/ml)

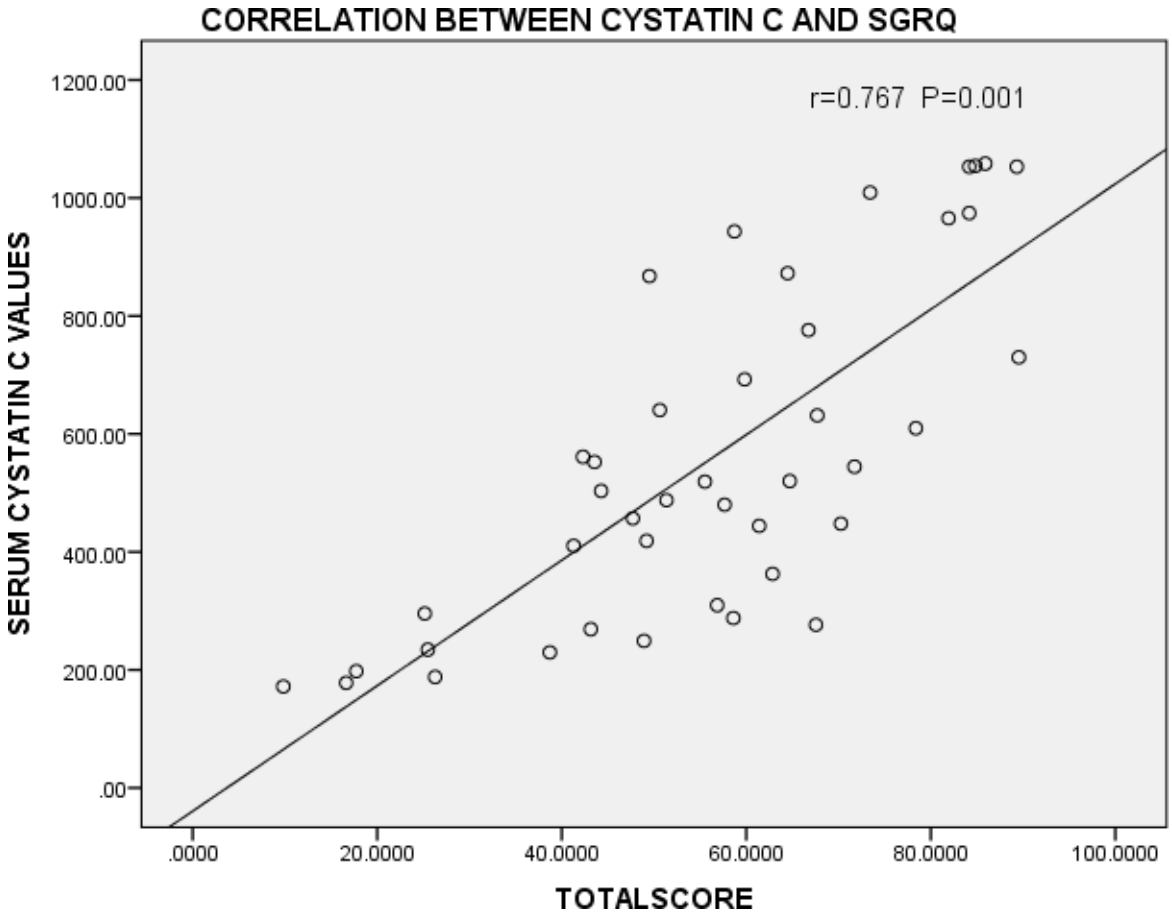
There is a positive correlation between serum Cystatin C level (ng/ml)and CCQ sore and it is statistically significant.



CCQ SCORE	SERUM CYSTATIN C VALUES
r co-efficient	0.743
P value	**0.001**

GRAPH :16 CORRELATION BETWEEN TOTAL SGRQ SCORE AND SERUM CYSTATIN C (ng/ml)

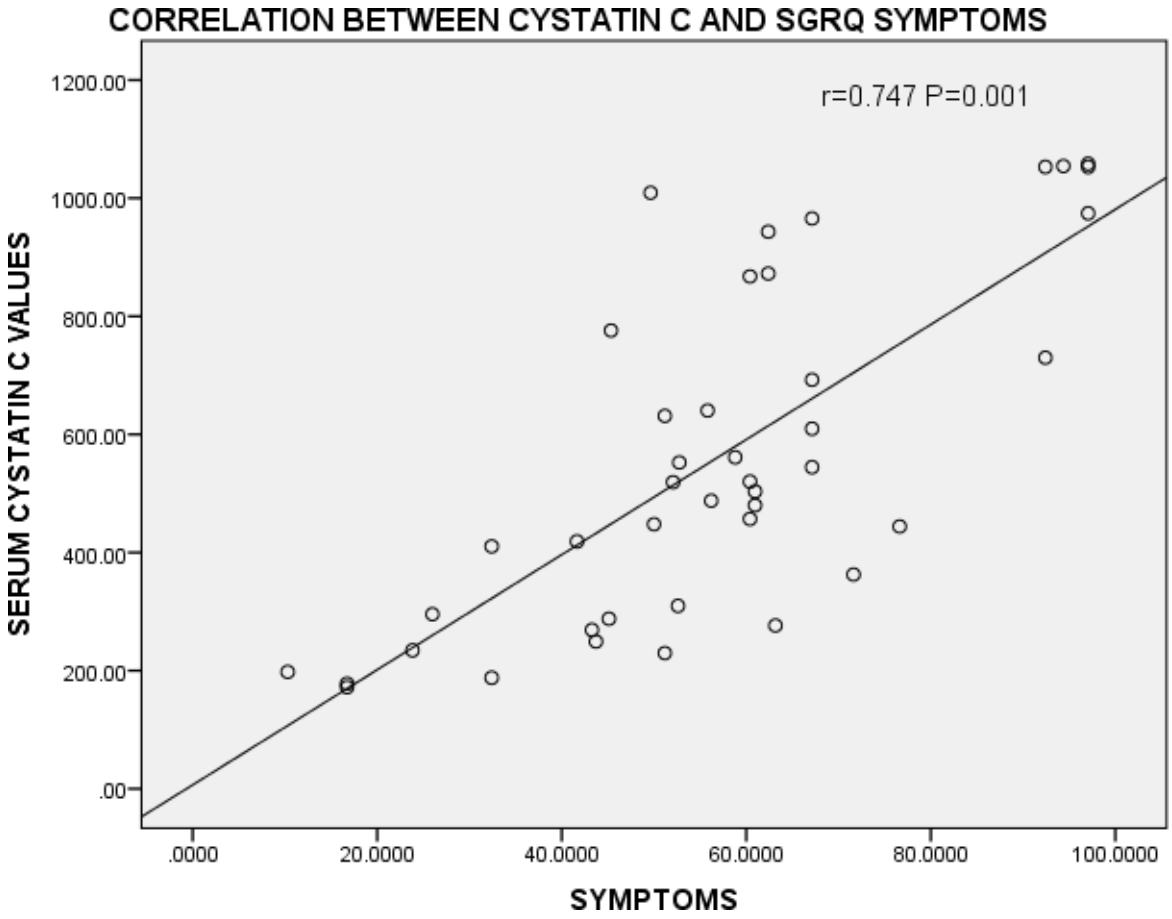
There is a positive correlation between serum Cystatin C level (ng/ml)and TOTAL SGRQ score and it is statistically significant.



SGRQ	SERUM CYSTATIN C VALUES
r co-efficient	0.767
P value	**0.001**

GRAPH :17 CORRELATION BETWEEN SYMPTOMS DOMAIN OF SGRQ AND SERUM CYSTATIN C (ng/ml)

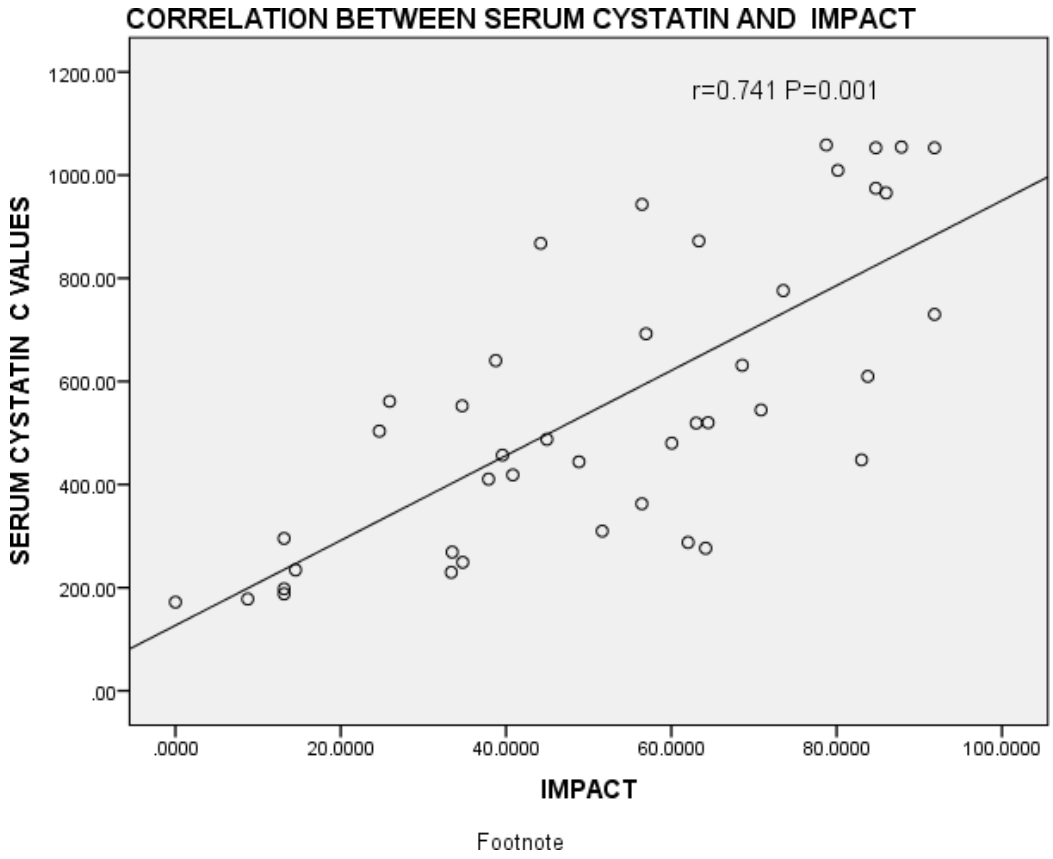
There is a positive correlation between serum Cystatin C level (ng/ml) and symptoms domain of SGRQ score and it is statistically significant



SYMPTOMS DOMAIN OF SGRQ	SERUM CYSTATIN C VALUES
r co-efficient	0.747
P value	**0.001**

GRAPH :18 CORRELATION BETWEEN IMPACT DOMAIN OF SGRQ AND SERUM CYSTATIN C (ng/ml)

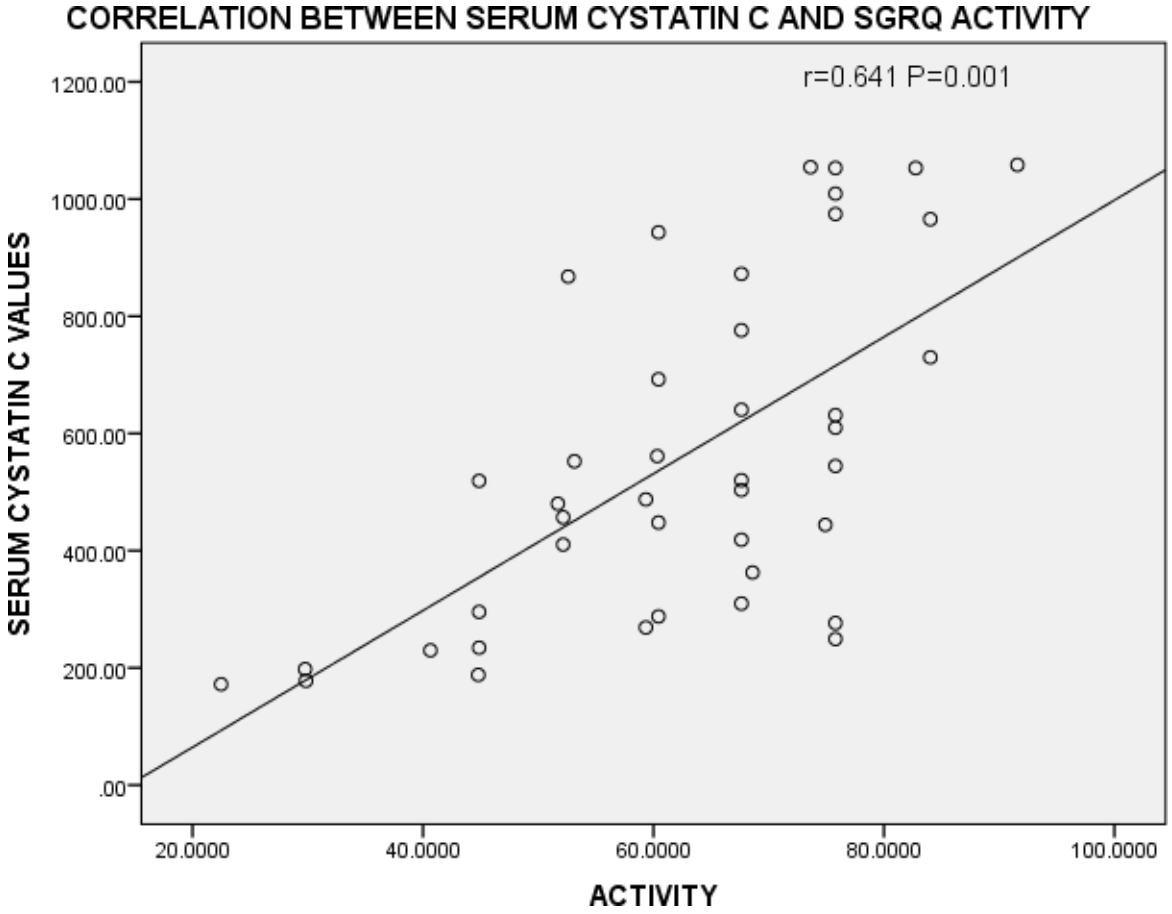
There is a positive correlation between serum Cystatin C level (ng/ml) and impact domain of SGRQ score and it is statistically significant



IMPACT DOMAIN OF SGRQ SCORE	SERUM CYSTATIN C VALUES
r co-efficient	0.741
P value	**0.001**

GRAPH :19 CORRELATION BETWEEN ACTIVITY DOMAIN OF SGRQ AND SERUM CYSTATIN C (ng/ml)

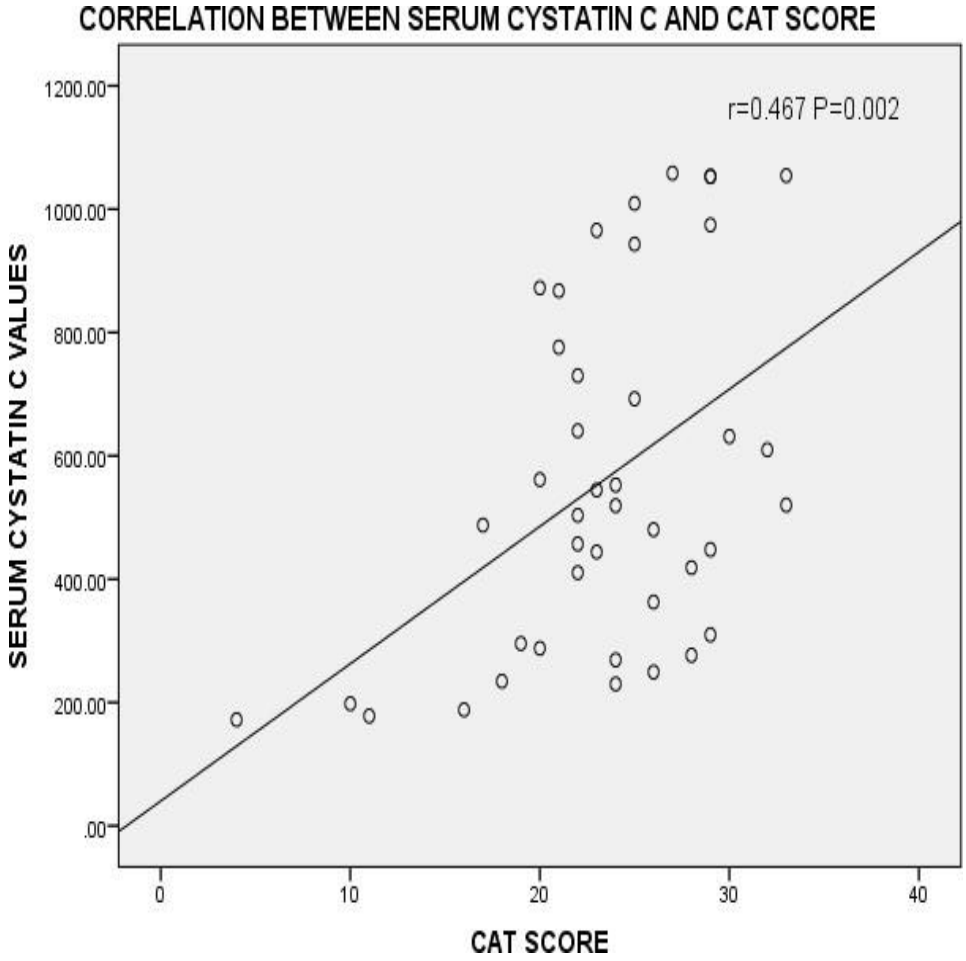
There is a positive correlation between serum Cystatin C level (ng/ml)and activity domain of SGRQ score and it is statistically significant



	SERUM CYSTATIN C VALUES
r co-efficient	0.641
P value	**0.001**

GRAPH :20 CORRELATION BETWEEN CAT SCORE AND SERUM CYSTATIN C (ng/ml)

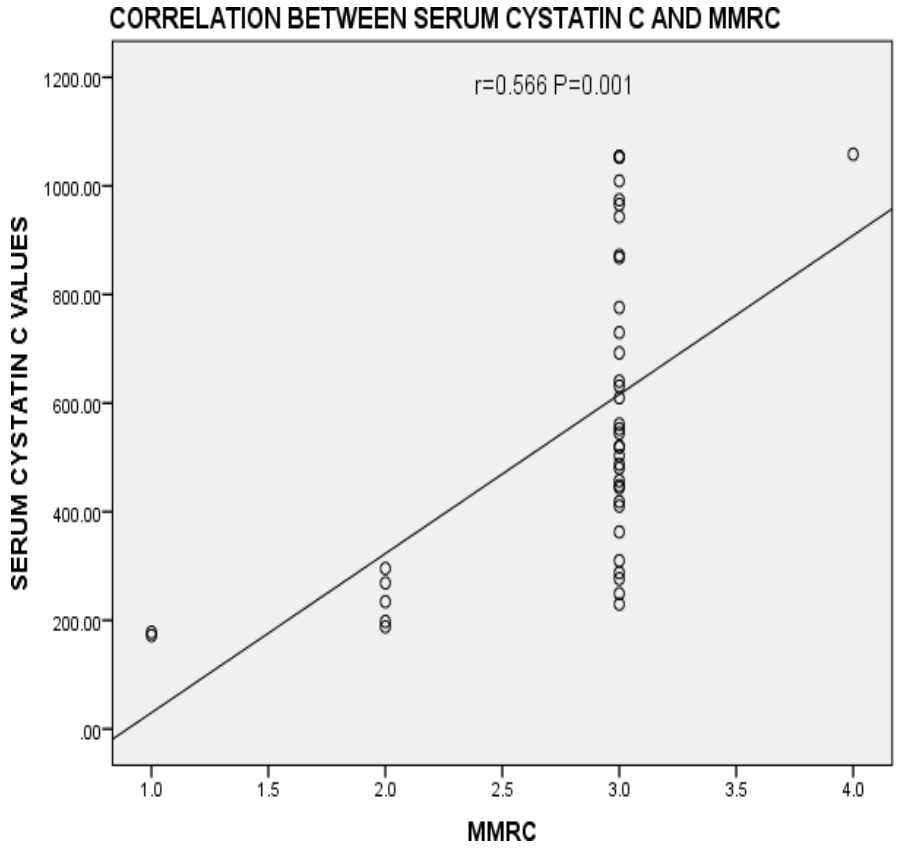
There is a positive correlation between serum Cystatin C level (ng/ml) and CAT score and it is statistically significant



CAT SCORE	SERUM CYSTATIN C VALUES
r co-efficient	0.567
P value	**0.002**

GRAPH :21 CORRELATION BETWEEN mMRC SCALE AND SERUM CYSTATIN C (ng/ml)

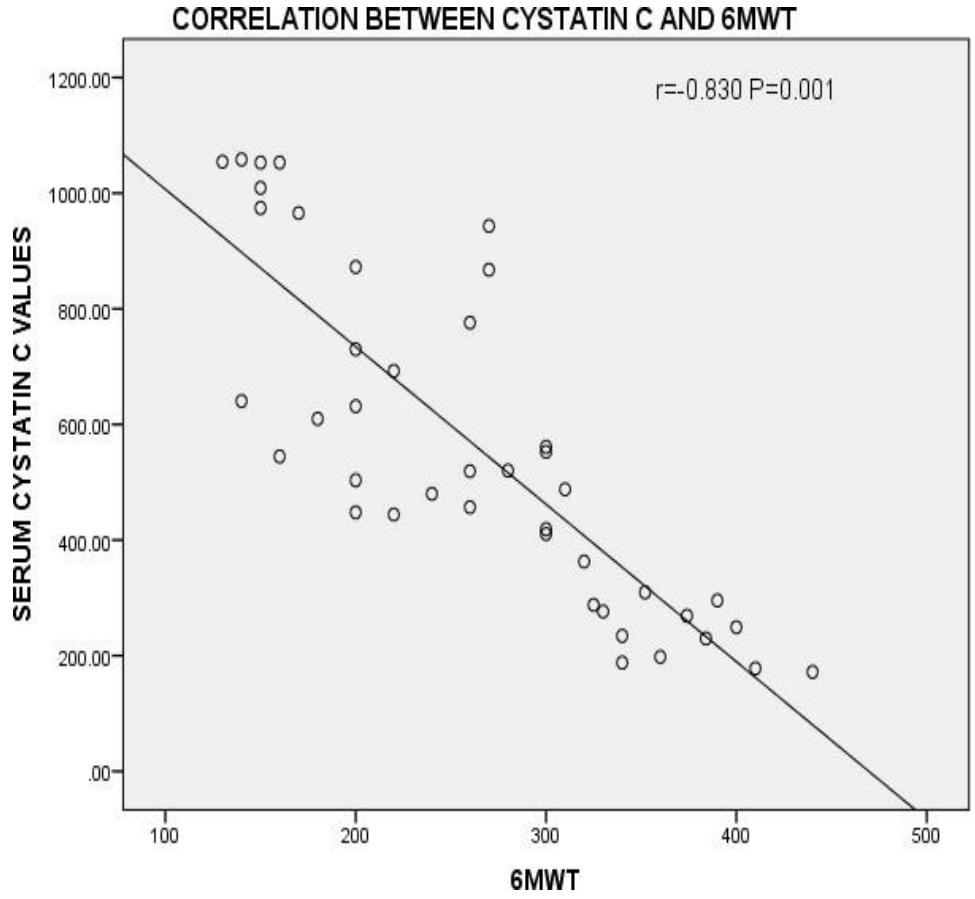
There is a positive correlation between serum Cystatin C level (ng/ml) and mMRC scale and it is statistically significant



mMRC	SERUM CYSTATIN C VALUES
r co-efficient	0.566
P value	**0.001**

GRAPH :22 CORRELATION BETWEEN SIX MINUTE WALK TEST AND SERUM CYSTATIN C (ng/ml)

There is a negative correlation between serum Cystatin C level (ng/ml) and six minute walk test it is statistically significant



Six minute walk test	SERUM CYSTATIN C VALUES
r co-efficient	-0.830
P value	**0.001**

DISCUSSION:

In this study, the significance of serum Cystatin C concentrations in Patients with copd as well as the connection between these levels and the spirometry test (PFT) and its influence on quality of life are being investigated.

Subjects with an exacerbation of copd had their lung function status determined by a spirometry and their serum Cystatin C concentrations measured. Serum Cystatin C levels were compared to a number of variables, including the Clinical COPD Questionnaire, Spirometry Test, CRP, Pack Years, and Duration of Disease.

Persistent inflammation in COPD patients may lead to inflammatory cells recruitment and also increases protease activity in the lungs. Serum Cystatin C levels may decrease in persons with Chronic cigarette smoking which is a cathepsin L inhibitor in the lungs, and this may be the cause of emphysematous changes [(44).]

In contrast, bronchoalveolar lavage and serum Cystatin C levels were increased in patients with emphysema, smokers, and in inflammatory lung disease [(45,46,47).] Also, Increased Cystatin C levels were shown in the culture medium of macrophages of smokers when compared to nonsmokers [(48)].

It was believed that the rise of Cystatin C was a result of the inflammatory processes occurring in the lung since several studies shown a substantial relationship between inflammatory markers including interleukin-6, tumour necrosis factor, and CRP and Cystatin C. [(47,2)]. Patients with COPD had elevated levels of serum Cystatin C, which may be a sign of systemic inflammation as the disease progresses [(76)]

SERUM CYSTATIN C LEVEL:

Characteristic of the studies:

Author and year	Study Design	Assay method	Age Mean ±SD	Men %	Ethnicity	Serum Cystatin C level ng/ml Mean ± SD		Co-morbidities Included
						CASE	CONTROL	
Rokadiaet al.[47] 2012	Cross sectional	Immuno Nephelometer	52.4	36.6	Caucasian	970± 340	883±580	CKD, Cardio vascular diseases
Zhang et al. 2014[5]	Case-control	Immuno nephelometer	81.7 ±6.6	100	Asian	1150± 50	1050±30	Hypertension CKD, Cardio vascular disease
Zhang et al. 2014[56]	Case-control	Immuno nephelometer	65	96.1	Asian	1040± 210	840±180	Renal disorders
Zhang et al.[2] 2015	cohort	Immuno nephelometer	63±7	78.9	Asian	1100 ±30	870±130	NIL
Yoshizawa et al.[77] 2015	Case-control	ELISA KIT	74.3± 7.1	83.3	Asian	1287 ±37	1084 ±26	Renal disorders
Selda et al.[3] 2018	Case-control	Immuno nephelometer	64.9±10	88.2	Asian	970± 20	470±130	NIL
Dickson et al.[78]	Case-control	Immuno nephelometer	72.5	69.5	Asia	1210 470	1180 471	Cardiovascular diseases

In our study	Cross-sectional	ELISA KIT	57.95±3.66	64.3	Indian	560.1± 285.5	No	NIL

In our study Mean serum Cystatin C level is 560.1± 285.5ng/ml which is less and contrast in cases and even in controls when compared to the other studies done by Zhang et al.[(2)] which was 1.31± 0.30 mg/l, Selda et al.[(3)] was 0.97 ± 0.29mg/l, Shu-Hong Fu et al[(5)] was 115.45µg/l and Yonghongzhnag et al.[(77)] was 1.09± 0.22mg/l.

Hence we performed ROC analysis to find specific cut-off values to determine normal and pathological levels. A serum Cystatin C level of 532.1 ng/L was accepted as the cut-off with the highest sensitivity of 100% and specificity of 79.3% as depicted in the graph6. The receiver operating characteristic (ROC) curve's area under the curve (AUC) is 0.942.

Cystatin C concentration of 0.69 mg/ml is selected as the cut-off value in the Selda et al. investigation with a 91percentage sensitivity and 80percentage specificity.

The cut-off value findings in this study are lower than those reported in other studies.

This might be because of the different assay methods used for measuring serum Cystatin C, study design, ethnicity, age, subjects, (%men), BMI, and Presence of co-morbidities.

Cystatin C levels have been studied in kidney and cardiovascular disease and are valuable in assessing renal function and predicting cardiovascular mortality, particularly in the elderly[78,32].

Cystatin C is strongly associated with renal function, so renal dysfunction might affect the concentration of COPD.

Increased serum Smoking, advanced age, male gender, C-reactive protein (CRP), and cardiovascular risk factors such hypertension, poor high-density lipoprotein cholesterol, and an elevated body mass index have all been linked to Cystatin C [32] .

Serum Cystatin C levels do seem to be impacted by a number of variables, including increased weight and height, according to Knight et al.

According to Rubina Bashir et al.,(54) both males and females in the overweight and obese groups had substantially higher blood Cystatin C levels than those in the control group, indicating a possible connection to BMI. Since all nucleated cells, including adipocytes, are known to generate Cystatin C, overweight and obese people are likely to have greater blood Cystatin C levels.

Muntner P et al.(56) and Al-Wakeell JS et al.(55) have also reported.

AGE DISTRIBUTION AND ITS ASSOCIATION WITH SERUM CYSTATIN C LEVELS (ng/ml):-

The age of the patients being studied ranged from 44 years to 60 years & the mean age was 57.95±3.66.

In our study, the mean age 56.8± 4, had serum Cystatin C levels less than or equal to 532.3ng/ml whereas the mean age 59±1, had serum Cystatin C levels more than 532.3 ng/ml.

High serum Cystatin C levels were seen as age increases and the association between them was statistically significant ($P < 0.05$) as depicted in table 4.

In other studies, Rokadia et al., (47) Zhang et al., (2) and Selda et al. (3) had a mean age of 52.4, 63 ± 7, and 64.19± 10.6 respectively & which correlated well with our study.

In the study done by Shu-Hong fu et al. (5) mean age was 81 .78 ±6.6 which is in contrast to our study.

The findings of the investigations by Shu-Hong Fu et al., [5] Gouping hu et al. [6] and Yonghong zhang et al. [58] showed a positive correlation between age and serum Cystatin C levels.

Michelle et al. [50] concluded the mean and variance are greater with each ascending decade of age without risk factors for kidney disease. Cystatin C levels were 46% higher in participants 80 and older compared with those aged <40 years (P<0.001).

GENDER DISTRIBUTION IN ASSOCIATION WITH SERUM CYSTATIN C LEVEL (ng/ml:

In our study, out of 42patients, 27 patients were males & 15 were females & the male: female ratio was 1.8:1 as depicted in graph 3.

In other population-based studies of COPD like Rokadia et al. [47] male to female prevalence, the ratio was 1.04: 1 concurrence to our study. Studies done by & Zhang et al. [2] and Shu-Hong fu et al. [5] included only men whereas in the study done by Selda et al. [3] ratio was 5:1 which was in contrast to our study. Eric L knight et al. concluded male gender, was independently associated with higher serum Cystatin C levels.

Among the 42 patients, the mean Serum Cystatin C levels distribution according to sex was 624±293 ng/ml in male patients and 444±237.5ng/ml in female patients as seen in table 5. Serum Cystatin C levels were notably increased in males and it was statistically significant (P <0.001).

BMI DISTRIBUTION AND ITS ASSOCIATION WITH SERUM CYSTATIN C LEVEL(ng/ml):-

In our study Mean BMI is 20±3 which is in the normal range, the distribution of patients according to BMI was mentioned in Graph 4.

Among the 42 patients,23 patients with a mean BMI of 20.47 had serum Cystatin C levels ≤532.1ng/ml whereas 19 patients with a mean BMI is 20.49Serum Cystatin C levels >532.1ng/ml there was no association between them as seen in table 6.

In other studies done by zhang et al., [2] Shu-Hong Fu et al., [5] and yonghong et al. (58) patients were in the normal BMI range (24 ±2). Whereas in the study by Selda et al.[3] patients were in the overweight BMI range (25.86± 7) and there was no association between serum Cystatin C levels and BMI which is concurrence with our study.

ASSOCIATION OF PACK YEARS WITH SERUM CYSTATIN C LEVEL (ng/ml)

Out of 42 patients, 27 patients were smokers & 15 patients were nonsmokers. Among the 15 non-smokers, 15 were females & 2 were males.

In our study, the mean pack years was 12.1 ± 13.1 years.

In other studies done by zhang et al.,[2] the mean pack year was 38.8±20.6, in Selda et al.,[3] the mean pack year was 19.06±10 which was higher and in contrast to our study.

Among 27 Patients, 7 patients with pack years less than equal to 10 had serum Cystatin C levels <532.1ng/ml levels whereas 20 patients with pack years had serum Cystatin C levels >532.1ng/ml.

In our study serum, Cystatin C levels increased as pack years increased. There is a positive association between pack years and serum Cystatin C. patients with more than 10 pack years have odds of 5.8 times increased chance of serum Cystatin C ng/ml levels which was statistically significant.

These increased levels of Cystatin C may be related to pulmonary inflammation caused on by smoking.

ASSOCIATION OF SERUM CYSTATIN C LEVEL (ng/ml) WITH SPIROMETERY:

Our study consists of 42 subjects who were divided into four categories depending on their FEV1/FVC ratio & Post-Bronchodilator FEV_1 predicted percentage into mild, moderate, severe, and very severe (According to GOLD CRITERIA for classification of COPD) mentioned in the graph 5.

Among the 42 patients,19 patients had serum Cystatin C levels above 532.1ng/ml and 23 patients had serum Cystatin C levels less than or equal to 532.1ng/ml. association between them is statistically significant as depicted in table 11.

The mean Serum Cystatin C levels in patients with moderate airway limitation was 250.02 ng/ml, 567.60 in patients with severe airflow limitation, and 861.25 ng/ml Serum Cystatin C levels in patients with very severe airflow limitation.

Serum Cystatin C was notably increased as airflow limitation (% FEV1 predicted) decreases and the association between them was statistically significant ($P<0.001$).

The serum concentration of Cystatin C was Negatively correlated with FEV1% predicted

($r= -0.802$, $p=0.0001$) as depicted in graph 12.

Serum Cystatin C levels can be used as an alternative diagnostic tool in patients with poor or inadequate effort for performing pulmonary function tests for the diagnosis of COPD.

In a study done by zhang et al. [(2)] the mean Serum Cystatin C levels distribution according to airway limitation was 1.10± 0.27 mg/l in the mild patient's category 1.20± 0.24 mg/l in the moderate patient's category, 1.43± 0.2 mg/l in severe patients category and1.59 ±0.25 mg/ml

Serum Cystatin C levels in the very severe patient category which were a contrast to our study and higher than our serum Cystatin C levels.

Mean Serum Cystatin C was notably increased as airflow limitation (% FEV_1 predicted) decreases and the negatively correlated between them was statistically significant (P <0.001).

In the studies by Zhang et al., [2] and Shu-Hong Fu et al., [5] Serum concentration of serum Cystatin C was negatively correlated with FEV_1 predicted (r= -0.475, p=0.0001).

ASSOCIATION OF REDEFINED ABCD TOOL WITH SERUM CYSTATIN C LEVEL (ng/ml)

According to the severity of the patients' symptom, H/O exacerbation, and hospitalisation, patients were staged in our study using the Redefined ABCD evaluation method.

Out of 42 patients, 3 (7%) of them were in class A, 5(11%) of them were in class B and 34 (81%) of them were in class D as depicted in table 14.

Serum Cystatin C levels were less than equal to 532.1 ng/ml in 8 patients belonging to the A and B classes.

Among 34 patients in class D, 15 had serum cystatin levels less than or equal to 532.1 ng/ml. These patients had ≥1 exacerbations history whereas 19 patients had serum Cystatin C levels of more than 532.1 ng/ml and had exacerbation history ≥2 during the duration of the disease.

Serum Cystatin C levels were increased with Disease severity and in patients with increased no of exacerbations and the association between them was statistically significant. (p<0.05).

According to a study by Selda et al., [3] 58 COPD who are stable, 26 patients (38.4%) fell into class B, while 42 patients (42%) fall into class C.

The mean serum Cystatin C level 1.05 ±0.56, 1.33 ±2.30 respectively and (P>0.05). and concluded that serum Cystatin C may be used only to determine and follow up on the severity of airflow limitation which is in contrast to our study.

ASSOCIATION OF DURATION OF DISEASE WITH SERUM CYSTATIN C LEVEL (ng/ml):-

In our study, the mean duration of illness is 4.9 ± 2.2 years. The distribution of patients according to the Duration of the disease was depicted in graph 8.

There is a positive association between serum Cystatin C ng/ml and Duration of disease and patients with a duration of disease more than 4 years have odds of 6.5 times increased chance of serum Cystatin C levels found to be statistically significant as mentioned the table 16.

There is a positive correlation between serum Cystatin C level (ng/ml) and Duration of disease and it is statistically significant as depicted in the graph13.

ASSOCIATION OF MODIFIED MEDICAL RESEARCH COUNCIL SCALE WITH SERUM CYSTATIN C LEVEL (ng/ml):-

Dyspnea is the most frequent symptom reported by patients suffering from COPD, and the Modified medical research scale is the most commonly used validated scale to assess dyspnea in patients.

The distribution of patients according to the Modified medical research scale is depicted in table 17. The distribution of patients according to the Modified medical research scale concerning serum Cystatin C levels is depicted in table 18.

Serum Cystatin C levels were higher in patients with mMRC score ≥3. There is an association between the Modified medical research scale and serum Cystatin C levels and it is statistically significant $p<0.05$ (table 18).

In the study done by Magno,F et al. (80) had mean serum Cystatin C level 550ng/ml with mMRC score 1.7±1.2.

ASSOCIATION OFSIX-MINUTE WALK TEST AND SERUM CYSTATIN C LEVEL (ng/ml):-

The 6-min walk test (6MWT) is commonly used to evaluate the functional exercise capacity in COPD patients. The distribution of patients according to the six-minute walk test was depicted in graph 9.

There was a positive association between the six-minute walk and serum Cystatin C levels and patients with a 6-minute walk test less than 250m have odds of 13 times increased chance of serum Cystatin C levels it was found to be statistically significant (table 19).

There is a negative correlation between serum Cystatin C level (ng/ml) and the six-minute walk test it is statistically significant ($r = -0.830$, $p= 0.001$) as depicted in graph 2.

ASSOCIATION OF BODE INDEX WITH SERUM CYSTATIN C LEVEL (ng/ml)

The BODE index is a multidimensional index that incorporates: the body mass index (BMI), the degree of airflow obstruction assessed by the Forced Expiratory Volume in one second (FEV_1), the modified Medical Research Council (mMRC) dyspnea scale, and the exercise capacity assessed by the 6-min walking distance (6MWD) test Bode Index ranged from 0-10

In our study among 42 patients, 26 patients had a BODE index score less than or equal to 6, whereas 16 patients' BODE index score is more than 6.

There is a positive association between BODE index and serum Cystatin C levels and patients with a BODE index of more than 6 have odds of 14 times increased chance of serum Cystatin C levels and it was statistically significant (table 20).

Serum Cystatin C level had a statistically significant positive association across all domains of the BODE index except BMI.

In the study done by Magno,F et al. (80) had mean serum Cystatin C level 550ng/ml with BODE index 4±2.1.

ASSOCIATION OF CRP LEVELS WITH SERUM CYSTATIN C LEVEL (ng/ml)

In our study as serum CRP levels increase with increased serum Cystatin C levels and are positively correlated and statically significant. (r=0.554, p,0.001).

Due to a significant association of CRP and Cystatin C in our study population, it might be speculated that elevation of Cystatin C occurs secondary to inflammatory processes in the lung.

Studies done rokadia et al.,[47] Selda et al.,[3] S-H Fu et al.,[5] and zhang et al., [2]also concluded, a progressive increase in the mean serum CysC level with serially increasing CRP concentrations and statically significant which is similar to our study.

ASSOCIATION OF SERUM CYSTATIN C LEVELS WITH QUALITY OF LIFE IN COPD PATIENTS.

In chronic diseases, health-related quality of life (HRQL) is an important patient-oriented measurement of the impact of health on well-being.

Health-related quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ) and clinical COPD Questionnaire (CCQ) and CAT score.

To our knowledge, this is the first study to evaluate the serum Cystatin C levels' impact on the quality of life in COPD patients.

The SGRQ is a standardized self-administered airways disease-specific questionnaire divided into three subscales: symptoms (eight items), activity (16 items), and impacts (26 items). For

each subscale and the overall questionnaire, scores range from zero (no impairment) to 100 (maximum impairment).

ASSOCIATION OF SERUM CYSTATIN C LEVEL WITH A TOTAL SCORE OF ST. GEORGE QUESTIONNAIRE (I.E SYMPTOMS, ACTIVITY AND IMPACT).

Among 42 patients, Distribution according to St. George Respiratory Questionnaire total score according to serum Cystatin C levels was shown in table 23.

To our knowledge, this is the first study to evaluate the serum Cystatin C levels' impact on the Total score of St. George questionnaire (i.e symptoms, activity and impact).

There was a positive association between SGRQ total score and serum Cystatin C ng/ml and patients with St George total score more than 50 have odds of 4.8 times chance of increased levels of serum Cystatin C levels and were found to be statistically significant shown in (table 23).

There is a positive correlation between serum Cystatin C level (ng/ml) and SGRQ Total score and it is statistically significant as shown in Graph 16.

In the study done by Magno,F et al. [80] had mean serum Cystatin C level was 550ng/ml with St. George total score 45.3±30.6.

ASSOCIATION OF SERUM CYSTATIN C LEVEL WITH INDIVIDUAL DOMAIN OF ST. GEORGE QUESTIONNAIRE (I.E SYMPTOMS, ACTIVITY, AND IMPACT).

Among 42 patients, the Distribution of patients according to the St. George Respiratory Questionnaire symptom score concerning serum Cystatin C levels was shown in table 24.

To our knowledge, this is the first study to evaluate the serum Cystatin C levels' impact on individual domain of St. George questionnaire.

There was a positive association between SGRQ symptom score and serum Cystatin C ng/ml and patients with St George symptom scores more than 50 had 9 times increased levels of serum Cystatin C levels and were found to be statistically significant shown in (table 24).

There is a positive correlation between serum Cystatin C level (ng/ml) and symptoms domain of SGRQ score and it is statistically significant ($r= 0.747$, $p< 0.05$) as depicted in graph 17.

Among 42 patients, the Distribution of patients according to the St. George Respiratory Questionnaire impact score according to serum Cystatin C levels was shown in table 25.

There was a positive association between SGRQ impact score and serum Cystatin C ng/ml and patients with St George total score of more than 50 have odds of 7.03 times chances of increased levels of serum Cystatin C levels and were found to be statistically significant shown in the (table 25).

There is a positive correlation between serum Cystatin C level (ng/ml) and impact domain of SGRQ score and it is statistically significant ($r= 0.741$, $p< 0.05$) as shown in graph 18.

Among 42 patients, the Distribution of patients according to the St. George Respiratory Questionnaire Activity score according to serum Cystatin C levels was shown in table 26.

There was a positive association between SGRQ activity score and serum Cystatin C ng/ml was found to be statistically significant shown in (table 26).

There is a positive correlation between serum Cystatin C level (ng/ml) and the activity domain of SGRQ score and it is statistically significant ($r= 0.741$, $p< 0.05$) as shown in graph 19.

In the study done by Magno,F et al. [80] had mean serum Cystatin C level 550ng/ml with symptom score53.9±24.4, activity score 62.1±26.4 and impact score 32.7±20.4.

ASSOCIATION OF CLINICAL COPD QUESTIONNAIRE SCORES WITH SERUM CYSTATIN C LEVEL (ng/ml)

In our study, the mean CCQ score was 2.73±0.7. Distribution of patients according to clinical COPD questionnaire with respect to serum Cystatin C levels (ng/ml).

To our knowledge, this is the first study to evaluate the serum Cystatin C levels' impact on the Clinical COPD questionnaire.

There is an association between the clinical COPD questionnaire and serum Cystatin C levels and patients with Clinical COPD questionnaire scores more than or equal to 3 have odds of 4.7 times increased chances of serum Cystatin C levels and found it was statistically significant ($p<0.05$) (table 21).

There was a positive correlation between the serum Cystatin C levels (ng/ml) and CCQ score ($r= 0.743$, $p< 0.001$) as shown in graph 15.

ASSOCIATION OF CAT SCORES WITH SERUM CYSTATIN C LEVEL (ng/ml):-

The CAT score assesses symptom burden in COPD patients. It comprises 8 questions, each presented as a semantic 6-point differential scale, providing a total score out of 40.

To our knowledge, this is the first study to evaluate the serum Cystatin C levels' impact on the CAT scores.

The distribution of patients according to CAT score with respect to serum Cystatin C levels as depicted in table 22.

There is a positive association between cat score and serum Cystatin C levels and patients with CAT scores more than 20 have odds of 4.5 times chances of increased serum Cystatin C levels and found it was statistically significant($p <0.05$) (table 22).

There was a positive correlation between the serum Cystatin C levels (ng/ml) and total CAT score ($r= 0.467$, $p< 0.002$) and it was statistically significant.

In the study done by Magno,F et al. [80] had mean serum Cystatin C level 550ng/ml with CAT score17.5±8.2.

LIMITATIONS:

1. Further prospective studies are required with long term follow ups.
2. This is a cross-sectional study but a case-control study would provide better knowledge about variations of serum Cystatin C levels between COPD patients and healthy subjects

3. This is the first Indian study, and hence many other studies from India are required to establish the standard values in the population.

CONCLUSION:

The mean serum Cystatin C level is 560.1± 285.5ng/ml in our study, which is far less than controls in other studies. So standardized values from our lab of serum Cystatin C has been taken with help of ROC analysis that is 532ng/ml.

In this study, most of the patients belonged to the age group more than 55 years, with male predominance with Ideal body weight, with pack years more than ten might have increased chances of raised serum Cystatin C levels and a duration of disease of more than 4 years have odds of 6.5 times chance of increased serum Cystatin C levels.

Mean Serum Cystatin C was notably increased as airflow limitation (% FEV_1 Predicted) decreases and the association between them was statistically significant . There is a positive association between BODE index and serum Cystatin C levels and patients with a BODE index of more than 6 have odds of 14 times chance of increased serum Cystatin C levels. Serum Cystatin C levels were increased with Disease severity (ABCD TOOL). 6-minute walk test less than 250m have odds of 13 times chance of increased serum Cystatin C levels

serum Cystatin C ng/ml and patients with St George total score more than 50 have odds of 4.8 times chance of increased levels of serum Cystatin C levels. St George symptom scores more than 50 have odds of 9 times the chance of increased levels of serum Cystatin C levels. Clinical COPD questionnaire scores more than or equal to 3 have odds of 4.7 times chance of increased serum Cystatin C levels. CAT scores more than 20 have odds of 4.5 times chance of increased serum Cystatin C levels

There was a negative correlation between FEV_1, six-minute walk test, and Cystatin C levels in a positive correlation between Cystatin C and CRP levels, duration of disease, CCQ score, mMRC, CAT score, and St George questionnaire

SUMMARY

Forty-two patients diagnosed with COPD attended the in-patient department of Respiratory Medicine, BLDE (Deemed to be University), Shri. B. M. Patil Medical College, Hospital and Research Centre, Vijayapura, between January 2021 and June 2022 were studied. The study

was conducted to evaluate serum Cystatin C levels in cases of COPD and its correlation with spirometry and impact on their quality of life

1. The most common age group was more than 55 years with 88.1%, followed by 9.5% in 50-55 years and 2.4% in ages less than 44 years.

2. In this study, more male patients (64.3%) were more than female (35.7%).

3. In this study 50% were of Ideal body weight, whereas 14.2%were overweight, and 35% were Underweight.

4. In this study 74% of male patients have pack years of smoking for more than 10 years

5. In this study, 31% had moderate airflow limitation whereas 38.1% were with severe air limitation and 31% were with very severe airflow limitation.

6. In this study Mean serum Cystatin C level is 560.1± 285.5ng/ml which is less when compared to other studies, so performed ROC analysis to find out the cut-off that is 532.1ng/ml with the highest sensitivity of 100% and specificity of 79.3% with area under the curve is 0.942.

7. 45.2%patients had serum Cystatin C levels above 532.1ng/ml and 54.7%patients had serum Cystatin C levels less than or equal to 532.1ng/ml. association between them is statistically significant.

8. Mean Serum Cystatin C was notably increased as airflow limitation (% FEV_1 Predicted) decreases and the association between them was statistically significant ($P<0.001$).

9. Serum Cystatin C levels were increased with Disease severity (ABCD TOOL) and in patients with increased number of exacerbations and the association between them was statistically significant. ($p<0.05$).

10. Patients with a duration of disease of more than 4 years have odds of 6.5 times chance of increased serum Cystatin C levels found to be statistically significant ($P<0.05$).

11. Serum Cystatin C levels were higher in patients with mMRC score ≥3. There is an association between the Modified medical research scale and serum Cystatin C levels and it is statistically significant ($P<0.05$).

12. There is a positive association between the six-minute walk and serum Cystatin C levels and patients with a 6-minute walk test less than 250m have odds of 13 times chance of increased serum Cystatin C levels it was found to be statistically significant($P<0.05$).

13. There is a positive association between BODE index and serum Cystatin C levels and patients with a BODE index of more than 6 have odds of 14 times chance of increased serum Cystatin C levels and it was statistically significant ($p<0.05$).

14. Serum Cystatin C level had a statistically significant positive association across all domains of the BODE index except BMI.

15.serum CRP levels increase with increased serum Cystatin C levels and are positively correlated and statically significant.

16. There was a positive association between SGRQ total score and serum Cystatin C ng/ml and patients with St George total score more than 50 have odds of 4.8 times chance of increased levels of serum Cystatin C levels and were found to be statistically significant. ($P<0.05$).

17. There was a positive association between SGRQ symptom score and serum Cystatin C ng/ml and patients with St George symptom scores more than 50 have odds of 9 times chance of increased levels of serum Cystatin C levels and were found to be statistically significant. ($P<0.05$).

18. There is a positive correlation between serum Cystatin C level (ng/ml) and impact domain of SGRQ score and it is statistically significant. ($P<0.05$).

19. There is an association between the clinical COPD questionnaire and serum Cystatin C levels and patients with Clinical COPD questionnaire scores more than or equal to 3 have odds of 4.7 times chance of increased serum Cystatin C levels and found it was statistically significant ($p<0.05$)

20. There is a positive association between cat score and serum Cystatin C levels and patients with CAT scores more than 20 have odds of 4.5 times chance of increased serum Cystatin C levels and found it was statistically significant ($p <0.05$).

RECOMMENDATIONS:

1. Serum Cystatin C level does not have clinical management impact, further studies in different population are required as data is available only from China.

2. Quality of life like BODE index, St.George Questionnaire to be used in all patients in every follow up to know the impact on patient.

3. CRP is also a good prognostic test and is easily available.

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ANNEXURE I

B.L.D.E. (DEEMED TO BE UNIVERSITY) IEC/NO-09/2021 Date- 22/01/2021

(Declared vide notification No. 1-9-37/2007-U-3 (N) Dated: 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)

The Constituent College

SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The ethical committee of this college met on 11-01-2021 at 11-00 am to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: A clinical study of serum cystatin C levels in cases of COPD and its correlation with spirometry and impact on their quality of life.

Name of PG student: Dr Ravi Apoorva, Department of Respiratory Medicine

Name of Guide/Co-investigator: Dr Ramesh.S.Babar, Professor & HOD of Respiratory Medicine

DR. S. V. PATIL
CHAIRMAN, IEC
Institutional Ethical Committee
B L D E (Deemed to be University)
Shri B.M. Patil Medical College,
VIJAYAPUR-586103 (Karnataka)

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

1

ANNEXURE II

INFORMED CONSENT FORM

B.L.D.E(DEEMED TO BE UNIVERSITY) SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA – 586103, KARNATAKA

TITLE OF THE PROJECT: " A CLINICAL STUDY OF SERUM CYSTATIN C LEVELS IN CASES OF COPD AND ITS CORRELATION WITH SPIROMETRY AND IMPACT ON THEIR QUALITY OF LIFE".

PRINCIPAL INVESTIGATOR: Dr. Ravi Apoorva
Department of Respiratory Medicine

PG GUIDE: Dr. RAMESH .S. BABAR,
Professor and Head,
Department of Respiratory Medicine,
B.L.D.E (Deemed to be University)'s
Shri B.M.Patil Medical College, Hospital and
Research Centre, Sholapur Road,
Vijayapura- 586103

PURPOSE OF RESEARCH:

I have been informed that the purpose of this study is to assess " A CLINICAL STUDY OF SERUM CYSTATIN C LEVELS IN CASES OF COPD AND ITS CORRELATION WITH SPIROMETRY AND IMPACT ON THEIR QUALITY OF LIFE ".

I have been explained the reason for conducting this study and selecting me/my ward as a subject for this study. I have also been given a free choice for either being included or not in the study.

PROCEDURE:

I understand that I will undergo a detailed history and clinical examination and investigations.

RISKS AND DISCOMFORTS:

I understand that I/my ward may experience hypersensitivity or anaphylaxis while doing the procedure. I understand that necessary measures will be taken to reduce these complications as and when they arise.

BENEFITS:

I understand that I/my ward's participation in this study will help find out a clinical study of serum Cystatin C levels in cases of copd and its correlation with spirometry and impact on their quality of life.

CONFIDENTIALITY:

I understand that this study's medical information will become a part of this hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records but will be stored in the investigator's research file and identified only by a code number. The code key connecting the name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purposes, no names will be used, and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may request more questions about the study at any time. Dr.RAVI APOORVA is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. And that a copy of this consent form will be given to me to keep for careful reading.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary, and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that Dr. RAVI APOORVA will terminate my participation in this study at any time after she has explained the reasons for doing so and has helped arrange for my continued care by my physician or therapist if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly in my participation in this study, if such injury were reported promptly, medical treatment would be available to me, but no further compensation will be provided.

I understand that I am not waiving any of my legal rights by my agreement to participate in this study.

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. RAVI APOORVA has explained the purpose of this research, the study procedure that I will undergo, and the possible discomforts and benefits that I may experience in my own language.

I have been explained all the above in detail in my own language, and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

I have explained to_____, the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Date: Dr. RAMESH. S. BABAR Dr. RAVI APOORVA

(Guide) (Investigator)

ANNEXURE III

PROFORMA

Name of the patient: Age:

Address: Sex:

IP no/OP no:

Occupation:

Presenting Complaints:

History of Present Illness:

Past history:

Personal history:

1. Diet- Veg/Mixed:
2. Appetite:
3. Sleep:
4. Bowel and bladder habits:

Family history:

Menstrual History:

GENERAL PHYSICAL EXAMINATION:

Conscious/ oriented/ co-operative:

Built:

Nourishment:

Ht (cm):

Wt (kg):

BMI:

Pallor

Icterus

Clubbing

Cyanosis

Lymphadenopathy

Edema

6. Vital parameters:

a. Temperature:

b. Pulse:

c. Respiratory rate:

d. BP:

e. SpO2:

SYSTEMIC EXAMINATION:

RESPIRATORY SYSTEM

ABDOMEN EXAMINATION

CARDIOVASCULAR SYSTEM

CENTRAL NERVOUS SYSTEM

INVESTIGATIONS:

Complete blood count:

Total Count	
Neutrophils %	
Lymphocytes %	
Monocytes %	
Eosinophils %	
Basophils %	
Hemoglobin (gm/dl)	
Platelet count (per cu.mm)	

Serum creatinine

Urea

Serum Cystatin C level:

Chest X-ray:

ECG:

Pulmonary Function Test:

FINAL DIAGNOSIS:

DATE SIGNATURE

ANNEXURE IV

MASTERCHART

											SGI Q								
S.NO	NAME	AGE	SEX	BMI	SMOKING STATUS	POST BRONCHODILATOR FEV1/FVC	POSTBRONCHODILATOR FEV1% PREDICTED	CRP	SERUM CYSTATIN C VALUES	6MWT	TOTALSCORE	SYMPTOMS	ACTIVITY	IMPACT	MMRC	CAT SCORE	CCQ SCORE	ABCD TOOL	DURATION OF DISEASE	BODE INDEX	pack years
1	SHEELA	55	FEMALE	19	ABSENT	69.4	51	10	188	340	26.28	32.41	44.8	13.14	2	16	1.5	B	0.5	4	0
2	SANGABASAPPA.KUMBAR	60	MALE	23.2	PRESENT	62.4	67	28	268.93	374	43.15	43.27	59.34	33.48	2	24	2.9	D	4	2	5
3	MAHADEVAPPA.MANDUR	60	MALE	21	PRESENT	68.3	60	28.3	229.78	384	38.71	51.17	40.65	33.38	3	24	2.4	B	5	4	4
4	SIDAMMA	52	FEMALE	22.2	ABSENT	57.2	63	21.2	309.71	352	56.85	52.6	67.63	51.64	3	29	2.7	D	5	3	0
5	SHANKAR	60	MALE	18.2	PRESENT	56.3	66	27	249.28	400	48.92	43.71	75.79	34.76	3	26	2.4	D	2	5	8
6	SOMNATHSOMNAL	60	MALE	18.7	PRESENT	67.2	56	15.5	276.43	330	67.55	63.16	75.79	64.15	3	28	3.3	D	4	4	7
7	MALLAPPA SAJJAN	60	MALE	18.4	PRESENT	45.8	31	22	444.07	220	61.4	76.62	74.91	48.82	3	23	2.4	D	8	8	12
8	LAMANI PARSU	60	MALE	21.1	PRESENT	59	70	5	172	440	9.83	16.73	22.48	0	1	4	0.9	A	0.5	1	3
9	ROKAMMA	60	FEMALE	20.7	ABSENT	49.7	55	22	362.75	320	62.85	71.62	68.6	56.43	3	26	2.5	D	7	6	0
10	BABANGOUDA	60	MALE	22.1	PRESENT	49.8	26	12	631.32	200	67.69	51.17	75.79	68.58	3	30	3.2	D	8	8	15
11	VAJABAI	60	FEMALE	20.1	ABSENT	64.4	53	21	234.3	340	25.49	23.83	44.87	14.53	2	18	1.8	B	3	3	0
12	RAMAPPA	60	MALE	18.1	PRESENT	46.5	29	12	729.84	200	89.54	92.41	84.03	91.84	3	22	2.3	D	6	8	24
13	RAMANGOUDA	60	MALE	24.2	PRESENT	62.9	39	44	692.46	220	59.82	67.13	60.44	56.94	3	25	3.3	D	6	6	18
14	MAHADEVAPPA.B	58	MALE	18	PRESENT	38.1	32	33	447.9	200	70.25	50	60.44	83.01	3	29	3.1	D	4	7	13
15	SHAKUNTALA	58	FEMALE	26	ABSENT	70.3	67	5	178	410	16.63	16.73	29.84	8.75	1	11	1.6	A	1	0	0
16	YALLAWAA	57	FEMALE	20.4	ABSENT	70.2	67	10	197.8	360	17.74	10.3	29.77	13.14	2	10	1.3	A	0.5	2	0
17	HARSING MADHU	50	MALE	15.6	ABSENT	56.3	40	20	456.95	260	47.7	60.4	52.16	39.57	3	22	2.8	D	5	6	16
18	DANAPPA NADASHETTI	60	MALE	17.2	PRESENT	51.8	47	25	410.5	300	41.29	32.41	52.16	37.88	3	22	2.4	D	6	6	12
19	MIRABAI	58	FEMALE	17.9	ABSENT	67.7	45	43	418.72	300	49.19	41.65	67.63	40.82	3	28	2.7	D	7	6	0
20	RANJANA	44	FEMALE	26.5	ABSENT	61.1	38	36	519.18	260	55.51	52.07	44.87	63.01	3	24	2.4	D	3	5	0
21	BASAPPA BIRADAR	60	MALE	18.4	PRESENT	53.2	44	20	520.07	280	64.71	60.4	67.63	64.45	3	30	2.8	D	5	6	18
22	DEVAKKI	55	FEMALE	25.8	ABSENT	56.8	28	36	609.71	180	78.38	67.13	75.79	83.77	3	32	3.3	D	7	7	0
23	KALYANSHETTI	60	MALE	21.8	PRESENT	53.4	60	12	295.49	390	25.15	25.98	44.87	13.14	2	19	1.8	B	2	2	8
24	BASAMMA	58	FEMALE	22.2	ABSENT	57.9	28	22	544.55	160	71.73	67.13	75.79	70.85	3	23	3.2	D	6	7	0
25	PADMAVATHI	50	FEMALE	18.1	ABSENT	65.7	32	17	480.15	240	57.65	60.95	51.7	60.05	3	26	3.6	D	5	8	0
26	SIDANNAGOUDA	60	MALE	29.3	PRESENT	57.3	36	18	552.46	300	43.55	52.74	53.14	34.69	3	24	2	D	4	5	22
27	SHIVASHARANAE	57	MALE	25.2	PRESENT	49.2	36	11.4	487.64	310	51.35	56.2	59.34	44.94	3	17	2.6	B	3	5	12
28	MALAPPA MUREGAPPA	60	MALE	14.9	PRESENT	44.4	29	301	974.43	150	84.17	97.05	75.79	84.74	3	29	3.6	D	8	8	25
29	SIDDARAY GOUDA BIRADAR	60	MALE	29.7	PRESENT	52.3	28	45	640.46	140	50.63	55.81	67.63	38.75	3	22	2.7	D	5	8	8
30	MALLAMMA	50	FEMALE	24.6	ABSENT	58.2	39	32	503.47	200	44.27	60.95	67.63	24.67	3	22	2.5	D	3	6	0
31	SAVITRI	59	FEMALE	19	ABSENT	41	50	12	287.81	325	58.6	45.11	60.44	62.02	3	20	2.1	D	8	5	0
32	SHIVAPPA	60	MALE	23.1	ABSENT	54	47	18	561.29	300	42.3	58.8	60.33	25.91	3	20	2.6	D	4	5	16
33	SANGAMMA MANNUR	60	FEMALE	13.8	ABSENT	50.5	26	37	965.6	170	81.93	67.13	84.03	85.98	3	23	3.1	D	6	8	0
34	SANGANGOUDA	56	MALE	19.5	PRESENT	41.3	21	107	1054.5	130	84.83	94.37	73.63	87.84	3	33	3.6	D	9	9	45
35	MALDEGARI	60	MALE	14.9	PRESENT	44.4	29	103	1053	150	84.17	97.05	75.79	84.74	3	29	3.6	D	8	8	40
36	CHANDRASHA	60	MALE	18.1	PRESENT	65.3	37	184	776.06	260	66.74	45.34	67.63	73.54	3	21	2.9	D	7	6	20
37	GOURABAI	60	FEMALE	21.4	ABSENT	68.3	38	43	867.63	270	49.5	60.4	52.6	44.19	3	21	2.9	D	5	5	0
38	MALLAPPA . IRAKAR	60	MALE	20.14	PRESENT	36.1	19	88	1058.3	140	85.9	97.05	91.58	78.75	4	27	4.2	D	6	10	40
39	ISHWARAPPA	60	MALE	15	PRESENT	33.6	26	25	872.34	200	64.48	62.38	67.63	63.33	3	20	3.2	D	5	8	24
40	MARTHANDARAO	58	MALE	21	PRESENT	52	49	180	943.19	270	58.72	62.38	60.44	56.45	3	25	3.2	D	5	6	25
41	SHARNAPPA KALAPPA	59	MALE	19.8	PRESENT	40.8	19	39	1009.2	150	73.42	49.63	75.79	80.15	3	25	2.9	D	6	8	34
42	SANGAPPA GURUBASAPPA	60	MALE	16	PRESENT	56.3	29	22	1053	160	89.32	92.41	82.76	91.84	3	29	4.6	D	7	8	36

ANNEXURE V

PLAGIARISM REPORT

A CLINICAL STUDY OF SERUM CYSTATIN C LEVELS IN CASES OF COPD AND ITS CORRELATION WITH SPIROMETRY AND IMPACT ON THEIR QUALITY OF LIFE

by Dr. Ravi Apoorva

Submission date: 27-Dec-2022 08:52PM (UTC+0530)
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A CLINICAL STUDY OF SERUM CYSTATIN C LEVELS IN CASES OF COPD AND ITS CORRELATION WITH SPIROMETRY AND IMPACT ON THEIR QUALITY OF LIFE

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