



A Prospective Study Of Eosinophilic Phenotype In Asthma And COPD With Comparison To Blood And Sputum.

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ABSTRACT

Asthma and Chronic Obstructive Pulmonary Disease are airway obstructive disease that causes both morbidity and mortality in the general population. Often it becomes difficult to know the cause of airway obstruction as sometimes asthma mimics chronic obstructive pulmonary disease. The well-defined feature that allows us to have a differential diagnosis is fixed airflow obstruction in asthma from COPD. Obstructive airway disease falls under an umbrella term due to the presence of a heterogeneous population and Asthma-COPD phenotype or Overlap syndrome (ACOS). Also, recent studies have shown that neither asthma nor COPD are single diseases but rather syndromes due presence of multiple endotypes and phenotypes. An Eosinophilic phenotype is a distinct form of type 2 airway obstructive disease in Asthma and whereas in COPD it is traditionally associated with neutrophilic infiltration in bronchi. But recent studies have shown that around 25-40 % of patients have severe exacerbation and decline of lung function with higher levels of eosinophil in COPD. Therefore this helps to personalize a targeted therapy based on traits and the role of ICS in this kind of phenotype.

KEYWORDS: Airway obstruction, Asthma, COPD, Eosinophilic phenotype, ACOS syndrome.

METHODOLOGY:

The study was conducted in Gandhi Medical College/Hospital, Secunderabad for six months. Out of 61 patients, 14 were females and 46 were males. 30 patients were known as COPD patients and 31 patients were known as asthmatics.

COPD DIAGNOSIS

COPD was diagnosed based upon GOLD criteria. The COPD patients were differentiated on a scale from A to D based upon dyspnea grade and previous exacerbations. Asthma was diagnosed according to the GINA guidelines.

SPUTUM INDUCTION

To check the Eosinophilic inflammation the sputum sample was induced and processed by a non-invasive method for the analysis of the airway cells with a success rate of 75%, Sputum induction is a safe well-tolerated, and non-invasive technique, but not commercially available only limited to research service. For sputum induction, the patient is treated with Duolin (Bronchodilator) and after some time inhalation of 3% hypertonic or isotonic saline is done. Sample collection is done and the sputum is treated with mucolytic (DTT) dithiothreitol for mucolytic. The treated sample is then processed to obtain a differential cell count to identify the type of cells present in the air lumen, which is further analyzed on sputum supernatant for investigations of the immune mechanism and inflammatory mediators by using spectral analysis like flow cytometry.

Blood cell count

Blood was collected from patients in K2EDTA tubes for Peripheral blood eosinophils and absolute cells were determined using a hematology analyzer for cell count and cell determination.

RESULTS:

Total of 61 patients, 30 COPD patients with acute exacerbation and 31 asthma patients with mild to moderate exacerbation. The baseline characteristics were compared between both groups.

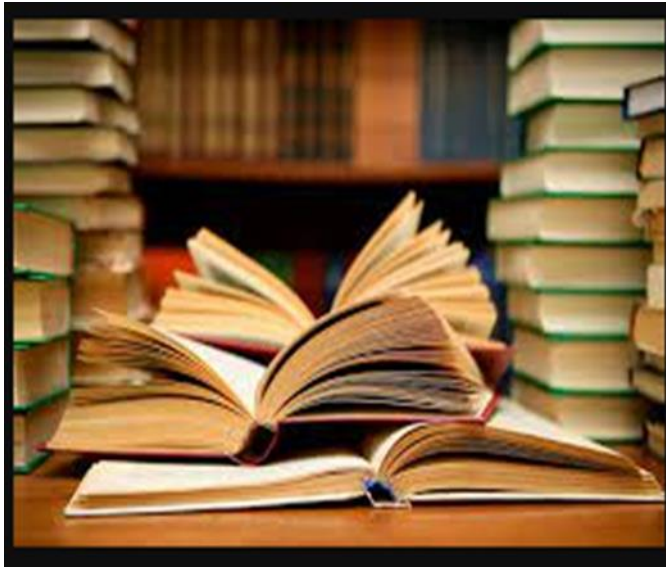
Sputum and Blood eosinophil of asthma did not correlate ($\rho = 0.721$ $p = 0.003$), COPD ($\rho = 0.266$; $P < 0.154$) which was statistically insignificant. The blood Eosinophil percentage show less correlation were as when expressed in the count the correlation was slightly better than that expressed as percentages in COPD ($\rho = 0.325$; $p = 0.007$) and in asthmatic patients it was not as significant as COPD ($\rho = 0.48$ $p < 0.007$).

Gender and age didn't show any significance in the role of eosinophils in blood and sputum. But there was slightly elevated eosinophil in COPD patients with Hypertension. There was no huge marked difference in eosinophil in blood and sputum with comorbidities in asthmatic patients.

Conclusion

The sputum and eosinophil did not correlate with each other within group and also between asthma and COPD. This is due to Eosinophilic biology that causes the airway inflammation differently in both the diseases. There is a need for more precise data which is clinically accurate. The Eosinophil characteristics of COPD patients could help in understanding the role of Eosinophilic Phenotype in COPD. This will help us to come up with a better treatment plan. This research is the first-ever attempted in the south zone and there was a lack of significance due to the small sample size and the presence of random noises in the group. This study will also pave a path for research of biologics targeting eosinophilic inflammation in COPD patients.

INTRODUCTION



Definition: Asthma is defined as a chronic inflammatory airway disease. . It is associated with airway hypersensitivity leading to wheezing, shortness of breath, chest tightness, and recurrent episodes of coughing. Symptom episodes are generally associated with widespread but fluctuating obstruction of pulmonary airflow, which is usually reversible, either spontaneously or with fastacting branching processes ⁽¹⁾.

In some cases, swelling in airways prevents oxygen from reaching the lungs. This means oxygen cannot enter the blood stream (or) reach vital organs. Therefore, people who experience severe symptoms need urgent medical attention.^[2]

Types of Asthma: -

There are four main categories of Asthma.

1. Intermittent.
2. Mild persistent.
3. Moderate persistent.
4. Severe persistent.

INTERMITTENT: -

- Mild symptoms and do not interfere with normal activities.
- Symptoms at night occur less than twice a month.
- Infrequent Asthmatic attacks.
- When a person is not having Asthma attack, the lung function tests are normal.

MILD PERSISTENT: -

- Symptoms at night occur three to four times a month.
- Symptoms occur 3 to 6 times a week.
- Lung function tests are normal when a person is not having an asthma attack.

MODERATE PERSISTENT: -

- Symptoms at night time occur more than once per week but not every day.
- Lung function tests are abnormal.
- Symptoms occur daily.
- Asthma attacks affect daily activities.

SEVERE PERSISTENT: -

- Symptoms at night occur frequently, sometimes every night.
- Lungs functions tests are abnormal.
- Symptoms occur throughout the day, every day.
- Asthma can also be classified as allergic (or) non- allergic.
- Allergic asthma id triggered by exposure to an allergen, such as pollen.

- Non- allergic asthma is triggered by factors such as illness, extreme weather, stress, intents in the air & some medicines. ^[3]

Some other numerous types of asthma:

1) Childhood asthma:

Asthma can develop at any age, but it is more common in the children than in adults.

According to the American Lung Association (ALA) some common triggers of childhood asthma includes allergies, sudden changes in temperature, excitement, stress, exercise, cigarette smoke, including secondhand tobacco smoke, respiratory infection, and colds, exposure to cold air, air pollutants such as ozone and particle pollution both indoors and outside

2) Adult-onset asthma;

Asthma can develop at any age including during adulthood.

Factors that affect the risk of developing asthma in adulthood include.

- Hormonal factors.
- Obesity.
- Stress.
- Smoking.
- Respiratory illness.
- Allergies and exposure to allergens.

3) Occupational asthma:

Occupational asthma occurs as a result of exposure to an allergen or irritant present in the workplace.

4) Seasonal asthma:

Seasonal asthma occurs in response to allergens that are in surroundings environment at certain time of the year.

Pollen in the spring (or) summer (or) cold air in the winter may trigger symptoms of seasonal asthma.^[4]

5) Exercise –induced asthma:

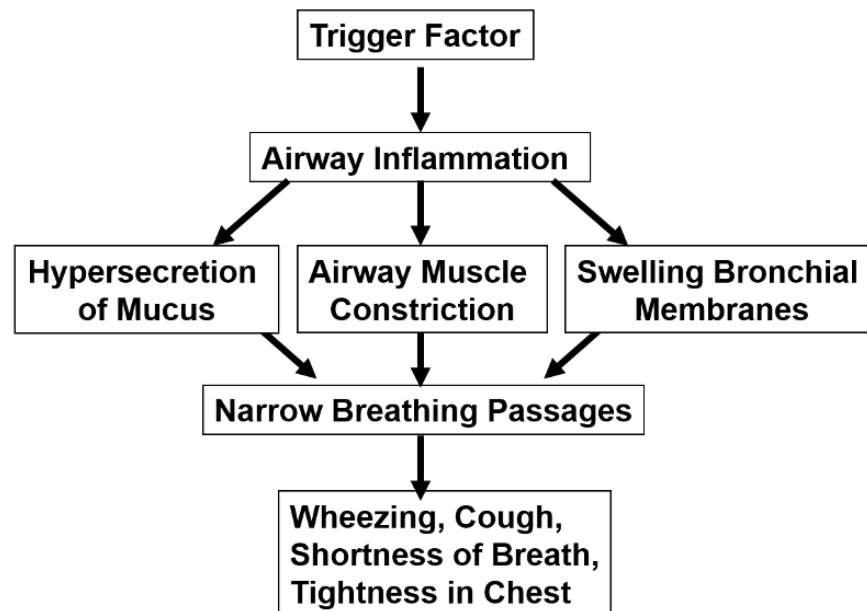
Exercise induced bronchial constriction (EIB) sometimes called exercise induced asthma.

ETIOLOGY:

- Asthma is common, if other family members also have asthma such as parent or sibling. ○ Children and adults who are obese are at a greater risk of asthma.
- Asthma is also common in people who have other allergic condition such as rhinitis (hay fever) and eczema.^[5]
- Asthma comprises a wide range of diseases and a variety of heterogeneous phenotypes. ○ The factors associated with asthma or genetic predisposition, personal or family history ⁽⁵⁾
- (6).
- On exposure to tobacco smoke and other inflammatory gases or particulate matter also triggers asthma. ○ The etiology is complex and fully understands.

Various triggers of asthma include:

- Chronic sinusitis.
- Tobacco smoke.
- Insects, chemical fumes and plants.
- Obesity.
- Emotional factors or stress.
- Gastro- esophageal reflux disease (GERD).
- Viral respiratory tract infections.
- Exercise.
- Use of beta –blockers, aspirin.^{[6][7]}

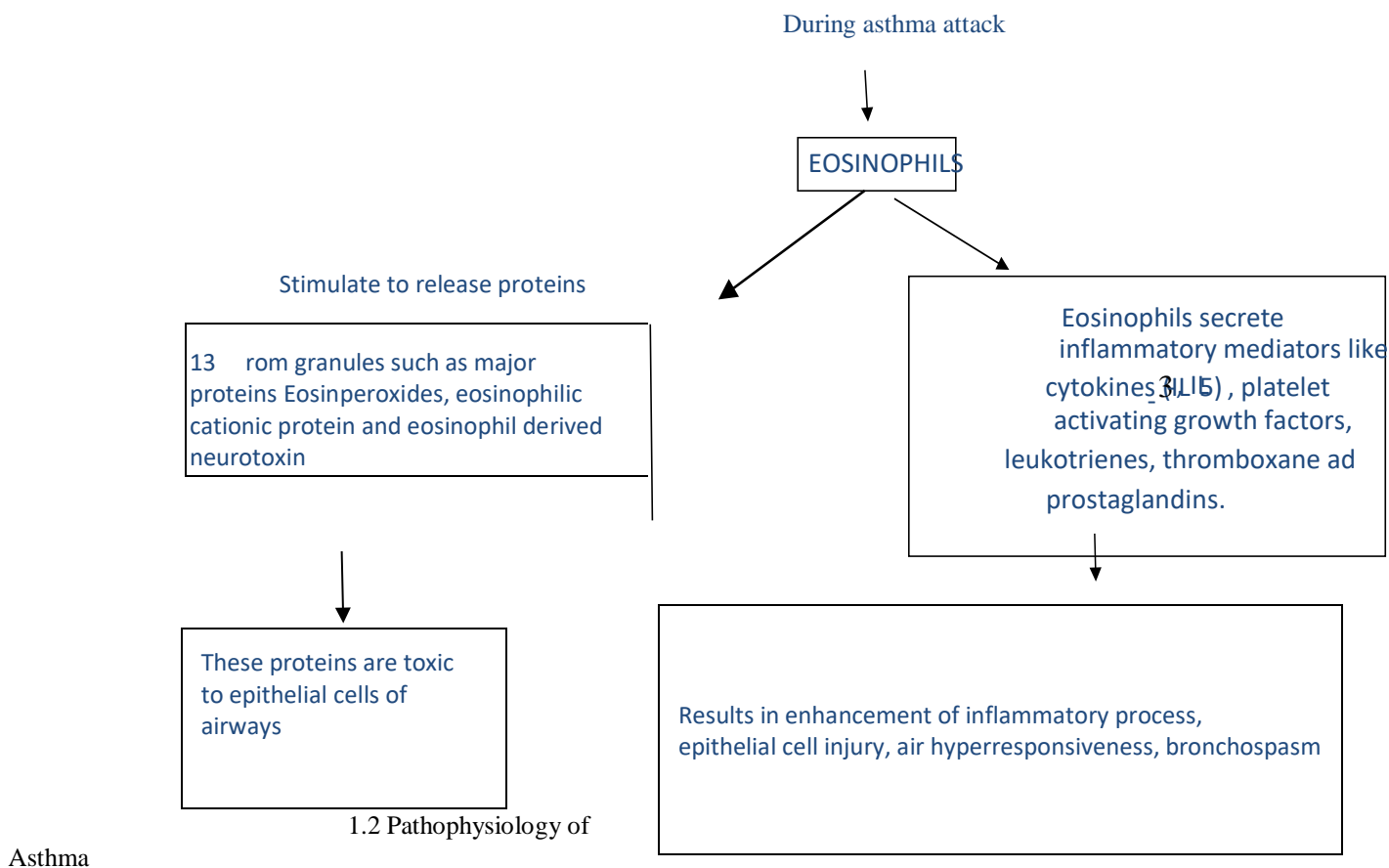
**1.1 Various trigger factors in asthma****Pathophysiology of Asthma:**

With the inhalation of an irritant or an allergen, the pathological process begins which then due to bronchial hypersensitivity leads to inflammation of airways and increased mucous production. Obstruction of airways occurs due to

- Smooth muscle contraction.
- Mucous hyper secretion with mucous plug formation
- Inflammatory infiltration ^[9]

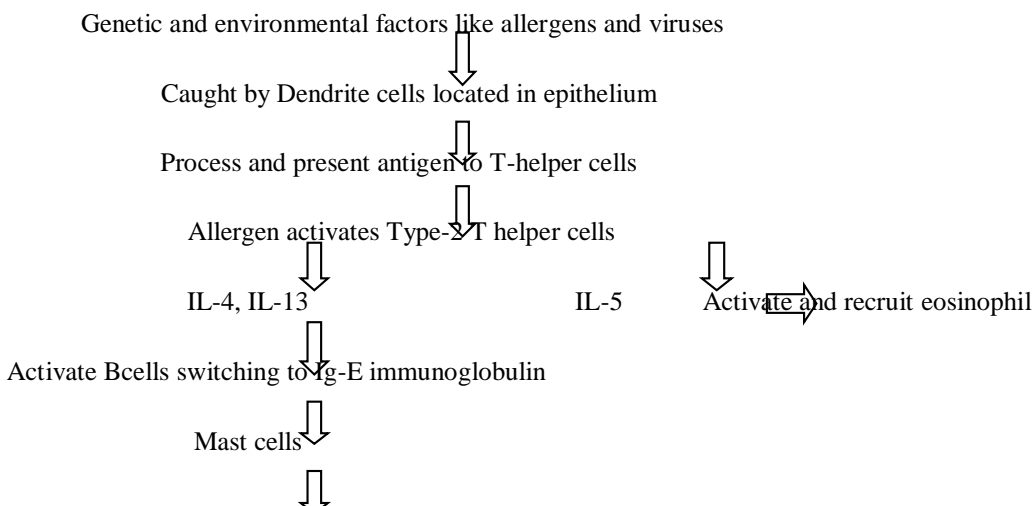
Asthma is associated with type-2 T helper cells, the elevation of these Th-2 cells in the airways release cytokines including interleukins IL-4, IL-5, IL-9, IL-13 promotes eosinophilic inflammation and immunoglobulin's E production (IgE) which triggers the release of inflammatory mediators like histamine, cysteinyl leukotrienes, causes Oedema, bronchospasm and increased mucous production. ^[10]

The release of cytokines and inflammatory mediators during an early phase of an initiating allergen triggers a further inflammatory response (late phase) leads to further inflammation of the airway and bronchial hyperactivity. [11]



Asthma

EOSINOPHILIC ASTHMA



IL-13.IL-5

Eosinophil recruitment and expansion in the non- allergic eosinophilic asthma ^[12]

1.3 Eosinophilic pathway of Asthma

Diagnosis: -

Although there is no gold standard single test to make a diagnosis of asthma, there are several objective tests that can be used to support the diagnosis including physiological measures such as obstructive spirometry associated with bronchodilator reversibility and airway hyperresponsiveness, non- invasive tests of airway – inflammation such as exhausted nitric oxide and/or periphery blood eosinophils.^[13]

MANAGEMENT OF ASTHMA

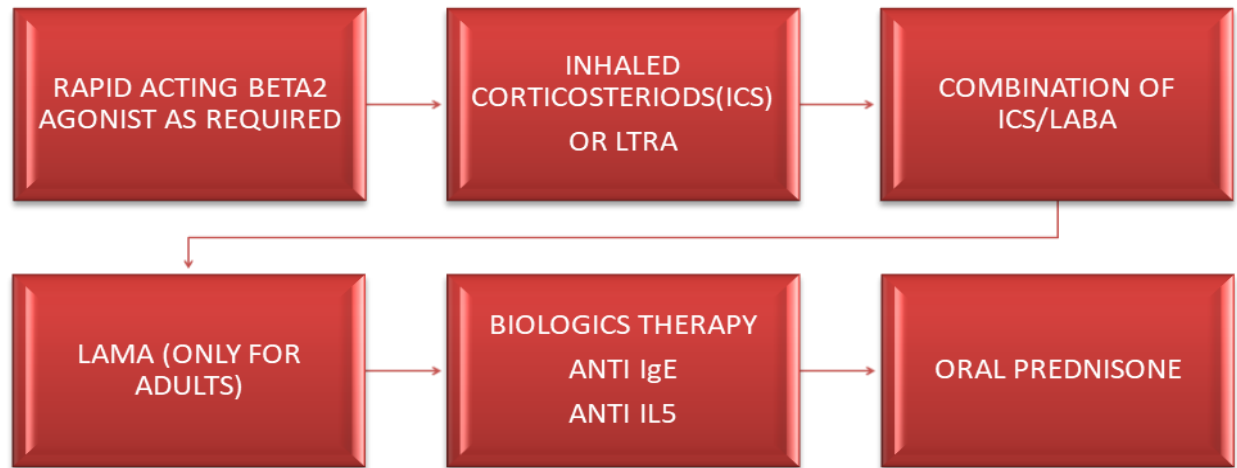
The goal of therapy in the management of asthma is to maintain and control the disease to prevent future exacerbations which require immediate medical attention and/or the use of oral steroid therapy which helps to reduce the risk of morbidity and mortality. The treatment should be such that which minimizes the frequency and severity of asthma and better management of the symptoms for maintaining a normal a by preventing airflow obstruction and reducing exacerbations and looking out the triggers.^[14] After a diagnosis of the activity level of Asthma, ICS therapy is initiated to improve the lung function which is later discontinued. The ICS/LABA therapy is recommended irrespective of disease severity.^[15]

AVOIDANCE METHODS

Avoiding exposure to tobacco smoke is the main step in controlling asthma. Most of the patients may have an allergic episode when they come into contact with dust mites are instructed to use hypo allergic bedding and keep the humidity levels be 50%. People allergic to pollen should wear a mask while going out and close the windows. Pet owners should vacuum the furniture and bedding frequently to keep away from animal dander. To install HEPA filters in the home, use dehumidifiers and fungicides to keep the allergens in check.

PHARMACOTHERAPY

The grade of asthma control should be looked carefully at each visit using the criteria and treatment should be forgiven accordingly to control. In most asthmatics, the incidence can be controlled by trigger avoidance as well as well-tailored pharmacological treatment. The agents that are commonly used for the treatment of asthma are classified into two categories. They are the controllers and relievers. Controller medications include ICSs, leukotriene receptor antagonists (LTRAs), LABAs in combination with an ICS, long-acting muscarinic receptor antagonists (LAMAs), and biologic agents including anti-IgE therapy and anti-IL-5 therapy. Reliever medications include rapid-acting inhaled beta2-agonists and inhaled anticholinergics ^[19 20]. Patients with allergic asthma should be given Allergen-specific immunotherapy (allergen-specific immunotherapy) ^[16 17 18]. Systemic ICS therapy may also be required for the of acute asthma exacerbations exacerbation.



1.4 Drug of choice based upon severity

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

COPD leading cause of mortality in many countries. According to (GOLD) Guidelines – COPD is a preventable and treatable disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. The pulmonary component is characterized by airflow limitation and it is not fully reversible. Abnormal inflammatory response of lungs to noxious gases and particles causes airflow limitation and it is progressive^[21]

- Firstly, COPD is a preventable disease. Primary, secondary, tertiary prevention strategies exist for COPD. They range from increasing smoking cessation and adequate treatment of asthma which is primary^[22] to early detection of disease and subsequent modification exposure to risk factors which is secondary to prevention of complications in patients with established disease which is tertiary.^[23]
- Secondly COPD is a treatable disorder. Treatment for stable COPD and exacerbations.
- Thirdly, in some of the COPD patients extra pulmonary effects are seen and other condition which are related to respiratory disorder, include fat free mass, muscle wasting ,osteopenia and chronic infections.^[24]
- Fourth, individuals with similar smoking and exposure history differ greatly in disease severity and response to intervention COPD has many different phenotypes. Lung function test is best way which is currently available to characterize the severity^[25]
- Fifth, airflow limitation in COPD is due to mixture of small airway disease, parenchymal destruction and in many cases increased airway responsiveness. They worsen with age and also effected by exacerbations or other events like acute worsening.^[26]
- Sixth, COPD is not fully reversible. Obstruction observed does not revert either in response to bronchodilators, anti-inflammatory treatment spontaneously .This lack of full reversibility is a means to distinguish Asthma\COPD ,although many have both features^[27]

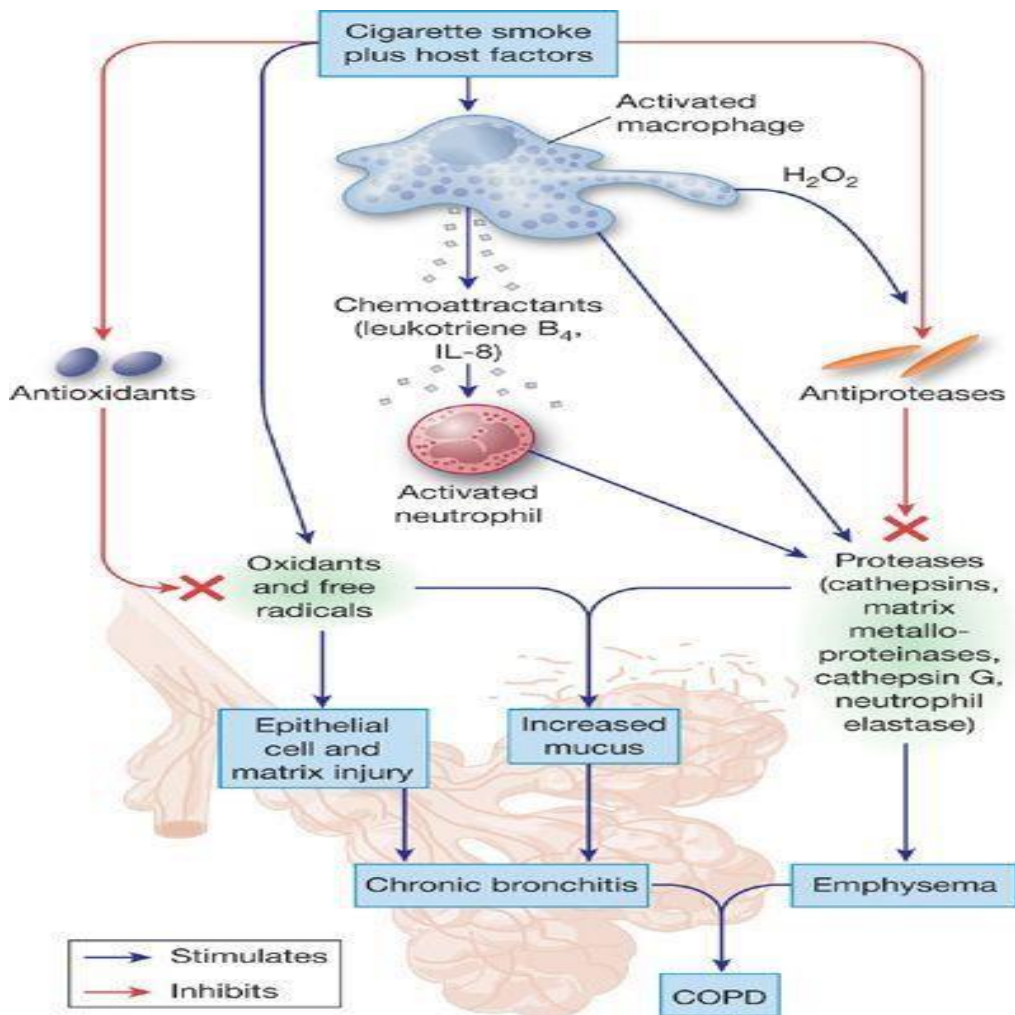
ETIOLOGY

The most common causes of COPD include cigarette smoking, environmental exposures like indoor air pollution and urban air pollution. Occupational exposure like organic and inorganic dusts e.g:- cadmium, silica, dust from grains, welding etc.

The development of COPD is mainly due to exposure to harmful pesticides and gases that initiate the lung causing inflammation.^[28]

AIRWAY PATHOPHYSIOLOGY OF COPD

The pathophysiology of COPD is complex due to multiple causes. Hence COPD is defined as multipotent disease consisting of mucociliary dysfunction, airway inflammation and structural changes leading to airflow limitation. COPD patients also presents extrapulmonary and systemic manifestations such as cachexia, weight loss, cardiovascular disease leading to airflow limitations and overall leading to systemic inflammation. Irrespective of systemic inflammation mechanism, elevated systemic inflammatory factors such as plasma fibrinogen leads to decreased lung function These are correlated with decline in lung function and increased risk may lead to COPD hospitalization. C-reactive protein, tumour necrosis factor alpha(TNF- α) these inflammatory conditions adversely affect pathophysiology with therapeutic conditions in severe COPD.^[29]

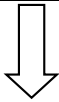
**1.5 Airway Pathophysiology of COPD****EOSINOPHILIC PATHWAY IN COPD**

Eosinophils are recruited into the airway by immunoregulatory cells and chemokines



Infiltration of eosinophils into the airway only occurs when inflammatory signals induce adhesion molecules on both the bronchial vascular epithelium and endothelium

Recruitment to the airway is under the control of chemokine and cognate receptors



Chemokine interaction plays a crucial role, together with chemoattractant receptor homologous molecule expressed on T-helper type-2 cells and its ligand prostaglandin D2



Due to inflammatory response, the quality and activation state of Eosinophils is likely more important than the absolute eosinophilic number



In patients with chronic airway disease, pulmonary eosinophilia was associated with elevated macrophage elastase levels, predictive of emphysema⁽³¹⁾

1.7 Eosinophilic pathway in COPD

STABLE STATE:

- Inflammation in COPD is associated with T-helper 1 lymphocyte (Th1) mediated driven by neutrophils, in response to bacterial colonization. when compared with asthma, copd presents a number of different clinical phenotypes and during stable state about 10-40% of patients have eosinophilic inflammation.
- Cell senescence play crucial role in copd because cytokines and other factors are released from senescent cells as they are involved in pathogenesis of COPD.
- In stable state, heterogenicity is seen in COPD exacerbations. In 28% of exacerbations, Eosinophilic-predominant phenotype is related with eosinophilia is mostly seen in exacerbations than in stable disease.
- In stable COPD, eosinophilic airway inflammation, sputum eosinophilia is about 20-40% ○ Increased number of Eosinophils is seen in chronic bronchitis and COPD is one bronchial biopsy study, lower BAL concentrations of ECP than in asthmatics; states that Eosinophils are present but less activated in COPD.
- In COPD sputum ECP concentrations are at higher level than with asthma in moderate to severe conditions. States that Eosinophils are activated in more severe disease.
- In some subjects, high levels of sputum eosinophilia is very difficult to explain, but an alternate is eosinophilic bronchitis ,it is common cause for chronic cough in middle age with sputum eosinophilia without symptoms and functional evidence of airflow obstruction and airway hyperresponsiveness.^[32]

EXACERBATIONS

COPD exacerbations are related with sputum and bronchoscopic bronchial biopsy evidence of eosinophilic inflammation. Bronchial biopsies taken from patients during acute exacerbations and compared with stable COPD show a 30-fold increase within total number of Eosinophils and a 3fold increase in neutrophils. The presence of high concentrations of tumour necrosis factor (TNF- α)-a proinflammatory cytokine that activates adhesion molecules on endothelial cells influencing eosinophil chemotaxis and the eosinophil product ECP and EPO in induced sputum also supports a role for the eosinophil in COPD exacerbations.^[33]

RISK FACTORS

Risk for COPD is related to an interaction between genetic factors and many different environmental exposures, which could also be affected by comorbid disease.

○ **Genetic factors:** The best-known genetic factor linked to COPD is a deficiency of the serine protease $\alpha 1$ antitrypsin, which arises in 1–3% of patients with COPD. Low concentrations of this enzyme, in combination with smoking or other exposures, increases the risk of emphysema [34].

○ Tobacco smoke: Tobacco smoke is the most important cause of COPD. WHO estimates that in high-income countries, 73% of COPD mortality is related to smoking, with 40% related to smoking in nations of low and middle income. It is affected highly by genes, because not all smokers go on to develop COPD.

○ Occupational dust, vapours, and fumes

Exposure to various dusts, chemicals, vapours, and fumes in the workplace is a factor for many people with COPD. ○ Indoor air pollutants

○ Outdoor air pollutants

○ Ageing

○ Asthma

○ Gender

○ Socioeconomic and related factor^[35]

DIAGNOSIS

Early symptom detection and evaluation provides for more effective treatment earlier intervention aimed at preserving lung function and slow disease progression. The diagnosis is primarily clinical,²⁵ and majority of patients are mainly diagnosed by primary care physicians. Suggestive symptoms include chronic cough, excessive sputum production, and dyspnea, especially if any of these symptoms are associated with the history of tobacco smoking or regular exposure to occupational or environmental pollutants or toxins. Special care should be taken to identify the patient those who have these insight and considering further evaluation faster than in the past^[36].

MANAGEMENT OF COPD:

To reduce the risk of exacerbations and management of the symptoms is the priority of the treatment. The management should be designed such that it should have appropriate pharmacotherapy, cessation of smoking, and pulmonary rehabilitation.

Various tools such as GOLD and ABCD are used to assess disease severity. COPD assessment score or modified medical research council and exacerbation risk help to determine the disease severity. It also helps in categorizing patients into risk groups to guide appropriate pharmacological treatment.

Bronchodilators are the heart for the management of COPD at all levels of disease severity. The initial treatment is based upon GOLD which recommends specific treatment options based upon ABCD Classification.

Combination of long-acting beta2-agonist (LABA) / long-acting muscarinic antagonist (LAMA) over Inhaled corticosteroid (ICS) regimens which are supported by evidence from several studies. The LANTERN study evaluated that LABA/LAMA (Indacaterol/glycopyrronium) had a better outcome when compared with LABA/ICS (Salmeterol/fluticasone) in patients with a history of COPD Exacerbation of <1 in the previous year which was also supported by the studies conducted by the ILLUMINATE^[37]

Glycopyronium/Indacaterol was more effective than Salmeterol/fluticasone in reducing COPD Exacerbation in the FLAME study.

The combination of LAMA/LABA showed a significantly reduced rate of exacerbation by 31% by 11% respectively. If the patients do not respond to the ICS therapy shift to LAMA/LABA is recommended. The triple therapy LAMA/LABA/ICS should be recommended if the patient does not respond to LAMA/LABA OR LABA/ICS therapy.^[38]

A high number of eosinophils is also associated with a better response to ICS and is a good biomarker. Biological treatment of asthma have a limited effect on the better out of COPD.

Eosinophil inflammation of the airways may prove to be the most treatable feature of COPD. Many monoclonal antibodies and small molecule therapies have recently been developed to target this inflammatory pathway. For example, there are monoclonal antibodies against IL5 (eg, mepolizumab), IL5 receptor alpha (eg, bevacizumab), IL13 (eg, tralokinumab), and IL4 receptor alpha (eg, dupilumab)^[39]

Corticosteroid response to Blood Eosinophils count is useful in predicting response to ICS and can be a treatable predictor of exacerbation frequency with COPD patients and ICS / LABA with a history of moderate/severe exacerbations^[40]

LITERATURE REVIEW



REVIEW LITERATURE

1. Patrizia pignatti et,al conducted a study titled “Do blood eosinophils strictly reflect airway inflammation in copd ?comparison with asthamtic patients”.A total of 146 patients 57 with copd and 89 with asthma are evaluated .blood and sputum eosinophils expressed as percentages and correlated in copd($\rho=0.40$, $p=0.004$) but the entity of correlation was lower compared with asthmatic subjects ($\rho=0.7$, $p<0.0001$). When blood eosinophils were expressed as counts the correlation was slightly lower than when expressed as percentage in copd ($\rho=0.35$, $p=0.01$) and in asthmatic patients ($\rho=0.68$, $p<0.0001$).blood Eosinophils correlated with sputum

Eosinophils to lesser degree in COPD than in asthmatic patients. Older age, high blood eosinophil, hypertension affected the correlation between the blood and sputum Eosinophils, more are needed to evaluate the role of other cardiac comorbidities.

2. Gibson, Woolley conducted a research study titled "Induced sputum Eosinophils cationic protein (ECP) measurement in asthma and COPD". ECP was measured in sputum supernatant and in the lysed cell pellet and was compared with sputum eosinophil count in 31 adults with asthma and COPD and the sputum absolute eosinophil count across a layer of subject group ($r=0.72, p=0.004$). Sputum eosinophil count is well correlated with supernatant ECP levels ($r=0.50, p<0.05$). The ratio of ECP was used as an index of eosinophil degranulation and found to be elevated in asthma exacerbations, COPD and but not in stable asthma. The ECP ratio may be a useful marker of eosinophil activation and was increased in asthma exacerbation and COPD. The increased ECP in COPD reflects a non selective accumulation of eosinophils in these conditions.

3. Jeffery Ho, Wajia He, Matthew T. V. Chan, conducted a research study titled "Eosinophilia and clinical outcome of chronic obstructive pulmonary disease: a meta-analysis". Importantly, the temporal variation of eosinophilia in COPD was largely ignored in the included studies. Longitudinal study of 1,483 patients with COPD revealed that 49% of the subjects had variable eosinophil counts. Only 37% and 14% of the individuals were persistently eosinophilic and eosinopenic, respectively. The level of this cellular marker can increase considerably soon after sputum induction. In this connection, spot sampling may lead to misclassification of case and control.

4. Trung N Tran, titled as "Persistence of Eosinophilic Asthma Endotype and Clinical Outcomes: A Real-World Observational Study", the data validate the use of blood eosinophil measurements to characterize a patient population at increased risk for severe asthma exacerbations. The consistency in risk elevation between the persistently high and intermittently high groups suggests that in patients with a single or multiple BEC measurements, 1 or more elevated BEC is sufficient to characterize a patient as having eosinophilic asthma, thus affirming the validity of categorizing patients in clinical practice, clinical trials, and real-world studies using the highest recorded BEC.

Conversely, a single eosinophil measurement ≤ 300 cells/ μ L cannot rule out the potential of having eosinophilic asthma. For these patients, additional measurement of BECs in clinical practice is needed to increase the identification and appropriate management of patients with eosinophilic asthma.

5. Sara R. A. Wijnant, titled "Prevalence of Asthma and COPD and Blood Eosinophil Count in a Middle-Aged Belgian Population" this study showed that, both asthma and COPD, are common diseases in the middle-aged population of the Asklepios study in Belgium, and that COPD is often under-diagnosed and under-treated, despite respiratory symptomatology. A greater awareness of lung-function deterioration in the middle-aged population, and adherence to clinical practice guidelines is needed. Interestingly, the systemic eosinophil count was increased in asthma cases, despite clinical remission. Future studies should focus on the utility of systemic eosinophil count to predict asthma relapse after clinical remission.



AIM AND OBJECTIVES

AIM AND OBJECTIVE

Aim:

To study and evaluate the role of Eosinophil as an inflammatory mediator in AECOPD with comparison to Acute Exacerbation of Asthma. The purpose of the study is to analyze Eosinophilic phenotype in airway obstruction to come up with a better pharmacotherapy.

Objective:

The primary objectives,

- The objective of this review to assess the role of eosinophil as an inflammatory phenotype in blood and sputum/airway to know its biology and its effect in Acute Exacerbation of Chronic Obstructive Pulmonary Disease and Asthma

The secondary objectives,

- To study the prognosis of the exacerbation in chronic obstructive pulmonary disease and Asthma.
- To have a better differential diagnosis to overcome Asthma COPD overlap syndrome.
- Assessment of Inhaled Corticosteroids in Acute Exacerbations.
- Proper pathological and cytological study of blood and sputum sample.
- Analyzing the severity of exacerbation.
- To prospectively assess the demographic, treatment, need of oxygen and laboratory parameters
- Sputum Eosinophil
- Blood Eosinophil
- Absolute Eosinophil Count

NEED FOR THE STUDY

- Studies suggested that up to 40 percent of the acute exacerbations in the COPD patients were due to eosinophil inflammation.
- Blood and sputum eosinophil count as inflammatory biomarker to study the responsiveness of therapy
- Will give information which will be useful in studying distinctive phenotypes and generation of biologics for better outcome.
- To study new Anti-Eosinophilic drugs for Asthma and COPD like
IL-5 receptor alpha (mepolizumab, IL-13 (lebrikizumab and tralokinumab), IL-4 receptor alpha (dupilumab), Ig E (omalizumab) etc.
- Eosinophilic biologic plays an important role as it has become a subject of research interest other than potential treatment like inhaled corticosteroid therapy.

PLAN OF WORK

- Selection of topic ○ Review of literature to consider objectives and outcomes of the study. ○ Get permission from the hospital authorities for the approval of study ○ To correlate the active state of inflammatory biomarker in comparison to AECOPD vs Asthma
- Designing the appropriate data collection form. ○ Drawing the limitations and strengths of the study ○ Having a proper assessment of the parameters that are being considered for the study for the merits and demerits of it.
- To make the lab work is being done with 100 accuracy.
- Statistical analysis ○ Interpretation of data ○ Report writing ○ Conclusion

METHODOLOGY

1. STUDY DESIGN

This study is single center, Cohort, Prospective, Open label study.

2. STUDY SITE

GANDHI MEDICAL COLLEGE/HOSPITAL – SECUNDERABAD

3. DURATION OF THE STUDY / STUDY POPULATION.

Data will be collected from the case records of the Pulmonology department that fits the inclusion criteria who have been diagnosed with AECOPD and asthma whose sputum and blood samples were tested for Eosinophil levels mainly within the period of October 15th 2021 to April 15th 2022.

4. STUDY CRITERIA INCLUSION CRITERIA:

1. Age > 18 - < 80yrs
2. Patients with acute exacerbation COPD
3. Patient with acute exacerbation of Asthma.
4. Patients with Grade SOB and require oxygen supplementation.

EXCLUSION CRITERIA:

- 1.** Patient who have other co-morbidities are excluded except Primary Hypertension and Type 2 Diabetes Mellitus.
- 2.** Pediatric patients and pregnant women are excluded.
- 3.** Patients with severe exacerbations and other lung disorders are excluded.
- 4.** Any uncontrolled bacterial fungal or viral infections
- 5.** History of Tuberculosis is excluded.

SOURCE OF DATA COLLECTION

STUDY MATERIAL:

All the relevant data will be obtained from the case records of all pulmonology wards for a period of 6 months after getting required permission from ethical committee.

STASTICAL ANALYSIS:

The sample data was entered into MS EXCEL. Quantitative variables will be summarized using descriptive statistics {number of observations percentages, mean, standard deviation [SD]}. To assess the relationship between eosinophils in the peripheral blood and in sputum spearman correlation was used. To assess the qualitative variables Chi-square and Fisher exact test was done. T-Test was done to assess the quantitative variables. The data will be statistically analyzed using package for the social sciences (SPSS) software and will be represented as graphs, pie diagrams, bar graphics.

METHODOLOGY:

The study was conducted in Gandhi Medical College/Hospital, Secunderabad for a period of six months. Out of 61 patients 14 were females and 46 were males. 30 patients were known COPD patients and 31 patients were known Asthmatic. COPD was diagnosed based upon GOLD criteria. The COPD patients were differentiated on a scale from A to D based upon dyspnea grade and previous exacerbations. Asthma was diagnosed according to the GINA guidelines.

SPUTUM INDUCTION

To check the Eosinophilic inflammation the sputum sample was induced and processed by a noninvasive method for the analysis of the airway cells with a success rate of 75%. Sputum induction is a safe well-tolerated and non-invasive technique, but not commercially available only limited to research service. For sputum induction, the patient is treated with Duolin (Bronchodilator) and after some time inhalation of 3% hypertonic or isotonic saline is done. Sample collection is done and the sputum is treated with mucolytic (DTT) dithiothreitol for mucolytic. The treated sample is then processed to obtain a differential cell count to identify the type of cells present in the air lumen, which is further analyzed on sputum supernatant for investigations for immune mechanism and inflammatory mediators by using spectral analysis like flow cytometry.

Blood cell count

Blood was collected from patients in K2EDTA tubes for Peripheral blood eosinophils and absolute cell were determined using haematology analyser for cell count and cell determination.



RESULTS

Out of 61 patients admitted in the hospital 30 (50%) patients with Acute Exacerbation of COPD were included on strict inclusion and exclusion criteria and 22 (70%) moderate exacerbation of asthma and 9(30%) with mild exacerbation of asthma as shown in Table 1

CHARACTERISTICS

	COPD (N=30)	ASTHMA (N=31)	P VALUE
AGE	56(30-85)	42(20-75)	0.004

GENDER MALE	27	20	0.005
FEMALE	3	11	
Oxygen support	56%	41%	0.105
Cough	86%	42%	0.454
BMI	21 (18-23)	23(17-25)	
SOB Grade 2	0%	7%	
Grade 3	50%	48%	
Grade 4	50%	45%	
ABG NORMAL	50%	60 %	0.129
ABNORMAL	50%	40%	
GOLD stages, %			
1	30.4		
2	43.2		
3	9	-	
GINA STEPS			
1		22.6	
2		43.3	
3		35.1	
4			
5			
Mean (SD) FEV1,	64(6.08)	<u>62 (11.7)</u>	<u>0.002</u>
Mean (SD) FVC%	65(10.3)	<u>67 (6.70)</u>	<u>0.034</u>
Mean (SD)			
Blood eosinophil, %	3.7(2.31)	<u>7.0 (1.89)</u>	<u>0.21</u>
Sputum eosinophil %	4.07(3.60)	4.7 (2.25)	<u>0.02</u>
Mean (SD)			
Blood Neutrophils, %	72 (10.5)	<u>62 (5.54)</u>	<u>0.001</u>
Sputum Neutrophils %	83 (11.4)	<u>62 (9.96)</u>	<u>0.03</u>

TAB 7.1 Showing Baseline Characteristics of patients of both groups.

GENDER

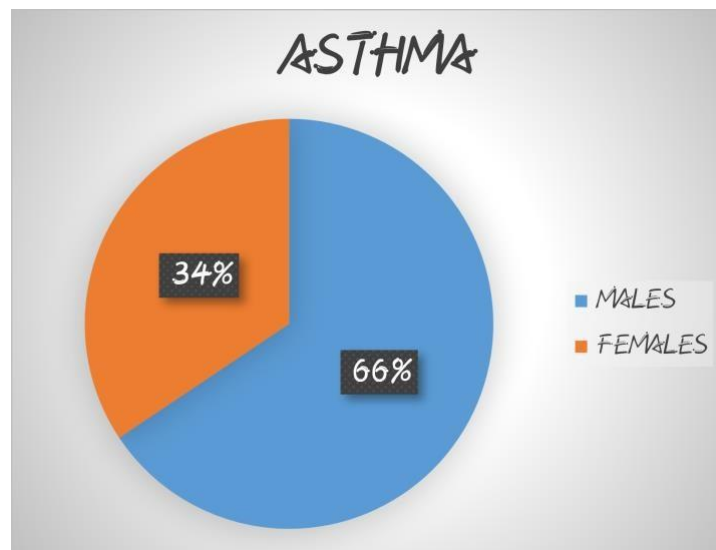


Figure:7.1.1 Gender distribution in Asthma

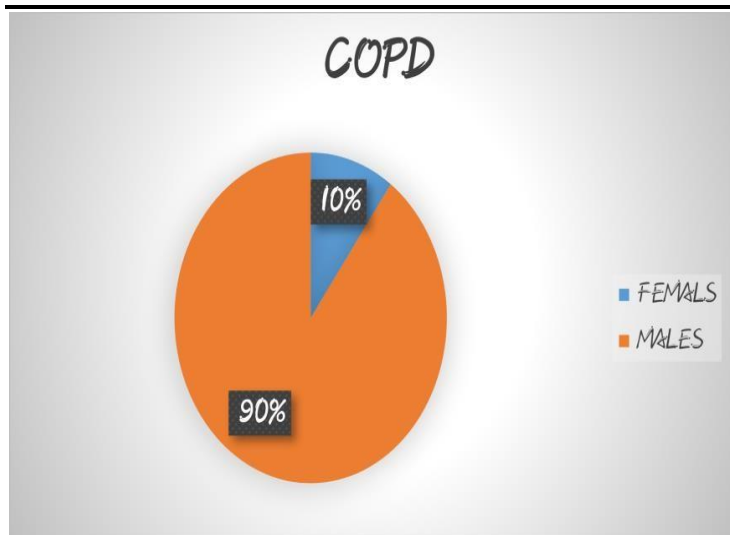


Figure 7.1.2 Gender distribution in COPD

We can see that there is equal distribution of the disease between the men 66% and 34% asthmatics and where as COPD 90% of the patients were male and a small part around 10% was females with a p-value of <0.005 . Gender did not influence the relation between the blood and sputum eosinophil in the subjects considered.

AGE

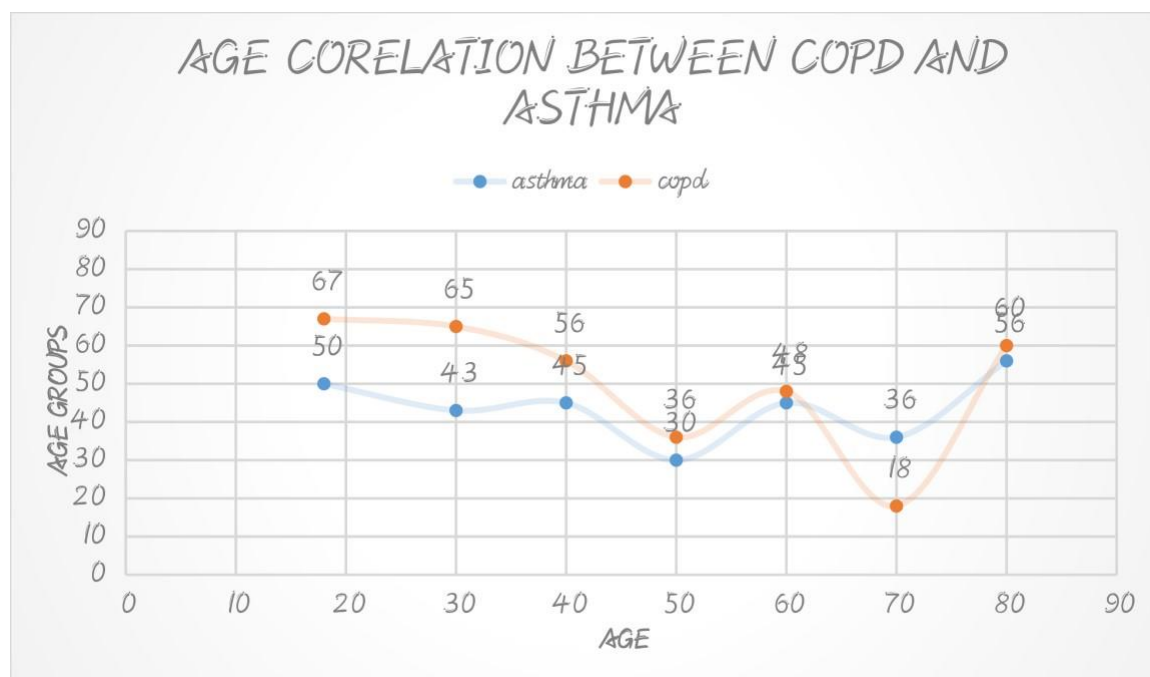


Fig.7.2 Correlation of age between COPD and Asthma

Also there was no age correlation between the groups as it was as Asthma was seen in all age groups and whereas COPD the median age 56.

Also there was no correlation found between the age and blood/sputum eosinophil was found in Chronic Obstructive pulmonary disease and asthmatic patients as the disease was present in different age groups.

COMORBIDITIES

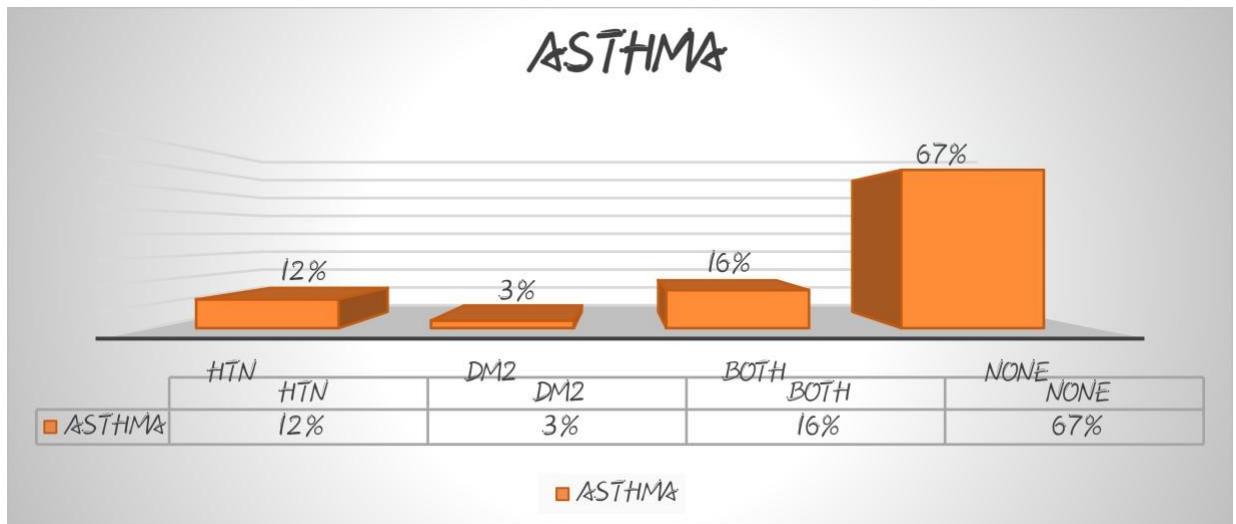


Fig 7.3.1 The distribution of comorbidities in asthma

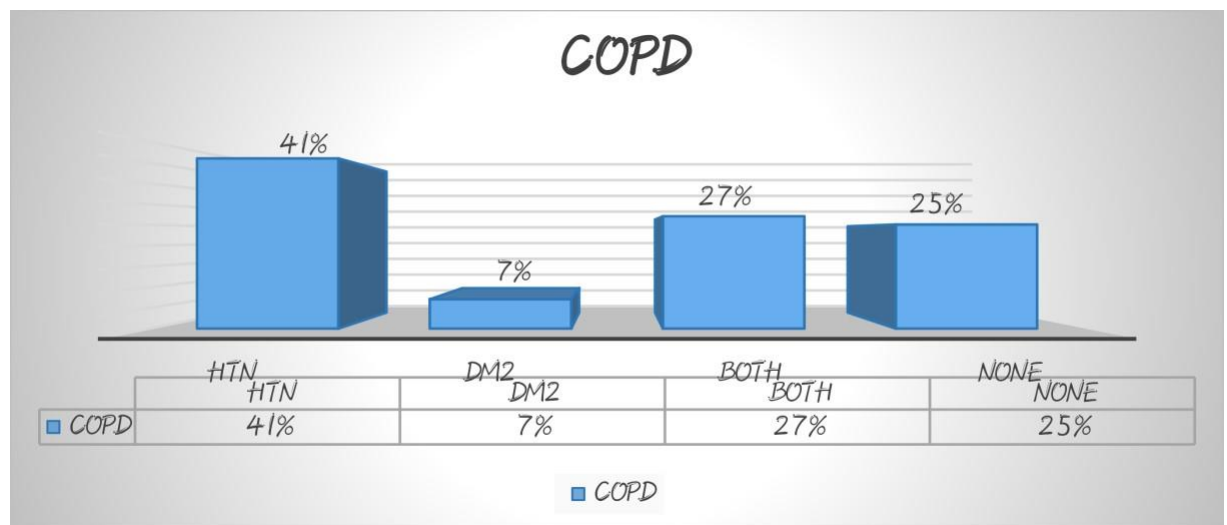


Fig7.3.2 The distribution of the comorbidities in COPD

Overall COPD patients had more comorbidities (75%) and (25%) in asthmatics. (41%) people suffered with hypertension, (7%) with Type 2 DM and (27%) people suffered with hypertension and diabetes mellitus whereas a very small percentage suffered with comorbidities in asthma group.

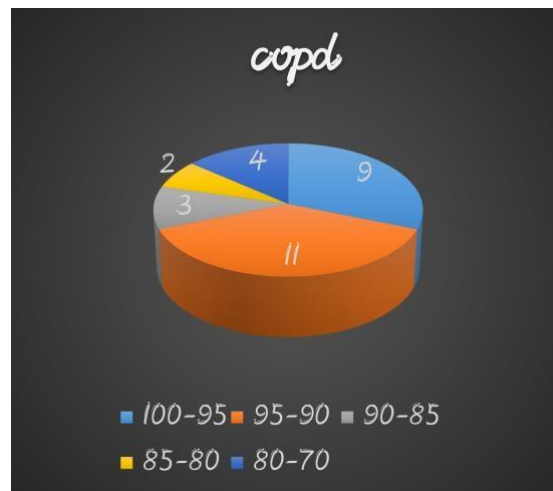
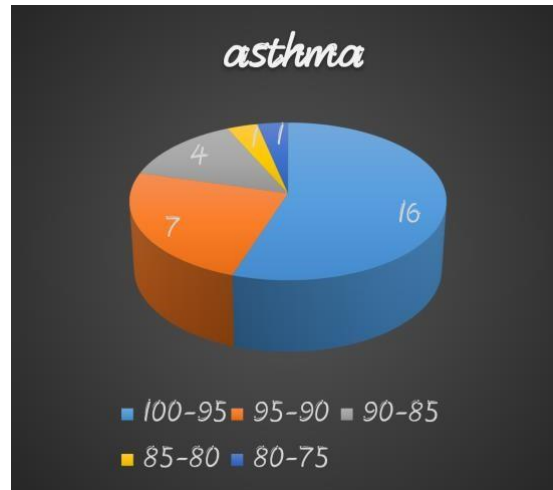
OXYGEN SATURATION

Fig 7.4.1 and 7.4.2 shows the SpO₂ levels in asthma and COPD

Both groups required oxygen as SpO₂ levels were low, but 55% of asthmatics had SpO₂ below 80 and required 6 liters oxygen when compared to COPD patients as blood remains well oxygenated to VQ mismatch defect in early stages.

ARTERIAL BLOOD GAS

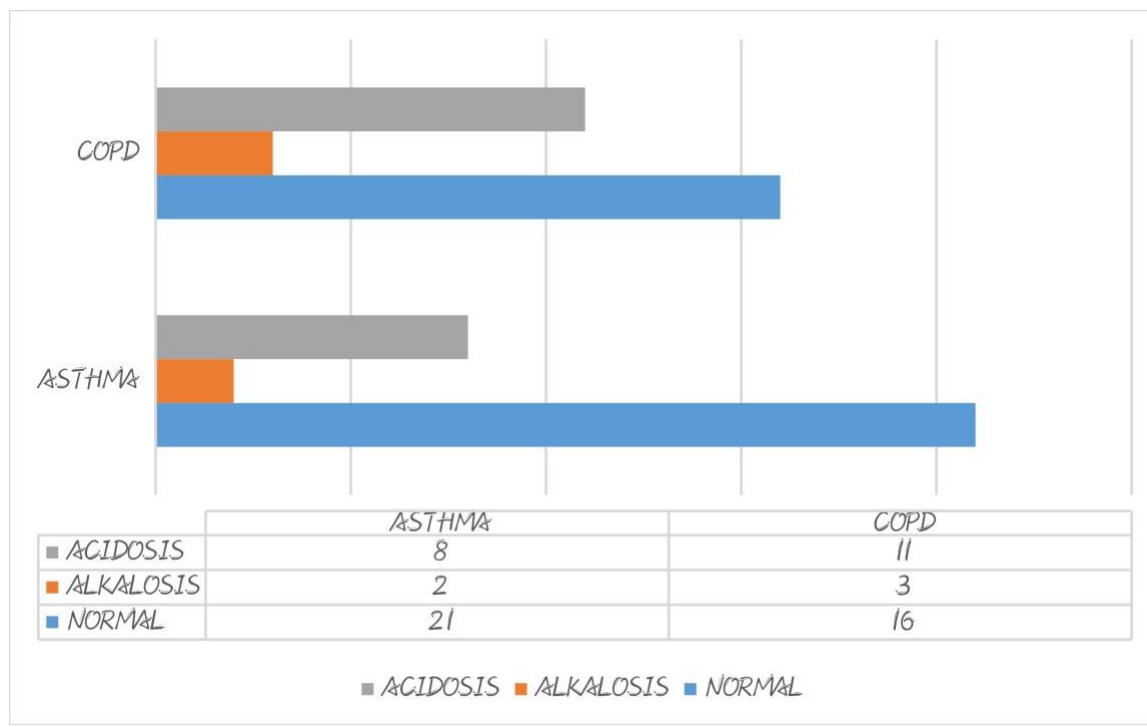


Fig 7.5 Distribution of respiratory alkalosis and acidosis between the groups

Usually respiratory alkalosis is more common in airway obstructive disease due to hyperventilation and hypoxia which is corrected with oxygen therapy, as the disease progresses we can see respiratory acidosis in the patients due acid base change and VQ mismatch. COPD and asthmatics had acid base changes with a P-value of 0.129 which had no significance.

SYMPTOMS

VARIABLES	ASTHMA	COPD
COUGH	42	86

DYSPNEA		
GRADE 2	7%	1%
GRADE 3	48%	49%
GRADE 4	45%	50%

Tab 7.2 showing the symptoms between the two groups

SHORTNESS OF BREATH

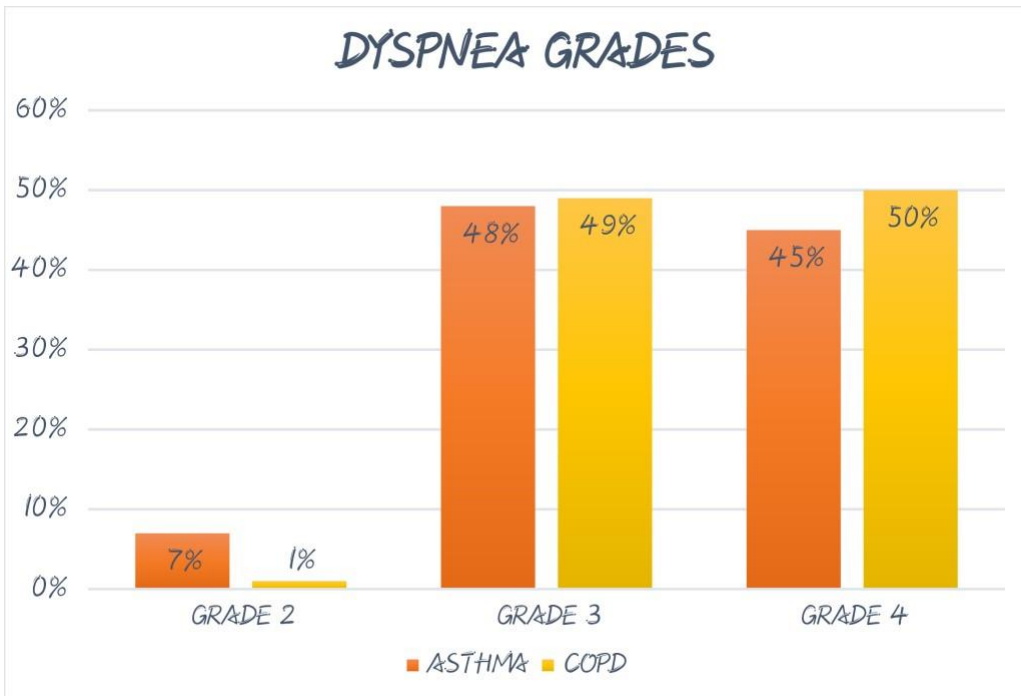


Fig 7.6.1 shows the different grades of dyspnea.

Both the groups showed grade 3-4 shortness of breath as they belong to the airway obstructive disease. Patients with severe bronchoconstriction showed marked increase in breathlessness and was improved after nebulization.

COUGH

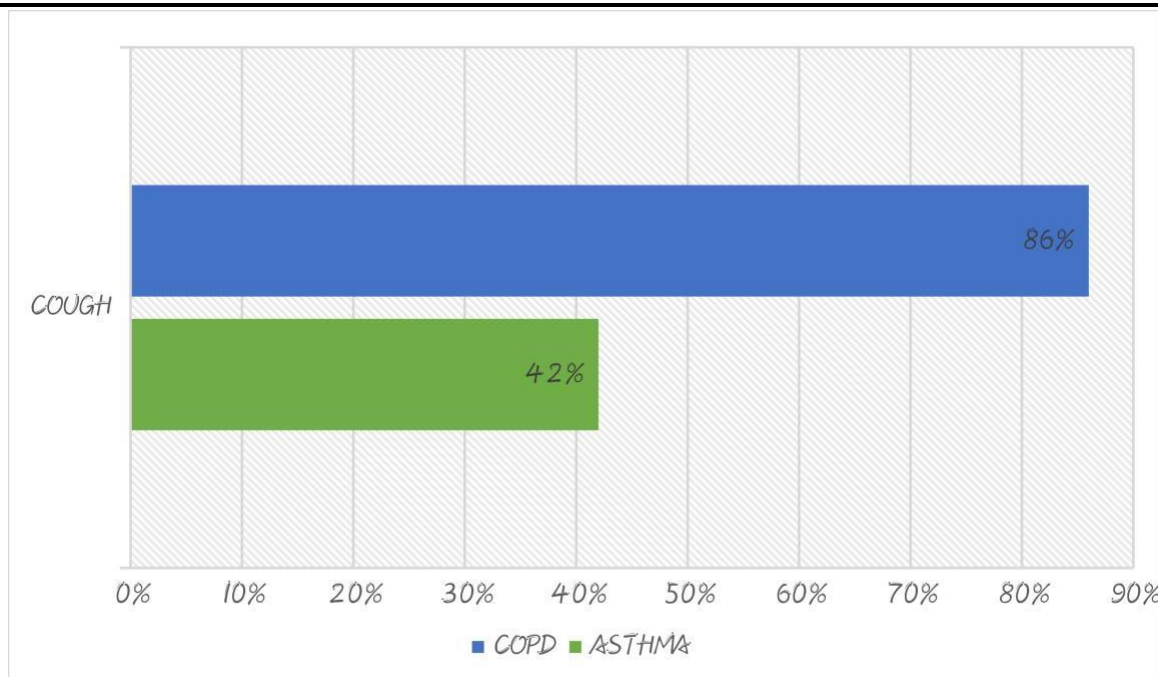


Fig 7.6.2 showing the percentage of people with cough in two groups

COPD group has higher percentage of patients suffering with cough (86%) which was productive (sputum) and whereas Asthmatics (42%) it was more of dry cough with inspiratory wheeze.

FEV1/FVC

VARIABLES	COPD	ASTHMA
FEV1	64(6.08)	62 (11.7)
FVC	65(10.3)	67 (6.70)

Tab 3 shows the distribution of respiratory alkalosis and acidosis between the groups

Both the groups had decrease FEV1/FVC levels due to obstruction with fev1 mean 64 in COPD and fev1 mean 62 in asthmatics.

CORRELATION BETWEEN BLOOD AND SPUTUM EOSINOPHILS IN ASTHMA AND COPD

Variables	Rh0 (P-VALUE)
-----------	----------------

COPD	
Blood eosinophils % and sputum eosinophils %	0.66 (0.001)
Blood eosinophils count and sputum eosinophils	0.32 (0.007)
Asthma	
Blood eosinophils % and sputum eosinophils %	0.266 (0.154)
Blood eosinophils count and sputum eosinophils %	0.48 (0.007)

Tab 4 showing the correlation between blood and sputum eosinophils in Asthma and COPD using Spearman Correlation.

Sputum and Blood eosinophil of asthma did not correlate ($\rho = 0.721$ $p = 0.003$), COPD ($\rho = 0.266$; $P < 0.154$) which was statistically insignificant. The blood Eosinophil percentage show less correlation were as when expressed in the count the correlation was slightly better than that expressed as percentages in COPD ($\rho = 0.325$; $p = 0.007$) and in asthmatic patients it was not as significant as COPD ($\rho = 0.48$ $p < 0.007$).

Gender and age didn't show any significance in role of eosinophil in blood and sputum. But there was slightly elevated eosinophil in COPD patients with Hypertension. There was not huge marked difference in eosinophil in blood and sputum with comorbidities in asthmatic patients.

COPD BLOOD AND SPUTUM EOSINOPHIL CORRELATION

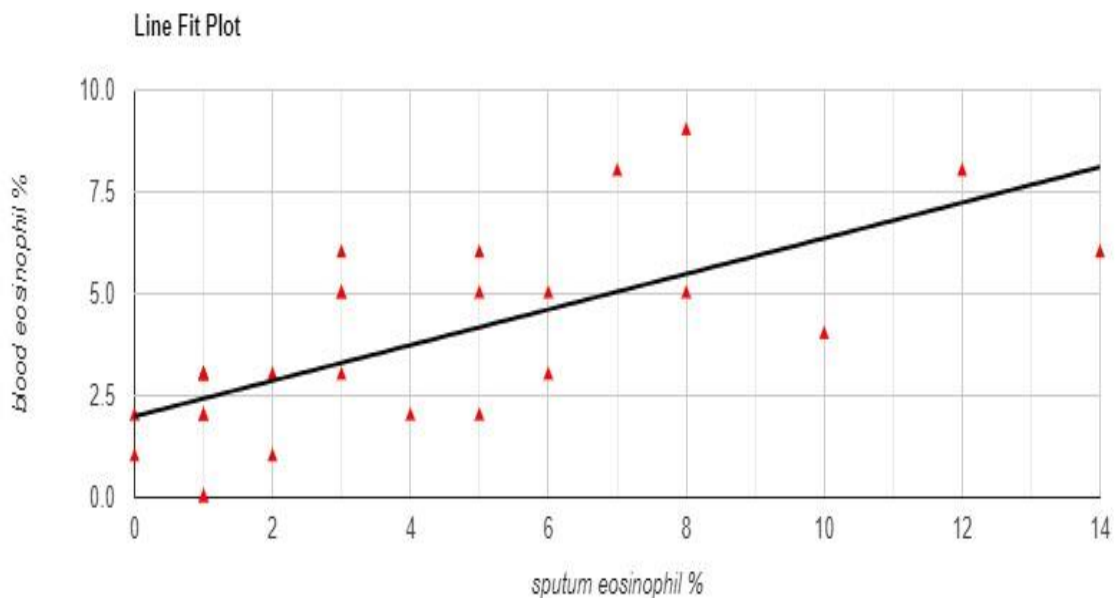


Fig 7.7.1 Correlation between blood and sputum eosinophil in COPD

Results of the Pearson correlation indicated that there is a significant large positive relationship between sputum eosinophil % and blood eosinophil %, ($r(27) = .693$, $p < .001$).

ASTHMA BLOOD AND SPUTUM EOSINOPHIL CORRELATION.

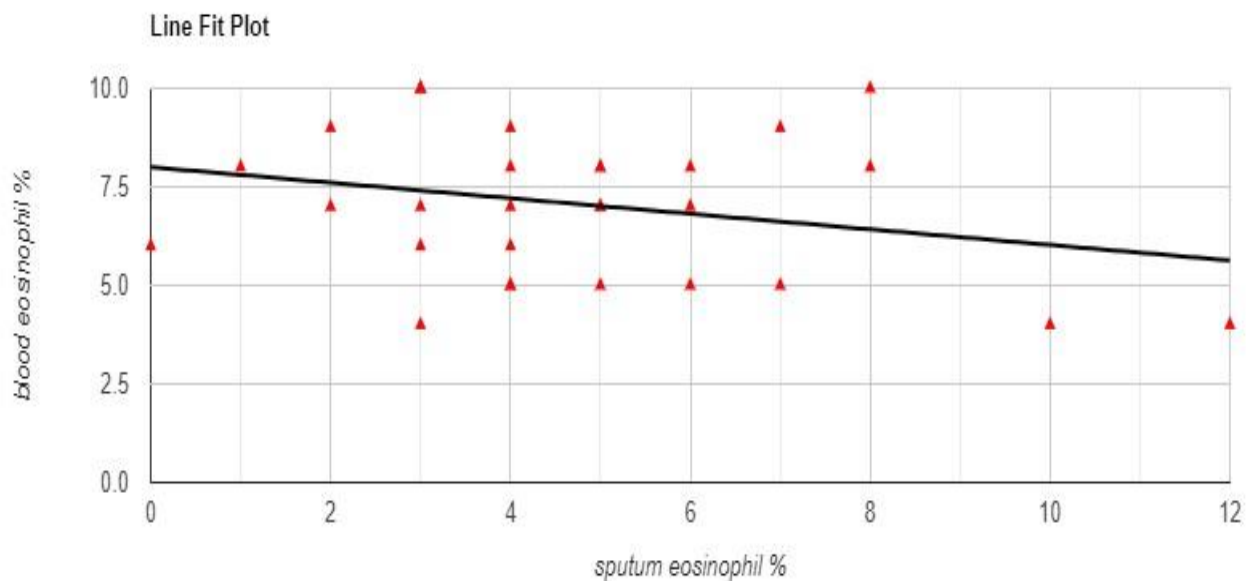
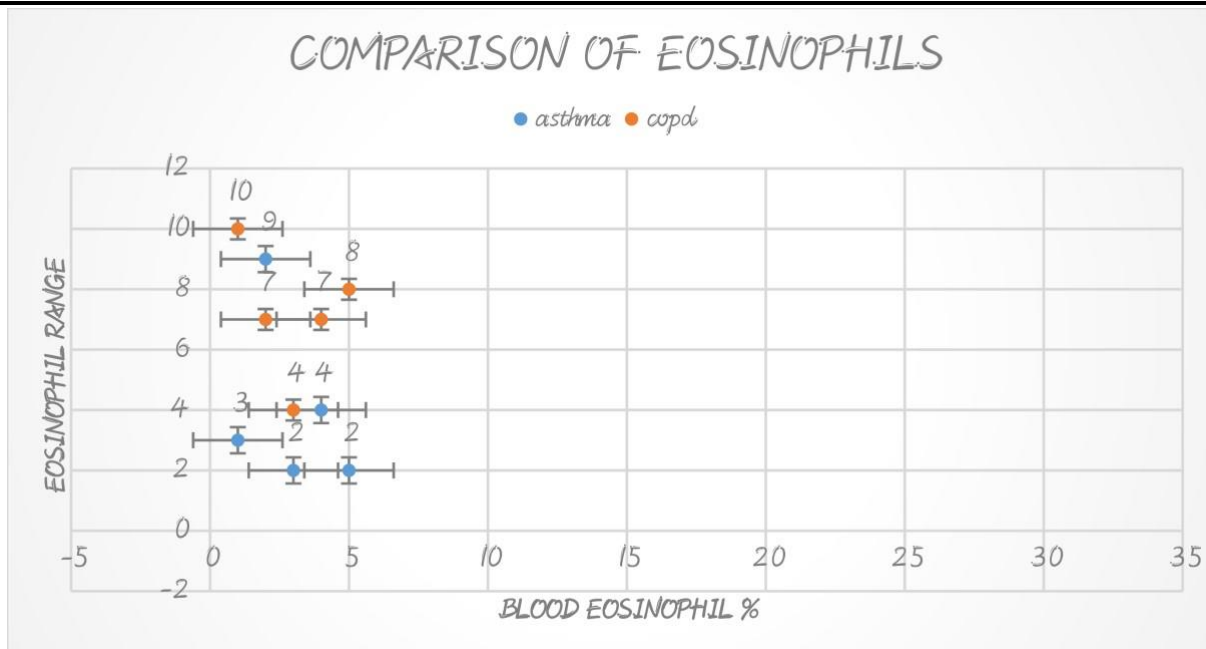


Fig 7.7.2 Correlation between blood and sputum in COPD

Results of the Pearson correlation indicated that there is a non-significant very small negative relationship between sputum eosinophil % and blood eosinophil %, ($r(28) = .267$, $p = .154$).

BLOOD EOSINOPHILS ASTHMA VS COPD



7.8.1 Comparison between blood Eosinophils

SPUTUM EOSINOPHILS ASTHMA VS COPD

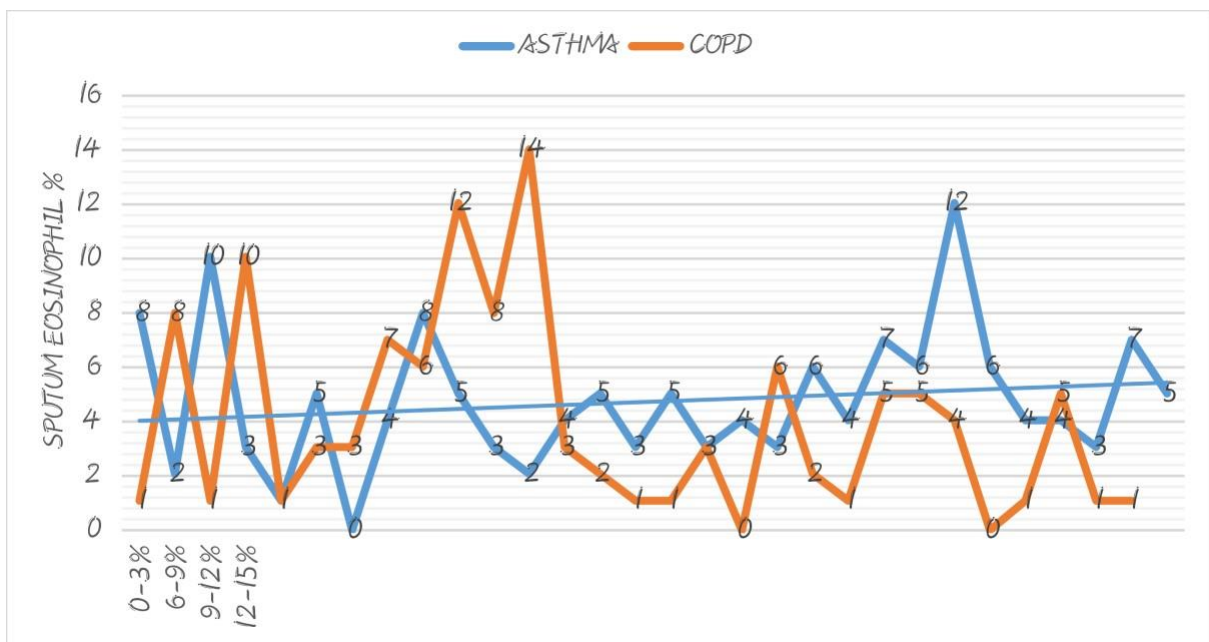


Fig 7.8.1 and 7.8.2 Comparison of blood and sputum Eosinophil in asthma vs COPD

NEUTROPHILS BLOOD VS SPUTUM IN COPD

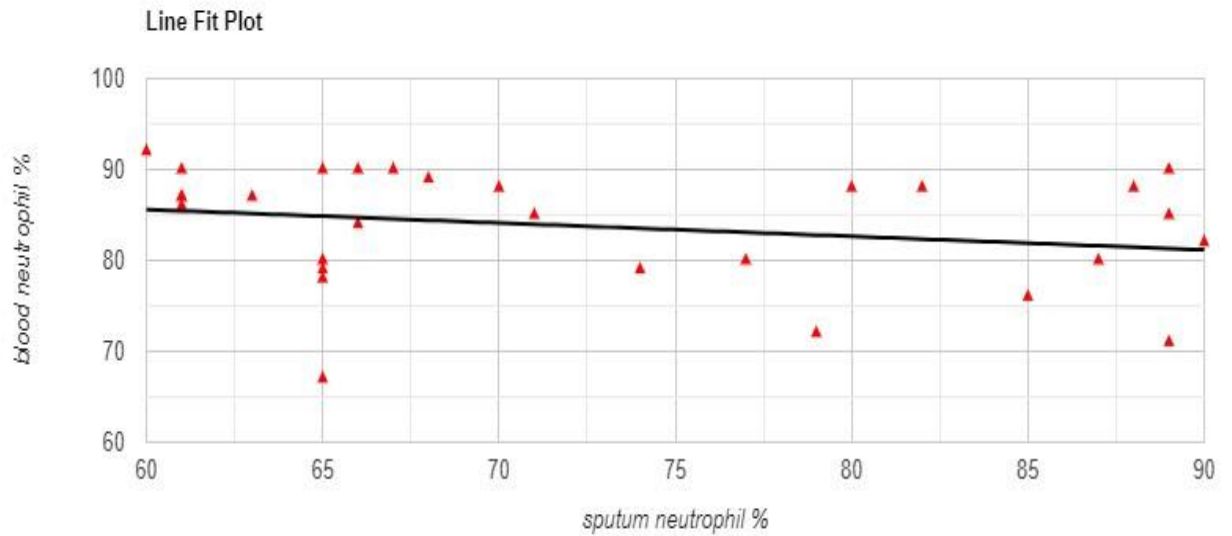


Fig 9 correlation between blood and sputum Neutrophils in COPD

Results of the Pearson correlation indicated that there is a non-significant very small negative relationship between sputum neutrophil % and blood neutrophil %, ($r(27) = .242$, $p = .205$)



Discussion

In this study, we investigated the correlation between blood and Sputum eosinophils in acute exacerbation COPD patients compared to asthma patients. Percentage of Blood eosinophils were less correlated with the proportion of sputum eosinophils in COPD than in asthmatics. The percentage of eosinophils in the blood it reflected slightly better than accounting to the eosinophilic inflammation of sputum. As far as we know, this is First study investigating correlation with blood Sputum eosinophils were simultaneously assessed by COPD and asthma patients. We also found that there was no correlation between blood and sputum in COPD patients. Patients with high blood eosinophils (above median) or co-diagnosed with hypertension. No relevant conclusions can be drawn about the role of these comorbidities. Diabetes can be another comorbidity that may affect the correlation between blood and sputum Eosinophils, but too infrequently in the evaluated cases. Most COPD and Asthma patients participated in this study were previously on ICS treatment which may have affected the correlation of eosinophil.

Blood eosinophils are a count has recently been used as a replacement marker for Airway inflammation in asthma and COPD. While in this correlation is not strong, but it is found in asthma patients as persuasive, but skepticism was greater in COPD patients. It is known that the strength of the correlation between blood and sputum eosinophils varies depending on the degree. Both asthma and COPD studies, none of them evaluated the correlation in two patient groups in the same study.

Blood eosinophils should be detected in COPD patients for treatment selection: patient selection treated with an ICS/bronchodilator combination needed to reduce the risk of pneumonia in patients without eosinophilic inflammation and to evaluate possible therapies with monoclonal antibodies against IL5 or its receptor, reducing T2 inflammation. Increase Blood eosinophils may represent a treatable trait in patient with COPD, but it is unclear whether this increase affects the outcomes.

The lung tissue eosinophils and blood eosinophils did not reflect each other. However high number of blood eosinophils always didn't have a worst outcome and sometimes it might also benefit the patient according to study from Turato et al.⁽¹⁸⁾

When COPD patients not treated with inhaled corticosteroid had a very weak correlation between sputum and blood eosinophils in study by Hartjes et al (m) the researcher also highlighted that due to high variance the is unreliable to predict airway eosinophilia.⁽¹⁹⁾

Comorbidities and its affect on blood eosinophils and on the correlation between blood and airway eosinophils has scarcely been evaluated. DiSantostefano RL et al., found in a cohort of COPD patients that blood eosinophils increased in older male subjects with (M).when compared to asthma.⁽²⁰⁾



Conclusion

The sputum and eosinophil did not correlate with each other within group and also between asthma and COPD. This is due to Eosinophilic biology that causes the airway inflammation differently in both the diseases. There is a need for more precise data which is clinically accurate. The Eosinophil characteristics of COPD patients could help in understanding the role of Eosinophilic Phenotype

in COPD. This will help us to come up with a better treatment plan. This research is the first-ever attempted in the south zone and there was a lack of significance due to the small sample size and the presence of random noises in the group. This study will also pave a path for research of biologics targeting eosinophilic inflammation in COPD patients.

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- [3] Medical Editor: John P. Cunha, DO, FACOEP Medically Reviewed on 4/15/2021
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Patient Data Collection FormGANDHI HOSPITAL SECUNDERBADDEMOGRAPHIC DETAILS

Name:	Age:	Gender:
Weight:	Height:	Occupation:
Smoking:		
History of present illness:		
Allergies:		
ASTHMA:		COPD:

Comorbidities:		
HTN:	DIABETES:	OTHER:

Vitals			
Temp:	Pulse Rate:	Respiratory rate:	Sp02:

LAB INVESTIGATIONS:

Absolute eosinophil count:

Sputum Eosinophils:

Arterial Blood Gas:	Spirometry
pCO2:	
pO2:	
HCO3:	