The frequency of eosinophilia in asthmatic hospitalized patients

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بسم الله الرحمن الرحيم

وَعَلَّمَكَ مَا لَمْ تَكُن تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا

صدق الله العظيم

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A special thanks to my lovely brother **Yusuf Adnan** for his help.

Dedication :

To my family for nursing me with affections and love and their dedicated partnership for success in my life .

abbreviations

AHR	Airway hyper responsiveness
IgE	Immunoglobulin E
ICS	Inhaled corticosteroids
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
PEF	Peak expiratory flow
RAST	Radio allergosorbent test

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Abstract

Back ground

Asthma is a chronic inflammatory disorder of the airways , associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night and in the early morning .

Eosinophil infiltration is a characteristic feature of asthmatic

airways . eosinophilia was defined as an eosinophil count >300 cells/microliter in peripheral blood at some time during the hospitalization.

Aim

The aim of this study was to evaluate eosinophil count in hospitalized patient with asthma exacerbation.

Patients and method

A cross sectional study was performed during a period between 10^{th} of October 2018 to 20^{th} of January 2019.

Twenty five patients whom admitted in the ward at Al-Imamain Al-Kadhumain medical city, Baghdad, Iraq.

Each patient was assessed for severity of attack by clinical examination and oximetry then send for complete blood count .

Result

The majority of patients were females representing 80% of sample, 32% of intermittent severity, 20% mild persistent ,and 24% sever and moderate severity asthma .

The majority of patients with oxygen saturation more than ninety two percent 64%,while those oxygen saturation less than ninety two percent were 36%.

Most of cases have normal eosinophil count ,only 12% had count more than 300 cell/microliter.

Conclusion

- Females liable to get more sever attack of asthma.

- Raised eosinophil count is recognized feature in asthma.

- Higher eosinophil count associated with more sever attack.

1. Introduction

1.1.Definition:

Asthma is a chronic inflammatory disorder of the airways, in which many cells and cellular elements play a role. Chronic inflammation is associated with airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction within the lung that is often reversible, either spontaneously or with treatment.[1]

1.2.Prevalence:

Asthma is one of the most common chronic diseases globally and currently affects approximately 300 million people worldwide. with approximately 10-12% of adults and 15% of children affected by the disease.[2]

In developing countries where the prevalence of asthma had been much lower,there is a rising prevalence, which is associated with increased urbanization.

Most patients with asthma in affluent countries are atopic, with allergic sensitization to the house dust mite Dermatophagoídes pteronyssínus and other environmental allergens ,such as animal fur and pollens.[2]

Asthma can present at any age, with a peak age of 3 years. In childhood, twice as many males as females are asthmatic, but by adulthood the sex ratio has equalized. Long-term studies that have followed children until they reach the age of 40 years suggest that many with asthma become asymptomatic during adolescence but that asthma returns in some during adult life, particularly in those with persistent symptoms and severe asthma. Adults with asthma,including those with onset during adulthood ,rarely become permanently asymptomatic.[2]

Types of asthma:

Many phenotypes have been identified,some of the most common include:

1. *Allergic asthma*: this is the most easily recognized asthma phenotype, which often commences in childhood and is associated with a past and/or family history of allergic disease such as eczema, allergic rhinitis, or food or drug allergy. Examination of the induced sputum of these patients before treatment often reveals eosinophilic airway inflammation.[3]
2. Non-allergic asthma: some adults have asthma that is not associated with allergy. The cellular profile of the sputum of these patients may be neutrophilic, eosinophilic or contain only a few inflammatory cells(paucigranulocytic).[3]
3. Late-onset asthma: some adults, particularly women, present with asthma for the first time in adult life. These patients tend to be non-allergic, and often require higher doses of ICS.[3]
4. Asthma with fixed airflow limitation: some patients with long-standing asthma develop fixed airflow limitation due to airway wall remodeling.[3]
5. Asthma with obesity: have prominent respiratory symptoms and little eosinophilic airway inflammation.[3]

1.3.Pathophysiology:

1.3.1.Airway inflammation:

there is good evidence that the specific pattern of airway inflammation in asthma is associated with airway hyper responsiveness (AHR),the physiologic abnormality of asthma, which is correlated with variable airflow obstruction. The pattern of inflammation in asthma is characteristic of allergic diseases, with similar inflammatory cells seen in the nasal mucosa in rhinitis .However, an indistinguishable pattern of inflammation is found in

intrinsic asthma, and this may reflect local rather than systemic IgE production. [2]

the mechanisms involved in persistence of inflammation in asthma are still poorly understood. Superimposed on this chronic inflammatory state are acute inflammatory episodes, which correspond to exacerbations of asthma. Although the common pattern of inflammation in asthma is characterized by eosinophil infiltration, some patients with severe asthma show a neutrophilic pattern of inflammation that is less sensitive to corticosteroids. However, many inflammatory cells are involved in asthma with no key cell that is predominant.[2]

1.3.2.Airway Remodeling :

Several changes in the structure of the airway are characteristically found in asthma, and these may lead to irreversible narrowing of the airways. Population studies have shown a greater decline in lung function over time than in normal subjects; however, most patients with asthma preserve normal or near-normal lung function throughout life if appropriately treated.[2]

There is some evidence that the early use of ICS may reduce the decline in lung function. The characteristic structural changes are increased airway smooth muscle, fibrosis, angiogenesis, and mucus hyperplasia.[2]

1.3.3.Airway hyper-reactivity (AHR):

the tendency for airways to narrow excessively in response to triggers that have little or no effect in normal individuals is integral to the diagnosis of asthma and appears to be related, although not exclusively, to airway inflammation . Other factors likely to be important in the behaviour of airway smooth muscle include the degree of airway narrowing and neurogenic mechanisms.[4]

The relationship between atopy (the propensity to produce IgE) and asthma is well established. Common examples of allergens include house dust mites, pets such as cats and dogs, pests such as cockroaches, and fungi. Inhalation of an allergen into the airway is followed by an early and late-phase bronchoconstrictor response.Allergic mechanisms are also implicated in some cases of occupational asthma.[4]

In persistent asthma, a chronic and complex inflammatory response ensues, characterised by an influx of numerous inflammatory cells, the transformation and participation of airway structural cells, and the secretion of an array of cytokines, chemokines and growth factors. Examination of the inflammatory cell profile in induced sputum samples demonstrates that, although asthma is predominantly characterised by airway eosinophilia , neutrophilic inflammation predominates in some patients while in others scant inflammation is observed: so-called 'paucigranulocytic' asthma .[4]

1.4.clinical feature:

Typical symptoms include recurrent episodes of wheezing, chest tightness, breathlessness and cough. Asthma is commonly mistaken for a cold or a persistent chest infection (e.g. longer than 10 days). Classical precipitants include exercise, particularly in cold weather, exposure to airborne allergens or pollutants,and viral upper respiratory tract infections. Wheeze apart, there is often very little to find on examination. An inspection for nasal polyps and eczema should be performed. Rarely, a vasculitic rash may suggest eosinophilic granulomatosis with polyangiitis(formerly known as Churg–Strauss syndrome).[4]

Patients with mild intermittent asthma are usually asymptomatic between exacerbations. Individuals with persistent asthma report ongoing breathlessness and wheeze but these are variable, with symptoms fluctuating over the course of one day, or from day to day or month to month.[4]

Asthma characteristically displays a diurnal pattern, with symptoms and lung function being worse in the early morning. Particularly when poorly controlled, symptoms such as cough and wheeze disturb sleep. Cough may be the dominant symptom in some patients, and the lack of wheeze or breathlessness may lead to a delay in reaching the diagnosis of so-called 'cough-variant asthma'.[4]

1.5.Diagnosis:

The diagnosis of asthma is predominantly clinical and is based on the combination of the history, lung function and 'other' tests,which allows high, intermediate or low probability of asthma to emerge.as in figure 1 .

Components of Severity		Classification of Asthma Severity ≥12 years of age			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
Normal FEV$_1$/FVC: 8–19 yr 85%, 20–39 yr 80%, 40–59 yr 75%, 60–80 yr 70%	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV$_1$ between exacerbations • FEV$_1$ >80% predicted • FEV$_1$/FVC normal	• FEV$_1$ >80% predicted • FEV$_1$/FVC normal	• FEV$_1$ >60% but <80% predicted • FEV$_1$/FVC reduced 5%	• FEV$_1$ <60% predicted • FEV$_1$/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV$_1$.			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
(See figure 4–5 for treatment steps.)		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

Figure (1):assessment of asthma severity.[4]

1.6.Investigations:

1.6.1.Lung function test:

Supportive evidence is provided by the demonstration of variable airflow obstruction, preferably by using spirometry to measure FEV1 and FVC.[4]

How to make a diagnosis of asthma
Compatible clinical history plus either/or: • FEV1 ≥ 12% (and 200 mL) increase following administration of a bronchodilator/trial of glucocorticoids. Greater confidence is gained if the increase is > 15% and > 400 mL • > 20% diurnal variation on ≥ 3 days in a week for 2 weeks on PEF diary • FEV1 ≥ 15% decrease after 6 mins of exercise
(FEV1 = forced expiratory volume in 1 sec;PEF = peak expiratory flow)

1.6.2.Airway Responsiveness:

The increased AHR(airway hyper responsiveness) is normally measured by methacholine or histamine challenge with calculation of the provocative concentration that reduces FEV1 by 20% (PC20),This is rarely useful in clinical practice, but can be used in the differential diagnosis of chronic cough and when the diagnosis is in doubt in the setting of normal pulmonary function tests.[2]

1.6.3.Hematologic Tests:

Blood tests are not usually helpful. Total serum IgE and specific IgE to inhaled allergens (radioallergosorbent test [RAST]) may be measured in some patients.[2]

1.6.4.Imaging:

Chest roentgenography is usually normal but in more severe patients may show hyperinflated lungs. In exacerbations, there may be

evidence of a pneumothorax. Lung shadowing usually indicates pneumonia or eosinophilic infiltrates in patients with bronchopulmonary aspergilosis. High-resolution computed tomography (CT) may show areas of bronchiectasis in patients with severe asthma, and there may be thickening of the bronchial walls, but these changes are not diagnostic of asthma.[2]

1.6.5.Skin Tests :

Skin prick tests to common inhalant allergens (house dust ,Mite,cat fur,grass pollen) are positive in allergic asthma and negative in intrinsic asthma,but are not helpful in diagnosis. Positive skin responses may be useful in persuading patients to undertake allergen avoidance measures.[5]

1.6.6.Exhaled Nitric Oxide:

F_ENO is now being used as a noninvasive test to measure airway inflammation. The typically elevated levels in asthma are reduced by ICS, so this may be a test of compliance with therapy.[5]

1.7.Eosinophils:

are phagocytic and their granules contain a peroxidase capable of generating reactive oxygen species and proteins involved in the intracellular killing of protozoa and helminthes, they are also involved in allergic reactions (e.g. atopic asthma). Eosinophils represent 1–6% of the circulating white cells. They are a similar size to neutrophils but have a bilobed nucleus and prominent orange granules on Romanowsky staining.[4]

eosinophilia was defined as an eosinophil count >300 cells/microliter in peripheral blood at some time during the hospitalization.[6]

A high eosinophil count of more than 0.5×10^9/L is usually

Due to:

1. Allergy: hay fever, asthma, eczema
2. Infection: parasitic

3. Drug hypersensitivity: e.g. gold, sulphonamides
4. Vasculitis: e.g. eosinophilic granulomatosis with polyangiitis (Churg–Strauss), granulomatosis with polyangiitis (Wegener's)
5. Connective tissue disease: polyarteritis nodosa
6. Malignancy: solid tumours, lymphomas
7. Primary bone marrow disorders: myeloproliferative disorders,hypereosinophilic syndrome (HES), acute myeloid leukaemia.[4]

Eosinophil in asthma:

Eosinophil infiltration is a characteristic feature of asthmatic airways. Allergen inhalation results in a marked increase in activated eosinophils in the airways at the time of the late reaction. Eosinophils are linked to the development of AHR through the release of basic proteins and oxygen-derived free radicals. Eosinophil recruitment involves adhesion of eosinophils to vascular endothelial cells in the airway circulation due to interaction between adhesion molecules,
migration into the submucosa under the direction of chemokines,and their subsequent activation and prolonged survival. Blocking antibodies to IL-5 causes a profound and prolonged reduction in circulating and sputum eosinophils, but is not associated with reduced AHR or asthma symptoms, a1though in selected patients with steroid-resistant airway eosinophils, there is a reduction in exacerbations. Eosinophils
may be important in release of growth factors involved in airway remodeling and in exacerbations but probably not in AHR.[7]

2.Aim :

The aim of this study was to evaluate eosinophil count in hospitalized patient with asthma exacerbation.

3.Patient and method:

3.1.study design:

A cross sectional study was performed during a period between 10th of October 2018 to 20th of January 2019.

3.2.population:

Inclusion criteria:

Twenty five patients whom admitted in the ward at Al-Imamain Al-Kadhumain medical city for management of acute asthma .

the diagnosis of confirmed history, examination, and pulmonary function test within one day after admission.

Each patient was assessed for severity of attack by clinical examination and oximetry then send for complete blood count for assessment of eosinophil count and percentage.

Exclusion criteria:

Those people with a defined cause of eosinophilia have been excluded , like: bone marrow disorder(myeloproliferative disorders ,hypereosinophilic syndrome (HES), acute myeloid leukaemia), vasculitis (e.g. eosinophilic granulomatosis with polyangiitis (Churg–Strauss), granulomatosis with polyangiitis (Wegener's), connective tissue disease(polyarteritis nodosa),

And including history of worm infestation, in addition any people with malignancy.

3.3.Data collection & analysis:

Data of each patient were collecting from the case sheet including :

demographics of each patient(age, gender ,duration of disease, precipitating factor), family history of atopy , history of smoking,

frequency of admission in the last 12 months patients were classified in to different classes of severity according to (symptoms, night awakening ,use of short acting beta agonist for symptoms control, and interference with normal activity) as in figure 1. investigation including complete blood count(by autoanalyzer machine), in addition to pulse oximetry for oxygen saturation (as reported in patient sheet).

3.4.statistical analysis:

The data were presented in simple measures of frequency, mean ± standard deviation ,and range.

Considering normal eosinophil count less than 300 cells/microliter, and normal oxygen saturation above 92%.

3.5.Ethical:

All patients were informed verbally about study , and the investigation was recorded from patient registry system.

There is no conflict of interest.

4.Result:

The majority of patients were females representing 80% of sample, mean age 53±13 as shown in table 1

Mean duration of asthma 16±11 as shown in table 1.

Only 8% of patients were smoker ,the majority 24% of them had URTI as precipitating factor ,and 44% had +ve family history of atopy as shown in table 1.

Variable		Description		
		Male no(%)	Female no(%)	Total no(%)
Gender		5(20)	20(80)	25(100)
Age(year)	Range	28-73	31-76	28-76
	Mean ±SD	56±17	53±11	53±13
Duration (year)	Range	15-36	1-38	1-38
	Mean ±SD	24±7	14±11	16±11
Smoking history	+ve	1	1	2
	-ve	4	19	23
Precipitating factor	URTI			16 (24)
	Gas inhalation			1 (4)
	Dust			5 (20)
	Cold weather			3 (12)
Family history	+ve			11 (44)
	-ve			14 (56)

Table 1:Demography variable of study sample.

The majority of admitted patients were of intermittent severity 32%,while the minority of mild type 20%,as shown in figure 2.

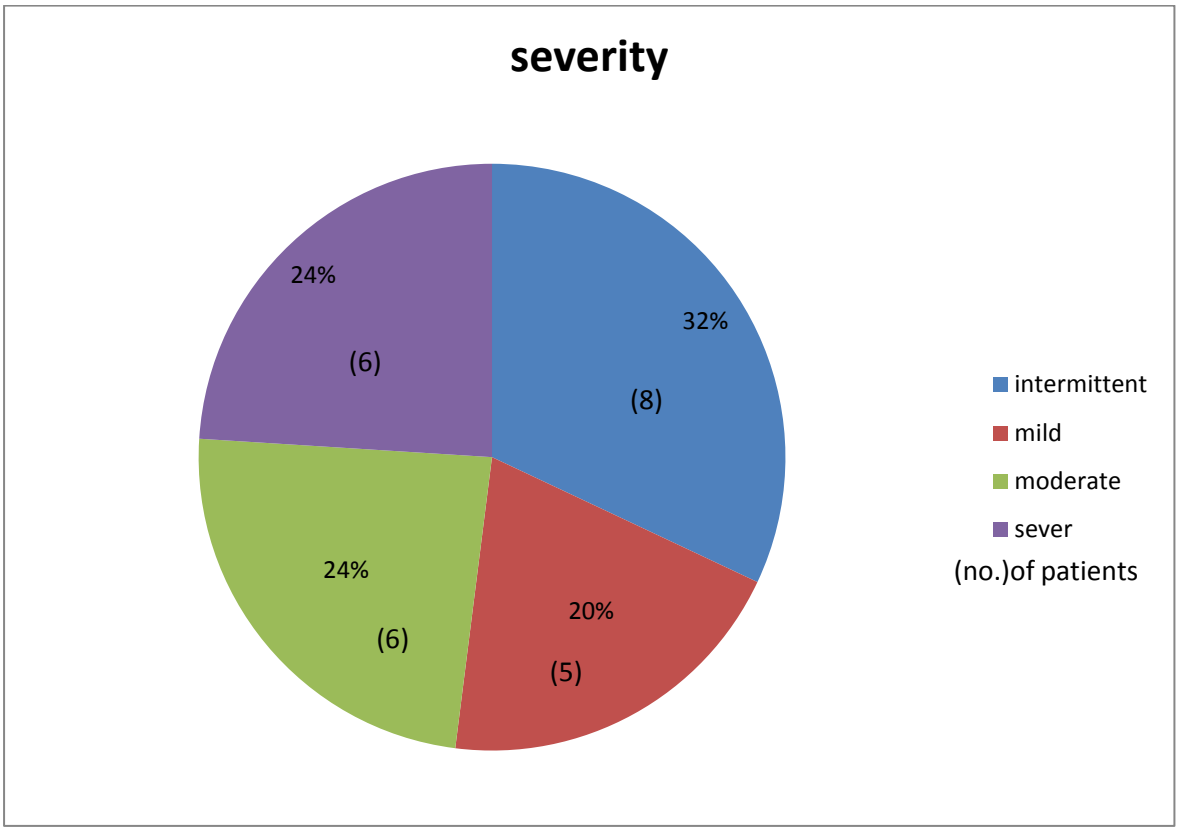

Figure 2: severity of asthma.

There is no male present with intermittent severity, and the majority of patients are females with intermittent severity, as shown in figure3.

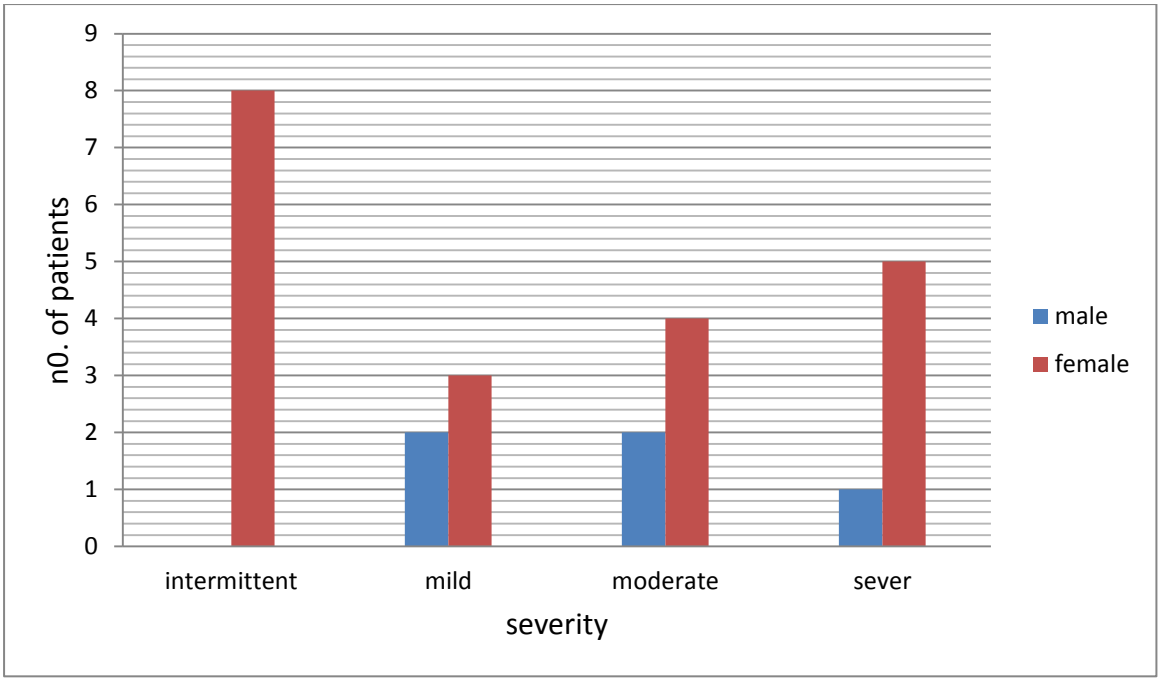

Figure3:gender difference in term of clinical presentation severity.

The majority of patients admitted for the first time were of intermittent severity, while the minority whom admitted for three and four times were of moderate and sever severity ,as shown in figure 4.

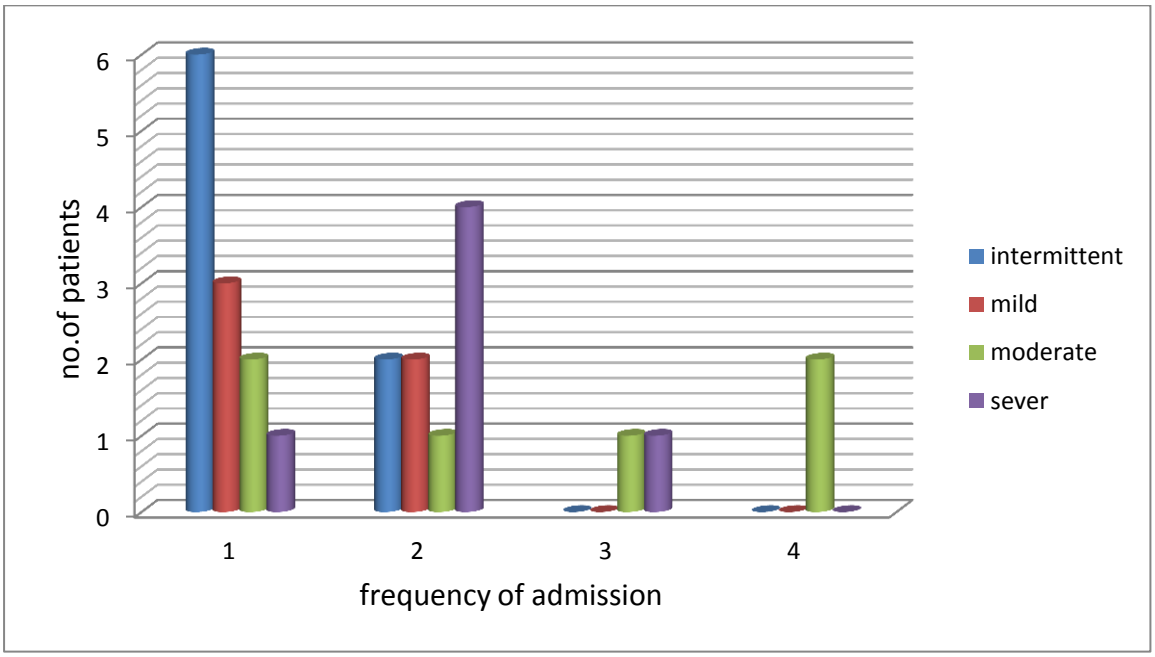

Figure 4:frequency of admission according to severity.

The majority of patients with oxygen saturation more than ninety two percent 64% in whom males were 8% & females were 56%, while those oxygen saturation less than ninety two percent 36% in whom males 12%& females 24%, as shown in figure 5.

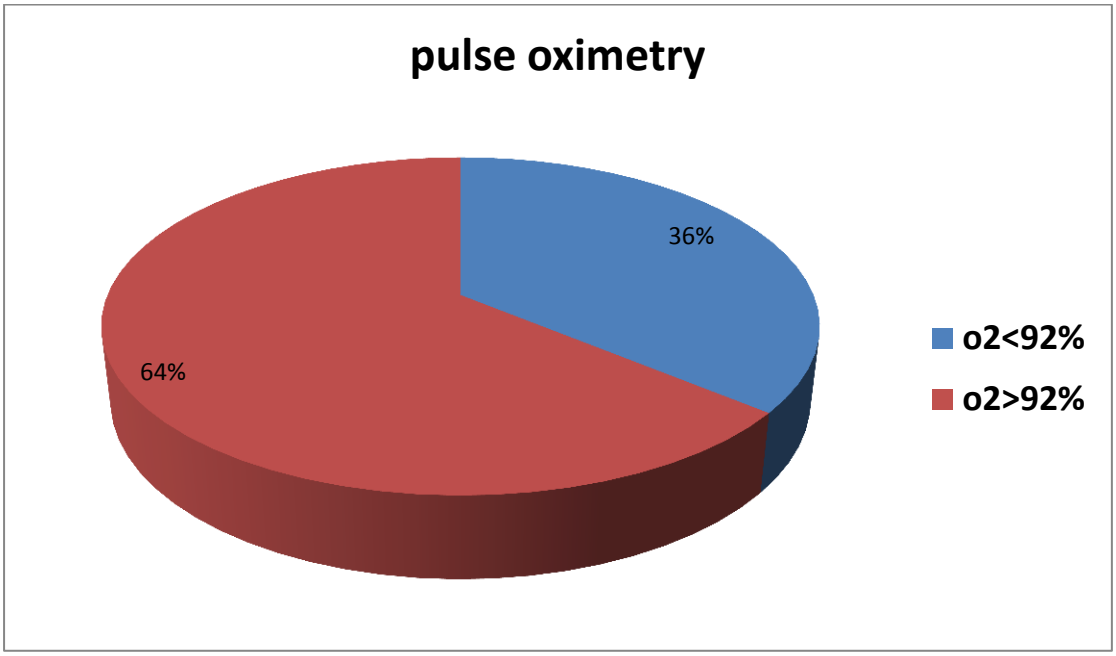

Figure 5:oxygen saturation according to pulse oximetry.

The majority of patients in whom oxygen saturation less than 92% of intermittent severity, as shown in figure 6.

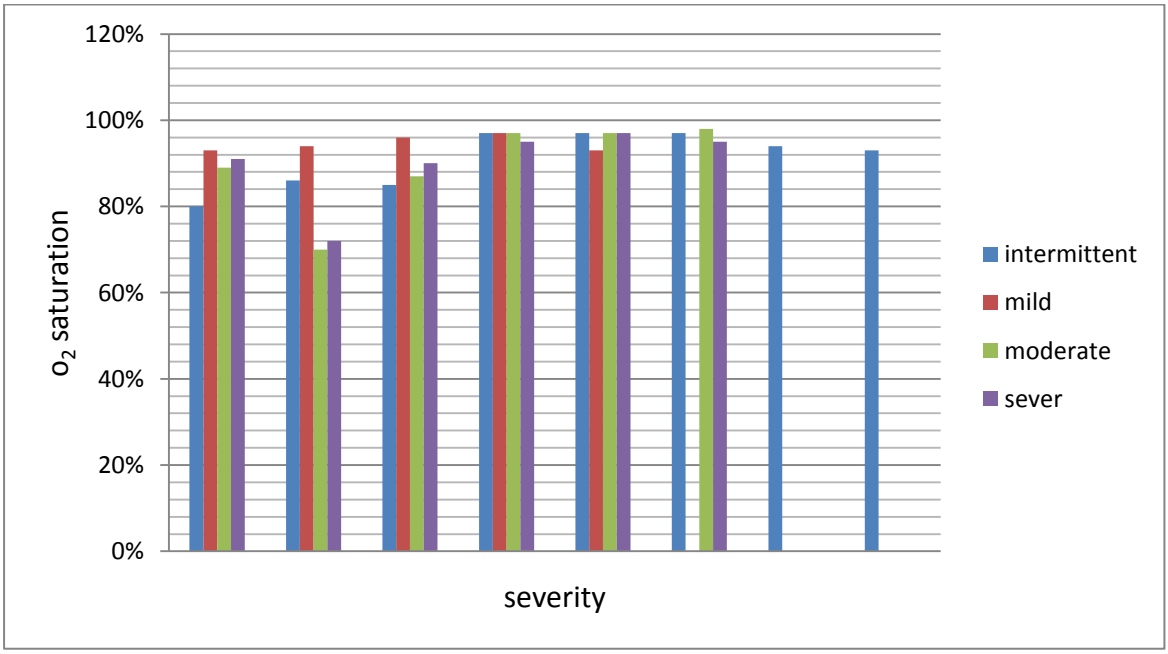

Figure 6:oxygen saturation according to severity.

The minority of patients were with eosinophil count more than 300 cell/mic L, while the majority were their eosinophil count less than 100 cell/mic L, as shown in figure 7.

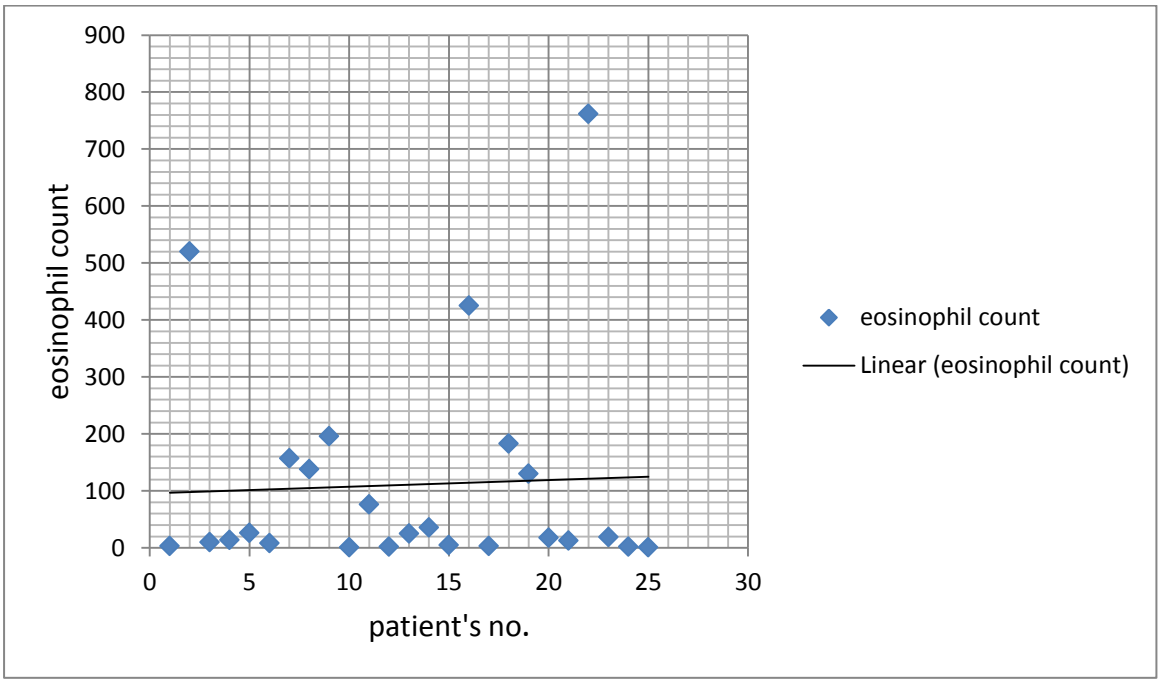

Figure 7:eosinophil count .

Most of patients show normal eosinophil count ,while only 12% of them had blood eosinophilia ,as shown in figure 8.

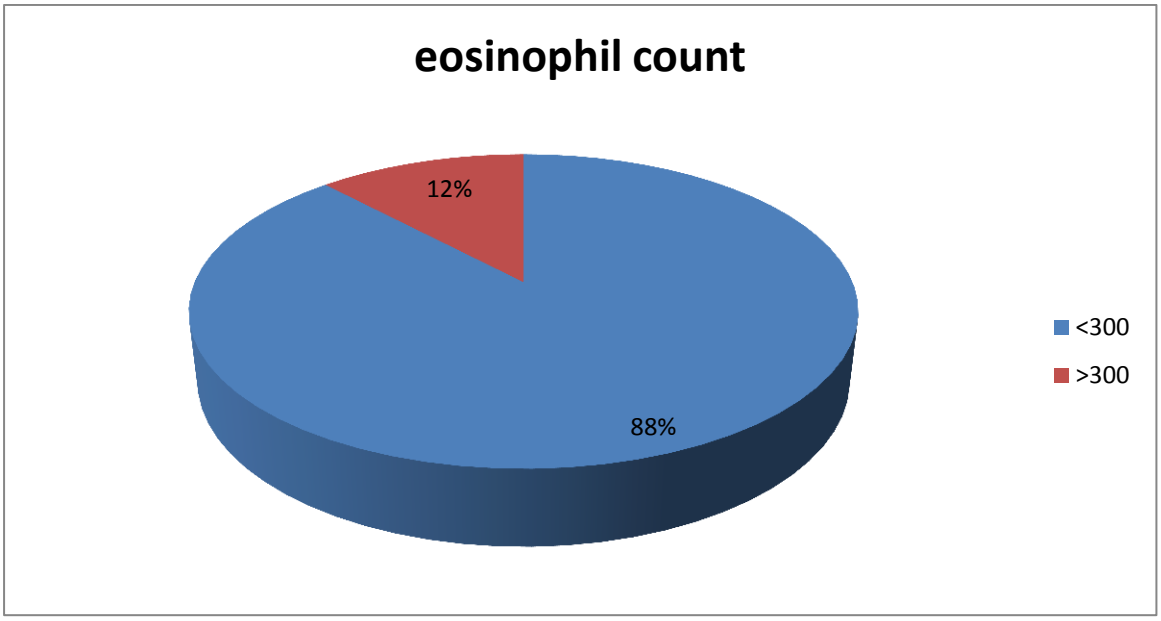

Figure 8: percentage of eosinophil count.

The minority of patients 12% had eosinophil count more than 300 cell/micL with mean 569 ,the mean of white blood cells count of each type of asthma shown in table 2.

		intermittent	mild	moderate	sever
WBC count	Mean	106280	14440	16983	16881
Eosinophil count>300	Fq	0	2	0	1
	Mean	0	641	0	425
Eosinophil count<300	Fq	8	3	6	5
	Mean	57.6	8	35.8	73.2

Table 2:eosinophil count and white blood cells count according to severity.

5.Discussion :

In this study females were forming the majority (80%) of asthmatic patients which is similar to David et al 66% [8] , it's assume that female hormones have a large impact on asthma, fluctuation in levels of estrogen can lead to airway inflammation. Thus, asthma attacks are more likely to occur right before a women's menstrual cycle when her estrogen is low. Most hospitalisations from asthma occur at the peri-menstrual state. In particular, girls during puberty can find that their asthma worsens before their cycle, though the frequency and severity may decrease with age[9].

In this study the most prevalence age group was middle age which is similar to Michael et al[10], it is recognized that aging is associated with a progressive decline in lung function, specifically decreases in the FEV1 as well as the FVC and the FEV1:FVC ratio, there are data to suggest that individuals with asthma have more severe decline in lung function over time , it is commonly attributed to the airway inflammation and airway remodeling that occur with asthma.[11]

Regarding severity; the majority of patients were in mild severity which is similar to Sandra et al[12] , and differ from Julian et al[13] This difference in asthma severity could also account for the difference from previous studies reporting that continuous corticosteroid therapy prevented a decline in airway function in patients with mild asthma.[14]

Regarding hospital admission ,the majority of patients were admitted for the first time , because the majority of them of mild severity.

Regarding precipitating factor of asthma exacerbation ,the majority of them were due to upper respiratory tract infection which is similar

to Donald et al [15] ,and this can be understood to result in corticosteroid resistance leading to occurrence of exacerbation in back ground of viral infection [16] ,further explanation any history of common cold or influenza like in this study can be the initial precipitating factor because respiratory viral infection can activate eosinophil in asthmatics, viral infections may have been a trigger of airway eosinophilic inflammation.[17]

Regarding family history of atopy more than half of patients were with negative family history for atopy which is similar to Michael et al .[10]

Regarding the pulse oximetry the majority of patient were discovered non hypoxic as most of them were in mild asthma.

It's well known that hypoxia SPO_2 <92%,associated with 6.3 fold greater relative risk for requiring additional treatment ,indicate more severity.[18]

Thus pulse oximetry is helpful in monitoring the severity of an acute exacerbation of asthma and has a prognostic value.[18]

Regarding eosinophil count ,in this study most of patients have normal eosinophil count only 12% of patients have count more than 300 cell/microliter in contrast to Kohei et al [6],how found 40% of patients with asthma present with eosinophilia.

Keeping in mind one patient show absolute eosinophilia 762 cell/microliter ,the patient had frequent emergency department admission and 2 in patient admission and her asthma was of mild persistent asthma ,which was exacerbated by dust and upper respiratory tract infection .

Eosinophils are linked to the development of airway hyper responsiveness through the release of basic proteins and oxygen-

derived free radicals. Eosinophil recruitment involves adhesion of eosinophils to vascular endothelial cells in the airway circulation due to interaction between adhesion molecules,migration into the submucosa under the direction of chemokines, and their subsequent activation and prolonged survival.[2]

Eosinophilia not necessarily in all cases of asthma, increased numbers of activated neutrophils are found in some patients with severe asthma and during exacerbations, although there is a proportion of patients even with mild or moderate asthma who have a predominance of neutrophils.[2]

The presence of eosinophilia may suggest otherdiseases like eosinophilic granulomatosis with polyangiitis (Churg–Strauss), granulomatosis with polyangiitis (Wegener's), Connective tissue disease: polyarteritis nodosa, allergic bronchopulmonary aspergillosis .[4]

Several studies have identified the "eosinophilic phenotype" that is characterized by persistent eosinophilic inflammation and frequent

exacerbations .Moreover, recent clinical trials with monoclonal antibodies against interleukin-5 and interleukin-4 receptor have demonstrated decreases in the rate of asthma exacerbations and the dose of systemic corticosteroids required in patients with blood eosinophilia .These data collectively support blood eosinophilia as away to identify patients with severe eosinophilic asthma who might benefit from a targeted therapy.[6]

6.limitations :

1.Data not collected prospectively and no follow up of the patients for response of treatment.

2.Analysis based on auto analyzer without peripheral blood smear.

3.No assessment for the role of corticosteroid used by the patients ,that may affect the blood eosinophil count.

7.Conclusion:

- Females liable to get more sever attack of asthma.

- Raised eosinophil count is recognized feature in asthma.

- Higher eosinophil count associated with more sever attack.

8.Recommendation:

1. Monitoring chronic asthma with acute attack asthma in larger study and the difference in eosinophil count.
2. Monitoring of eosinophil count in assessment response to treatment and follow up of the patient and frequency of admission to hospital.

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