Original Research Article

"A STUDY ON CLINICAL PHENOTYPES OF ASTHMA IN ASTHMA PATIENTS ATTENDING TO A TERTIARY CARE HOSPITAL"

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ABSTRACT:

Background: Asthma is a common airway disease, but it has been often questioned whether it's a single disease or a group of asthmatic diseases with different underlying disease processes. Asthma is currently defined as a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

OBJECTIVES:

1. To study clinical phenotypes of asthma.

2. To classify patients of asthma into various clinical phenotypes.

MATERIAL & METHODS: Study Design: Prospective hospital based cross - sectional study.**Study area:**The present study was conducted in the department of TB & Respiratory medicine,Subbaiah Institute of Medical Sciences, Shimoga, Karnataka.**Study Period:** Mar. 2021 – Feb. 2022.

Study population: It is a cross-sectional study on patients attending respiratory medicine outpatient department (OPD) in Subbaiah Institute of Medical Sciences, Shimoga, Karnataka.

Sample size:A total of 500 diagnosed cases of Bronchial asthma were analyzed in the study.

Sampling method: Universal Sampling Technique.

Study tools and Data collection procedure: The selected patients were briefed about the study, written and informed consent was obtained.A questionnaire concerning: Age, gender, height, weight, BMI, presenting symptoms, past history and duration of asthma, current medications, history of smoking, presence of comorbidities – diabetes, hypertension, ischemic heart disease, number of previous admissions were recorded. All patients with a diagnosis of bronchial asthma as per inclusion criteria were included in the study.

Results: Higher proportion of cases with severe disease had an early onset of the disease too (n=179, 60.9%) as compared to late onset with severe disease (n=91, 44.2%)& higher

proportion of cases with late onset were noted to have less severe disease (n= 115, 55.8%). Chi-square analysis revealed a highly significant correlation between the two parameters (p=0.0001)**.**

CONCLUSION: From our study, we Identified 4 phenotypes of asthma as:

- Early Onset Asthma
- Late onset asthma
- Severe Asthma
- Asthma with obesity

Significant correlation exists between severe asthma phenotype and early onset asthma phenotype.Significant correlation exists between severe asthma phenotypes and asthma with obesity.
Keywords: clinical phenotypes of asthma, adverse effects, Asthma with obesity

INTRODUCTION:

Asthma is one of the most common chronic diseases affecting children and young adults. Asthma is a serious global health problem affecting all age groups, with global prevalence ranging from 1% to 21% in adults and with up to 20% of children aged 6-7 years experiencing severe wheezing episodes within a year. Although some countries have seen a decline in asthma-related hospitalizations and deaths, the global burden for patients from exacerbations and day-to-day symptoms has increased by almost 30% in the past 20 years.[1]

Asthma is a common airway disease, but it has been often questioned whether it's a single disease or a group of asthmatic diseases with different underlying disease processes. Asthma is currently defined as a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[1]

Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called "asthma phenotypes".[1] It is now recognized as a heterogeneous disorder, having various phenotypes. Each of these phenotypes are defined by its unique interaction between genetic and environmental factors.

The term "asthma" is now deliberately used as an umbrella term like "anemia", "arthritis" and "cancer"; these terms are very useful for communication with patients and for advocacy, and they facilitate clinical recognition of heterogeneous diseasesthat have readily recognizable clinical features in common. But evidence about the underlying mechanisms in asthma is much less well-established.[1]

Identification of heterogeneity and classification of asthma by phenotypes provides a foundation from which to understand disease causality and ultimately to develop management approaches that can lead to improved asthma control while avoiding adverse effects and decreasing the risk of serious asthma outcomes (e.g., exacerbations and loss of pulmonary function).[2]

In patients with more severe asthma, phenotype-guided treatments are available. However, to date, no strong relationship has been found between specific pathological features and particular clinical patterns or treatment responses.[3]

Recognition of these phenotypes and defining them, will help us in better understanding of asthma its treatment response and prognosis. It will also help us in providing individual tailored treatment to the patients of asthma. Hence the present study was undertaken to study the clinical phenotypes of asthma in the study population.

OBJECTIVES:

1. To study clinical phenotypes of asthma.

2. To classify patients of asthma into various clinical phenotypes.

MATERIAL & METHODS:

Study Design: Prospective hospital based cross - sectional study.

Study area: The present study was conducted in the department of TB & Respiratory medicine,Subbaiah Institute of Medical Sciences, Shimoga, Karnataka.

Study Period: Mar. 2021 – Feb. 2022.

Study population: It is a cross-sectional study on patients attending respiratory medicine outpatient department (OPD) in Subbaiah Institute of Medical Sciences, Shimoga, Karnataka.

Sample size:A total of 500 diagnosed cases of Bronchial asthma were analyzed in the study.

Sampling method: Universal Sampling Technique.

Inclusion criteria: All patients attending Respiratory medicine OPD and are diagnosed as Bronchial asthma according to GINA guidelines 2014.

Exclusion criteria: Patients who are:

1) Currently smokers.

2) Having active tuberculosis.

3) Having post tubercular lung disease sequelae.

4) Having associated heart diseases.

5) Having chest wall abnormalities.

6) Having parenchymal lung diseases.

7) Having associated COPD.

Ethical consideration: Institutional Ethical committee permission was taken prior to the commencement of the study.

Study tools and Data collection procedure:

The selected patients were briefed about the study, written and informed consent was obtained. A questionnaire concerning: Age, gender, height, weight, BMI, presenting symptoms, past history and duration of asthma, current medications, history of smoking, presence of comorbidities – diabetes, hypertension, ischemic heart disease, number of

previous admissions were recorded. All patients with a diagnosis of bronchial asthma as per inclusion criteria were included in the study.

Statistical analysis

This is a Cross sectional study in which BMI, age of asthma onset, severe disease history was assessed. Comparison of age, body mass index, duration and severity of the illness between both the groups was done. Data was compiled and analysed using SPSS software Version 17.0. Chi Square test. Results with a p value of <0.05 was considered statistically significant.

OBSERVATIONS & RESULTS:

Table 1: Gender Wise Distribution of Cases

GENDER	Frequency	Valid Percent (%)
F	298	59.6
M	202	40.4
Total	500	100.0

Among total 500 cases, 298(59.6%) were females and 202(40.4 %) were males.

Table 2: Distribution of Cases according to BMI

BMI	Frequency	Valid Percent (%)
Underweight	37	7.4
Normal	178	35.6
Overweight	195	39.0
Obese	90	18.0
Total	500	100.0

Among 500 asthma cases, 37 cases (7.4%) were Underweight, 178 cases (35.6%) had normal BMI, 195 cases (39%) were found to be overweight, 90 cases (18.0%) fell in in Obese category.

Table 3: Distribution of Cases based on SEVERITY

SEVERE DISEASE	Frequency	Valid Percent (%)
Yes	270	54.0
No	230	46.0

Total	500	100.0

270 cases (54.0%) were found to have severe disease.

Table 4: Distribution of Cases based on Time of Onset

TIME OF ONSET	Frequency	Valid Percent (%)
Early Onset	294	58.8
Late Onset	206	41.2
Total	500	100.0

Out of the study population, 294 cases (58.8%) had an early onset of the disease as compared to 206 cases (41.2%) who had late onset of the disease.

Table 5:Correlation between severity of disease & gender (n=500)

GENDER	SEVERITY		TOTAL (n =)	p-Value
	YES n = (%)	NO n = (%)		
Male	**113 (55.9%)**	**89 (44.1%)**	**202**	**0.473**
Female	**157 (52.7%)**	**141 (47.3%)**	**298**	
Total	**270**	**230**	**500**	

Out of the study population, it was found that higher proportion of males (n=113, 55.9%) experienced severe disease compared to females (n=157, 52.7%) but Chi-square analysis did not reveal any significant correlations between gender & severity of disease. (p=0.473).

Table 6: Correlation between severity of disease & time of onset (n=500)

ONSET OF	SEVERITY	TOTAL	

DISEASE	YES n = (%)	NO n = (%)	(n =)	p-Value
Early Onset	179 (60.9%)	115 (39.1%)	294	0.0001
Late Onset	91 (44.2%)	115 (55.8%)	206	
Total	270	230	500	

The table reveals that a higher proportion of cases with severe disease had an early onset of the disease too (n=179, 60.9%) as compared to late onset with severe disease (n=91, 44.2%)& higher proportion of cases with late onset were noted to have less severe disease (n= 115, 55.8%). Chi-square analysis revealed a highly significant correlation between the two parameters (p=0.0001)**.**

Table 7: Correlation between severity of disease & BMI (n=500)

ONSET OF DISEASE	SEVERITY		TOTAL (n =)	p-Value
	YES n = (%)	NO n = (%)		
Underweight	14 (37.8%)	23 (62.2%)	37	0.007
Normal	86 (48.3%)	92 (51.7%)	178	
Over-weight & Obese	170 (59.6%)	115 (40.4%)	285	
TOTAL	270	230	500	

The table reveals that a higher proportion of cases with severe disease were noted to be in overweight & obese category (n=179, 60.9%) as compared to those with underweight and normal BMI. Chi-square analysis revealed a highly significant correlation between the two parameters (p=0.007)**.**

DISCUSSION:

Asthma is a complex heterogeneous disease that likely comprises several distinct disease phenotypes. Phenotypes can be classified by analyzing single or multiple manifestations of disease including symptoms and clinical measurements using various clustering approaches.

Phenotypes classified in this way show differences in associations with clinical outcomes and with underpinning genetic pathways. Big data will add to the complex multidimensionality of these approaches but the challenge is to identify interventions that are specific to one or more of these phenotypes to realize the potential of personalized medicine.[4]

Asthma phenotypes have been developed to address the complexities of the disease. However, owing to a lack of longitudinal studies, little is known about the onset as well as the stability of phenotypes. Distinguishing phenotypes with regard to the severity or duration of the disease is essential. A phenotype covers the clinically relevant properties of the disease, but does not show the direct relationship to disease etiology and pathophysiology.[5]

In our study we have identified 4 phenotyes of asthma:

• Early Onset Asthma

• Late onset asthma

• Severe Asthma

• Asthma with obesity

In a study conducted by Wendy C.Moore , Anne M. Fitzpatrick et al.[6], on Clinical Heterogeneity in the Severe Asthma Research Program, had comprehensively characterized 1,644 patients with asthma over a period of 10 years, including 583 individuals with severe asthma and 300 children below the age of 18 years.

The diversity in clinical characteristics, physiologic measures, and biomarkers in a large number of subjects across the ages provides an ideal cohort in which to investigate asthma heterogeneity. Using both biased and unbiased approaches, multiple asthma phenotypes have been described in SARP. There may be large groups of patients, especially those with milder asthma, that can be grouped into a clinical phenotype to guide therapy.

The SARP cohort exemplifies asthma heterogeneity. All levels of the asthma severity spectrum are represented in SARP from the mildest intermittent asthma to the most severe persistent disease in both children and adults. As such, the SARP cohort provides a platform to investigate asthma heterogeneity. Phenotyping analyses in SARP have been performed in a layered step-wise fashion. Initial analyses used to hypothesis-drive, biased approaches with *a priori* separation of subjects before comparison investigating differences in not severe and severe asthma, as well as differences within the severe asthma subgroup.

Yet another study conducted byMoore WC, Meyers DA, Wenzel SE, et al[7] under Severe Asthma Research Program on Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program compared severe with mild and moderate asthma patients, analyzing 726 patients with variables such as forced expiratory volume in 1 second (FEV_1), sputum neutrophils and eosinophils, asthma duration, and body mass index (BMI) via a cluster analysis and identified 5 clinical phenotypes.

1. Early-onset atopic asthma, predominately female and normal lung function, younger subjects.

2. Early-onset atopic asthma, predominately female, slightly older subjects with more medication use, normal or reversible lung function.

3. Older obese women, late-onset asthma, less likely to be a topic, decreased lung function, highly symptomatic.

4. More severe asthma, both sexes, many of early onset and atopic, long duration of disease, severely reduced lung function.

5. More severe asthma, more women, less atopy, longest duration of disease, the most severely reduced lung function.

In a study done byHaldar P, PavordID et al.[8] on Cluster analysis and clinical asthma phenotypes, where they hadanalysed184 patients with mild to moderate asthma followed in a primary care clinic and 187 patients diagnosed with refractory asthma and referred to an asthma specialty clinic for management. The study identified 3 phenotypes in mild to moderate asthma patients in the primary care group and 4 phenotypes in patients with refractory asthma. The primary care phenotypes were overall less symptomatic & were divided into 3 phenotypes:

• Early-onset atopic asthma with eosinophilic airway inflammation. This group had the most exacerbations and used the greatest amount of oral steroids among the 3 phenotypes in the primary care group.

• Obese subgroup, mostly female, with noneosinopilic asthma and

• Benign asthma with little active disease. Patients in this group had minimal symptoms, often normal lung function and 58% had no evidence of airway hyper responsiveness at assessment. These patients had few exacerbations.

In another study conducted byMoore WC, Hastie AT, Li X, et al; under Severe Asthma Research Program on Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis**.** A follow-up study was conducted in a subset of 423 patients to better understand interactions between sputum inflammatory cellular markers and clinical variables. In this cluster analysis, 4 phenotypes were identified, differentiated by inflammatory cell phenotypic patterns and clinical characteristics.[3]

According to the study conducted byAmelink M, de Nijs SB, de Groot JC, et al.[9]; identified three phenotypes of adult-onset asthma based on cluster analysis that was undertaken in 200 adult-onset asthma patients including clinical lung function parameters (FEV_1, forced vital capacity, total lung capacity), age at onset, asthma duration, race, BMI, smoking pack-year history, and inflammatory markers (sputum and blood eosinophils and neutrophils, fractional exhaled nitric oxide, and atopy) as variables.

According to study conducted byBoudierA,Curjuric I, Basagaña X, et al, which was a pooled analysis of three cohort studiesconducted onTen-year follow-up of cluster-based asthma phenotypes in adults,identified7 phenotypes based on respiratory symptoms, allergic status, and pulmonary function, but not inflammatory markers, varied from 54% to 88% across phenotypes during a 10-year period, with transitions toward increased asthma symptoms being more common in non allergic than allergic phenotypes.[10]

In a retrospective study done byJames Lee Kuhlen Jr.[11] on Identification of Asthma Phenotypes in a Tertiary Care Medical Center, study comprised of 139 patients with mild, moderate, and severe persistent asthma. Variables including baseline and maximal FEV1 and age of asthma onset were used to classify patients. The study identified five clusters(C) similar to SARP.

According to a review article byWenzel SE, on "Asthma phenotypes: the evolution from clinical to molecular approaches"; it was noted that though different studies selected different variables to analyze and, as a result, different phenotype classifications were identified, some consistencies between study findings have been observed. Many study findings show age at onset to be a frequently observed phenotype; with early-onset disease often associated with a more atopic and allergic condition over a range of severities, whereas later-onset disease is often associated with noneosinophilic inflammation, may be associated with obesity and is often more common in women, with less association with atopy.[12]

Among our study population that comprised of 298(59.6%) females and 202(40.4 %) males; 157 females experienced severe disease.In the study conducted byJessica A. Kynyk; John G. Mastronarde et al.[13] on "Asthma, the Sex Difference "revealed a striking difference in asthma prevalence and severity closely related to sex and age, which interestingly seem to follow key transition points in the reproductive cycle of women. The lifetime likelihood of developing asthma is about 10.5% greater in women than men. When examined at specific time points, asthma is more common and more severe in prepubertal boys, with boys less than 18 years of age having a 54% higher rate of asthma than girls of the same age. However, the prevalence of asthma and its severity increases significantly in women after puberty, with asthma becoming more common in women by age 20 in the United States. 2009 estimates from the National Health Interview Survey in the United States demonstrate a prevalence of asthma in those less than 15 years of age of 11.9% in boys and 7.7% in girls. In young adults aged 15–34 years, the pattern shifts, with a prevalence of 6.3% in men and 9.6% in women. The difference continues to widen in adults older than 35 years with a prevalence of 5.6 versus 10.1% in men and women, respectively.

In our study, when we tried to find correlations between severity of disease & time of onset it was noted that higher proportion of cases with early onset (60.9%) was found to have severe disease compared to those with late onset (44.2%).In a cross-sectional analytical study conducted byMiranda C.,Busacker A. et al.[14], on "Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation." , from 80 subjects with severe asthma , it was found that subjects with early-onset, severe asthma had significantly more allergen sensitivity (skin test positivity, 98% vs 76%, P <.007) and more allergic symptoms (P values all <or=.02) than subjects with late-onset asthma.

Among our study population, it was noted that 285 cases were categorized under overweight & obesity out of which 170 cases were noted to have severe asthma. Statistical analysis showed significant correlation between Obesity & severe disease (p-value= 0.007).A study conducted byDavid A.Beuther and E.[15] Rand Sutherland on " Overweight, Obesity and Incident Asthma"with an objective to quantify the relationship between categories of body mass index (BMI) and incident asthma in adults and to evaluate the impact of gender on this relationship.The study also stated that the phenotype of asthma seen with overweight and obesity is unique with regard to clinically-meaningful parameters such as the nature or perception of symptoms, specific physiologic impairments, or response to therapy.

In yet another cross-sectional study conducted by David M. Mose et al[16] on "The relationship between obesity and asthma severity and control in adults" with a study population of 1113 cases of age 35 years and above with active asthma using Mini-Asthma Quality of Life Questionnaire, the Asthma Therapy Assessment Questionnaire, and self-reported asthma-related hospitalization. Several other factors known to influence asthma outcomes also were collected: demographics, smoking status, oral corticosteroid use in the past month, evidence of gastroesophageal reflux disease, and inhaled corticosteroid use in the past month. Results

suggested that obese adults were more likely than those with normal BMIs (<25 kg/m2) to report poor asthma-specific quality of life (odds ratio, poor asthma control, and multiple history of asthma-related hospitalizations). The study concluded that obesity is associated with worse asthma outcomes like increased risk of asthma related hospitalizations.

CONCLUSION:

From pur study, we Identified 4 phenotypes of asthma as:

- Early Onset Asthma
- Late onset asthma
- Severe Asthma
- Asthma with obesity

Significant correlation exists between severe asthma phenotype and early onset asthma phenotype.Significant correlation exists between severe asthma phenotypes and asthma with obesity.

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