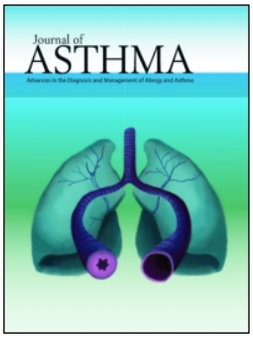

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Distinct asthma phenotypes with low maximal attainment of lung function on cluster analysis

Smriti Bhargava, MBBS[a], Amrutha D. Holla, MBBS, DAA[b], Biligere S. Jayaraj, MD, DM[a], Attahalli S. Praveena, PhD[c], Sreenivasan Ravi, PhD[c], Sandhya Khurana, MD[d], and Padukudru A. Mahesh, DTCD, DNB (Respiratory Diseases)[a]

[a]Department of Pulmonology, JSS Medical College, JSS Academy of Higher Education and Research, Mysore, India; [b]Allergy Asthma and Chest Center, Mysore, India; [c]Department of Studies in Statistics, University of Mysore, Mysore, India; [d]Division of Pulmonary & Critical Care Medicine, University of Rochester Medical Center, Rochester, NY, USA

ABSTRACT

Objective: Asthma is a heterogeneous disease with varying clinical presentations, severity and ability to achieve asthma control. The present study aimed to characterize clinical phenotypes of asthma in an Indian cohort of subjects using a cluster analysis approach.

Methods: Patients with confirmed asthma ($N = 100$) and at least 6-months of follow-up data, identified by retrospective chart review, were included in this study. Demographics, age at disease onset, disease duration, body mass index, serial spirometry and allergen sensitization were assessed. Asthma control was assessed prospectively using Global Initiative for Asthma and Asthma Control Test. R version 3.4.3 was used for statistical analysis. Ward's minimum-variance hierarchical clustering method was performed using an agglomerative (bottom-up) approach. To compare differences between clusters, analysis of variance using Kruskal-Wallis test (continuous variables) and chi-square test (categorical variables) was used.

Results: Cluster analysis of 100 treatment-naive patients with asthma identified four clusters. Cluster 1, ($N = 40$), childhood onset of disease, normal body weight, equal gender distribution and achieved normal lung function. Cluster 2 ($N = 16$) included adolescent disease-onset, obese, majority males and had poor attainment of maximum lung functions. Cluster 3 ($N = 20$) were older, late-onset of disease, obese, majority male and had poor attainment of maximum lung function. Cluster 4 ($N = 24$) had adult-onset of disease, obese, predominantly female and achieved normal lung function.

Conclusions: In an Indian cohort of well-characterized patients with asthma, cluster analysis identified four distinct clinical phenotypes of asthma, two of which had poor attainment of maximum lung functions.

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Lung function; allergy; treatment responsiveness; genetics; categorize

Introduction

The prevalence of asthma has increased by 12.6% since 1990 making it the most common chronic respiratory disease worldwide (1). In 2015, 400,000 people died from asthma globally. There were 37.9 million cases of asthma in India in 2016 (2). The contribution of chronic respiratory diseases to the total DALYs (Disability-Adjusted Life Year) in India increased from 4.5% in 1990 to 6.4% in 2016. Of these, asthma was responsible for 20% of the chronic respiratory disease DALYs (2). The Global Initiative for Asthma (GINA) provides a stepwise approach for adjusting treatment based on disease severity, control and response to therapy (3). Despite availability of evidence-based updated guidelines, studies show that asthma control remains poor across multiple healthcare settings. A study conducted by Kearney et al. on residents of North Carolina found that a total of 2,066 decedents had an underlying cause of death as asthma for an overall death rate of 12.5 per 1,000,000 persons (4).

In a substantial number of patients, asthma is uncontrolled due to poor treatment-responsiveness independent of baseline disease severity (5). In a study conducted by Gonzalez-Barcala et al. of the 1316 patients analyzed, 36 (2.7%) had one early readmission (within 15 days of discharge) and 313 (23.8%)

CONTACT Padukudru A. Mahesh mahesh1971in@yahoo.com Professor and Head of Department of Pulmonology, JSS Medical College, JSS Academy of Higher Education and Research, Mysore, Karnataka, India.

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What this study adds: This is the first cluster analysis of asthma in the Indian population. A large percentage of subjects with asthma had low maximal attainment of lung function after 6 months of guidelines-based treatment (Clusters 2 & 3).

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one late readmission. The only factor independently associated with a higher probability of an early readmission was poor lung function. A higher probability of late readmission was associated with a greater severity of the asthma and the use of a combination of inhaled corticosteroid (ICS) and long acting beta agonist (LABA) as maintenance treatment (6). Current guidelines from GINA (3), British Thoracic Society (7), National Institute for Clinical Excellence (8) and National Asthma Education and Prevention Program (9) provide excellent population-based protocols on asthma management that are effective for majority of patients. However, there is a paucity of guidance on how to define, diagnose and manage patients who do not achieve normal lung function.

The clinical presentation, pathophysiology and treatment-responsiveness are all important variables in asthma. Studies have categorized asthma patients into subgroups using both pre-defined variables and unbiased cluster analysis (10–13). The objective of cluster analysis is to identify, without bias, groups of patients that are similar with respect to variables or attributes of interest, and the groups themselves stand apart from one-another (14). Majority of the cluster analyses have been based on cross-sectional data on patients with mixed duration of asthma (10–12).However, asthma is a disease with a high degree of variability, making one time point a fragile basis for cluster analysis. Reliability of the results and confidence in consistency of a phenotype would be increased by including clinical data from several time points (13). Recognition of specific sub-phenotypes may further our understanding of the pathophysiology, treatment response, prognosis and underlying genetic basis for the disease, and also pave the way for targeted therapy. In this study, we aimed to identify distinct clusters in patients with asthma and evaluate if they differed based on maximum lung function attained after guidelines-based management over 6-months. Some of the results of this study have been previously reported in the form of an abstract (15).

Materials and methods

This is a retrospective study of treatment naïve asthmatics evaluated at a tertiary care center between January 2015 and February 2016. Judgmental non-probabilistic sampling technique was applied. Confidentiality of the data was maintained according to the clinical research guidelines. The institution's ethics committee approved the study (JSSMC/IEC/02/0603/2017–18). Subjects were identified by review of institution's medical database. These patients had chest symptoms suggestive of airway disease and did not have previous spirometries to confirm their asthma. Therefore, during the first visit to the tertiary care center, these subjects were referred for spirometry to confirm the diagnosis of asthma. The inclusion criteria were asthmatics who had been treated at primary and secondary care levels only with intermittent oral bronchodilators, oral steroids and nebulization during the acute attacks. None of these patients were on daily ICS therapy as per the GINA guidelines at the time of presentation. The age of onset of clinical symptoms suggestive of asthma as elicited in history is taken as the age of onset of asthma. Patients who had at least 6 months of follow up and a minimum of four spirometry tests during this time, were included. The exclusion criteria was defined by patients with respiratory diseases other than asthma, <6 months of follow-up, non-adherent with treatment, or <4 serial spirometry. Patients, which were referred back to family physician, were also excluded from the study.

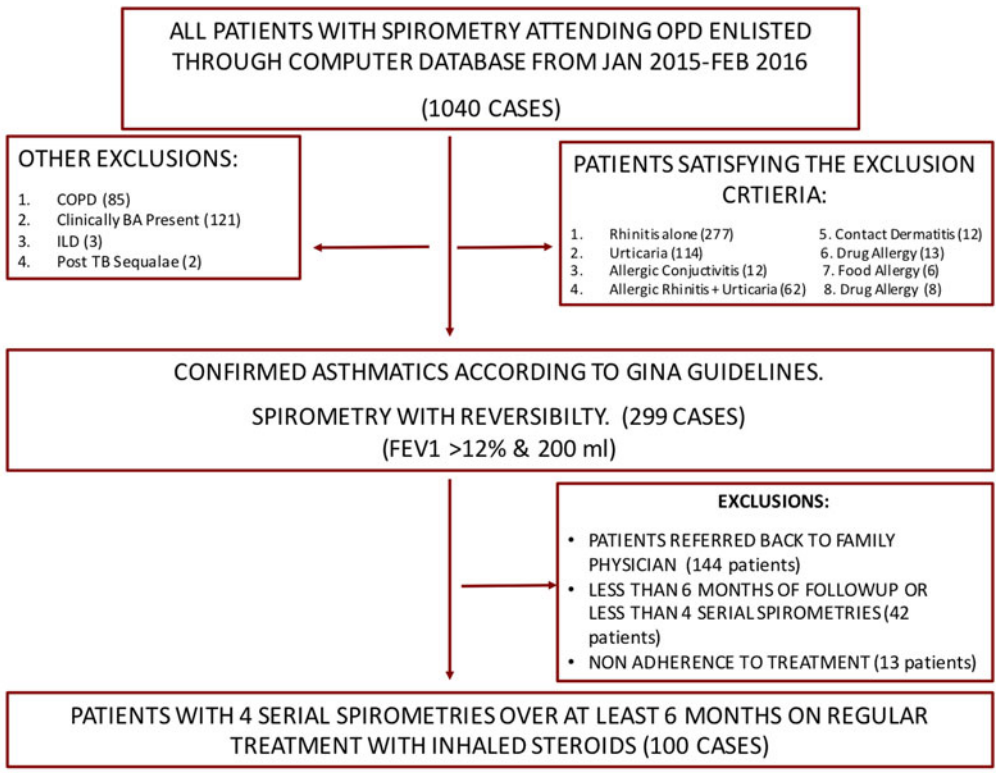
The patients were treated according to GINA guidelines (3). Maximal lung function was defined according to the maximum value obtained during the period of study. When the lung functions did not reach 80%, subjects received a short course of oral steroids. Adherence to pharmacotherapy was assessed from pharmacy refills.

Subjects were assessed using a standardized protocol that included the recording of demographics and performance of pulmonary function tests that satisfied American Thoracic Society (ATS) quality criteria. Spirometry was performed with Easy-One spirometer (NDD Medizintechnik; Zurich, Switzerland), and post-bronchodilator testing was performed 15 min after administration of 400 μg of salbutamol. Asthma was diagnosed according to GINA guidelines with patients having a post-bronchodilator FEV1 reversibility of >12% and 200 ml. The reference values used were Asian (16). Serial lung functions were recorded to identify the time taken to achieve maximum lung function. The 'Revised Consensus of Body Mass Indices for Asian Indians' criteria was used (17). Patients with body mass index (BMI) between 18 and 23 kg/m^2 were categorized as normal, 23 and 24 kg/m^2 as overweight and ≥25 kg/m^2 as obese. Patients were categorized as atopic if they had a skin prick test to one or more allergen measuring ≥3 mm of the saline control. The skin prick test was performed using Hollister Stier (Spokane, USA) allergens with a 1 mm prick lancet (Hollister Stier) for different allergens (pollens, grasses, trees/shrubs, pets, fungi/molds and dust mite). Total serum IgE levels were measured using Genesis Diagnostics ELISA Kit (Cambridgeshire, England). Total and differential white cell counts

including absolute eosinophil count were performed with Sysmex automated cell counter.

Allergic rhinitis and conjuctivitis were diagnosed according to the Allergic Rhinitis and its Impact on Asthma guidelines and 'American Optometric Association' (18,19). Subjects with symptoms of rhinitis were classified as allergic rhinitis if they were atopic and were classified as non-allergic rhinitis if they were non-atopic. Patients were asked about exposure to biomass fuels for cooking and heating, mosquito repellents and incense sticks all of which are known to cause indoor pollution similar to that of smoking indoors that can lead to poor treatment responsiveness (20). The number of exacerbations during the follow-up period was noted. Asthma exacerbations were defined according to ATS/ERS statement on standardization of outcomes. Patients having either (a) use of systemic corticosteroids or an increase from a stable maintenance dose, for at least 3 days, or (b) a hospitalization or ER visit because of asthma requiring systemic corticosteroids, were classified as having an asthma exacerbation (21).

CDC defines a 'former smoker' as an adult who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview and a 'never smoker' if smoked <100 cigarettes in their lifetime (22). Follow up was prospective, using GINA and Asthma control test (ACT) questionnaire to determine asthma control (23,24). This was assessed at 6 months, during the last visit of the patients. Patients were classified as well controlled, partially controlled and uncontrolled according to GINA. Using the ACT questionnaire for patients >12 years of age, asthma control was categorized as uncontrolled (score < 20) or controlled (score ≥ 20). An ACT score of 19 or lower is useful for identifying patients with poorly controlled asthma (GINA) (25). Data on the treatment levels of patients according to GINA guidelines at the beginning of the study versus at the end of 6 months were also collected (3). All the subjects underwent a detailed educational program about asthma, risk factors, triggers, various medications, need for regularity of medications, device options and training on the use of the device lasting 30–35 min at the initiation of



OPD: Out Patient Department
COPD: Chronic Obstructive Pulmonary Disease
ILD: Interstitial Lung Diseases
Post TB: Post Tuberculosis

Figure 1. Flow chart of patient recruitment with reasons for exclusion.
OPD: out patient department; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung diseases; Post TB: post tuberculosis

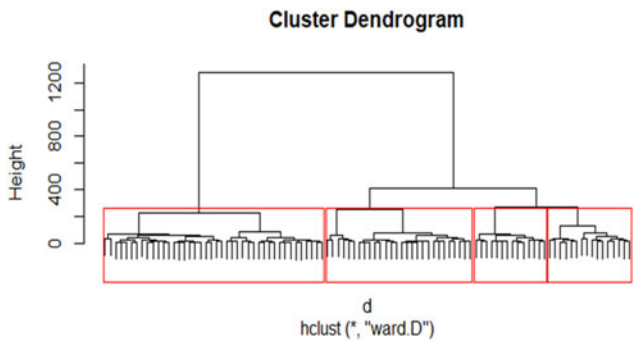


Figure 2. Cluster dendrogram identified four distinct asthma clusters.

treatment. During each follow-up visit, the subject was requested to demonstrate the use of their device.

Statistical analysis

Data were standardized using method of medians, as the variables were measured on different scales. The median was subtracted from each observation and the difference was divided by the median absolute deviation. R version 3.4.3 was used to perform statistical analysis.

This was followed by application of cluster analysis methodology in which unsupervised machine-learning method is used to identify similar characteristics in patients and to group them together on that basis. The essential aim is to minimize intra-group variance while simultaneously maximizing inter-group variance. The methodology was applied to each population using a two-step approach. In the first step, Ward's minimum-variance hierarchical clustering method (14) was performed using an agglomerative (bottom-up) approach. Hierarchical clustering did not require the number of clusters to be specified *a priori* and cluster assignment was based on similarity of measured characteristics. The agglomerative method then applied started with each data point assigned to its own cluster, and iteratively merges the two closest clusters until all the data belong to a single cluster (26).

The dendrogram (Figure 1) then generated was used to estimate the number of likely clusters within the studied population and four distinct clusters were identified. Once clusters were formed, there was no inter-cluster switching. The choice of which clusters to combine is determined by measuring distances, similarities/dissimilarities, and/or using linkage criteria (27). Cluster stability is an important aspect of validity, because cluster methods can generate groups in fairly homogenous data sets hence, trial of 5 clusters was also considered, but little difference was appreciated between the fourth cluster and fifth cluster, thus we retained only four clusters. This estimate was pre specified in k-means cluster analysis that was used as the principal clustering technique. K-means clustering method was used by taking the centroids as seeds of the clusters obtained. Variables chosen for cluster modeling were selected on the basis of their considered contribution to characterizing the asthma phenotype. Analysis of variance using Kruskal-Wallis test for continuous variables and chi-square test for categorical variables were used to compare these clusters.

Table 1. Demographic and clinical variables of the study population.

Parameter	Female	Male	Total
No. of subjects	55	45	100
Baseline FEV1 before treatment (% predicted)	59.05 (21.22)	58.5 (22.85)	58.81 (21.96)
Max. post treatment FEV1 achieved (% predicted)	76.31 (17.13)	74.3 (19.9)	75.39 (18.46)
BMI (kg/m^2)	25.28 (7.20)	20.94 (4.865)	23.33 (6.62)
Age at baseline (years)	33.85 (18.2)	33.0 (21.42)	33.45 (19.72)
Age at onset of disease (years)	25.65 (17.6)	21.0 (19.23)	23.54 (18.5)
Duration of disease (Years)	9.04 (8.73)	12.72 (14.05)	10.7 (11.6)
Non-smokers (%)	92.73 (0.26)	86.7 (0.34)	90.0 (0.3)
Presence of Indoor air pollution (%)	15.5 (0.352)	11.1 (0.314)	13.0 (0.336)
Presence of Atopy (%)	83.64 (0.34)	80.0 (0.4)	81.82 (0.39)
Serum IgE levels (IU/ml)	534.3 (559.3)	668.6 (605.82)	581.7 (583.9)
Absolute eosinophil count (Cells/μl)	386.9 (174.8)	315.4 (188.1)	356.2 (183.45)
WBC count (Cells/mm^3)	8265.8 (1192.8)	8000 (1198.67)	8139.1 (1204.6)
Allergic Rhinitis (%)	83.64 (0.34)	80.0 (0.4)	81.8 (0.31)
Non-Allergic Rhinitis (%)	9.16 (0.74)	6.7 (0.66)	7.18 (0.687)
Perennial symptoms (%)	74.55 (0.4356)	66.66 (0.4714)	72.0 (0.449)
Sensitive to House dust mite (%)	94.45 (0.2271)	88.9 (0.3143)	93.0 (0.2551)
Asthma Control according to GINA (%)			
(1) Controlled	(1) 30.9	(1) 33.33	(1) 32.0
(2) Partially controlled	(2) 10.9	(2) 28.9	(2) 19.0
(3) Uncontrolled	(3) 58.2	(3) 37.77	(3) 49.0
Asthma Control according to ACT (ACT) (% of controlled patients)	35.42 (0.478)	38.24 (0.486)	40.24 (0.56)

Notes. The continuous variables are calculated as average while the others have percentage calculations. The values in the bracket are standard deviations.
For Asthma control according to GINA.
(1) Well controlled.
(2) Partially controlled.
(3) Uncontrolled.

Results

Out of the 1040 patients screened, 741 patients did not meet inclusion criteria (Figure 2). Confirmed asthmatics according to GINA guidelines were 299

Table 2. Comparison of demographic and clinical variables of the four distinct asthma clusters.

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	*p* Value
Size	40	16	20	24	–
Baseline Pre-bronchodilator FEV1 before treatment % predicted	68.9	43.4	45.7	63.3	<0.00001
Max. post treatment FEV1 achieved % predicted	87.57	58.12	61.6	78.1	<0.00001
% FEV1 improvement with bronchodilator on first visit (%)	16.5	24.2	14.6	12.25	<0.00001
Age at onset of disease (average) (Years)	7.6	16.1	51.9	31.8	<0.00001
Age at baseline (average) (Years)	13.2	41.7	61.2	38.5	<0.00001
BMI (average) (kg/m^2)	18.72	23.9	26.8	27.8	<0.00001
Duration of disease (average) (Years)	6.9	27.1	9.9	6.7	0.00014
House dust mite sensitivity (%)	85.0	62.5	50.0	79.1	0.0218
Percentage of subjects with at least one moderate or severe Asthma exacerbations in 6 months (%)	5.0	18.8	15.0	33.3	0.0282
Asthma Control according to GINA* (%)	(1) 45.0 (2) 32.5 (3) 22.5	(1) 50.0 (2) 12.5 (3) 37.5	(1) 0.0 (2) 5.0 (3) 95.0	(1) 25.0 (2) 12.5 (3) 62.5	<0.00001
Asthma Control according to ACT (%) of uncontrolled (ACT)	63.6 *n* = 22/40°	37.5 *n* = 16/16	85 *n* = 20/20	62.5 *n* = 24/24	0.03422
Atopy (%)	90.0	86.7	65.0	79.2	0.1395
Perennial symptoms (%)	80.0	75.0	65.0	62.5	0.407
Allergic Rhinitis (%)	90.0	86.7	65.0	79.2	0.139
Non-allergic Rhinitis (%)	2.0	0.8	20.0	8.3	<0.00001

Notes. *GINA (1) Well controlled (2) Partially controlled (3) Uncontrolled.
°ACT was only administered to subjects above the age of 12.

with spirometry-confirmed reversible airflow obstruction. Of these, 144 patients were referred back to the family physician, 42 patients had <6 months follow up and/or <4 spirometry studies. Thirteen patients were excluded based on non-adherence to treatment. One hundred subjects met all the inclusion criteria (55 female; 45 male). Average age was 33.4 (19.72) years and age of asthma onset 23.54 (18.5) years. The detailed demographic features are presented in Table 1. Cluster dendrogram identified four distinct clusters (Figure 1) and their characteristics are detailed in Table 2. Additional information of cluster characteristics is available as a Supplementary Table. As per GINA treatment protocol, step wise escalation was done at each visit if asthma was uncontrolled or partially controlled. If subjects did not tolerate the dose escalation due to adverse events, which in many cases, were more troublesome than their asthma symptoms (muscle cramps, tremors, palpitations due to LABA, oral candidiasis and loss of taste in-spite of use of a spacer and immediate mouth gargling due to ICS), de-escalation was done and patients were maintained with the highest tolerated dose. None of the patients received biologics due to cost and poor access in a low resource setting. Most of the subjects had achieved their maximum lung function (personal best) after 3 months of treatment. According to Asthma control by GINA, 32% were well controlled, 19% were partially controlled and 49% were uncontrolled.

Cluster 1, the largest cluster ($N = 40$), was characterized by early onset of disease, normal weight, equal gender distribution and achievement of normal lung function after treatment. This cluster had the highest pretreatment baseline FEV1 (68.9% predicted). The maximum post treatment FEV1 achieved (% predicted) was 87.57 and % FEV1 improvement with bronchodilator on first visit was 16.5%. Twenty percent of subjects in cluster 1 were exposed to indoor air pollution and 10% were current smokers. Ninety-two percent of patients had comorbid rhinitis out of which 80% had perennial symptoms of rhinitis.

Cluster 2 ($N = 16$), the smallest cluster, included subjects with higher BMI and longer duration of disease. There were more males (56.3%) in this group. Subjects had the lowest baseline pre-BD FEV1(43.4% predicted). The maximum post treatment FEV1 achieved (% predicted) was 58.12% and % FEV1 improvement with bronchodilator on first visit was 24.2%.

They had the lowest FEV1 after 6 months of treatment. On average, patients achieved their maximum FEV1 at 2 months of treatment.

Subjects in cluster 3 ($N = 20$) had late onset asthma (average age: 51.9 years) and were older (average age: 61.2 years); majority were obese. This cluster had the pretreatment baseline FEV1 as 45.7 (% predicted). The maximum post treatment FEV1 achieved (% predicted) was 61.6 and % FEV1 improvement with bronchodilator on first visit was 14.6%.

Ten percent were exposed to indoor air pollution and 10% were smokers. Subjects had poor baseline FEV1. This cluster had the lowest percentage (65%) of patients with atopy with 85% patients having co-morbid rhinitis.

Subjects in cluster 4 ($N = 24$) were predominantly female (75%), obese, middle-aged, and with late onset of disease. This cluster had pretreatment baseline FEV1 of 63.3 (% predicted). The maximum post treatment FEV1 achieved (% predicted) was 78.1

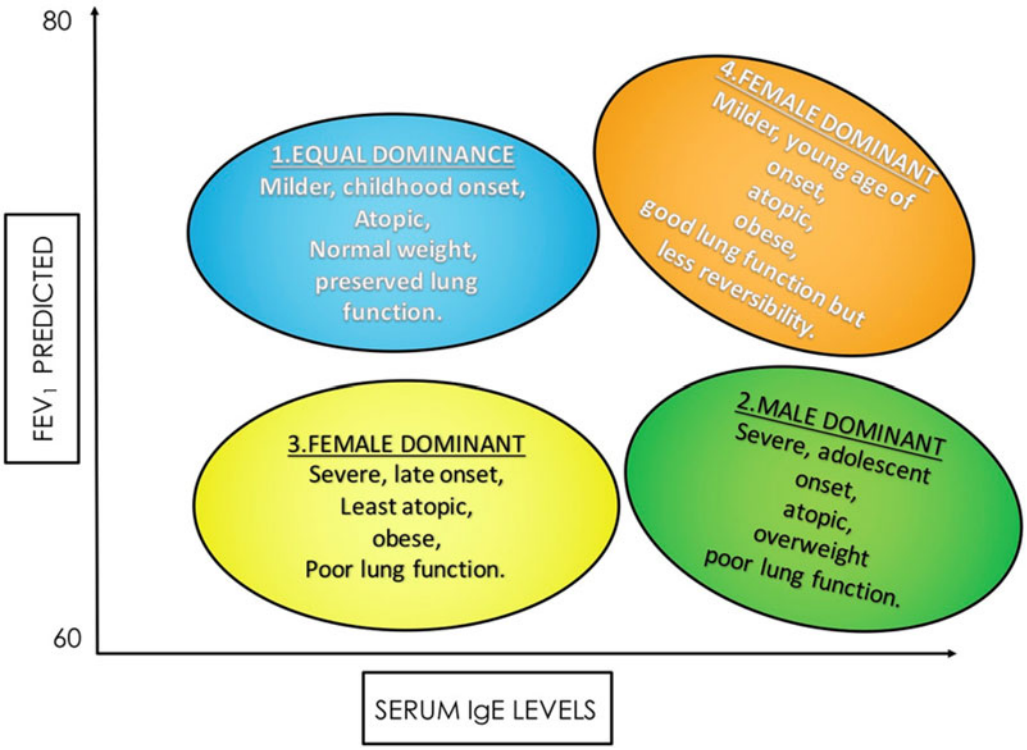


Figure 3. Four distinct asthma clusters plotted according to maximum attained FEV1 and total IgE.

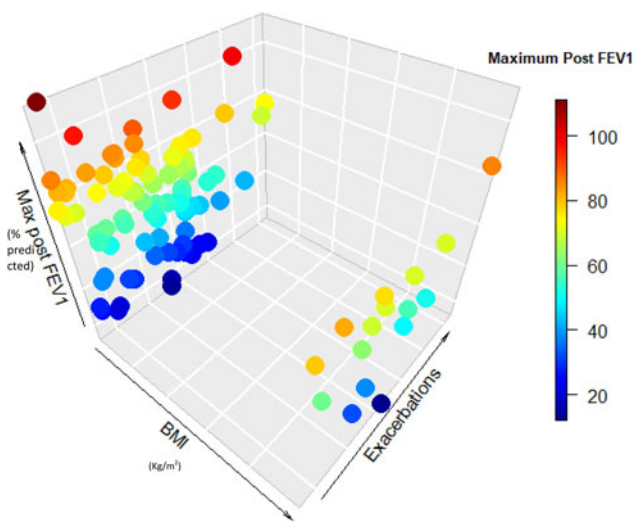


Figure 4. A 3D model using maximum attained lung functions, BMI and exacerbations as variables.

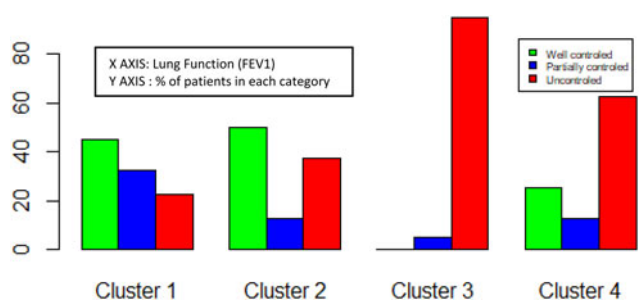


Figure 5. A histogram graph depicting GINA control in the four clusters after 6 months of treatment.

and % FEV1 improvement with bronchodilator on first visit was 12.25%.

This group had the highest percentage of smokers (12.5%). Normal lung functions were achieved after treatment, with maximum FEV1 achieved after 3.2 months of therapy. They also had the maximum number of subjects with at least one moderate or severe asthma exacerbations.

The four clusters are plotted in a 2 D graph (Figure 3) with total serum IgE level on the X-axis and predicted FEV_1 values on the Y-axis. Figure 4 shows a 3 D model, plotted using R version 3.4.3 software, where a sphere represents each of the 100 subjects in the cluster analysis. The color of the sphere indicates the assigned phenotype. The axes are those used in the allocation rule: maximum post FEV_1, BMI and exacerbations. Examination of the model in different planes highlights that the 'obese atopic' group separates out on BMI and highest number of asthma exacerbations, whereas the remaining three clusters are differentiated based on disease severity. Figure 5 shows proportion of subjects with various degrees of asthma control according to GINA in the various clusters. Patients in cluster 3 were largely uncontrolled (95%) and 85% of these subjects were receiving GINA Step 4 or 5 treatment and the remaining 10% did not

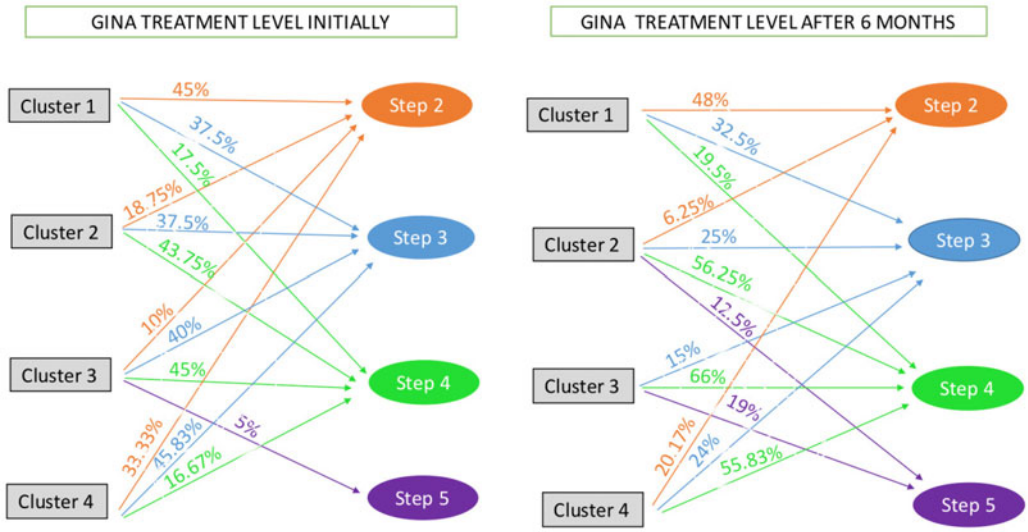


Figure 6. GINA treatment steps at the beginning of the study versus after 6 months.

tolerate dose escalation. The GINA stepwise treatment received by the various clusters at the beginning of the treatment and at the end of 6 months are presented in Figure 6.

Discussion

To our knowledge, this is the first cluster analysis of Indian patients with asthma. In our cohort of 100 well-characterized patients with at least 6 months follow-up and four serial spirometries, we identified four distinct clusters. Cluster 1 with early onset of disease and normal weight, normal lung functions; Cluster 2 with poor lung function, overweight patients and predominantly males; Cluster 3 with females, obese subjects, poor lung function; Cluster 4 with obese and predominantly female with good lung functions. The differences in variables between the four clusters that achieved statistical significance were baseline pretreatment FEV1, Max. post BD FEV1 during 6 months, percentage FEV1 improvement with bronchodilator on first visit, age of onset of disease, duration of disease, BMI, house dust mite sensitivity and percentage of subjects with at least one asthma exacerbation in last 6 months. Clusters 2 and 3 failed to achieve normal lung functions after guideline-based therapy, both characterized by low post-treatment lung function but there was a dichotomy in maintaining asthma control between clusters. Cluster 4 achieved near normal lung function. The worst asthma control was seen in cluster 3 with 95% of subjects being uncontrolled according to GINA guidelines, whereas subjects in cluster 2 with similar poor attainment of maximum FEV1 had far better asthma control (37.5% subjects uncontrolled) than cluster 4 (62.5% subjects uncontrolled) who had attained near normal FEV1. We observed that patients in all the 4 clusters took about 3 months to attain their maximum lung function. Cluster 4 was unusual since they had achieved near-normal lung functions, but also had the highest number of subjects (one in three) with at least one moderate to severe asthma exacerbations in spite of having achieved near normal lung functions. They had the highest BMI among four clusters and the highest total IgE, but it is not clear whether these attributes resulted in the observed greater number of exacerbations in this group. Another interesting observation was that Cluster 3, which was female predominant, had the highest number of patients with non-allergic rhinitis (20%). A study conducted by Gauthier and colleagues emphasized that a later onset of disease in obese patients with less atopy showed poor responsiveness to treatment with corticosteroids (28). For the current study, asthma control was assessed using ACT questionnaire and GINA guidelines. A dichotomy was seen in Cluster 2 where, despite low lung function, 50% of patients reported their asthma to be well controlled. Good correlation between the two assessment tools was observed in clusters 2, 3 and 4. Poor correlation was seen for cluster 1 perhaps because, as previously published, accepted ACT cutoff score for uncontrolled asthma likely overestimates asthma control in children (29).

In our study, two clusters were unable to reach normal lung functions after 6 months of guideline-based therapy, suggesting two possibilities. One, development of fixed airways disease/airway remodeling and the second, low baseline lung function and/or low lung function trajectory (30,31). Both of these groups

(clusters 2 and 3) had low FEV1 in similar range (43.4 and 45.7, respectively) before initiating guideline-based therapy and improved to similar levels (58.1 and 61.6, respectively) after treatment. However, subjects in cluster 2 had earlier onset of asthma and longer duration of the disease (Mean 27.1 years SD) when compared to cluster 3 with later onset and shorter duration (Mean 9.9 years SD). It is possible that fixed airway disease develops earlier in older subjects, though the exact mechanism needs further study. Although subjects in cluster 3 were less atopic compared to cluster 2, both groups had a high proportion of subjects with co-morbid rhinitis and fewer subjects with house dust mite sensitivity, as compared to the groups that attained normal lung functions. Both groups also had similar proportion of subjects with asthma exacerbations and exposure to indoor air pollution.

Another possibility is that these two clusters had low baseline lung function and therefore their maximum achieved FEV1, even with treatment, is much lower than predicted for their age. A recent study by Lange et al. (32) analyzed spirometry from three large cohorts (Framingham offspring cohort, Copenhagen city heart study and the Lovelace smokers cohort) and confirmed that in the general population 62% had FEV1 < 80% predicted at baseline before entering into the study. They observed that at the final follow-up several decades later, the FEV1 was 61% (±15) predicted in all the cohorts combined. On analyzing the life course trajectories among these subjects, it was observed that 12% of the subjects had small lungs (evidenced by low maximal attainment of FEV1 before decline) compared to the rest of the population. To our knowledge, there are no published data on the prevalence of small lungs in Indian population, though Indians have been observed to have lower lung functions than Caucasians. According to the PURE study, mean lung function parameters of Indians are seen to be ∼30% less as compared to healthy, white American or European individuals (33). Earlier studies have also observed that the lung functions in Indians are lower than the Caucasians (34,35). FEV1 in all four clusters in our population improved similarly, between 14.7 and 18.6% after 6 months of treatment compared to baseline. It is possible that these two clusters, constituting 36% of our study population, could have small lungs, which could explain their lower maximum FEV1 attained (58.1% and 61.6% predicted for clusters 2 and 3, respectively).

Published studies of cluster analysis in asthma are summarized in Table 3 (13,36,37,39–52). In a longitudinal 12-year follow-up study of new-onset adult asthma, Ilmarinen et al. (13) identified 5 clusters of which subjects in cluster 2 were less treatment-responsive. These subjects were predominantly smokers, middle aged, nearly half of them were obese, had mostly uncontrolled asthma, had the most exacerbations and hospitalizations, and also had the maximum decline in lung function from baseline. Howrylak et al. (36), in the longitudinal childhood asthma management program study, found five clusters that maintained remarkable consistency over a period of two years. The study did not include adults, or children with severe asthma. They observed one cluster that was poorly treatment-responsive to inhaled budesonide (cluster 5) and one that was partially treatment-responsive (cluster 4). They used only disease-specific variables for their cluster analysis. The poorly treatment-responsive cluster included children with high burden of atopy (atopic dermatitis, allergic rhinitis, asthma), airway obstruction and exacerbations. Fingleton et al. (37) identified five phenotypes, including a distinct asthma-COPD overlap group with features of atopic asthma, marked variability in airflow obstruction, emphysema and chronic bronchitis in current or former smokers. This group had the most severe airflow obstruction but benefitted from ICS treatment with marked bronchodilator reversibility to both inhaled beta-agonist and anti-muscarinic therapy. Another phenotype with adult-onset disease, obesity, systemic inflammation and multiple comorbidities was identified but, in contrast to other published cluster analyses, this group did not have marked female predominance. They showed minimal bronchodilator responsiveness to beta-agonist and anti-muscarinic treatments but marked improvement in SGRQ scores after 12 weeks of ICS treatment. The other two clusters of childhood-onset disease were consistent with our cluster 1, while the fifth cluster phenotype showed adult-onset disease with intermittent airflow obstruction.

Patients with asthma present with different disease severity. Despite varying levels of asthma severity, the treatment goals are similar and focus on reducing impairment and risk. A patient who has severe persistent asthma or a patient who is less responsive to therapy requires more intensive intervention to achieve these goals. An important adverse consequence of longstanding asthma is airway remodeling, which is associated with worse clinical outcomes and poor treatment responsiveness (38). Guidelines do not currently provide guidance on early recognition of patients who are partially or wholly treatment-unresponsive and may represent distinct clinical phenotypes. The first step is to arrive at a globally accepted

Table 3. Summary of previous studies on cluster analysis on asthma.

Study name	Factors considered	Clusters formed	Country; year; sample size; duration of study	Assessment of treatment responsiveness
Cluster Analysis on Longitudinal Data of Patients with Adult-Onset Asthma Ilmarinen et al. (13)	Sex, smoking history, atopy, lung functions, comorbidities, age, treatment responsiveness	5	Finland; 2017; 171; 12 years	Yes
Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medication Howrylak et al. (36)	Pulmonary function, treatment responsiveness, atopy, baseline exacerbation history, prior hospitalizations	5	USA; 2014; 1041; 4 years	Yes
Treatment responsiveness of phenotypes of symptomatic airways obstruction in adults Fingleton et al. (37)	Age of onset atopy, asthma-COPD overlap, BMI, comorbidities.	5	New Zealand; 2015; 389(for cluster analysis) 127 (for follow up), 12 Weeks	Yes
Ten-year follow-up of cluster-based asthma phenotypes in adults. A pooled analysis of three cohorts. Boudier et al. (39)	Asthma symptoms, Allergic status, Pulmonary function	10	ECRHS data, Switzerland, France; 2013; 3320; 10 years	No*
Asthma phenotypes in inner-city children. Zoratti et al. (37)	Age, asthma and rhinitis severity, pulmonary physiology, allergy (sensitization and total serum IgE), and allergic inflammation.	5	USA; 2016; 616; One year	No*
Persistent airflow obstruction in patients with asthma: Characteristics of a distinct clinical phenotype Konstantellou et al. (41)	Age, sex, pulmonary function tests, inflammatory cells in induced sputum, bronchial hyper-responsiveness (BHR, PD15 to methacholine) treatment regimens, atopy.	3	Greece; 2015; 170; 6 months	No*
Classification and implementation of asthma phenotypes in elderly patients. Park et al. (42)	Sex, Acute asthma exacerbation, symptom duration airway obstruction, lung function, smoking, BMI.	4	Korea; 2014; 872; 2 years	No*
Distinct clinical phenotypes of airways disease defined by cluster analysis. Weatherall (43)	Age, sex, pulmonary function tests, nitric oxide measurements, blood tests, chest computed tomography atopy, history of chronic bronchitis and emphysema, eosinophilic airways inflammation, smoking.	5	Wellington Respiratory Survey (Europe); 2009; 175; 12 months	No*
Validated and longitudinally stable asthma phenotypes based on cluster analysis of the ADEPT study. Loza et al. (44)	Lung functions, age of onset, eosinophilic inflammation, gene expression for type 2 asthma.	4	North America & Europe; 2016; ADEPT & U-BIOPRED; 238	No*
Cluster analysis and clinical asthma phenotypes. Haldar et al. (45)	Lung function, smoking, eosinophilic inflammation, age of onset, asthma exacerbations, sex.	4	United Kingdom; 2008; 429	No
Cluster analysis identifies characteristic phenotypes of asthma with accelerated lung function decline. Sakagami et al. (46)	Sex, age of onset, Lung function, atopy, duration, age.	3	Japan; 2014; 86	No
Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Moore et al. (47)	Lung function, Atopy, Age of onset, Oral corticosteroids, comorbidities, Age.	4	North Carolina (USA); 2010; 726	No
Identification and validation of asthma phenotypes in Chinese population using cluster analysis. Wang et al. (48)	SES, Sex, Smoking, Psychological, Factors, First asthma exacerbation, unplanned and emergency visits, hospital admission.	5	China; 2017; 284	No
Severe or life-threatening asthma exacerbation: patient heterogeneity identified by cluster analysis. Sekiya et al. (49)	Age, sex, Severity of symptoms at baseline, frequency of treatment with oral corticosteroids and short-acting beta-agonists, frequency of asthma hospitalizations in the past year. Evidence of chronic hyperplastic rhinosinusitis/nasal polyposis, duration of disease, atopy, history of allergic rhinitis and furred pet hypersensitivity, concomitant chronic obstructive pulmonary disease	5	Japan; 2016; 175	No
Cluster analysis of sputum cytokine-high profiles reveals diversity in T(h)2-high asthma patients Seys et al. (50)	T (h) 2-sputum cytokine profile. sputum eosinophil and neutrophil counts lung function parameters at baseline and 2 years later	5	Belgium; 2016; 205	No
Phenotypes of asthma in low-income children and adolescents: cluster analysis. Cabral et al. (51)	Pulmonary function, eosinophil inflammation, exacerbations, age at asthma onset, atopy.	3	Brazil; 2017; 206	No
Quantitative computed tomography-derived clusters: redefining airway remodeling in asthmatic patients. Gupta et al. (52)	Quantitative CT analysis Air trapping (RB1 WV and LV values)	3	UK; 2013; 65 Cases; 30 cohorts	No

Notes. *Data for follow up collected but not analyzed for treatment responsiveness.

definition that will then increase the likelihood of clinical trials focused on evaluating treatment options for patients with treatment-unresponsive asthma. As we observed in our study population, the different clusters varied significantly in their clinical presentation, and treatment response. With recent advances in available treatment options in asthma, it has become even more important to recognize this heterogeneity in treatment- responsiveness. Tailored treatment protocols that address therapeutic challenges in these patients are urgently needed.

Strengths and limitations of the study

There are many strengths of our study. We included patients with well-characterized asthma with objective confirmation of asthma diagnosis and guidelines-based treatment. Adherence to prescribed therapy was confirmed. Cross-sectional and longitudinal data were included. Information on exposure to indoor air pollution, which is very relevant to this population, was included. There are also some limitations to our study. The data were collected retrospectively except for the assessment of current asthma control (GINA) and ACT. In many patients, the control of asthma was not achieved. In these patients, the maximal lung function may well be higher than that achieved during the study.

Some false negative diagnosis of asthma is possible, as the methacholine challenge was not performed. Additional analysis to inform endo-genotypes of low and high maximal attainment of lung functions in these asthmatics could not be performed.

Conclusion

To our knowledge, this is the first cluster analysis of Indian patients with asthma across varying ages and disease severity. The study identified distinct phenotypes of asthma associated with low maximal attainment of lung functions despite guidelines-based therapy and underscores an urgent need for further studies in this subgroup. Similar clustering approach can be used to identify longitudinally consistent and clinically relevant asthma phenotypes, with implications for targeted therapeutic strategies and clinical trials designing.

Declaration of interest

Dr. Sandhya K (Division of Pulmonary & Critical Care Medicine, University of Rochester Medical Center, Rochester, United States of America) has participated in clinical trials of biologicals with GSK and Sanofi.

Notes on contributor

S.B., A.D.H., B.S.J. and P.A.M. conceptualized, designed the study and collected the data. A.S.P., S.R., S.K. and P.A.M. were involved in data analysis. All authors contributed in the writing of the manuscript and reviewed the content critically.

ORCID

Smriti Bhargava http://orcid.org/0000-0001-6055-4580

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Supplementary Tables:

Comparison of demographic and clinical variables of the four distinct asthma clusters- Non significant variables

Variable	Cluster 1	Cluster 2	Cluster 3	Cluster 4	p value
Serum IgE levels (IU/ml)	472.7	591.2	325.0	681.0	0.0904
Indoor air pollution (%)	20.0	6.2	10.0	8.3	0.09788
Gender(%) of females	47.5	43.7	55.0	75.0	0.1324
Absolute Eosinophil count (Cells/microliter)	417.5	336.4	283.6	340.4	0.2257
Time taken to reach maximum lung function (Months)	3.0	2.0	3.0	3.2	0.2753
WBC counts (Cells/mm^3)	8195.8	8354.3	7757.1	8246.7	0.6196
Non-Smoker (%)	90.0	93.7	90.0	87.5	0.9368