

Distinct Asthma Phenotypes Among Older Adults with Asthma



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What is already known about this topic? Older adults with asthma have high morbidity and mortality rates. There may be distinct phenotypes among older adults, but currently this is unknown.

What does this article add to our knowledge? A cluster analysis of 180 older adults with persistent asthma identified 4 distinct phenotypes. Subjects in these phenotypes differed by lung function, duration of asthma, obesity, comorbidities, asthma control, and ethnicity.

How does this study impact current management guidelines? Asthma is not a uniform condition, but rather a heterogeneous disease. Older adults with asthma have distinct phenotypes, and determination of a therapeutic difference between clusters may help to maximize outcomes.

BACKGROUND: Older adults have high rates of asthma morbidity and mortality. Asthma is now recognized as a heterogeneous disease, yet the distinct phenotypes among older adults are unknown.

OBJECTIVE: The objective of this study was to identify asthma phenotypes in a diverse population of elderly patients with asthma.

METHODS: Using cluster analysis, 180 older adults with persistent asthma were analyzed. Subjects completed detailed questionnaires, skin prick testing, and spirometry with reversibility. Twenty-four core variables were analyzed.

RESULTS: Four groups were identified. Subjects in cluster 1 ($n = 69$) typically had asthma diagnosed after the age of 40 and the shortest duration of asthma. Cluster 2 ($n = 40$) had the mildest asthma defined by spirometry, Asthma Control test (ACT), and Asthma Quality of Life Questionnaire (AQLQ). They also had the lowest body mass index (BMI), lowest

depression score, and least number of comorbidities. Cluster 3 ($n = 46$) had the longest duration of asthma (56 years) and the highest atopic skin test sensitization (74%). Cluster 4 ($n = 25$) had the most severe asthma, with extremely low FEV₁% predicted (37.8%), lowest ACT, and lowest AQLQ scores. They were more likely to be black and had the highest comorbidities. Using BMI, posttreatment FEV₁% predicted, and duration of asthma, 95.6% of subjects were able to be correctly classified. **CONCLUSIONS:** In older adults with asthma, distinct phenotypes vary on key features that are more pronounced among the elderly, including comorbidities, fixed airway obstruction, and duration of asthma ≥ 40 years. Further work is required to determine the clinical and therapeutic implications for different asthma phenotypes in older adults. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:244-9)

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Asthma is a major public health problem that affects more than 3 million people over the age of 65 in the United States.¹ Often thought to be a disorder of young people, older patients with asthma have been repeatedly overlooked or excluded from many trials.² In fact, the prevalence of asthma among older adults is greater than 10%,³ similar to other age groups. Age is a significant predictor of morbidity and mortality in asthmatics including in-hospital mortality during exacerbations.^{4,5} Older asthmatic patients account for more than 1 million hospital days and more than 50% of all asthma fatalities annually.⁶ In addition, a recent study demonstrated a higher number of emergency department visits, hospitalizations, and near fatal events in patients above the age of 55 compared with younger adults.⁷ Despite the tremendous burden of morbidity and mortality, asthma in the elderly has been inadequately studied and treated.⁸

Abbreviations used

ACT- Asthma Control Test
AQLQ- Asthma Quality of Life Questionnaire
ATS- American Thoracic Society
BMI- Body mass index
CDC- Centers for Disease Control and Prevention
COPD- Chronic obstructive pulmonary disease
FAO- Fixed airway obstruction
FVC- Forced vital capacity
NIH- National Institutes of Health

Although previously thought to be a uniform condition, asthma is a heterogeneous multidimensional disease with substantial variability in demographic and immunological profiles. Previous literature has noted limitations in the current classification approach based on the National Asthma Education and Prevention Program, and the Global Initiative for Asthma guidelines as not being reflective of the true heterogeneity of the disease.⁹⁻¹¹ Identification of distinct asthma phenotypes is important as it may improve our understanding of the disease pathogenesis and facilitate improved targeted therapies.^{12,13} Previous studies have attempted to identify asthma phenotypes with somewhat varied results, likely due to different patient populations and variables assessed.¹³⁻¹⁵

To date, only one previous study has specifically studied the heterogeneity of phenotypic expression of asthma in elderly patients, and this was performed in a Korean population, the majority of whom were smokers.¹⁶ Such research is crucial as there may be important differences in both clinical presentation and management of asthma between young and old patients, and between those with different phenotypes. The primary objective of this study was to identify distinct asthma phenotypes from a diverse population of elderly patients with asthma.

METHODS

Study population

Participants included in this study were part of an ongoing blinded, randomized controlled trial of asthma self-management in older adults. To be included in the study, participants had to be 55 years or older, with persistent asthma. Although various authors have used differing age limits (ie, 55, 60, 65, and 70 years), a cutoff of 55 years was chosen as many datasets from the Centers for Disease Control and Prevention (CDC), as well as other recent trials, have previously used the same cutoff when studying asthma in older adults.^{7,17-21} Persistent asthma was defined as the need for a controller medication on a daily basis or the use of albuterol on at least 3 days of the week. Exclusion criteria included any other pulmonary disease (including chronic obstructive pulmonary disease [COPD]), current smoking, or greater than a 20-pack year smoking history as this level has been associated with COPD.²² Subjects were recruited from 2 academic centers from November 2013 through April 2016. One of the institutions was located in downtown Detroit, Mich, whereas the other was located in Ann Arbor, Mich, thus providing a diverse socioeconomic population. Institutional review board approval was obtained, and each participant provided written informed consent.

Study participants were assessed through the completion of a detailed questionnaire related to asthma and general health. Patient demographic data were collected, including age, sex, and race. A value for comorbidities was based on the total sum of self-reported heart disease, high blood pressure, stroke, or cancer. Given our previous research indicating the

importance of depression in older adults with asthma,²³ this self-reported comorbidity was coded separately. The presence of allergic rhinitis was assessed through self-reported seasonal allergies or hay fever, similar to the questioning method utilized by the CDC in the third National Health and Nutrition Examination Survey (NHANES III).²⁴ Education level was self-reported and divided into 5 categories according to their highest education level (1 = below high school, 2 = high school, 3 = 2-year college, 4 = 4-year college, and 5 = postgraduate).

National Institutes of Health (NIH) asthma severity was graded from 1 to 6 (6 = most severe) based on medication use per the NIH guidelines (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).¹⁰ FEV₁, forced vital capacity (FVC), and FEV₁/FVC (both pre- and postbronchodilator treatment) were measured via spirometry performed per American Thoracic Society (ATS) guidelines. Reversibility testing using nebulized albuterol and ipratropium was also completed according to ATS guidelines. Fixed airway obstruction (FAO) was defined as the FEV₁/FVC postbronchodilator value of less than 70%.^{25,26} Atopy was assessed by skin prick testing using the ComforTen device (HollisterStier LLC, Spokane, Wash) and a panel of 8 allergens. If any of the tests were positive (≥ 3 mm larger than the negative control), the patient was considered to be atopic. Based on the NIH core asthma outcomes, asthma exacerbations were a binary outcome defined the requirement for an asthma hospitalization, emergency department presentation, or urgent care visits over the past 1 year.²⁷ Oral corticosteroid use was self-reported and defined as requiring a course of oral corticosteroids for asthma in the past 12 months. Subjects also completed an Asthma Control Test (ACT) and a mini Asthma Quality of Life Questionnaire (AQLQ) at baseline.

The entire dataset contained a number of variables that were reduced for optimal performance in a cluster analysis. All variables with missing data were also excluded leaving a total of 24 variables. The final list of variables included (1) sex, (2) age, (3) age of diagnosis ≥ 40 years, (4) duration of asthma, (5) education level, (6) race, (7) number of comorbidities, (8) number of cigarette pack years, (9) body mass index (BMI), (10) depression, (11) asthma severity score, (12) asthma exacerbations, (13) atopic sensitization, (14) allergic rhinitis, (15) FAO, (16) oral corticosteroid use, (17) ACT score, (18) AQLQ score, (19) FEV₁ pretreatment % predicted, (20) FVC pretreatment % predicted, (21) FEV₁/FVC ratio pretreatment % predicted, (22) FEV₁ posttreatment % predicted, (23) FVC posttreatment % predicted, and (24) FEV₁/FVC ratio posttreatment % predicted. Variables were either dichotomized or treated as continuous as appropriate.

Statistical analysis

Ward's method,²⁸ an agglomerative clustering algorithm, was utilized and pseudo *F* statistics were used to determine the optimal number of clusters as previously performed in the Severe Asthma Research Program (SARP) study.¹⁴ ANOVA was used to compare the differences among all 4 clusters and 24 variables, and a χ^2 test was used for dichotomized variables. Decision tree analysis²⁹ was performed on all 24 variables to predict the cluster for each subject, and misclassification rates were calculated. The pruning criterion for the decision tree analysis was "minimal cost-complexity pruning." Cross-validation was performed to determine the prediction performance. Clustering analysis was analyzed in SAS version 9.3 (SAS Institute Inc., Cary, NC), and tree analysis was performed in R version 3.0.1 with R package "tree."³⁰

RESULTS

There were a total of 180 patients evaluated of 189 recruited initially (9 patients were omitted because of missing data). Of

TABLE I. Cluster analysis of all participants

	Total cohort	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P value
Number of subjects	180	69	40	46	25	
Male gender, n (%)	47 (26.1)	20 (29.0)	6 (15.0)	14 (30.4)	7 (28.0)	.34
Age of enrollment, y	65.9 (7.4)	65.7 (6.7)	64.6 (6.3)	67.1 (7.5)	66.7 (10.1)	.44
Age diagnosis >40, n (%)	84 (46.7)	52 (75.4)	19 (47.5)	3 (6.5)	10 (40.0)	<.0001*
Asthma duration, y	31.7 (20.9)	18.1 (10.3)	22.5 (13.0)	56.3 (11.1)	38.4 (23.7)	<.0001*
Education level†	3.6 (1.2)	3.5 (1.2)	4.0 (1.1)	3.7 (1.2)	2.9 (1.2)	.004*
Race, n (%)						
White	116 (64.4)	50 (72.5)	34 (85.0)	26 (56.5)	6 (24.0)	<.0001*
Black	58 (32.2)	18 (26.1)	4 (10.0)	18 (39.1)	18 (72.0)	
Other	6 (3.3)	1 (1.5)	2 (5.0)	2 (4.3)	1 (4.0)	
Comorbidities‡	0.9 (0.7)	0.8 (0.7)	0.7 (0.7)	0.9 (0.8)	1.2 (0.6)	.009*
Tobacco pack years	2.5 (5.7)	2.3 (5.6)	2.1 (4.5)	2.9 (6.2)	3.2 (6.8)	.81
Body mass index (BMI)	31.2 (7.4)	32.0 (6.8)	28.3 (5.1)	30.5 (7.3)	35.0 (10.1)	.003*
Depression, n (%)	42 (23.3)	19 (27.5)	6 (15.0)	10 (21.7)	7 (28.0)	.46
NIH severity score§	3.5 (1.2)	3.7 (1.2)	3.4 (1.1)	3.7 (1.3)	3.2 (1.4)	.25
Asthma exacerbations, (%)	77 (42.8)	31 (44.9)	15 (37.5)	19 (41.3)	12 (48.0)	.82
Hospitalization	20 (11.2)	7 (10.1)	2 (5.0)	5 (11.1)	6 (24.0)	.12
Emergency visit	31 (17.2)	13 (18.8)	5 (12.5)	8 (17.4)	5 (20.0)	.82
Unscheduled visit	59 (33.2)	26 (38.2)	12 (30.0)	13 (28.9)	8 (32.0)	.72
Oral corticosteroid use in past year, n (%)	86 (47.8)	37 (53.6)	16 (40.0)	21 (45.7)	12 (48.0)	.57
Atopic sensitization, n (%)	107 (59.4)	31 (44.9)	25 (62.5)	34 (73.9)	17 (68.0)	.01*
Allergic rhinitis, n (%)	132 (73.3)	42 (60.9)	32 (80.0)	40 (87.0)	18 (72.0)	.01*
FAO, n (%)	55 (30.6)	16 (23.2)	0 (0.0)	21 (45.7)	18 (72.0)	<.0001*
FEV ₁ /FVC ratio, pretreatment %	93.2 (13.8)	94.8 (10.9)	101.8 (7.3)	89.9 (14.1)	81.1 (18.0)	<.0001*
FEV ₁ /FVC ratio, posttreatment %	95.5 (15.5)	98.9 (9.3)	105.3 (6.1)	90.3 (18.5)	80.4 (18.9)	<.0001*
FEV ₁ pretreatment % predicted	70.1 (20.7)	67.5 (10.7)	95.3 (9.9)	69.8 (16.2)	37.8 (8.4)	<.0001*
FEV ₁ posttreatment % predicted	75.4 (19.3)	73.4 (9.8)	97.8 (9.2)	76.4 (13.9)	43.0 (8.0)	<.0001*
FVC pretreatment % predicted	74.4 (17.7)	71.0 (8.3)	93.1 (7.8)	78.0 (17.0)	47.4 (9.2)	<.0001*
FVC posttreatment % predicted	77.8 (15.7)	74.3 (9.3)	92.8 (8.3)	82.5 (13.2)	54.8 (12.5)	<.0001*
Asthma control test	17.5 (4.6)	17.2 (4.7)	19.9 (3.8)	17.5 (4.7)	14.7 (3.6)	<.0001*
Asthma quality of life	5.1 (1.2)	5.1 (1.2)	5.6 (0.9)	5.1 (1.2)	4.3 (1.1)	.0004*

FAO, Fixed airway obstruction; FVC, forced vital capacity; NIH, National Institutes of Health.

Data presented as mean $\pm$ SD unless otherwise noted.

*P value < .05.

†Education: highest education level with 1 = below high school, 2 = high school, 3 = 2-y college, 4 = 4-y college, 5 = postgraduate.

‡Comorbidities based on the counts of comorbidities of heart disease, high blood pressure, stroke, or cancer.

§NIH severity score on the scale of 1 to 6, with 6 = the most severe.

||FAO defined by postbronchodilator FEV₁/FVC < 70%.

these, 26.1% were males, 32.2% were black, and the mean age was 65.9 ± 7.4 years. The mean duration of asthma in study participants was 31.7 ± 20.9 years. A total of 46.7% of the patients were diagnosed with asthma after the age of 40. Based on the pseudo *F* statistics obtained from cluster analysis, 4 clusters were identified. The clinical characteristics defining each cluster are provided in detail in Table I.

Cluster 1

A total of 38.3% (*n* = 69) of the study participants were included in cluster 1. The majority of subjects (75.4%) in this cluster were diagnosed with asthma at a later age (>40 years) and thus had a shorter duration of asthma (18.1 ± 10.3 years). Patients in this cluster were noted to have the lowest rates of allergic rhinitis (60.9%) and atopic sensitization (45%) among any cluster. A total of 26.1% of the study participants in this cluster were African American. After a bronchodilator challenge, 23.2% of the patients in this cluster had inadequate reversibility, and were classified as FAO. The pretreatment FEV₁% predicted was

67.5% predicted, whereas the posttreatment FEV₁% predicted improved only to 73.4%.

Cluster 2

The second cluster included 40 patients. This cluster included subjects with mildest asthma defined by FEV₁ pretreatment 95.3% predicted, and the posttreatment FEV₁% predicted was similarly high at 97.8%. None of the patients in this cluster were found to have FAO after a bronchodilator challenge. Moreover, this cluster included the healthiest patients with the lowest burden of comorbidities (score of 0.7 ± 0.7 , *P* < .01), highest ACT score (19.9 ± 3.8 , *P* < .01), and highest AQLQ score (5.6 ± 0.9 , *P* < .01). Approximately half of the subjects in this cluster were above the age of 40 when diagnosed with asthma, and the mean duration of asthma was 22.5 years.

Cluster 3

This cluster consisted of 46 participants, or 25.6% of the study population. These subjects had a relatively younger age of

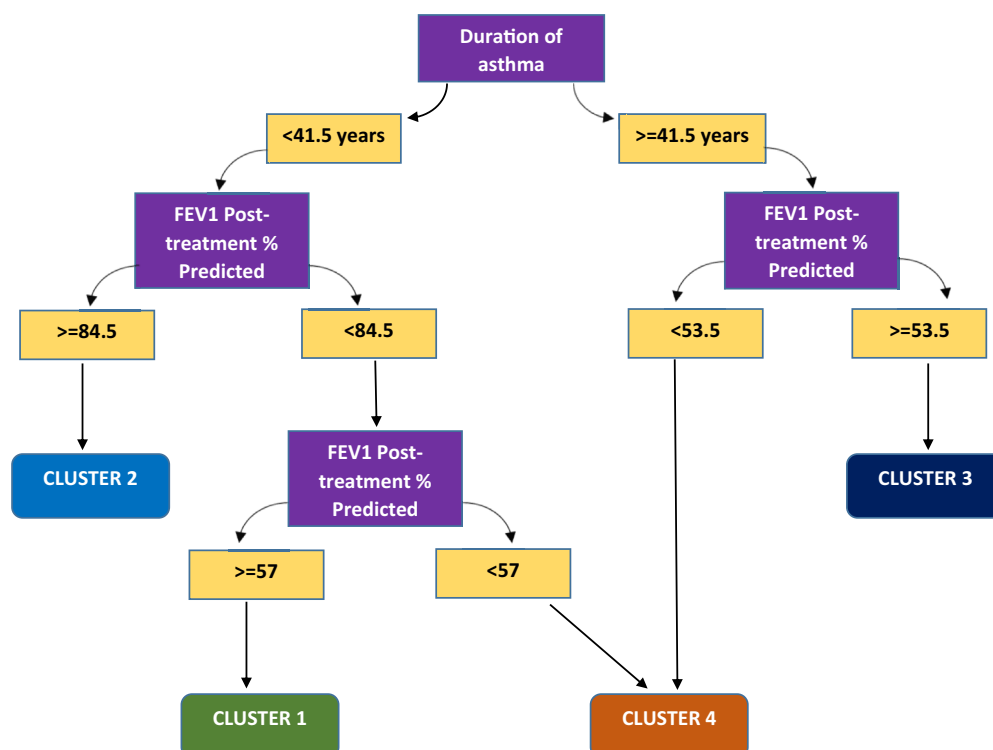


FIGURE 1. Decision tree analysis using 2 factors (duration of asthma and FEV₁ posttreatment % predicted).

asthma onset (only 3 patients in this cluster [6.5%] had asthma onset at greater than 40 years of age). The mean duration of asthma was longer than other clusters (56.3 ± 11.1 years) and included a higher proportion of African Americans (39.1%). Both allergic rhinitis and atopic sensitization were highest in this cluster, with 73.9% of subjects testing positive to at least one allergen. The pretreatment FEV₁ was 69.8%, whereas the post-treatment FEV₁ % predicted showed an increase to 76.4%, and 45.7% of subjects met spirometric criteria for FAO.

Cluster 4

The fourth cluster included 25 subjects with most severe asthma. The pretreatment FEV₁ was extremely low at 37.8% predicted, whereas the posttreatment FEV₁ % predicted only increased to 43%. A total of 72% of the subjects in this cluster had a positive FAO status. The subjects also had the lowest ACT (14.7 , $P < .01$) and AQLQ scores (4.3 ± 1.1 , $P < .01$). A total of 40% of the patients were >40 years of age when diagnosed with asthma. The mean duration of asthma was 38.4 ± 23.7 years. A large proportion of the study participants were African American (72%) and had the highest burden of comorbidities (1.2 ± 0.6). Asthma hospitalizations and emergency department visits were highest in cluster 4, though this did not reach statistical significance.

Decision tree analysis

After offering all 24 variables in the decision tree analysis, 3 variables were selected by the recursive algorithm for classification trees for optimization at each step. The 3 variables identified were duration of asthma, FEV₁ posttreatment % predicted, and FVC pretreatment % predicted, and these variables were used in the construction of the decision tree with a misclassification rate of

3.8%. For ease of utilizing the tree in clinical practice, a final decision tree was constructed with the elimination of FVC pretreatment % predicted as a variable. Using FEV₁ posttreatment % predicted and duration of asthma, 91.7% of subjects were correctly placed into the appropriate cluster (Figure 1). Figure 2 shows the misclassification rate for each cluster. Cross-validation was performed using all 24 variables 100 times and showed a mean error rate of 11.8%.

BMI is commonly assessed in clinical practice, and obesity is pronounced among the elderly.³¹ With the addition of BMI as a variable in the decision tree (along with FEV₁ posttreatment % predicted and duration of asthma), 95.6% of the subjects were correctly classified. This decision tree had a misclassification rate lower than the previously discussed 2-variable decision tree (Figure E1 and E2, available in this article's Online Repository at www.jaci-inpractice.org). Thus, adding BMI to the decision tree not only allows for continued ease of applicability in the clinical setting but also more accurate classification of subjects into their respective clusters.

DISCUSSION

Asthma is a heterogeneous disease with significant variability in disease expression, severity, and response to therapeutic measures. The current NIH classification of asthma from mild to severe, intermittent to persistent, assumes that patients within these categories share similar clinical characteristics and can be managed uniformly. This traditional scheme ignores the variability in clinical characteristics and subtypes within categories. There are especially sparse data on the phenotypic profiles of asthma in elderly patients. This study evaluated the heterogeneity of asthma by dividing older adults with asthma into clusters, each with specific clinical profiles.

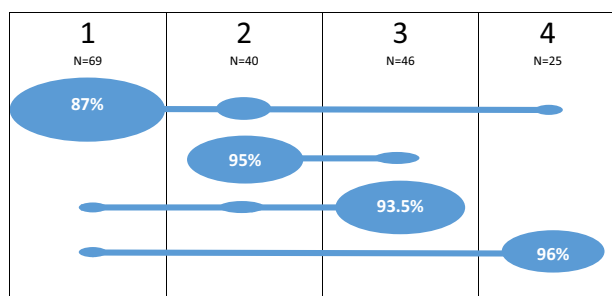


FIGURE 2. Decision tree misclassification rate. Individual figure size is proportional to frequency of a specific cluster. The percent of subjects correctly assigned is indicated numerically within the cluster, whereas the tail region indicates where the incorrectly assigned subjects were placed.

Among all the variables studied, pulmonary function was one of the most important differentiating factors between clusters. As shown in Table 1, both pre- and postbronchodilator values varied widely between the cohorts, from normal (cluster 2) to severely impaired, with a pretreatment FEV₁% predicted of 38% (cluster 4). The importance of spirometric function as a differentiating factor is similar to cluster analyses of younger populations, including those with severe asthma¹⁴ and in children.³² Therefore, although while some authors have recommended placing less emphasis on spirometric findings when determining therapy and severity,^{33,34} this study indicates that in older adults, consideration of lung function is an important factor.

Although spirometric findings have been noted to be an important differentiating feature for other populations, FAO has not. However, in this population of older adults, the rates of FAO varied greatly between 0% and 72%. In general, older adults are more likely to have FAO compared with younger age groups.³⁵ In this study, the FAO rates were highest among those with more severe asthma as defined by a greater rate of asthma exacerbations, lower ACT scores, and lower AQLQ scores. It is possible that subjects in this cluster will exhibit a differential response to medications, and further research is needed. Also of note, older subjects with FAO and concurrent atopy may have the Asthma-COPD overlap syndrome,³⁶ and this should be explored in future studies.

Another feature unique to older adults with asthma is duration of asthma—simply due to enhanced longevity allowing for the examination of such an outcome. As shown in Figure 1, a duration of asthma of approximately 40 years or longer was a key differentiating factor between asthma clusters. However, a longer duration of asthma was not necessarily associated with more severe asthma. For example, cluster 3 had the longest duration of asthma, yet fairly normal spirometric results, ACT, and AQLQ scores.

Late-onset asthma was another significant finding in this study. Although late-onset asthma is typically considered more severe than early-onset asthma, our study shows that even patients with late-onset disease can have normal spirometric values and high levels of quality of life.^{37,38} In cluster 2, 47.5% of the patients had late-onset disease, yet this cluster was also found to have the highest spirometric values, ACT scores, and AQLQ scores. These findings are an indication of how cluster analysis can change our understanding of a disease process.

Other factors that are more pronounced in older adults were also noted to play important differentiating roles in our cluster analysis. The number of serious comorbidities is typically higher among the elderly as compared with younger age groups. Interestingly, the most severe cluster in this study also had the greatest number of comorbidities. Although obesity is a significant problem for all age groups, rates are rising among the elderly at a rate greater than nearly every other age group.³¹ In this study, the most severe cluster had the highest BMI at 35, and BMI served as an important factor to optimize the decision tree analysis (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Finally, depression has been linked to asthma, and our previous work has shown a significant link between depression and poor outcomes among older adults.²³ As with obesity and total comorbidities, depression was highest in cluster 4. Taken together, this study provides preliminary evidence that these factors may aggregate in more severe asthma, and serve as important targets to improve outcomes.

There are a number of differences in comparing the results of this cluster analysis with the previously conducted cluster analyses. The SARP study was one of the hallmark studies in the cluster analysis of asthma phenotypes and found that age, gender, BMI, duration of asthma, lung function, medication use, and atopic status were the key differentiating features.¹⁴ Many key differentiating variables in our study overlap with those of the SARP study. The majority of the baseline populations were women in both studies, but our analysis did not demonstrate that gender was a key differentiating feature among older adults unlike the SARP study. In contrast to the findings from SARP, race was found to be a significant factor in our study. Asthma severity based on medication use was not significant, but it is worth noting that this measure has not been validated. Many of these differences may be attributable to the fact that our study comprised exclusively older adults, whereas SARP included participants aged 12 and above, making it less applicable and specific for the older adult population.¹⁴ In addition, important features of asthma in the elderly, such as obesity, educational level, and depression, were not considered in the SARP study further reiterating its lack of applicability to older adults.

There are several limitations in this study. Because it is an observational cross-sectional analysis, explanations or causal associations for the collected data cannot be deduced. For example, cluster 4 was noted to have the lowest ACT and AQLQ scores, yet the NIH severity score for this group was no different than other clusters. It is possible that individuals in this cluster were therefore undertreated, and following such patients may answer such questions. Similarly, although BMI was highest in the most severe cluster, this could have been a consequence of higher cumulative use of systemic steroids or decreased physical activity. In regard to the patient population, this study included a greater percentage of African Americans when compared with the general US population.³⁹ Subjects with other lung conditions such as COPD were excluded, and biomarkers such as serum eosinophil count and exhaled nitric oxide were not evaluated. Furthermore, although data regarding allergic rhinitis were collected, this study did not account for various rhinitis subtypes. The inclusion of such criteria may have further altered the cluster differentiation. Genomic analyses were not performed, and such information may

reveal important endotypes present among older adults with asthma.

The ultimate purpose of cluster analysis would be to not only identify differences in older adults with asthma, but to also have a specific approach to treatment for each of the phenotypes. As an example, given the high rate of FAO and low ACT scores in cluster 4, we speculate that one approach may be early aggressive multidrug treatment including inhaled anticholinergic medications.⁴⁰ Although this cluster analysis has expanded our current knowledge of a disease state in novel ways, further investigation is required to draw any conclusive therapeutic implications for each of these identified phenotypes.

In conclusion, we defined 4 distinct clusters of elderly patients with asthma, each with distinct clinical phenotypes. Key features that are more pronounced in older adults with asthma were found to be important differentiating factors for each cluster. These include a duration of asthma of 40 years, obesity, and number of comorbidities. In addition, features seen in other age groups also played a prominent role in cluster differentiation, such as lung function, race, and asthma control. To individualize care and maximize outcomes in the future, it will be important to determine therapeutic differences between these clusters.

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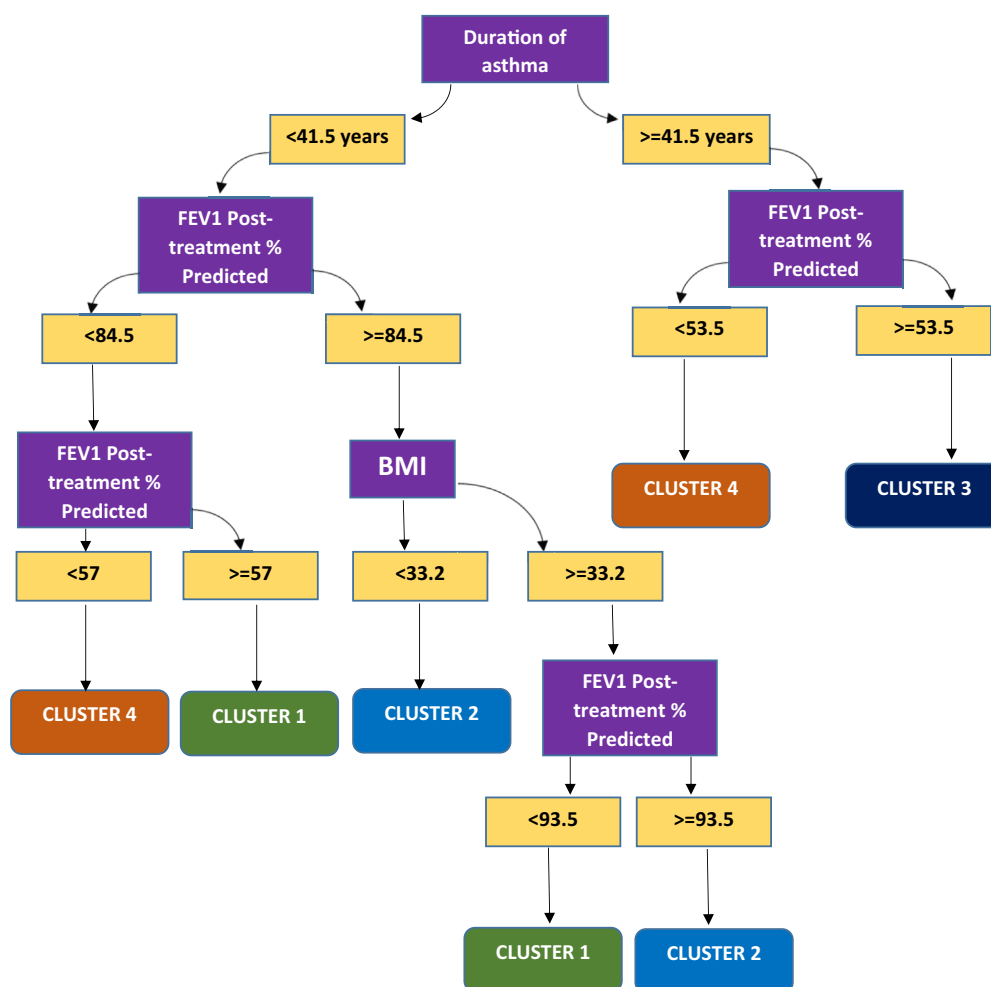


FIGURE E1. Decision tree analysis using 3 factors (duration of asthma, FEV₁ posttreatment % predicted, and BMI). *BMI*, Body mass index.

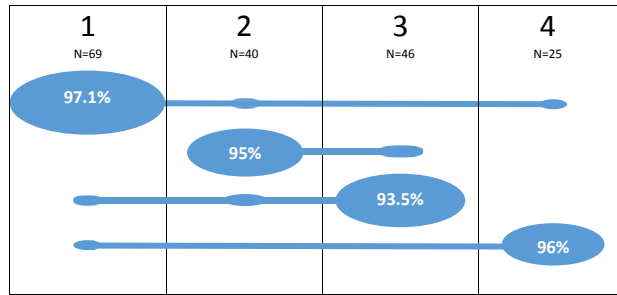


FIGURE E2. Decision tree misclassification rate. Individual figure size is proportional to frequency of a specific cluster. The percent of subjects correctly assigned is indicated numerically within the cluster, whereas the tail region indicates where the incorrectly assigned subjects were placed.

TABLE E1. Asthma severity scoring based on medication use

Severity score	Asthma medication
1	SABA
2	Low-dose ICS or cromolyn or montelukast
3	Medium-dose ICS
4	Medium-dose ICS and LABA or montelukast
5	High-dose ICS and LABA or montelukast
6	High-dose ICS and LABA or montelukast and oral systemic glucocorticoids

ICS, Inhaled corticosteroid; *LABA*, long-acting β -agonist; *SABA*, short-acting β -agonist.

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