Original Article

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 FEV_1% predicted (37.8%), lowest ACT, and lowest AQLQ scores. They were more likely to be black and had the highest comorbidities. Using BMI, posttreatment FEV_1% 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 2017;■:■-■)

Key words: *Asthma; Older adults; Phenotypes; Cluster analysis; Fixed airway obstruction; Atopic sensitization; Asthma classification*

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]

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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] FEV_1, forced vital capacity (FVC), and FEV_1/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 FEV_1/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 (≥3mm 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) FEV_1 pretreatment % predicted, (20) FVC pretreatment % predicted, (21) FEV_1/FVC ratio pretreatment % predicted, (22) FEV_1 posttreatment % predicted, (23) FVC posttreatment % predicted, and (24) FEV_1/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 analysis[29] 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