Original Article

Cluster Analysis on Longitudinal Data of Patients With Adult-Onset Asthma

Pinja Ilmarinen, PhD[a], Leena E. Tuomisto, MD, PhD[a], Onni Niemelä, MD, PhD[b,c], Minna Tommola, MD[a], Jussi Haanpää, MSc[d], and Hannu Kankaanranta, MD, PhD[a,e] *Seinäjoki and Tampere, Finland*

What is already known about this topic? Many phenotypes of asthma have been identified in previous cluster analyses, mostly on the basis of cross-sectional data with limited inclusion of patients. Some studies have provided short-term 1- to 3-year prognosis for the phenotypes.

What does this article add to our knowledge? This is the first study that reports long-term 12-year prognosis for clusters of adult-onset asthma starting from diagnosis. We report different disease prognoses for smoking, obesity-related, female, atopic, and nonrhinitic asthma.

How does this study impact current management guidelines? Information on long-term outcome of asthma can be used to inform and motivate patients. We show the poorest outcome and the most unmet needs in the therapy of smoking and obesity-related asthma, suggesting need for special guidance.

BACKGROUND: Previous cluster analyses on asthma are based on cross-sectional data.
OBJECTIVE: To identify phenotypes of adult-onset asthma by using data from baseline (diagnostic) and 12-year follow-up visits.
METHODS: The Seinäjoki Adult Asthma Study is a 12-year follow-up study of patients with new-onset adult asthma. K-means cluster analysis was performed by using variables from baseline and follow-up visits on 171 patients to identify phenotypes.
RESULTS: Five clusters were identified. Patients in cluster 1 (n = 38) were predominantly nonatopic males with moderate smoking history at baseline. At follow-up, 40% of these patients had developed persistent obstruction but the number of patients with uncontrolled asthma (5%) and rhinitis (10%) was the lowest. Cluster 2 (n = 19) was characterized by older men with heavy smoking history, poor lung function, and persistent obstruction at baseline. At follow-up, these patients were mostly uncontrolled (84%) despite daily use of inhaled corticosteroid (ICS) with add-on therapy. Cluster 3 (n = 50) consisted mostly of nonsmoking females with good lung function at diagnosis/follow-up and well-controlled/partially controlled asthma at follow-up. Cluster 4 (n = 25) had obese and symptomatic patients at baseline/follow-up. At follow-up, these patients had several comorbidities (40% psychiatric disease) and were treated daily with ICS and add-on therapy. Patients in cluster 5 (n = 39) were mostly atopic and had the earliest onset of asthma, the highest blood eosinophils, and FEV_1 reversibility at diagnosis. At follow-up, these patients used the lowest ICS dose but 56% were well controlled.
CONCLUSIONS: Results can be used to predict outcomes of patients with adult-onset asthma and to aid in development of

[a]Department of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland
[b]Department of Laboratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland
[c]University of Tampere, Tampere, Finland
[d]Department of Clinical Physiology, Seinäjoki Central Hospital, Seinäjoki, Finland
[e]Department of Respiratory Medicine, University of Tampere, Tampere, Finland

This study was supported by the Finnish Anti-Tuberculosis Association Foundation (Helsinki, Finland), the Tampere Tuberculosis Foundation (Tampere, Finland), the Jalmari and Rauha Ahokas Foundation (Helsinki, Finland), the Research Foundation of the Pulmonary Diseases (Helsinki, Finland), the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (Tampere, Finland), and the Medical Research Fund of Seinäjoki Central Hospital (Seinäjoki, Finland). None of the sponsors had any involvement in the planning and execution of this study or in the writing of this article.

Conflicts of interest: P. Ilmarinen has received lecture fees from MundiPharma. L. E. Tuomisto has received lecture fees from Mundipharma and has received travel support from Takeda, Chiesi, and Orion. M. Tommola has received lecture fees from AstraZeneca and GlaxoSmithKline. H. Kankaanranta has received lecture and consultancy fees and travel support from Almirall, AstraZeneca, and Boehringer Ingelheim; has received consultancy fees from Chiesi Pharma AB; has received lecture and consultancy fees from GlaxoSmithKline, Leiras-Takesa, and Novartis; has received lecture fees from MSD, Mundipharma, Medith, Resmed Finland, and Orion Pharma; has received travel support from Intermune; and has received consultancy fees from Roche. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 25, 2016; revised January 3, 2017; accepted for publication January 31, 2017.
Available online ■■

Corresponding author: Pinja Ilmarinen, PhD, Department of Respiratory Medicine, Seinäjoki Central Hospital, Hanneksenrinne 7, Seinäjoki 60220, Finland. E-mail: pinja.ilmarinen@epshp.fi.

2213-2198

http://dx.doi.org/10.1016/j.jaip.2017.01.027

Abbreviations used
ACOS- Asthma-COPD overlap syndrome
ACT- Asthma control test
AQ20- Airways Questionnaire 20
BD- Bronchodilator
COPD- Chronic obstructive pulmonary disease
FVC- Forced vital capacity
ICS- Inhaled corticosteroid
$Max_{0-2.5}$- Maximum lung function during the first 2.5 years after diagnosis (and start of anti-inflammatory therapy)
SAAS- Seinäjoki Adult Asthma Study

personalized therapy (NCT02733016 at ClinicalTrials.gov). **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Asthma; Adult-onset; Late-onset; Cluster analysis; Phenotypes; Follow-up; Longitudinal; Smoking; Obesity; Early-onset*

Adult- or late-onset asthma has been suggested to be a distinctive phenotype of asthma.[1,2] Patients with adult-onset asthma have lesser allergic processes, lower lung function despite shorter duration of disease, and more often a pronounced eosinophilic inflammation without evidence of T_H2–associated inflammation when compared with patients with childhood-onset asthma.[1] These findings suggest that adult-onset asthma is more heterogeneous when compared with childhood-onset asthma. In previous studies, subphenotypes of adult-onset asthma such as eosinophil-predominant, mild to moderate well-controlled, obesity-related, smoking, and severe obstructive asthma have been proposed.[3,4]

To identify phenotypes of asthma, unsupervised hierarchical cluster analyses have been carried out. However, the cluster analyses have mostly been based on cross-sectional data on patients with mixed duration of asthma.[2,4-6] Asthma is known as a disease with a high degree of variability, making one time point a fragile basis for cluster analysis. Furthermore, no information on the diagnostic phase has been included in the previous analyses. In addition, many previous analyses have clustered patients with severe asthma,[7,8] leaving milder forms with less attention. Some studies have involved short follow-ups (1-3 years).[6,7,9,10] In a previous prospective longitudinal analysis of severe asthma, the clusters did not show cluster-specific disease courses regarding outcome of asthma, suggesting a potential limitation in the way of performing current cluster analyses.[9] In addition to the natural disease variability, many factors such as therapy, lifestyle, and comorbidities may modify the disease course. Reliability of the results of a cluster analysis would be increased by including clinical data from several time points of the disease follow-up into the analysis.

Here, we used a long-term follow-up approach to construct phenotypes of adult-onset asthma by carrying out a cluster analysis with inclusion of variables from diagnosis to a 12-year follow-up visit. This approach provides novel insights into the phenotypes of asthma with prognostic significance.

METHODS

Patients and study design

The present study was part of the Seinäjoki Adult Asthma Study (SAAS), which is a prospective, single-center (Seinäjoki Central Hospital, Seinäjoki, Finland), 12-year follow-up study of a cohort of consecutive white patients having new-onset asthma diagnosed at adult age (≥15 years). SAAS has been registered on ClinicalTrials.gov with ID NCT02733016. Institutional permissions (TU1114 and LET) were obtained and the participants gave written informed consent to the study protocol approved by the Ethics Committee of Tampere University Hospital, Tampere, Finland (R12122). The protocol, inclusion and exclusion criteria, and the background data of SAAS have been published elsewhere.[11] Briefly, asthma was diagnosed by a specialized respiratory physician during the period 1999 to 2002 on the basis of typical clinical symptoms and confirmed by objective lung function measurements.[11,12] The main diagnostic features of asthma in each cluster are presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org. Smokers and patients with comorbidities were not excluded. After diagnosis, the patients were treated and monitored in specialized or primary care as required. The total cohort consisted of 257 patients and 203 patients completed the follow-up visit (mean follow-up time, 12.2 years; range, 10.8-13.9 years). At 12-year follow-up visit, asthma status and disease control, comorbidities, and medication were evaluated using structured questionnaires and lung function was measured. Data on asthma-related visits to health care and hospitalizations were also collected from primary care, occupational health care, private clinics, and hospitals. After excluding those with missing data, 171 patients with adult-onset asthma remained in the cohort for cluster analysis (Figure 1).

Lung function, comorbidities, inflammatory parameters, and other clinical measurements

Lung function was measured with a spirometer according to international recommendations.[13] The following were the lung function measurement points: (1) baseline (time of asthma diagnosis), (2) the maximum prebronchodilator FEV_1 (Pre-BD FEV_1) during the first 2.5 years after diagnosis ($Max_{0-2.5}$) (and after start of anti-inflammatory therapy), and (3) 12-year follow-up.[14] Detailed information on determination of lung function, inflammatory parameters, and comorbidities can be found in this article's Online Repository at www.jaci-inpractice.org. Asthma control was assessed according to the Global Initiative for Asthma 2010 report.[15] Patients filled out the Airways Questionnaire 20 (AQ20) at baseline visit and AQ20 and asthma control test (ACT) questionnaires at the follow-up visit. The AQ20 is a short and simple well-validated questionnaire to measure and quantify disturbances in the airway-specific quality of life.[16] ACT is a widely used patient self-administered tool for identifying those with poorly controlled asthma.[17]

Variable selection

Input variables for the cluster analysis were selected on the basis of factor analysis (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Basic and clinical variables included in factor analysis were chosen to cover as wide a range as possible from diagnosis to 12-year follow-up visit and are further discussed in this article's Online Repository at www.jaci-inpractice.org.

Cluster analysis and discriminant analysis

Cluster analysis was carried out by using a 2-step process. First, Ward hierarchical cluster analysis was performed for preevaluation of