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Editorial



# Implication of Cluster Analysis in Childhood Asthma

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▸ See the article "Heterogeneity of Childhood Asthma in Korea: Cluster Analysis of the Korean Childhood Asthma Study Cohort" in volume 13 on page 42.

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Asthma is characterized by heterogeneity involving a wide variety of phenotypes.[1] Accurate assessment of asthma phenotypes is essential because it can guide asthma treatment properly and predict future risks and complications.[1] However, asthma was simply divided into nonatopic/atopic or intrinsic/extrinsic asthma in the past, which also simplified asthma treatment and did not help treat heterogeneous asthma effectively.[2,3] However, at present, through several clustering studies, it has been possible to confirm that there are specific groups that share similar characteristics among asthmatic patients, and asthma can be classified into several phenotypes.[2,3] Even clustering based on phenotype was not sufficient, and the concept of endotype, a group reflecting the underlying mechanism, appeared.[2,4] Categorizing asthma by phenotype or endotype is beneficial to find the most appropriate treatment for various aspects ofairway inflammation or to find ways to deal with a variety of clinical situations, as each phenotype has a different clinical characteristic or prognosis.[1,2,5]

In the UK, Haldar et al.[3] clustered asthmatic patients. Primary care patients with asthma were classified into clusters 1, 2, and 3 representing early-onset atopic asthma, obese noneosinophilic asthma, and benign asthma, respectively, and secondary care patients were classified into clusters 1–4 representing early-onset atopic asthma, obese noneosinophilic asthma, early symptom predominant asthma, and eosinophilic inflammation dominant asthma. From this study, symptom-predominant and eosinophilic inflammation-predominant types began to be distinguished in earnest.[3] In addition, in the US, Moore et al.[1] classified asthmatic patients enrolled in the Severe Asthma Research Program (SARP) into 5 clusters through unsupervised modeling. Cluster 1 represented early-onset atopic asthma with normal lung function, cluster 2 represented early-onset atopic asthma with preserved lung function but increased medication requirements and healthcare utilization, cluster 3 represented older obese women with late-onset nonatopic asthma with moderate reduction in FEV1 and frequent exacerbations, cluster 4 represented early-onset atopic asthma with severe airflow obstruction and bronchodilator response, and cluster 5 represented later-onset less atopic asthma with severe airflow obstruction.[1] Although airway inflammation was not measured in all patients, sputum eosinophils increased in clusters 3, 4, and 5, and sputum neutrophils increased in cluster 5. Serum total immunoglobulin E (IgE) also increased in clusters 1, 2, and 4, which represent atopic asthma, and was low in clusters 3 and 5, showing different inflammation types.[1] In Europe, Unbiased Biomarkers for the Prediction of

Respiratory Disease Outcomes (U-BIOPRED) also confirmed that mild, moderate, and severe asthma have different clinical types, and higher sputum eosinophil counts were noted in severe asthmatics.[6] In Korea, there is also a study on clustering of adult asthma. The authors analyzed clusters of asthmatic patients enrolled in the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA) and Soonchunhyang University Asthma Genome Research Centre (SCH). In that cohort, asthmatic patients were clustered as smoking asthma, severe obstructive asthma, early-onset atopic asthma, and late-onset mild asthma.[7]

There have been studies of cluster analysis abroad targeting children. In the pediatric asthma cluster analysis using the SARP cohort in which registered patients mainly had difficult atopic asthma, 4 clusters with atopy degree and lung function were categorized as late-onset symptomatic asthma with normal lung function, early-onset atopic asthma with normal lung function, early-onset atopic asthma with mild airflow limitation, and early-onset atopic asthma with advanced airflow limitation.[8] In that study, the degree of atopic sensitization was determined by the number of aeroallergen skin prick responses, and information on inflammation levels, such as serum IgE and blood eosinophils, was also included.[8] There was also a study to examine the response to asthma treatments through cluster analysis of childhood asthmatics.[9] Howrylak et al.[9] clustered pediatric asthmatics participating in the Childhood Asthma Management Program (CAMP). They divided asthmatic patients into 5 clusters using atopic burden, degree of airway obstruction, and history of exacerbation as follows: cluster 1, mild asthma with low atopy, obstruction, and exacerbation rate; cluster 2, atopic asthma with low levels of obstruction and medium rates of exacerbation; cluster 3, atopic asthma with high levels of obstruction and medium rates of exacerbation; cluster 4, moderately atopic asthma with high levels of obstruction and high rates of exacerbation; and cluster 5, highly atopic asthma with high levels of obstruction and high rates of exacerbation. The authors were able to differentiate between responding (cluster 4) and non-responding clusters (cluster 5) to inhaled asthma therapies (budesonide and nedocromil) through 48-month longitudinal follow-up.[9] In France, there was also a cluster analysis study of childhood asthmatics who participated in the Trousseau Asthma Program.[10] The following 3 independent clusters were identified: cluster 1, asthma with severe exacerbations, multiple allergies, and pronounced blood eosinophils; cluster 2, severe asthma with bronchial obstruction and pronounced blood neutrophils; and cluster 3, mild asthma.

While a number of clustering studies have been conducted on pediatric asthma abroad, there has been no such trial yet in Korea.[11-13] In this issue of *Allergy, Asthma and Immunology Research*, Yoon et al.[14] conducted the first cluster analysis of childhood asthma in Korea, and it is a study with great significance in this respect. The authors analyzed the Korean childhood asthma study (KAS) cohort and classified it into the following 4 clusters: cluster 1, male-dominant atopic asthma; cluster 2, early-onset atopic asthma with atopic dermatitis; cluster 3, puberty-onset, female-dominant atopic asthma with low lung function; and cluster 4, early-onset, non-atopic asthma. Unlike the SARP cohort, which only targeted patients with atopic severe asthma, the KAS cohort has the advantage of being able to study various types of asthma more comprehensively because it covers all the characteristics of asthma patients, including various severities ranging from mild intermittent to severe persistent asthma, and even nonatopic asthma patients. In this study, it was observed that early-onset atopic asthma was male predominant and puberty-onset atopic asthma was female predominant and had a more severe pattern. This suggests that sex hormones are involved differently in the mechanism of asthma by age. In addition to differences in gender and age of onset, there was a group of asthma patients with milder symptoms and accompanied atopic dermatitis in 99%


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of patients, suggesting atopic march. On the contrary, there was also a group of nonatopic and more severe asthmatics. This suggests that asthma with a nonallergic mechanism also exists in a considerable part of childhood asthma, and it may affect severity and prognosis. Unlike the CAMP clusters, there is no mild nonatopic asthma group in the KAS clusters. It is not known whether this difference is actually due to the ethnic difference in the characteristics of asthmatic patients between the US and Korea or the difference in variables used in the cluster analysis. This is the limitation of cluster analysis because it is difficult to directly compare each study due to different variable sets. In addition, this study did not include any biomarker that reflects airway inflammation, and the short follow-up study period of 6 months is considered to be a limitation. It will be more reliable if the cluster of asthmatics can be observed for a longer period with assessment of inflammation indicators.

Cluster analysis of asthmatic patients generally has the following limitations: 1) lack of evidence for stability of the clusters over time; 2) cross-sectional study design and little longitudinal study; 3) lung function being a confounder; 4) different variable sets and inconsistencies across different populations; and 5) lack of inflammation indicators.[15] In order to overcome these limitations, longitudinal cluster analysis is necessary, and a trajectory study can be suggested as an alternative. In another study, Park et al.[16] used COREA data to identify longitudinal trajectories of lung function in asthmatic patients for 3 years, and found that 4 different trajectory groups maintained a consistent course of lung function. In addition, while the concept of asthma phenotype was confined to clinical characteristics previously, it is now expanding to the concept of asthma phenotype linked to underlying biological mechanisms.[17] Many integrated omics studies, such as genomics, proteomics, transcriptomics, and metabolomics, are being conducted to elucidate the mechanism of asthma, and molecular-based phenotyping and targeted asthma treatment may be possible through these studies.[17]

Nevertheless, the reason why cluster analysis is particularly important in childhood asthmatics is that it is currently unknown whether the clinical features they show are changeable or fixable over time. Information on whether their traits persist into adulthood through future longitudinal studies will be an important clue to when the traits of asthmatics are determined. In addition, cluster analysis of pediatric asthma will enable us to apply the appropriate treatment for the cluster from the early point of the disease course.

In conclusion, this study is the first to cluster childhood asthma patients in Korea and elucidate that there are various subtypes of pediatric asthma. This will be significant basic data for personalized treatment that should be applied differently for each cluster in childhood asthma.

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