

Editorial



Is a Longitudinal Trajectory Helpful in Identifying Phenotypes in Asthma?

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► See the article "Lung Function Trajectory Types in Never-Smoking Adults With Asthma: Clinical Features and Inflammatory Patterns" in volume 10 on page 614.



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Asthma is an extremely heterogeneous chronic airway disease. Accordingly, classification and understanding of heterogeneous phenotypes are the starting point of establishing management plans and predicting prognosis in asthma. Considering that new specific, targeted biologic agents for asthma have recently been emerging, precision medicine based on precise phenotyping is definitely needed to achieve better clinical outcome. That is, proper phenotyping should predict long-term outcomes and find out which specific treatments may benefit selected phenotypes for personalized medicine.

Unbiased cluster phenotyping is a very interesting approach to effectively avoid pre-established hypotheses.¹ Cluster analysis is a statistical modeling technique in which patients are successfully grouped into “clusters” based on their similarities. The greater the similarity within a group or the greater the difference between the groups, the better and more distinct clustering. Thus, the term “cluster” has been used interchangeably with the term “phenotype.”

There was a landmark study of cluster analysis in asthma, which was performed by Haldar *et al.*² in Leicester, UK. They found 2 clusters characterized by a marked discordance between symptom and eosinophilic inflammation, which were specific to refractory asthma.² Clusters derived from the Severe Asthma Research Program (SARP) in the USA have been well disseminated in asthma world,^{1,3} which has provided an opportunity to further activate cluster analysis research.

In Korea, there have been several asthma cluster phenotyping studies. The first study performed by my colleagues and me identified 4 distinct clusters from the COREA cohort: (1) smoking asthma, (2) severe obstructive asthma, (3) early-onset atopic asthma and (4) late-onset mild asthma.⁴ The editors stated that this study for the first time performed cluster phenotyping on asthmatics in Asia; it included smoking asthmatics, even though smoking is frequently regarded as an exclusion criterion in other asthma studies. In addition, this result was successfully replicated in 2 different large cohorts. Consequently, a longitudinal follow-up study using these clusters in the COREA cohort was performed to investigate the clinical significance of asthma clusters over 1 year, showing that FEV1 does not decline in the follow-

up year and rather increases in the most severe cluster. Use of systemic corticosteroids during the follow-up period was well preserved across the clusters, meaning that this cluster may be useful and significant in phenotype classification in asthma.⁵ There is a cluster analysis in severe refractory asthma in Korea.⁶

How stable are clusters identified at time points 10 years apart? Boudier *et al.*⁷ compared the stability of clusters in asthma a decade apart and addressed the individuals' transition across the clusters, using a large number of subjects in 3 different cohorts in Europe. They found that the probability of remaining in the same phenotype at both time points varied from 54% to 88%. In other words, about 20%–30% of the subjects moved to other phenotypes.

Meanwhile, can cross-sectionally defined clustering discriminate asthma outcomes in the future? One study aimed to identify which asthma outcomes are associated with different phenotypes in a prospective longitudinal cohort: in 112 severe asthma patients, 5 clusters were identified by the SARP algorithm. They investigated several outcomes related with asthma control after 1 year. However, there were no differences in any outcome including ACQ, lung function, medication requirement, or even time to the first exacerbation.⁸ Taken together, the clusters could not discriminate future risks in severe asthma. Therefore, different strategies are needed to perform cluster analysis.

Cluster phenotyping is an excellent way to better understand asthma, but clinical use in a daily practice still remains debatable. There are several drawbacks to cluster phenotyping in asthmatics: (1) little data obtained from longitudinal close follow-up studies, (2) lung function being a major confounder, (3) different variable sets and encodings,⁹ (4) heterogeneity within a cluster,¹⁰ (5) lack of inflammatory markers and (6) inconsistencies across different populations. The important point is that current clustering approach is not sufficient to reflect real practical phenotypes. Therefore, we need to find a novel approach to overcome these drawbacks by further collecting useful longitudinal data.

A trajectory is the path that a moving object follows through space as a function of time. Group-based trajectory analysis assumes that the population is composed of a mixture of distinct groups defined by their developmental trajectories.¹¹ Allen *et al.*¹² published 5 distinct blood pressure trajectories by age and analyzed long-term patterns of blood pressure and their effect on cardiovascular disease risk.

In this issue of the *Allergy, Asthma and Immunology Research*, Kim *et al.*¹³ successfully used a trajectory clustering method to identify lung function trajectory phenotypes in non-smoking adult asthmatic patients in Korea. They found that trajectories 1 and 2 were associated with normal lung function during the study period, while trajectory 3 was associated with a reversal to normal of the moderately decreased baseline FEV1 within 3 months. Trajectories 4 and 5 were associated with severe asthma with a marked reduction in baseline FEV1. Especially, it is interesting that eosinophilic inflammation in both blood and sputum in trajectory 4 may be predictive of the response to conventional asthma treatment, whereas non-atopy and neutrophilic inflammation in trajectory 5 were related to persistent airflow obstruction. Probably, trajectory 5 seems to have characteristics of asthma-COPD overlap, which is similar to those of those longitudinally defined as persistent airway limitation in the COREA cohort (currently under revision). This article is also valuable in longitudinally analyzing data in order to overcome the weakness of previous cross-sectional cluster analyses, which has not yet been performed in studies from Europe and the USA.

My colleagues and I also analyzed trajectories in almost 500 subjects who were regularly followed up every 3 months for 3 years in the COREA cohort in 2014 (unpublished data). We identified 4 distinct trajectories in pre-bronchodilator FEV1. The patterns of FEV1 trajectories look so similar across the trajectories. The change in mean FEV1 was consistently maintained over time in each trajectory. We also identified persistent fixed severe asthma clusters from this longitudinal trajectory analysis. The trajectories were associated with unexpected hospital visits and the use of steroid bursts due to exacerbation. Interestingly, mild to moderate asthma clusters of this and other studies clusters⁴ in Korean asthma populations were quite unique in that the subjects were less atopic, older at asthma onset, and more frequently had normal BMI compared to asthmatics in Western countries.^{3,14} In fact, many asthmatic patients continue to smoke in spite of physicians' advice. Therefore, clusters including smoking asthmatics are more applicable in real practice. In that study, the authors excluded smoking asthma patients from the analysis, since they were not able to be sure about how smoking affect trajectories. However, the effect of smoking on longitudinal changes in asthma should be considered in future studies.

To my thought, the authors successfully initiated a trajectory clustering method to reach the potential "Holy Grail" as mentioned by Bourdin and Chanez.¹ I strongly believe that this approach will be the starting point for accurate phenotyping and clinical implementation in asthma, leading to one step closer to precision medicine.

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