

Can We Define Asthma-COPD Overlap (ACO) by Biomarkers?



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Asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) is both old and new as a concept. For a long time, it has been accepted that asthma and COPD are distinct diseases that have different pathological mechanisms; asthma is characterized by airway hyperresponsiveness, leading to reversible airflow obstruction based on type 2 inflammation with eosinophils, whereas COPD shows progressive and irreversible airflow obstruction typically caused by smoking and associated with neutrophilic inflammation involving CD8⁺ lymphocytes and macrophages.¹ However, clinicians have long recognized that some patients have characteristics of both asthma and COPD and this may make diagnosis difficult. Some patients with asthma may have irreversible airflow obstruction together with neutrophilic infiltration, whereas some patients with COPD may have reversible airflow obstruction together with eosinophil-dominant inflammation. Orie et al² first proposed the concept of ACO in 1961, which was later referred to as the Dutch Hypothesis. They hypothesized that various forms of airway obstruction, such as asthma, chronic bronchitis, and emphysema, can be recognized as one disease entity called chronic nonspecific lung disease and different environmental factors drive it into different phenotypes. The Dutch Hypothesis was controversial because asthma and COPD were thought to be different entities with different pathological mechanisms, but in the 1990s, it was demonstrated that airway hyperresponsiveness is associated with the development of chronic respiratory symptoms.³ Gibson and Simpson⁴ proposed the term asthma COPD overlap syndrome (ACOS) in 2009 to describe patients with both features of asthma and COPD. Then the Global Initiative for Asthma and the Global Initiative for Chronic Obstructive Lung Disease proposed guidelines for ACOS in 2014 defining persistent airflow limitation with features of asthma and COPD and later recommended the modified term, ACO.⁵

Although the concept of ACO is now well accepted, no generally agreed diagnostic criteria have been established. Many criteria of ACO have been proposed and most of them are based on clinical symptoms and lung function.^{1,6} However, it is not certain how ACO should be defined by biomarkers. Shirai et al⁷ show in this issue of the journal that combined assessment of serum periostin and YKL-40 may have potential value in identifying ACO. Periostin is a matricellular protein downstream of the IL-4 and IL-13 signals.⁸ Periostin is highly expressed in various allergic diseases—asthma, atopic dermatitis, chronic rhinosinusitis, and allergic conjunctivitis—and serum periostin has been proposed as a biomarker of asthma showing type 2 inflammation. YKL-40 is a member of the chitinase family although it lacks enzymatic activity.⁹ YKL-40 was first reported to be associated with asthma^{10,11}; however, it was later demonstrated that serum YKL-40 is upregulated in patients with COPD to a greater extent than in patients with asthma.¹²⁻¹⁴

Shirai et al showed that serum periostin is high in both patients with ACO and those with asthma but not in patients with COPD, whereas serum YKL-40 is high in both patients with ACO and those with COPD compared with patients with asthma. These results suggest that ACO has both pathogenesis of asthma and COPD, type 2 inflammation, and neutrophilic inflammation, leading to high expression of periostin and YKL-40, representative biomarkers of these 2 types of inflammation. This is an interesting finding from the point of view of the ACO pathogenesis. Moreover, practically, these results suggest that combined assessment of serum periostin and YKL-40 may help in the diagnosis of ACO.

However, this study raises several issues. (1) It is known that both asthma and COPD are heterogeneous. Consistent with this notion, serum periostin and YKL-40 are not upregulated in all patients with asthma or those with COPD. Periostin and YKL-40 are not biomarkers of asthma and COPD, but biomarkers of subtypes of asthma and COPD. Therefore, it is no wonder that some patients with ACO diagnosed based on clinical symptoms and lung functions do not show elevation of serum periostin or YKL-40 in this study. We need to examine the characteristics of patients with “atypical” ACO (low periostin or low YKL-40) together with patients with atypical asthma (low periostin) and those with COPD (low YKL-40). (2) ACO as well as asthma and COPD is a heterogeneous disease. Although ACO is defined as mixed features of asthma and COPD, the contribution of each component is different amongst patients with ACO. The patients with COPD who have features of asthma are clearly different from patients with asthma who have characteristics of COPD.¹⁵ Shirai et al⁷ showed that the levels of serum YKL-40, but not serum periostin, are different between patients with ACO who were first diagnosed with asthma or COPD, respectively, which supports the heterogeneity of ACO, which is an important area of research to be examined in the future. (3) The

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receiver operating characteristic analysis in this article shows that the areas under the curve of serum periostin and YKL-40 to distinguish ACO from COPD or asthma, respectively, were not very high (approximately 0.6 for periostin and approximately 0.7 for YKL-40). This suggests that combined assessment of serum periostin and YKL-40 alone is not sufficient to diagnose ACO accurately. To refine the diagnosis of ACO, other parameters may need to be included. Further work is therefore needed in diagnosing and classifying ACO, and this will be important for deciding the most appropriate therapies for these patients.

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