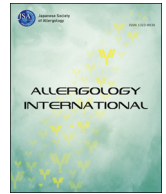




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Letter to the Editor

Utility of serum YKL-40 levels for identification of patients with asthma and COPD

Dear Editor

Bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) are separate disease entities; however, the condition in which these diseases overlap has recently attracted much attention. In 2014, the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) have jointly proposed the concept of asthma–COPD overlap syndrome (ACOS)¹ because patients with concomitant BA and COPD tend to be non-uniformly excluded from large-scale studies of either of these diseases. Scientific evidence for treatment response, prognosis, and natural history in cases of asthma–COPD overlap (ACO) is, therefore, inadequate. Untreated ACO patients have been reported to have a higher frequency of exacerbation than do patients with either COPD or BA and are prone to progression of persistent airway obstruction.² In contrast, the CHAIN study found that ACO patients under proper therapeutic management have a better prognosis than do COPD patients with a comparable level of airway obstruction.² It supports that classifying patients with a combination of clinical BA and COPD characteristics according diagnostic criteria would be important for appropriate management. Differentiation of patient populations with ACO characteristics from BA and COPD patients is often done on the basis of clinical symptoms; presence of airway obstruction; history of smoking; and indicators of Th2 inflammation, such as IgE, eosinophil, and fractional exhaled nitric oxide (FeNO), as proposed in the GINA guidelines. However, it is difficult to clearly define the condition of ACO by using these traits alone.³

Chupp GL *et al.* demonstrated that serum YKL-40 levels correlated with asthma severity and inversely correlated with level of airway obstruction in all three studies.⁴ Additionally, a BIOAIR Consortium study that compared YKL-40 levels in BA and COPD patients found that serum YKL-40 levels increased in both BA and COPD but were higher in COPD.⁵ In that study, serum YKL-40 levels and airway obstruction were found to be correlated, as in previous reports; however, there were no correlations with biomarkers of Th2 inflammation, such as FeNO, blood eosinophils, periostin, and IgE. Hinks TS *et al.* also reported that a correlation between YKL-40 levels and markers associate with neutrophilic airway inflammation in the sputum.⁶ Serum YKL-40 levels rise with systemic inflammation in various diseases, and are recognized as a serum marker of systemic inflammation.⁷⁻⁹ All of the above suggests that increases in serum YKL-40 levels in BA indicate the presence of overlapping neutrophilic airway inflammation, systemic

inflammation, and airway obstruction.¹⁰ These features are generally acknowledged to be strongly associated with the pathogenesis of COPD.¹¹ Then, we examined the significance of serum YKL-40 levels in diagnosing ACO patients.

A total of 176 BA and COPD patients visiting Nihon University Itabashi Hospital were randomly selected and enrolled. The study protocol was approved by the institutional review board, and written informed consent was obtained from all patients. Of the BA and COPD patients who were classified into BA, COPD, and ACO groups according to the following procedure. First, 131 of all 176 enrolled patients were diagnosed as having BA in accordance with the GINA guidelines. Next, the remaining 45 patients were diagnosed as having COPD in accordance with the GOLD guidelines. Of the patients with BA, those aged >50 years with a post-bronchodilator

Table 1
Patients characteristics of BA, ACO, and COPD patients.

	All (n = 176)	BA (n = 91)	ACO (n = 40)	COPD (n = 45)	p Value
Age (years)	61.1 ± 1.14	53.2 ± 1.62	66.2 ± 1.51	72.6 ± 1.12	<0.0001*
Gender (F/M)	91/85	70/21	11/29	10/35	
BMI (Kg/cm ²)	22.8 ± 0.30	23.2 ± 0.45	23.4 ± 0.60	21.3 ± 0.49	0.0154*
Smoking habit					
Never	72	66	4	2	<0.0001*
Pack/year	21.9 ± 2.28	3.28 ± 0.90	32.5 ± 4.33	50.2 ± 5.16	<0.0001*
Blood test					
White blood cell no. (×10 ³)	6.22 ± 153.8	6.08 ± 192.3	6.29 ± 250.3	6.42 ± 401.6	0.6325
Neutrophil no. (×10 ³)	3.78 ± 120.5	3.68 ± 148.8	3.83 ± 220.3	3.93 ± 307.6	0.684
Eosinophil (no.)	283.2 ± 23.6	309.2 ± 41.4	264.1 ± 26.2	248.1 ± 31.3	0.5119
(%)	4.55 ± 0.30	4.86 ± 0.49	4.57 ± 0.58	3.90 ± 0.39	0.4216
CRP (mg/dL)	0.40 ± 0.15	0.54 ± 0.28	0.18 ± 0.03	0.31 ± 0.09	0.5983
YKL40 (ng/ml)	125.3 ± 7.23	75.8 ± 7.68	157.4 ± 13.6	197.1 ± 13.1	<0.0001*
(percentile)	65.4 ± 2.43	49.9 ± 3.26	79.4 ± 4.09	84.1 ± 3.42	<0.0001*
log total IgE (IU/ml)	2.25 ± 0.06	2.28 ± 0.08	2.40 ± 0.10	2.04 ± 0.11	0.0680
Lung function test					
FEV1.0 (L)	1.90 ± 0.06	2.18 ± 0.08	1.65 ± 0.09	1.56 ± 0.09	<0.0001*
%FEV1.0 (% predicted)	82.6 ± 1.90	91.9 ± 2.26	71.7 ± 3.73	73.8 ± 3.94	<0.0001*
FEV1.0/FVC (%)	61.2 ± 1.24	71.3 ± 1.30	53.0 ± 1.95	48.4 ± 1.93	<0.0001*
FENO (bbp)					
	27.4 ± 2.40	32.7 ± 4.16	24.5 ± 3.08	18.3 ± 1.55	0.0477*

* $p < 0.05$ comparison between BA, ACO, and COPD patients.

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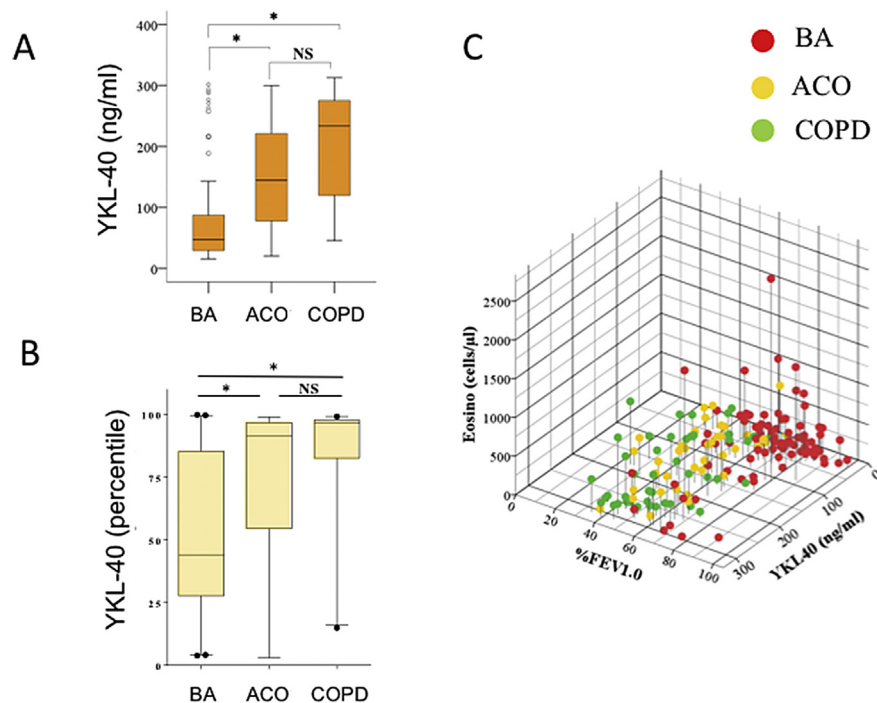


Fig 1. Serum YKL-40 levels in BA, ACO and COPD. Serum YKL-40 concentrations (A), and percentile value (B) in BA, ACO and COPD patients. * $p < 0.05$ comparison to asthmatics. Three dimensional patterns of 3 components for identification of BA, ACO, or COPD (C). Axes show principal components (eosinophils number, FEV1.0%, serum YKL-40 concentrations) for each patients. Red, yellow, green circles show each BA, ACO, COPD patients, respectively.

forced expiratory volume in 1 s (FEV1) of $<70\%$ who met at least two of the following three additional criteria—1: history of smoking ≥ 10 packs per year; 2: diffusing capacity for carbon monoxide [DLCO]/alveolar volume <0.7 ; 3: low-attenuation areas corresponding to emphysema on high-resolution computed tomography—were diagnosed as having ACO. Next, of the patients diagnosed as having COPD, those that met at least two of the following four criteria—1: atopic status; 2: history of asthma; 3: FeNO >35 bpb; 4: blood eosinophils $>5\%$ —were diagnosed as having ACO. We used the aforementioned methods to diagnose 94 BA patients, 37 ACO patients, and 45 COPD patients.

Patient profiles for BA, ACO, and COPD are presented in Table 1. White blood cells, eosinophils, C-reactive protein levels, and IgE levels did not differ significantly among BA, ACO, and COPD (Table 1). Serum YKL-40 measurements and comparisons among BA, ACO, and COPD are presented in Figure 1A. The median YKL-40 levels were $80.5 \text{ ng/mL} \pm 7.95$ in BA, $152.0 \text{ ng/mL} \pm 14.2$ in ACO, and $197.1 \pm 13.1 \text{ ng/mL}$ in COPD. Although there was no difference in YKL-40 levels between ACO and COPD (Fig. 1A), YKL-40 levels were significantly higher in patients with ACO compared to those with BA alone. Serum YKL-40 levels are reportedly affected by age.¹² The mean age was lower for BA patients than for ACO and COPD patients, so YKL-40 levels were converted into age percentiles of healthy individuals and compared (Fig. 1B). The median percentiles for YKL-40 levels were 44.1 ± 28.8 in BA patients, 91.3 ± 21.0 in ACO patients, and 96.5 ± 7.57 in COPD patients. Although there was no significant difference in the percentiles for YKL-40 levels between the ACO and COPD groups (Fig. 1B), the percentiles for YKL-40 levels were significantly higher in ACO than in BA. In the multivariate logistic regression analysis, the significant association with the incidence of ACO was observed (adjusted OR 1.023 [95% CI, 1.003–1.044]; $p = 0.025$) after adjusting for age, smoking, BMI, and FeNO.

The area under the curve (AUC) from receiver operating characteristic curve of YKL-40 percentile for ACO identify from BA (age > 50) patients was 0.687 (95% confidence interval [CI], 0.584–0.790). We attempted to determine if ACO patients could be more clearly differentiated from BA patients by serum YKL-40 levels, in the identification of ACO in addition to FEV1, and blood eosinophil count. Unlike diagnoses that used only airway obstruction and eosinophils as the parameters, diagnoses that included serum YKL-40 levels were better able to differentiate ACO and COPD from BA patients (Fig. 1C).

This study was limited because there are currently no clear criteria for diagnosing ACO. This problem is also linked to the difficulty of differentiating BA from COPD in physiological tests and image analyses. This study showed that the use of serum YKL-40 levels as a blood biomarker of neutrophilic airway and systemic inflammation, which overlap in Th2 cytokine-dominant BA, enabled easy evaluation of one of the characteristics of COPD that overlaps with BA.

Conflict of interest

SH received honoraria from Nippon Boehringer Ingelheim, GlaxoSmithKline, Kyorin Pharmaceutical, AstraZeneca, Astellas Pharma, Novartis Pharmaceuticals, Abbott Japan, MSD. YG and SH received research funding from Philips Respironics. The rest of the authors have no conflict of interest.

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References

1. Global Initiative for Asthma (GINA). Diagnosis of Diseases of Chronic Airflow Limitation: Asthma COPD and Asthma-COPD Overlap Syndrome (ACOS). Updated 2015. Available from: http://www.ginasthma.org/local/uploads/files/ACOS_2015.pdf. [Accessed 7 May 2015].
2. Cosío BG, Soriano JB, López-Campos JL, Calle M, Soler JJ, de-Torres JP, et al. Distribution and outcomes of a phenotype-based approach to guide COPD management: results from the CHAIN cohort. *PLoS One* 2016;**11**:e0160770.
3. Zeki AA, Schivo M, Chan A, Albertson TE, Louie S. The asthma-COPD overlap syndrome: a common clinical problem in the elderly. *J Allergy (Cairo)* 2011;**2011**:861926.
4. Cazzola M, Rogliani P. Do we really need asthma-chronic obstructive pulmonary disease overlap syndrome? *J Allergy Clin Immunol* 2016;**138**:977–83.
5. Chupp GL, Lee CG, Jarjour N, Shim YM, Holm CT, He S, et al. A chitinase-like protein in the lung and circulation of patients with severe asthma. *N Engl J Med* 2007;**357**:2016–27.
6. James AJ, Reinius LE, Verhoek M, Gomes A, Kupczyk M, Hammar U, et al., BIOAIR (Longitudinal Assessment of Clinical Course and Biomarkers in Severe Chronic Airway Disease) Consortium. Increased YKL-40 and chitotriosidase in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2016;**193**:131–42.
7. Hinks TS, Brown T, Lau LC, Rupani H, Barber C, Elliott S, et al. Multidimensional endotyping in patients with severe asthma reveals inflammatory heterogeneity in matrix metalloproteinases and chitinase 3-like protein 1. *J Allergy Clin Immunol* 2016;**138**:61–75.
8. Wiwanitkit V. YKL-40 as new cardiac biomarker. *Anadolu Kardiyol Derg* 2014;**14**:98–9.
9. Pedersen SJ, Sørensen IJ, Lambert RG, Hermann KG, Garner P, Johansen JS, et al. Radiographic progression is associated with resolution of systemic inflammation in patients with axial spondylarthritis treated with tumor necrosis factor α inhibitors: a study of radiographic progression, inflammation on magnetic resonance imaging, and circulating biomarkers of inflammation, angiogenesis, and cartilage and bone turnover. *Arthritis Rheum* 2011;**63**:3789–800.
10. Andreassen M, Raymond I, Hildebrandt P, Kistorp C, Rathcke C, Vestergaard H, et al. Associations between plasma insulin-like growth factor-I and the markers of inflammation interleukin 6, C-reactive protein and YKL-40 in an elderly background population. *Inflamm Res* 2010;**59**:503–10.
11. Agustí A, Faner R. Systemic inflammation and comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2012;**9**:43–6.
12. Bojesen SE, Johansen JS, Nordestgaard BG. Plasma YKL-40 levels in healthy subjects from the general population. *Clin Chim Acta* 2011;**412**:709–12.

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