YKL-40 and adult-onset asthma: Elevated levels in clusters with poorest outcome

Pinja Ilmarinen, PhD[a], Leena E. Tuomisto, MD, PhD[a], Onni Niemelä, MD, PhD[b,c], Mari Hämäläinen, PhD[d], Eeva Moilanen, MD, PhD[d], and Hannu Kankaanranta, MD, PhD[a,c]

Clinical Implications

- This study shows that non-T2 marker YKL-40 could be used in identifying clinical phenotypes associated with poor prognosis in adult-onset asthma.

TO THE EDITOR:

Asthma may be divided into different phenotypes. Adult-onset asthma constitutes of phenotypes including less allergic processes, poorer responsiveness to inhaled corticosteroid therapy, and poorer prognosis compared with childhood-onset asthma. We previously carried out a cluster analysis and identified 5 subphenotypes of adult-onset asthma with variable long-term prognosis, namely, smoking asthma, obese asthma, atopic asthma, nonrhinitic asthma, and female asthma.[1] Poorest 12-year prognosis was found in smoking and obese asthma. Novel targeted approaches are needed for these patient groups.

YKL-40 (chitinase-3–like protein 1) is a secreted glycoprotein produced by macrophages, neutrophils, and airway epithelium. YKL-40 levels are increased in patients with asthma and chronic obstructive pulmonary disease when compared with levels in healthy controls, and a negative correlation was shown between lung function and serum YKL-40 level.[2,3] Furthermore, YKL-40 has been associated with asthma severity[2] and is a potential marker of asthma-chronic obstructive pulmonary disease overlap.[4] Previous cluster analysis[5] identified 2 YKL-40–high clusters characterized by severe asthma and airflow obstruction but separated by age of asthma onset. Based on sputum and transcriptional profiling, it was suggested that YKL-40 might be a non-T2 biomarker.[5] In patients with severe asthma, YKL-40 was associated with neutrophilic inflammation and correlated with IL-8 and IL-6.[6]

We aimed to study levels of plasma YKL-40 in our previously defined clusters of adult-onset asthma,[1] and the association of YKL-40 with clinical parameters and biomarkers.

This study is part of Seinäjoki Adult Asthma Study (ClinicalTrials.gov ID NCT02733016), which is a prospective,

TABLE I. Main characteristics of clusters at 12-y follow-up visit

Characteristic	Cluster 1: Atopic	Cluster 2: Female	Cluster 3: Nonrhinitic	Cluster 4: Obese	Cluster 5: Smoking	*P* value
Subjects	39	50	38	25	19	
Sex: female, n (%)	18 (46.2)	49 (98)*	15 (39.5)	16 (64)	2 (10.5)†	<.001
Age of onset (y)	33 ± 11*	43 ± 12*	50 ± 12	57 ± 8	55 ± 9	<.001
BMI (kg/m^2)	26.8 ± 3.9	27.1 ± 4.8	29.9 ± 6.5	32.8 ± 5.3‡§‖	28.1 ± 4.9	<.001
With smoking history, n (%)	21 (53.8)	18 (36)	20 (52.6)	11 (44)	15 (78.9)§	<.001
Current smokers, n (%)	8 (20.5)	8 (16.0)	7 (18.4)	0	3 (15.8)	.225
Atopic, n (%)	22 (57.9)†	19 (40.4)	9 (27.3)	2 (9.1)	5 (31.3)	<.001
Rhinitis, n (%)	35 (89.7)	44 (88)	4 (10.5)*	24 (96)	14 (73.7)	<.001
Uncontrolled asthma,¶ n (%)	6 (15.4)	11 (22)#	2 (5.3)	12 (48)‖#	16 (84.2)§‖#	<.001
ICS dose of daily users (μg budesonide equivalent)	800 (400-800)	800 (575-1000)	800 (400-1000)	1000 (475-1525)	900 (700-1400)	.163
Pre-BD FEV_1 (%ref)	86 (12)	96 (13)*	85 (14)	79 (16)	63 (19)*	<.001
Blood eosinophils ($\times 10^9$/L)	0.20 (0.12-0.28)	0.16 (0.10-0.28)	0.14 (0.09-0.25)	0.13 (0.06-0.25)	0.23† (0.13-0.43)	.035
No. of comorbidities	0 (0-1)	0.5 (0-1)	1 (0-2)‖	3 (2.5-4)§‖#	3 (1-4)§‖#	<.001
Diabetes, n (%)	2 (5.1)	3 (6.0)	4 (10.5)	11 (44.0)§‖#	7 (36.8)§‖	<.001
YKL-40 (ng/mL)	37 (25-48)	41 (28-63)	53 (38-86)	59 (40-96)‖	83 (43-176)§‖	<.001
IL-8 (pg/mL)	5.4 (4.2-6.3)	5.3 (4.3-8.1)	6.8 (5.1-9.0)	7.0 (5.5-8.4)	8.1 (6.8-13.1)§‖	<.001
IL-6 (pg/mL)	1.2 (0.9-1.9)	1.7 (1.0-2.5)	1.8 (1.2-2.6)	4.0§‖# (2.1-5.5)	3.1 (2.1-4.9)§‖	<.001

BD, Bronchodilator; *BMI*, body mass index; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid.
Part of data has been previously published.[1]
Continuous variables are shown as mean ± SD or median (interquartile range). Group comparisons were performed by 1-way ANOVA with Tukey post hoc test (age of onset, BMI, pre-BD FEV_1), Kruskal-Wallis test adjusted by Bonferroni correction for multiple tests (ICS dose, blood eosinophils, number of comorbidities, YKL-40, IL-8, and IL-6), or χ^2 test with comparison of column proportions by *z* test and adjusting *P* values by Bonferroni method (all categorical variables).
*$P < .05$ to all other clusters.
†$P < .05$ vs obese cluster.
‡$P < .05$ vs smoking cluster.
§$P < .05$ vs female cluster.
‖$P < .05$ vs atopic cluster.
¶Asthma control based on GINA 2010.
#$P < .05$ vs nonrhinitic cluster.

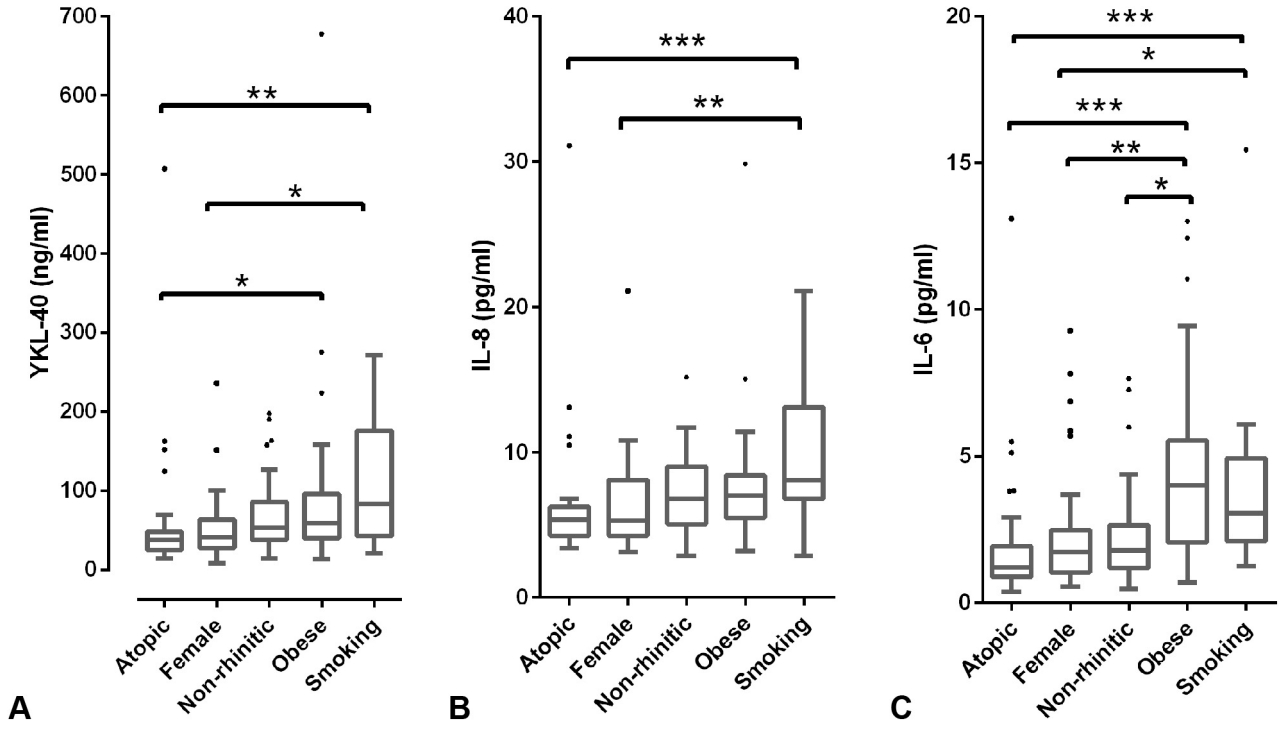

FIGURE 1. Blood levels of YKL-40, IL-8, and IL-6 in clusters of adult-onset asthma. Group comparisons were performed by Kruskal-Wallis test.

single-center (Seinäjoki Central Hospital, Seinäjoki, Finland) study in which 203 patients with new-onset adult asthma were followed for 12 years. Asthma was diagnosed by respiratory specialists and confirmed by lung function measurements. Detailed methodology is presented in this article's Online Repository at www.jaci-inpractice.org.

Main features of the clusters are as follows (Table I[1]): (1) *atopic* well-controlled asthma with earliest age of onset, (2) *female* asthma with normal clinical parameters but high use of health care, (3) *nonrhinitic* partially controlled or controlled asthma with low use of medication and health care, (4) *obese* asthma with comorbidities, frequent symptoms, and use of medication and health care, and (5) *smoking* asthma or asthma-chronic obstructive pulmonary disease overlap with the poorest lung function, frequent symptoms, and use of medication and health care.

In patients with adult-onset asthma, YKL-40 levels measured at 12-year follow-up visit were highest in the smoking cluster, second highest in the obese cluster, and lowest in atopic and female clusters (Figure 1, *A*; Table I). Plasma IL-8 levels behaved in a manner similar to YKL-40 levels in the clusters (Figure 1, *B*; Table I). Levels of IL-6 were highest in obese asthma (Figure 1, *C*; Table I). YKL-40 levels correlated with age ($\rho = 0.402$; $P < .001$), number of comorbidities ($\rho = 0.376$; $P < .001$), IL-6 level ($\rho = 0.449$; $P < .001$), and IL-8 level ($\rho = 0.410$; $P < .001$). Regarding traditional asthma-related parameters, YKL-40 level was found to correlate with increasing symptoms (Asthma Control Test: $\rho = -0.228$; $P = .001$; Airways Questionnaire 20: $\rho = 0.256$; $P < .001$) and negatively with lung function (pre-BD FEV_1: $\rho = -0.305$; $P < .001$; post-BD FEV_1: $\rho = -0.317$; $P < .001$). YKL-40 level also weakly correlated with number of add-on drugs, number of hospitalizations, and high sensitivity C-reactive protein, and negatively correlated with diagnostic lung function (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). There was no correlation between YKL-40 and biomarkers of T2-asthma (blood eosinophils, fraction of exhaled nitric oxide, total IgE) (Table E1).

Smoking and obese clusters shared many features such as older age, comorbidities, high respiratory symptoms, and reduced lung function. Linear regression analysis on clinical or physiological parameters associated with high YKL-40 levels in adult-onset asthma showed significant associations with age ($\beta = 0.006$; 95% CI, 0.003 to 0.009; $P < .001$), postbronchodilator FEV_1 ($\beta = -0.003$; 95% CI, −0.006 to −0.001; $P = .004$), diabetes ($\beta = 0.148$; 95% CI, 0.037 to 0.259; $P = .009$), and Airways Questionnaire 20 score ($\beta = 0.011$; 95% CI, 0.002 to 0.021; $P = .019$). Sex, body mass index, smoking or pack years, blood eosinophils, neutrophils, IgE, fraction of exhaled nitric oxide, or lung function decline during 12-year follow-up were not associated with YKL-40 levels.

Our previously defined clusters of adult-onset asthma based on long-term clinical data were distinguished by the levels of YKL-40. Smoking and obese clusters with the poorest 12-year outcome had the highest YKL-40 levels at 12-year follow-up visit and can be considered as "YKL-40 high" clusters. The result supports the association between YKL-40 and asthma severity,[2] previously defined by using cross-sectional data. Atopic and female clusters containing the highest proportion of atopic patients had the lowest YKL-40 levels, being "YKL-40 low" clusters. Previous studies have suggested YKL-40 as a biomarker

of non-T2 inflammation,[5,7] and our study supports this concept. Furthermore, differing levels of YKL-40, IL-6, and IL-8 validate our previous cluster analysis[1] by suggesting that the clusters originally defined on the basis of clinical parameters also share pathobiological features.

Higher age, comorbidities (such as diabetes), symptoms, and poor lung function were common in the obese and smoking clusters and the main features associated with elevated YKL-40 levels. However, pack years of smoking was not associated with YKL-40, and body mass index only weakly (Table E1), as suggested previously.[3] The association of YKL-40 level with diabetes was stronger when compared with body mass index or obesity, consistent with a previous study in subjects without asthma.[8] We previously showed worse respiratory symptoms in multimorbid patients with asthma, which might be related to higher level of IL-6.[9] Now we found an association between multimorbidity, higher symptoms, and YKL-40 level, adding YKL-40 as a possible player into this multifactorial phenomenon. Weak correlation between asthma symptom score and YKL-40 level has been shown before,[3] but our study strengthens this relationship by showing that the association between YKL-40 level and symptoms remains after adjusting for age, sex, smoking, lung function, and comorbidities.

The exact biological role of YKL-40 in asthma remains unknown, but it has consistently been shown to be associated with lung function[3] (the present study) and parameters of airway remodeling.[2] YKL-40 was shown to be induced by IL-6/sIL-6R but not by IL-4/IL-13 pathway[7] and stimulated IL-8 production in bronchial epithelial cells, presenting a possible pathway leading to bronchial smooth muscle proliferation and airway remodeling.[10] Consistently, in our study, YKL-40 level correlated with IL-6 and IL-8 levels, supporting the mechanisms proposed. Even though sputum YKL-40 and sputum neutrophils have been reported to correlate in patients with severe asthma, in studies with all levels of severity included as the present study, no clear relationship has been found between airway or blood YKL-40 level and neutrophils.[2,3,5]

Altogether, highest YKL-40 levels were found in previously defined clinical clusters of adult-onset asthma with the poorest long-term outcomes and were associated with more severe symptoms, poor lung function, and multimorbidity. In this era where many attempts are being made to identify clinical phenotypes and their biomarkers, our study extends previous findings by showing a link between a biomarker, clinically defined phenotypes, and disease prognosis. Our study suggests that YKL-40 could be used in identifying asthma phenotypes with poor prognosis and support a role for YKL-40 in non-T2 asthma.

Acknowledgments

Mrs Aino Sepponen, RN, is gratefully acknowledged for her help through all the stages of this work. Ms Terhi Salonen and Ms Heini Sood are acknowledged for excellent technical assistance.

[a]Department of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland
[b]Department of Laboratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland
[c]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
[d]The Immunopharmacology Research Group, Faculty of Medicine and Health Technology, Tampere University and Tampere University Hospital, Tampere, Finland

This study is supported by Tampere Tuberculosis Foundation (Tampere, Finland), the Finnish Anti-Tuberculosis Association 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), the Medical Research Fund of Seinäjoki Central Hospital (Seinäjoki, Finland), and the Paulo Foundation (Helsinki, Finland). None of the sponsors had any involvement in the planning, execution, drafting, or write-up of this study.

Conflicts of interest: P. Ilmarinen reports personal fees from MundiPharma, Orion, Astra Zeneca, and GlaxoSmithKline. L. E. Tuomisto reports nonfinancial support from Chiesi, Orion Pharma, TEVA, and Boehringer-Ingelheim; personal fees from Astra Zeneca; and other fees from Novartis, outside the submitted work. H. Kankaanranta reports grants, personal fees, and nonfinancial support from AstraZeneca; personal fees and nonfinancial support from Almirall, Orion Pharma, and Boehringer-Ingelheim; personal fees from Chiesi Pharma AB, GlaxoSmithKline, Leiras-Takeda, MSD, Novartis, MundiPharma, Medith, Resmed Finland, Roche, and SanofiGenzyme outside the submitted work; and nonfinancial support from Intermune.

Received for publication December 20, 2018; revised March 13, 2019; accepted for publication March 27, 2019.

Available online April 4, 2019.

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

2213-2198

https://doi.org/10.1016/j.jaip.2019.03.043

REFERENCES

1. Ilmarinen P, Tuomisto LE, Niemelä O, Tommola M, Haanpää J, Kankaanranta H. Cluster analysis on longitudinal data of patients with adult-onset asthma. J Allergy Clin Immunol Pract 2017;5:967-78.
2. 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.
3. James AJ, Reinius LE, Verhoek M, Gomes A, Kupczyk M, Hammar U, et al. Increased YKL-40 and chitotriosidase in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2016;193:131-42.
4. Shirai T, Hirai K, Gon Y, Maruoka S, Mizumura K, Hikichi M, et al. Combined assessment of serum periostin and YKL-40 may identify asthma-COPD overlap. J Allergy Clin Immunol Pract 2019;7:134-145.e1.
5. Gomez JL, Yan X, Holm CT, Grant N, Liu Q, Cohn L, et al. Characterisation of asthma subgroups associated with circulating YKL-40 levels. Eur Respir J 2017;50:1700800.
6. 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.
7. Jevnikar Z, Ostling J, Ax E, Calven J, Thorn K, Israelsson E, et al. Epithelial IL-6 trans-signaling defines a new asthma phenotype with increased airway inflammation. J Allergy Clin Immunol 2019;143:577-90.
8. Catalan V, Gomez-Ambrosi J, Rodriguez A, Ramirez B, Rotellar F, Valenti V, et al. Increased circulating and visceral adipose tissue expression levels of YKL-40 in obesity-associated type 2 diabetes are related to inflammation: impact of conventional weight loss and gastric bypass. J Clin Endocrinol Metab 2011;96:200-9.
9. Ilmarinen P, Tuomisto LE, Niemelä O, Danielsson J, Haanpää J, Kankaanranta T, et al. Co-morbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. Eur Respir J 2016;48:1052-62.
10. Tang H, Sun Y, Shi Z, Huang H, Fang Z, Chen J, et al. YKL-40 induces IL-8 expression from bronchial epithelium via MAPK (JNK and ERK) and NF-kappaB pathways, causing bronchial smooth muscle proliferation and migration. J Immunol 2013;190:438-46.

ONLINE REPOSITORY

METHODS

Study design and patients

The present study was part of Seinäjoki Adult Asthma Study (SAAS). SAAS is a prospective, single-center (Seinäjoki Central Hospital, Seinäjoki, Finland) 12-year follow-up study of a cohort of patients having new-onset asthma that was diagnosed at adult age (≥15 years). 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 separately,[E1] as well as results of cluster analysis.[E2] Briefly, asthma was diagnosed by a respiratory physician during the period 1999-2002 on the basis of typical symptoms and confirmed by objective lung function measurements.[E1] After diagnosis, the patients were treated and monitored by their own treating physician either in specialized care or in primary care. The total cohort consisted of 257 patients and 203 patients returned to the follow-up visit 12 years (mean, 12.2 years; range, 10.8-13.9 years) after diagnosis. At follow-up visit, asthma status and control, comorbidities, and medication were evaluated using structured questionnaires and lung function and blood YKL-40, IL-8, and IL-6 levels were measured. Data on asthma-related visits to health care and hospitalizations were collected from primary care, occupational health care, private clinics, and hospitals from the whole 12-year follow-up period. All 203 patients were included in most correlation analyses but 171 patients in clinical clusters due to missing data.

Lung function, inflammatory parameters, and other clinical measurements

Lung function measurements were performed with a spirometer (Vmax Encore 22, Viasys Healthcare, Palm Springs, Calif) according to international recommendations.[E3] The spirometer was calibrated daily. Postbronchodilator measurements were taken 15 minutes after inhalation of salbutamol (400 μg). Finnish reference values were used.[E4] Fractional exhaled nitric oxide was measured with a portable rapid-response chemiluminescent analyzer according to ATS standards[E5] (flow rate, 50 mL/s; NIOX System, Aerocrine, Sweden). Venous blood was collected and white blood cells differential counts were determined. Total IgE levels were measured by using ImmunoCAP (Thermo Scientific, Uppsala, Sweden). Plasma YKL-40 and IL-8 concentrations were measured by an ELISA using reagents from R&D Systems Europe Ltd, Abingdon, UK, and BD Biosciences, Erembodegem, Belgium, respectively.[E6-E8] The detection limit and interassay coefficient of variation were 7.8 pg/mL and 2.7% for YKL-40 and 0.8 pg/mL and 7.5% for IL-8. Serum IL-6 levels were measured by using ELISA (R & D Systems, Minneapolis, Minn), and lower limit for detection was 0.7 pg/mL. High-sensitivity C-reactive protein was measured by using particle-enhanced immunoturbidometric method on Roche Cobas 8000 automated clinical chemistry analyzer (Roche Diagnostics, Basel, Switzerland) with lower limit of detection of 0.3 mg/L. Patients completed Airways Questionnaire 20[E9] and Asthma Control Test. Assessment of asthma control was performed according to the Global Initiative for Asthma report.[E10] Information on the conditions included as comorbidities has been previously published.[E11]

Statistical analysis

A multivariate linear regression was performed when analyzing factors associated with YKL-40 levels. Because of skewed YKL-40 distribution, YKL-40 levels were log-transformed for linear regression analysis. The correlation matrix was analyzed and the explanatory variables not strongly correlated ($R < 0.7$) were included in the analysis. Predictors were selected on the basis of univariate analysis and the combination of variables giving the best R^2 chosen by using the enter method. Also, forward and backward methods were carried out to aid selection of the best model. Statistical analyses were performed by using SPSS software, version 25 (IBM SPSS, Armonk, NY).

TABLE E1. Correlations of plasma YKL-40 with clinical clusters/phenotypes of adult-onset asthma, basic characteristics, and clinical parameters of asthma

Characteristic	Spearman ρ	*P* value
At 12-y follow-up visit		
Age	0.402	<.001
BMI	0.213	.002
Pack years	0.099	.171
No. of comorbidities	0.376	<.001
Pre-BD FEV_1	−0.305	<.001
Post-BD FEV_1	−0.317	<.001
Pre-BD FVC	−0.218	.002
Post-BD FVC	−0.175	.013
Post-BD FEV_1/FVC ratio	−0.238	.001
FEV_1 Reversibility	0.078	.270
ACT	−0.228	<.001
AQ20	0.256	<.001
Blood eosinophils	0.031	.664
Blood neutrophils	0.125	.076
Total IgE	−0.058	.411
F_{ENO}	−0.042	.563
IL-6	0.449	<.001
IL-8	0.410	<.001
hsCRP	0.248	<.001
ICS dose	0.119	.144
No. of add-on drugs	0.273	<.001
At diagnosis		
Pre-BD FEV_1	−0.225	.001
Post-BD FEV_1	−0.232	.001
Post-BD FEV_1/FVC ratio	−0.248	.001
During 12-y follow-up period		
Lung function decline*	−0.154	.020
Hospitalizations†	0.208	.003
No. of oral steroid courses‡	0.063	.377

ACT, Asthma Control Test; *AQ20*, Airways Questionnaire 20; *BD*, bronchodilator; *F_{ENO}*, fractional exhaled nitric oxide; *FVC*, forced vital capacity; *hsCRP*, high sensitivity C-reactive protein; *ICS*, inhaled corticosteroid.

*Pre-FEV_1 from maximum point of lung function within 2.5 y after start of therapy to 12-y follow-up visit.

†Number of hospitalizations during the 12-y follow-up period.

‡Within 2 y before 12-y follow-up visit. Most correlation analyses include 203 patients.

REFERENCES

E1. Kankaanranta H, Ilmarinen P, Kankaanranta T, Tuomisto LE. Seinajoki adult asthma study (SAAS): a protocol for a 12-year real-life follow-up study of new-onset asthma diagnosed at adult age and treated in primary and specialised care. NPJ Prim Care Respir Med 2015;25:15042.

E2. Ilmarinen P, Tuomisto LE, Niemelä O, Tommola M, Haanpää J, Kankaanranta H. Cluster analysis on longitudinal data of patients with adult-onset asthma. J Allergy Clin Immunol Pract 2017;5:967-78.

E3. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.

E4. Viljanen AA, Halttunen PK, Kreus KE, Viljanen BC. Spirometric studies in non-smoking, healthy adults. Scand J Clin Lab Invest Suppl 1982;159:5-20.

E5. American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005;171:912-30.

E6. Väänänen T, Lehtimäki L, Vuolteenaho K, Hämäläinen M, Oksa P, Vierikko T, et al. Glycoprotein YKL-40 levels in plasma are associated with fibrotic changes on HRCT in asbestos-exposed subjects. Mediators Inflamm 2017;2017:1797512.

E7. Väänänen T, Kallio J, Vuolteenaho K, Ojala A, Luukkaala T, Hämäläinen M, et al. High YKL-40 is associated with poor survival in patients with renal cell carcinoma: a novel independent prognostic marker. Scand J Urol 2017;51:367-72.

E8. Väänänen T, Koskinen A, Paukkeri EL, Hämäläinen M, Moilanen T, Moilanen E, et al. YKL-40 as a novel factor associated with inflammation and catabolic mechanisms in osteoarthritic joints. Mediators Inflamm 2014;2014:215140.

E9. Barley EA, Quirk FH, Jones PW. Asthma health status measurement in clinical practice: validity of a new short and simple instrument. Respir Med 1998;92:1207-14.

E10. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2010. Available from: http://www.ginasthma.org/. Accessed October 27, 2014.

E11. Ilmarinen P, Tuomisto LE, Niemelä O, Danielsson J, Haanpää J, Kankaanranta T, et al. Co-morbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. Eur Respir J 2016;48:1052-62.