

Serum high-sensitivity C-reactive protein can be an airway inflammation predictor in bronchial asthma

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ABSTRACT

It is controversial that the serum high-sensitivity C-reactive protein (hs-CRP) can be a useful marker of airway inflammation in bronchial asthma, because various factors have been reported to affect hs-CRP levels. We conducted a study in patients with mild bronchial asthma without complications to determine whether hs-CRP is a useful indicator of airway inflammation. The induced sputum cell differentiation, respiratory function tests, bronchial hyperresponsiveness tests, and hs-CRP measurement were performed in the subject population consisted of 40 healthy volunteers and 45 patients with bronchial asthma. The log-transformed (log) serum hs-CRP level was higher in asthmatic patients compared with healthy controls (2.49 ± 0.41 versus 2.21 ± 0.39 ; $p = 0.002$). A receiver-operating characteristic (ROC) analysis showed a sensitivity of 0.69 and specificity of 0.70 for a log serum hs-CRP of 2.3 to distinguish asthmatic patients from healthy controls. The log serum hs-CRP level negatively correlated with forced volume in 1 second ($FEV_{1.0}\%$)_{pred} ($r = -0.31$, $p = 0.04$), positively correlated with sputum eosinophils ($r = 0.34$, $p = 0.02$), negatively correlated with sputum macrophages ($r = -0.56$, $p < 0.001$), and did not correlate with log 20% fall in $FEV_{1.0}$ (PC_{20}) ($r = -0.09$, $p = 0.56$). A multiple regression analysis revealed that the log serum hs-CRP concentration significantly correlated with eosinophils ($p = 0.019$) and neutrophils ($p = 0.042$) in the sputum, respectively. Serum hs-CRP may be a useful marker of airway inflammation in nonsmoking asthmatic patients without complications, such as heart disease, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, or infection.

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Cytokines released from inflammatory cells, such as interleukin (IL)-6, IL-1, and tumor necrosis factor- α , stimulate hepatocytes to produce C-reactive protein (CRP).¹ CRP is an acute phase reactant with a molecular mass of approximately 21,500 Da and was identified as a substance that precipitates with the C-polysaccharides of pneumococcal cell walls. CRP is also used in clinical practice as a marker to diagnose and monitor the course of inflammatory diseases and infections and also can predict the risk of coronary artery heart disease.¹ The high-sensitivity CRP (hs-CRP) assay is highly responsive (reported to have a 100-fold higher sensitivity compared with conventional CRP detection methods) and can measure CRP at extremely low concentrations (0.01–0.02 mg/dL).²

Whether hs-CRP is reflected the airway inflammation is not clarified, and the relationship of hs-CRP with bronchial hyperresponsiveness is controversial.^{2–4} Because serum hs-CRP is a nonspecific marker of systemic inflammation, and many factors can increase hs-CRP levels, it is difficult to demonstrate the direct

correlations with wheezing, asthma control scores, and forced volume in 1 second ($FEV_{1.0}$) in asthma patients.^{5,6} Increases of serum hs-CRP can be found in all systemic inflammatory diseases,⁶ and it is reported to increase with age.⁵ In addition, females tend to have higher hs-CRP levels than males.³ In addition to cardiovascular disease, hs-CRP is reported to have a relationship with diabetes and obesity stemming from the IL-6 derived from adipocytes.⁷

Therefore, use of hs-CRP as a marker for inflammation in asthmatic patients with these complications and physiologic factors can be difficult and should be taken into account when using this protein for diagnostics.^{8–10} To clarify whether hs-CRP can detect airway eosinophilic or neutrophilic inflammation in asthmatic patients, we excluded the patients with any of these complications and investigated the possible correlations of hs-CRP levels with airway obstruction, inflammation, and hyperresponsiveness in nonsmokers aged 20–60 years with mild persistent asthma by comparison with the gender, age-matched healthy persons.

MATERIALS AND METHODS

Subjects

The study included 45 asthmatic patients aged 20–60 years and 40 gender and age-matched healthy volunteers as control subjects. All of the asthmatic patients

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Table 1 Patient characteristics

	Healthy Controls (n = 40)	Bronchial Asthmatics (n = 45)	p-Value
Male/female	21 / 19	18/27	0.25
Age, years	32.2 ± 11.0	36.6 ± 10.3	0.16
Body mass index	21.6 ± 2.3	22.1 ± 2.8	0.37
Duration, years	—	5.9 ± 9.6	
Atopic/nonatopic	—	31/14	
FEV _{1.0} %predicted	—	77.4 ± 9.8	
FEV _{1.0} /FVC, %	—	91.1 ± 16.4	
V _{50%} predicted	—	71.0 ± 29.0	
V _{25%} predicted	—	53.0 ± 25.6	
Log PC ₂₀	—	2.71 ± 0.55	
Sputum eosinophils, %	—	18.1 ± 22.3	
Log serum hs-CRP	2.21 ± 0.39	2.49 ± 0.41	0.002

FVC = forced volume capacity.

were first seen at our hospital for mild persistent asthma that was not previously treated.

Bronchial asthma was diagnosed according to the Global Initiative for Asthma Guidelines.¹¹ Specifically, patients were required to meet the next eligibility criteria to enter the study, including a history of wheezing and/or dyspnea, an improvement of at least 12% and 200 mL in FEV_{1.0} after bronchodilator therapy, and/or concentrations of acetylcholine (Ach) that produced a 20% fall in FEV_{1.0} (PC₂₀) should be less than or equal to 8000 mcg/mL in a test of bronchial hyperresponsiveness. None of the patients used antiasthma medication (oral or inhaled corticosteroids, long- or short-acting β -antagonists, leukotriene modifiers, or antihistamines) within the 24 hours before enrollment.

All of the healthy volunteers and asthmatic patients were nonsmokers without complications of chronic obstructive pulmonary disease. The subjects with hypertension (n = 17 of asthmatics and 10 of healthy controls), hyperlipidemia (n = 3 and 4), heart disease, diabetes mellitus (n = 2 and 0), or other diseases, except atopic disposition, and the subjects with a serum hs-CRP more than or equal to 10,000 ng/mL (n = 3 and 1; all of them had low-grade fever) were excluded from the study. No significant differences were observed for sex, age, or body mass index between asthmatic patients and healthy controls. In the asthmatic patients, atopic patients (a positive test was defined as an IgE capsulated hydrophobic carrier polymer-radioallergosorbent test score of two or higher for at least one allergen, except pollen) accounted for 68.9% of the cohort (Table 1). Of 45 asthmatics, 31 were positive to *Dermatophagoides farinae*, 31 were positive to house dust, 26 were positive to Japanese cedar pollen, and 8 and 6 were positive to dog and cat, respectively.

The study was performed at Fukuoka National Hospital. The study protocol was approved by the ethics

committee of Fukuoka National Hospital. All the participants received verbal and written study information before giving their informed consent. The protocol approval number is 20-14.

Study Design

Blood sampling, respiratory function test, bronchial hyperresponsiveness test, and sputum induction with the use of inhaled 3% hypertonic saline were performed in all the asthmatic patients in the same order.

Measurement of Flow-Volume Curves

Each flow-volume curve was measured with a spirometer (Chest Graph HI-701; Chest M.I., Tokyo, Japan). The results are expressed as a percentage of the predicted values (FEV_{1.0}/FVC, FEV_{1.0}%predicted, V_{50%}predicted, and V_{25%}predicted) determined from relevant reference standards.¹²

Measurement of Bronchial Hyperresponsiveness to Ach

The challenge test was performed using standardized methodology after that fact that the patient did not take any antiasthma medication was confirmed. The subjects inhaled aerosolized Ach from a hand-held nebulizer (PARI BOY 038; PARI GmbH, Starnberg, Germany) while performing tidal breathing for two minutes. The operating airflow rate was 5 L/min. Isotonic saline was inhaled first as a control, followed by a progressive doubling of the Ach concentration from 39 to 20,000 mcg/mL. The FEV_{1.0} was measured after each inhalation with a spirometer (Chest Graph HI-701; Chest M.I.). The test was continued until the FEV_{1.0} had decreased by more than 20% or until the maximum concentration of Ach had been administered. Bronchial hyperresponsiveness was expressed as

the PC₂₀. At the end of the test, any decrease in the FEV_{1.0} was reversed with an inhalation of salbutamol (0.3-mL Venetlin for inhalation; GSK, Tokyo, Japan). The subjects with a PC₂₀ of less than 8000 mcg/mL were considered to have bronchial hyperresponsiveness.¹¹

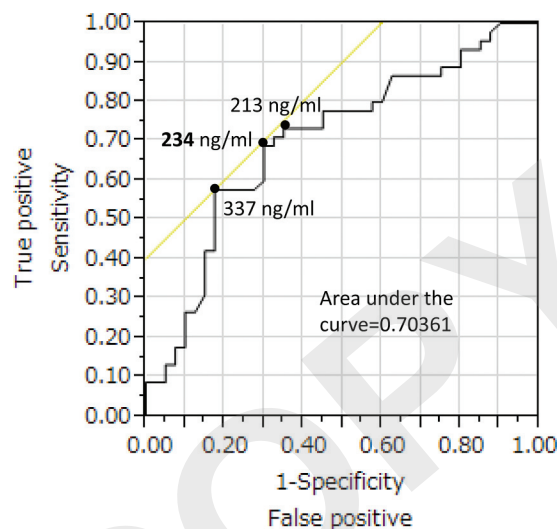
Measurement of High-Sensitivity CRP (hs-CRP)

Levels of serum hs-CRP were measured using latex-based nephelometry. The serum was frozen at -80°C until subsequent testing. Latex nephelometry was performed with the Behring Nephelometer II [Dade Behring, Inc., Tokyo, Japan (currently operating as Siemens Health care Diagnostics, Inc., IL)] and an hs-CRP reagent with mouse anti-CRP monoclonal antibodies absorbed on latex particles (N-Latex CRP II; Dade Behring, Inc.). According to the United States Food and Drug Administration requirements for hs-CRP assay reagents, the sensitivity of measurement should be 200 ng/mL or less, and the coefficient of variation at a CRP concentration of 100 ng/mL should not exceed 3%.¹³

Sputum Induction and Processing

The participants inhaled 5 mL of a 3% NaCl solution through a small ultrasonic nebulizer (Nescosonic nebulizer; UN-511; Azwell, Tokyo, Japan) to induce sputum.¹⁴ According to the manufacturer, the output was approximately 5 L/min. The subjects rinsed their mouths and were asked to cough and expectorate into empty containers during and after over a 20-minute period inhalation.

The sputum samples were processed within 30 minutes. The samples were transferred to a Petri dish, and particularly viscous parts were collected using forceps. The samples were then processed using a method described by Metso *et al.*¹⁴ to collect cells for the cytospin procedure. The samples were diluted with 6.5 mmol/L dithiothreitol (diluted 10-fold in distilled water, Sputolysin; Calbiochem, La Jolla, CA). The mixture was filtered through a 53- μm mesh nylon filter (SEFAR Mesh+Technology NYTAL 21T-53; Sefar, Heiden, Switzerland). The sputum cells were separated by centrifugation at $2000 \times g$ for 10 minutes and resuspended in 1-mL PBS, and the total number of cells was determined using a hemocytometer. The cell suspension was cytocentrifuged (Cytospin 3; Shandon, Astmoor, UK) onto microscope slides (Super Frost S2441; Matsunami, Tokyo, Japan) at 450 rpm for six minutes and then stained using the Giemsa staining method (Muto Pure Chemicals Co., Ltd., Tokyo, Japan). At least 400 nonsquamous cells, including eosinophils, neutrophils, lymphocytes, macrophages, and ciliated epithelial cells, were differentially counted. The results are expressed as a percentage of the total nonsquamous cell counts.



Cut-off value : 234ng/ml (sensitivity 0.69, specificity 0.70)

Figure 1. ROC (Receiver-operator characteristic). Ability to differentiate between healthy subjects and asthmatic patients. The point on the ROC curve closest to (0, 1) was 234 ng/mL.

Statistical Analysis

Lung function values, the log-transformed (log) PC₂₀ for bronchial hyperresponsiveness, and the sputum cell differentiation ratio are expressed as the mean $\pm$ standard deviation. Differences between the asthmatic patients and healthy controls were analyzed using the Wilcoxon signed rank test with the level of significance (*p*-value) set at 0.05. The receiver-operating characteristic (ROC) curves were generated to determine the cut-off value for the ability of serum hs-CRP to differentiate between healthy controls and asthmatic patients based on the point on the ROC curve closest to (0, 1).¹⁵ Single relationships of hs-CRP and the other factors were performed using Spearman rank correlation test. Multivariate statistics were performed using a least squares linear regression with selection of all possible subsets. We performed a variable selection based on the multicollinearity. The ROC analysis and multivariate statistics were completed using JMP8 (Statistical Discovery; SAS Institute, Cary, NC).

RESULTS

Serum hs-CRP Levels of Asthmatic Patients and Healthy Subjects

The serum hs-CRP ranges in asthmatic patients and healthy controls were wide. The means (95% confidence interval) of them were 476 ng/mL (327–625) and 257 (155–359). The log serum hs-CRP levels were significantly higher in asthmatic patients compared with healthy controls (2.49 ± 0.41 versus 2.21 ± 0.39 , respectively; *p* = 0.002) (Table 1).

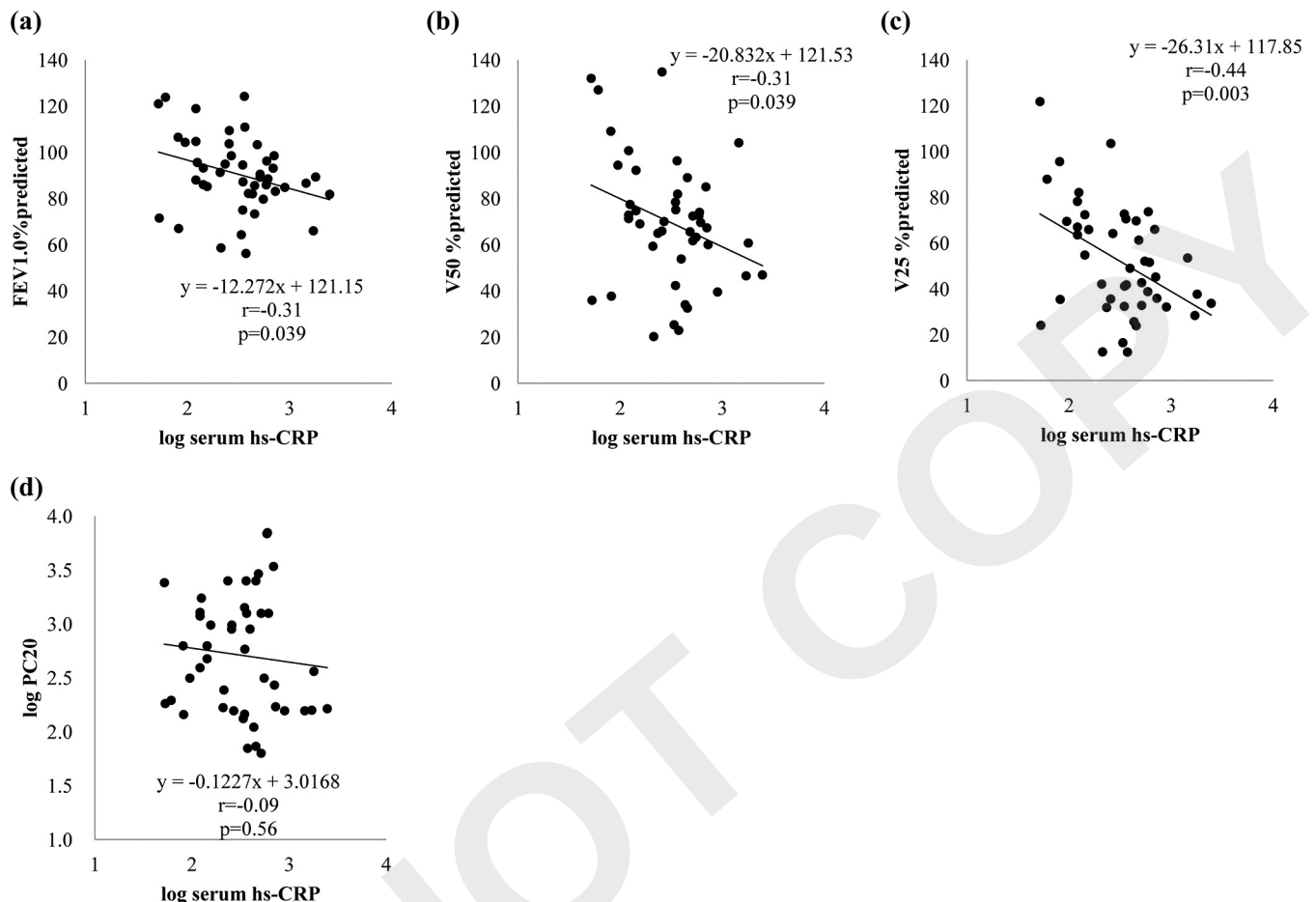


Figure 2. Single correlations between serum log hs-CRP and respiratory functions in asthmatic patients. (a) Correlation between the log serum hs-CRP and forced volume in one second ($FEV_{1.0}$)_{r,pred.} (b) Correlation between the log serum hs-CRP and $V50_{r,pred.}$ (c) Correlation between the log serum hs-CRP and $V25_{r,pred.}$ (d) Correlation between the log serum hs-CRP and log concentrations of acetylcholine that produced a 20% fall in $FEV_{1.0}$ (PC_{20}).

ROC Curves to Evaluate the Sensitivity and Specificity of Serum hs-CRP to Detect Asthmatic Patients from Healthy Subjects

For the prediction of a healthy subjects or asthmatic patient, the maximum area under the curve was 0.70. We found that a lower hs-CRP cutoff of 234 ng/mL had an improved combination of sensitivity and specificity (0.69 and 0.70, respectively) (Fig. 1).

Single Correlations and Multiple Regression Analyses Between Log Serum hs-CRP and Other Factors in Asthmatic Patients

The log serum hs-CRP levels negatively correlated with respiratory function based on the $FEV_{1.0\%predicted}$ ($r = -0.31$, $p = 0.04$), $V50_{\%predicted}$ ($r = -0.31$, $p = 0.04$), and $V25_{\%predicted}$ ($r = -0.44$, $p = 0.003$). In contrast, the log serum hs-CRP values did not correlate with log PC_{20} ($r = -0.09$, $p = 0.56$) (Fig. 2).

In the fractional analysis of induced sputum, the log hs-CRP levels negatively and positively correlated with sputum macrophages ($r = -0.56$, $p < 0.001$) and

sputum eosinophils ($r = 0.34$, $p = 0.02$), respectively (Fig. 3) for single correlations between serum log hs-CRP and sputum cell differentiations in asthmatic patients.

Multiple regression statistics revealed that the log serum hs-CRP levels positively correlated with sputum eosinophils ($p = 0.019$) and neutrophils ($p = 0.042$) (Table 2).

DISCUSSION

Several studies have reported increased serum hs-CRP concentrations in patients with asthma, which is characterized with bronchial inflammation and bronchial hyperresponsiveness.^{9,10,16,17} We found significantly higher hs-CRP levels in nonsmoking patients aged 20–60 years with mild persistent asthmatic patients compared with healthy subjects. We also determined that the cut off value for serum hs-CRP to distinguish asthmatic patients from healthy subjects is 234 ng/mL with sensitivity of 0.69 and specificity of 0.70. The multiple analysis revealed that hs-CRP was related

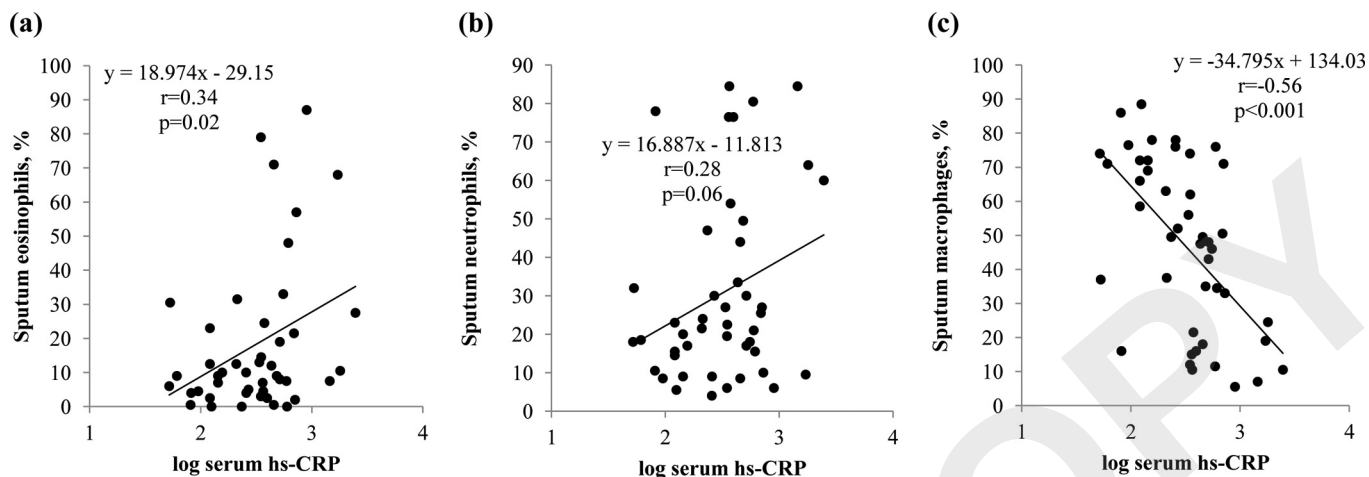


Figure 3. Single correlations between serum log hs-CRP and sputum cell differentiations in asthmatic patients. (a) Correlation between the log serum hs-CRP and sputum eosinophils ratio. (b) Correlation between the log serum hs-CRP and sputum neutrophils ratio. (c) Correlation between the log serum hs-CRP and sputum macrophages ratio.

Table 2 Multiple regression statistics for log serum hs-CRP

	Estimate	SE	t-Value	p-Value
Sex, male	0.110	0.060	1.84	0.074
Age, years	0.007	0.007	0.94	0.354
BMI	-0.016	0.022	-0.73	0.470
Atopic/nonatopic (atopic)	-0.012	0.066	-0.18	0.856
FEV _{1.0%} predicted	-0.005	0.004	-1.08	0.289
log PC ₂₀	0.138	0.125	1.1	0.278
Sputum neutrophils, %	0.006	0.003	2.11	0.042
Sputum eosinophils, %	0.008	0.003	2.47	0.019

$R^2 = 0.239$, probability of obtaining a greater *F*-value: $p = 0.0185$ (analysis of variance).

with eosinophilic and neutrophilic inflammation of airway independently in asthmatic patients.

A positive correlation was found between airway eosinophilic inflammation and serum hs-CRP levels, providing evidence that the serum hs-CRP level is a reflection of eosinophilic inflammation in the airway. This finding also supports the results of Takemura *et al.*, who reported that increased serum hs-CRP concentrations were correlated with increased eosinophil counts and decreased respiratory function in steroid-naïve patients.² Our multiple regression analysis revealed a significant correlation of serum hs-CRP with both sputum neutrophils and eosinophils, indicating that the level of serum hs-CRP is increased in both eosinophil-dominated and neutrophil-associated inflammations. Therefore, serum hs-CRP levels are shown to increase when airway inflammation accom-

panies obstruction, regardless of the cell type associated with bronchial asthma.

Whether the serum hs-CRP correlates with respiratory functions or airway hyperresponsiveness is not clarified.^{3,4} A previous study demonstrated correlations between an increased serum hs-CRP level and decreased respiratory function.¹⁸ In the present study, a negative correlation was found between serum hs-CRP values and respiratory function, suggesting that hs-CRP levels increase as a result of airway obstruction and inflammation in even mild bronchial asthma. The present results did not demonstrate a significant correlation between serum hs-CRP levels and bronchial hyperresponsiveness.

Olafsdottir *et al.* reported that serum hs-CRP was significantly higher in patients with nonallergic asthma than the patients with allergic asthma.¹⁶ Butland *et al.* also reported that the prevalence of nonatopic asthma was increased according to increased hs-CRP concentrations but that of atopic asthma was not.¹⁹ Smoking is another cause of increased serum hs-CRP, and smoking cessation is reported to reduce hs-CRP.²⁰ One study reported that smoking affects hs-CRP levels independently of asthma.³ However, another study demonstrated a correlation between smoking and hs-CRP level only in nonatopic asthma patients.¹⁹ That study also reported that body mass index influenced serum hs-CRP concentrations in nonatopic asthma patients but not the atopic population as a whole. In the present study, atopic factor did not affect hs-CRP in multiple regression analysis.

The hs-CRP may be not a very good indicator for asthma diagnosis itself.¹¹ Some markers of exhaled breath condensates or fractional nitric oxide can estimate the airway information specifically.^{11,21–23} However, hs-CRP increased by various systematic inflam-

mation, including airway eosinophilic and neutrophilic inflammation, hs-CRP measurement might be useful to detect of the beginning of the asthma worsening triggered by allergic exposure and/or airway infection, both of them are essential for the disease control. We are planning another study for this purpose.

The primary limitation was still whether we could exclude the effect of the other factors. We strictly excluded the subjects with complications that were likely to increase the level of hs-CRP, such as heart disease, hypertension, autoimmune disease, and hyperlipidemia, even they were very mild severity. As a result, the only 45 asthmatic patients were selected from 68 candidates, and only 40 healthy controls from 53 candidates were included to the study.

In conclusion, the serum hs-CRP value is useful in assessing airway inflammation in nonsmoking asthmatic patients aged 20–60 years without complications, such as heart disease, hypertension, autoimmune disease, hyperlipidemia, chronic obstructive pulmonary disease, and infection. Serum hs-CRP levels are elevated in asthma patients with either eosinophil-mediated or neutrophil-associated inflammation and could be informative sign of the very early phase of asthma exacerbation.

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