

Original Article



Staphylococcal Enterotoxin-Specific IgE Sensitization: A Potential Predictor of Fixed Airflow Obstruction in Elderly Asthma

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ABSTRACT

Purpose: *Staphylococcus aureus* enterotoxin-specific immunoglobulin E (SE-sIgE) sensitization tends to increase with age and is known to be associated with asthma and severity in older adults. However, the long-term impact of SE-sIgE in the elderly remains unknown. This study aimed to examine the relationships between SE-sIgE and fixed airflow obstruction (FAO) in a cohort of elderly asthmatics.

Methods: A total of 223 elderly asthmatics and 89 controls were analyzed. Patients were assessed for demographics, history of chronic rhinosinusitis (CRS), asthma duration, acute exacerbation frequency, and lung function at baseline and then were prospectively followed up for 2 years. Serum total IgE and SE-sIgE levels were measured at baseline. Airflow obstruction was defined as forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio < 0.7 at baseline and FAO was defined as FEV1/FVC ratio < 0.7 over the 2-year follow-up.

Results: At baseline, the prevalence of airflow obstruction was 29.1%. Patients with airflow obstruction were significantly more likely to be male, and have a positive smoking history, comorbid CRS, and higher levels of SE-sIgE than those without airflow obstruction. Multivariate logistic regression analysis showed that airflow obstruction was significantly associated with current smoking and SE-sIgE sensitization at baseline. After the 2-year follow-up, baseline SE-sIgE sensitization was consistently related to FAO. Meanwhile, the number of exacerbations per year was significantly correlated with SE-sIgE levels.

Conclusions: Baseline SE-sIgE sensitization was significantly associated with the number of asthma exacerbations and FAO after the 2-year follow-up in elderly asthmatics. These

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There are no financial or other issues that might lead to conflict of interest.

findings warrant further investigation of the direct and mediating roles of SE-sIgE sensitization on airway remodeling.

Keywords: Asthma; immunoglobulin E; enterotoxins; *Staphylococcus aureus*

INTRODUCTION

Staphylococcus aureus (SA) is a normal human flora and frequent colonizer. SA is a species of gram-positive cocci, and facultative aerobic-anaerobic bacterium, mainly found in human skin and upper airways.¹ It is known that about 20%–25% of the general population are persistent colonizers and 60% are intermittent carriers.^{2–4} A meta-analysis on nasal colonization of SA reported that the mean prevalence was about 30% in 5 different geographic locations.⁵ More than 70% of SA secrete exotoxin (*e.g.*, toxic shock syndrome toxin, TSST-1) and staphylococcal enterotoxins (SE) such as SEA, SEB, SEC, SED, SEE, and SEG, which are known as potent T cell superantigens. These superantigens directly interact with T cells and class II major histocompatibility complex molecules (MHC class II) to induce polyclonal T cell proliferation and activation. Activated T cells secrete type 2 cytokines such as interleukin (IL)-4, IL-5, and IL-13, which lead to eosinophilic inflammation and polyclonal immunoglobulin E (IgE) formations.⁶ They are considered to play a crucial disease-modifying role in upper and lower airway diseases.

Recent studies have reported that staphylococcal enterotoxin-specific immunoglobulin E (SE-sIgE) sensitization is associated with airway diseases such as allergic rhinitis, chronic rhinosinusitis (CRS), and asthma.^{2,7} In asthma, SE-sIgE sensitization is associated with the disease onset and severity, especially in the elderly. In the community-based population, SE-sIgE concentration was significantly associated with asthma.^{8,9} A recent meta-analysis study corroborated the relationship between asthma and SE-sIgE sensitization.¹⁰ Meanwhile, a European cohort study showed that SE-sIgE sensitization was related to asthma severity and acute exacerbations (AEs), use of oral corticosteroids, and lower lung functions.¹¹ Additionally, our previous study using the same data as the current study showed that SE-sIgE was significantly linked to eosinophilic asthma and its severity in late-onset elderly patients.¹²

Asthma is a heterogeneous disease which involves chronic airway inflammation and presents with variable expiratory airflow limitation, particularly in older adults.¹³ The variable airflow limitation can develop into persistent airflow limitation or fixed airflow obstruction (FAO) in some patients, and FAO is found in about 55%–60% of severe or difficult-to-treat adult asthmatics.^{14,16} Generally, FAO in asthma has been mainly thought as a consequence of airway remodeling due to persistent airway inflammation. In clinical practice, pulmonary function test is commonly used to assess physiologic airway remodeling.¹⁷ However, there has been no longitudinal study elucidating the association between SE-sIgE sensitization and FAO in elderly asthmatics. In consideration of the cross-sectional associations between SE-sIgE sensitization and lower lung functions, we hypothesized that SE-sIgE sensitization is associated with FAO. Also, the long-term impact of SE-sIgE sensitization remains unknown in the elderly. Thus, the present study aimed to examine how SE-sIgE sensitization is associated with FAO in elderly asthmatics based on a prospective cohort design.

MATERIALS AND METHODS

Study sample

Our prospective cohort study analyzed the data from late-onset elderly asthmatics and non-asthmatic controls (onset age ≥ 40 years and baseline age ≥ 65 years). Elderly asthmatics were recruited from a previously reported cohort study.¹⁸ It was a prospective observational multicenter study with a 5-year follow-up (2009–2013) and asthmatics were recruited from nine referral hospitals in South Korea. Among the participants in the cohort, this study included patients recruited from the Seoul National University Hospital, who had been evaluated for CRS, nasal polyp (NP), and follow-up pulmonary function outcomes.

Asthma was diagnosed by allergists, based on the clinical history and positive bronchodilator responsiveness (BDR) in pulmonary function test at baseline or after anti-asthmatic treatment. Comorbidities were defined using the following question; “Have you ever been diagnosed with or treated by a doctor?”

The same exclusion criteria were applied to both asthma patients and controls. Subjects were excluded when they had any comorbidities that could affect respiratory symptoms or serum IgE levels, including eosinophilic granulomatosis with polyangiitis, allergic bronchopulmonary aspergillosis, atopic dermatitis, recent treatment with anti-IgE monoclonal antibody or corticosteroid, congestive heart failure, and malignancy plus cases with concomitant diseases. Also, those without serum collection or follow-up were excluded. The final sample included 223 elderly patients with asthma.

Non-asthmatic elderly controls were recruited through bulletin board advertisements. The absence of asthma was confirmed based on a questionnaire and methacholine challenge test (MCT). The questionnaire asked if they had previously had asthma or wheezing. Subjects with negative results both for the questionnaire and MCT (provocative concentration causing a 20% fall in FEV1 [PC20] > 16 mg/mL by a 5-breath dosimeter method) were recruited as controls.¹⁹ Informed consent was obtained from all participants and the study protocol was approved by the Institutional Review Boards of all participating institutions (IRB number: H-0812-045-266).

Baseline assessment

Demographic information of participants such as age, sex, smoking history, body mass index (BMI), and disease duration were collected. Smoking status was defined as follows. A never smoker was a non-smoker or who smoked less than 5 pack-year over the lifetime, and a former smoker was who smoked more than 100 cigarettes over the lifetime and had stopped smoking for more than 6 months. Current smoker was who smoked 100 or more cigarettes over the lifetime and was currently smoking or had quit smoking for less than 6 months. BMI was calculated by dividing weight (kg) by the square of height (m^2).

CRS was operationalized as a condition in which 2 or more of the following symptoms persisted for more than 12 weeks over the past year; nasal discharge/obstruction, anosmia, and/or facial pain.²⁰ The NP was evaluated through rhinoscopy or a history of NP surgery. Based on this, subjects were classified into 3 categories: no CRS, CRS without NP (CRSsNP), and CRS with NP (CRSsNP). The predicted FEV1 and FVC were measured with about 3-month intervals based on the methods of Morris.²¹ Atopy was defined based on a positive skin test result, meaning that the allergen-induced wheal is 3 mm or greater than the negative control in tests performed with 55 common allergens.

Medication adherence was checked by the research coordinator at each visit to maintain compliance and correct use of inhalers. Study participants were asked how often they used inhalers on days with and without asthma symptoms, and they were asked to bring their inhalers to check the dose counter and appropriateness of inhaler usage. They received a formal training whenever they found that they had difficulty using their inhalers.

Outcome assessment

Asthma duration was defined as the time between the initial asthma diagnosis and the baseline assessment. Late-onset asthma was defined as asthma diagnosed at and after the age of 40 years. After the baseline assessment, asthma outcome was prospectively evaluated. AE was determined 1) when systemic corticosteroids were increased for at least 3 days after the maintenance dose, or when a subject who had not been previously treated with systemic corticosteroids was treated with systemic corticosteroids for at least 3 days, or 2) when a subject was hospitalized or visited the emergency room due to an asthma attack. The annual frequency of AE was based on the last 1 year of data.

A pulmonary function indicator of pre-bronchodilator (BD) FEV1/FVC < 0.7 at baseline was used to determine airflow obstruction. Pulmonary function tests were conducted as a part of routine clinical practice and the test results data were collected sequentially. It was determined as FAO if the best pre-BD FEV1/FVC ratio during the 2-year follow-up was less than 0.7.

Serum IgE measurement

Serum total IgE and SE-sIgE were measured using an immunoCAP 250 analyzer (ThermoFisher, Uppsala, Sweden). To measure the level of SE-sIgE, staphylococcal enterotoxin mix was used (SEA, SEC, TSST-1; ThermoFisher).⁹ SE-sIgE sensitization was defined as serum SE-sIgE $\geq$ 0.35 kU/L.

Statistical analyses

Descriptive data were expressed as means $\pm$ standard deviations, medians (interquartile ranges), or percentages. Group comparisons were performed using t-test, χ^2 test, and one-way analysis of variance. Correlations among nonparametric variables were examined using Spearman correlation analysis. Univariate logistic regression analyses were performed to examine the risk factors for airflow obstruction and FAO, and multivariate logistic regression analyses were performed after adjusting for confounding factors. All statistical tests, performed using Stata 15.1 (Stata Corporation, College Station, TX, USA), were 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics of 223 elderly asthmatics and 89 controls at the time of cohort enrollment are summarized in **Table 1**. The proportion of airflow obstruction was about 29.1% among the elderly asthmatics at baseline. The mean ages of those with and without airflow obstruction were 71.4 ± 5.0 and 70.9 ± 4.9 years, respectively. Also, those with airflow obstruction were significantly more likely to be male, use bronchodilators, and have a positive smoking history, CRS, heightened levels of SE-sIgE and SE-sIgE sensitization than their counterparts. However, there were no significant differences between the 2 groups in terms of atopy, blood eosinophils, mean inhaled corticosteroid dose, and use of leukotriene receptor antagonist.

Table 1. Baseline characteristics of the study subjects

At baseline	Control	Asthma without FEV1/FVC < 0.70	Asthma with FEV1/FVC < 0.70	P value
Number of subjects	89	158	65	
Age (yr)	70.4 ± 4.7	71.4 ± 5.0	70.9 ± 4.9	0.363
Female sex (%)	66.3	75.9	26.2	< 0.001
Smoking (%)				< 0.001
Never	71.9	83.5	53.8	
Former	21.4	10.1	26.2	
Current	6.7	6.3	20.0	
BMI (kg/m ²)	23.7 ± 3.5	24.6 ± 3.2	23.7 ± 3.0	0.067
CRS				< 0.001
No CRS	84.3	49.4	35.4	
CRSsNP	15.7	38.0	49.2	
CRSwNP	0.0	12.6	15.4	
Asthma duration (yr)	NA	7 (3–11)	6 (2–11)	0.788
Atopy (%)	NA	32.2	42.4	0.166
Blood eosinophils (/mm ³)	NA	201 (110–384)	209 (169–418)	0.245
Total IgE (kU/L)	91.0 (28.9–218.2)	76.1 (28.1–175.5)	143.9 (36.7–348.8)	0.160
SE-sIgE (kU/L)	0.10 (0.00–0.18)	0.13 (0.04–0.45)	0.34 (0.09–0.98)	< 0.001
SE-sIgE sensitization (%)	14.6	27.2	49.2	< 0.001
Baseline FEV1% pred.	NA	92.1 ± 19.4	78.5 ± 17.0	< 0.001
Baseline FEV1/FVC ratio	NA	0.76 ± 0.07	0.65 ± 0.08	< 0.001
ICS dose (µg of fluticasone equivalent/day)	NA	588.8 ± 269.0	669.6 ± 270.1	0.060
LABA (%)	NA	74.4	90.9	0.021
LAMA (%)	NA	10.8	23.7	0.049
LTRA (%)	NA	61.7	56.8	0.566

Data are presented as means ± standard deviations, medians (interquartile ranges), or percentages.

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyp; CRSwNP, chronic rhinosinusitis with nasal polyp; IgE, immunoglobulin E; SE-sIgE, *Staphylococcus aureus* enterotoxin-specific immunoglobulin E; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist; NA, not available.

Association between SE-sIgE sensitization and airflow obstruction

Univariate logistic regression analysis showed that former (odds ratio [OR] = 4.01; 95% confidence interval [CI], 1.84–8.72) and current smoking (OR, 4.90; 95% CI, 1.98–12.12) were significantly associated with airflow obstruction (**Supplementary Table S1**). In addition, being male (OR, 3.65; 95% CI, 2.0–6.77), low FEV1 (< 80%, OR, 3.58; 95% CI, 1.91–6.7), use of long-acting beta2-agonists (LABA) (OR, 3.44; 95% CI, 1.14–10.34), and SE-sIgE sensitization (OR, 2.59; 95% CI, 1.42–4.72) were significantly associated with airflow obstruction. Multivariate logistic regression was performed to examine the risk factors for airflow obstruction in elderly asthmatics (**Table 2**). Current smoking was found as a significant risk factor (OR, 3.50; 95% CI, 1.19–10.30). Additionally, SE-sIgE sensitization was significantly associated with airflow obstruction after adjusting for smoking status as well as age, sex, and CRS. However, atopy, blood eosinophilia, and asthma medications were not significantly related to airflow obstruction after adjusting for the same confounding factors. Meantime, the SE-sensitized group had significantly lower baseline FEV1/FVC ratio than the SE-negative group (**Supplementary Table S2**).

Clinical characteristics of asthmatics regarding FAO after the 2-year follow-up

After the 2-year follow-up, the proportion of asthmatics with FEV1/FVC ratio < 0.7 was 22.4%. The proportion of those with consistently low FEV1/FVC ratio (< 0.7) was 17.5% while the proportion of those with worsened airflow obstruction compared to baseline was 4.9% (**Fig. 1**). However, the proportion of low FEV1 (< 80%) decreased by more than 50% over the 2-year follow-up (**Supplementary Fig. S1**). **Table 3** shows the clinical characteristics of the subjects with and without FAO based on the results of the lung function test after the 2-year follow-up. Though being only marginally significant ($0.05 < P < 0.10$), subjects with FAO were older

Table 2. Factors associated with airflow obstruction in elderly asthmatics: multivariate logistic regression analysis

Baseline FEV1/FVC $\geq$ 0.70 (n = 158) vs. < 0.70 (n = 65) in asthma	Adjusted OR (95% CI)	P value
Age (yr)	0.97 (0.91–1.03)	0.313
Male sex	1.95 (0.85–4.49)	0.117
Smoking		
Never	Reference	
Former	2.52 (0.94–6.74)	0.065
Current	3.50 (1.19–10.30)	0.023
CRS		
No CRS	Reference	
CRSsNP	1.58 (0.78–3.19)	0.204
CRSwNP	1.19 (0.42–3.39)	0.740
Asthma duration	1.01 (0.97–1.06)	0.607
Atopy	1.33 (0.67–2.64)	0.420
Blood eosinophilia ($\geq$ 300/mm ³)	1.26 (0.31–5.04)	0.746
Total IgE $\geq$ 100 kU/L	1.12 (0.56–2.25)	0.739
SE-sIgE sensitization ($\geq$ 0.35 kU/L)	2.05 (1.05–4.01)	0.036
Baseline FEV1% pred. < 80%	2.64 (1.34–5.22)	0.005
Mean ICS dose	1.00 (0.99–1.00)	0.323
LABA	2.76 (0.87–8.71)	0.084
LAMA	1.63 (0.56–4.75)	0.372
LTRA	0.85 (0.40–1.81)	0.677

Adjusted for age, sex, smoking, and CRS.

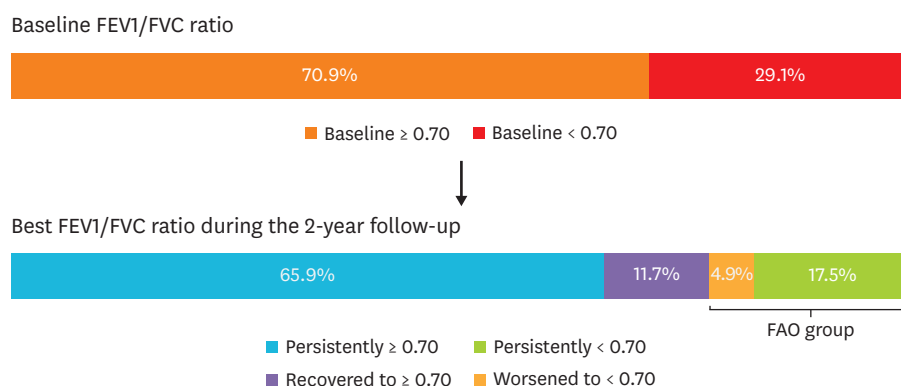
FEV1, forced expiratory volume in 1 second; FVC, forced volume capacity; OR, odds ratio; CI, confidence interval; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyp; CRSwNP, chronic rhinosinusitis with nasal polyp; SE, staphylococcal enterotoxin; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonist.

and had lower BMI than those without FAO. In addition, those with FAO were significantly more likely to be male and have a positive smoking history and a longer asthma duration than their counterparts. SE-sIgE sensitization rate and total IgE levels were significantly higher in the FAO group than the non-FAO group. The lung function of the FAO group was significantly lower than the non-FAO group, but there were no significant differences in atopy, eosinophilic inflammations, and the number of AEs per year.

Relationship between SE sensitization and FAO in elderly asthmatics after the 2-year follow-up

A univariate logistic regression analysis showed that the subjects with FAO after the 2-year follow-up were more likely to be male and have a longer asthma duration, a positive smoking history, CRSwNP, and greater SE sensitization than those without FAO (**Supplementary Table S3**).

A multivariate logistic regression analysis (**Table 4**) showed that asthma duration and former

**Fig. 1.** Changes of FEV1/FVC ratio over the 2-year follow-up.

FEV1, forced expiratory volume in 1 second; FVC, forced volume capacity; FAO, fixed airflow obstruction.

Table 3. Clinical features among elderly asthmatics depending on the presence of fixed airflow obstruction after the 2-year follow-up

Elderly asthma	FEV1/FVC $\geq$ 0.70	FEV1/FVC $<$ 0.70	P value
Subjects, n (%)	173 (77.6)	50 (22.4)	
Age (yr)	70.9 $\pm$ 4.8	72.3 $\pm$ 5.4	0.095
Female sex (%)	74.6	42.0	$<$ 0.001
Smoking (%)			$<$ 0.001
Former	12.7	22.0	
Current	4.6	30.0	
BMI (kg/m ²)	24.5 $\pm$ 3.2	23.6 $\pm$ 2.8	0.080
CRS			0.118
CRSsNP	41.6	40.0	
CRSwNP	11.0	22.0	
Asthma duration (yr)	6.6 (2.8–10.5)	10.4 (3–11.8)	0.030
Atopy (%)	33.7	37.7	0.593
Blood eosinophils (/mm ³)	201.5 (110–403)	200.0 (104–380)	0.474
Total IgE (kU/L)	75.2 (27.0–209.8)	144.3 (41.4–415.6)	0.027
SE-sIgE (kU/L)	0.13 (0.04–0.46)	0.35 (0.10–1.24)	0.002
SE-sIgE sensitization (%)	28.9	50.0	0.005
Best FEV1% pred.	100.2 $\pm$ 17.4	81.1 $\pm$ 13.3	$<$ 0.001
Best FEV1/FVC ratio	0.80 $\pm$ 0.05	0.63 $\pm$ 0.06	$<$ 0.001
Acute exacerbation of asthma (number/year)	0 (0–2)	1 (0–2)	0.134

Data are presented as means $\pm$ standard deviations, medians (interquartile ranges), or percentages.

FEV1, forced expiratory volume in 1 second; FVC, forced volume capacity; BMI, body mass index; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyp; CRSwNP, chronic rhinosinusitis with nasal polyp; IgE, immunoglobulin E; SE-sIgE, staphylococcal enterotoxin-specific immunoglobulin E.

smoking were only marginally ($0.05 < P < 0.10$) associated with FAO. However, current smoking and SE-sIgE sensitization were consistently and significantly associated with FAO (Model 1 in **Table 4**). Additionally, when FAO was regressed on CRS and SE-sIgE sensitization, the association between FAO and CRSwNP was non-significant, while the relationship between FAO and SE-sIgE sensitization was consistently significant (Model 2 in **Table 4**). Both baseline and follow-up FEV1/FVC ratios were significantly lower in the group sensitized to SE in univariate (data not shown) and multivariate logistic regression analyses (**Supplementary Table S4**). Meantime, the number of AEs per year showed a significant correlation with the level of SE-sIgE ($r = 0.43$ for asthmatics without FAO; $r = 0.40$ for asthmatics with FAO, both correlations significant with $P < 0.01$; **Fig. 2**). In never smokers, SE-sIgE and the frequency of AEs was significantly correlated in asthma patients without FAO, but it was non-significant in asthma patients with FAO (**Supplementary Fig. S2**).

Table 4. SE-sIgE sensitization and other factors associated with fixed airflow obstruction in elderly asthmatics after the 2-year follow-up: multivariate logistic regression analysis

Best FEV1/FVC ratio $\geq$ 0.70 (n = 173) vs. $<$ 0.70 (n = 50) in asthma	Adjusted OR (95% CI)	P value
Model 1		
Smoking		
Former	2.33 (0.92–5.88)	0.074
Current	8.90 (3.23–24.51)	$<$ 0.001
Asthma duration (yr)	1.04 (0.99–1.09)	0.070
SE-sIgE sensitization ($\geq$ 0.35 kU/L)	2.40 (1.16–5.00)	0.019
Model 2		
CRS		
CRSsNP	0.99 (0.47–2.05)	0.971
CRSwNP	1.81 (0.70–4.65)	0.221
SE-sIgE sensitization ($\geq$ 0.35 kU/L)	2.24 (1.13–4.43)	0.020

Model 1: Adjusted for smoking and asthma duration, Model 2: Adjusted for CRS.

FEV1, forced expiratory volume in 1 second; FVC, forced volume capacity; OR, odds ratio; CI, confidence interval; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyp; CRSwNP, chronic rhinosinusitis with nasal polyp; SE, staphylococcal enterotoxin.

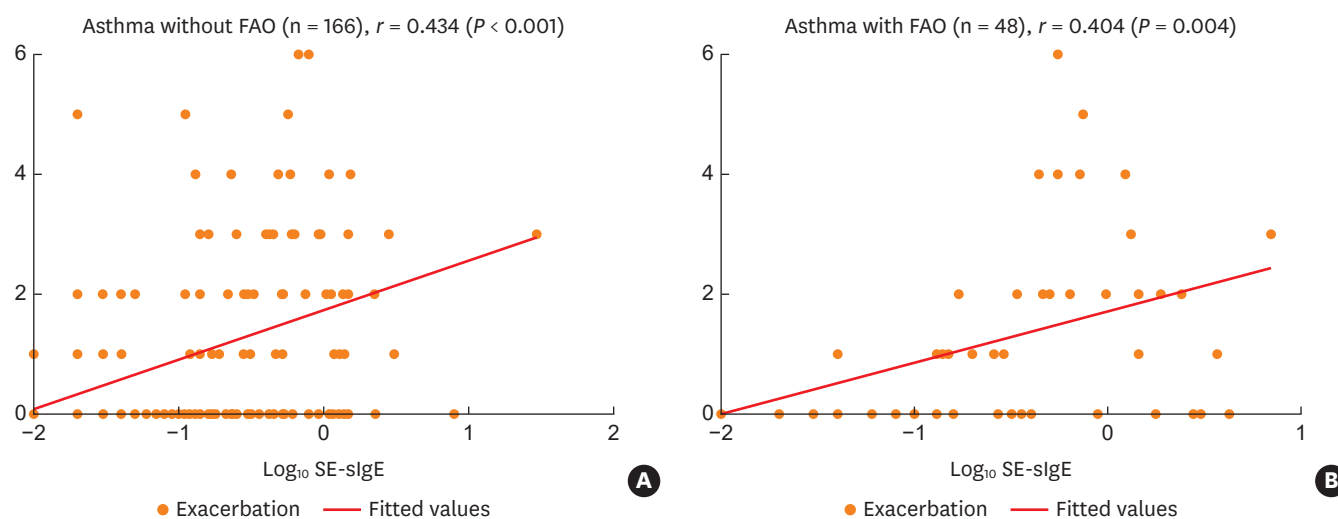


Fig. 2. Correlations between the frequency of annual asthma exacerbations and level of SE-sIgE depending on the presence of FAO. (A) Asthma without FAO ($n = 166$), $r = 0.434$ ($P < 0.001$). (B) Asthma with FAO ($n = 48$), $r = 0.404$ ($P = 0.004$). FAO, fixed airflow obstruction; SE-sIgE, staphylococcal enterotoxin-specific immunoglobulin E.

DISCUSSION

The present prospective cohort study examined the risk factors for FAO in elderly asthma patients. Elderly asthmatics had higher rates of CRS and SE-sIgE sensitization than controls. Among the elderly asthmatics at baseline, a significant association between current smoking and airflow obstruction was detected, and SE-sIgE was also significantly associated with airflow obstruction. In addition, pulmonary function test over the 2-year follow-up showed that subjects with persistent or worsened airflow obstruction were significantly more likely to be male and have a smoking history, longer asthma duration, greater SE-sIgE sensitization, and lower lung function than their counterparts. Multivariate logistic regression analysis also showed that FAO was significantly linked to current smoking and SE-sIgE sensitization, and the number of AEs per year showed a positive correlation with the levels of SE-sIgE. In never smokers, the number of AEs per year was consistently and significantly correlated with the levels of SE-sIgE. Our findings suggest that SE-sIgE may be a biomarker predicting FAO and asthma severity in elderly asthmatics.

Smoking is a well-known major risk factor for the decline of lung function, accelerating the negative effects of asthma. Besides, it increases the chance of airway inflammation in asthmatics, impairing asthma controls and compromising the corticosteroid treatment responsiveness.^{22,23} Additionally, smoking status is associated with sensitization to SEs in both general population and asthmatics, particularly in current smokers.^{8,24} Thus, in asthma patients with a positive smoking history, smoking itself not only affects airway inflammation and poor asthma controls, but also increases the risk of SE-sIgE sensitization, which may eventually contribute to the increased asthma severity and decreased lung function. FAO accompanied by airway remodeling may be attributable to smoking and SE-sIgE.

Meantime, it is worth noting the functional features of SE-sIgE reported in previous studies. Mucosal tissue polyclonal IgE from 14 NP subjects, but not serum, was able to activate mast cells on exposure to inhalant allergens and SEB.⁶ In atopic dermatitis patients with SE-sIgE sensitization, basophils from peripheral blood induced histamine secretion upon exposure

to SE.²⁵ Further, SEs may increase the chance of eosinophil survival by inhibiting eosinophil apoptosis and activate macrophages by inducing the secretion of cytokines like IL-8 and IL-12.^{26,27}

In terms of exacerbations, Tanaka found that SEA-IgE was closely associated with asthma control status and high level of FeNO.²⁸ Also, Sintobin *et al.*'s longitudinal cohort study²⁹ reported that SE-sIgE was related to an increased risk of asthma severity and AE. As in previous studies, notable finding of this study was the significant correlation between the level of SE-sIgE and the number of AEs per year. These findings suggest that SE-sIgE is a risk factor for the increased asthma severity. It was shown that superantigens such as SEs and TSST-1 were particularly immunogenic and intensified eosinophilic inflammation by releasing excessive cytokines including Th2 cytokines, which induced mast cell and basophil activation when SE-sIgE was present.^{6,30} Ultimately, these can lead to the aggravation of inflammation and asthma severity as well as frequent exacerbations, accelerating the decline in lung function. Therefore, we infer that persistent inflammation and repeated exacerbations may contribute to airway remodeling through both intrinsic and extrinsic factors such as decreased epithelial integrity, goblet cell hyperplasia, and mechanical injury, which can subsequently lead to FAO.

Meanwhile, there have been a few studies showing that SE-sIgE sensitization may be involved in chronic obstructive pulmonary disease (COPD), rather than asthma. Lymphocytes and neutrophils in bronchoalveolar lavage, CD8+ lymphocytes and granulocytes in lung tissue, as well as IL-13 mRNA expression in lung and goblet cell hyperplasia in airway wall were increased with the combined exposure to smoking and SEB in mice models.³¹ Additionally, SE-sIgE level was significantly higher in smoker subjects with both stable and exacerbated COPD, compared to healthy controls and smoker subjects without COPD.³² Moreover, SE-sIgE decreased significantly as FEV1 improved in hospitalized subjects due to exacerbated COPD. Although further studies are needed, the contribution of SE-sIgE in COPD to airway inflammation and airway remodeling is suggested. However, there has been no study directly examining the longitudinal association between asthma-COPD overlap (ACO) and SE-sIgE. Jointly considering our findings and previously demonstrated associations in asthma and COPD, SE-sIgE is suggested to be a biomarker for FAO, and involved in airway inflammation and airway remodeling, contributing to FAO and the ACO phenotype.

Our results showed that SE-sIgE sensitization was closely associated with airflow obstruction at baseline and persistent or worsened airflow obstruction after the 2-year follow-up. We also showed the significant correlation between SE sensitization and frequent AEs in line with previous studies. Therefore, we speculate that asthmatics with high SE-sIgE levels are more likely to experience severe asthma symptoms, poor asthma control, and frequent AEs, contributing to airway remodeling due to persistent airway inflammation, frequent bronchoconstriction, and mechanical injury. In sum, SE-sIgE sensitization might be a potential risk factor for FAO accompanied by airway remodeling in elderly asthmatics.

Besides SE-sIgE sensitization, Staphylococcal protein A secreted by SA can act as a B-cell superantigen, degranulating mast cells by binding them to V_H3-positive IgE. SA can stimulate innate lymphoid cells-2 (ILC-2) by secreting alarmins such as IL-25, IL-33, and thymic stromal lymphopoietin from the epithelium.¹ Subsequently, IL-5 released from ILC-2 or Th2 cells activates eosinophilic inflammation, followed by a series of reactions resulting in substances like extracellular eosinophilic traps, galectin 10, and Charcot-Leyden crystals, inducing persistent inflammation of the airway epithelium. These responses may eventually lead to

FAO accompanied by airway remodeling by worsening respiratory epithelial inflammation and undermining epithelial integrity.^{33,34} However, evidence from human studies is still lacking and further *in vivo* and mechanistic studies are needed on the interrelations between SA, including SE-sIgE, and respiratory epithelium.

This study is the first follow-up study on the associations between SE-sIgE sensitization and FAO in elderly patients with asthma. In particular, a previous study showed that the rate of SE-sIgE sensitization was significantly higher in smoking asthmatics compared to never smokers, and it was associated with eosinophilic inflammation and asthma severity.^{9,35} Consistently, the present study demonstrated that SE-sIgE sensitization was associated with smoking and frequent exacerbation, and further, it was closely related to airflow obstruction and FAO in conjunction with airway remodeling. FAO accompanied by airway remodeling accelerates the deterioration of lung function and increases morbidity, but proactive prevention methods or symptomatic treatment approaches for FAO are not readily available yet. This is due to our lack of understanding of the underlying pathophysiology of FAO.³⁶ At the same time, the prevalence of elderly asthma has recently been increasing, and it is considered to be a different disease entity characterized by more severe symptoms, poorer control, and lower quality of life than non-elderly asthma.³⁷ For the development of novel treatment strategies, a mechanistic understanding of the causes of FAO, especially in elderly asthmatics, is required. To this end, our study examined the relationship between SE-sIgE sensitization and FAO, offering a new insight on the associations between SE-sIgE sensitization and airway remodeling in elderly asthmatics.

However, there are several limitations in the present study. First, our study subjects were patients who visited the tertiary referral hospital and they were likely to have relatively high severity. Second, the definition of FAO was not based on post-BD values but on the best pre-BD FEV/FVC ratio over the 2-year follow-up. In the present study, lung function was measured sequentially as a part of routine clinical practice in which post-BD response was oftentimes not assessed. Nonetheless, the participants were sequentially assessed for pre-BD lung function at the tertiary referral hospital, and the best pre-BD value might be a reasonable approximation of post-BD value. Third, demographic information such as race and geographic location was not considered in this study. Fourth, type 2 biomarkers such as sputum eosinophil counts or fractional exhaled nitric oxide levels were not analyzed. Future studies need to address these limitations for the enhanced internal and external validity. Additionally, studies with longer-term follow-up are needed to further elucidate the relationship of SE-sIgE sensitization with airway remodeling and FAO.

In conclusion, SE-sIgE sensitization was significantly associated with FAO in elderly patients with asthma independent of other known risk factors for FAO such as asthma duration or smoking history. Moreover, SE-sIgE levels were significantly related to the frequency of AEs, suggesting that persistent inflammations and mechanical injury associated with SE-sIgE during exacerbations might be a potential FAO mechanism. Thus, SE-sIgE could have a pathogenic role in the development of persistent airflow obstruction in elderly patients with asthma and is deemed a biomarker of FAO. These findings warrant further investigation of the direct and mediating roles of SE-sIgE on airway remodeling and FAO.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1

Factors associated with airflow obstruction in elderly asthmatics: univariate logistic regression analysis

[Click here to view](#)

Supplementary Table S2

Changes in lung functions depending on SE sensitization in elderly asthmatics

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Supplementary Table S3

Factors associated with fixed airflow obstruction in elderly asthmatics after the 2-year follow-up: univariate logistic regression analysis

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Supplementary Table S4

Associations between SE sensitization and changes in lung functions in elderly asthmatics: multivariate logistic regression analysis

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Supplementary Fig. S1

Changes of FEV1 (%) over the 2-year follow-up.

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Supplementary Fig. S2

Correlations between the frequency of annual asthma exacerbations and level of SE-sIgE depending on the presence of FAO in never smokers.

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