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Staphylococcus aureus enterotoxin sensitization is associated with declined capsaicin cough sensitivity in chronic obstructive pulmonary disease

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Sensitization to *Staphylococcus aureus (S. aureus)* enterotoxins (SEs) A (SEA) and B (SEB) is associated with the pathogenesis of several chronic airway diseases, including asthma and chronic rhinosinusitis, but its role in chronic obstructive pulmonary disease (COPD) remains unclear. This cohort study aimed to investigate the impact of sensitization to SEs on total IgE levels, and capsaicin cough reflex sensitivity (C-CS) in COPD. This study prospectively enrolled 68 patients with COPD from the outpatient department at Nagoya City University Hospital and Shizuoka General Hospital, Japan, from June 2018 to January 2020 for posthoc analysis. Patient characteristics and biomarkers, including total IgE, and C-CS, were collected. We additionally measured and serum SEA-IgE and SEB-IgE levels for this analysis. Total IgE and SEs-IgE levels in individuals with COPD were compared to those of 20 healthy individuals. The correlation between C-CS and IgE levels was evaluated using Pearson's correlation coefficient. Multivariate analyses were used to adjust the impact on SE sensitization in total IgE levels and C-CS. The prevalence of SEs sensitization was higher in patients with COPD (23.5%, *N* = 16) than in healthy individuals (0%, *N* = 0) at a cut-off value of 0.35 UA/mL or more (*p* = 0.018). There was a negative correlation between total serum SEB-IgE levels and declined C-CS values. Multivariate analysis showed that SEs sensitization was associated with increased total IgE levels, and declined C-CS values. This study indicated that SEs sensitization was associated with increased IgE levels and decreased C-CS in COPD. This study was approved by the ethics committee of Nagoya City University (60-18-0012) and registered in the UMIN Clinical Trials Registry (Registry ID UMIN000032497).

Keywords Capsaicin cough reflex sensitivity, Chronic obstructive pulmonary disease, *Staphylococcus aureus*, *Staphylococcus aureus* enterotoxins, IgE

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide[1]. COPD is a complex disease influenced by a multitude of factors, including environmental and genetic components[2]. Additionally, COPD exacerbations are associated with various pathogens and allergens[2].

Allergens may be associated with the development of a Type-2 inflammatory environment in COPD. Sensitization to *S. aureus* enterotoxins (SEs), including SEA and SEB, is linked to the development of chronic upper and lower airway inflammation[3]. *S. aureus* colonization on the skin and nasopharyngeal membranes is commonly observed in approximately 25–30% of the healthy population[4]. *S. aureus* carriage and SEs sensitization are associated with allergic multimorbidity[5]. SEs can act as superantigens, triggering T-cell activation without conventional antigen presentation, thereby orchestrating airway inflammation[6]. Notably, previous research has suggested a role for SEs sensitization in the pathophysiology of chronic rhinosinusitis (CRS) with nasal polyps and asthma[7–10]. However, a recent study reported that SEs sensitization did not induce elevated eosinophil or

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fractional nitric oxide (FeNO) levels in patients with COPD[11]. Thus, potential impact of SEs sensitization on the pathophysiology of COPD remains unclear at present.

Acute exacerbation (AE) of COPD and pneumonia are the leading causes of death in patients with COPD. We have recently shown that declined capsaicin cough reflex sensitivity (C-CS) is associated with hospitalization in patients with COPD[12]. Meanwhile, we did not evaluate what factors were associated with declined C-CS in the original study. In asthma, lower levels of serum total IgE were associated with heightened C-CS in patients with asthma[13]. Since SE sensitization could facilitate IgE production, it could trigger the decline in C-CS in patients with COPD. However, no studies have investigated the association between SE sensitization and C-CS in either asthma or COPD.

Considering that SEs facilitate IgE production in COPD acting as superantigens, SE sensitization could contribute to declined C-CS. Furthermore, SE sensitization may be a risk factor for AE. Therefore, we performed a posthoc study to evaluate the impact of SE sensitization on the clinical outcomes of COPD.

Methods

Patients

We recruited patients with COPD from the outpatient departments at Nagoya City University Hospital and Shizuoka General Hospital, from June 2018 to January 2020 to assess the impact of C-CS on hospitalization due to community-acquired pneumonia (CAP) and AE in these patients[12]. COPD and comorbid asthma were diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 and the Japanese Respiratory Society Guidelines for the Management of Asthma-COPD overlap 2018[14], respectively. Inclusion criteria were as follows[12]: (1) a postbronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of <0.70; (2) persistent respiratory symptoms such as dyspnea, cough, sputum production, or wheezing; and (3) substantial exposure to noxious stimuli such as tobacco smoke or other environmental particles. Furthermore, we excluded patients if (1) they denied participation in the study; (2) had chronic respiratory diseases other than asthma; (3) had a postbronchodilator FEV_1/FVC ratio of ≥ 0.70; (4) resided in a nursing care home, were bedridden at home; (5) had a history of aspiration pneumonia; (6) underwent tubal feeding; or (7) had a respiratory infection within four weeks of enrollment or hospitalization due to AE-COPD or CAP within 12 weeks prior to enrollment. Out of the 80 patients initially considered, 69 were eligible for enrollment, and 68 completed the study follow-up (Fig. S1). This study was approved by the ethics committee of Nagoya City University (60-18-0012) and registered in the UMIN Clinical Trials Registry (Registry ID UMIN000032497). All methods were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. This study was conducted in accordance with the STROBE guidelines.

In our previous study, biomarkers, such as fractional exhaled nitric oxide (FeNO) and serum levels of total IgE, were measured in 28 healthy individuals between October 2015 and December 2017[15]. In addition, serum SEs-IgE levels were measured in 20 healthy individuals using stored samples[10]. All healthy individuals had no history of upper or lower respiratory disease. They provided consent for secondary use of anonymized data. (approval number of the Ethics Committee of Nagoya City University: 1165).

Measurements

Biomarkers, including blood eosinophil counts, FeNO, serum total IgE, and C-CS, and pulmonary and cardiac functions were measured at enrollment. The capsaicin cough challenge involved testing ten doubling concentrations of capsaicin (ranging from 0.61 to 312.5 μM)[16]. Higher values of C2 and C5 represented a decline in C-CS[15]. The detailed method of the capsaicin cough challenge test is described in the online supplementary manuscript.

Disease control, symptoms, and cough-specific quality of life (QoL) were evaluated at the time of enrollment using the COPD Assessment Test, a modified version of the Medical Research Council dyspnea scale, and Leicester Cough Questionnaire. AE and admissions due to severe AE and/or CAP were prospectively monitored for 12 months after enrollment. AE was defined as an acute worsening of respiratory symptoms requiring additional treatments, such as bronchodilators, antibiotics, and systemic corticosteroids, for ≥ 3 consecutive days. Additionally, a history of AE, CAP, and hospitalization within two years prior to enrollment were also evaluated[12].

SEs-IgE measurements

We measured serum levels of SEs-IgE (SEA-IgE and SEB-IgE, respectively) in titers (ImmunoCAP®; Phadia K.K., Tokyo, Japan) using the collected samples. The detection limit for each specific IgE titer was 0.10 UA/mL.

Sputum culture

Sputum samples were cultured to increase colonization by pathogenic microorganisms if it could be collected from patients. Bacterial culture was performed according to the national guideline issued by the Japan Registered Clinical Laboratories Association (uploaded in Japanese: https://www.jrcla.or.jp/).

Statistical analysis

Statistical analysis was performed using JMP 14.3 software (SAS Institute Japan, Tokyo, Japan). Continuous variables were presented as median (interquartile range), and categorical variables as numbers (%). Although total IgE levels were not measured at enrollment in four patients, values were obtained from stored samples. Two C-reactive protein values were missing, but were not measured and treated as blanks because they did not affect the main results of this study. COPD patients were divided into SEs sensitization (+) [SE (+)] and SEs sensitization (−) [SE (−)] groups. Comparisons between the two groups were made using the Wilcoxon rank-

sum test, Chi-squared test, and Fisher's exact test, as appropriate. Total IgE levels were compared among SE (+), SE (−), and healthy individuals using the Steel–Dwass test.

Correlations between IgE levels (total IgE and SEs-IgE) and C-CS (C2 and C5) were evaluated using Pearson's correlation coefficient. Levels of serum total IgE and SEs-IgE were log-transformed when assessing such correlations.

To adjust for the influence of confounders on the association of SEs sensitization with total IgE levels, declined C-CS, and AE, multiple logistic regression analyses were performed. Confounders identified were incorporated into each analysis. Current smoking was considered a confounder for all outcomes. Additionally, other potential confounders included: (1) total IgE levels: age, asthma, and rhinitis; (2) declined C-CS: cerebrovascular disease, male gender, and use of antidepressant drugs; (3) AE during the follow-up period: history of AE within the past two years, not taking inhaled corticosteroids, eosinophils $\geq 300/\mu L$, and severe airflow limitation (postbronchodilator FEV_1/FVC). We considered that SE-IgE was associated with them if the p value was ≤ 0.05 in the multiple logistic regression analyses.

Patient's characteristics

Table 1 presents the characteristics of the patients. The cohort included patients with severe COPD, with 29 (39.7%) having severe AE and/or community-acquired pneumonia that necessitated hospitalization within the two years preceding enrollment, and nine (13.4%) receiving home oxygen therapy. According to the GOLD 2018 guidelines, twenty (29.4%) patients were classified in Group D. Additionally, ten (14.7%) had comorbid asthma. Sputum samples were collected from 36 (52.9%) patients. *S. Aureus* was found in seven patients. When compared to the healthy individuals (Table S1), ages were older, the proportion of males were higher, and lung function were lower in patients with COPD ($p < 0.0001$ for all). Meanwhile, body mass index and levels of total IgE and FeNO were similar between the two groups.

In the previous study, we considered that levels of SEs-IgE ≥ 0.10 UA/mL were clinically meaningful in patients with CRS, particularly when they had comorbid asthma[10]. However, the rate of individuals whose values of SEs-IgE were ≥ 0.10 UA/mL was similar between patients with COPD and healthy individuals (Fig. 1 A and C). In contrast, no healthy individuals showed levels of SEs-IgE ≥ 0.35 UA/mL (Fig. 1D and F). Sensitization

	All patients ($n=68$)	SE (−) ($n=52$)	SE (+) ($n=16$)	p values
Age	75 (70, 75)	74 (70, 77)	75 (70, 80)	0.36
Body Mass Index, kg/m^2	21.8 (19.1, 24.0)	21.9 (19.5, 24.0)	21.3 (18.8, 24.2)	0.57
Sex, male	58 (85.3)	43 (82.7)	15 (93.8)	0.43
Smoking, ex/ current	54 (79.4)/14 (20.6)	44 (84.6)/ 8(15.4)	10 (62.5)/ 6(37.5)	0.078
Pack-years	51.5 (36, 73.5)	52.5 (37.5, 73.5)	46.5 (24.6, 83.3)	0.66
GOLD classification, A/ B/ C/ D	19 (27.9)/ 23 (33.8)/ 6 (8.8)/ 20 (29.4)	14 (27)/17 (33)/ 6 (12)/15 (29)	5 (31)/6 (38)/ 0 (0)/5 (31)	0.33
COPD stage 1/2/3/4	14 (20.6)/38 (55.9)/ 12 (17.6)/4 (5.9)	12 (23)/29 (56)/ 8 (15)/3 (6)	2 (13)/9 (56)/ 4 (25)/1 (6)	0.72
Sputum, +	36 (52.9)	26 (50.0)	10 (62.5)	0.41
SA colonization, +*	7 (10.3)	3 (11.5)	4 (40.0)	0.076
LAMA, +	48 (70.6)	35 (67.3)	13 (81.3)	0.36
LABA, +	57 (83.8)	42 (80.8)	15 (93.8)	0.44
ICS, +	21 (30.9)	14 (26.9)	7 (43.8)	0.23
Home oxygen use, +	9 (13.2)	6 (11.5)	3 (18.8)	0.43
Antidepressant drugs, +	3 (4.4)	2 (3.9)	1 (6.3)	0.56
ACE inhibitors, +	1 (1.5)	1 (1.9)	0 (0)	> 0.99
Pneumococcal vaccination, +	34 (50)	27 (51.9)	7 (43.8)	0.78
Asthma, +	10 (14.7)	10 (19.2)	0 (0)	0.10
Cerebrovascular disease, +	7 (10.3)	4 (7.7)	3 (18.8)	0.34
Pneumonia < 2 year, +	20 (29.4)	16 (30.8)	4 (25.0)	0.76
A history of pneumonia ≥ 2, +	5 (7.4)	3 (5.8)	2 (12.5)	0.58
AE < 2 year, +	19 (27.9)	15 (28.8)	4 (25.0)	> 0.99
A history of AE ≥ 2, +	8 (11.8)	7 (13.5)	1 (6.3	0.67
Hospitalization < 2 year, +	27 (39.7)	21 (40.4)	6 (37.5)	> 0.99
A history of hospitalization ≥ 2, +	10 (14.7)	7 (13.5)	3 (18.8)	0.69
mMRC scale, Grade	1 (1, 3)	1 (1, 3)	1.5 (1, 3)	0.52
mMRC ≥ Grade 2, +	33 (48.5)	25 (48.1)	8 (50)	> 0.99
CAT, point	13 (6, 18)	14 (6, 19)	12 (6, 18)	0.88
CAT ≥ 10, +	39 (57.4)	22 (42.3)	7 (43.8)	> 0.99
LCQ, point	19.1 (17.3, 20.2)	19.1 (16.9, 20.2)	19.3 (17.4, 20.3)	0.67

Table 1. Patient's characteristics. *$n=36$ (SE [−]: $n=26$/ SE [+]: $n=10$)

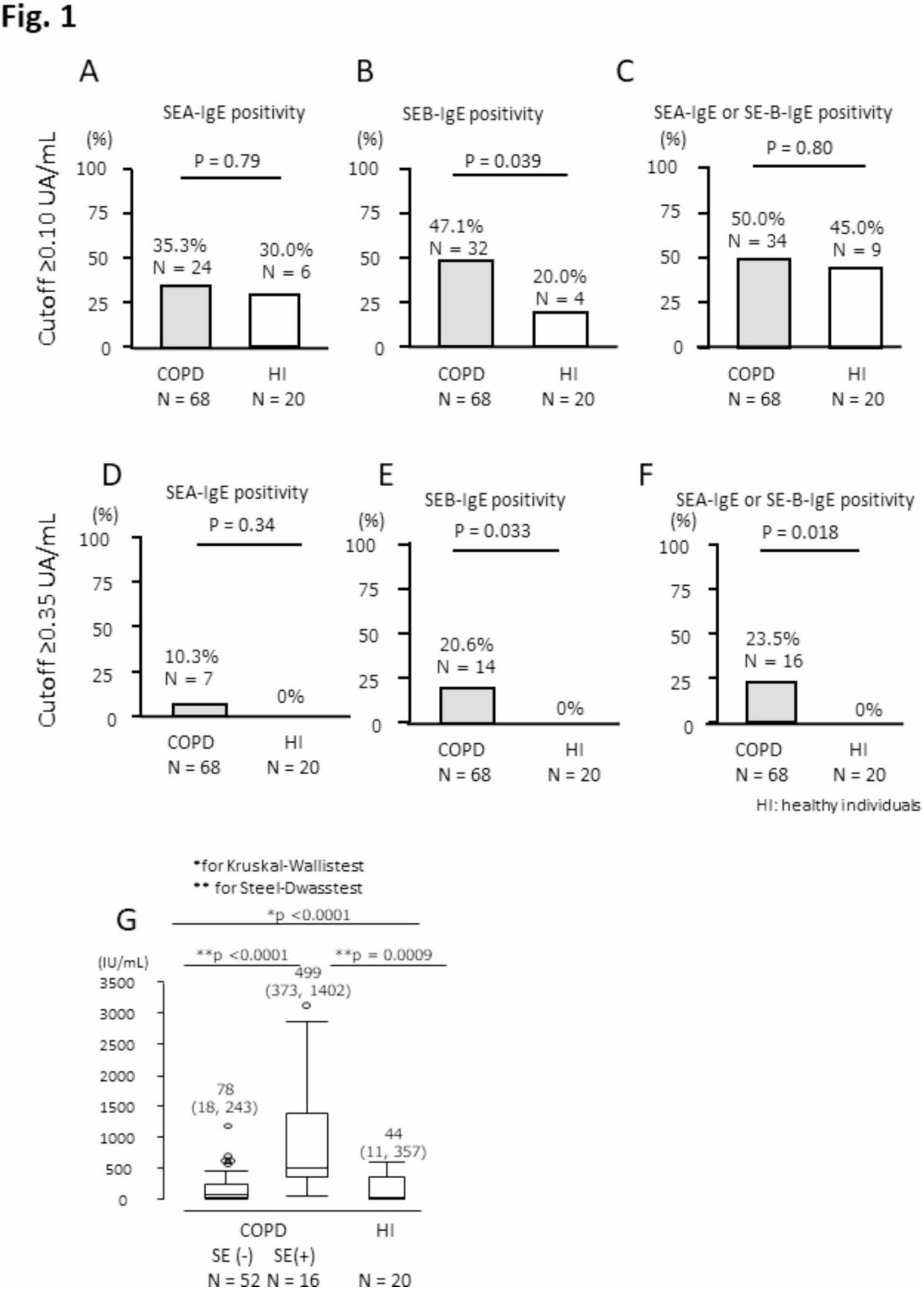

Fig. 1. An impact of SEs sensitization on COPD and IgE levels. The SEs-IgE cut-off values were set at ≥0.10 UA/mL (**A**–**C**) and ≥0.35 UA/mL(**D**–**F**). Comparison of total IgE levels among SE(+), SE(−), and HI(G).

to SEs ($n=16$ [23.5%]), especially SEB ($n=14$ [20.6%]), was more frequent in patients with COPD than in healthy individuals (0%) when the cut-off value was set at 0.35 UA/mL ($p=0.033$ for SEB and $p=0.018$ for SEs, respectively. Figure 1E and F).

Stratifying patients based on the presence or absence of SEs sensitization revealed no differences in terms of disease severity, COPD-related symptoms, cough-specific QoL, history of AE, pneumonia, hospitalization

within the past two years, or comorbid asthma. However, *S. aureus* colonization tended to be more prevalent in the SE (+) group compared to the SE (−) group (Table 1).

Results

Biomarkers and physiological functions

Serum total IgE levels were significantly higher in the SE (+) group compared to both the SE (−) group and healthy individuals (Fig. 1G). In patients with COPD, a significant, but moderate correlation was observed between serum IgE levels and SEs-IgE levels (Fig. 2A), a correlation not detected in healthy individuals (Fig. 2B). Blood eosinophil counts and FeNO, both biomarkers of Type-2 inflammation, showed no significant differences between the SE (+) and the SE (−) groups. Notably, concentrations of both C2 and C5 were higher in the SE (+) group than in the SE (−) group, indicating a more prominent decline in C-CS levels in the SE (+) group (Table 2). Higher levels of serum total IgE and SEB-IgE were significantly correlated with higher values of C2 and C5, suggesting an association between increased levels of serum total IgE, SEs sensitization, and a decline in C-CS (Fig. 2C and D).

AE, hospitalization, and pneumonia during one-year follow-up period

During the 12-month follow-up period, 15 patients experienced AE, with eight of them requiring hospitalizations due to severe AE and/or CAP. A higher proportion of individuals in the SE (+) group experienced AE compared to those in the SE (−) group (Fig. S2A). However, SEs sensitization did not have an impact on hospitalization or pneumonia (Figures S2B, C).

The influence of total IgE levels, C-CS, and AE in stratification with SEA/SEB

When analyses of the influence of total IgE levels, C-CS and AE were performed for the stratification with SEA and that with SEB, the trends observed were consistent with the combined analysis. However, some of the variables (the proportion of AE, and C5 for both, and C2 for SEB) lacked statistical significance ($p < 0.05$) likely because of the limited sample size (SEA-IgE positive: $n = 7$, SEB-IgE positive $n = 14$).

Role in SE sensitization on elevated total IgE levels, declined C-CS, and AE-COPD

To determine the association of SEs sensitization with elevated total IgE levels, declined C-CS, and AE, we performed multivariate analyses adjusting for confounders. The results of the multivariate analysis after adjusting confounders suggested that SEs sensitization contributed to elevated levels of serum total IgE, decline in C-CS, and increased frequency of AE during the follow-up period in patients with COPD (Tables 3A–3D).

During the follow-up, we further evaluated whether C-CS was associated with AE through SE sensitization. However, we found no evidence supporting this hypothesis (data not shown).

Discussion

This posthoc study is the first to reveal that SEs sensitization at a threshold of ≥ 0.35 UA/mL, particularly SEB sensitization, is more prevalent in patients with COPD than in healthy subjects. Importantly, we found that SEs sensitization was associated with a lower C-CS. Although *S. aureus* colonization is potentially more relevant to clinical outcomes, SE sensitization may influence the decline in C-CS in patients with COPD by inducing IgE production. A recent study by Karakioulaki et al.[11] reported that SEs sensitization did not impact eosinophil and FeNO levels under stable patient conditions, it led to elevated levels of serum total IgE. Although the results were inconclusive because of the small sample size, SE sensitization may worsen the clinical condition of patients with COPD.

In our previous study, we observed that SE-IgE levels of ≥ 0.10 UA/mL influenced clinical phenotype of patients with CRS[10]. Even at low sensitization levels, SEs induced increased expression of Type-2 inflammation systemically and locally in these patients[10]. Moreover, other studies have demonstrated that SE-IgE levels of ≥ 0.10 UA/mL are associated with the development and exacerbation of asthma, in terms of severity, use of oral corticosteroids, hospitalization, and lower lung function[7,17,18]. The current study revealed a difference in SEs sensitization, especially SEB sensitization, between patients with COPD and healthy controls when the cut-off value was set at 0.35 UA/mL. Meanwhile, Karakioulaki et al. did not observe a difference in SEs-IgE positivity between COPD patients and healthy individuals[11]. This discrepancy may be explained by the characteristics of healthy individuals. Most of the healthy individuals in our cohort comprised never smokers ($n = 18$), and Karakioulaki's cohort included current smokers. The GA^{2}LEN study clearly demonstrated that heavy smoking was associated with sensitization to SEs[18]. Thus, different rate of smokers may lead to a conflict outcome between ours and Karakioulaki's. Age may also influence the rate of SE sensitization between patients with COPD and healthy individuals. However, the relationship between age and SE sensitization in the adult population remains controversial. A recent study showed that older age was a risk factor for SE sensitization in the general population[19], whereas age had no effect in patients with asthma[18]. These findings suggest that the minimum levels of serum SEs-IgE necessary to trigger a response might vary across different diseases.

Elevated levels of total IgE have been correlated with an increased risk of dyspnea, AE, and a decline in lung function in patients with COPD[20,21]. Prevalence of SEs sensitization is higher in patients with COPD during stable and exacerbated conditions, compared to nonsmoking and smoking healthy individuals[22]. Although we did not observe a difference in the levels of total IgE between patients with and without COPD, we observed a moderate correlation in patients with COPD between the levels of total IgE and SEs-IgE. However, this correlation was absent in either nonsmoking or smoking healthy individuals[22]. Thus, SEs sensitization may stimulate the production of IgE during a chronic inflammatory response by acting as superantigens.

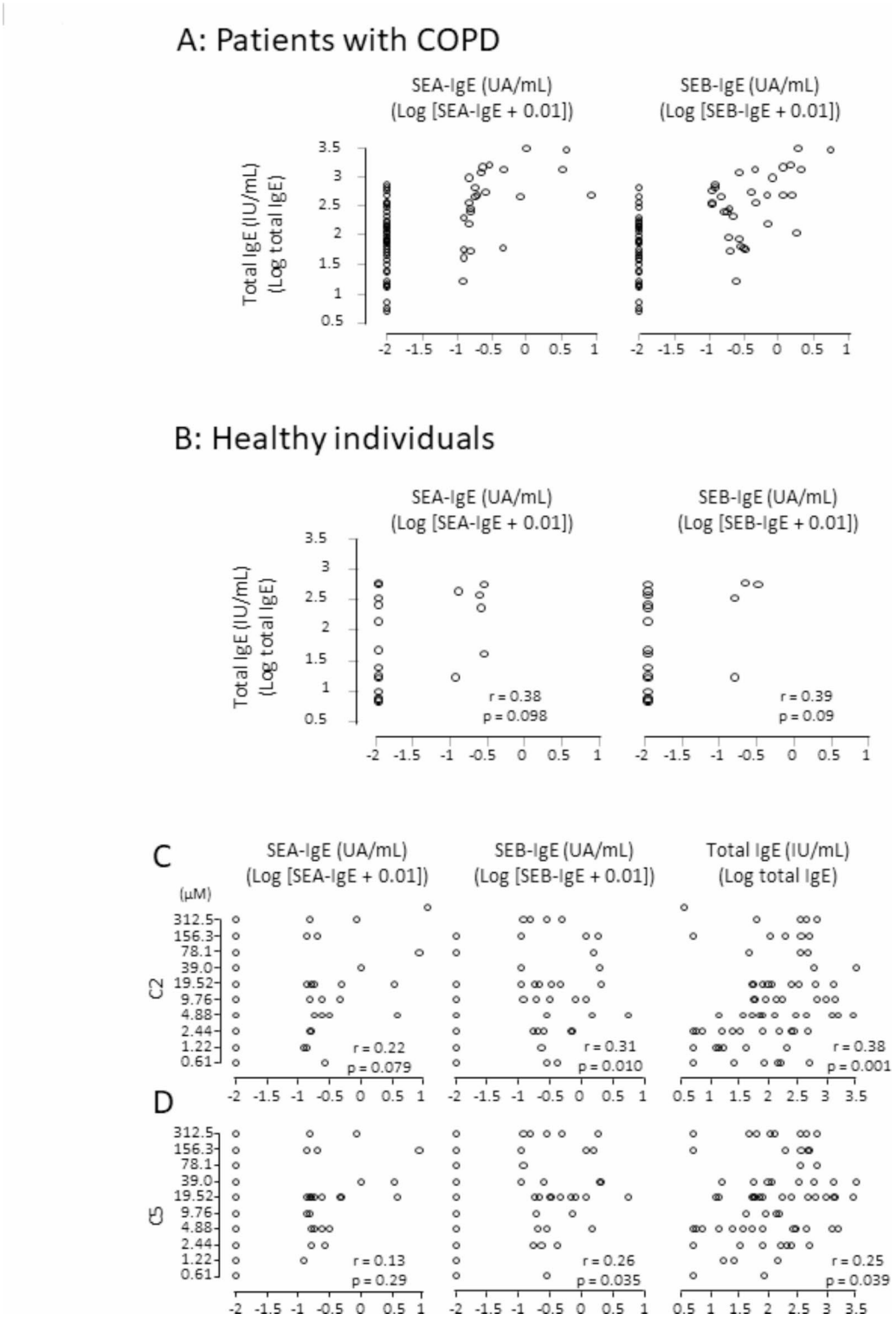

Fig. 2. Correlations between SEs-IgE and total IgE/C-CS. Patients with COPD (**A**), healthy individuals (**B**), C2 (**C**) and C5 (**D**).

C-CS recognized as a biomarker of airway neuronal dysfunction in asthma, and heightened C-CS was associated with the pathophysiology of nonatopic asthma, poorly controlled asthma, asthma severity, and asthma exacerbation[13,16]. Lower levels of total IgE have contributed to heightened C-CS[13]. In this study, we observed a similar trend in the influence of total IgE levels on C-CS in patients with COPD, as higher levels of total IgE correlated with a decline in C-CS (Fig. 2B). These suggest that the nonallergic response is associated with airway neuronal dysfunction. In contrast, direct challenge with house dust mites into the airways could increase

	All patients ($n=68$)	SE (-) ($n=52$)	SE (+) ($n=16$)	p values
Neutrophils, /μL	3709 (2921, 4768)	3746 (2967, 4672)	3450 (2489, 5871)	0.83
Eosinophils, /μL	196 (119, 259)	196 (116, 252)	195 (134, 330)	0.72
Eosinophils ≥ 300 /μL, +	12 (17.6)	8 (15.4)	4 (25)	0.46
Albumin, g/dL	4.1 (3.8, 4.3)	4.1 (3.9, 4.3)	4.0 (3.6, 4.1)	0.061
Lactate dehydrogenase, IU/L	192 (170, 212)	194 (175, 213)	184 (158, 205)	0.27
Hemoglobin A1c, %	5.8 (5.6, 6.2)	5.8 (5.6, 6.2)	6.8 (5.4, 6.4)	0.70
Brain natriuretic peptide, pg/mL	34 (18, 67)	42 (20, 73)	28 (13, 58)	0.46
C-reactive protein, mg/L*	0.12 (0.07, 0.29)	0.12 (0.07, 0.28)	0.19 (0.06, 0.52)	0.54
FeNO, ppb	23.2 (14.4, 31.2)	21.7 (13.3, 31.2)	26.0 (16.2, 32.7)	0.47
C2, Number of doubling concentrations†	4 (3, 5)	4 (3, 6)	5.5 (4, 8.75)	0.036
C5, Number of doubling concentrations†	6 (4, 7)	5 (4, 7)	6 (6, 9)	0.038
Ejection Fraction, %	64 (61, 70)	66 (61, 71)	62 (61, 66)	0.20
Postbronchodilator FEV_1, mL	1535 (1153, 1905)	1560 (1285, 1956)	1280 (943, 1803)	0.22
Postbronchodilator FEV_1 predicted, %	63.8 (50.4, 76.2)	64.7 (51.7, 76.2)	54.5 (43.7, 75.4)	0.14
Postbronchodilator FEV_1/FVC, %	51.2 (41.0, 60.2)	53.7 (43.4, 60.5)	46.5 (32.7, 55.7)	0.073
Reversibility, %	3.2 (0, 9.2)	2.9 (0, 8.5)	4.2 (−4.0, 14.3)	> 0.99

Table 2. Biomarkers (except for serum total IgE) and physiological functions when stratified according to SE sensitization. *$n=66$(SE [−]: $n=50$/ SE [+]: $n=16$), †The number of doubling concentrations of capsaicin ranges from 1 (0.61 μM) to 10(312.5 μM), with a higher number indicating decreased cough sensitivity to inhaled capsaicin. It reflects base 2 logarithmic values of C2 and C5, respectively.

the cough response through airway hyperresponsiveness[23]. Thus, allergens may alter airway nerve fiber hyper- and hyporesponsiveness. SE may cause food poisoning by inducing the release of neuropeptides from sensory neurons[24]. SE-IgE may induce airway nerve hyporesponsiveness to capsaicin by triggering neuropeptides such as substance P and CGRP. However, the mechanism by which SE-IgE decreases C-CS remains unknown. Further studies are warranted to elucidate this.

Our previous work demonstrated that declined C-CS was a predictor of AE and/or community-acquired pneumonia requiring hospitalization in patients with COPD[12]. Aligning with these data, previous literature reported an association between heightened C-CS and AE-COPD[25,26]. The cough reflex is a natural and inevitable function to protect the lower airways from external particles, microorganisms, and aspirates. Viral infections, a well-known cause of AE-COPD, can trigger heightened C-CS[27], while declined C-CS causes recurrent pneumonia[28]. Therefore, we speculated that both heightened and declined C-CS may contribute to the worsening of COPD. However, no association was observed between SE sensitization and hospitalization in this study. The association of SE sensitization with C-CS may be small in terms of future hospitalization or AE. Although the difference in C5 between the SE (+) and SE (−) groups was small, there is a difference of two doubling doses of C2 between the two groups. The European Respiratory Society guidelines for the management of cough published in 2007 clearly stated that not only C5 but also C2 should be recorded when performing the cough challenge test[29]. The C2 value may be preferred over the C5 value when patients reach C5 near the maximum inhaled doses of capsaicin. In our cohort, only five patients had heightened C-CS [C5 ≤ 2.44 μM (the third lowest concentration among the 10 doubling concentrations)]. When most of the population has normal cough reflex sensitivity, the difference in C2 values between the two groups may be more crucial than that in C5 values. SE sensitization contributed to the decline in C5 as well as C2 values after adjusting for confounders. Thus, we believe that SE sensitization contributed to the decline in C-CS in patients with COPD.

This study has some limitations. First, we did not measure aeroallergens, such as those from house dust mites, molds, dogs, or cats. Sensitization to rhinitis-related allergens was associated with SEs-IgE positivity in patients with COPD[11]. Increased exposure to sensitized aeroallergens has been associated with a higher risk of adverse clinical outcomes, including perceived wheezing, cough, dyspnea, emergency department visits, and the use of antibiotics, in patients with COPD[30]. A recent report identified higher levels of allergen-specific IgE, measured using the S1 screening panel, as a risk factor for a decline in lung function[21]. While sensitization to SEs facilitates the production of IgE in patients with COPD[22], other allergens may also contribute to exacerbation of the condition. Second, it remains unclear whether SEs can enhance Type-2-dependent inflammatory responses and the decline of C-CS during COPD exacerbations. Unfortunately, we could not assess this hypothesis as we did not collect samples from patients with exacerbated COPD during the study. Third, due to the small sample size in our study, we were unable to evaluate the association between colonization of *S. aureus* and sensitization to SEs due to the small study sample size. *S. aureus* colonization, but not SE sensitization, is associated with the decline in C-CS because of less effective airway defenses. Therefore, we cannot exclude the possibility that colonization of *S. aureus* may play a more important role than sensitization. Meanwhile, measuring serum SE-IgE levels is easier than collecting sputum samples because some patients have difficulty expectorating sputum. Therefore, SE sensitization may be a marker for declined C-CS in patients with COPD. Last, SE sensitization is associated with the pathophysiology of CRS. CRS may confound the high IgE levels in patients with COPD. However, we did not evaluate comorbid CRS using sinus CT. Meanwhile, the relationship between allergy and

	(A) Elevation of total IgE*			
	Estimates	**95% C. I.**	**Standardized β**	***p* value**
SE sensitization, +	0.50	0.30, 0.69	0.57	< 0.0001
Smoking, current smoking	−0.02	−0.23, 0.18	−0.03	0.80
Age	0.002	−0.02, 0.02	0.02	0.82
Asthma, +	0.10	−0.12, 0.33	0.10	0.36
Rhinitis, +	−0.15	−0.34, 0.04	−0.17	0.11
	(B) Decline in C-CS (C2†)			
	Estimates	95% C. I.	Standardized β	p value
SE sensitization, +	0.85	0.07, 1.62	0.28	0.033
Smoking, current smoking	−0.17	−0.98, 0.65	−0.05	0.68
Cerebrovascular disease, +	−0.06	−1.11, 0.99	−0.01	0.91
Sex, males	0.07	−0.86, 0.99	0.02	0.88
Antidepressant drugs, +	−1.00	−2.55, 0.55	−0.16	0.20
	(C) Decline in C-CS (C5†)			
	Estimates	95% C. I.	Standardized β	p value
SE sensitization, +	0.80	0.06, 1.53	0.27	0.035
Smoking, current smoking	−0.23	−0.55, 1.01	−0.07	0.56
Cerebrovascular disease, +	0.28	−0.72, 1.28	0.07	0.58
Sex, males	0.09	−0.96, 0.80	−0.02	0.85
Antidepressant drugs, +	−1.31	−2.78, −0.17	−0.22	0.083
	(D) AE during follow-up period			
	Estimates	95% C. I.	Standardized β	p value
SE sensitization, +	13.8	2.43, 25.2	0.28	0.018
Smoking, current smoking	−9.33	−21.5, 2.83	−0.18	0.13
A history of AE < 2 year, +	11.3	0.38, 22.1	0.24	0.043
ICS, -	0.48	−10.4, 11.3	0.01	0.93
Eosinophil ≥ 300 /μl, +	4.79	−7.28, 16.9	0.09	0.43
Post bronchodilator FEV_1/FVC	−0.80	−1.57, −0.04	−0.24	0.039

Table 3. An association of SE sensitization with elevation of total IgE (A), decline in capsaicin cough reflex sensitivity (C-CS) (B, C), and acute exacerbation (AE) during follow-up period (D). *Total IgE was log-transformed because it was not normally distributed. †The number of doubling concentrations of capsaicin ranges from 1 (0.61 μM) to 10(312.5 μM), with a higher number indicating decreased cough sensitivity to inhaled capsaicin. It reflects base 2 logarithmic values of C2 and C5, respectively.

pathophysiology of CRS remains inconclusive[31]. Thus, CRS may not have a substantial effect on high IgE levels in COPD.

Although further studies are needed to address these limitations, we propose that SEs sensitization may lead to declined C-CS, resulting in future AE in patients with COPD. In conclusion, sensitization to SEs could be a therapeutic target for COPD, as targeting IgE levels might be effective in improving respiratory symptoms and preventing AE in patients with COPD.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

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Declarations

Competing interests

There is no conflict of interest in the submitted work. The authors have competing interests outside the submitted work. Y.K. received research grants from MSD life foundation and personal fees from GSK, Novartis Pharma, AstraZeneca, Sanofi, and Kyorin. K.F. received research grants from Novartis Pharma and GSK. S.F. received personal fees from AstraZeneca and Eli Lilly. H.O. received a research grant from Boehringer Ingelheim. A.N. reports personal fees from Astellas, AstraZeneca, Kyorin, GSK, MSD, Shionogi, Bayer, Sanofi, Taiho, and Boehringer Ingelheim, and research grants from Astellas, Kyorin, Boehringer Ingelheim, Novartis, MSD, Daiichi Sankyo, Taiho, Teijin, Ono, Takeda, and Sanofi Pharmaceutical. R.K., T. A., Y.I., Y. A., T. S., K.I., Y. M., T. U., T.T., or T.S. did not receive any grants or personal fees.

Ethics approval and consent to participate

This study was approved by the ethics committee of Nagoya City University (60-18-0012) and registered in the UMIN Clinical Trials Registry (Registry ID UMIN000032497). Written informed consent was obtained from all participants. All methods were performed in accordance with the Declaration of Helsinki.

Additional information

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