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ORIGINAL ARTICLE

Lung Functions of Japanese Patients with Chronic Rhinosinusitis Who Underwent Endoscopic Sinus Surgery

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ABSTRACT

Background: Chronic rhinosinusitis (CRS), which is clinically classified into CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP), shows considerable geographic differences and heterogeneity. Eosinophilic (E) CRS with nasal polyps (ECRSwNP) has a higher degree of disease severity and higher frequency of comorbid asthma. Epidemiologic studies in different ethnic populations have improved understanding of the pathophysiology of the disease. Here we report the clinical characteristics of Japanese patients with medically refractory CRS undergoing endoscopic sinus surgery (ESS).

Methods: We recruited a total of 210 CRS patients and assessed them by nasal endoscopy, the Lund-Mackay score using computed tomography (CT), peripheral eosinophilia and smoking status. We also examined the comorbidity of asthma, effects of age and lung functions in the patients.

Results: In this study, 13% of CRSwNP patients and 20% of CRSwNP patients with peripheral blood eosinophilia exhibited obstructive lung dysfunction (FEV_1/FVC <70%) despite the absence of an asthma diagnosis. Among elderly nonsmoker patients (≥ 60 years) who had never been diagnosed with asthma, 50% of CRSwNP patients with peripheral blood eosinophilia showed decreased FEV_1/FVC <70%.

Conclusions: Our findings suggest that asthma is under-diagnosed in CRS patients who undergo ESS, especially the elderly. Although the association between CRS and asthma has been recognized, increased attention to the comorbidity of obstructive airway diseases such as asthma is still needed for management of medically refractory CRS.

KEY WORDS

asthma, chronic rhinosinusitis, eosinophils, lung functions, nasal polyps

INTRODUCTION

Chronic rhinosinusitis (CRS), a common disease associated with persistent inflammation of the nasal and paranasal sinuses, is a public health problem resulting in a socioeconomic burden throughout the world.[1,2] CRS is commonly classified into two groups, CRSsNP and CRSwNP. Considerable heterogeneity within CRSwNP has been recognized and there are geographic differences in the condition.[3,4] Tissue from Caucasian patients with CRSwNP is characterized by eosinophilic inflammation, whereas samples from Asian patients are biased toward neutrophilic inflammation.[3,4] Eosinophilic (E) CRSwNP has been found in 65-90% of subjects with CRSwNP in Caucasians and in 50% of them in East Asian populations.[1-3] ECRSwNP represents a higher degree of disease severity, with an impaired sense of smell, higher recurrence rate after surgery and higher frequency of comorbid asthma.[2] The association of ECRSwNP and asthma is well recognized in western countries; [5,6] however, asthma comorbidity in CRSwNP patients in

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Table 1 Clinical characteristics of patients with chronic rhinosinusitis

	CRSsNP $n = 40$	CRSwNP $n = 170$	*P*-value
Age (median, range)	57 (35-64)	54.5 (44-63)	NS
Sex (male/female) (female %)	31/9 (23)	109/61 (36)	NS
Smoker, no. (%)	21 (53)	56 (33)	<0.05
Current smoker, no. (%)	21 (53)	46 (27)	<0.01
Brinkman index of smokers	430 (290-728)	560 (300-854)	NS
Asthma, no. (%)	2 (5)	44 (26)	<0.01
Aspirin-induced asthma, no. (%)	0 (0)	10 (6)	NS
Allergic rhinitis, no. (%)	8 (20)	48 (28)	NS
Rhinorrhea, no. (%)	34 (85)	124 (73)	NS
Nasal congestion, no. (%)	23 (58)	138 (81)	<0.01
Headache, no. (%)	17 (43)	38 (22)	<0.05
Olfactory dysfunction, no. (%)	11 (28)	112 (66)	<0.0001

P values were determined using the Mann-Whitney U test, or Fisher's exact test as appropriate. CRSwNP, chronic rhinosinusitis with nasal polyps; CRSsNP, chronic rhinosinusitis without nasal polyps; NS, not significant.

Asian countries has not been fully studied. Nor are the clinical features of CRS such as sinus scores evaluated by CT scanning and lung functions in Asian populations well investigated.

Epidemiologic studies have shown that asthma and rhinitis often coexist in the same patients and suggest the 'united airways' concept.[4,7-11] Underdiagnosis and undertreatment of asthma is a significant public problem all over the world, especially in the elderly.[12] The awareness of asthma is frequent in those with comorbid rhinitis,[13] and it has also been suggested that symptoms may predominate in one organ and be unrecognized in other organs even though they exist.[8] A higher CT score and more nasal polyp formation are observed in elderly patients with CRS.[14] However, the influence of aging on the clinical features of CRS in Japanese patients has not been examined.

ESS is the treatment choice for medically refractory CRS with or without nasal polyposis.[15] To clarify the clinical features of refractory CRS in Japanese patients, we conducted a cross-sectional study with a total of 210 CRS patients who underwent ESS. We assessed their clinical phenotypes through the use of nasal endoscopy, considering peripheral eosinophilia, CT scores based on the Lund-Mackay system, smoking status, comorbidity of asthma, effects of age and lung functions.

METHODS

SUBJECTS

CRS was defined as a condition with at least two of the following symptoms: anterior and/or posterior rhinorrhea, nasal obstruction, decreased sense of smell, and nasal pressure existing for 12 weeks despite medical management.[1,2] We recruited all patients with CRS who underwent ESS at the University of Yamanashi Hospital from January 2002 to October 2011. All individuals were Japanese, and we excluded patients with autoimmune disease, cancer, papilloma, fungal infection, postoperative maxillary cysts, choanal polyps, and nasal foreign bodies before enrollment. We excluded patients with allergic fungal rhinosinusitis based on CT and/or histopathological findings from the start. We included patients with unilateral CRS and those with nasal polyps. The presence or absence of nasal polyps was confirmed by endoscopy. Finally, a total of 210 subjects were analyzed (Table 1). CRS patients were classified into CRSwNP and CRSsNP groups based on the criteria of the American Academy of Otolaryngology-Head and Neck Surgery Chronic Rhinosinusitis Task Force.[1] Comorbidity of asthma was determined from the patients' medical histories based on doctors' interviews. We defined individuals who had asthma diagnosed by a doctor at any point in their lifetime as having bronchial asthma. This study was approved by the ethics committee of the University of Yamanashi Hospital. We informed patients that any clinical data would be used for research analyses by placing a notice on walls in the medical examination room and hospital lobby in the University of Yamanashi Hospital. We individually responded to patients who dissented from such use. In this study, we recruited subjects who did not dissent from use of the clinical data. This process of obtaining informed consent was approved by the ethics committee of the University of Yamanashi Hospital.

PERIPHERAL EOSINOPHIL COUNT

A total of 19 patients (9%) were treated with systemic corticosteroids in the two months before the operation, and 91 patients (43%) were treated with intranasal steroids in the month before the operation. Since the eosinophil count is sensitive to steroid treatment, we recorded the highest peripheral blood eosinophil percentage among all the blood tests done before operation.

LUNG FUNCTION AND COMPUTED TOMOGRAPHY

Spirometry was performed for all patients using a DISCOM 21 FXII spirometer (CHEST MI., Inc., Tokyo, Japan). Forced expired volume in one second (FEV_1)/forced vital capacity (FVC) (FEV_1%) was calculated. Maximum expiratory flow rates at 50% and 25% of the FVC (V50 and V25) were obtained from flow/volume curves. FEF25-75 and lung functions after application of a bronchodilator were not available for this study. CT scans of the sinuses were available for 54 patients with CRSwNP and were graded based on the Lund-Mackay staging system.[16] We used the average of the right and left side scores in the following analyses.

HISTOLOGICAL ANALYSIS

It is well known that infiltration of eosinophils in nasal polyps is a characteristic of ECRSwNP. However, it remains unclear whether eosinophilic infiltration exists in nasal mucosal tissue of CRS without nasal polyp involvement. To assess eosinophil infiltration in sinonasal mucosal tissues without polyps, we examined the maxillary mucosa histologically. Among the 210 CRS patients enrolled in this study, non-polyp mucosal tissues from the maxillary sinuses were obtained from 46 CRSwNP patients. Paraffin-embedded sections were stained with hematoxylin and eosin, and the number of infiltrating eosinophils were counted in four randomly selected high power (×400) magnification fields.

STATISTICAL ANALYSIS

Demographic data, lung functions, and CT scores were compared using the Mann-Whitney U test or Fisher's exact test. The correlational validity of the peripheral blood eosinophil percentage with the mucosal eosinophil count was assessed using Spearman rank correlations. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using R (R Development Core Team, http://www.r-project.org/).

RESULTS

SUBJECTS' CHARACTERISTICS

Of the 210 CRS patients who underwent ESS, 40 (19%) had CRSsNP and 170 (81%) had CRSwNP. Clinical features of each group are shown in Table 1. Current smokers were more frequent in the CRSsNP group (53%) than in the CRSwNP group (27%). The comorbidity of asthma was significantly higher for CRSwNP (26%) than for CRSsNP (5%). Among subjective symptoms, olfactory dysfunction was more frequent in CRSwNP (66%) than in CRSsNP (28%).

Recent studies have shown that the blood eosinophil percentage is the most accurate clinical factor to distinguish the eosinophilic type of CRSwNP from the non-eosinophilic type;[17,18] however, precise clinical diagnostic criteria including the peripheral eosinophil percentage for ECRSwNP have not been determined. In this study, we divided the patients with CRSwNP into two groups to clarify the clinical characteristics of each group. Since the median value of the eosinophil percentage of the total leukocyte count in subjects with CRSwNP was 5%, we defined subjects with an eosinophil percentage <5% as having CRSwNP without peripheral blood eosinophilia and subjects with ≥5% as having CRSwNP with peripheral blood eosinophilia. A total of 87 subjects (51%) were classified into the CRSwNP group without peripheral blood eosinophilia, and 83 subjects (49%) were classified into the group having CRSwNP with peripheral blood eosinophilia (Table 2). The comorbidity of asthma was significantly higher for CRSwNP with peripheral blood eosinophilia (43%) than for CRSwNP without peripheral blood eosinophilia (9%), and the comorbidity of aspirin-induced asthma (AIA) or allergic rhinitis was significantly higher for CRSwNP with peripheral blood eosinophilia than for the CRSwNP without peripheral blood eosinophilia (Table 2). Olfactory dysfunction was also frequently observed in the group having CRSwNP with peripheral blood eosinophilia (Table 2).

CT SCORES IN PATIENTS WITH CRSwNP

The Lund-Mackay score is commonly used for assessment of the stage and severity of CRS.[16] We examined the severity of the disease in subjects with CRSwNP using CT scores based on the Lund-Mackay system. The total score for CRSwNP with peripheral blood eosinophilia had a tendency to be higher than that for CRSwNP without peripheral blood eosinophilia (Fig. 1) but the difference was not statistically significant ($P = 0.051$). There was no significant difference between CRSwNP without peripheral blood eosinophilia and CRSwNP with peripheral blood eosinophilia for the maxillary sinus score, sphenoid sinus score, frontal sinus score, and ostiomeatal complex score (data not shown). However, the anterior ethmoid (AE) sinus score and posterior ethmoid (PE) sinus score of CRSwNP with peripheral blood eosinophilia were significantly higher those for CRSwNP without peripheral blood eosinophilia ($P < 0.05$ and < 0.001, respectively) (Fig. 1).

CORRELATION BETWEEN EOSINOPHIL INFILTRATION IN SINONASAL MUCOSA AND PERIPHERAL BLOOD EOSINOPHIL COUNT IN PATIENTS WITH CRSwNP

Infiltration of eosinophils in nasal polyps is a characteristic of ECRSwNP. Since whether eosinophilic infiltration exists in nasal mucosal tissue of CRS without nasal polyp involvement remains unknown, we investigated the correlation between blood and mucosal eosinophilia in a total of 46 patients with CRSwNP. The count of mucosal eosinophils strongly correlated

Table 2 Clinical characteristics of patients with CRSwNP

	CRSwNP (n = 170)		P-value
	without peripheral blood eosinophilia n = 87	with peripheral blood eosinophilia n = 83	
Age (median, range)	58 (45-66)	52 (44-61)	NS
Sex (male/female) (female %)	54/33 (38)	55/28 (34)	NS
Smoker, no. (%)	31 (36)	25 (31)	NS
Current smoker, no. (%)	25 (29)	21 (26)	NS
Brinkman Index of smokers (median, range)	730 (330-900)	460 (293-620)	NS
Asthma, no. (%)	8 (9)	36 (43)	<0.000001
Aspirin-intolerant asthma, no. (%)	1 (1)	9 (11)	<0.01
Allergic rhinitis, no. (%)	16 (18)	32 (39)	<0.01
Rhinorrhea, no. (%)	64 (74)	60 (72)	NS
Nasal congestion, no. (%)	70 (81)	68 (82)	NS
Headache, no. (%)	23 (26)	15 (18)	NS
Olfactory dysfunction, no. (%)	49 (56)	63 (76)	<0.01

P values were determined using the Mann-Whitney U test or Fisher's exact test as appropriate. NS, not significant.

with the peripheral blood eosinophil percentage (R = 0.67, $P < 0.000001$) (Fig. 2).

LUNG FUNCTIONS OF THE CRS PATIENTS

The close relationship between asthma and CRS is widely recognized. We therefore assessed lung functions of the CRS patients. We first excluded nine patients whose smoking histories were unknown from the analysis. FEV_1/FVC was significantly lower in subjects with CRSwNP than in subjects with CRSsNP, and was also lower in the group having CRSwNP with peripheral blood eosinophilia than in the group having CRSwNP without peripheral blood eosinophilia (Fig. 3a, Table 3). There were 18 patients being treated with corticosteroids among the subjects whose lung functions were assessed. One patient with CRSsNP (2.6%), two patients with CRSwNP without peripheral blood eosinophilia (2.4%) and 15 patients who had CRSwNP with peripheral blood eosinophilia (19%) had received systemic corticosteroid treatment prior to surgery. Although there were more patients receiving corticosteroids in the group having CRSwNP with peripheral blood eosinophilia than in the groups having CRSsNP and CRSwNP without peripheral blood eosinophilia, FEV_1/FVC was significantly lower in the subjects who had CRSwNP with peripheral blood eosinophilia than in the subjects of the other two CRS groups. Furthermore, %V25 was lower in the CRSwNP group than in the CRSsNP group, and both %V25 and %V50 were lower for CRSwNP with peripheral blood eosinophilia than for CRSwNP without peripheral blood eosinophilia (Table 3).

Decreased FEV_1/FVC is a clinical feature of obstructive lung diseases such as bronchial asthma and chronic obstructive pulmonary disease (COPD). Since smoking is the leading cause of COPD, we next examined the influence of smoking status on lung functions of subjects with CRSsNP and CRSwNP. There was no significant difference in lung functions (FEV_1/FVC, %V25, and %V50) between current smokers, former smokers (smokers) and never smokers (nonsmokers) among the entire group with CRS (Fig. 3b, Table 3). After excluding current and former smokers, FEV_1/FVC was lower in the CRSwNP group than in the CRSsNP group, and was lower in the CRSwNP group with peripheral blood eosinophilia than in the CRSwNP group without peripheral blood eosinophilia (Fig. 3c). Both %V25 and %V50 were lower in patients who had CRSwNP with peripheral blood eosinophilia than in those who had CRSwNP without peripheral blood eosinophilia (Table 3).

We next stratified the CRS patients who had never been diagnosed with asthma prior to ESS by the comorbidity of asthma, and focused on their lung functions. Since obstruction has been traditionally defined by an FEV_1/FVC ratio of less than a certain percentage, usually 70 to 75%,[19] we divided subjects into three classes according to their lung function: $FEV_1/FVC < 70\%$, $70\% \leq FEV_1/FVC < 75\%$ and $FEV_1/FVC \geq 75\%$ (Fig. 4). In 13% of patients with CRSwNP who had never been diagnosed as having asthma, FEV_1/FVC was less than 70% (Fig. 4a). Furthermore, 20% of patients having CRSwNP with peripheral blood eosinophilia had FEV_1/FVC of less than 70% despite the absence of a previous asthma diagnosis (Fig. 4a). The same tendency was observed even after excluding current and former smokers, and smoking status did not influence the obstructive lung dysfunction in subjects who had CRSwNP and CRSwNP with peripheral blood eosinophilia (Fig. 4b).

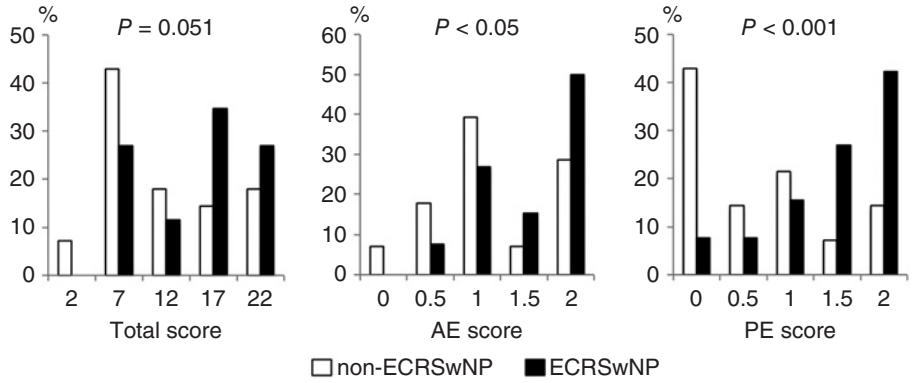

Fig. 1 Comparison of CT scores for CRSwNP with and without peripheral blood eosinophilia. CT scores based on the Lund-Mackay staging system were compared between subjects who had CRSwNP without peripheral blood eosinophilia (n = 28) and CRSwNP with peripheral blood eosinophilia P (n = 26). P values were determined using the Mann-Whitney U test. AE score, anterior ethmoid sinus score; PE score, posterior ethmoid sinus score.

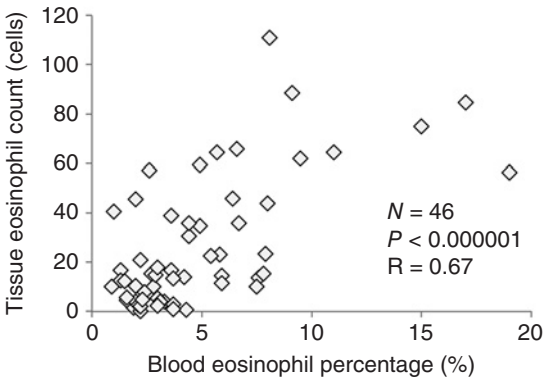

Fig. 2 Correlation between percentage of eosinophils in peripheral blood and the tissue eosinophil count in the mucosa of the maxillary sinus. The tissue eosinophils of patients with CRSwNP (n = 46) were counted at high power maginification (×400). Correlation validity was assessed by using Spearman rank correlations.

Underdiagnosis of asthma is an important problem, especially in the elderly.[12] Therefore we further examined whether there were age-related differences in the prevalence of each subgroup or in FEV_1/FVC. We divided nonsmoker patients who had never been diagnosed with asthma into nonelderly (<60 years) and elderly groups (≥60 years). In the elderly group, obstructive lung dysfunction (FEV_1/FVC <70%) was more frequently seen in those with CRSwNP (28%) than in those with CRSsNP (0%), and for CRSwNP with peripheral blood eosinophilia (50%) than for CRSwNP without peripheral blood eosinophilia (18%) (Fig. 4c).

DISCUSSION

There is considerable heterogeneity within the CRSwNP subgroup,[3,4] and importance of understanding CRS within the context of racial and ethnic populations has been suggested.[20] This study revealed the clinical characteristics of Japanese patients with medically refractory CRS who underwent ESS. Epidemiologic studies have reported that rhinitis and asthma often coexist in the same patients.[1,5,6,8] The 'united airways' concept implies that there is a link between upper and lower airway inflammation.[8,9,21] A recent study reported the asthma comorbidity in patients with CRSwNP who underwent ESS (n = 19) to be 32% in Japanese patients.[22] In the United States, the frequencies of comorbidity of asthma were reported to be 11% in those with CRSsNP and 44% in those with CRSwNP.[23] In this study, the frequency was 26% for CRSwNP, and it was significantly higher for CRSwNP with peripheral blood eosinophilia (43%) than for CRSwNP without peripheral blood eosinophilia (9%). The frequency of comorbidity of asthma observed in the group having CRSwNP with peripheral blood eosinophilia (43%) in our study was similar to that in the CRSwNP group (44%) in the United States. Furthermore, it has been reported that ECRSwNP has a higher degree of disease severity in western countries.[1] AIA represents a severe phenotype of asthma and we found significantly higher comorbidity of AIA for CRSwNP with peripheral blood eosinophilia than for the CRSwNP without peripheral blood eosinophilia in this study.

A recent report has shown that CRS patients with anosmia have a higher density of eosinophils infiltrating the olfactory epithelium, and exhibit more abnormalities on CT and endoscopic examination, including being more likely to exhibit nasal polyposis than other CRS patients.[24] We observed olfactory dysfunction with high frequency in subjects with CRSwNP (66%), especially in those who had CRSwNP with peripheral blood eosinophilia (76%). Our findings support previous research results. CT scanning is useful

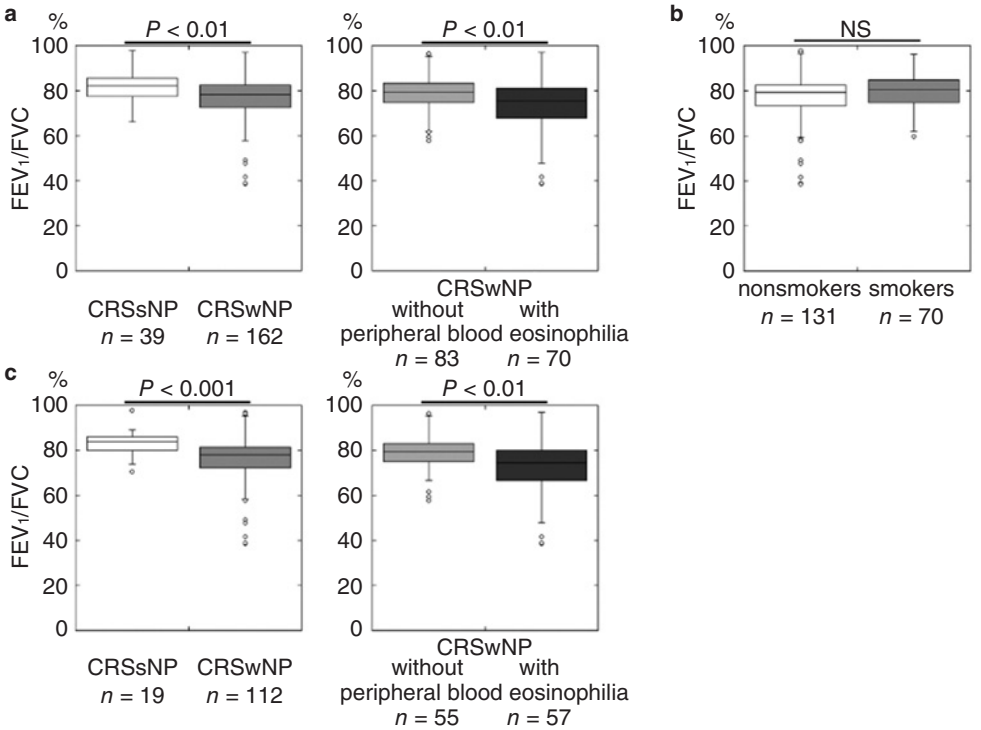

Fig. 3 Comparison of FEV_1/FVC ratios among subgroups of CRS. **a**) Comparison between CRSsNP and CRSwNP, and between CRSwNP with and without peripheral blood eosinophilia. **b**) Comparison between nonsmokers and (current and former) smokers among the entire group with CRS. **c**) Comparison between CRSsNP and CRSwNP, and between CRSwNP with and without peripheral blood eosinophilia after excluding current and former smokers. Rectangles include the range from the 25th to 75th percentiles, horizontal lines indicate the median and vertical lines indicate the 10th to 90th percentiles. *P* values were determined using the Mann-Whitney U test. FVC, forced vital capacity; FEV_1, forced expired volume in one second.

Table 3 Lung functions of subgroups of CRS

	CRS		*P*-value	Nonsmokers with CRS		*P*-value
	CRSsNP (*n* = 39)	CRSwNP (*n* = 162)		CRSsNP (*n* = 19)	CRSwNP (*n* = 112)	
%FVC	105.0 (93.5-111.8)	106.7 (95.2-118.3)	NS	102.0 (88.2-110.9)	107.8 (95.3-118.5)	<0.05
$\%FEV_1$	102.5 (95.7-109.7)	101.5 (89.6-110.8)	NS	106.5 (94.0-111.2)	103.3 (88.5-112.1)	NS
FEV_1/FVC	82.3 (77.4-85.6)	78.4 (72.5-82.6)	<0.01	83.9 (80.2-86.3)	78.1 (72.4-81.4)	<0.001
%V50	68.5 (61.4-85.7)	67.3 (45.7-83.9)	NS	68.4 (60.7-76.1)	64 (43.8-81.9)	NS
%V25	58.8 (44.2-66.2)	42.7 (29.3-55.3)	<0.001	60.8 (52.7-66.2)	42.7 (27.7-54.5)	<0.001
	CRSwNP		*P*-value	Nonsmokers with CRSwNP		*P*-value
	without peripheral blood eosinophilia P (*n* = 83)	with peripheral blood eosinophilia (*n* = 79)		without peripheral blood eosinophilia (*n* = 55)	with peripheral blood eosinophilia (*n* = 57)	
%FVC	106.4 (94.7-113.2)	108.2 (97.5-121.0)	NS	106.7 (95.1-113.2)	110.3 (97.6-121.6)	NS
$\%FEV_1$	101.8 (91.9-112.9)	101.5 (80.1-108.5)	NS	105.1 (92.6-114.4)	98.2 (78.1-108.8)	NS
FEV_1/FVC	79.5 (74.7-83.3)	75.3 (67.8-81.2)	<0.01	79.4 (75.1-83.2)	74.4 (66.7-80.1)	<0.01
%V50	69.6 (55.2-85.7)	58.5 (37.7-81.7)	<0.01	68.3 (57.3-84.7)	53.5 (36.8-74.0)	<0.01
%V25	45.6 (36.8-59.5)	40.9 (25.8-51.4)	<0.01	45.1 (37.5-56.3)	38.7 (22.4-48.4)	<0.01

Lung functions are expressed as percentages of predicted values and are presented as medians (interquartile ranges). *P* values were determined using the Mann-Whitney U test. FVC, forced vital capacity; FEV_1, forced expired volume in one second; V50 and V25 of FVC, maximum expiratory flow rates at 50% and 25%; $FEV_1\%$, FEV_1/FVC %.

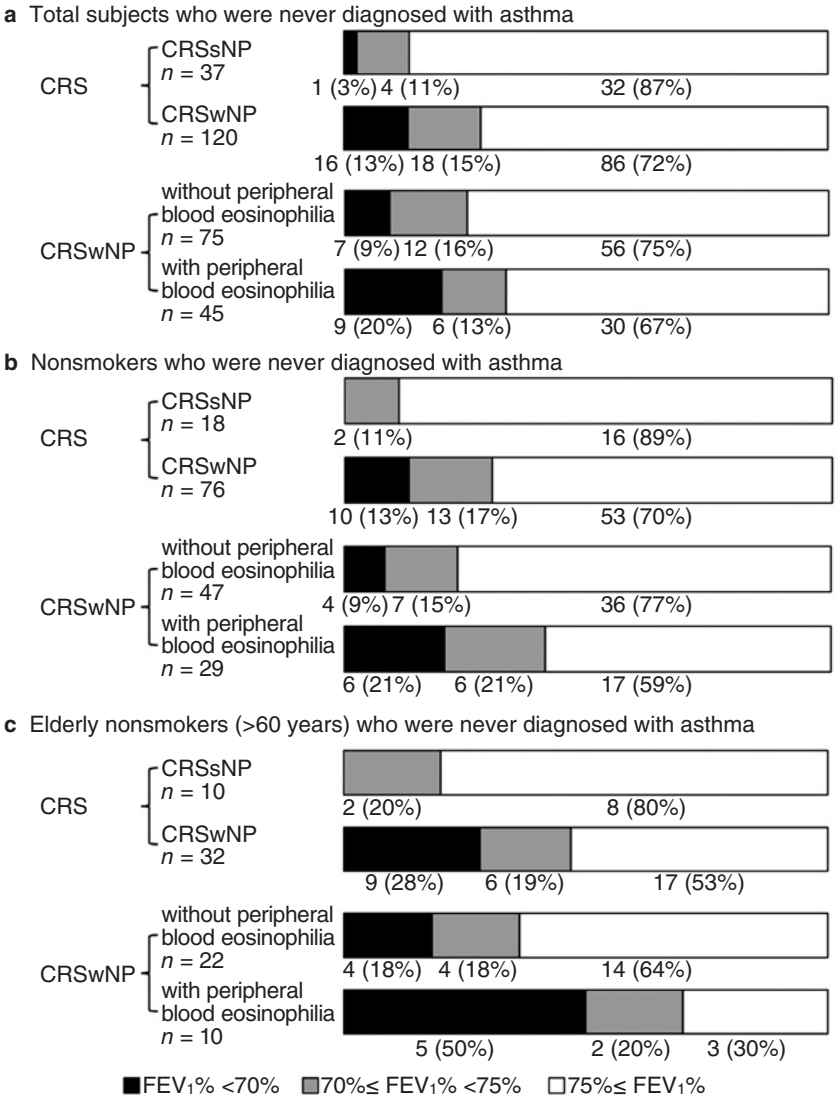

Fig. 4 Obstructive lung dysfunctions of CRS patients who had never been diagnosed with asthma prior to ESS. **a-c**) Comparison between CRSsNP and CRSwNP, and between CRSwNP with and without peripheral blood eosinophilia. **a**) In total subjects. **b**) In subjects excluding current and former smokers. **c**) In elderly nonsmoker subjects (>60 years) who had never been diagnosed with asthma.

for the visualization of disease and enables us to determine the extent of rhinosinusitis accurately. The Lund-Mackay score evaluated on CT scans is widely used in assessment of CRS.[16] A recent study has shown that an increased blood eosinophil percentage and the CT image scores for the PE sinus and the olfactory cleft are good predictors of ECRSwNP.[18] In this study, although the total score for CRSwNP with peripheral blood eosinophilia did not significantly differ from that for CRSwNP without peripheral blood eosinophilia, the AE sinus and PE sinus scores of CRSwNP with peripheral blood eosinophilia were significantly higher than those for CRSwNP without peripheral blood eosinophilia. Thus, our results support previous findings on involvement of the posterior ethmoid sinus in ECRSwNP.

Infiltration and activation of eosinophils in nasal polyps is a characteristic of eosinophilic CRSwNP, and it has been reported that the peripheral blood eosinophil percentage is positively correlated with the number of eosinophils in nasal polyps.[25] In this study, we found eosinophilic infiltration in nasal mucosal tissue not involving nasal polyps and a positive correlation between blood and mucosal eosinophilia in patients with CRSwNP. Thus, it is necessary to be aware of the possibility of eosinophilic inflammation not only in nasal polyps but also in nasal mucosa for the treatment of CRSwNP patients with high blood

eosinophil levels.

A recent report showed a high prevalence of asymptomatic lower airway dysfunctions in patients with CRSwNP in the United Kingdom.[26] In this study, 28% of CRSwNP patients exhibited FEV_1/FVC of less than 75%, and 20% of patients who had CRSwNP with peripheral blood eosinophilia had FEV_1/FVC of less than 70% despite the absence of an asthma diagnosis. Decreased FEV_1/FVC (<70%) was more frequently observed in patients having CRSwNP with peripheral blood eosinophilia (21%) than in those having CRSwNP without peripheral blood eosinophilia (9%), even after excluding current and former smokers. Never smokers comprise a substantial proportion of patients with COPD; however, asymptomatic decreased lung function suggestive of an asthmatic phenotype was frequently observed in CRSwNP, especially in CRSwNP with peripheral blood eosinophilia. Most patients with asthma have symptoms of rhinitis, but in many cases symptoms may predominate in one organ and be unrecognized in other organs even though they exist.[8] Our findings also suggest the necessity of paying increased attention to the possible comorbidity of obstructive airway diseases such as asthma for management of refractory CRS.

The underdiagnosis and undertreatment of asthma are serious problems throughout the world,[13,27-30] especially in the elderly.[29] About half of elderly people with asthma have not been diagnosed, and the underuse of objective testing such as spirometry has been considered to be one reason.[30] In this study, after excluding patients who had ever been diagnosed with asthma and current or former smokers, decreased FEV_1/FVC (<70%) tended to be more prevalent in elderly patients in the CRSwNP and CRSwNP groups with peripheral blood eosinophilia. Although FEV_1/FVC normally decreases with age and FEV_1/FVC lower than 70% might be a normal finding, an FEV_1/FVC ratio of less than 70% increases the probability of asthma in elderly patients with asthma symptoms.[30] Careful assessment of asthma by means of systemic inquiries about respiratory symptoms and objective testing by spirometry seems to be necessary in subjects with refractory CRS, especially elderly patients. Early diagnosis and good asthma control are important to reduce morbidity and healthcare costs as well as minimize the development of chronic illnesses,[13] and appropriate diagnosis and management of asthma would contribute to mitigating the severity of their CRS.

In conclusion, we found that 19% of subjects with CRS who underwent ESS had CRSsNP, and 81% CRSwNP. We confirmed that both the AE and PE sinus CT scores of the Lund-Mackay staging system were helpful for identifying CRSwNP with peripheral blood eosinophilia. Obstructive lung dysfunctions are frequently observed in CRSwNP with peripheral blood eosinophilia, especially in elderly persons, despite the absence of an asthma diagnosis. Although further studies are needed, our findings will contribute to better understanding of the pathophysiology of CRS.

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