

Impaired small airway function in non-asthmatic chronic rhinosinusitis with nasal polyps

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Abstract

Background: There is clinical evidence for impaired lung function in chronic rhinosinusitis with nasal polyps (CRSwNP) patients, which may be due to a high incidence of asthma comorbidity. The lung function characteristics of non-asthmatic CRSwNP patients are not known. Small airway dysfunction (SAD) is involved in the pathogenesis of asthma. However, whether SAD is detected in non-asthmatic patients with CRSwNPs remains unclear.

Objective: This study analysed the lung function of non-asthmatic patients with CRSwNPs and evaluated its clinical relevance in CRSwNPs.

Methods: The clinical data for 191 consecutive CRSwNP patients (73 asthmatic and 118 non-asthmatic) and 30 control subjects were prospectively collected. The patients were followed up for at least 3 years (mean [standard deviation], 42.47 ± 8.38 months). Serum and tissue total IgE levels were measured in 95 and 93 patients, respectively. Tissue eosinophil counts were documented in 63 patients.

Results: Non-asthmatic CRSwNP patients had decreased forced expiratory flow at 75% of the FVC (FEF₇₅) and FEF₅₀ compared to the control subjects, and this difference was related to the severity of CRSwNP. The risk factors for impaired lung function in asthmatic and non-asthmatic patients were duration of asthma and smoking. A multivariate logistic analysis showed that decreased FEF₅₀ was associated with the recurrence of non-asthmatic CRSwNPs. The lung function of CRSwNP patients negatively correlated with the degree of type-2 inflammation, which was defined by the levels of Eos and IgE in polyp tissues and blood. The SAD of non-asthmatic CRSwNP patients was related to serum IgE levels.

Conclusions and clinical relevance: This study provides evidence that non-asthmatic CRSwNP patients may have SAD, which correlated with the severity and recurrence of CRSwNP. The decreased lung function of patients with CRSwNP was related to the degree of type-2 inflammation.

KEYWORDS

asthma, immunoglobulin E, nasal polyp, small airway dysfunction

1 | INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNPs) is a type-2 inflammatory disease caused by innate lymphoid cells (ILC2s), T-helper type-2 cell (Th2)-biased responses, eosinophilia, and IgE synthesis,^{1,2} and it has a high prevalence of asthma comorbidity.³ Because the upper and lower airways are considered a morphological and functional entity,⁴ the link between CRSwNPs and lower airway dysfunction represents a topic of clinically relevant interest. However, there is a paucity of published reports on lower airway function in patients with nasal polyps (NPs).

Although there is clinical evidence for impaired lung function in CRSwNP patients,⁵ the present study failed to exclude asthma as a possible confounding factor. However, the lung function characteristics of asthmatic and non-asthmatic patients with NPs remain unclear. The lower airway is segmentally divided to include the area ranging from the trachea (generation 1) to the alveoli (generation 23).⁶ The downstream airways with an internal diameter <2 mm are small airways, which are the major sites of airflow limitation in lower airway diseases (eg asthma and chronic obstructive pulmonary disease).^{7,8} Small airways are more sensitive sites for the detection of airway impairment than large airways.⁹ Subjects may suffer from small airway dysfunction (SAD) when early-stage pulmonary disease occurs.⁶ Amaryllis et al¹⁰ reported that non-asthmatic allergic rhinitis (AR) patients with SAD may have a normal ventilation function, which is different from the lung function characteristics of asthma patients. Given the "united airways" concept, whether CRSwNP patients exhibit a similar pattern of SAD is not known. SAD is also involved in the pathogenesis of asthma,⁶ and it is associated with poor clinical outcomes of asthma.^{11,12} Therefore, it is important to investigate whether SAD exists in non-asthmatic CRSwNP patients to monitor the development of asthma comorbidity.

Due to the limitations of forced expiratory volume in one second (FEV1) and FEV1/forced vital capacity (FVC) in detecting SAD,¹³ the present study used forced expiratory flow between 25% and 75% of the FVC (FEF₂₅₋₇₅), which is a more sensitive marker for mirroring small airway function.⁸ We hypothesized that non-asthmatic CRSwNP patients would have impaired small airway function. To evaluate the clinical implications of decreased lung function in CRSwNP patients, we analysed its relevance to CRSwNP.

Some existing evidence supports relationships between type-2 inflammation and lower airway disorders in patients with upper airway diseases. Amaryllis et al¹⁰ found that localized type-2 inflammatory changes in the lower airway of patients with AR may be an aetiology that links upper and lower airway functions. Kambara et al¹⁴ identified a correlation between the fractional concentration of exhaled nitric oxide (FeNO) and eosinophilic markers, including the blood eosinophil (Eos) percentage and the number of Eos in nasal polyps. Therefore, we measured total IgE levels and Eos numbers in blood samples and polyp tissues to obtain information on the degrees of systemic and topical type-2 inflammation.

Taken together, this study evaluated the lung function characteristics of asthmatic and non-asthmatic CRSwNP patients. Clinical and immunological factors potentially related to decreased lung function were analysed.

2 | MATERIALS AND METHODS

2.1 | Subjects

This study was based on 205 consecutive CRSwNP patients (with or without asthma) who underwent endoscopic sinus surgery (ESS) performed by the same surgeon (Dr Xiangdong Wang) at Beijing TongRen Hospital from January 2013 to December 2016. Thirty healthy volunteers without upper and lower airway diseases served as a control group. All of the enrolled CRSwNP patients were diagnosed in accordance with the current European EAACI Position Paper on Rhinosinusitis and Nasal Polyps.¹⁵ Patients with unilateral polyps, cysts, allergic fungal rhinosinusitis, systemic autoimmune diseases, acute upper or lower respiratory tract infections before ESS, and patients who were treated with systemic antibiotics/glucocorticoids during the four weeks prior to surgery were excluded. Patients with incomplete clinical data and non-asthmatic CRSwNP patients with new-onset lower airway symptoms were also excluded. The comorbidity of asthma was diagnosed by pulmonologists and based on the Global Initiative for Asthma guidelines, that is the presence of principal respiratory symptoms (eg shortness of breath and wheezing, recurrent cough, and excessive airway mucus production) and at least one positive asthma test.¹⁶ All of the non-asthmatic CRSwNP patients lacked lower airway symptoms, and their asthma comorbidity were excluded by a negative bronchial challenge test. The study protocol was approved by the Ethics Committee of Beijing Tongren Hospital (TREC 2011-21), and each enrolled subject provided their written informed consent.

2.2 | Study design

This was a retrospective study. The patients were followed up for at least 3 years after ESS (mean [standard deviation], 42.47 ± 8.38 months). During the follow-up period, the first outpatient visit was carried out within 14 days then once every 1-2 months thereafter, until six months after surgery. Subsequently, all patients were periodically reassessed during routine outpatient visits every 3 to 6 months. On the 7th day after ESS, all patients began treatment with saline irrigation (250 mL twice daily), clarithromycin (250 mg/day), and topical corticosteroids (budesonide, mometasone, or fluticasone, 2 sprays in each nostril twice daily) for the first three months after surgery.^{15,17} When nasal polyps or severe mucosal oedema were observed during visits after the first 3 months, the patients were given systemic corticosteroids (methylprednisolone tablets, 0.5 mg/kg, 20-24 mg/day) for at least one pulse treatment of 7 days and were subsequently given topical

corticosteroids to take in combination with clarithromycin (250 mg/day) for another 3 months.¹⁸

Six months after ESS, recurrence was diagnosed as remaining evidence of bilateral pedunculated lesions as opposed to cobblestoned mucosa, on an endoscopic examination performed after the maximum amount of medication described above was used.^{15,19} The minimum follow-up period was three years, and endpoints were recorded at the closest date from the last follow-up visit.

2.3 | Clinical data

A complete blood count, information on the sensitization to aeroallergens, lung function test, and computed tomography (CT) scan were performed for all enrolled patients prior to surgery. The percentage of Eos in circulating blood was determined using a Sysmex XE-2100 Automated Hematology System (Sysmex, Kobe, Japan).

Sensitization to aeroallergens was determined using a test of serum IgE levels for 15 respiratory allergens from 6 different categories: mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), cockroach, cat, dog, fungi (*Cladosporium* sp, *Alternaria* sp, *Aspergillus*, *Penicillium* sp), *artemisiifolia*, *Artemisia argyi*, and an arbour pollen mix (willow, poplar, and elm). The test was performed using a fluoroenzyme immunosorbent assay (UniCAP, Uppsala, Sweden), and a positive value was determined when the serum-specific IgE ≥ 0.35 kU/L.

For lung function tests, data for FVC, FEV1, FEV1/FVC, peak expiratory flow (PEF), forced expiratory flow between 25% and 75% of the FVC (FEF₂₅₋₇₅), and maximum mid-expiratory flow between 25% and 75% of FVC (MMEF) were obtained using a spirometer (SensorMedics, Yorba Linda, CA, USA). All of these lung function parameters were tested for three manoeuvres and recorded as a percentage of the best value/predicted value.

Images obtained from CT scans (Philips Heath care, the Netherlands) were scored according to the Lund-Mackay scoring system (LMS).²⁰ An investigator who was blind to the information about the subjects assessed the baseline clinical data and the 3-year follow-up outcomes.

2.4 | Immunological measurements of topical and systemic IgE levels, and Eos numbers in nasal polyp tissue

During ESS, a sample of peripheral blood and a portion of fresh nasal polyp tissue were obtained from each patient. The samples were immediately frozen in liquid nitrogen and stored at -80°C until immunological testing. Another portion of fresh polyp tissue was fixed in 10% neutral formalin and used for histopathological testing.

Tissue homogenates were prepared as previously described.²¹ Briefly, a 100-mg sample of frozen polyp tissue was weighed and cut into a 2 mm $\times$ 2 mm specimen in a Petri dish containing liquid nitrogen. After 15 minutes of processing in a homogenization meter

(B. Braun-melsungen, Melsungen, Germany), 1 mL of a 0.9% saline solution containing 1% protease inhibitors (Sigma-Aldrich, St. Louis, MO, USA) was added, and the tissue homogenate was centrifuged for 10 minutes (3000 rpm, 4°C). The supernatant was collected and stored at -80°C until use. The ImmunoCAP test (Phadia, Uppsala, Sweden) was used to quantitatively analyse the levels of total IgE in tissue specimens and blood serum.

Tissue specimens used for obtaining Eos counts were cut into 5- μm sections and stained with H&E. One pathologist who was blinded to the study read 10 randomly selected microscopic fields under an x400 microscope and recorded the absolute number of Eos per high-power field (HPF).

2.5 | Assessment of small airway function

FEV1 is a crucial parameter that reflects the function of large and small airway ventilation, and FEV1/FVC is the most critical parameter for identifying an obstructive impairment.²² However, FEV1 and FEV1/FVC do not properly mirror the function of small airways.²³ FEF₂₅₋₇₅ and MMEF is useful and reproducible markers for examining the function of small airways in the clinic.^{13,24} Because the relevant data are easily obtained, FEF₂₅₋₇₅ is the most common parameter used to identify small airway dysfunction (SAD),²⁵ and FEF₅₀ and FEF₇₅ are the most sensitive markers.⁸ Although variations in the values of these two parameters limit their use for diagnostic purposes, these variations do not preclude their use in aetiological studies where differences between groups may provide valuable clues.²⁶

2.6 | Statistical analysis

All data were analysed using IBM SPSS Statistics for Windows, Version 25.0 software (IBM Corp., Armonk, NY, USA). The results pertaining to categorical data are expressed as percentages, and the significance of differences between groups was analysed using the χ^2 test or Fisher's exact test. The results pertaining to continuous variables are presented as the mean $\pm$ standard deviation (SD) or the median and interquartile range (IQR), depending on whether the data showed a normal distribution as determined by the Kolmogorov-Smirnov test. Analysis of variance (ANOVA) comparisons performed with a Bonferroni correction (for normal distributions) or Kruskal-Wallis test (for non-normal distributions) were used when more than two mean or median values were compared. The independent sample *T* test (2-tailed) or non-parametric Mann-Whitney *U* test was used for comparisons between 2 groups. Pearson or Spearman correlation coefficients were applied to the correlation analyses of the variables with or without a normal distribution, respectively. Prior to correlation analysis, the data for levels of IgE, Eos and lung function parameters were normalized as Z-scores using R statistical software (version 3.5.1). Univariate and multivariate logistic regression analyses were performed to identify factors associated with CRSwNP recurrence.

3 | RESULTS

3.1 | Small airway function was impaired in non-asthmatic patients with CRSwNPs

A total of 14 patients were excluded and 191 CRSwNP patients (73 asthmatic, 118 non-asthmatic), and 30 control subjects were finally enrolled in this study (a flow diagram for screening is shown in Figure 1). The characteristics of the patients are shown in Table 1. CRSwNP patients with asthma had significantly decreased lung function in large airway ventilation (FEV1 and FEV1/FVC) and small airway function (FEF₂₅₋₇₅) compared to the non-asthmatic NP patients and control subjects. The asthmatic NP patients had significantly higher Lund-Mackay scores (LMS), higher blood Eos percentages, and lower blood neutrophil percentages than their non-asthmatic NP counterparts. The FEF₅₀ and FEF₇₅ values, but not the FVC, FEV1, or FEV1/FVC values, for the non-asthmatic patients were significantly lower than the control subjects.

3.2 | Risk factors for impaired small airway function in asthmatic and non-asthmatic patients with CRSwNPs

To evaluate the risk factors for decreased lung function and impaired small airway function in asthmatic and non-asthmatic CRSwNP patients, we investigated the clinical relevance of lung function parameters of these patients (see Tables 2 and 3). No correlation between the LMS and lung function was found in the asthmatic CRSwNP patients. However, the duration of asthma negatively correlated with lung function parameters ($P < .05$). For the non-asthmatic CRSwNP patients, all of the lung function parameters showed a correlation

with the LMS (See Table 3). The r values for FEF₇₅ and FEF₅₀ were -0.274 and -0.255 , respectively ($P < .05$). The highest r value was -0.316 for MMEF. Most of the lung function parameters showed a negative correlation with smoking ($P < .05$) (Table 3).

3.3 | A decrease in FEF₅₀ is a risk factor for the recurrence of CRSwNPs in non-asthmatic patients after ESS

To further identify the clinical relevance of SAD in non-asthmatic patients, we investigated whether decreased FEF₇₅ and FEF₅₀ were risk factors for NP recurrence in non-asthmatic patients. Of the 118 non-asthmatic patients, 115 were followed up for at least 3 years after endoscopic sinus surgery, during which time, 18 (15.7%) of those patients experienced recurrence. A univariate logistic regression analysis showed that FEF₇₅, FEF₅₀, and prior ESS surgery, but not the blood Eos percentage, were risk factors for recurrence (See Table 4). To calculate adjusted OR values for all of these parameters, we performed a multivariate analysis and found that the decrease in FEF₅₀ was an independent risk factor. The adjusted odds ratio (95% CI) for FEF₅₀ was 0.965 (0.933-0.998) ($P < .05$, Table 4).

3.4 | The correlation of type-2 inflammation with impaired lung function in CRSwNPs

Among the enrolled patients, serum and tissue total IgE levels were measured in 95 and 93 patients, respectively. Tissue eosinophil counts were documented for 63 patients, and the percentage of blood Eos for all 191 patients was recorded. The levels of these type-2 inflammation markers are shown in Figure 2A. The values

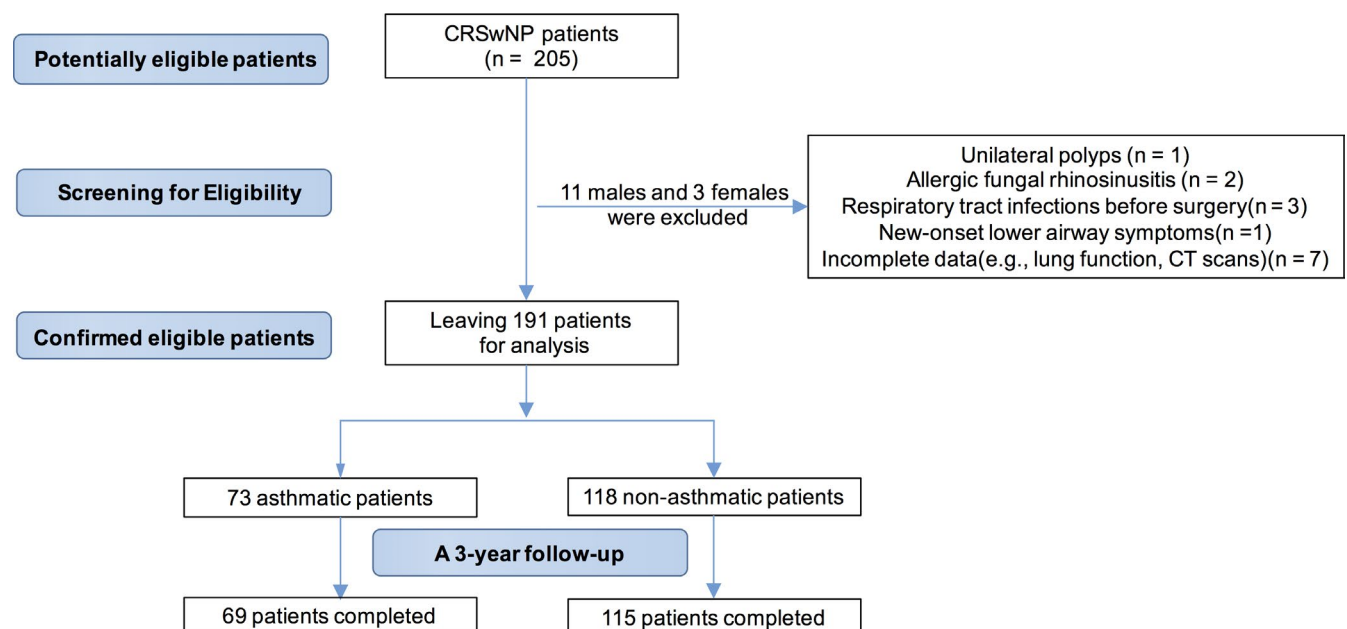


FIGURE 1 A flowchart of screening for eligible CRSwNP patients. CRSwNP, chronic rhinosinusitis with nasal polyps

TABLE 1 The clinical characteristics of CRSwNP patients with or without asthma

Characteristics	Asthmatic n = 73	Non-asthmatic n = 118	Control n = 30	P- value
Male, n (%)	46 (63.01) ^{***}	96 (81.36) ^{***}	18 (60) ^{**}	.006
Age (y)	47.21 ± 11.37	50.78 ± 14.34	49.77 ± 14.02	.204
Eos in blood (%)	9.73 ± 5.83 ^{***}	5.16 ± 3.48 ^{***}	2.41 ± 1.89 [*]	<.001
Lymphocytes in blood (%)	32.89 ± 7.59	34.14 ± 8.11	33.44 ± 8.19	.573
Neu in blood (%)	49.87 ± 10.13 ^{***}	53.48 ± 9.19 ^{***}	55.67 ± 9.20 ^{**}	.008
Smoker, n (%)	14 (19.18) ^{***}	49 (41.53) ^{***}	5 (16.67) ^{**}	.001
Allergy, n (%)	24 (32.88)	41 (34.74)	5 (16.67)	.158
Prior ESS for NP, n (%)	26 (35.62)	28 (23.73)	NA	.076
Duration of CRSwNPs (y)	7 (3-14)	8 (2.25-15)	NA	.468
Duration of asthma (y)	5 (2-10)	NA	NA	NA
ICS treatment, n (%)	32 (43.84)	NA	NA	NA
LMS	18.25 ± 5.49 ^{***}	13.74 ± 5.95 ^{***}	NA	<.001
FVC (% predicted)	86.35 ± 9.24 ^{***}	91.02 ± 10.85 ^{***}	94.18 ± 13.15 ^{**}	<.001
FEV1 (% predicted)	80.17 ± 16.92 ^{***}	97.95 ± 14.69 ^{***}	101.73 ± 11.68 ^{**}	<.001
FEV1/FVC (%)	76.69 ± 12.19 ^{***}	88.24 ± 8.96 ^{***}	90.16 ± 5.10 ^{**}	<.001
PEF (% predicted)	81.07 ± 19.29 ^{***}	90.88 ± 19.51 ^{***}	97.47 ± 15.59 ^{**}	<.001
FEF ₇₅ (% predicted)	64.17 ± 28.25 ^{***}	90.97 ± 24.16 ^{***}	101.20 ± 15.76 [*]	<.001
FEF ₅₀ (% predicted)	52.68 ± 26.82 ^{***}	88.95 ± 28.50 ^{***}	100.80 ± 20.11 [*]	<.001
FEF ₂₅ (% predicted)	43.26 ± 24.47 ^{***}	90.18 ± 40.05 ^{***}	95.92 ± 36.68 ^{**}	<.001
MMEF (% predicted)	48.65 ± 24.87 ^{***}	88.02 ± 29.46 ^{***}	96.82 ± 20.40 ^{**}	<.001

Note: Data are expressed as numbers (%) and means ± standard deviation.

Abbreviations: ESS, endoscopic sinus surgery; ICS, inhaled corticosteroid; LMS, Lund-Mackay score; NP, nasal polyps.

*There were significant differences ($P < .05$) between the control group and the other two CRSwNP groups.

**A significant difference ($P < .05$) was found between the two marked groups (control vs. CRSwNPs with or without asthma).

***A significant difference ($P < .05$) was found between the two marked groups (asthmatic and non-asthmatic).

for FEV1, FEV1/FVC, FEF₂₅, FEF₅₀, FEF₇₅, and MMEF all correlated with tissue and serum IgE levels in CRSwNP patients ($P < .05$) (see Figure 2B and Figure S1). As small airway parameters, MMEF and FEF₅₀ showed the relatively strongest correlations with tissue IgE levels ($r = -.341$, $P < .001$) and serum IgE levels ($r = -.357$, $P < .001$), respectively. Values for FEV1, FEF₂₅, FEF₅₀, FEF₇₅, and MMEF also correlated with tissue and blood Eos levels ($P < .05$) (Figure 2C and Figure S2). Similarly, MMEF and FEF₅₀ showed the strongest correlations with tissue Eos counts ($r = -.362$, $P = .004$) and blood Eos percentages ($r = -.301$, $P < .001$). We also identified a relationship

between type-2 inflammation biomarkers (Eos and IgE) in polyp tissue and those in blood, of which the r values were .423 and .530, respectively ($P < .01$) (Figures S1 and S2).

CRSwNP patients with asthma comorbidity showed a more severe type-2 response as compared to their non-asthmatic CRSwNP counterparts²⁷ (Figure 2A). Therefore, we further investigated whether the decreased lung function and LMS among non-asthmatic CRSwNP patients were also related to type-2 inflammation (see Table 5). We found that values for FEV1, FEV1/FVC, FEF₂₅₋₇₅, and MMEF were related to serum IgE levels, and FEF₅₀ showed the

TABLE 2 Correlation coefficients of lung function in the asthmatic CRSwNP group

Variable	FVC	FEV1	FEV1/ FVC	PEF	FEF ₇₅	FEF ₅₀	FEF ₂₅	MMEF
DON	-0.083	-0.060	-0.141	-0.028	-0.212	-0.209	-0.142	-0.175
DOA	-0.121	-0.312*	-0.320*	-0.153	-0.332*	-0.384*	-0.296*	-0.340*
Pack-year	0.083	0.017	-0.022	-0.024	0.079	0.057	-0.048	0.015
LMS	0.057	0.086	0.126	0.145	0.003	0.028	0.054	0.028

* $P < .05$. DON, duration of nasal disease; DOA, duration of asthma; ICS treatment, inhaled corticosteroid treatment before lung function examination; Pack-year, a unit for measuring the amount that a person has smoked over a long period of time, which is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked; LMS, Lund-Mackay score.

strongest correlation ($r = -.348$, $P = .004$). No correlations were found between lung function parameters and other type-2 inflammation markers, including tissue IgE levels, tissue Eos numbers, or blood Eos percentages.

4 | DISCUSSION

To our knowledge, this is the first study to systematically analyse distinct characteristics of the decreased lung function found in asthmatic and non-asthmatic CRSwNP patients. We confirmed that asthmatic CRSwNP patients had higher LMS than their non-asthmatic counterparts. CRSwNP patients with asthma had impairments in of large and small airway function. Non-asthmatic CRSwNP patients had lower LMS, and their impairments in the lower airway were primarily due to asymptomatic SAD. Previous studies found evidence of possible asymptomatic airway impairments in non-asthmatic CRSwNP patients,²⁸ and small airways represent a silent zone in the lungs where a disease can increase in severity without notice.⁸ Therefore, SAD in CRSwNP patients may be an early sign of lower airway disease. SAD significantly contributes to the pathophysiology of asthma,⁶ and it is associated with the development of asthma.^{11,12} When SAD in CRSwNP patients develops into asthma, disease severity in the upper and lower airways becomes simultaneously enhanced. The main finding of our study is the presence of SAD in non-asthmatic patients with CRSwNP. Our findings confirmed that the upper and lower airways are vital components of the "united airways" and that more attention should be paid to lower airway function in CRSwNP patients, regardless of concomitant asthma. It is important to monitor the small airway function of CRSwNP patients without asthma.

In this study, we identified a negative correlation between SAD and Lund-Mackay scores in non-asthmatic CRSwNP patients, which verified that the presence and severity of CRSwNPs were related to a decrease in lower airway function. Smoking was identified as a risk factor for impaired lung function in non-asthmatic CRSwNP patients, which is consistent with previous studies.^{29,30} Although exposure to smoke contributes to SAD, its effect seems independent of the intensity of smoking and may persist even after a patient stops smoking.^{31,32} Our finding of a relationship between LMS and FEF₂₅₋₇₅ values suggests that the severity of NPs reflects small airway function. Therefore, patients with CRSwNPs and who undergo ESS should have their small airway function re-evaluated after surgery, because it is involved in the pathogenesis of asthma.⁶

No correlations were found between lung function parameters and the Lund-Mackay scores of asthmatic CRSwNP patients. The only risk factor for impaired lung function in asthmatic CRSwNP patients was the duration of asthma, which suggests that asthma comorbidity was the dominant cause of abnormal lung function in these patients. Asthma is a dominant risk factor for CRSwNP recurrence.³³ It remains unknown whether SAD is a risk factor for NP recurrence in non-asthmatic CRSwNP patients. Because the values for FEF₇₅ and FEF₅₀ were decreased in non-asthmatic CRSwNP patients, we used these two parameters to investigate the relationship between SAD and polyp recurrence. We identified FEF₅₀ as an independent risk factor for recurrence. Our findings confirmed the clinical relevance of SAD, which is a risk factor for the recurrence of CRSwNPs.

To further investigate the immunological relevance of decreased lower airway function in CRSwNP patients, we measured IgE and Eos levels in samples of polyp tissue and blood. As expected, we found negative correlations between the lung function parameters

TABLE 3 Correlation coefficients of lung function in the non-asthmatic CRSwNP group

Variable	FVC	FEV1	FEV1/ FVC	PEF	FEF ₇₅	FEF ₅₀	FEF ₂₅	MMEF
DON	0.121	0.169	0.127	0.048	0.048	0.085	0.153	0.125
Pack-year	-0.249*	-0.286*	-0.231*	0.011	-0.143	-0.250*	-0.289*	-0.285*
LMS	-0.200*	-0.282*	-0.261*	-0.220*	-0.274*	-0.255*	-0.276*	-0.316*

* $P < .05$. DON, duration of nasal disease; Pack-year, a unit for measuring the amount that a person has smoked over a long period of time, and is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked; LMS, Lund-Mackay score.

TABLE 4 Univariate and multivariate logistic regression analyses related to NP recurrence in 115 non-asthmatic CRSwNP patients

Variable	Univariate		Multivariate		
	OR (95% CI)	P-value	β coefficient	OR (95% CI)	P-value
Gender, (male vs. female)	1.218 (0.320-4.638)	.773	NA	NA	NA
Age, (y)	0.984 (0.952-1.018)	.984	NA	NA	NA
Prior ESS for NPs, (n)	1.779 (1.304-3.061)	.038	0.642	1.900 (1.073-3.363)	.038
Allergy, (yes vs. no)	0.970 (0.334-2.816)	.955	NA	NA	NA
Pack-years	1.013 (0.983-1.044)	.407	NA	NA	NA
Blood Eos (%)	0.980 (0.846-1.136)	.792	NA	NA	NA
LMS	1.025 (0.983-1.119)	.587	NA	NA	NA
FEF ₇₅	0.970 (0.948-0.992)	.008	0.001	1.001 (0.966-1.038)	.943
FEF ₅₀	0.968 (0.948-0.988)	.002	-0.035	0.965 (0.933-0.998)	.041

Note: Pack-year, a unit for measuring the amount that a person has smoked over a long period of time, which is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

Abbreviations: ESS, endoscopic sinus surgery; FEF₅₀, forced expiratory flow at 50% of the forced vital capacity; FEF₇₅, forced expiratory flow at 75% of the forced vital capacity; LMS, Lund-Mackay score; OR, odds ratio.

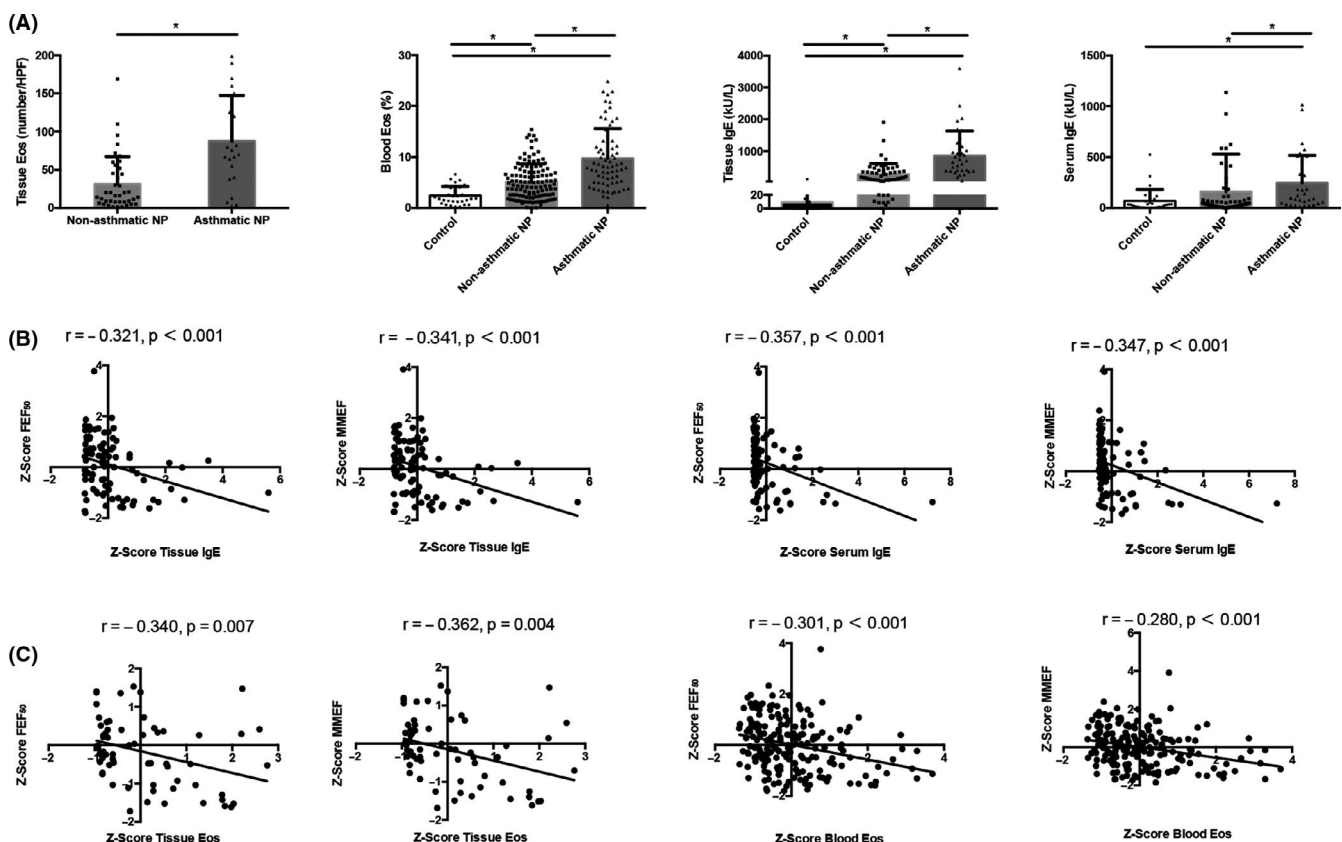


FIGURE 2 Impaired small airway function in non-asthmatic CRSwNP patients is related to the degree of type-2 inflammation. A, Comparison of type-2 inflammatory agents (mean $\pm$ SD) between the three groups (asthmatic and non-asthmatic patients, and controls). Kruskal-Wallis test, *: $P < .05$. B, Correlation between small airway parameters and IgE levels (Spearman test). C, Correlation between small airway parameters and Eos levels (Spearman test), FEF₅₀, forced expiratory flow at 50% of forced vital capacity; MMEF, maximum mid-expiratory flow between 25% and 75% of forced vital capacity

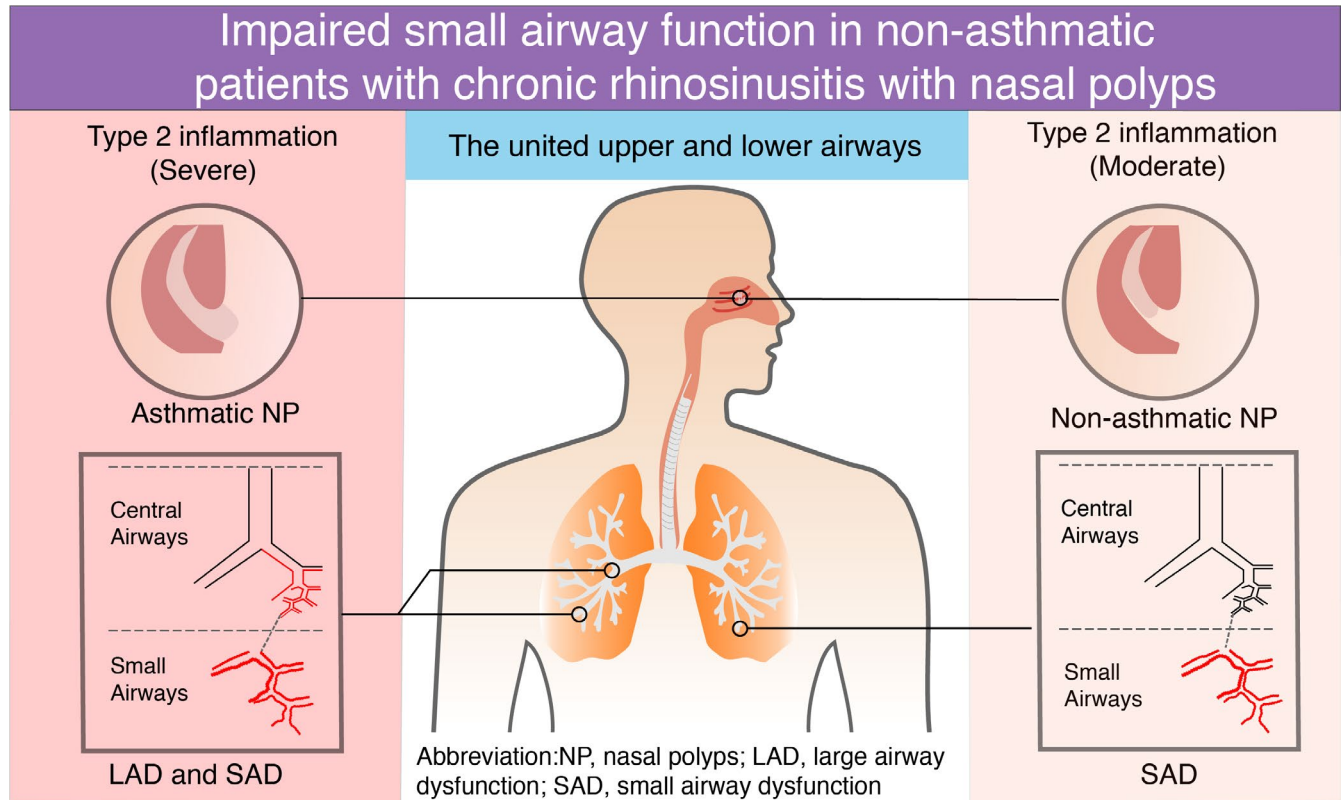
(eg FEV₁, FEF₇₅, and FEF₅₀) and type-2 inflammation markers (eg tissue and serum IgE, and tissue and blood Eos). Some evidence suggests that the degree of type-2 inflammation in the lower

airway and circulation is related to lower airway dysfunction. Kozlik et al³⁴ found that patients with airflow limitations had greater degrees of eosinophilia in blood and bronchoalveolar lavage samples,

TABLE 5 Correlations between lung function and type-2 inflammation markers in the non-asthmatic CRSwNP group

Variable	FVC	FEV1	FEV1/ FVC	PEF	FEF ₇₅	FEF ₅₀	FEF ₂₅	MMEF
Tissue Eos count (Number/ HPF, n = 40)	-0.210	-0.097	0.234	-0.056	0.079	0.078	0.162	0.108
Blood Eos (%; n = 118)	0.000	0.013	-0.041	0.128	0.002	-0.050	0.041	-0.005
Tissue IgE (kU/L, n = 58)	-0.048	-0.142	-0.197	0.133	-0.089	-0.174	-0.167	-0.182
Serum IgE (kU/L, n = 64)	-0.230	-0.346*	-0.324*	-0.068	-0.284*	-0.348*	-0.248*	-0.319*

Abbreviation: HPF, high-power field.

* $P < .05$.**FIGURE 3** Schematic overview of impaired small airway function in non-asthmatic CRSwNP patients and its relationship to the degree of type-2 inflammation

and Mauro et al³⁵ reported that asthma patients with impaired lung function had increased blood Eos numbers and values for fractional exhaled NO (FeNO). Asthma patients with nasal polyps show a more severe type-2 response than asthma patients without nasal polyps.³⁵ Because the degree of type-2 inflammation in non-asthmatic patients is lower than asthmatic patients,²⁷ we hypothesized that the immunological relevance of SAD in non-asthmatic CRSwNP patients would be different. However, we failed to find any correlations between lung function parameters and markers of eosinophilic inflammation, including Eos counts in nasal polyps and blood Eos percentages. Instead, we found that the FEF₂₅₋₇₅ values for non-asthmatic CRSwNP patients were significantly related to their blood IgE levels. The upper and lower airways certainly form a

morphological and functional entity.⁴ The mechanism by which the upper and lower airways most likely interact with each other is via localized inflammatory changes that occur in both airways, followed by a systemic response.⁴ Recent studies revealed that lower airway inflammation, as assessed by FeNO, was related to Eos counts in nasal polyps and the blood Eos percentage,¹⁴ and the level of FeNO was associated with a decline in lung function.³⁶ As a supplement to the current knowledge gap, we also found a correlation between lower airway function and nasal and systemic type-2 inflammation, and a correlation between the levels of Eos and IgE in nasal polyps and peripheral blood. Taken together, our results indicate that the parallel upper and lower airway disorders of CRSwNPs, nasal polyps, and impaired lung function are related to nasal and systemic

type-2 inflammation and nasal inflammation and bronchitis may be linked via peripheral blood. Serum IgE may be a link between nasal polyps and SAD in non-asthmatic CRSwNP patients.

When interpreting our findings, there are some limitations need to be considered. First, the measurement of SAD is a big challenge, and a unanimously agreed-upon approach to investigate small airway functions is lacking.⁶ Although FEF₂₅₋₇₅ is widely available in clinical practice, large airway obstruction and volume changes influence its values. Therefore, we failed to set a cut-off value for FEF₂₅₋₇₅ to identify the numbers of patients with SAD. The number of the CRSwNP patients without asthma was also relatively small in this retrospective study. A larger multi-centre prospective study is required to confirm and expand on our observations.

In conclusion, asthmatic and non-asthmatic CRSwNP patients had impaired lung function. The lower airway dysfunction found in non-asthmatic patients occurred in small airways, and smoking was identified as a risk factor. The SAD found in non-asthmatic patients correlated with the presence and severity of nasal polyps. The duration of asthma was identified as a major risk factor for decreased lung function in asthmatic CRSwNP patients. The existence of persistent lower airway dysfunction correlated with the presence of upper airway disease and the degree of nasal and systemic type-2 inflammation (Figure 3).

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CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

KD wrote the manuscript. KD, MZ and WBX analysed the data. KD, NZ, XDW, LZ, and CB designed the study and revised the manuscript. Y.Z and YH tested the specimens. K.D, YW, YH, and JMZ collected the clinical data and made the follow-up.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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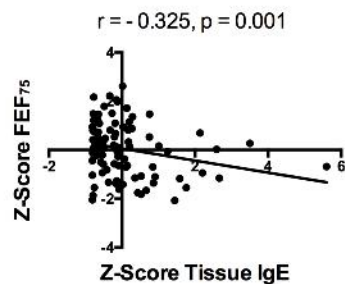
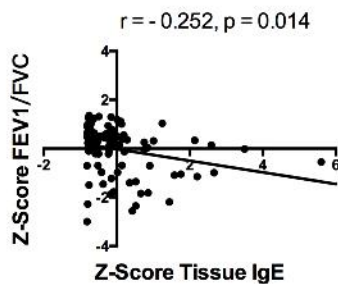
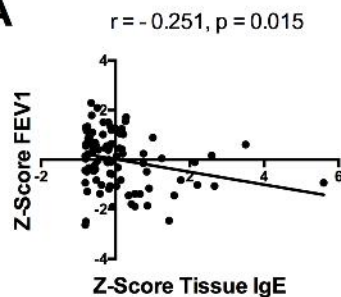
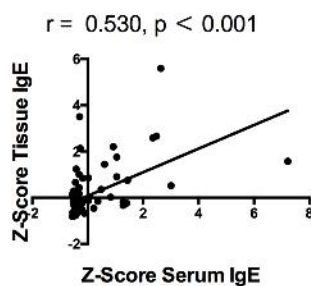
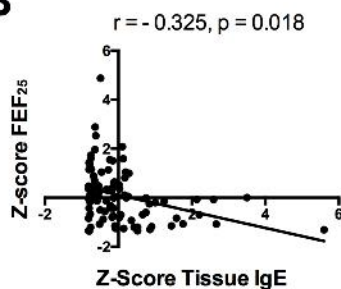
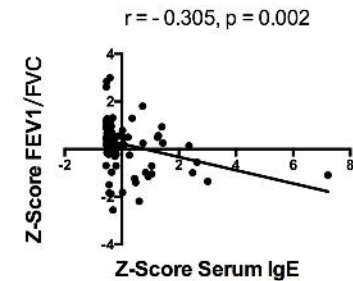
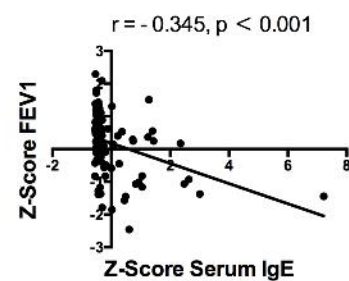
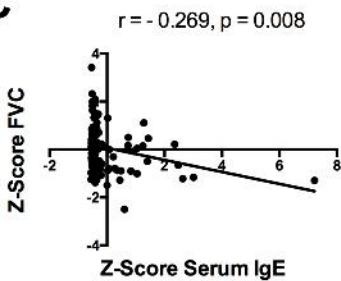
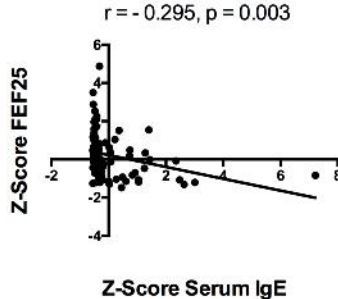
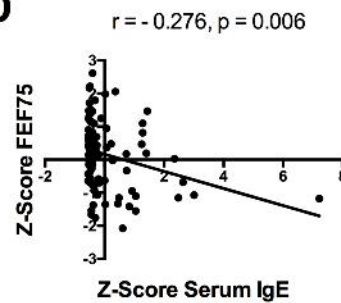
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

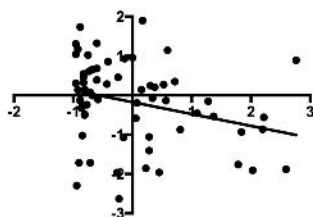
How to cite this article: Du K, Zheng M, Zhao Y, et al. Impaired small airway function in non-asthmatic chronic rhinosinusitis with nasal polyps. *Clin Exp Allergy*. 2020;00:1–10. <https://doi.org/10.1111/cea.13747>

A**B****C****D**

A

$$r = -0.288, p = 0.022$$

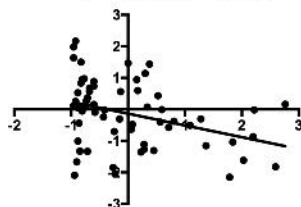
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Z-Score Tissue Eos

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Z-Score FEF75

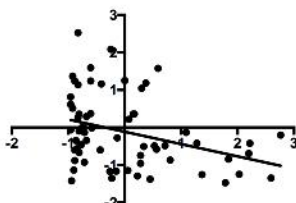


Z-Score Tissue Eos

B

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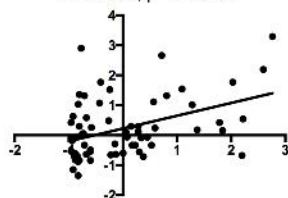
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Z-Score Tissue Eos

$$r = 0.423, p < 0.001$$

Z-Score Blood Eos

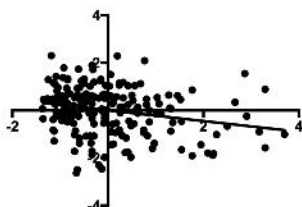


Z-Score Tissue Eos

C

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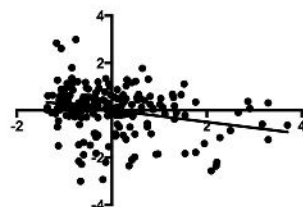
Z-Score FEV1



Z-Score Blood Eos

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Z-Score FEV1/FVC

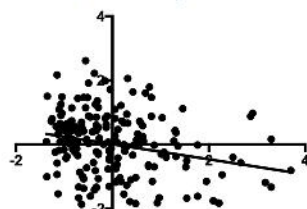


Z-Score Blood Eos

D

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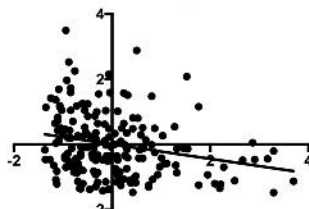
Z-Score FEF75



Z-Score Blood Eos

$$r = -0.228, p = 0.002$$

Z-score FEF25



Z-Score Blood Eos