



## Two inflammatory phenotypes of nasal polyps and comorbid asthma

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### ABSTRACT

**Background:** Nasal polyps and comorbid asthma (NPCA) is a common united airway disease. However, the inflammatory phenotypes of NPCA are not clear.

**Objective:** To identify inflammatory phenotypes of NPCA.

**Methods:** A total of 106 patients diagnosed with NPCA were recruited from rhinologic clinics. A combined method of biopsies from nasal polyps and fractional exhaled nitric oxide (FeNO) was used to explore inflammatory phenotypes of NPCA. Patients were evaluated with respect to clinical, functional, and inflammatory parameters. Clinical outcomes after medical treatment were also assessed.

**Results:** Two distinct inflammatory phenotypes (eosinophilic [64.15%] and noneosinophilic phenotypes [35.85%]) were identified. Inflammatory patterns of upper and lower airways were consistent in NPCA. Patients with eosinophilic NPCA had a higher nasal polyps recurrence rate than did patients with noneosinophilic NPCA, a more severe asthma phenotype ( $P < .001$ ), higher exhaled nitric oxide levels ( $P < .001$ ), higher IgE levels ( $P < .001$ ), higher Lund-Mackay scores ( $P < .05$ ), and more blood eosinophilia ( $P < .001$ ). In addition, eosinophilic NPCA was associated with worse pulmonary function and responded well to an 8-week course of medical treatment based on computed tomographic findings and the ratio of forced expiratory volume in 1 second to forced vital capacity. The total IgE concentration was a marker for eosinophilic NPCA (optimal cutoff,  $>55.5$  kU/L; sensitivity, 86.2%; specificity, 85.4%).

**Conclusion:** Patients with NPCA had 2 inflammatory phenotypes with distinct clinical profiles. Total IgE is a marker of eosinophilic NPCA.

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### Introduction

Chronic rhinosinusitis is a chronic inflammatory disease that affects the nasal cavity and paranasal sinuses and greatly affects the quality of life of patients. Nasal polyps (NPs) are a severe phenotype of chronic rhinosinusitis.<sup>1</sup> Comorbid asthma is considered a predictor of recurrence of NPs.<sup>2</sup> Approximately 20% to 60% of patients with NPs have asthma,<sup>3,4</sup> and approximately 7% to 25.4% of patients with asthma have NPs.<sup>5</sup> During the natural evolution of this disease combination, a clinical history of NPs usually precedes asthma, and up to 45% of patients with NPs develop asthma.<sup>6,7</sup>

NPs can be classified as either eosinophilic or noneosinophilic NPs based on the dominant inflammatory cell type in tissues.<sup>8</sup> The clinical and immunopathologic characteristics of eosinophilic NPs have been thoroughly researched, and eosinophilic NPs are thought to be a refractory phenotype, characterized by a high reversion rate and good responses to corticosteroid therapy.<sup>9–11</sup> Nasal polyps and comorbid asthma (NPCA) is a common severe airway disease.<sup>12</sup> Patients with both upper and lower respiratory tract diseases have gained special attention. Although NPs and asthma often coexist, the mechanism of this disease entity is poorly understood. Previous studies have indicated the existence of a systemic pathway that links the upper and lower airways in nasal and bronchial allergic disease.<sup>13–15</sup> The nasal and bronchial airway tend to react consistently on being challenged with allergen in terms of the inflammatory response. A large amount of evidence indicates that NPs and asthma are closely related in terms of the clinical epidemiology, pathophysiology, and immunology.<sup>16–18</sup> Actually, both NPs and asthma can be divided into eosinophilic and noneosinophilic phenotypes. In regard to NPCA, whether the inflammatory patterns of upper and lower airways is consistent is not clear.

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Many studies of NPCA have usually focused on the prevalence, mutual effect of disease severity, and combined treatment of both upper and lower airway diseases.<sup>19–21</sup> The effect of chronic rhinosinusitis in patients with NPs on asthma treatment is controversial,<sup>22–25</sup> and a possible cause was heterogeneity. These studies did not divide NPCA into different inflammatory patterns and instead considered both diseases as a single entity.

Identification of the phenotype that characterizes NPCA in individual patients might be diagnostically and therapeutically useful because causative mechanisms and treatment response may vary across NPCA subtypes. The present study was designed to investigate the inflammatory phenotypes of NPCA and their response to medical treatment.

## Methods

In this prospective cohort study, patients were recruited from January 1, 2011, through December 31, 2015, from the Rhinology Clinics, Department of Otorhinolaryngology of Beijing Chaoyang Hospital or Beijing Anzhen Hospital at the Capital Medical University (Beijing, China). NPCA was diagnosed using nasal mass biopsy specimens (NPs) and airway hyperreactivity (a 20% reduction in forced expiratory volume in 1 second [FEV<sub>1</sub>] after administration of up to 16 mg/mL of methacholine) or by airway reversibility (a >12% improvement in FEV<sub>1</sub> after administration of a  $\beta$ -agonist) according to the criteria of the European Position Paper on Rhinosinusitis and Nasal Polyps 2012<sup>1</sup> and Global Initiative for Asthma guidelines.<sup>26</sup> The study design is shown in Figure 1.

Exclusion criteria were acute upper or lower respiratory tract infections within 2 weeks before the inclusion visit, use of corticosteroids (including oral and inhaled corticosteroids) within 4 weeks before the inclusion visit, a clinically significant comorbidity (systemic vasculitis and granulomatous diseases, hypereosinophilic syndrome, and neoplasia), significant psychological diseases, pregnancy, and lactation. All patients were aged 23 to 68 years. Study site visits occurred at screening and at week 8 after the first clinical visit. Patients who had ever undergone previous endoscopic sinus surgery in our department and were under long-term follow-up were

included in the study. The status and time of NP recurrence after surgery were also recorded. This study was approved by the ethics committee of Beijing Chaoyang Hospital, Capital Medical University. All patients provided written informed consent before participating in the study.

## Inflammatory Phenotype Evaluation and Atopic Status

Tissue specimens were obtained from the NPs in the clinic, immediately formalin fixed, and then paraffin embedded. Paraffin sections (4- $\mu$ m thick) were stained with hematoxylin-eosin. A total of 5 randomly selected field of views were evaluated for each stain at a magnification of  $\times 400$  by 2 experienced pathologists. NPs were classified as eosinophilic when the frequency of tissue eosinophils exceeded 10% of the total infiltrating cells per high-power field.<sup>8</sup> Exhaled nitric oxide was measured using an LR2000 analyzer (Logan Research Ltd). The patient was asked to inhale deeply and then exhale slowly and steadily through the mouthpiece, keeping 80% of the biofeedback indicator lighting on to attain a constant exhalation flow rate of 200 mL/s and maintain a mouth pressure of approximately 5 cm H<sub>2</sub>O, as recommended by the European Respiratory Society task force.<sup>27</sup> Eosinophilic asthma was defined when FeNO values were greater than 50 ppb.<sup>28</sup> A combination of eosinophilic NPs and eosinophilic asthma was used to define the eosinophilic NPCA. Noneosinophilic NPCA was defined when both NPs and asthma had noneosinophilic subtypes. Subtypes of eosinophilic NPs with noneosinophilic asthma and noneosinophilic NPs with eosinophilic asthma were also evaluated and calculated.

A total of 15 mL of peripheral venous blood was collected in EDTA anticoagulated tubes from each participant before treatment. The atopic status of the patients was evaluated using skin prick test to a standard panel of aeroallergens or using the ImmunoCAP Phadiatop test (Phadia, Uppsala, Sweden) for detecting total IgE antibodies against various common inhalant allergens. A complete peripheral blood cell count was performed by an automated analyzer (Beckman Coulter, Miami, Florida), and the percentages of neutrophils (reference range, 40%–75%) and eosinophils (reference range, 0.4%–8%) were calculated.

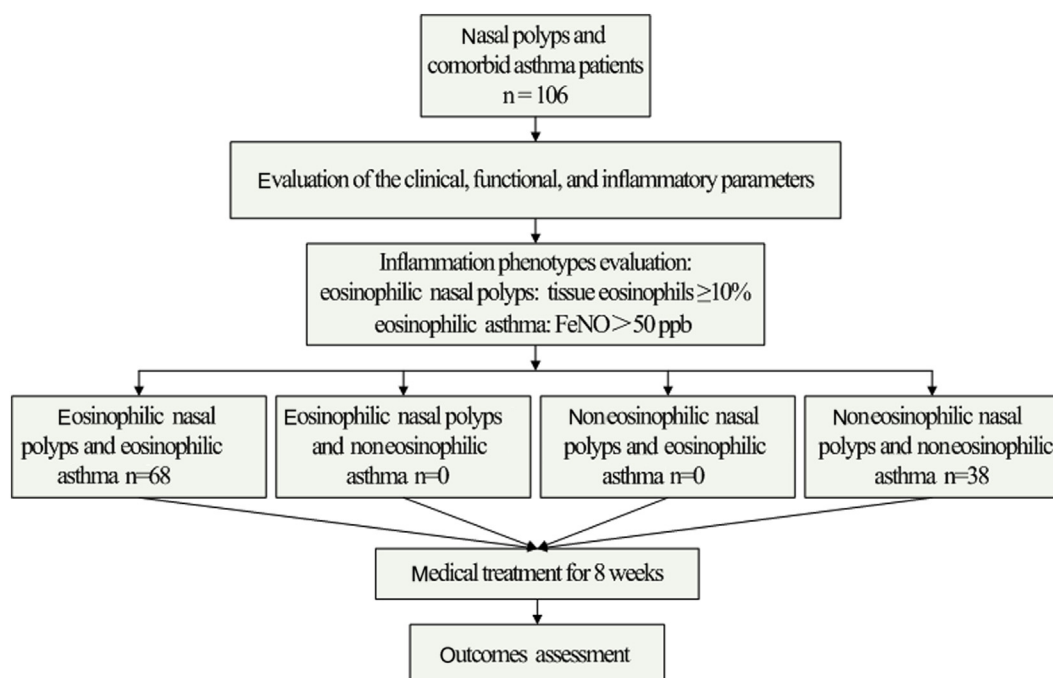


Figure 1. Study design. FeNO, fractional exhaled nitric oxide.

## Subjective Assessment

Patients filled out questionnaires that assessed demographic data, medical history, history of nonsteroidal anti-inflammatory drug (NSAID) sensitivity, history of nasal endoscopic surgery, family history of asthma, and medication use. The severity of asthma was defined by the Global Initiative for Asthma guidelines.<sup>26</sup> Patients were divided into 2 groups according to their age at asthma onset: childhood onset (<18 years old) or adult onset ( $\geq$ 18 years old) as previously described.<sup>29</sup>

## Objective Upper and Lower Airway Evaluation

Computed tomography (CT) was performed to assess the inflammatory state and anatomical structure of the nasal cavity and sinuses. CT was staged according to the Lund-Mackay scoring scale.<sup>30</sup> Respiratory function parameters, including FEV<sub>1</sub> (percentage predicted), ratio of forced vital capacity (FVC) to FEV<sub>1</sub>, and peak expiratory flow, were evaluated using a spirometer (model 2160; Vitalograph, Buckingham, England). The spirometric standards complied with the European Respiratory Society recommendations.<sup>31</sup> An FEV<sub>1</sub> and forced expiratory flow at 25% to 75% of less than 80% of the predicted value were considered indications of impairment of lung function. An astograph methacholine provocation test was conducted to assess the airway responsiveness, as previously described.<sup>32</sup> The cumulative dose of inhaled methacholine measured at the inflection point at which respiratory conductance started to decrease ( $D_{min}$ ) was recorded.

## Medical Treatment

Conservative medical therapy consisted of oral prednisone for 4 weeks (1 week each of 30.00, 25.0, 12.5, and 5.0 mg/d), topical steroids in spray or irrigation form for another 4 weeks (once daily), and saline irrigation for 8 weeks (twice daily). We recommended that patients visit the same respiratory clinic to receive standard treatment for asthma. Follow-up was arranged in 8 weeks to assess the response to medical therapy. A clinical asthma exacerbation was defined as an FEV<sub>1</sub> decrease of 20% or more from baseline or worsening of asthma requiring emergency treatment, hospital admission, or 3 or more days of oral corticosteroid treatment. Patients with exacerbations were treated according to the recommendations of the respiratory physicians.

## Statistical Analysis

Continuous variables were presented as mean (SD), median (with range or interquartile range), or number (percentage) according to the data distribution.  $P < .05$  was considered statistically significant. The 2-sample  $t$  test was applied for parametric data that followed a normal distribution. A nonparametric test (the Mann-Whitney test) was applied for parametric data that did not follow a normal distribution. Differences in frequencies between groups were examined using the  $\chi^2$  test. For efficacy evaluation, baseline variables were analyzed with 1-way analysis of variance followed by the paired  $t$  test for differences before and after treatment. A receiver operating characteristic (ROC) curve was plotted by calculating the sensitivity and specificity of each clinical marker to identify the best cutoff point. The diagnostic ability of each marker was calculated based on the area under the ROC curve (AUC). An AUC greater than 0.9 was considered to represent high accuracy, 0.7 to 0.9 represented moderate accuracy, and 0.5 to 0.7 represented low accuracy. The Youden index (sensitivity + specificity – 1) was used to evaluate the diagnostic predictive ability of markers. Statistical analyses were performed using SPSS statistical software, version 17.0 (SPSS Inc, Chicago, Illinois).

## Results

### Clinical Characteristics of Enrolled Patients

A total of 106 patients with NPCA were enrolled in the study based on the inclusion and exclusion criteria. In this study, 68 patients present with an eosinophilic phenotype, and 38 patients had a noneosinophilic phenotype. No patients had subtypes of eosinophilic NPs and noneosinophilic asthma or noneosinophilic NPs and eosinophilic asthma. The clinical characteristics of all patients are summarized in Table 1. No significant differences were found between the patients with eosinophilic NPCA and those with noneosinophilic NPCA with respect to age, sex, smoking habit, history of NSAID sensitivity, family history of asthma, concurrent rate of atopy, duration of chronic rhinosinusitis, asthma duration, or rate of adult-onset asthma. However, patients with eosinophilic NPCA had a significantly higher NP recurrence rate ( $P < .01$ ) and more severe asthma ( $P < .001$ ) than did patients with noneosinophilic NPCA.

### Features of Upper and Lower Airway Disease Severity and Inflammatory Characteristics

The features of upper and lower airway disease severity and inflammatory characteristics are summarized in Table 2. With respect to the pulmonary function of the lower airway, FEV<sub>1</sub> and FEV<sub>1</sub>/FVC were significantly lower in patients with eosinophilic NPCA than in those with noneosinophilic NPCA ( $P < .001$  for both). However, no significant differences were found in the FVC or  $D_{min}$  value between the 2 groups. Patients with eosinophilic NPCA had a significantly higher level of total IgE than did patients with noneosinophilic NPCA ( $P < .001$ ). The Lund-Mackay scores were calculated to evaluate the severity of upper airway disease. We found that patients with eosinophilic NPCA had significantly higher scores than did patients with noneosinophilic NPCA (mean, 21.44 vs 17.42;  $P < .05$ ) (Fig 2). We also evaluated the degree of eosinophil infiltration within NPs. The frequency of eosinophil infiltration in patients with eosinophilic NPCA was significantly higher than that in patients with noneosinophilic NPCA (median, 21.40 vs 8.00;  $P < .001$ ) (Table 2 and Fig 3). With respect to markers of airway inflammation, patients with eosinophilic NPCA had higher levels of FeNO than did those with noneosinophilic NPCA (median, 105 vs 61 ppb;  $P < .05$ ). Patients with eosinophilic NPCA had more evidence of systemic inflammation based on the higher blood eosinophil percentage than in patients with noneosinophilic NPCA (median, 6.2% vs 2.5%;  $P < .001$ ). However, the 2 groups had similar percentages of blood neutrophils.

### Different Response to Medical Treatment

As shown in Figure 2 and Figure 4, patients with eosinophilic NPCA had different responses to medical treatment than did patients with noneosinophilic NPCA based on CT and pulmonary function testing. Patients with eosinophilic NPCA had significantly decreased Lund-Mackay scores after treatment ( $P < .001$ ), whereas those with noneosinophilic NPCA had a decreasing trend, but it did not reach statistical significance ( $P = .38$ ). Both groups had an increasing FEV<sub>1</sub> after treatment, but the finding was not statistically significant. Patients with eosinophilic NPCA had a significant increase in the FEV<sub>1</sub>/FVC after treatment ( $P < .05$ ), whereas patients with noneosinophilic NPCA also had an increased FEV<sub>1</sub>/FVC after treatment, but without statistical significance.

### ROC Analysis and Determination of Optimal Cutoff

The ROC curve analysis of clinical markers for diagnosing eosinophilic NPCA is presented in Table 3 and Figure 5. The total IgE level had a higher accuracy as a predictor of eosinophilic NPCA (AUC = 0.894) than did other markers, such as reciprocal of FEV<sub>1</sub> (AUC = 0.812), percentage of blood eosinophils (AUC = 0.808),

**Table 1**  
Clinical Characteristics of Patients With Eosinophilic NPCA vs Patients With Noneosinophilic NPCA

| Characteristic                        | NPCA (n = 106)    | Eosinophilic NPCA (n = 68) | Noneosinophilic NPCA (n = 38) | P value |
|---------------------------------------|-------------------|----------------------------|-------------------------------|---------|
| Age, mean (SD), y                     | 47.25 (9.99)      | 47.50 (11.22)              | 46.79 (7.56)                  | .81     |
| Male, No. (%)                         | 74 (69.81)        | 48 (70.59)                 | 26 (68.42)                    | .87     |
| Atopy, No. (%)                        | 40 (37.74)        | 26 (38.24)                 | 14 (36.84)                    | .92     |
| Duration of CRS, median (IQR), y      | 5.00 (1.00–15.00) | 4.00 (10.00–11.00)         | 5.00 (2.00–20.00)             | .23     |
| Asthma duration, median (IQR), y      | 3.00 (0.21–6.00)  | 3.00 (0.26–10.00)          | 2.00 (0.08–6.00)              | .79     |
| Age at asthma diagnosis, mean (SD), y | 41.71 (11.60)     | 41.75 (12.49)              | 41.64 (10.12)                 | .97     |
| Adult-onset asthma, No. (%)           | 76 (71.70)        | 52 (74.47)                 | 24 (63.16)                    | .30     |
| Smoker, No. (%)                       | 34 (32.08)        | 20 (29.41)                 | 14 (34.84)                    | .58     |
| History of NSAID sensitivity, No. (%) | 10 (9.43)         | 6 (8.83)                   | 4 (10.53)                     | >.99    |
| Family history of asthma, No. (%)     | 8 (7.55)          | 4 (5.88)                   | 4 (10.53)                     | .94     |
| Nasal polyp recurrence rate, No. (%)  | 64 (60.38)        | 50 (64.10)                 | 14 (36.84)                    | .009    |
| Severe asthma, No. (%)                | 50 (47.17)        | 44 (64.71)                 | 6 (15.79)                     | <.001   |

Abbreviations: CRS, chronic rhinosinusitis; IQR, interquartile range; NPCA, nasal polyps and comorbid asthma; NSAID, nonsteroidal anti-inflammatory drug.

Lund-Mackay score (AUC = 0.795), reciprocal of FEV<sub>1</sub>/FVC (AUC = 0.791), and FeNO (AUC = 0.749). The evaluation indexes for the cutoff point of each predictor are given in Table 3. A higher Youden index (sensitivity + specificity – 1) indicated a higher diagnostic predictive ability. As shown in Table 3, a total IgE cutoff point greater than 55.5 kU/L indicated a higher predictive accuracy (sensitivity of 86.2%, specificity of 85.4%, and Youden index of 0.716), whereas an FeNO cutoff point greater than 71.0 ppb indicated the lowest predictive accuracy (sensitivity of 80.6%, specificity of 64.7%, and Youden index of 0.453).

## Discussion

This study found that patients with NPCA had eosinophilic and noneosinophilic phenotypes (64.15% vs 35.85%). These 2 distinct phenotypes were identified using biopsies of NPs and FeNO. In the present study, we found that the inflammatory patterns of upper and lower airways were consistent in patients with NPCA, which further support the unified airway theory. Besides, eosinophilic NPCA and noneosinophilic NPCA have different clinical profiles. In term of the response to medical treatment, patients with eosinophilic NPCA responded well as shown by significant improvements in their CT findings and FEV<sub>1</sub>/FVC ratio. These results suggested that eosinophilic NPCA might have an underlying pathophysiologic mechanism that differed from that of noneosinophilic NPCA. We used FeNO rather than bronchial biopsy or induced sputum cell count to define the inflammatory subtypes of asthma, which might have resulted in a deviation. In this study, a combined method was used to explore inflammatory subtypes of NPCA, which should be examined and verified using a more objective method (biopsy or induced sputum) in the future study.

Eosinophilic NPCA is a severe airway disease that involves active eosinophilic airway inflammation that extends from the nose and

sinuses to the peripheral airways. Approximately 64.10% of patients with eosinophilic NPCA have a history of NP recurrence, and approximately 64.71% have a severe asthma phenotype; these ratios greatly differs from those of patients with noneosinophilic NPCA. It is widely recognized that patients with NPCA are characterized by a longer duration of nasal symptoms, older age, bronchial obstruction, more severe Lund-Mackay CT scores, more revision sinonasal operations (higher CT scores, higher numbers of sinonasal operations), and higher incidence of comorbid aspirin-sensitive disease.<sup>19,33</sup> However, more detailed studies of NPCA with a classification of inflammatory phenotypes are relatively rare. In previous studies, late-onset eosinophilic asthma was often associated with NPs,<sup>33–35</sup> and NPs were an independent factor associated with blood eosinophilia in patients with asthma.<sup>35</sup> In addition, anti-interleukin 5 therapy with reslizumab for the treatment of patients with poorly controlled and eosinophilic asthma was effective in improving pulmonary function and tended toward greater asthma control, especially in patients with NPs.<sup>34</sup> Interleukin 5 is a key mediator in the maturation, recruitment, and activation of eosinophils.<sup>36</sup> These studies indicated that an eosinophilic airway of NPCA was a special phenotype and may benefit more from systemic anti-inflammatory therapy (specifically directed at eosinophils), which was confirmed by our findings.

The radiologic features of nasal cavities and sinuses, pulmonary function, and related inflammatory parameters of the patients were assessed to characterize further the severity of airway diseases and inflammatory conditions. Patients with eosinophilic NPCA had significantly higher Lund-Mackay scores than patients with noneosinophilic NPCA, suggesting that the paranasal sinus CT abnormalities in patients with eosinophilic phenotype were worse than those in patients with noneosinophilic phenotype. Moreover, eosinophilic NPCA was associated with poor lung function (FEV<sub>1</sub> and FEV<sub>1</sub>/FVC). A mutual association exists between NPs and asthma.

**Table 2**  
Features of Upper and Lower Airway Disease Severity and Inflammatory Characteristics

| Characteristic                                         | NPCA (n = 106)        | Eosinophilic NPCA (n = 68) | Noneosinophilic NPCA (n = 38) | P value |
|--------------------------------------------------------|-----------------------|----------------------------|-------------------------------|---------|
| FEV <sub>1</sub> , median (IQR), % predicted           | 86.30 (74.05–97.30)   | 80.15 (70.90–92.50)        | 97.30 (85.10–100.90)          | .003    |
| FVC, median (IQR), % predicted                         | 100.20 (90.10–112.30) | 100.20 (88.90–112.30)      | 103.30 (95.80–113.3)          | .30     |
| FEV <sub>1</sub> /FVC ratio, median (IQR), % predicted | 70.67 (61.77–78.39)   | 67.56 (59.23–74.91)        | 77.31 (63.18–83.40)           | .005    |
| D <sub>min</sub> , median (IQR)                        | 2.13 (0.27–3.44)      | 2.62 (0.13–4.00)           | 1.91 (1.22–2.63)              | .68     |
| Total IgE, median (IQR), kU/L                          | 60.00 (33.00–132.00)  | 89.00 (50.20–159.00)       | 30.50 (28.00–55.50)           | <.001   |
| LM score, mean (SD)                                    | 20.00 (3.64)          | 21.44 (2.30)               | 17.42 (3.89)                  | .041    |
| FeNO, median (IQR), ppb                                | 67.00 (38.00–101.00)  | 94.00 (65.00–124.00)       | 35.30 (28.00–46.50)           | <.001   |
| Tissue eosinophils, median (IQR), n                    | 16.54 (8.37–19.62)    | 21.40 (10.50–33.40)        | 8.00 (5.00–11.00)             | <.001   |
| BEP, median (IQR), %                                   | 5.45 (2.93–7.90)      | 6.20 (4.55–9.10)           | 2.50 (1.40–3.70)              | <.001   |
| BNP, median (IQR), %                                   | 58.45 (52.18–61.78)   | 56.40 (51.35–60.55)        | 60.00 (53.60–62.00)           | .089    |

Abbreviations: BEP, blood eosinophil percentage; BNP, blood neutrophil percentage; D<sub>min</sub>, cumulative dose of inhaled methacholine measured at the inflection point at which respiratory conductance started to decrease; FeNO, fractional exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; LM score, Lund-Mackay score; NPCA, nasal polyps and comorbid asthma.

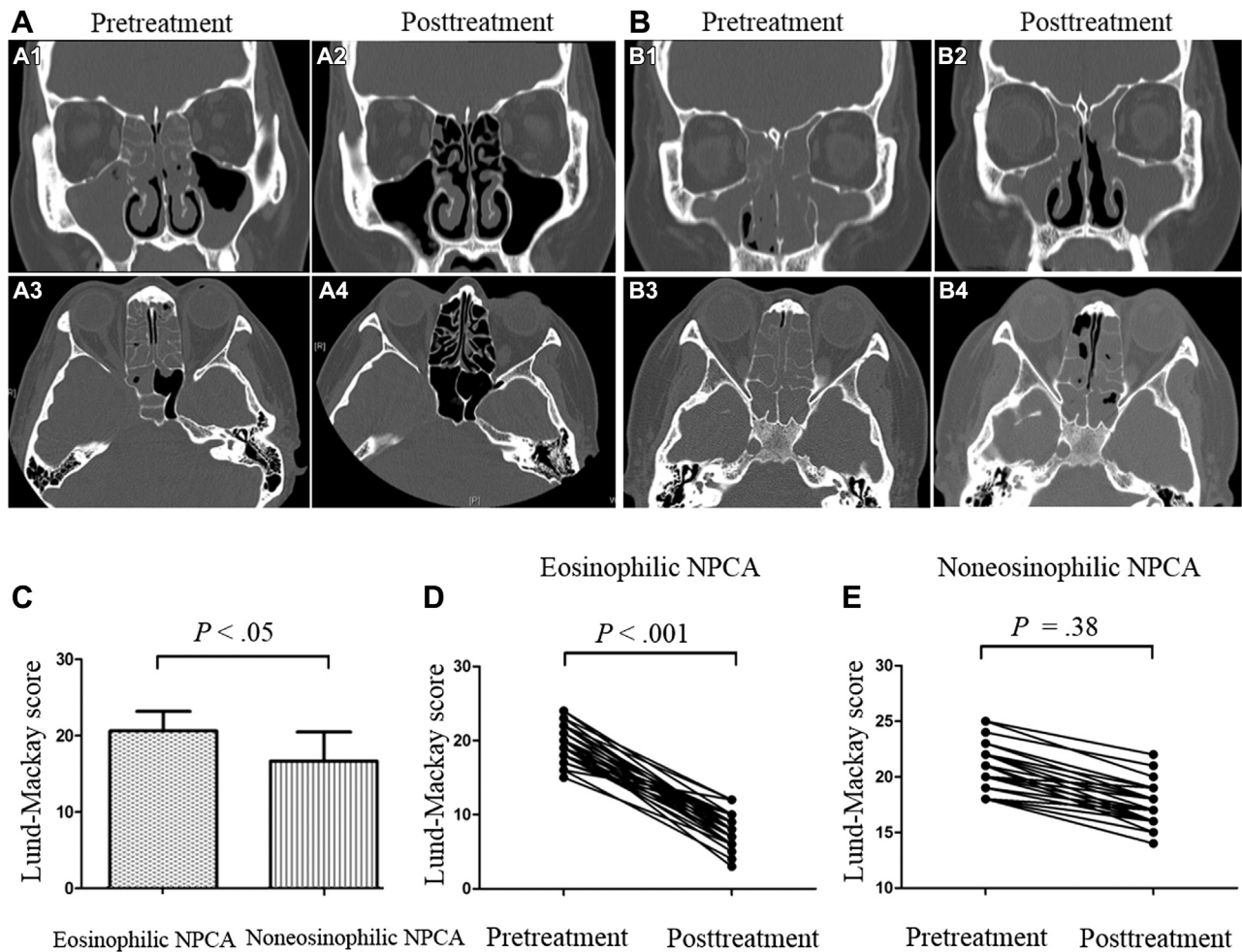


**Figure 2.** Computed tomography change in eosinophilic nasal polyps and comorbid asthma (NPCA) (A) and noneosinophilic NPCA (B). Coronal position scanning change before and after treatment (A1 and A2, B1 and B2). Horizontal position scanning change before and after treatment (A3 and A4, B3 and B4).  $P < .05$  was considered statistically significant.

The coexistence of these 2 diseases is worse than either disease alone as shown by worse Lund-Mackay scores and pulmonary function parameters.<sup>19,37,38</sup> Only one study found that comorbid asthma had no effect on the severity of NPs in terms of the Lund-Mackay score.<sup>39</sup> Inflammatory NPCA was first considered in the

present study, which found that different inflammatory phenotypes had different disease severity and inflammatory conditions.

IgE has a central role in the pathophysiology of allergic responses.<sup>40</sup> Previous studies have found that the total IgE concentration is significantly higher in patients with eosinophilic NPs

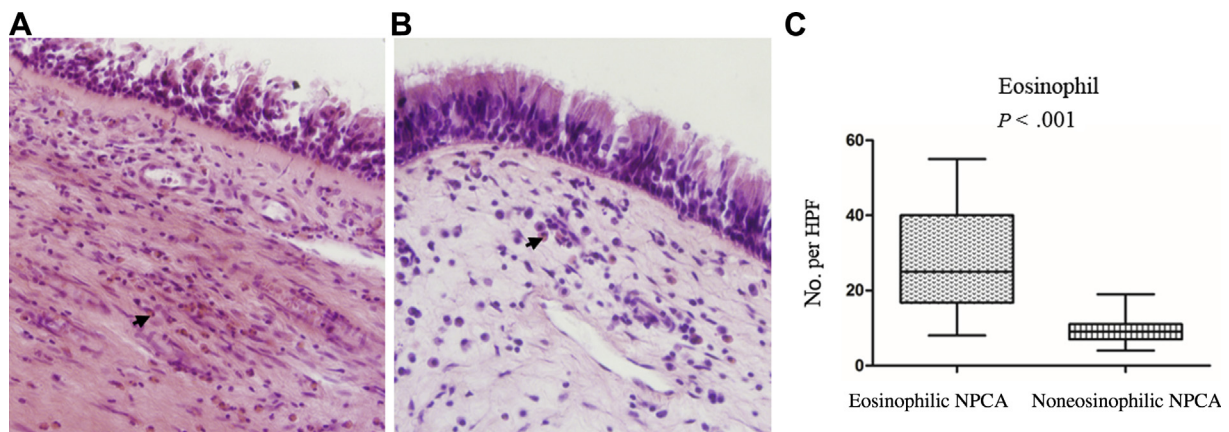


**Figure 3.** Histopathologic sections from nasal polyps in patients with eosinophilic nasal polyps and comorbid asthma (NPCA) and patients with noneosinophilic NPCA (hematoxylin-eosin, original magnification  $\times 200$ ). A, Eosinophilic nasal polyps infiltrated by a large number of eosinophils (indicated by arrows). B, Noneosinophilic nasal polyps infiltrated by large numbers of neutrophils, plasma cells, lymphocytes, and a few eosinophils (indicated by arrows). C, Comparisons of number of tissue eosinophils per high-power field (HPF) between patients with eosinophilic NPCA and noneosinophilic NPCA. Data represent the median (interquartile range).  $P < .05$  was considered statistically significant.

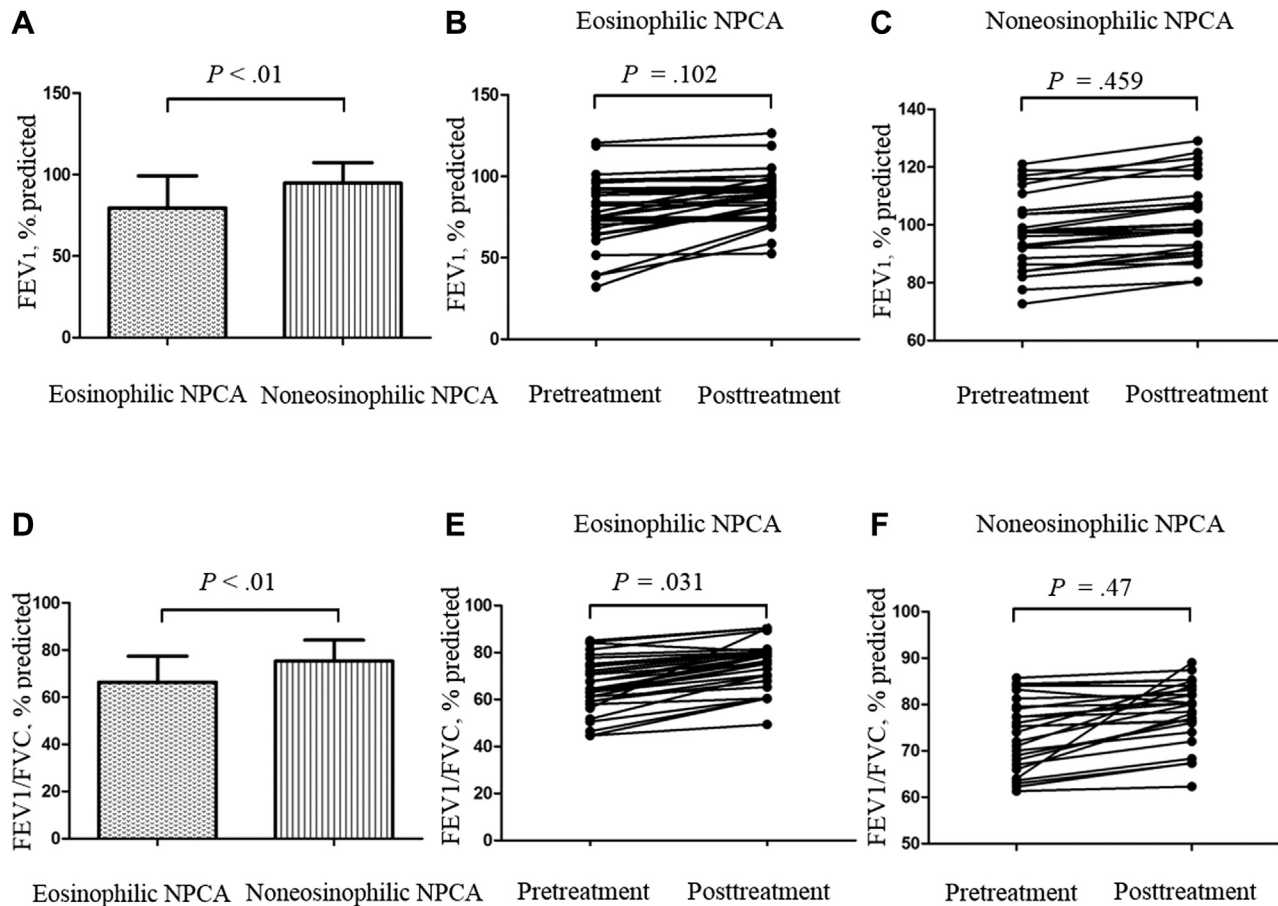


**Figure 4.** Forced expiratory volume in 1 second (FEV<sub>1</sub>) and ratio of FEV<sub>1</sub> to forced vital capacity (FVC) change in eosinophilic nasal polyps and comorbid asthma (NPCA) and noneosinophilic NPCA before and after treatment (panels A, B, C, D, E, F).  $P < .05$  was considered to indicate statistical significance.

than in those with noneosinophilic NPs.<sup>41,42</sup> Eosinophilic asthma is characterized by elevated IgE levels, a high FeNO, and atopy.<sup>43</sup> A direct comparison of the total IgE concentration between 2 inflammatory phenotypes of NPCA was rare. The present study found the total IgE concentration to be significantly higher in patients with eosinophilic NPCA than in those with noneosinophilic NPCA, indicating that IgE was more closely involved in the pathogenesis of eosinophilic than noneosinophilic NPCA. Notably, a recent study found that anti-IgE therapy was effective in the treatment of NPs with comorbid asthma,<sup>44</sup> further supporting the important functionality of IgE in the pathogenesis of NPCA. It was speculated that atopy might play an important role in the formation of eosinophilic NPCA.

Nitric oxide is an important biological mediator and plays a key role in modulating inflammatory response with the airway.<sup>45</sup> FeNO, as a noninvasive and convenient means, is recommended as a biomarker in the diagnosis and monitoring of eosinophilic airway

inflammation and in determination of corticosteroid responsiveness.<sup>28</sup> The present study found the level of FeNO to be significantly higher in patients with eosinophilic NPCA than in those with noneosinophilic NPCA, suggesting that eosinophilic NPCA was a more severe eosinophilic inflammatory condition. A recent study found that patients with asthma with high FeNO levels (>50 ppb) had coexistent eosinophilic chronic rhinosinusitis, and higher FeNO levels were linked to patients with more severe eosinophilic chronic rhinosinusitis and asthma,<sup>46</sup> which was consistent with the present findings.

The medical and surgical management of NPCA has been widely studied.<sup>12,20,21,24,44</sup> However, few studies have further divided NPCA into different inflammatory phenotypes. A study by Bachert et al<sup>44</sup> found that omalizumab was effective in patients with NPs and asthma, irrespective of the presence of allergy. In our study, according to the changes in the CT findings and pulmonary function parameters, patients with eosinophilic NPCA had significant

**Table 3**  
Receiver Operating Characteristic Curve Analysis of Clinical Markers for Diagnosing Eosinophilic NPCA

| Predictor                           | AUC (95% CI)        | Cutoff value | Specificity, % | Sensitivity, % | Youden index |
|-------------------------------------|---------------------|--------------|----------------|----------------|--------------|
| BEP                                 | 0.808 (0.688–0.928) | 4.3          | 82.4           | 75.0           | 0.574        |
| FeNO                                | 0.749 (0.618–0.881) | 71.0         | 64.7           | 80.6           | 0.453        |
| Total IgE                           | 0.894 (0.825–0.956) | 55.5         | 85.4           | 86.2           | 0.716        |
| Lund-Mackay score                   | 0.795 (0.665–0.925) | 18.5         | 70.6           | 77.8           | 0.484        |
| Reciprocal of FEV <sub>1</sub>      | 0.812 (0.713–0.942) | 84.26        | 83.5           | 76.1           | 0.596        |
| Reciprocal of FEV <sub>1</sub> /FVC | 0.791 (0.615–0.874) | 64.37        | 69.5           | 77.3           | 0.468        |

Abbreviations: AUC, area under the receiver operating characteristic curve; BEP, blood eosinophil percentage; CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity.

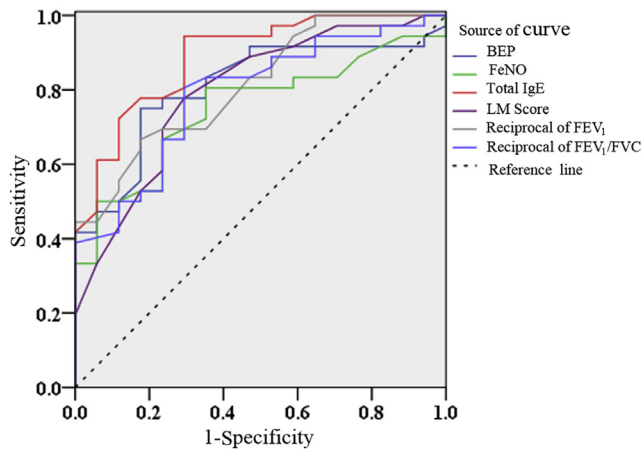


**Figure 5.** Receiver operating characteristic for significant clinical characteristics, including blood eosinophil percentage (BEP), fractional exhaled nitric oxide (FeNO), total IgE, Lund-Mackey (LM) score, reciprocal of forced expiratory volume in 1 second ( $FEV_1$ ) and reciprocal of  $FEV_1/FVC$ . The total IgE had the highest accuracy for eosinophilic nasal polyps and comorbid asthma (area under the curve = 0.815), followed by reciprocal of  $FEV_1$ , BEP, LM score, reciprocal of  $FEV_1/FVC$ , and FeNO.

improvement of Lund-Mackay scores and  $FEV_1/FVC$  after treatment, whereas those with noneosinophilic NPCA had poor responses to the medical treatment. Neither their CT findings nor pulmonary function parameters were significantly improved after treatment in patients with noneosinophilic NPCA. In previous studies, an eosinophilic phenotype in patients with NPs or asthma usually implied a good response to glucocorticoid therapy.<sup>9,47,48</sup> Besides, both noneosinophilic NPs and noneosinophilic asthma respond poorly to glucocorticoid therapy.<sup>49,50</sup> In the present study, by considering NPs and asthma as an entity and dividing it into 2 inflammatory phenotypes, we found that noneosinophilic NPCA also had a poor response to the medical treatment. Previous studies have found that a neutrophil-predominant inflammation was resistant to steroid treatment<sup>51</sup> and tended to be a more severe form of asthma.<sup>52,53</sup> Similarly, a neutrophil-predominant inflammation was considered the best-characterized phenotype in noneosinophilic chronic rhinosinusitis with NPs (approximately 20% to 46% of noneosinophilic chronic rhinosinusitis with NPs in Asia),<sup>8,11</sup> and increased neutrophilia in NPs has been established to reduce responses to oral corticosteroid therapy.<sup>49</sup> We speculate that patients with noneosinophilic NPCA may be a neutrophil-predominant phenotype, although further validation is required.

This study found that the AUC of 0.894 for total IgE had a higher accuracy for all markers investigated. The optimal cutoff point of greater than 55.5 kU/L demonstrated a sensitivity of 86.2% and specificity of 85.4% for eosinophilic NPCA. Besides, the Youden index of the cutoff point was the highest one (0.716). However, few studies have addressed the diagnosis of eosinophilic NPCA. Markers of the eosinophilic phenotypes of both NPs and asthma have been widely studied. The blood eosinophil count, ratio of the CT scores for the ethmoid and maxillary sinuses, and tissue eosinophil infiltration have been identified as markers of eosinophilic NPs.<sup>42,54</sup> Noninvasive methods for assessing airway inflammation in patients with asthma, such as FeNO, sputum eosinophil count, and blood eosinophil count, have been widely studied to identify markers of eosinophilic asthma.<sup>55,56</sup> This study found that the total IgE concentration was a useful predictor in diagnosing eosinophilic NPCA.

The present study had several limitations. First, this study used FeNO to define the inflammatory subtypes of asthma as presented above. This method should be verified in future studies. Second, the sample size was relatively small; multicenter and large sample

randomized clinical trial studies are needed. Third, the 8-week course of medical treatment was short. Finally, our study did not involve mechanism research, and further studies are required to elaborate on the molecular mechanisms responsible for the findings.

In conclusion, eosinophilic and noneosinophilic phenotypes of NPCA, which have different clinical profiles, were identified in this study using a combined method to evaluate the upper and lower airway inflammation. In addition, the total IgE concentration was identified as a marker for diagnosing eosinophilic NPCA.

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