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Diagnostic biomarkers for chronic rhinosinusitis in adult asthmatics in real-world practice

Jae-Hyuk Jang, MD, Eun-Mi Yang, MS, Youngsoo Lee, MD, Yoo Seob Shin, MD, PhD, Young-Min Ye, MD, PhD and Hae-Sim Park, MD, PhD*

ABSTRACT

Background: Chronic rhinosinusitis (CRS) is a common comorbid condition of asthma that affects the long-term outcome of asthmatic patients. CRS is a heterogeneous disease requiring multiple biomarkers to explain its pathogenesis. This study aimed to develop potential biomarkers for predicting CRS in adult asthmatic patients in a real-world clinical setting.

Methods: This study enrolled 108 adult asthmatic patients who had maintained anti-asthmatic medications, including medium-to-high doses of inhaled corticosteroid plus long-acting β2-agonists, and compared clinical characteristics between patients with CRS (CRS group) and those without CRS (non-CRS group). CRS was diagnosed based on the results of paranasal sinus X-ray and/or osteomeatal-unit CT as well as clinical symptoms. Type-2 parameters, including blood eosinophil count, serum levels of periostin/dipeptidyl peptidase 10 (DPP10) and clinical parameters, such as FEV1% and fractional exhaled nitric oxide (FeNO), were analyzed. All biomarkers were evaluated by logistic regression and classification/regression tree (CRT) analyses.

Results: The CRS group had higher blood eosinophil counts/FeNO levels and prevalence of aspirin-exacerbated respiratory disease (AERD) than the non-CRS group (n = 57, 52.8% *vs.* n = 75, 47.2%; $P < 0.05$), but no differences in sex/smoking status or asthma control status were noted. The CRS group had higher serum periostin/DPP10 levels than the non-CRS group. Moreover, logistic regression demonstrated that serum periostin/DPP10 and the AERD phenotype were significant factors for predicting CRS in asthmatic patients (adjusted odds ratio, 2.14/1.94/12.39). A diagnostic algorithm and the optimal cutoff values determined by CRT analysis were able to predict CRS with 86.27% sensitivity (a 0.17 negative likelihood ratio).

Conclusion: Serum periostin, DPP10 and the phenotype of AERD are valuable biomarkers for predicting CRS in adult asthmatic patients in clinical practice.

Keywords: Asthma, Rhinitis, Sinusitis, Eosinophils, Biomarkers, Periostin, Dipeptidyl-peptidases and tripeptidyl-peptidases, Fractional exhaled nitric oxide testing

Department of Allergy & Clinical Immunology, Ajou University School of Medicine, Suwon, Republic of Korea
*Corresponding author. Department of Allergy and Clinical Immunology, Ajou University School of Medicine, 164 World cup-ro, Yeongtong-gu, Suwon 16499, Republic of Korea, E-mail: hspark@ajou.ac.kr
Full list of author information is available at the end of the article

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INTRODUCTION

Chronic rhinosinusitis (CRS) is a prevalent condition affecting over 10% of the population in European countries and the United States and is characterized by inflammation of the nasal mucosa and paranasal sinuses with heterogeneous phenotypes.[1,2] Patients with asthma are more susceptible to developing CRS, with up to 45% experiencing the condition.[3,4] These 2 diseases are known to have a bidirectional relationship, where 1 disease increases the risk of the other and *vice versa*.[5] Sharing a common pathophysiology with asthma, CRS is involved in the higher prevalence and disease severity in patients with asthma.[6–8] CRS has typically been classified into 2 phenotypes depending on the presence of nasal polyps (NPs).[9]

Currently, the diagnosis of CRS is based on clinical symptoms, findings from nasal endoscopy, and the results of imaging studies, including CT, providing evidence of the presence of NPs. Although these modalities enable clinicians to evaluate the presence of CRS with/without NPs, they possess significant disadvantages. In particular, the invasiveness of endoscopy and the potential radiation exposure risk associated with CT scans have considerable challenges.[10,11] However, the traditional phenotypical classification of CRS has proven to be of limited utility in the treatment of patients with CRS.[12] Furthermore, the understanding and management of CRS have advanced, and the classification of CRS into specific endotypes has become crucial for predicting the natural course of the disease and for determining adequate treatment options, including pharmacotherapy, surgical intervention, and biologics.[13]

Recently, a shift toward endotypic stratification, specifically distinguishing between type 2 and nontype 2 endotypes, has been suggested in the European Position Paper on Rhinosinusitis and Nasal Polyps.[14] There are 2 major inflammatory phenotypes of CRS: the eosinophilic and noneosinophilic/neutrophilic types. The eosinophilic phenotype was found to be more prevalent in CRS patients with NPs than in those without NPs, and it is associated with different characteristics. Tissue eosinophilia in CRS with NP has been significantly associated with extensive sinus disease, higher postoperative symptom scores, lower improvement in quality of life, and a higher NP recurrence rate.[15–24]

The diagnosis of type 2/eosinophilic CRS is primarily based on nasal mucosal biopsy for analyzing the degree of eosinophil or neutrophil infiltration and type 2 or nontype 2 cytokines.[25] However, the diagnosis of these endotypes largely depends on the results from tissue biopsy, and the results can vary based on the biopsy site.[26] Alternative biomarkers, such as the blood eosinophil count and serum total IgE level, can be challenging to use accurately due to the overlapping phenotypes/endotypes in patients with CRS.[27] It is also believed that epithelial-derived inflammation contributes to the pathogenesis of CRS regardless of the specific endotype.[28] Moreover, the diversity and heterogeneity of CRS are further amplified by its various inflammatory profiles (type 1, type 2, or type 3), which are based on effector cells and primary cytokines, irrespective of the presence of NPs.[26,27,29–31] Therefore, the conventional classification could not fully explain the heterogeneity of CRS. Both CRS phenotypes have been differentiated based on immune pathways, indicating that CRS is a complex and heterogeneous disease marked by a range of distinct inflammatory endotypes.[26,31] Although there has been very little studies to suggest biomarkers for CRS,[25] the urgent need are present for the development of reliable diagnostic biomarkers to diagnose and guide CRS treatment strategies in patients with asthma. Such biomarkers would need to be more easily applicable than radiologic findings for the management of CRS.

Several biomarkers, including serum periostin, dipeptidyl peptidase 10 (DPP10), transforming growth factor (TGF-β) and matrix metalloproteinase 9 (MMP9), were suggested to be potential diagnostic biomarkers in patients with CRS.[16,32–37] This study aimed to validate these biomarkers for predicting CRS in an adult asthmatic cohort in daily clinical practice.

METHODS

Study subjects

This study enrolled adult asthmatic patients who had had moderate-to-severe asthma with maintaining anti-asthmatic medications, including medium-

to-high doses of ICS plus long-acting beta2 agonist (LABA) with/without leukotriene receptor antagonists, in the Department of Allergy and Clinical Immunology at a tertiary university hospital. Patents who had used biologics were excluded from the study. The clinical characteristics of the CRS and non-CRS groups were compared. The diagnosis and control status of asthma were determined according to the recent GINA guidelines.[38] The diagnosis of CRS was determined according to both of the following criteria: 1) the presence of clinical symptoms, such as nasal congestion, mucus discharge, facial pain, pressure, or fullness, and a decreased sense of smell; and 2) radiologic findings of paranasal sinus involvement on X-ray and/or ostiomeatal unit computed tomography (OMU-CT), persisting for a minimum of 12 weeks with at least 2 of the symptoms mentioned above.

The demographic characteristics were analyzed. Atopy was defined as a positive result of the skin prick test and/or an elevated serum allergen-specific IgE level ($\geq$0.35 IU/mL) to at least 1 common environmental allergen. Aspirin-exacerbated respiratory disease (AERD) was defined by clinical history, recurrent exacerbations of upper and lower respiratory symptoms after exposure to aspirin/NSAIDs and/or a positive result of the lysine-aspirin bronchial provocation test (Lys-ASA BPT).[39,40] More than a 20% decrease in FEV1 (%) after the challenge was considered a positive result of Lys-ASA BPT. An aspirin-tolerant asthmatic was defined as a subject who showed negative results to the Lys-ASA BPT or denied any changes in upper or lower respiratory tract symptoms on previous exposure to aspirin/NSAIDs.

Serum total immunoglobulin E levels were measured by using the ImmunoCAP® system (Thermo Fisher Scientific, Waltham, MA, USA). The cytokine levels were measured using a commercially available ELISA kit (periostin: SHINO-Test Corporation, Sagamihara, Japan; DPP10: MyBioSource, San Diego, CA, USA; TGF-β1: DuoSet, Minneapolis, MN, USA) according to the respective manufacturer's protocol. A spirometer (Jaeger, Würzburg, Germany) was used for pulmonary function tests. Fractional exhaled nitric oxide (FeNO) was measured by using Niox® (Circassia, Sollentuna, Sweden). This study was approved by the Institutional Review Board, and informed consent forms were obtained from all participants.

Statistical analysis

Depending on the type of variables, comparisons were made by Student's *t*-test (parametric values) or the Mann–Whitney *U* test (nonparametric values) and the chi-square test (categorical values). The correlations between variables were assessed using the Pearson method. Logistic regression was used to identify factors associated with CRS by estimating odds ratios (ORs) and 95% confidence intervals. The multivariable logistic analysis included elements that showed statistical significance in univariate association with CRS. Classification and regression tree (CRT) analysis was used to define a rule of grouping patients with the optimal cutoff value of each biomarker. The CRT analysis was performed for all variables evaluated in univariate logistic regression using a minimum of 10 cases for the parent node, pruning to reduce overfitting. All data were analyzed, and graphs were created using R 4.2.2 (R Core Team, 2022). $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of the study subjects

Table 1 compares clinical parameters of patients with CRS and those without CRS. A total of 108 patients (57 CRS patients and 51 non-CRS patients) were enrolled in the study. The CRS group was older than the non-CRS group (55.0 [44.0; 62.0] years *vs*. 48.0 [35.0; 57.5] years, $P = 0.04$), and no differences were noted in sex, smoking status, or asthma control status. The prevalence of bilateral CRS was 70.18% in the CRS group. In total, 38 patients were diagnosed with AERD. Of these, 12 were confirmed to have Lys-ASA BPT, and 26 exhibited recurrent hypersensitivity reactions following exposure to NSAIDs. The CRS group had a higher prevalence of AERD (33/57, 57.9% *vs*. 5/51, 9.8%, $P < 0.0001$) and a lower prevalence of atopy (25/57, 43.9% *vs*. 37/51, 72.5%, $P = 0.01$) than the non-CRS group (Table 1).

The CRS group had a higher blood eosinophil count (300.0 [200.0; 500.0] cells/μL *vs*. 200.0 [100.0; 300.0] cells/μL, $P < 0.01$), FeNO level (23.0 [14.0; 47.0] ppb *vs*. 16.0 [8.5; 28.0] ppb, $P < 0.05$), serum periostin level (79.8 [66.9; 99.5] ng/mL *vs*. 60.1 [50.2; 73.3] ng/mL, $P < 0.0001$), and serum

DPP10 level (7.5 [5.3; 12.8] ng/mL *vs.* 4.7 [2.8; 9.0] ng/mL, $P = 0.001$) than the non-CRS group (Fig. 1 and Table 1). The ratio of FEV1 to FVC (%) values was lower in the CRS group than in the non-CRS group (83.8 [75.1; 88.2] *vs.* 85.6 [79.8; 92.6], $P < 0.05$, Table 1). No significant differences in FEV1 (%), maximum mid-expiratory flow (%), or serum levels of total IgE were noted between the 2 groups (Table 1). A significant correlation between serum periostin and TGF-β1 was noted in the CRS group ($r = -0.42$, $P < 0.01$, eTable 1) but not in the non-CRS group (eTable 1). In addition, no significant correlations were found among other biomarkers.

Biomarkers for predicting CRS in asthmatic patients

In the univariate logistic regression, factors such as AERD phenotype, atopy, age, the ratio of FEV1 to FVC (%), blood eosinophil count, serum total IgE, serum periostin, and serum DPP10 were found to predict CRS (Table 2). Following a stepwise approach, multivariate logistic regression revealed that serum periostin, serum DPP10, and the AERD phenotype were predictors of CRS in asthmatic patients. The AERD phenotype had the highest adjusted odds ratio (aOR) (12.39, 95% CI, 4.32–42.33), with significant positive associations between CRS and serum periostin (aOR, 2.14, 95% CI, 1.28–3.86) and between CRS and serum DPP10 (aOR, 1.94, 95% CI, 1.17–3.53). Other biomarkers, such as blood eosinophil count, FeNO, and serum total IgE, did not show significant associations (Table 2).

The ROC analysis for predicting the CRS group, based on logistic regression, demonstrated that the AERD phenotype and serum periostin had higher prediction accuracy as individual parameters (area under ROC: 0.74, 95% CI, 0.66–0.82 and 0.74, 95% CI, 0.65–0.84, respectively) than other biomarkers, such as blood eosinophil count, serum total IgE, and serum DPP10 (Table 3, Supplementary Figure). However, no statistically significant differences were observed when comparing individual AUROCs for each single biomarker (Table 3). Combining the AERD phenotype with either serum periostin or DPP10 significantly improved the predictive accuracy (periostin, 0.84, 95% CI, 0.77–0.92; DPP10, 0.83, 95% CI, 0.76–0.91, Table 3, Supplementary Figure).

Classification and regression tree (CRT) analysis of potential biomarkers for predicting CRS

A combination of potential biomarkers for predicting CRS in asthmatic subjects was further evaluated by CRT analysis, which included all the

Characteristics	The CRS group (n = 57)	The non-CRS group (n = 51)	*P* value
Age (year)	55.0 [44.0; 62.0]	48.0 [35.0; 57.5]	0.04
Female, n (%)	36 (63.2)	33 (64.7)	NS
Bilateral CRS, n (%)	40 (70.18)	0	
Atopy, n (%)	25 (43.9)	37 (72.5)	0.01
Ex-smoker, n (%)	13 (22.80)	10 (19.61)	NS
Uncontrolled asthma, n (%)	7 (12.3)	5 (9.8)	NS
AERD, n (%)	33 (57.9)	5 (9.8)	<.0001
FEV1 (%)	94.0 [84.7; 101.2]	90.6 [82.4; 101.8]	NS
FEV1/FVC (%)	83.8 [75.1; 88.2]	85.6 [79.8; 92.6]	<.05
MMEF (%)	69.6 ± 24.8	76.3 ± 29.8	NS
FeNO (ppb)	23.0 [14.0; 47.0]	16.0 [8.5; 28.0]	<.05

Table 1. Comparisons of clinical parameters between patients with CRS (CRS group) and those without CRS (non-CRS group). *Non-parametric values are presented as median [IQR] and parametric values or mean ± SD. P-values were evaluated by the t-test or the Mann-Whitney test or the Chi-squared test with Yates' continuity correction depending on the variables. AERD, aspirin exacerbated respiratory disease; CRS, chronic rhinosinusitis; FEV1, forced expiratory volume in 1sec; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; MMEF, maximal mid-expiratory flow rate*

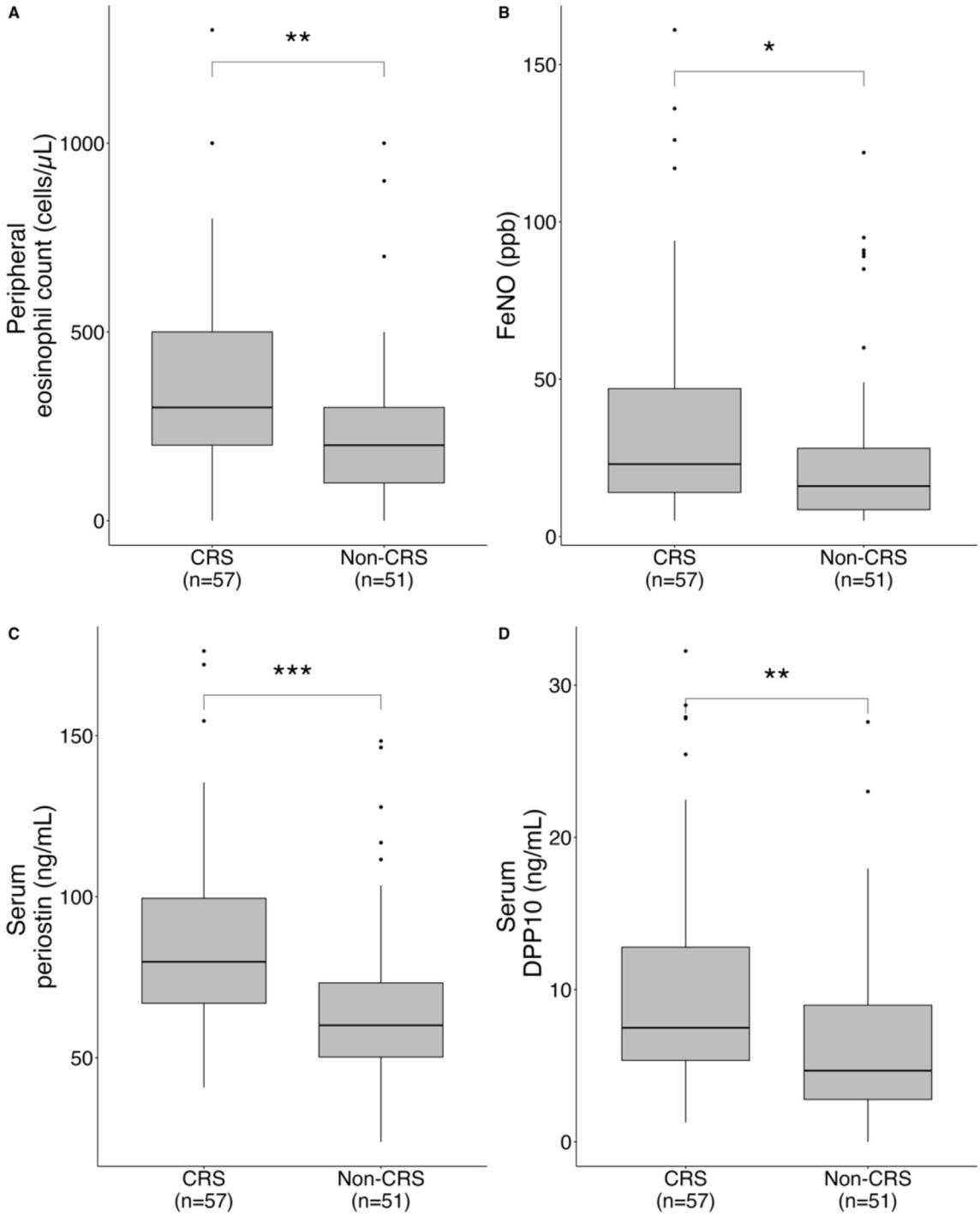

Fig. 1 Comparisons of blood eosinophil counts (A), FeNO(B), and serum levels of periostin (C) and DPP10 (D) between patients with CRS (CRS group) and those without CRS (non-CRS group) in asthmatic subjects. P values were computed using the Wilcoxon-Mann Whitney test *$P < 00.05$; **$P < 0.01$; ***$P < 0.0001$. CRS, chronic rhinosinusitis; DPP10, dipeptidyl-peptidase 10

variables as in the univariate logistic regression analysis. CRT analysis identified a model that included the AERD phenotype, serum DPP10 level, and serum periostin level (optimal cutoff values, 4.05 and 66.53 ng/mL, respectively) for predicting CRS (Fig. 2). The diagnostic algorithm based on the phenotype of AERD, serum DPP10, and serum periostin predicted the CRS group with a sensitivity of 86.27% and a negative likelihood ratio of 0.17 (Fig. 2).

Variables	Univariate Logistic Regression		Multivariate Logistic Regression	
	P value	OR (95% CI)	*P* value	aOR (95% CI)
Age	0.04	1.52 (1.03–2.29)		
Female	0.87	0.94 (0.42–2.06)		
Atopy	0.003	0.30 (0.13–0.65)		
AERD	<.001	12.65 (4.70–40.78)	<.0001	12.39 (4.32–42.33)
FEV1 (%)	0.98	0.99 (0.68–1.46)		
FEV1/FVC (%)	0.04	0.66 (0.43–0.97)		
FeNO	0.12	1.40 (0.94–2.18)		
Peripheral eosinophil count	0.02	1.76 (1.15–2.90)		
Serum total IgE	0.06	0.60 (0.34–0.95)	0.08	0.54 (0.24–0.94)
Serum periostin	0.001	2.35 (1.47–4.07)	0.006	2.14 (1.28–3.86)
Serum DPP10	0.01	1.86 (1.20–3.11)	0.02	1.94 (1.17–3.53)
Serum MMP-9	0.09	0.72 (0.48–1.05)		
Serum TIMP-1	0.62	0.91 (0.62–1.33)		

Table 2. The univariate and multivariate logistic regression analysis for predicting the CRS group in asthmatic subjects. *Factors with P-values less than 0.05 in the univariate analysis were included to a multivariate logistic regression analysis and deleted in a stepwise manner. AERD, aspirin exacerbated respiratory disease; CRS, chronic rhinosinusitis; OR, odds ratio; FeNO, fractional exhaled nitric oxide; DPP10, dipeptidyl-peptidase 10; MMP-9, matrix metalloproteinase-9; TIMP-1, tissue inhibitor of metalloproteinase-1*

Variables	AUROC (95% CI)		
	Single parameter	(+) Periostin	(+) DPP10
Aspirin exacerbated respiratory disease	0.74 (0.66–0.82)	0.84 (0.77–0.92)*	0.83 (0.76–0.91)*
Peripheral eosinophil count (cells/μL)	0.66 (0.56–0.76)	0.74 (0.65–0.84)	0.70 (0.61–0.80)
Serum periostin (ng/mL)	0.74 (0.65–0.84)		0.76 (0.67–0.85)
Serum DPP10 (ng/mL)	0.68 (0.58–0.78)		

Table 3. Diagnostic accuracy of a single parameter and combined parameters (with serum periostin or DPP10) for predicting the CRS group in asthmatic subjects. *$P < 0.01$. *P value comparing a single parameter AUROC vs. the clinical parameters combined with periostin or DPP10 AUROC.DPP10, dipeptidyl-peptidase 10*

DISCUSSION

Identifying biomarkers for predicting CRS is essential for the accurate diagnosis and appropriate treatment of CRS in patients with asthma. CRS is a multifaceted and heterogeneous disease characterized by various inflammatory endotypes.[28] Current biomarkers for endotypes still have limitations. The present study assessed various potential biomarkers derived from airway epithelial cells, suggesting that 2 serum biomarkers, periostin and DPP10, along with the phenotype of AERD, were effective for predicting CRS in adult asthmatic subjects.

CRS is a common comorbidity of asthma that typically involves chronic inflammation of the nasal mucosa and the paranasal sinuses. A nationwide cohort study reported that individuals with asthma had an increased risk of developing CRS and that those with CRS had an increased risk of developing asthma, demonstrating a bidirectional association between asthma and CRS.[5] Furthermore, CRS has been identified as a factor that can exacerbate symptoms and negatively impact the control status in asthmatic patients.[41,42] Patients with severe asthma had more severe CRS both endoscopically and radiologically than those with nonsevere asthma.[43] The present study showed that CRS was not associated with control status, which is possibly due to the heterogeneity of the study population, but was significantly associated with decreased lung function (lower FEV1/FVC) and increased T2 airway inflammation (higher FeNO) in real-world practice. Individuals with CRS exhibited significant obstructive changes in lung function regardless of the presence of asthma.[44] Decreased lung function is 1 of the asthma exacerbation factors. Therefore, we suggest that CRS is associated with asthma exacerbation more than asthma control status. There is a need to detect chronic sinonasal involvement, which can potentially exacerbate asthmatic symptoms in the chronic management of asthma.

The present study provides convincing evidence that 2 serum biomarkers, periostin and DPP10, are both derived from airway epithelial cells.[45] They are helpful biomarkers for the early detection of CRS in patients with asthma even on maintenance medications. Periostin, an

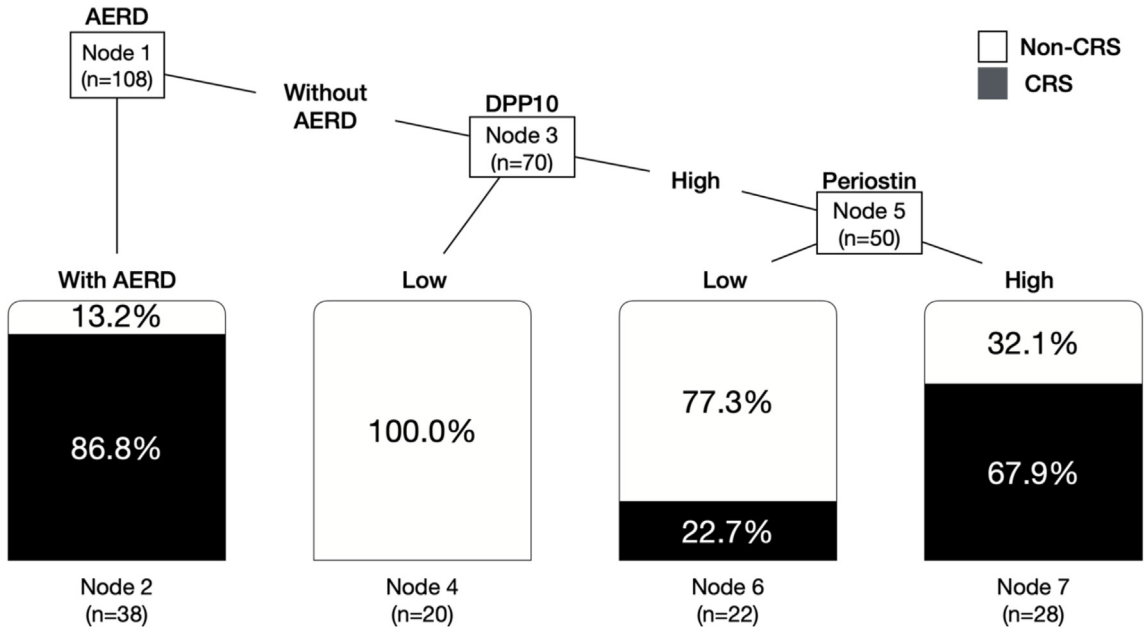

Fig. 2 Classification and regression tree (CRT) analysis algorithms for predicting the CRS group in asthmatic subjects. CRT analysis identified a model that included the phenotype of AERD, serum DPP10 level, and periostin level (A). This model suggested optimal cutoff values of DPP10 and periostin for predicting the CRS group (4.05 and 66.53 ng/mL, respectively). DPP10, dipeptidyl peptidase10; CRT, classification and regression tree analysis

extracellular matrix protein, can activate eosinophils and perpetuate eosinophil-mediated type 2 inflammation. Therefore, it is a representative biomarker of type 2 airway inflammation in asthmatic airways.[12,46] Periostin expression is induced by type 2 cytokines, such as IL-4 and IL-13, in patients with asthma and CRS.[16,46] The present study revealed higher serum periostin levels in the CRS group than in the non-CRS group, which is consistent with previous studies demonstrating a close association between serum periostin and the presence of asthma in CRSwNP patients or that of CRS in asthmatic patients.[32,47] The cutoff values for serum periostin have been reported in previous studies.[48,49] A value of 95 ng/mL was suggested for diagnosing CRSwNP, while values of 115.5 ng/mL and 130 ng/mL were suggested to predict the risk of recurrence after endoscopic sinus surgery.[48,49] In the present study, the cutoff value for serum periostin was lower than those values, which may be because all the study subjects had maintained anti-asthmatic medications. Moreover, the CTA analysis suggests the combined effect of serum periostin with other markers.

DPP10 is a member of the dipeptidyl peptidase family and is expressed in the bronchi and trachea. The origin of DPP10 is believed to be eosinophils, neutrophils, T cells, and B cells. Our previous studies have suggested that DPP10 expression is affected by genetic variations in DPP10 genes,[50] and serum DPP10 levels are associated with lung function decline as well as the prevalence of CRS in patients with AERD.[35] In an experimental *in vivo* study using DPP10 knockout mice, exposure to house dust mites was found to affect airway hyperresponsiveness.[51] The present study demonstrated a significant association between serum DPP10 levels and the phenotype of CRS in asthmatic patients even on anti-asthmatic medications. Airway epithelial cells are an additional source of DPP10 (induced by TGF-B1) and periostin. Moreover, periostin increases TGF-β1 production, contributing to airway remodeling.[52] These findings suggest that both periostin and DPP10 mediate airway epithelial cell-derived inflammation by interacting with TGF-β1 in the pathogenesis of CRS.[45] These findings suggest that these markers may be applied as potential serum biomarkers for CRS in the management of asthma and AERD patients.

Blood eosinophil count and FeNO have been suggested for evaluating CRS. The blood eosinophil count is a widely recognized biomarker for

predicting allergic disorders, including asthma, and it has also been proposed as a potential biomarker for CRS.[53] A cross-sectional study reported that blood eosinophilia (more than 300 cells/μL) is significantly associated with CRS, whether NPs coexist or not (OR, 3.05 *vs*. 1.7).[15] Eosinophilic CRS, a subgroup of CRS, is characterized by eosinophil infiltration and tissue remodeling driven by Th2-related cytokines. This subtype has been more prevalent in recent years in both Western and East Asian countries.[54–56] FeNO is another biomarker for CRS. In a previous study, it was documented that FeNO is associated with type 2-related epithelial inflammation in asthmatic patients.[57] Preoperative FeNO may be a significant biomarker for predicting the development of asthmatic symptoms after endoscopic sinus surgery.[58] The present study showed higher blood eosinophil counts and FeNO values in the CRS group than in the non-CRS group. However, a multivariate analysis revealed no significant association between CRS and blood eosinophil count/FeNO value. As this study targeted patients with asthma, eosinophil counts and FeNO results were increased even in patients without CRS, and no significant association was noted for other indicators. Moreover, geographical and epidemiological differences among CRS patients could influence the prevalence of type 2 inflammation, thereby resulting in varied impacts due to eosinophils.[59] In addition, the enrolled patients consistently maintained their asthma medications; therefore, the suppression of FeNO due to ICS may have resulted in its lower impact compared to other biomarkers.[60,61] Taken together, these findings show that blood eosinophils and FeNO may not be the most effective markers for differentiating CRS in patients with asthma in real-world practice.

AERD is a well-documented phenotype in patients with severe asthma. In such cases, a higher prevalence of CRS with persistent eosinophilic inflammation in both the upper and lower airways has been observed.[39] Recent updated practice parameters suggest that AERD diagnosis can be principally established based on clinical history and/or aspirin challenges.[40] In the present study, a high prevalence of AERD was confirmed among asthmatic patients comorbid with CRS, suggesting a potential progression toward severe asthma in these patients. Some AERD patients (9.8%) did not have CRS (Table 1), which is consistent with previous studies demonstrating that the existence of the AERD subtype was not associated with CRS.[62] Taken together, the results of the present study reveal that the phenotype of AERD is a stronger predictor for CRS than other biomarkers, including blood eosinophil count and FeNO value. Interestingly, the predictive accuracy of either biomarker alone was not significant, implying that a single biomarker may not adequately explain the heterogeneity of CRS in asthma.[63] However, the present study demonstrated that the combination of serum periostin, serum DPP10, and the phenotype of AERD significantly improved the prediction accuracy for CRS. This suggests that this approach could assist in identifying the phenotype of CRS in patients with asthma, which may in turn prove beneficial in the risk assessment for severe asthma.

There are several limitations to this study. First, the lack of data on the clinical characteristics of NP and the small number of patients enrolled at a single center may reduce the clinical significance and statistical power of the biomarkers. Second, sample bias was not excluded, and the CRS group was likely to have a higher prevalence of AERD, which can be a confounding factor. Third, although we suggest the diagnostic algorithm of CRS in the present study, further validation studies in other cohorts are needed to confirm our results. Despite these limitations, this study suggests potential biomarkers and a diagnostic algorithm for CRS in adult asthmatic patients. Further studies are warranted to completely validate these biomarkers and to fully understand the clinical implications of CRS in asthma.

In conclusion, it is suggested that the combination of 2 serum biomarkers (periostin and DPP10) and the phenotype of AERD could help clinicians evaluate the implications of CRS in adult asthmatic patients in real-world practice.

Abbreviations

AERD, aspirin-exacerbated respiratory disease; CRS, chronic rhinosinusitis; CRT, classification and regression tree; DPP10, dipeptidyl-peptidase 10; FeNO, fractional exhaled nitric oxide; NP, nasal polyp; TGF-β, transforming growth factor-β.

Availability of data and materials
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Author contributions
JH Jang has coordinated the study, collected patient data, was involved in statistical analysis, and drafted the manuscript.
EM Yang performed laboratory tests and was involved in the proof-reading of the manuscript.
Y Lee, Yoo Seob Shin and YM Ye were involved in manuscript preparation and proof-reading of the manuscript.
HS Park was the overall study coordinator and was involved in manuscript preparation and the proof-reading of the manuscript.

Ethics approval
This study was approved by the Institutional Review Board of Ajou University Hospital. (AJIRB-BMR-SUR-15-498).

Authors' consent for publication
All the authors reviewed the final draft and provided consent for publication.

Declaration of competing interest
None.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100879.

Author details
Department of Allergy & Clinical Immunology, Ajou University School of Medicine, Suwon, Republic of Korea.

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