

Serum Periostin as a Potential Biomarker in the Evaluation of Allergic Rhinitis: A Pilot Study

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Purpose: Although periostin has recently emerged as a new mediator in chronic allergic diseases, particularly in upper airway disease, its significance as a biomarker for allergic rhinitis (AR) is still unclear. Therefore, we aimed to assess the potential of periostin as a novel candidate biomarker for diagnosing and assessing the severity of AR.

Patients and Methods: A total of 40 patients with AR and 22 healthy controls, all aged over 18 years, were recruited for the study. Participants underwent examinations to assess serum levels of total IgE (tIgE), specific IgE (sIgE), periostin, and remodeling-related factors, as well as fractional exhaled nitric oxide (FeNO) and fractional nasal nitric oxide (FnNO). Additionally, clinical characteristics questionnaire and nasal function assessments were completed by AR patients.

Results: The levels of serum periostin were significantly higher in patients with AR compared to healthy controls ($Z=-3.605$, $p<0.001$). There was a notable positive correlation between serum periostin and FeNO ($r=0.398$, $p=0.012$), FnNO ($r=0.379$, $p=0.017$), as well as the visual analogue scale (VAS) score for ocular tearing ($r=0.351$, $p=0.026$) in AR patients. Furthermore, the serum periostin levels were higher in moderate-to-severe AR compared to mild AR cases ($Z=-2.007$, $p=0.045$). The level of serum periostin in AR patients showed a sequential increase corresponding to shortness of breath scores from 0 to 3 ($Z=10.137$, $p=0.017$). The predicted probability of serum periostin demonstrated moderate diagnostic accuracy in detecting AR ($AUC=0.773$, $p<0.001$).

Conclusion: Serum periostin shows potential as a candidate biomarker for detecting AR and can serve as a surrogate biomarker for assessing airway inflammation in AR patients.

Keywords: allergic rhinitis, biomarkers, fractional exhaled nitric oxide, inflammation, periostin

Introduction

Allergic rhinitis (AR) is a common global allergic disorder dominated by eosinophil infiltration and type 2 inflammation.¹ As AR progresses, structural and phenotypic changes occur in the patient's airway, leading to airway remodeling, which may result in chronic, severe and refractory AR.^{1,2} Current treatments for AR focus on individualized, precise medical approach based on distinct immunophenotypes. Increasingly, studies are dedicated to identifying biomarkers that can distinguish different endotypes of AR, and reflect treatment response and prognosis.

Periostin, a downstream molecule of IL-4 and IL-13, has emerged as a novel mediator in chronic allergic diseases. It plays a significant role in type 2 inflammation, contributing to fibrosis and airway tissue remodeling during allergic inflammation.^{3,4} Previous studies have demonstrated periostin's significant role in chronic inflammation including asthma,⁵ atopic dermatitis,^{6,7} type 2 chronic rhinosinusitis (CRS) and eosinophilic CRS,⁸⁻¹⁰ allergic conjunctivitis,¹¹ and eosinophilic esophagitis.¹² Furthermore, periostin has been established as an important biomarker of type 2 inflammation and a potential predictor of airway eosinophilia.^{8,9,13,14} Ongoing studies continue to reveal its involvement

in airway eosinophil infiltration in asthma patients, where it exacerbates airway remodeling, enhances airway responsiveness, and shows promise as both a biomarker and a therapeutic target for asthma detection and treatment.^{5,13,15,16}

AR and asthma share similar chronic inflammatory processes and mutually influencing each other.¹ Current research on periostin in the upper respiratory tract predominantly focuses on CRS, limited attention has been paid to its role in AR. Preliminary studies have revealed a high expression of periostin in the sinonasal tissues and serum of AR patients.^{10,17} Additionally, eosinophil inflammation and subepithelial fibrosis were reduced in the periostin knockout mice models of AR.¹⁸ Serum periostin could also serve as a valuable biomarker for predicting the clinical response to sublingual immunotherapy for house dust mite in AR patients.¹⁹ These discoveries implicate periostin as a promising new candidate for the diagnosis and treatment of AR.

In the present study, we examined the serum periostin levels in AR patients and healthy controls and correlated the findings with nitric oxide (NO) and the clinical characteristics of AR. We aimed to assess the potential significance of periostin as a biomarker for predicting and assessing the severity of AR.

Materials and Methods

Study Subjects

A total of 40 unrelated AR patients (19 women and 21 men; age, 31.05±12.03 years) were recruited from the First Affiliated Hospital of Nanjing Medical University. AR was diagnosed according to the criteria described in Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis.¹ All patients completed the questionnaire detailing their clinical characteristics. 22 age- and sex-matched controls (16 women and 6 men; age, 29.73±10.87 years), with no history of nasal or lower airway diseases and no history of allergy, were recruited from the healthy physical examinations. Allergy testing exhibited negative allergen-specific IgE (sIgE) in their serum. A four-point scale and the visual analogue scale (VAS) for 4 nasal symptoms, 2 ocular symptoms and 4 respiratory symptoms were used to assess the AR symptoms. The four-point scale rated each symptom from 0 to 3 (none=0, mild=1, moderate=2, severe=3).¹ The severity of AR was assessed using a total symptom VAS, which ranged from 0 to 10 cm and was used to evaluate the combined nasal symptoms' severity.^{1,20}

According to the questionnaire results, 5 cases (12.5%) had a history of asthma and were currently in a stable stage. For patients suspected of having asthma, we consulted with the respiratory department and conducted pulmonary function tests to rule out an asthma diagnosis. Based on the frequency of symptoms, 16 cases (40.0%) were assigned to intermittent AR (<4 days/week or <4 weeks/year) and 24 cases (60.0%) were assigned to persistent AR (≥4 days/week and ≥4 weeks/year).¹ 13 cases (32.5%) were assigned to mild AR (VAS score ≤5), 27 cases (67.5%) were assigned to moderate/severe AR (VAS score >5).²⁰

Exclusion criteria were pregnant and lactating women; use of corticosteroids and antiallergic drugs within 2 weeks; current or past immunotherapy; patients with rhinosinusitis, nasal neoplasms, respiratory infection, autoimmunity and immune deficiency, cardiovascular diseases, liver and kidney diseases, and patients with trauma and malignant tumor history. The study protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (approval number: 2021-SRFA-088). All participants signed written informed consent prior to recruitment. The study complies with the principles of the Declaration of Helsinki.

Allergy Testing

Approximately 5 mL of peripheral blood was collected from each subject for in vitro allergy testing, along with assessments for serum periostin and remodeling related factors testing. Both serum total IgE (tIgE) and sIgE were measured using AdvanSure™ AlloStation S (LG Life Sciences, Ltd., Seoul, Korea). The sIgE antibodies to common inhalant allergens, including *Dermatophagoides pteronyssinus* (*Der p*), *Dermatophagoides farinae* (*Der f*), Cat dander, Dog dander, *Blatella germanica*, *Alternaria alternata*, *Artemisia vulgaris*, Birch-Alder, Oak white, Ragweed, Humulus, and Grass mix, were determined in all subjects. The serum sIgE level higher than 0.35 kU_A/L was considered positive. Atopy was defined as serum sIgE positive to at least one common inhalant allergen. Of the AR patients, 34 of cases (85.0%) were sensitized to dust mites (*Der p* and/or *Der f*) or combined with other aeroallergens, while 6 of cases

(15.0%) were sensitized to aeroallergens other than dust mites. Serum tIgE detection was semi-quantitative, with >100 IU/mL considered positive and <100 IU/mL negative.

Enzyme-Linked Immunosorbent Assay (ELISA)

Serum periostin levels were determined utilizing Human POSTN/OSF2 (Periostin) ELISA kit (Thermo Fisher Scientific, Waltham, MA, USA). Serum chitinase-3-like protein 1 (CHI3L1/YKL-40) levels were measured by Human CHI3L1 ELISA Kit (Thermo Fisher Scientific, Waltham, MA, USA). Serum transforming growth factor- β 1 (TGF- β 1) levels were measured by Human TGF-beta 1 ELISA kit (R&D Systems, Minneapolis, MN, USA).

Luminex Assay

The levels of serum vascular endothelial growth factor-A (VEGF-A), tissue inhibitor of metalloproteinase-1 (TIMP-1), matrix metalloproteinase-2 (MMP-2), MMP-9, platelet-derived growth factor-AA (PDGF-AA), PDGF-BB, fibroblast growth factor-2 (FGF-2), and hepatocyte growth factor (HGF) were measured using Luminex assays (R&D Systems, Minneapolis, MN, USA).

Exhaled Nitric Oxide Measurement

Measurements of fractional exhaled nitric oxide (FeNO) and fractional nasal nitric oxide (FnNO) were performed by Nano Coulomb Breath Analyser (Sunvou-CA2122, Sunvou Medical Electronic, Wuxi, China). Specific moisture mask, filters and nasal plug probe were used for measurements. The unit of measurement was parts per billion (ppb). FeNO value ≥ 25 ppb and the FnNO value ≥ 500 ppb were considered indicative of airway eosinophilic inflammation.^{21,22}

Nasal Function Examination

Nasal resistance was measured by four-phase rhinomanometry (NR6, GM Instruments Ltd., Kilwinning, UK) at 75 Pa and 150 Pa, respectively. The total nasal resistance was calculated using the formula $RL \times RR / (RL + RR)$ (RL is the unilateral nasal resistance values of left and RR is right). The unilateral nasal resistance value was obtained according to formula $(RL + RR) / 2$. Rhinospirimeter (NV1, GM Instruments Ltd., Kilwinning, UK) was used to measure bilateral nasal respiratory capacity (NCbi). Rhinometer (A1, GM Instruments Ltd., Kilwinning, UK) was used to measure the minimum cross-sectional area (MCA) of the bilateral nasal cavity, the distance between nostril and MCA (MD) and the nasal volumes from 0–6cm (NV0-6).

Statistical Analysis

All data were analyzed using SPSS software version 21.0 (IBM SPSS, Chicago, IL, USA). *P* values < 0.05 were considered statistically significant. Categorical data were expressed as n (number) and percentages (%), while quantitative data were expressed as mean \pm standard error (SEM) or median and interquartile range (IQR). Student's *t*-test was used for quantitative data conforming to normal distribution and χ^2 test for categorical variables to compare the differences between groups. The Mann–Whitney *U*-test was used for non-normal distribution quantitative data. Spearman correlation analysis was used to analyze the correlation between indicators. The receiver operating characteristic (ROC) curve was plotted to obtain the cutoff value of periostin for diagnosing AR and assessing its severity.

Results

Characteristics of Study Population

The study comprised 40 AR patients and 22 age- and sex-matched healthy controls. Demographic clinical characteristics and serum cytokine/mediator levels of all subjects are shown in Table 1. AR patients had significantly higher FeNO, FnNO, and serum periostin levels compared to controls ($p < 0.001$) (Figure 1). No significant differences were observed in other cytokine and mediator levels between the two groups ($p > 0.05$).

Table 1 Demographic, Clinical and Laboratory Characteristics in AR and Control Groups

Variables	Control (n = 22)	AR (n = 40)	p value
Gender, n (%)			0.055 ^a
Male	6 (27.3%)	21 (52.5%)	
Female	16 (72.7%)	19 (47.5%)	
Age (yr)	29.73 ± 10.87	31.05 ± 12.03	0.670 ^b
Duration of AR (yr)	–	8.12 ± 5.46	
slgE (kU _A /L)			
Der p	–	18.28 (1.46–37.29)	
Der f	–	3.96 (0.54–18.57)	
FeNO (ppb)	13 (9.00–17.25)	39 (24.00–62.00)	<0.001^c
FnNO (ppb)	360 (270.50–420.25)	607 (500.00–904.00)	<0.001^c
Periostin (ng/mL)	18.95 (17.43–23.26)	26.18 (20.85–49.21)	<0.001^c
TGF-β1 (ng/mL)	33.61 (27.30–40.54)	30.00 (22.94–37.91)	0.217 ^c
YKL-40 (ng/mL)	29.00 (25.51–32.44)	30.23 (25.74–32.48)	0.774 ^c
VEGF-A (ng/mL)	0.21 (0.14–0.26)	0.20 (0.13–0.27)	0.512 ^c
TIMP-1 (ng/mL)	100.16 (89.51–113.68)	100.64 (83.03–117.77)	0.977 ^c
MMP-9 (ng/mL)	35.32 (26.98–55.32)	38.73 (27.49–62.36)	0.369 ^c
MMP-2 (ng/mL)	76.36 (66.00–81.42)	74.82 (71.33–79.09)	0.912 ^c
PDGF-AA (ng/mL)	3.31 (2.49–3.70)	3.00 (2.21–3.70)	0.513 ^c
PDGF-BB (ng/mL)	5.93 (4.22–8.92)	5.41 (3.69–6.93)	0.245 ^c
FGF-2 (pg/mL)	9.94 (6.74–11.41)	8.01 (5.40–9.34)	0.083 ^c
HGF (pg/mL)	149.89 (124.11–167.56)	122.50 (107.99–161.95)	0.276 ^c

Notes: ^aTwo-sided χ^2 test; ^bUnpaired Student's *t*-test; ^cMann–Whitney *U*-test. Bold values denote statistical significance at the $p < 0.05$ level.

Abbreviations: AR, allergic rhinitis; Der p, *Dermatophagoides pteronyssinus*; Der f, *Dermatophagoides farinae*; FeNO, fractional exhaled nitric oxide; FnNO, fractional nasal nitric oxide; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; MMP, matrix metalloproteinase; PDGF, platelet derived growth factor; slgE, specific immunoglobulin E; TIMP, tissue inhibitor of metalloproteinase; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; VAS, visual analogue scale; YKL-40, chitinase-3-like protein 1.

Stratification Analysis of Serum Periostin Levels in AR Patients

As shown in Table 2, moderate/severe AR patients had significantly higher serum periostin levels (27.18 [22.16–51.21] ng/mL) compared to mild AR patients (21.42 [17.76–40.48] ng/mL) ($p = 0.045$). No statistical significance was observed in serum periostin levels among other stratification ($p > 0.05$).

Comparison of Serum Periostin Levels with Symptom Scores in AR Patients

As shown in Table 3, serum periostin levels in AR patients increased from 0 to 3 scores (four-point scale) of shortness of breath ($Z = 10.137$, $p = 0.017$). No statistically significant association was observed between the other symptom scores and serum periostin levels ($p > 0.05$).

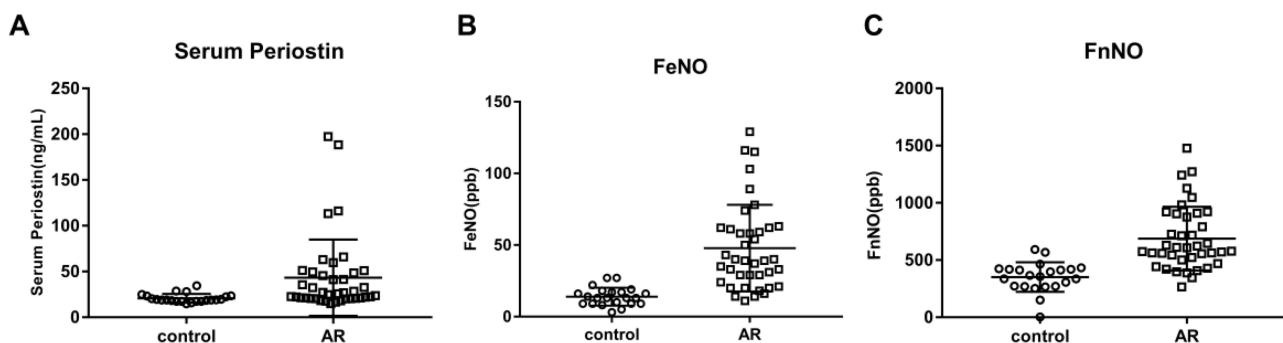


Figure 1 Comparison of Indicators in AR and Control Groups. Concentrations of periostin (A), fractional exhaled nitric oxide (FeNO) (B), and fractional nasal nitric oxide (FnNO) (C) in the patients with allergic rhinitis (AR) and control subjects. Mann Whitney *U*-test showed significant higher in patients with AR ($p < 0.001$).

Table 2 Stratification Analysis of Serum Periostin Levels in AR Patients

Variables	N (%)	Median (IQR) (ng/mL)	p value ^a
Gender			0.755
Male	21 (52.50)	22.52 (20.64–50.19)	
Female	19 (47.50)	27.18 (21.09–48.39)	
Classification of AR			0.087
Intermittent AR	16 (40.00)	22.25 (18.68–45.25)	
Persistent AR	24 (60.00)	30.44 (21.60–59.37)	
Severity of symptoms			0.045
Mild (VAS≤5)	13 (32.50)	21.42 (17.76–40.48)	
Moderate/severe (VAS>5)	27 (67.50)	27.18 (22.16–51.21)	
The stage of attack			0.088
Stable	6 (15.00)	21.09 (18.72–29.26)	
Attack	34 (85.00)	27.84 (21.15–50.98)	
Mite allergy			0.544
No	6 (15.00)	28.04 (19.95–3.29)	
Yes	34 (85.00)	26.18 (21.01–50.98)	
Concomitant asthma			0.425
No	35 (87.50)	26.74 (21.09–49.48)	
Yes	5 (12.50)	21.42 (15.72–114.86)	
Concomitant other allergic diseases			0.261
No	20 (50.00)	25.15 (21.56–47.70)	
Yes	20 (50.00)	27.84 (20.50–59.64)	
Concomitant family history of atopy			0.359
No	20 (50.00)	24.68 (20.00–45.62)	
Yes	20 (50.00)	27.18 (21.13–55.34)	
Concomitant eye symptoms			0.833
No	9 (22.50)	27.18 (21.10–43.35)	
Yes	31 (77.50)	25.63 (20.52–50.91)	
Concomitant respiratory system symptoms			0.345
No	17 (42.50)	28.50 (22.25–50.19)	
Yes	23 (57.50)	22.41 (20.41–41.33)	
Smoking status			0.067
Never smoker	19 (47.50)	32.57 (23.70–59.77)	
Ex-smoker	6 (15.00)	31.05 (20.39–134.18)	
Current smoker	5 (12.50)	20.26 (17.39–21.84)	
Passive smoker	10 (25.00)	23.42 (21.33–48.66)	

Notes: ^aMann–Whitney *U*-test. Bold values denote statistical significance at the $p < 0.05$ level.

Abbreviations: AR, allergic rhinitis; IQR, interquartile range; VAS, visual analogue scale.

Table 3 Comparison of Serum Periostin Levels with Symptom Scores in AR Patients

Variables	N	Median (IQR) (ng/mL)	p value ^a
Sneeze score			0.165
0	4	19.69 (16.90–39.57)	
1	13	28.50 (21.65–48.94)	
2	13	22.16 (20.46–46.12)	
3	10	33.92 (23.80–132.05)	

(Continued)

Table 3 (Continued).

Variables	N	Median (IQR) (ng/mL)	p value ^a
Rhinorrhea score			0.415
0	1	16.54 (16.54–16.54)	
1	11	32.57 (21.42–48.39)	
2	19	23.70 (20.415–1.21)	
3	9	24.68 (20.80–110.39)	
Nasal itching score			0.160
0	9	28.50 (21.09–47.01)	
1	11	20.52 (18.24–27.18)	
2	15	35.45 (22.16–63.03)	
3	5	26.74 (18.03–192.85)	
Nasal obstruction score			0.122
0	5	20.26 (17.76–22.92)	
1	13	28.50 (21.25–50.19)	
2	14	25.22 (21.75–52.78)	
3	8	36.86 (21.71–100.70)	
Ocular itching/grittiness/redness score			0.823
0	10	24.79 (21.01–42.21)	
1	11	26.74 (22.16–50.91)	
2	13	28.50 (19.25–64.49)	
3	6	22.43 (20.39–71.39)	
Ocular tearing score			0.553
0	16	24.66 (20.93–34.73)	
1	12	31.74 (20.44–60.00)	
2	8	40.94 (22.94–97.75)	
3	4	22.92 (20.29–147.46)	
Wheezing score			0.745
0	28	26.96 (21.56–49.21)	
1	9	22.16 (18.27–74.34)	
2	1	21.17 (21.17–21.17)	
3	2	104.40 (20.41-)	
Cough score			0.262
0	28	24.19 (20.58–49.22)	
1	6	26.87 (18.07–55.62)	
2	3	26.74 (22.41-)	
3	3	113.26 (32.39-)	
Shortness of breath score			0.017
0	31	22.52 (20.41–41.07)	
1	7	41.33 (32.39–116.11)	
2	1	113.26 (113.26–113.26)	
3	1	188.39 (188.39–188.39)	
Chest distress score			0.317
0	31	28.50 (21.99–50.91)	
1	6	21.25 (20.39–24.76)	
2	1	21.17 (21.17–21.17)	
3	2	104.40 (20.409-)	

Notes: ^aMann–Whitney *U*-test. Some scores cannot calculate the 75% quantile value. Bold values denote statistical significance at the $p < 0.05$ level.

Abbreviations: AR, allergic rhinitis; IQR, interquartile range.

Table 4 Correlations with Serum Periostin Levels in AR Patients

Variables	Mean \pm SD/ Median (IQR)	R	p value
Age (years)	31.05 \pm 12.03	-0.032	0.844
Duration of AR, (years)	8.12 \pm 5.46	-0.039	0.812
FeNO (ppb)	39.00 (24.00, 62.00)	0.398	0.012
FnNO (ppb)	607.00 (500.00, 904.00)	0.379	0.017
Der p (kU _A /L)	18.28 (1.46–37.29)	0.304	0.057
Der f (kU _A /L)	3.96 (0.54–18.57)	0.202	0.212
VAS of sneeze	6.10 (3.00–8.00)	0.212	0.189
VAS of rhinorrhea	7.00 (3.50–8.38)	0.085	0.601
VAS of nasal itching	5.00 (2.13–7.73)	0.211	0.190
VAS of nasal obstruction	5.25 (2.00–8.00)	0.268	0.094
VAS of total nasal symptoms	22.50 (12.50–31.50)	0.243	0.130
VAS of ocular itching/grittiness/redness	3.00 (0.25–7.38)	0.074	0.650
VAS of ocular tearing	2.00 (0.00–4.88)	0.351	0.026
VAS of total ocular symptoms	4.15 (1.40–11.00)	0.203	0.209
VAS of wheezing	0.00 (0.00–0.75)	-0.125	0.444
VAS of cough	0.00 (0.00–2.00)	-0.002	0.992
VAS of shortness of breath	0.00 (0.00–1.00)	0.167	0.304
VAS of chest distress	0.00 (0.00–0.00)	-0.207	0.201
VAS of total respiratory symptoms	0.75 (0.00–5.00)	-0.006	0.968
VAS total symptoms	7.00 (4.03–8.38)	0.171	0.291
75Pa total nasal resistance (Pa/cm ³ /s)	0.25 (0.17–0.65)	0.155	0.367
75Pa unilateral nasal resistance (Pa/cm ³ /s)	1.00 (0.40–2.00)	0.244	0.146
150Pa total nasal resistance (Pa/cm ³ /s)	0.42 (0.24–0.85)	0.179	0.344
150Pa unilateral nasal resistance (Pa/cm ³ /s)	1.20 (0.63–2.56)	0.262	0.117
NV0-6 (cm ³)	14.48 (11.79–18.00)	-0.190	0.260
MCA (cm ²)	0.25 (0.16–0.40)	-0.188	0.265
MD (cm)	2.25 (2.07–2.42)	0.005	0.979
Bilateral nasal respiratory capacity (L)	7.93 (4.76–10.60)	0.184	0.269

Notes: Bold values denote statistical significance at the $p < 0.05$ level.

Abbreviations: AR, allergic rhinitis; Der p, *Dermatophagoides pteronyssinus*; Der f, *Dermatophagoides farinae*; FeNO, fractional exhaled nitric oxide; FnNO, fractional nasal nitric oxide; IQR, interquartile range; MCA, minimum cross-sectional area; MD, the distance between nostril and MCA; NV0-6, the nasal volumes from 0–6cm; VAS, visual analogue scale.

Correlations with Serum Periostin Levels in AR Patients

When correlation analysis was made among age, AR duration, the serum sIgE levels, levels of FeNO and FnNO, symptom scores of VAS, the indexes of nasal function examination, and serum periostin levels in the patient group, significant positive correlations were found between serum periostin levels and FeNO ($r=0.398$, $p=0.012$), FnNO ($r=0.379$, $p=0.017$), as well as VAS ocular tearing scores ($r=0.351$, $p=0.026$) (Table 4, Figure 2).

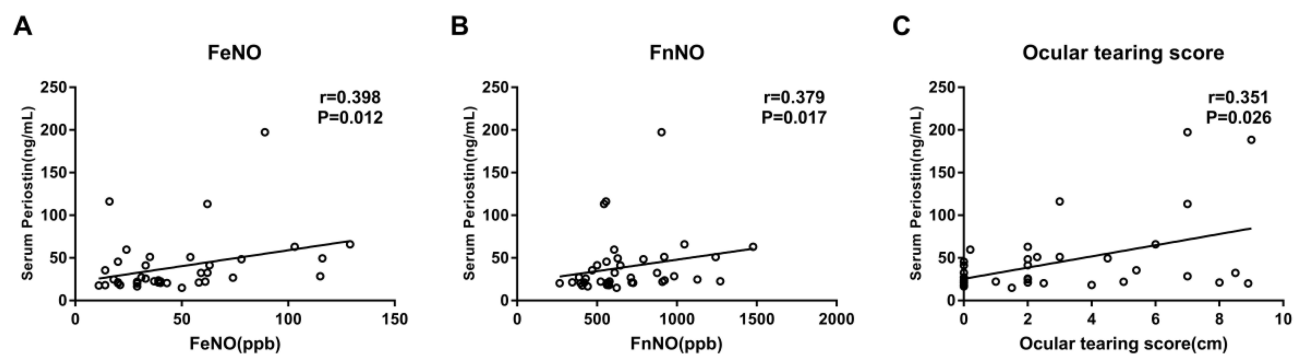


Figure 2 Correlations with Serum Periostin Levels in AR Patients. Scatter plots showing the correlations between serum periostin and fractional exhaled nitric oxide (FeNO) (A), fractional nasal nitric oxide (FnNO) (B) and ocular tearing score of visual analogue scale (VAS) (C) in allergic rhinitis (AR) patients. Spearman's rank correlation was used to assess the associations. Results were reported as significant when $p < 0.05$.

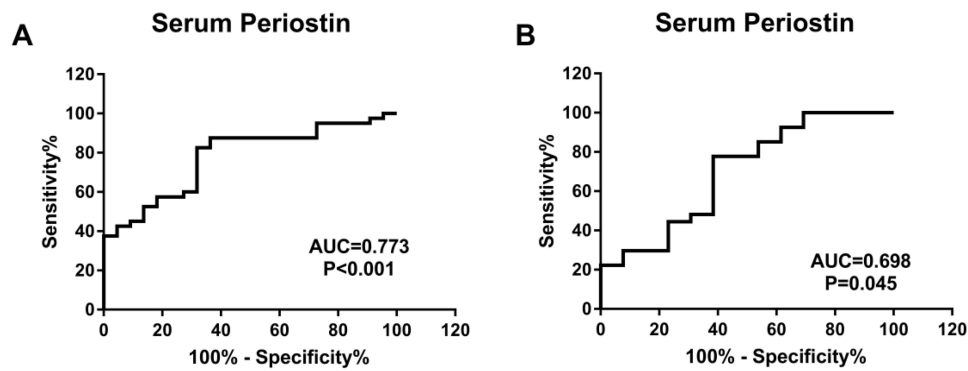


Figure 3 ROC Curve Analysis of Serum Periostin Levels in AR Patients. Receiver operating characteristic (ROC) curves to demonstrate the utility of serum periostin for predicting the diagnosis of allergic rhinitis (AR) (A) and AR severity (B). The results were examined by calculating area under the curve (AUC) which was considered statistically significant when $p < 0.05$.

ROC Curve Analysis of Serum Periostin Levels

As shown in Figure 3A, ROC analysis showed moderate diagnostic accuracy of serum periostin for detecting AR (AUC=0.773, $p < 0.001$) with a cutoff value of 20.360 ng/mL (sensitivity 82.1%, specificity 68.2%) (Table 5). For AR severity, the diagnostic accuracy was slightly lower (AUC=0.698, $p = 0.045$) (Figure 3B) with a cutoff value of 22.074 ng/mL (sensitivity 77.8%, specificity 61.5%) (Table 5).

Discussion

While IgE-mediated type I hypersensitivity reactions are the predominant mechanism in allergic rhinitis (AR), non-IgE-mediated inflammatory responses may also contribute to the initiation and progression of AR.²³ Recent studies have expanded our understanding of these complex interactions. Berghi et al²⁴ discovered that *Solanum melongena* allergens may induce respiratory symptoms via pollen-related reactions through multiple mechanisms, involving the lipid transfer protein pathway, profilin pathway, polyphenol oxidase mechanism and other molecules. This suggests that further exploration of the pathogenesis of AR is still needed.

Periostin, an extracellular matrix (ECM) protein encoded by the *POSTN* gene, is gaining recognition as a biomarker and therapeutic target in asthma and CRS.²⁵ Periostin can act as an ECM protein to maintain tissue structure and facilitate fibrosis formation.²⁶ It can also act as a matricellular protein to transduce signals in cells and regulate the expression of numerous downstream genes.^{27,28} Current studies have shown that periostin can regulate fibrosis and collagen deposition, upregulate the production of MMPs, facilitate myofibroblast differentiation and eosinophil tissue infiltration, or stimulate TGF- β activation in airway epithelial cells, thus playing an important role in accelerating airway inflammation and remodeling.^{5,15,16}

In the present study, AR patients exhibited significantly higher serum periostin levels compared to controls. Notably, periostin levels were also elevated in patients with moderate/severe AR compared to those with mild AR, implicating periostin in the occurrence and development of airway allergic inflammation in AR. Moreover, ROC curve analysis revealed that serum periostin had moderate diagnostic accuracy for detecting AR (AUC, 0.773) with an optimal cut-off value of 20.36 ng/mL. However, serum periostin performed substantially less well for detecting AR severity (AUC,

Table 5 Sensitivity and Specificity of Serum Periostin for Diagnosing AR and AR Severity

Predictors	AUC	Std. error	p value	95% CI	Cut-off point	Sensitivity	Specificity
AR	0.773	0.061	<0.001	0.653–0.892	20.360	0.821	0.682
AR severity	0.698	0.093	0.045	0.516–0.880	22.074	0.778	0.615

Abbreviations: AR, allergic rhinitis; AUC, area under the curve; CI, confidence interval.

0.698). These findings suggest that serum periostin is a valuable indicator for AR detection but less effective for assessing severity.

Meta-analysis revealed elevated serum periostin levels in asthma patients compared to healthy individuals.²⁵ Kimura et al¹⁷ demonstrated a gradient increase in periostin levels across non-AR/non-asthmatic, non-asthmatic AR, non-AR asthmatic, and asthmatic AR subjects, suggesting periostin's role in both conditions. Nonetheless, our stratified analysis found no significant difference in periostin levels between AR patients with and without asthma. Considering the small number of AR patients with asthma in this study and they were in remission, future studies should include a broader cohort of AR patients with asthma, especially those not in asthma remission.

As a potential reliable biomarker for AR, serum periostin offers distinct advantages. It can be easily accessed in clinical settings with little variability and appropriate concentration.²⁵ However, the inherently high levels of serum periostin in children, which fluctuate with age due to bone metabolism, complicate its application in pediatric populations.^{25,29} Additionally, gender differences in serum periostin have been reported, though not observed in our study.²⁵ Reports also show that smoking may downregulate the serum periostin levels.^{17,30,31} Our analysis showed a decreasing trend in the serum periostin levels among never smokers, ex-smokers, passive smokers and current smokers in AR patients, which was consistent with previous observations by James et al,³⁰ who found significant differences in periostin levels between smoking statuses only in non-asthmatics. We speculate that the elevated periostin in AR patients might obscure smoking's impact.

FeNO has been used to monitor eosinophilic inflammation in lower airway diseases and help to identify patients with Th2 mediated airway inflammation,³² while FnNO assesses upper airway inflammation.^{22,33} Our findings revealed elevated FeNO and FnNO levels in AR patients compared to controls, along with notable positive correlations between periostin and both FeNO and FnNO. These observations align with previously published studies on respiratory tract disorders.^{30,33,34} One study found that periostin was positively correlated with FeNO and blood eosinophil count in cough variant asthma (CVA).³⁴ Another study revealed that periostin was positively correlated with higher FeNO and tIgE levels in both asthmatic and non-asthmatic individuals.³⁰ Additionally, studies have found that eosinophilia, high NO levels, aspirin intolerance, nasal diseases, and late-onset asthma as distinctive features of asthmatic patients exhibiting high serum periostin levels.^{35,36} Collectively, these studies, along with our own findings, support the use of periostin in evaluating airway inflammation in AR. As inhaled corticosteroids can rapidly reduce the level of FeNO in asthmatic patients, while serum periostin decreased slowly,³⁷ Izuhara et al²⁵ proposed that inhaled corticosteroids alleviate superficial inflammation by reducing FeNO secreted by epithelial cells, while deep inflammation persists, in this way, periostin deposited subepithelially decreases slowly. Consequently, FeNO may reflect acute inflammation, whereas periostin indicates chronic or underlying inflammation and remodeling, supporting their combined use for a comprehensive assessment of airway inflammation in AR patients in clinical practices.

Our study also examined symptom correlations, but we did not find a relationship between serum periostin and nasal symptoms, which raises questions about its role and value as a biomarker of AR. This necessitates a larger sample size for future research. However, our findings revealed significant increases in serum periostin levels with higher scores for shortness of breath. This is similar with periostin's role in identifying patients with declining pulmonary function in asthma.³⁵ Moreover, our findings indicated a significant positive correlation between the VAS score for ocular tearing and serum periostin levels. Previous studies have highlighted the potential of tear periostin as a biomarker for diagnosing conjunctivitis in allergic patients and assessing disease severity.¹¹ These findings, combined with our findings, suggest that AR patients with severe shortness of breath or tearing symptoms may exhibit elevated serum periostin levels. This provides valuable insight for considering the impact of these symptoms on serum periostin levels of AR patients in clinical practice. In addition, nasal function tests showed no significant correlation with periostin levels. Factors such as environment, physiology, body status, and nasal cycle may influence these results,³⁸ warranting further investigation with larger samples and controlled confounding factors.

The purpose of our study was to preliminarily explore whether periostin can be used as a biomarker of AR for further research, and we focused on the correlation between serum periostin levels and AR symptoms, as well as inflammation levels. Given that the distinctive clinical presentations in asthma and CRS patients significantly differ from those in AR, and considering the inherent complexity of nonallergic rhinitis, which lacks definitive diagnostic parameters and

encompasses a broad spectrum of subtypes, we only included healthy individuals in the control group. With the deepening of research, we can expand the sample size and consider setting up more groups (such as an asthma group, CRS group, nonallergic rhinitis group, etc) to further verify the specificity and sensitivity of periostin as an AR biomarker.

Additional limitations inherent to our study encompass the absence of eosinophil and quantitative tIgE measurements in AR patients. Considering elevated production of periostin in nasal secretions during symptom exacerbation in AR patients with atopic asthma,^{39,40} nasal periostin can be included in future research. Comprehensive studies that focus on the dynamic monitoring of periostin levels are necessary to validate and broaden our results. These studies would also aid in determining the variability of periostin levels during and after allergen challenge, as well as pre- and post-treatment such as corticosteroids and/or other antiallergic drugs. Additionally, we need to pay attention to the geographical variability and racial differences of the serum levels of periostin. Studies have indicated that in comparison with the Caucasian non-asthmatic group, the serum periostin levels were notably higher in the Chinese group, suggesting that ethnic considerations should be factored into the interpretation of periostin levels.⁴¹

Conclusion

Serum periostin may participate in the process of nasal allergic inflammation and remodeling, making it a potential biomarker for predicting AR. Combined with FeNO and FnNO, periostin can provide an evaluation of airway inflammation in AR patients, aiding clinical interpretation and management. We will also expand our research to include a wider study group for further exploration.

Abbreviations

AR, allergic rhinitis; sIgE, allergen-specific IgE; CRS, chronic rhinosinusitis; CVA, cough variant asthma; *Der f*, *Dermatophagoides farinae*; *Der p*, *Dermatophagoides pteronyssinus*; ELISA, enzyme-linked immunosorbent assay; FeNO, fractional exhaled nitric oxide; FnNO, fractional nasal nitric oxide; FGF, fibroblast growth factor; HGF, hepatocyte growth factor; IQR, median and interquartile range; MCA, minimum cross-sectional area; MD, distance between nostril and MCA; MMP, matrix metalloproteinase; NO, nitric oxide; NV0-6, nasal volumes from 0–6cm; PDGF, platelet-derived growth factor; ROC, receiver operating characteristic; SEM, mean \pm standard error; tIgE, total IgE; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; VAS, visual analogue scale; VEGF, vascular endothelial growth factor; YKL-40, chitinase-3-like protein 1.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

Ethical approval for this study was obtained from the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2021-SRFA-088). All participants provided written informed consent before all experiments.

Consent for Publication

The authors obtained informed consent for publication from all participants in the study. The participants understand that their personal information will not be published.

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Author Contributions

All authors made a significant contribution to the work reported, took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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