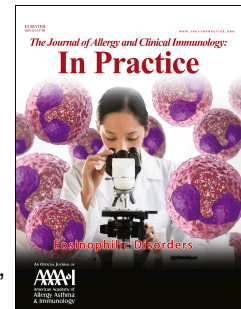


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Serum periostin as a biomarker for predicting clinical response to house dust mite sublingual immunotherapy in allergic rhinitis

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Abstract

Background: House dust mite (HDM) sublingual immunotherapy (SLIT) has proven to be effective for allergic rhinitis (AR), but its efficacy varies among patients. No candidate biomarkers for prediction of response to SLIT are available. Periostin, a matricellular protein, is involved in pathophysiology of AR, and its serum levels reflect airway allergic inflammation.

Objective: To evaluate the relationship between serum periostin levels and current rhinitis control before and after standardized quality (SQ)-HDM SLIT, and to investigate the role of periostin in predicting clinical response.

Methods: One hundred eleven subjects with HDM-induced AR were randomized to receive either SLIT plus pharmacotherapy or pharmacotherapy alone, for 48 weeks. At enrollment and the end of study, clinical characteristics and biomarkers that included serum periostin, serum HDM-specific IgE (s-IgE), total IgE, blood eosinophil counts and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) were measured. Association between clinical indices or biomarkers and clinical response to SLIT were analyzed.

Results: A response to SLIT was recorded in 64% (32 of 50) patients. High serum periostin levels (> 30.2 ng/mL) was associated with an effective response to SLIT, and the magnitude of RQLQ improvement was correlated with the level of serum periostin. The sensitivity and specificity based on receiver operating characteristic analysis for periostin were higher than those of s-IgE.

Multivariate regression analysis showed that serum periostin was independent factor for SLIT responders.

Conclusions: Serum periostin appears to be a useful biomarker for predicting the response to SQ-HDM SLIT in patients with AR.

Highlights Box

1. What is already known about this topic?

House dust mite (HDM) sublingual immunotherapy (SLIT) is an effective treatment option for allergic rhinitis (AR), but its efficacy varies across patients. To date, no validated biomarkers for the clinical response to SLIT are available.

2. What does this article add to our knowledge?

High serum periostin levels at enrollment predict clinical response to SLIT, and this value correlated with the magnitude of improvement in rhinoconjunctivitis quality of life.

3. How does this study impact current management guidelines?

This study highlights the importance of serum periostin as a biomarker of successful SLIT for patients with AR.

Key words: Allergic rhinitis; Biomarker; House dust mite; IgE; Periostin; Rhinoconjunctivitis Quality of Life Questionnaire; Sublingual immunotherapy

Abbreviations:

AE, adverse event; AIT, allergen immunotherapy; AR, allergic rhinitis; AUC, Area under the curve; *Der f*, *Dermatophagoides farinae*; *Der p*, *Dermatophagoides pteronyssinus*; EAACI, European Academy of Allergy and Clinical Immunology; ELISA, Enzyme-linked immunosorbent assay; FAS, full analysis set; HDM, house dust mite; ICH, International Conference on Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use; ICS, inhaled corticosteroid; ILC2, Group 2 innate lymphoid cells; JAU, Japanese allergy units; LME, linear mixed effects; QoL, Quality of life; ROC, Receiving operating characteristic; RQLQ,

69 Rhinoconjunctivitis Quality of Life Questionnaire; SCIT, subcutaneous immunotherapy; s-IgE,
70 specific IgE; SLIT, sublingual immunotherapy; SQ, standardized quality; t-IgE, total IgE; T regs,
71 regulatory T cells.

72

Introduction

Allergen immunotherapy (AIT) is an effective therapeutic modality for allergic diseases, particularly allergic rhinitis (AR) and asthma.¹ Sublingual immunotherapy (SLIT) is a treatment option with disease-modifying properties for allergic diseases, is more convenient and has less severe systemic reactions than subcutaneous immunotherapy (SCIT).² House dust mites (HDMs) are prevalent worldwide and are major cause of perennial AR. The efficacy and safety of the standardized quality (SQ)-HDM SLIT tablet has been demonstrated in Western countries for HDM-induced AR.³⁻⁶ While meta-analyses has demonstrated clear overall benefit compared to placebo, it is recognized that SLIT does not work effectively for all users. Thus, SLIT is recognized as a suitable treatment modality for AR, its efficacy varies across patients, and is known to be ineffective in a certain population of patients. The identification and validation of predictive biomarkers of SLIT response is a topic of major interest. A recent study reported that the serum specific IgE (s-IgE)/total IgE (t-IgE) ratio could be a candidate for predicting clinical response to AIT.⁷ However, other potential biomarkers of efficacy for SLIT remain unknown.

Periostin is a one of matricellular protein⁸ and is downstream molecule of IL-13,⁹ a signature cytokine of type 2 responses in allergic disease. Thus, periostin may play an important role in the pathogenesis of allergic diseases including AR. Since IL-4 and IL-13 are dominantly expressed in the inflamed sites of allergic diseases. Type 2 inflammation is characterized by increased release of IL-4, IL-5 and IL-13 likely from Th2 and Group 2 innate lymphoid cells (ILC2) resulting in eosinophilic airway infiltration.¹⁰ The local expression of periostin is significantly increased in patients with AR¹¹ and nasal polyps¹² compared to controls. These findings support the concept that periostin is involved in Th2-driven inflammation.¹³

The primary mechanisms of SLIT include reducing Th2 inflammation, enhancing Th1 inflammation and modulating allergen specific IgE mediated responses.¹⁴ Recent studies showed

that regulatory T cells (T regs) may be key regulators of immunological processes in peripheral tolerance to allergens during immunotherapy.¹⁵ Several studies have demonstrated that *Dermatophagoides pteronyssinus* (Der p)-driven IFN- γ and IL-10 were significantly increased in culture supernatants of peripheral blood mononuclear cells in successful SLIT.^{16,17} Therefore, we hypothesized that serum periostin would be a potential novel biomarker of predicting the clinical response to SLIT.

In this study, we examined baseline characteristics and changes in biomarkers for patients receiving SQ-HDM SLIT. Specifically, we sought to better characterize rhinitis outcomes after SLIT initiation and evaluate whether a biomarker profile or specific patient characteristics would be predictive of treatment response.

Methods

Trial design

This was a randomized, open-label controlled trial designed and conducted in accordance with the principle of the Declaration of Helsinki and in compliance with the Good Clinical Practice of the International Conference on Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use (ICH). Using a computer-generated randomization method, subjects were randomized to receive the SQ-HDM SLIT tablet, as add-on therapy to drug treatment (SLIT group) or drug treatment alone (control group) for up to 48 weeks, preceded by a run-in phase of 4 weeks. Blood examination and assessment of a quality of life (QoL) using a questionnaire were conducted at baseline and at the end of the study. The study protocol was approved by the ethics committee of International University of Health and Welfare (16-A-65). Written informed consent was obtained from all subjects.

Subjects

The trial population was comprised of adults 20 to 65 years of age, with a clinical history of HDM-induced AR, a positive result in a nasal provocation test using a house dust disk, and a positive s-IgE level against *Der p* or *Der farinae* (*Der f*), or both (> 0.7 kU/L). Subjects were excluded from the study if they were suspected of having symptomatic AR due to allergens other than HDM or high s-IgE against allergens other than HDM. Patients were also excluded if they had mild-persistent or more severe asthma that required treatment with inhaled corticosteroid (ICS); had systemic immunological diseases, malignancies that required long-term treatment with oral steroids; or had previous courses of immunotherapy.

Intervention medication

The HDM SLIT tablets (Torii, Tokyo, Japan/ALK-Abello, Horsholm, Denmark) contained allergen extracts derived from *Der f* and *Der p* at a 1:1 ratio, and formulated as a rapidly dissolving oral lyophilisate for sublingual administration. HDM SLIT tablets were administered as an initial dose of 2 SQ-HDM (equivalent dose of 3300 Japanese allergy units: [JAU]) for 1 week followed by a maintenance dose of 6 SQ-HDM (equivalent dose of 10,000 JAU). This is the approved dose in Japan, whereas the approved dose in the USA and Europe is 12 SQ-HDM. Pharmacotherapy for rhinitis or conjunctivitis, i.e., antihistamine tablets and eye drops or nasal steroids were provided to subjects only when needed for control of their symptoms. Once symptoms were alleviated, the subject had to stop taking these medications.

Assessments

Several biomarkers for blood eosinophil count, serum periostin and IgE were measured. A whole blood sample was submitted for a white blood cell count with differentiation. Serum s-IgE to HDM (ImmunoCAP, Thermo Fischer, Phadia, Uppsala, Sweden) and t-IgE levels were determined. Periostin levels were measured by an enzyme-linked immunosorbent assay (ELISA) with the DuoSet Human Periostin/OSF-2 (R&D Systems, Minneapolis, MN, USA). This ELISA kit is specific for the measurement of natural and recombinant human periostin. The lowest detection level of periostin was 0.97 ng/mL in diluted samples (1:25). The limit of detection was determined by adding 3 standard deviations to the mean value of 30 zero standard measurements. Details about data measurement are described elsewhere.¹⁸ Disease-specific QoL was assessed by using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The RQLQ is consist of 28 items in 7 domains, with each score on a 7-point scale. The 7 domains were activities, sleep, non-nose and non-eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional.¹⁹ A change of > 0.5 point compared to baseline represents a clinically meaningful improvement in QoL.

157

158 **Responder analysis**

159 Overall mean RQLQ score and seven domain scores with each domain weighted equally, were
160 calculated for each patient individually comparing baseline to the end of the 48-week period. HDM
161 SLIT responders were defined as those who had an improvement of 0.5 or more in overall and each
162 domain RQLQ from baseline compared to the end of the study. Numbers and percentage of patients
163 defined responders by the aforementioned criteria were calculated.

164

165 **Outcomes**

166 The primary outcome was symptoms scores on the RQLQ. The efficacy assessment period took
167 place from July to October to avoid overlapping symptoms caused by Japanese cedar pollen.
168 Demographic characteristics such as gender, age, disease duration, body mass index, blood
169 eosinophil counts, serum periostin, HDM s-IgE, t-IgE, and sensitization to other allergens besides
170 HDM were measured. The safety profile was regularly monitored regarding treatment adverse
171 events (AEs).

172

173 **Statistical analysis**

174 Normally distributed data were expressed as mean and standard deviation (SD), and non-normal
175 distributed data were expressed as median (interquartile range). The full analysis set (FAS) included
176 all randomized subjects by assigned treatment in accordance with the ICH intent-to-treat principle.
177 The primary analysis compared treatment groups using a linear mixed effects (LME) model. The
178 primary analysis set was the FAS with multiple imputations for missing data (FAS-MI), which
179 conservatively treated all subjects with missing data as having no treatment effect. Additional
180 analyses for the primary end point were performed on the FAS. Multiplicity for the primary and

secondary analyses were controlled for by using the Fisher least significant difference procedure. Receiver operating characteristic (ROC) analysis was performed to determine the utility of biomarkers in detecting the response to SLIT. Linear regression models were used to describe the relationship between changes (Δ : posttreatment minus pretreatment) in RQLQ score and clinical indices. Statistical significance was set at a *P* value of less than .05. Univariate analysis followed by multivariate logistic regression analysis was to evaluate which one predict Δ RQLQ. All statistical tests were performed with SAS version 9.1 software (SAS Institute, Cary, NC) with a 5% significance level, and all tests and 95% CIs were 2-sided.

Results

Population

Subject disposition is shown in Figure 1. A significantly higher proportion of subjects discontinued because of AEs in the SLIT group compared with control group. Subjects' baseline characteristics are presented in Table I. Patient demographics and baseline characteristics were similar in the 2 groups. The percentage of subjects with monosensitization to HDM was 26.7% in the SLIT group and 32.7% in the control group. In polysensitized subjects, the most prevalent allergens based on s-IgE levels were Japanese cedar pollen (64%), Japanese cypress pollen (42%), orchard grass (23%), ragweed and cat (14%).

Comparison of change in biomarkers and symptoms between SLIT and control

The level of serum periostin significantly decreased from baseline to the end of treatment in the SLIT group ($P < .001$). No significant changes in serum periostin levels were observed in the control group ($P = .477$). There was a significant difference in the change of periostin between SLIT and control group ($P < .01$, Table II). In the SLIT group, there was a significant increase in s-IgE levels ($P < .01$), whereas no significant changes in s-IgE values were observed in the control group ($P = .276$). The difference in the change of s-IgE between SLIT and control was significant ($P < .05$, Table II). There were no significant changes in t-IgE or blood eosinophil counts between baseline and the end of the study in either group. Overall, add-on SQ-HDM significantly improved AR related quality of life: the mean improvement in RQLQ score of 0.6 ($P < .001$) was clinically significant. Comparing the SLIT group to the control group, statistically significant differences were seen for all 7 RQLQ domains (Table II).

Prediction responders from biomarkers

Sixty-four percent of patients (32 of 50) were responders on the basis of clinical improvement in QoL. The ROC analysis revealed that serum periostin levels distinguished responders from non-responders with a cutoff value of 30.2 ng/mL, a sensitivity of 76.9%, a specificity of 80.8%, and an area under the curve (AUC) of 0.79 (95% CI, 0.62 - 0.95, $P < .001$, Figure 2A). Serum s-IgE levels also distinguished responders from non-responders with a cutoff value of 8.2 kU/L, a sensitivity of 63.6%, a specificity of 68.0%, and an AUC of 0.62 (95% CI, 0.39 - 0.81, $P < .001$, Figure 2B). The sensitivity and specificity of AUC for serum periostin were higher than for serum s-IgE. However, no predictive value for serum t-IgE (AUC 0.56) or blood eosinophil (AUC 0.50) was found (data not shown). Based on the optimal cutoff values obtained by ROC analysis, patients were classified into high or low of serum periostin (≥ 30.2 or < 30.2 ng/mL) and s-IgE (≥ 8.2 or < 8.2 kU/L). The proportion of patients with both high serum periostin and s-IgE levels was significantly greater in responder than in non-responder (odds ratio, 7.06; 95% CI, 1.51 - 31.63, $P = .013$; sensitivity, 88.2%; and specificity, 48.5%; Figure 3).

Association between biomarkers and clinical response

Univariate analysis was performed to evaluate the relationship between the patient characteristics, biomarkers and the improvement in RQLQ (Table III). The changes in RQLQ score (Δ RQLQ) was associated with serum periostin and s-IgE levels. No significant correlation between baseline patient characteristics and efficacy of SLIT was observed. Variables with a P value of $< .10$ in the univariate analysis and other potentially candidate biomarkers were included in the multiple logistic regression. Multivariate analysis revealed that serum periostin and s-IgE were independently associated with an improvement in RQLQ ($r^2 = .617$, $P < .05$, respectively, Table IV).

Safety

238 In general, the SQ-HDM SLIT tablet was well tolerated. The most frequently reported
239 treatment-related AEs were mild to moderate local reactions referred to sublingual administration of
240 the tablet, the most common being oral pruritus, throat irritation, and mouth swelling. The 4
241 dropouts because of AEs in the SLIT group were 2 oral itching, 1 ear pruritus and 1 gastroenteritis.
242 There were no reports of anaphylactic shock, airway obstruction, or administration of epinephrine.
243

Discussion

We demonstrated that the serum periostin levels are useful for detecting responders for SQ-HDM SLIT in patients with AR. A significant reduction of serum periostin levels was observed after SLIT initiation. It is also shown that high serum periostin was an independent factor for improvement in QoL. To the best of our knowledge, this is the first study to identify a possible role of serum periostin as a predictor of clinical response to SLIT.

The available biomarkers for predicting the outcomes of SLIT would be useful in clinical practice. In particular, ideal biomarkers for SLIT should favor patient selection and identification of responders and predict clinical response during SLIT. The recently published European Academy of Allergy and Clinical Immunology (EAACI) Position Paper reviewed candidate biomarkers related to AIT, including SLIT.²⁰ However, there is currently no consensus on surrogate biomarkers that would be prognostic and predictive of clinical response in successful AIT. In this study, we evaluated clinical characteristics and biomarkers, and analyzed the variables that distinguish the patients with effective from ineffective clinical response to SLIT.

Recent studies have revealed that the relevance of periostin in allergic diseases,^{9,13,21} and it has been established that periostin is indeed a biomarker reflecting type 2 inflammation.²² Association between the level of serum periostin and concomitant AR or chronic rhinosinusitis in patients with asthma have been reported.^{23,24} A previous study on the role of periostin in the pathophysiology of AR using nasal tissue specimens revealed that overexpression of periostin mRNA.¹¹ Therefore, serum periostin is a sensitive biomarker for detecting nasal allergic disorders. Based on ROC curve analysis, high serum periostin (> 30.2 ng/mL) detected clinical response to HDM SLIT in patients with AR. The change in RQLQ score correlated with serum periostin level at baseline. In addition, the present study showed that serum periostin level decreased after patients underwent SLIT. Mechanistically, it has been shown that SLIT will skew the Th2-type response, characterized by

cytokines IL-4 and IL-13, to a Th1 response with an increase in specific IgG4.¹⁴ Grass pollen immunotherapy showed that inhibition of IL-5/IFN- γ mRNA⁺ cells infiltration in the nasal mucosa and increases of IFN- γ mRNA⁺ cells during seasonal allergen provocation.²⁵ Our recently published study demonstrated that HDM SLIT provides a significant reduction of fractional exhaled nitric oxide (a maker of eosinophilic airway inflammation) and improvement in airflow limitation in patients with asthma.²⁶ These finding suggests that successful SLIT may inhibit periostin production, and that serum periostin may be not only a biomarker for detecting AR, but a predictor for clinical response in SLIT.

Although AUC was not higher than that of periostin, serum HDM s-IgE levels significantly differentiated responders from non-responders and the level of HDM s-IgE was also associated with the clinical response to SLIT. Our data is in accordance with previous reports; serum s-IgE could be a useful biomarker for predicting response to SLIT.^{7, 27, 28} Increased serum allergen s-IgE levels, along with a history of symptoms on exposure to allergens, represent the major inclusion criteria for intervention of immunotherapy.²⁹ Furthermore, Di Lorenzo *et al.* found that AIT was significantly effective in patients with high serum s-IgE/t-IgE ratio and low t-IgE values.⁷ In our study, there was no significant difference of serum t-IgE between responder and non-responder and t-IgE also could not predict efficacy of SLIT. The discrepancy of the usefulness of t-IgE as a predictor might be explained by the difference in the population and methods of AIT. That is, that study was conducted in a selected cohort of monosensitized allergic patients, and AIT administered either by means of SCIT or SLIT. It has been reported that the percentage of s-IgE is approximately 25% of t-IgE.³⁰ Although it is possible to quantify both serum s-IgE and t-IgE levels, t-IgE levels are not measured because they are not useful in the clinical diagnosis of allergy to common aeroallergens.³¹ Our findings support that assessment of s-IgE may be predictive of the response to SLIT without the need to assess t-IgE. The HDM s-IgE level increased significantly 48-weeks after SLIT. It is known

that allergen s-IgE level is not constant during the course of SLIT,^{3,6,32} in general, levels of s-IgE increase at the early stage of AIT and followed by a gradually decrease.¹⁴ This phenomenon would suggest that the suppression of Th2 response is related to the mechanisms of SLIT, whereas HDM s-IgE level remained essentially unchanged in the control group. Importantly, we found that combining the biomarkers of HDM sIgE and serum periostin levels was by far the strongest predictor of response to HDM SLIT.

In contrast to our study, a previously published report showed that blood eosinophil counts were associated with the efficacy of AIT.⁷ The difference in findings may be due to differences in patient selection, treatment methods and the severity of rhinitis. Indeed the majority of our subjects had mild to moderate rhinitis.

Patients with allergic disorders are often sensitized to multiple allergens. Polysensitization can affect the choices made regarding the formation of an allergen extract and the effectiveness of the choices made is a matter of some debate. In this study, we found 73% of patients were sensitized to allergens other than HDM. Of course, the presence of clinical symptoms to another perennial allergen to which the subject is regularly exposed was an exclusion criteria because sensitization to other indoor allergens could affect the efficacy of our intervention. Our results showed a significant effect of SQ-HDM tablet regardless of sensitization status. This is in agreement with a recent published several studies on the SQ-HDM SLIT, suggesting that polysensitization should not be a contraindication for immunotherapy.^{3,5,33,34}

There are some limitations in the study. First, we did not include a placebo arm. The potential for bias to be introduced by patients and investigators in the assessment of outcomes and response should be considered when interpreting open-label data. To avoid observer bias, after removing patient's name and the date of examination, and blood samples were coded and analyzed randomly. However, the aim of the study was to explore a potential explanation for why patients who have

received SLIT could be responders and thus to search for possible predictors of such varied responses. Second, the small number of subjects included in each arm could result in a Type II error. However, it was important to ensure that we used strict criteria to define our patients for this study, all of whom were carefully followed, allowing for a high follow-up rate at the end of the study. Third, although SLIT is recommended to be continued for 3 to 5 years, the treatment period of this study was short. Nevertheless, we believe that this limitation do not significantly confound the main finding of our study. Further study is necessary to perform the analysis in a larger number of subjects and for a longer duration.

In conclusion, serum periostin is useful for detecting the clinical response to SLIT in patients with HDM induced AR. These findings warrant further study of the mechanisms of periostin suppression due to immunotherapy including patient's molecular profile.

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Figure legends

Figure 1. Patient deposition

SLIT, sublingual immunotherapy; SQ, standardized quality; HDM, house dust mite.

Figure 2. Receiver operating characteristic (ROC) curves for serum periostin (A), HDM specific IgE (B) distinguishing responder from non-responder in asthmatic patients with SLIT

The optimal cutoff values (sensitivity, specificity): serum periostin of 30.2 ng/mL, HDM specific IgE of 8.2 kU/L respectively.

Figure 3. Proportions of patients classified as high or low of serum periostin (≥ 30.2 or < 30.2 ng/mL) and HDM specific IgE (s-IgE) (≥ 8.2 or < 8.2 kU/L)

The proportion of patients with both high serum periostin and s-IgE levels was significantly greater in responders than in non-responders.

Table I. Demographics and baseline patient characteristics

	SLIT (n = 56)	Control (n = 55)
Age (yr)	40 (13)	44 (17)
Male/female	23/33	20/35
Body mass index (kg/m ²)	24.3 (3.4)	22.7(3.8)
Disease duration (yr)	15 (16)	13 (15)
Blood eosinophil (/μL)	276.3 (208.1)	324.0 (306.2)
Total IgE (IU/mL)	283.5 (84.4, 690.2)	219.0 (67.2, 339.0)
Specific IgE HDM (kU/L)	14.4 (3.7)	15.6 (4.4)
Serum periostin (ng/mL)	30.7 (6.6)	29.6 (6.7)
RQLQ score		
Activities	2.2 (1.1)	2.2 (1.0)
Sleep	2.3 (1.0)	2.5 (1.3)
Non nose/eye	2.9 (1.2)	3.0 (1.4)
Practical	3.1 (1.1)	3.2 (1.6)
Nasal	3.5 (0.8)	3.8 (1.2)
Eye	3.0 (0.9)	2.9 (1.0)
Emotional	2.2 (0.9)	2.4 (1.2)
Sensitization		
Monosensitized, n (%)	15 (26.7)	18 (32.7)
Polysensitized, n (%)	41 (73.3)	37 (67.3)

Data are presented as mean (SD) or median (IQR).

SLIT, sublingual immunotherapy; IgE, immunoglobulin E; HDM, house dust mite;

RQLQ, rhinoconjunctivitis quality of life questionnaire.

Table II. Changes of parameters from baseline subjects with AR after SLIT and control, and analysis of efficacy

	<u>SLIT</u>	<u>Control</u>			
Variables	Change from baseline		Difference of SLIT and control	95% CI	P value
Serum periostin (ng/mL)	-4.7 (0.4)	0.1 (1.1)	5.33	(0.29 to 10.37)	.004
Specific IgE HDM (kU/L)	9.2 (3.4)	3.4 (1.9)	7.85	(-29.12 to 13.42)	.039
Total IgE (IU/mL)	1.7 (-50.9, 39.1)	5.0 (-32.0, 23.0)	22.86	(-113.74 to 157.46)	.985
Blood eosinophil (/ μ L)	-21.4 (12.6)	21.5 (16.0)	43.02	(-154.34 to 240.39)	.183
RQLQ score					
Activities	0.56 (0.96)	0.06 (0.50)	0.63	(-0.27 to 1.44)	.001
Sleep	0.45 (0.82)	0.01 (0.84)	0.46	(0.43 to 0.48)	.009
Non nose/eye	0.59 (0.96)	0.01 (0.85)	0.58	(0.38 to 0.79)	.003
Practical	0.58 (1.04)	-0.25 (0.96)	0.73	(0.66 to 0.99)	< .001
Nasal	0.81 (1.04)	-0.43 (0.86)	1.24	(0.87 to 1.61)	< .001
Eye	0.69 (0.78)	-0.19 (0.61)	0.88	(0.53 to 1.22)	< .001
Emotional	0.44 (0.84)	-0.14 (0.68)	0.54	(0.25 to 0.91)	.004

Data are presented as mean (SD) or median (IQR).

AR, allergic rhinitis; SLIT, sublingual immunotherapy; IgE, immunoglobulin E; HDM, house dust mite; RQLQ, rhinoconjunctivitis quality of life questionnaire.

Table III. Univariate analysis of factors affecting RQLQ score after SLIT

Variables	<i>r</i>	<i>P</i> value
Age (yr)	0.111	.247
Male/female	0.062	.350
Body mass index (kg/m ²)	0.118	.246
Disease duration (yr)	-0.139	.208
Serum periostin (ng/mL)	0.743	< .001
Specific IgE HDM (kU/L)	0.568	.014
Total IgE (IU/mL)	-0.068	.345
Blood eosinophil (/μL)	0.081	.318

IgE, immunoglobulin E; HDM, house dust mite; RQLQ, rhinoconjunctivitis quality of life questionnaire; SLIT, sublingual immunotherapy.

Table IV. Multivariate logistic regression models for prediction of symptoms after SLIT

	Model r^2	β	95% CI	<i>P</i> value
	0.617			
Serum periostin (ng/mL)		0.136	(0.059 to 0.213)	.018
Specific IgE HDM (kU/L)		0.054	(0.018 to 0.091)	.040
Total IgE (IU/mL)		-0.003	(-0.001 to 0.008)	.535
Blood eosinophil (/ μ L)		0.002	(-0.001 to 0.021)	.783

IgE, immunoglobulin E; HDM, house dust mite; SLIT, sublingual immunotherapy.

Figure 1