

Clinical significance of serum MRGPRX2 as a new biomarker in allergic asthma

To the Editor,

Allergic asthma, the most common phenotype of asthma, is clinically defined by the presence of allergic sensitization and a correlation between asthma symptoms and allergen exposure.^{1,2} Although several biomarkers for allergic asthma have been proposed, their role in reflecting treatment efficacy is controversial.^{3,4} Mas-related G protein-coupled receptor-X2 (MRGPRX2), expressed in mast cells, is an endogenous receptor associated with IgE-independent activation of mast cells. MRGPRX2 has specific characteristics that induce degranulation of mast cells and regulate inflammatory responses.⁵⁻⁷ We evaluated the potential of MRGPRX2 as a biomarker for predicting treatment outcomes in allergic asthma.

We enrolled asthmatic patients from the ongoing multicenter cohort study, Cohort for Reality and Evolution of adult Asthma in Korea (COREA).⁸ All subjects exhibited airway hyperresponsiveness, indicated by a 20% reduction in the forced expiration volume in 1 second (FEV1) after 16 mg/mL (PC 20) methacholine administration during a provocation test or airway reversibility of FEV1 > 12% (and at least 200 mL) following inhalation of 180 µg albuterol. Patients with severe lung damage, bronchiectasis, or a history of lung resection were excluded. Allergic asthmatic patients were defined as those having positive skin prick test reactivity to at least one common aeroallergens or a history of atopic dermatitis or allergic rhinitis. MRGPRX2 levels were determined using an ELISA kit from MyBioSource, in accordance with the manufacturer's instructions. Among the patients, some were prescribed the adequate ICS dose decided by the clinician, considering the patient's lung function and symptoms at the time of registration, according to the GINA guideline. Allergic asthmatic patients who were not controlled at least once during follow-up (6 and 12 months) were classified into the uncontrolled group. This study was approved by the institutional review board of Asan Medical Center (2018-1330), and all patients provided written informed consent.

Differences in MRGPRX2 levels in healthy, asthma, or allergic asthma groups were calculated using Student's *t* tests. Receiver operating characteristics (ROC) curve analysis was used to determine the optimal MRGPRX2 cutoff to discriminate between the controlled and uncontrolled groups. We used a binary logistic regression model for verifying whether the MRGPRX2 level was an independent predictor after adjusting for age. Differences in clinical variables between both groups were evaluated using chi-square tests. Linear regression models were used to investigate whether

laboratory profiles were associated with MRGPRX2 level. Data were analyzed using the STATA (version 15) and MedCalc (version 15.5) statistical software.

The study included 102 healthy controls and 242 asthmatic patients. The mean serum MRGPRX2 level in the asthma group was significantly higher than that of the control group (95.2 ± 54.8 vs 12.9 ± 9.8 , $P < .001$). The serum MRGPRX2 levels of 164 (68%) patients with asthma included in the allergic asthma group were significantly higher than that of the nonallergic asthma group (102.4 ± 54.5 vs 79.8 ± 52.5 , $P = .002$) (Figure 1A). In the allergic asthma group, MRGPRX2 levels in patients requiring moderate-to-high-dose ICS was higher than in those requiring low-dose ICS (108.1 ± 52.9 vs 76.6 ± 43.9 , $P = .033$) (Figure 1B). Among the allergic asthma group, 70% patients were categorized into the well-controlled group. Their MRGPRX2 levels were significantly higher than those of the uncontrolled group (113.3 ± 53.8 vs 83.4 ± 56.4 , $P = .041$) (Figure 1C). ROC curve analysis showed that MRGPRX2 level could well predict uncontrolled allergic asthma patients (AUC = 0.672; 95% confidence interval (CI), 0.525-0.798; Figure 1D). Furthermore, MRGPRX2 was an independent biomarker for predicting asthma status with ICS response during the 12-month follow-up after adjusting for age ($P = .0367$, Odds ratio = 4.13, 95% CI 1.09-15.6).

The allergic asthma group was classified into two subgroups with high and low MRGPRX2 levels using the optimal cutoff value of 100 ng/mL. Distributions of clinical variables between these two subgroups are summarized in Table 1. Patients with higher MRGPRX2 levels were significantly associated with an onset age higher than 40 years ($P = .008$) and well-controlled responses to ICS ($P = .033$) compared with their counterparts. Otherwise, no significant variables associated with MRGPRX2 levels existed. MRGPRX levels did not correlate with absolute blood eosinophil count ($r = .008$, $P = .929$), sputum eosinophil percentage ($r = -.318$, $P = .582$), C-reactive protein ($r = .118$, $P = .32$), and FEV1 ($r = .001$, $P = .986$).

We demonstrated that serum MRGPRX2 levels were significantly higher in asthma patients than in healthy subjects. In particular, they were higher in the allergic asthma group than in the nonallergic asthma group. Additionally, high levels of MRGPRX2 were significantly associated with allergic asthma requiring moderate-to-high ICS doses and those with good responses (well-controlled) to ICS for the 12-month follow-up period (especially those with MRGPRX2 value ≥ 100 ng/mL). Furthermore, we confirmed

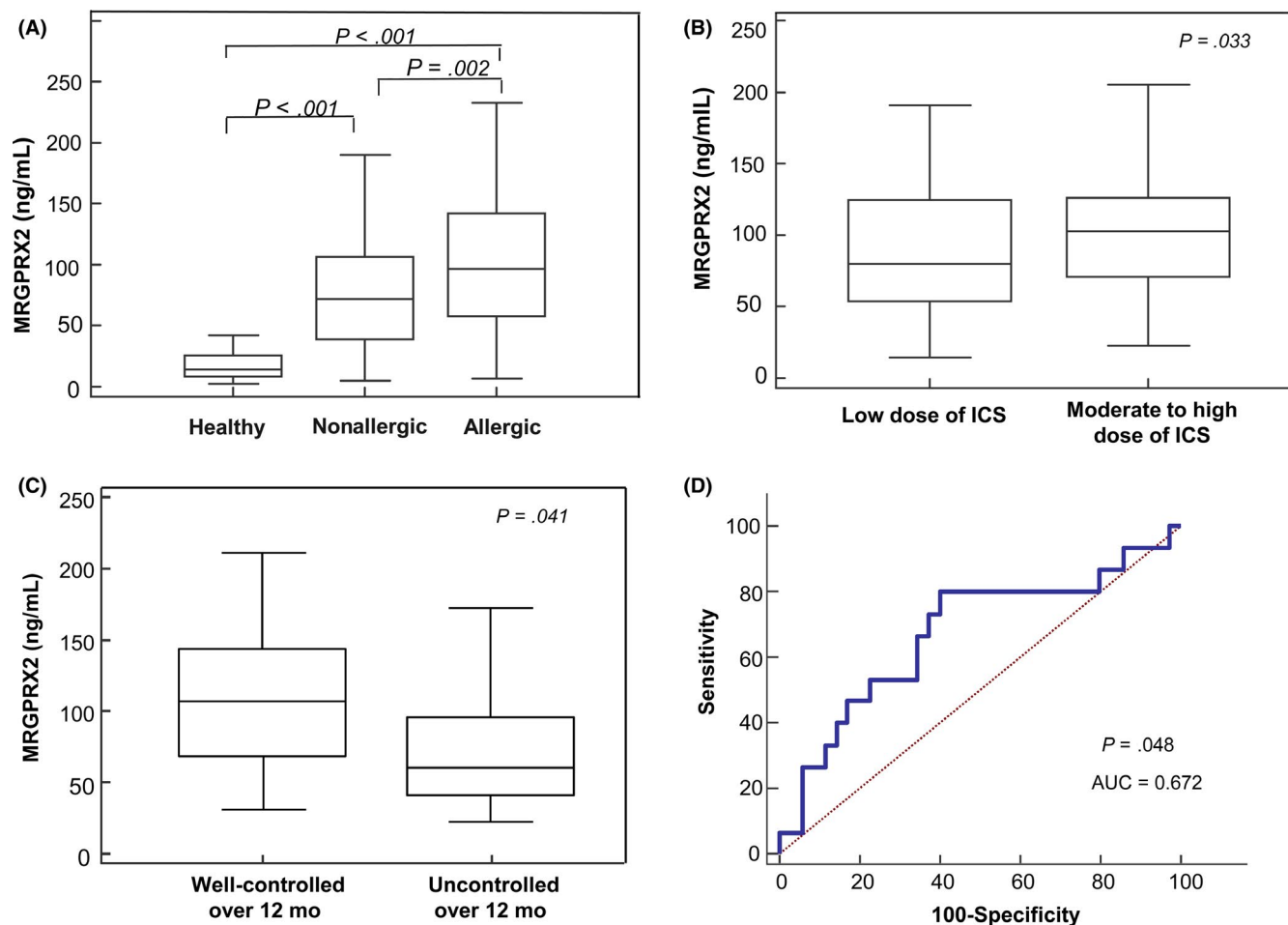


FIGURE 1 Differences in MRGPRX2 levels between healthy controls and nonallergic and allergic asthma groups (A). Mean serum MRGPRX2 level of the allergic asthma group (102.4 ± 54.5) was significantly higher than that of the nonallergic asthma (79.8 ± 52.5) and the control group (12.9 ± 9.8). Serum MRGPRX2 levels in allergic asthma patients according to (B) required ICS dose, and (C) asthma control status according to ICS response. MRGPRX2 levels in patients requiring moderate-to-high-dose ICS were higher than those requiring low-dose ICS (108.1 ± 52.9 vs 76.6 ± 43.9). Higher MRGPRX2 levels were observed in patients from the well-controlled group (6- and 12-mo follow-up, good response to ICS) than in patients from the uncontrolled group (113.3 ± 53.8 vs 83.4 ± 56.4). ROC curve for response to ICS treatment in the allergic asthma group (D). The cutoff MRGPRX2 value was 100 ng/mL for predicting the responses of patients uncontrolled by the 12-mo follow-up

that MRGPRX2 is an independent biomarker for predicting asthma control status with ICS response for the 12-month follow-up in allergic asthmatic patients. Interestingly, MRGPRX2 concentrations were higher in the well-controlled group than in the uncontrolled group probably because of patients with stronger nature of nonallergic asthma (usually difficult to control) among the allergic asthmatic patients.

Although several biomarkers have been proposed for diagnosis and phenotyping, currently few are available to guide precise and personalized allergic asthma treatment. MRGPRX2 levels may guide treatment because high levels suggest the use of higher ICS doses for desirable outcomes. Additionally, MRGPRX2 may be a valuable target molecule for therapy in patients with uncontrolled severe allergic asthma requiring additional treatment options that block the IgE-independent pathway.

This study has several limitations. Firstly, only serum samples were used to estimate MRGPRX2 levels, and local airway inflammation may not be confirmed. Second, a bias existed in sample collection at enrollment because we only collected data for patients in stable states, not in acutely exacerbated states. Furthermore, the sample size for ROC analysis was small. Third, this study has missing values for some parameters because some patients dropped out during follow-up. Lastly, the follow-up period was relatively short (12 months).

In conclusion, we investigated serum MRGPRX2 levels in allergic asthma, and its potential as a useful biomarker for monitoring treatment outcome and determining personalized ICS doses. The role of MRGPRX2 as a prognostic biomarker needs to be further studied using a larger population and for a longer period.

TABLE 1 Differences between clinical characteristics and optimal serum MRGPRX2 levels in allergic asthmatic patients

	Serum MRGPRX2 < 100 ng/mL (n = 85)	Serum MRGPRX2 ≥ 100 ng/mL (n = 79)	Total (n = 164)	P value
Age, years	46.0 ± 13.9	41.6 ± 14.1	43.9 ± 14.1	.047
Female sex, n (%)	56 (65.9)	47 (59.5)	103 (62.8)	.494
Smoking status, n (%)				
Current	10 (11.8)	9 (11.4)	19 (11.6)	.901
Former	21 (24.7)	22 (27.8)	43 (26.2)	
Never	54 (63.5)	48 (60.8)	102 (62.2)	
Age at onset, n (%)				
<40 y	36 (42.4)	50 (63.3)	86 (52.4)	.008
≥40 y	49 (57.6)	29 (36.7)	78 (47.6)	
Exacerbations over 12 mo [†] , n (%)				
No	13 (68.4)	13 (65.0)	26 (66.7)	.823
Yes	6 (31.6)	7 (35.0)	13 (33.3)	
ICS use at registration, n (%)				
No (naïve)	57 (66.3)	55 (69.6)	112 (67.9)	.647
Yes	29 (33.7)	24 (30.4)	53 (32.1)	
Required dose of ICS [‡] , n (%)				
Low	11 (39.3)	5 (20.8)	16 (30.8)	.155
Moderate to high	17 (60.7)	19 (79.2)	36 (69.2)	
Response to ICS over 12 mo [§] , n (%)				
Well-controlled	14 (56.0)	21 (84.0)	35 (70.0)	.033
Uncontrolled	11 (44.0)	4 (16.0)	15 (30.0)	
Blood eosinophil, absolute count, n (%)				
<300 cells/μL	22 (32.4)	29 (41.4)	51 (37.0)	.271
≥300 cells/μL	46 (67.6)	41 (58.6)	87 (63.0)	
Sputum eosinophil, n (%)				
<2%	4 (22.2)	3 (15.8)	7 (18.9)	.622
≥2%	14 (77.8)	16 (84.2)	30 (81.1)	
FEV1, pred, n (%)				
FEV1 ≥ 80%	36 (42.4)	32 (40.5)	68 (41.5)	.960
60% ≤ FEV1 < 80%	31 (36.5)	29 (36.7)	60 (36.6)	
FEV1 < 60%	18 (21.1)	18 (22.8)	36 (22.0)	

Abbreviations: FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid.

[†]Exacerbations over 12 mo: one or more acute exacerbation events during the follow-up year.

[‡]Required dose of ICS indicates the dosage of ICS at registration and was confirmed by comparing with the equivalent budesonide dosage.

[§]Response to ICS was assessed by a clinician and patients were classified as follows: (a) well-controlled, and (b) uncontrolled response (defined as those who were not well-controlled at least once during regular follow-up [6 and 12 mo]), including partly controlled, uncontrolled, and exacerbated patients.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

KEYWORDS

allergic asthma, biomarker, inhaled corticosteroid, MRGPRX2, prognosis

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