

Skin prick test and serum specific IgE in predicting dust mite-induced allergic rhinitis diagnosed from nasal provocation test in chronic rhinitis children

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Abstract

Background: Allergen skin prick test (SPT) and serum specific immunoglobulin E (sIgE) are effective diagnostic tests in allergic rhinitis (AR), however, positive results may not always correlate with clinical allergies. A nasal provocation test (NPT) can identify the causative allergen for immunotherapy, but it's not routinely performed.

Objective: To establish the cutoff value for the house dust mite (HDM) SPT mean wheal diameter (MWD) and HDM sIgE level for identifying children with HDM-induced AR diagnosed from NPT.

Methods: Children aged 5 to 18 years old with chronic rhinitis were evaluated by HDM SPT, sIgE, and NPT. Children with positive NPT results indicated HDM-induced AR. The cutoff values of the HDM SPT and sIgE level for predicting positive NPT were determined using a receiver operating characteristic curve.

Results: A total of 245 children with a mean age of 9.53 ± 3 years were enrolled. HDM SPT results were positive (≥ 3 mm) in 160 (65.3%) children. HDM NPT results were positive in 176 (71.8%) children. Among children with positive HDM SPT ($n = 160$), 153 children (95.6%) were confirmed as having AR on NPT findings. The cutoff values for positive NPT responses were 6.6 mm for HDM SPT (yielding 100% specificity and 100% positive predictive value) and 17.0 kUA/L for sIgE (98.6% specificity and 99.2% positive predictive value).

Conclusions: This study proposes HDM SPT and sIgE cutoff values for use in the diagnosis of HDM-induced AR based on NPT. These cutoff values can be used to identify HDM-induced AR children who might benefit from immunotherapy.

Key words: nasal provocation test, house dust mite, skin prick test, serum specific IgE, allergic rhinitis

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Introduction

Rhinitis is broadly classified as allergic and nonallergic rhinitis, of which allergic rhinitis (AR) is nasal inflammation that immunoglobulin (Ig) E mediates to environmental allergens. Epidemiologic studies have demonstrated that a considerable part of the population suffers from AR and the prevalence of AR in children is growing in most countries.^{1,2} AR symptoms severely compromised children's quality of life.³

An accurate diagnosis and appropriate treatment, including specific allergen avoidance, could significantly improve the quality of life for children with AR.

The diagnosis of AR is usually made on the basis of a history of symptoms associated with causative allergen exposure in combination with evidence of aeroallergen sensitization as assessed by a skin prick test (SPT) or serum specific IgE (sIgE).^{4,5} However, positive findings from a SPT or the detection of sIgE to an aeroallergen may not always correlate with clinical allergic illness.⁶ A recent study found that 42% of patients with positive SPT results had no allergic symptoms related to the tested allergen.⁷ A nasal provocation test (NPT) is the standard method used for confirming the allergen responsible for AR symptoms. However, NPTs are not routinely employed in clinical practice because they are time consuming and require patient cooperation, which children especially may not provide. House dust mite (HDM) is the aeroallergen to which rhinitis patients in Southeast Asian countries, including Thailand, most commonly exhibit sensitization.⁸ The current study aimed to establish cutoff values for the HDM SPT mean wheal diameter (MWD) and sIgE level for identifying children with HDM-induced AR based on HDM NPT results.

Material and Methods

This retrospective study was conducted in the Pediatric Allergy and Immunology Unit, Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand. SPT, sIgE to HDM, and HDM NPT data obtained from children with rhinitis from 2017 to 2020 were reviewed. Study protocols were reviewed and approved by the Human Rights and Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (ID: MURA2021/750).

Study subjects

All chronic rhinitis children who were evaluated for SPT, sIgE to HDM, and HDM NPT at the Pediatric allergy clinic, Ramathibodi Hospital from 2017 to 2020 were included in the current retrospective study. All enrolled children had chronic rhinitis as defined by the presence of at least two nasal symptoms for at least 1 h per day for more than 12 weeks per year. All children reviewed for the current retrospective study were interviewed to obtain a detailed history, evaluated for rhinitis symptoms using a total nasal symptom score questionnaire (including nasal congestion, sneezing, nasal itching, and rhinorrhea), and had a nasal physical examination at their outpatient visit. Participant demographics and baseline characteristics, e.g., sex, age, allergic comorbidities, and total nasal symptom scores (TNSS) were recorded. The HDM NPT and SPT results and HDM sIgE levels were reviewed.

TNSS assessment

The TNSS is the total score for nasal congestion, sneezing, nasal itching, and rhinorrhea over the previous 12 h. It uses a four-point scale (0–3), where a score of 0 indicates no symptoms, 1 indicates mild symptoms, 2 indicates symptoms

that cause some problems but are tolerable, and 3 indicates severe symptoms that interfere with daily activity.

Skin prick test (SPT)

Each SPT was performed on the volar aspect of the forearm with a blood lancet (Feather Safety Razor, Osaka, Japan) using a positive control solution of 0.1% histamine, a negative control solution of normal saline, and 12 commercial extracts of aeroallergens (Johnson grass, Bermuda grass, Careless weed, *Cladosporium sphaerospermum*, *Alternaria*, *Aspergillus fumigatus*, *Curvularia*, American cockroach, German cockroach, cat hair, dog pelt, HDM [*Dermatophagoides pteronyssinus*]) (ALK-Abello Pharm., Inc., USA). The wheal size was assessed after 15 min, and a positive SPT result was defined as a wheal diameter that was 3 mm larger than that produced by the negative control.

Specific IgE measurement

The serum levels of sIgE to HDM allergen [Der p (d1)] were analyzed with Immunocap (Phadia, Biomed Diagnostics, Bangkok, Thailand); levels of > 0.35 kUa/L were considered positive.

HDM nasal provocation test (NPT)

A NPT to Der p was performed on all participants. The NPT protocol was based on our previous report.⁹⁻¹¹ Using 0.9% NaCl as a negative control, the Der p allergen extract was delivered to both nostrils at concentrations of 50, 200, 500, and 2,000 AU/ml at 15-min intervals to determine the maximum tolerated dosage. Total nasal symptom scores for 5 symptoms (sneezing, nasal pruritus, rhinorrhea, nasal obstruction, and ocular symptoms), peak nasal inspiratory flow (PNIF), and nasal airway resistance were recorded during NPT. NPT results were considered positive if one of the following criteria were met: 1) the PNIF/nasal airway resistance flow was changed by at least 20% from the baseline value, plus change in the total nasal symptom scores from the baseline value by at least 3 points, 2) the PNIF/nasal airway resistance flow was changed by at least 40% of the baseline value, regardless of the total nasal symptom scores.⁹⁻¹¹

Statistical analysis

Demographic data were presented as the mean \pm SD, median (IQR), or frequency (percent). To compare a difference among continuous variables, a Student's *t*-test or Mann-Whitney U-test was used. Receiver operating characteristic (ROC) curves were used to assess the performance of HDM SPT and sIgE assessment in the diagnosis of HDM-induced AR using NPT as the reference test. The optimal cutoff values for the HDM SPT MWD and sIgE level were derived from the ROC curve with the shortest distance to sensitivity and specificity with the maximum value of the Youden index. Data analysis was conducted using the SPSS 18.0 (IBM, Chicago, IL, USA) and STATA 16.0 software package. *P*-values of < 0.05 were considered to indicate statistical significance.

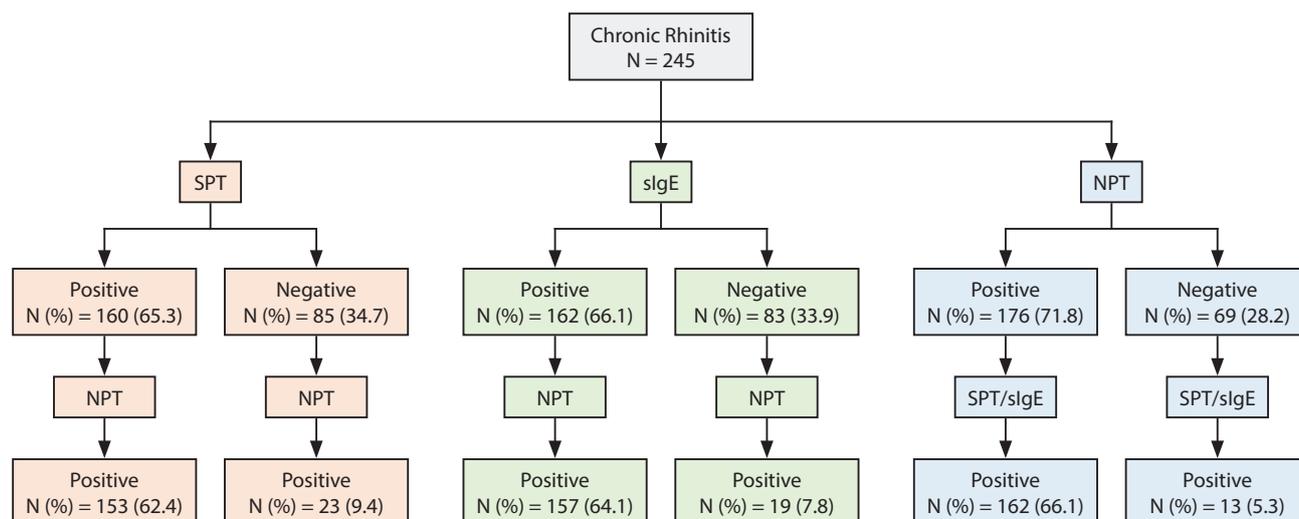


Figure 1. Diagram illustrating the results of three investigations on children with chronic rhinitis: HDM skin prick test (SPT), specific immunoglobulin E (sIgE) to HDM, and nasal provocation test (NPT) to HDM.

Results

The mean age of the 245 enrolled children with chronic rhinitis, 119 (48.6%) of whom were male, was 9.53 ± 2.97 years. HDM SPT results were positive in 160 (65.3%) children (median of MWD: 4.5 [0–8.0] mm), and 162 (66.1%) children were positive for sIgE to HDM (median level: 13.4 [0–70.9] kUA/L). HDM NPT results were positive in 176 (71.8%) children (**Figure 1**). Among 160 children with positive SPT to HDM, 153 of them (95.6%) had positive results for NPT. While 85 children had a negative SPT, 23 (27.1%) had a positive NPT. Regarding sIgE, 157 (96.9%) of 162 children with positive sIgE to HDM had positive NPT findings. Whereas 19 (22.9%) of 83 children with a negative sIgE to HDM had a positive NPT. The maximum tolerated dose of HDM was 50 Au/ml in 110 (44.9%) children and 200 Au/ml in 41 (16.7%), and that of Der p was 500 Au/ml in 22 (9%) children and 2000 Au/ml in 3 (1.2%) children. Rhinitis children with positive NPT to HDM have significantly higher TNSS and allergic comorbidities, including allergic conjunctivitis, atopic dermatitis, and food allergy than those with negative NPT to HDM. (**Table 1**).

HDM SPT MWD and sIgE level cutoff values for detecting HDM-induced AR according to NPT

A ROC curve was generated to determine the HDM SPT MWD and sIgE level for achieving 99% predicted probability of HDM-induced AR as assessed by NPT. A HDM SPT MWD of 6.6 mm provided a specificity of 100%, positive predictive value (PPV) of 100%, sensitivity of 50.6%, negative predictive value (NPV) of 44.2%, and accuracy of 64.5% for diagnosis of HDM-induced AR according to NPT, with an area under the curve (AUC) of 0.753 (95% confidence interval [CI]: 0.716–0.790). A sIgE to HDM of 17.0 kUA/L provided a specificity of 98.6%, PPV of 99.2%, sensitivity of 67.05%, NPV of 54%, and accuracy of 75.92%, with an AUC of 0.828 (95%CI: 0.790–0.866) (**Figure 2**).

Table 1. Comparison of demographic characteristics of patients who positive and negative NPT.

	Positive NPT to HDM (N = 176)	Negative NPT to HDM (N = 69)	P value
Age (years)	9.67 (2.93)	9.17 (3.04)	0.229
Gender: male	82 (46.59)	37 (53.62)	0.322
MWD Der p (mm)	7.0 (4.0, 8.5)	0 (0.0, 0.0)	< 0.001
MWD Der f (mm)	6.8 (4.0, 9.4)	0 (0.0, 0.0)	< 0.001
sIgE Der p (kUA/L)	40.8 (6.1, 95.6)	0 (0.0, 0.1)	< 0.001
Allergic comorbidities			
- Allergic conjunctivitis	68 (38.64)	11 (15.94)	0.001
- Atopic dermatitis	33 (18.75)	4 (5.79)	0.011
- Food Allergy	10 (5.68)	0 (0.00)	0.043
TNSS ^a	3.0 (1.8, 5.2)	1.2 (0.6, 3.0)	0.002

Data was presented as mean (SD), N (%) and median [IQR]

^aTotal nasal symptom score was recorded in 132 children (105 children with positive NPT to HDM).

Abbreviations: NPT, nasal provocation test; TNSS, total nasal symptom score; MWD, mean wheal diameter; sIgE, specific immunoglobulin E; Der p, *Dermatophagoides pteronyssinus*; Der f: *Dermatophagoides farinae*;

Agreement between sIgE and SPT results

Of the 162 children positive for sIgE to Der p, 151 (93.2%) had positive HDM SPT results. Additionally, of the 160 children with positive HDM SPT results, 151 (94.4%) were positive for sIgE. The Kappa agreement between sIgE and HDM SPT was 0.819 ($p < 0.001$).

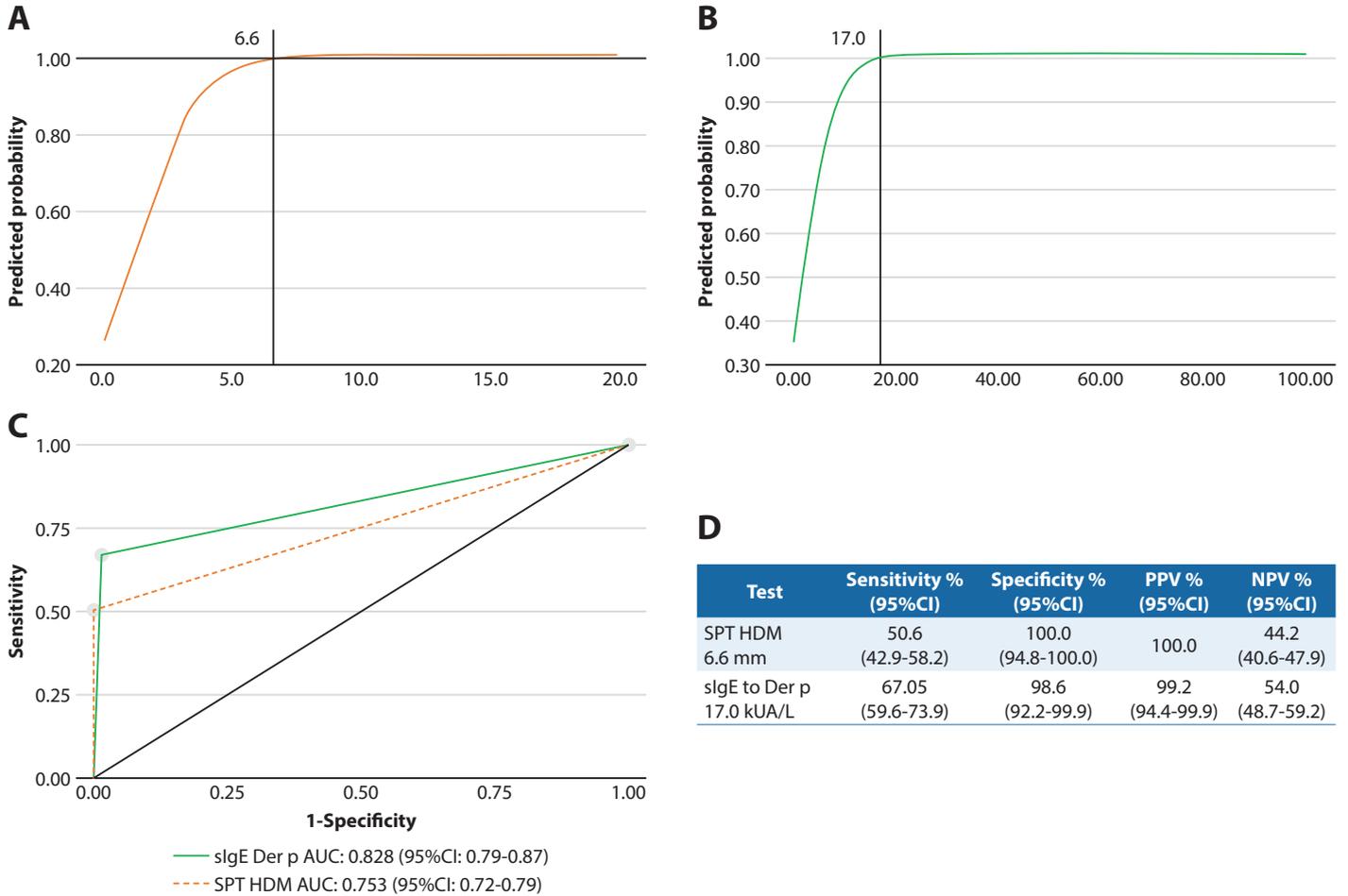


Figure 2. Cutoff for 99% predicted probability for positive HDM NPT A) the MWD of HDM SPT B) the level of specific immunoglobulin E (sIgE) to Der p. C) ROC curve for HDM-induced AR diagnosis based on NPT results using SPT MWD of HDM, and specific IgE to Der p. D) The accuracy of MWD of HDM SPT and Der p sIgE cutoff values based on HDM NPT.

Abbreviations: SPT, skin prick test; sIgE, specific immunoglobulin E; HDM, house dust mite; PPV, positive predictive value; NPV, negative predictive value; 95%CI, 95% confident interval; AUC, area under the curve;

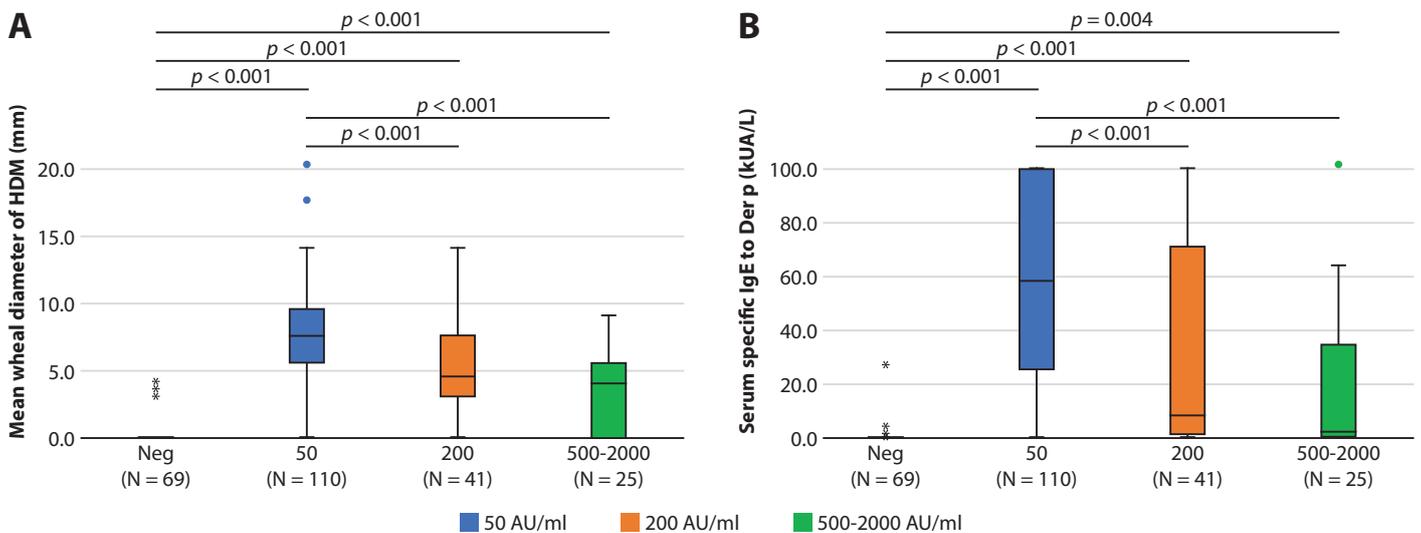


Figure 3. Comparison of A) MWD of HDM SPT B) serum specific immunoglobulin E to Der p and the maximum tolerated doses of HDM NPT.

Abbreviations: MWD, mean wheal diameter; SPT, skin prick test; sIgE, specific immunoglobulin E; Der p, *Dermatophagoides pteronyssinus*; NPT, nasal provocation test;

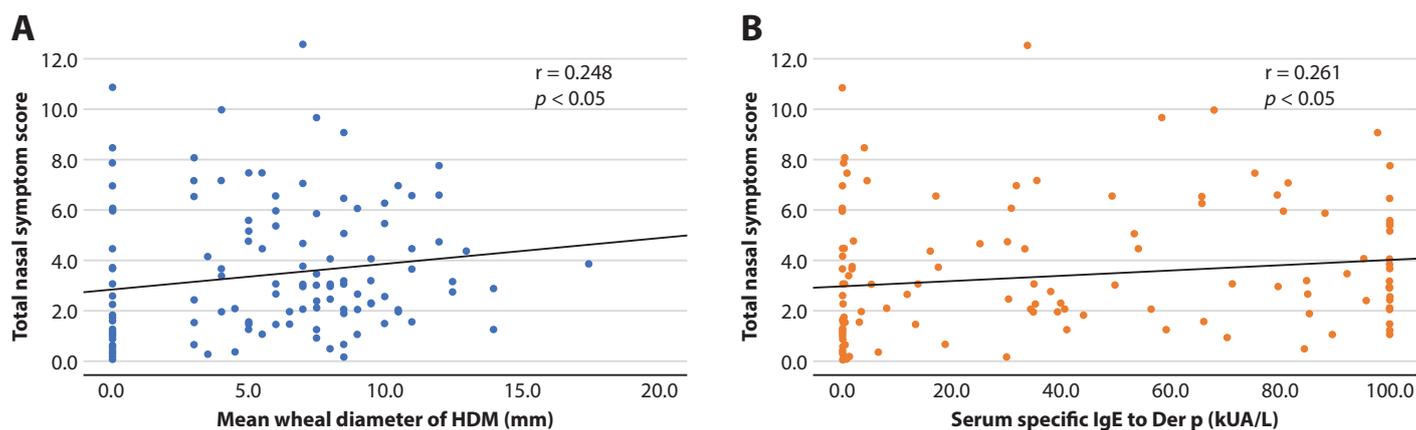


Figure 4. Dot plots show the correlations between TNSS and A) SPT MWD of HDM and B) serum specific IgE to Der p.

Abbreviations: TNSS, total nasal symptom score; SPT, skin prick test; sIgE, specific immunoglobulin E; Der p, *Dermatophagoides pteronyssinus*; MWD, mean wheal diameter;

Comparison of HDM SPT MWD, HDM sIgE level, and HDM NPT result

Children who had positive NPT results at a dose of 50 Au/ml had a significantly larger HDM SPT MWD compared with children who had a higher positive NPT dose ($p < 0.001$) (Figure 3A). Likewise, individuals who had a low positive NPT dose had a significantly higher level of Der p sIgE ($p < 0.001$) (Figure 3B). Patients with negative NPT results or positive NPT results at doses of 50, 200, or 500–2,000 Au/ml had HDM SPT MWDs of 0 (IQR 0.0–0.0) mm, 7.5 (5.5–9.5) mm, 4.5 (3.0–7.8) mm, and 4.0 (0.0–5.5) mm, respectively. Patients with negative NPT results or positive NPT at doses of 50, 200, or 500–2,000 Au/ml had a median level of sIgE to Der p of 0.0 (IQR: 0.0–0.1) kUA/L, 57.8 (24.8–100.0) kUA/L, 8.1 (0.8–76.4) kUA/L, and 2.0 (0.1–34.8) kUA/L, respectively.

Correlation between rhinitis severity and HDM SPT MWD, Der p sIgE level, and NPT result

A subgroup analysis was performed on the 132 children who had recorded TNSS. The median TNSS was 2.77 (1.4–4.7). The TNSS had a weak correlation with the HDM SPT MWD and sIgE level ($r = 0.248$, $p < 0.05$; $r = 0.261$, $p < 0.05$, respectively) (Figure 4), but no significant correlation with the maximum tolerated NPT dose.

Discussion

This study established HDM SPT MWD and sIgE level cutoff values for predicting HDM-induced AR according to HDM NPT results for children presenting with chronic rhinitis. The HDM SPT MWD cutoff value of 6.6 mm provided 100% specificity and PPV. Our results indicate that for children with chronic rhinitis who have a HDM SPT MWD above 6.6 mm, HDM is likely the causative allergen for their rhinitis symptoms. Notably, NPT is more difficult to perform in children than in adults, so it would be preferable to use cutoff value instead of NPT testing in this population. However, to the best of our knowledge, no previous study in rhinitis children has established a cutoff value for confirming HDM-induced AR based on the results of HDM NPT.

Our result differs slightly from that of a recent study in adults and children who presented with chronic rhinitis, in which Xiao et al found that the optimal cutoff value for Der p SPT was 5.5 mm, with a sensitivity and specificity of 92.5% and 64.7%, respectively.¹² Haxel et al. found that 80% of adults with clinically suspected HDM allergy and a MWD for Der p of > 5 mm had positive NPT results.¹³ However, these minor differences in cutoff levels may be explained by the age groups of the study participants. Xiao et al. investigated patients aged 5–60 years, but the majority of them were adults, whereas Haxel et al. examined only adults; in contrast, our study focused only on children. According to prior research, SPT wheal size is often smaller in senior individuals, indicating that there may be age-dependent differences in SPT wheal size.^{14–16}

Additionally, we purposed a sIgE to Der p cutoff value of 17.0 kUA/L, with a specificity and PPV of 98.6% and 99.2%, respectively. Our finding suggests that if we use this cutoff value without performing a NPT, we could still determine if HDM is the true causal allergen of the patient. This finding differs from earlier studies. Xiao et al., who studied primarily adult patients, identified a sIgE to Der p cutoff value of 2.77 kUA/L for a NPT-positive response, with a sensitivity of 76.7% and specificity of 72.5%.¹² Other research conducted on AR in children and adults but using methods other than NPT revealed some different values, such as a sIgE to Der p cutoff value of 0.69 kU/L for diagnosing AR based on SPT results¹⁷ and a cutoff level of 8.4 kU/L for diagnosing AR based on history and questionnaire.¹⁸ Possible reasons for this difference in cutoff values include the variations in study participant age groups and the method used as the criteria standard. Furthermore, allergen sIgE levels have been found to decline with age.^{19,20}

In this study, among the 160 children with positive HDM SPT results (≥ 3 mm), 7 (4.4%) had negative HDM NPT results, indicating asymptomatic HDM sensitization. However, of the 89 children with a HDM SPT MWD of > 6.6 mm (our cutoff level), all had positive NPT results (false-positive rate: 0%). Using our HDM SPT cutoff value

could help to differentiate symptomatic AR from asymptomatic HDM sensitization. For example, by applying our HDM SPT cutoff value in this study, we can reduce the number of HDM NPT 89 situations. Similar results were observed for serum sIgE testing. Among the 162 children with positive sIgE to HDM (≥ 0.35 kUA/L), 5 (3.1%) had negative HDM NPT results, indicative of silent HDM sensitization. In contrast, 118 of 119 children with Der p sIgE levels of > 17.0 kUA/L (our cutoff level) exhibited positive NPT results, and only 1 (0.8%) had silent HDM sensitization. By applying our cutoff Der p sIgE level in this study, we can limit the number of HDM NPT 118 occasions. Our findings indicate that we can use these cutoff values to identify HDM-induced AR patients who are suitable for undergoing allergen immunotherapy without performing a NPT. Additionally, SPTs and blood tests are frequently performed to identify allergies. While SPTs are less expensive and provide faster results, they require trained staff; alternatively, serum allergen sIgE testing is more costly but does not interfere with medication. Even though the NPT is the diagnostic gold standard for AR, it is impractical in general practice. Our proposed SPT and sIgE to HDM cutoff value could be a tool for general pediatricians to confirm HDM as a causative allergen for children's rhinitis symptoms, particularly in those with multiple allergen sensitization. Knowing accurate causative allergen leads to appropriate allergen avoidance and environmental control.

Although it is often not practical to apply NPT clinically, a NPT should be used as a diagnostic confirmation of AR when the allergen is highly suspected of being causative for rhinitis symptoms but the SPT or sIgE result is negative. In this study, 16 (21.6%) of 74 children with negative results for both HDM SPT and sIgE had positive NPT results. These cases may be explained by local AR.²¹ With them, a NPT with the suspected allergen should be performed to confirm the diagnosis, as positive NPT results are associated with more successful therapy.

Regarding the comparison between NPT response and degree of HDM sensitization, this study found that the maximum tolerated dose of NPT was in line with the HDM SPT MWD and level of sIgE for Der p, which is consistent with previous studies.^{22,23} However, we found that TNSS had a weak correlation with the HDM SPT MWD and serum sIgE level. When adults with HDM allergies were studied previously, no association was found,²³⁻²⁵ but there was controversy regarding this conclusion.²⁶ Notably, a previous study in children with HDM allergies demonstrated a correlation between AR severity and HDM SPT MWD or sIgE level.²⁷ Nonetheless, our findings revealed only a weak correlation; future extensions of our studies might verify this association in children.

The main strength of this study is that it included all children who presented with chronic rhinitis. Thus, it included children who had no evidence of sensitization but were eventually diagnosed with local allergic rhinitis (LAR). Unlike prior studies that relied on history of rhinitis symptoms and evidence of allergen sensitization, in this study, all children with rhinitis were assessed for allergen sensitization via SPT and a blood test for sIgE, and the clinical significance of sensitization was confirmed by NPT. Furthermore, the NPT procedure used here evaluated both subjective and objective data to maximize testing accuracy. The NPT results were interpreted using nasal and ocular symptom scores, PNIF, and rhinomanometry. Our study limitation is that most of the children with chronic rhinitis who were included in our study had only done NPT to HDM allergen, so they may have had concurrent sensitization to other aeroallergens that we did not do NPT. However, because HDM is the most common allergen in Southeast Asian countries, the number of AR children caused by other allergens is considered to be low. Since most of our patients with positive SPT results were also sensitive to HDM, it's likely that there were not many children with rhinitis who had negative HDM NPT but rhinitis from other allergens. Therefore, the study patients could represent the general pediatric population with HDM-induced nasal allergies. Further study with a larger sample size is needed to validate our proposed cutoff values.

In conclusion, this study proposed a HDM SPT MWD and a serum Der p sIgE level cutoff value in the diagnosis of HDM-induced AR based on NPT. Our cutoff values could help to identify children with HDM-induced AR, without the need for NPT, who would benefit from allergen immunotherapy.

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Declaration of Conflicting Interests

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