# Diagnostic accuracy and safety of *Dermatophagoides pteronyssinus* extracts used for skin prick test

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**Abstract**

**Background:** *Dermatophagoides pteronyssinus* is a common allergen causing allergic diseases in China. The aim of this study was to evaluate the efficacy and safety of *D. pteronyssinus* extracts produced by Peking Union Medical College Hospital (PUMCH) for the skin prick test (SPT) in the diagnosis of *D. pteronyssinus* allergy.

**Methods:** A total of 910 subjects with allergic diseases were prescribed *D. pteronyssinus* SPT and specific sIgE (sIgE) test among the Outpatients of Department of Allergy, PUMCH from August 10, 2015 to August 30, 2017. Receiver operating characteristic curve (ROC) analysis was performed according to the results of *D. pteronyssinus*-sIgE detection. The accuracy of *D. pteronyssinus* extracts used for SPT in the diagnosis of *D. pteronyssinus* allergy was evaluated under different cutoff values. Adverse events after SPT were recorded to evaluate safety.

**Results:** There were 796 and 618 subjects in the full analysis set (FAS) and the per protocol set (PPS), respectively. The areas under the curve of FAS and PPS were 0.871 and 0.873, respectively. According to the ROC of PPS, the optimal and 95% specificity diagnostic cutoff values of *D. pteronyssinus* SPT mean wheal diameter were 3.25 and 3.75 mm, respectively. No adverse events occurred.

**Conclusion:** The extracts of *D. pteronyssinus* for SPT were simple, highly accurate, and safe and should be considered for recommendation in the clinical diagnosis of *D. pteronyssinus* allergy.

**Keywords:** *Dermatophagoides pteronyssinus*; Allergen extract allergy; Skin prick test; Immunoglobulin E; Allergy

## Introduction

Dust mites are one of the most commonly inhaled allergens. It was reported that *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* were the most common mites.[1,2] *D. pteronyssinus* is a common allergen causing allergic diseases in China. From January 2015 to December 2016, Wang *et al*[3] conducted skin prick tests (SPTs) with 19 kinds of inhaled allergens in 2416 patients with suspected allergic rhinitis in Central China, and the sensitization rate to house dust mites was as high as 67.5%. A 200,000-fold increase in specific IgE (sIgE) test results based on the outpatient department found that the positive sensitization rate to dust mites in inhaled allergens was as high as 38.4%.[4]

Skin tests are commonly used to diagnose allergic diseases, including intradermal tests and SPTs. The SPT is widely used in clinical practice for the diagnosis of allergic diseases caused by type I hypersensitivity, such as rhinoconjunctivitis, asthma, and urticaria, due to its minimal invasiveness, simple operation, high repeatability, high safety, and low price.[5,6] However, the SPT is rarely used in clinical practice in China, and a standard allergen extracts for SPT is lacking. At present, the diagnostic standard of the SPT is 3 mm,[7,8] but some studies believe that a sensitivity of 3 mm is not high enough.[9]

The purpose of this study was to evaluate the diagnostic accuracy and safety of Peking Union Medical College

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**Table 1: Content of the main allergen proteins in PUMCH allergen extracts of *Dermatophagoides pteronyssinus*.**

| Items | Manufactor | Article number | Batch number | Content of main allergen proteins (μg/mL) |
|---|---|---|---|---|
| Der p 1 test kit | Indoor | EL-DP1A | 39361 | 2.80 |
| Der p 2 test kit | Indoor | EL-D2 | 42506 | 2.39 |

PUMCH: Peking Union Medical College Hospital.

**Table 2: Research process.**

| Content | Screening | Estimation | |
|---|---|---|---|
| | | Follow-up 1 (same day) | Follow-up 2 (the next day) |
| Medical history | × | | |
| Intradermal test or sIgE results | × | | |
| Informed consent | × | | |
| Prick results | | × | |
| Prick result record | | × | |
| *Dermatophagoides pteronyssinus* sIgE | | × | |
| Adverse event records | | ×* | ×† |
| Compliance evaluation | | × | × |

* Adverse events occurring on the same day as the SPT, 15 min and 1 h after pricking. † Adverse events occurring on the day after the SPT and 6 h after pricking. × This symbol indicates that the row step was finished at the column time. sIgE: Specific IgE; SPT: Skin prick test.

Hospital (PUMCH) *D. pteronyssinus* allergen extracts used in SPTs with sIgE as diagnostic criteria and to explore its diagnostic cutoff value.

## Methods

### Ethical approval

This study was approved by the ethics committee of PUMCH (No. JS-858). We confirmed that this research was performed in accordance with relevant guidelines/regulations and confirmed that informed consent was obtained from all participants and/or their legal guardians.

### Patients

All participants were outpatients of the Department of Allergy, PUMCH, from August 10, 2015 to August 30, 2017. The participants were diagnosed with allergic diseases by allergists, including allergic rhinitis, allergic asthma, allergic conjunctivitis, and atopic dermatitis, among others. Inclusion criteria were four- to 70-year-old patients; patients who finished the *D. pteronyssinus* intradermal test or sIgE test. Exclusion criteria were pregnant and lactating women; patients who did not stop taking antihistamines before the trial or whose withdrawal time was less than five half-lives of antihistamines; those who were taking systemic glucocorticoids; patients for which skin scratch signs were positive; patients with skin infection, dermatitis, trauma, scarring, and other pathological changes at the test site; patients with psoriasis; patients with acute episodes of allergic diseases (such as acute episodes of allergic asthma); patients with serious diseases (including severe hypertension and coronary heart disease) that affect the whole body; those who were currently in use of β receptor blocker therapy (including local application); those who had participated in clinical trials of other drugs within 3 months; and other circumstances that the researchers considered unsuitable for the trial. Data culling criteria were those who did not meet the inclusion or exclusion criteria; the results of sIgE were absent; SPT data were missing; the mean wheal diameter (MWD) of the SPT positive control was less than 3 mm, or the MWD of the negative control was equal to or more than 3 mm. Subjects were divided into groups according to sIgE of *D. pteronyssinus*. The positive group was sIgE ≥0.35 kUA/L, and the negative group was sIgE <0.35 kUA/L.

### SPTs

All participants underwent SPTs with *D. pteronyssinus* extracts, a negative control, and a positive control simultaneously. All materials were prepared in the allergen preparation room of PUMCH and kept at 2 °C to 8 °C for a long time. The contents of the main allergen proteins in PUMCH allergen extracts of *D. pteronyssinus* are shown in Table 1. The negative control was allergen preparation buffer glycerin, and the positive control was 5 mg/mL histamine phosphate. The chip pricking needle was purchased from Huaian Blue Star Plastic Instrument Development Co., Ltd (Huaian, China).

The research process is shown in Table 2, and SPTs were carried out according to European standards.[6] SPTs were performed on the palm of the forearm, at least 2 to 3 cm away from the wrist and anterior cubital fossa. The distance between the two prick tests was 2 cm to avoid cross-interference. The results were observed after 15 min of pricking and continuously observed for 1 h. The results of pricking were judged by the size of the wheal and expressed by the MWD. MWD = (D + d)/2, where D is the longest diameter of the wheal and d is the diameter obtained by taking the midpoint of D as the vertical line. Adverse events were recorded 15 min, 1 h, and 6 h after

pricking. Serum sIgE was detected by a Phardia 1000 system from Thermo Company (Waltham, USA).

### Statistical analysis

According to the following equation, the sample size of the positive group was calculated using sensitivity, and the sample size of the negative group was calculated using specificity.

$$n = \frac{Z^2_{1\alpha/2}P(1P)}{\Delta^2}$$

Formula $n$ was the sample size of the positive group/negative group. $Z_{1\text{-}\alpha/2}$ was the quantile of the standard normal distribution. $P$ was the expected value of sensitivity or specificity, and $\Delta$ was the allowable error size of $P$. $\Delta = 0.05$, when $\alpha = 0.05$ (bilateral), $Z_{1\text{-}\alpha/2} = 1.96$. The expected sensitivity and specificity were set according to similar products on the market.[10,11] The expected sensitivity was 70.0%, with a minimum sample size of 323 cases in the positive group. The expected specificity was 90.0%, with a minimum sample size of 139 cases in the negative group.

All data were analyzed by SPSS 22.0 (IBM, Armonk, USA). The receiver operating characteristic curve (ROC) was analyzed with sIgE as the gold standard to evaluate the specificity and sensitivity of different diagnostic cutoff values of SPT. Data related to adverse events were expressed separately.

## Results

### General information

A total of 910 participants were enrolled in this study. There were 910 participants in the safe set (SS), among which 114 participants were not included in the full analysis set (FAS) due to the lack of sIgE results, and 796 cases were included in the FAS. On this basis, 60 participants who did not meet the inclusion criteria were culled. Eighty participants with negative reactions to the positive control and 86 participants with positive reactions to the negative control were also culled. There was a partial overlap in the culled participant data. A total of 618 participants finally met the per protocol set (PPS).

The average age of the participants in FAS was 24.1 ± 14.5 years. The age range was 4.0 to 66.9 years. There were 458 males (57.5%) and 338 females (42.5%). The MWD of the SPT histamine positive control was 4.43 ± 1.26 mm, with a median of 4.5 mm, a minimum of 0.5 mm, and a maximum of 11.0 mm.

### Diagnostic accuracy evaluation

With the sIgE results of *D. pteronyssinus* as criteria, the ROC analysis of SPTs with PUMCH *D. pteronyssinus* allergen extracts was carried out. The results are shown in Supplementary Figure 1, http://links.lww.com/CM9/B304. The areas under the curve (AUC) of FAS was 0.871, and the 95% confidence interval (95% confidence interval [CI]) was 0.845 to 0.897; the AUC of PPS was 0.873, 95% CI 0.844 to 0.903.

According to the analysis of the PPS ROC curve, the optimal diagnostic cutoff value of SPTs for *D. pteronyssinus* was an MWD of 3.25 mm, with a specificity of 90.85% (95% CI 86.44%–92.57%) and a sensitivity of 72.03% (95% CI 67.90%–76.16%). When the diagnostic specificity was 95%, the diagnostic cutoff value had an MWD of 3.75 mm. Tables 3 and 4 show the accuracy of SPT with PUMCH *D. pteronyssinus* allergen extracts in the diagnosis of allergies in PPS when the MWD was 3, 3.25, and 3.75 mm, respectively.

### Safety evaluation

There were 910 participants with SS, and no adverse events occurred.

## Discussion

This study evaluated one kind of *D. pteronyssinus* allergen extract product for SPTs, which targeted the most common allergen in China, and was conducted in an experienced allergy medical center. The diagnostic accuracy and safety of the participants were both satisfactory. In addition, this study also discovered that the optimal MWD cutoff of SPT might not be the traditional cutoff of 3 mm, but is instead 3.25 mm.

This allergen extract caters to the huge need for inexpensive, localized puncture products in China. Skin testing was first reported by Charles Blackley in 1867, and now it has developed into a reliable, economic, and effective technology for the diagnosis of IgE-mediated allergic diseases. In China, intradermal testing has been widely used for many years. However, some research indicated that intradermal testing should be the next step of SPT.[12] Compared with the prick test, intradermal testing has higher sensitivity and

**Table 3: Case distribution of PUMCH allergen extracts of *Dermatophagoides pteronyssinus* used for SPTs in the diagnosis of *Dermatophagoides pteronyssinus* allergy (case distribution of PPS).**

| | | SPT | | |
|---|---|---|---|---|
| MWD | sIgE | Positive | Negative | Total |
| 3.00 mm | Positive | 356 | 98 | 454 |
| | Negative | 32 | 132 | 164 |
| | Total | 388 | 230 | 618 |
| 3.25 mm | Positive | 327 | 127 | 454 |
| | Negative | 15 | 149 | 164 |
| | Total | 342 | 276 | 618 |
| 3.75 mm | Positive | 292 | 162 | 454 |
| | Negative | 8 | 156 | 164 |
| | Total | 300 | 318 | 618 |

MWD: Mean wheal diameter; PPS: Per protocol set; PUMCH: Peking Union Medical College Hospital; sIgE: Specific immunoglobulin E; SPT: Skin prick test.

**Table 4: Accuracy of PUMCH allergen extracts of *Dermatophagoides pteronyssinus* used for SPTs in the diagnosis of *Dermatophagoides pteronyssinus* allergy (PPS).**

| MWD | Index | Sensitivity (%) | Specificity (%) | Concordance rate | Positive predictive value | Negative predictive value |
|---|---|---|---|---|---|---|
| 3.00 mm | Estimated value | 78.41 | 80.49 | 78.96 | 91.75 | 57.39 |
| | Standard error | 0.02 | 0.03 | 0.02 | 0.01 | 0.03 |
| | Lower limit of 95% CI | 74.63 | 74.42 | 75.75 | 89.02 | 51.00 |
| | Upper limit of 95% CI | 82.20 | 86.55 | 82.18 | 94.49 | 63.78 |
| 3.25 mm | Estimated value | 72.03 | 90.85 | 77.02 | 95.61 | 53.99 |
| | Standard error | 0.02 | 0.02 | 0.02 | 0.01 | 0.03 |
| | Lower limit of 95% CI | 67.90 | 86.44 | 73.71 | 93.44 | 48.11 |
| | Upper limit of 95% CI | 76.16 | 95.27 | 80.34 | 97.78 | 59.87 |
| 3.75 mm | Estimated value | 64.32 | 95.12 | 72.49 | 97.33 | 49.06 |
| | Standard error | 0.02 | 0.02 | 0.02 | 0.01 | 0.03 |
| | Lower limit of 95% CI | 59.91 | 91.83 | 68.97 | 95.51 | 43.56 |
| | Upper limit of 95% CI | 68.72 | 98.42 | 76.01 | 99.16 | 54.55 |

CI: Confidence interval; MWD: Mean wheal diameter; PPS: Per protocol set; PUMCH: Peking Union Medical College Hospital; SPT: Skin prick test.

lower specificity, and the dosage is larger, which leads to more false-positive results when using an intradermal test.[5,13] Moreover, intradermal testing is more difficult. The SPT, as a widely used allergen *in vivo* test method,[14,15] is rarely used in China and lacks inexpensive localized puncture allergen extracts. Therefore, this study evaluating a new allergen extract for SPTs met the need for such extracts in the Chinese SPT field.

The detection of sIgE of *D. pteronyssinus* was used as the gold standard in this study. There were two reasons for using this method. One was that Thermo's ImmunoCAP system had good repeatability and clinical relevance in the *in vitro* detection of serum allergen sIgE.[16-19] The other was that a large number of clinical studies have shown that the results of serum allergen sIgE detection were in good agreement with the SPT results,[15,20-22] which was recognized as the gold standard of allergen *in vitro* diagnosis in the field. Although the provocation test is the gold standard for the diagnosis of allergic diseases, it lacks standardized clinical procedures in China and has the risk of inducing severe allergic reactions. Therefore, this study evaluated the effectiveness and safety of SPTs in the diagnosis of *D. pteronyssinus* allergy based on the results of serum allergen sIgE detection by the ImmunoCAP system.

We adopted strict operational quality control in the SPT method. In addition to the allergen allergy itself, the accuracy of the SPT results is affected by many factors, including skin reactivity, age,[23] medication,[24] needle material,[25] and manipulation.[26] The purpose of the skin scratch test is to exclude false-positive results caused by a positive skin scratch sign. In addition, positive control and negative control were performed simultaneously to ensure the accuracy of the SPT results. Medication can cause negative reactions in positive controls, especially antihistamines. Therefore, this study required patients to stop taking medication for more than five half-lives before receiving the prick test. The chip pricking needle used in this study was the only pricking needle with a medical device registration certificate in China, although it was not a special allergen pricking needle; this lack of a specialized needle may have led to false negatives or false positives, where too light of a pricking force may have caused a false negative, and too heavy of a pricking force may have caused a false positive. Therefore, the participant data with unqualified results were screened out of this study, but there was little influence on the analysis results before and after screening.

The diagnostic accuracy of these allergen extracts was satisfactory in the ROC analysis. In this study, the AUC of FAS was 0.871, close to 0.9, and the 95% CI was 0.845 to 0.897, which indicated that the PUMCH allergen extracts of *D. pteronyssinus* had high accuracy in diagnosis. In 2019,[22] Nicola Wagner reported that the AUC of the SPT for *D. pteronyssinus* allergy diagnosis was 0.84, 95% CI 0.80 to 0.88, which was close to the result of this study [Table 5].

According to the ROC curve, the best diagnostic cutoff value was estimated to be an MWD of 3.25 mm, while the internationally recommended diagnostic cutoff value was generally an MWD of 3 mm. In a study including 529 children in Singapore, the highest agreement ($\kappa = 0.44$) was found with a cutoff value of 3 and 5 mm for SPT.[27] In this study, when an MWD of 3 mm was used as the diagnostic cutoff, the sensitivity was 78.41% (95% CI 74.63%–82.20%), with a specificity of 80.49% (95% CI 74.42%–86.55%). Using 3.25 mm MWD as the cutoff, the specificity was 90.85%, 95% CI 86.44%–95.27% with a sensitivity of 72.03%, 95% CI 67.90%–76.16%. Compared to the preset sensitivity of 70.0% and specificity of 90.0% in the sample size calculation in the "Methods" section, the actual sensitivity and specificity were satisfactory. The cutoff of 3.25 mm resulted in higher specificity but a slightly lower sensitivity. It is important to take measures to balance the sensitivity and specificity in clinical practice.

To balance the sensitivity and specificity, it was necessary to adapt stratified diagnostic steps according to the size of the MWD. If there was a relevant clinical history, the results of MWD ≥3.25 mm obtained by using SPT with

**Table 5: Studies describing the diagnostic accuracy of *Dermatophagoides pteronyssinus* allergen extracts for SPTs.**

| Author-year | Country | Sample size | AUC (95% CI) | Cutoff (mm) | Sensitivity (%), 95% CI | Specificity (%), (95% CI) |
|---|---|---|---|---|---|---|
| This study | China | 910 | 0.871 (0.845–0.897) | 3.25 | 72.03 (67.90–76.16) | 90.85 (86.44–95.27) |
| Wagner and Rudert (2019)[22] | Germany | 387 | 0.84 (0.80–0.88) | 3.00 | 71.7* | 91.5* |
| Chauveau *et al* (2017)[27] | Singapore | 529 | 0.58 (0.51–0.64) | 3.00 | 58.2* | 76.5* |
| Wu *et al* (2001)[10] | Denmark | 95 | NR | 3.00 | 83.58* | 78.57* |
| | China | 95 | NR | 3.00 | 80.60* | 96.40* |
| Visitsunthorn *et al* (2017)[11] | America | 84 | NR | 3.00 | 98.67* | 0* |
| | Thailand | 84 | NR | 3.00 | 100* | 0* |

* 95% CI was not reported. AUC: Areas under the curve; CI: Confidence interval; NR: Not report; SPT: Skin prick test.

**Table 6: Main allergen protein concentrations of major *Dermatophagoides pteronyssinus* allergen extracts on the market.**

| Author-year | Country | Manufacturer | Der p 1 (μg/mL) | Der p 2 (μg/mL) |
|---|---|---|---|---|
| This study | China | PUMCH | 2.80 | 2.39 |
| Huber *et al* (2021)[28] | Indian | M1- Creative Diagnostic Medicare Pvt. Ltd. | 0 | 0 |
| | | M2a- All Cure Pharma Pvt. Ltd. | 0 | 0 |
| | | M2b- All Cure Pharma Pvt. Ltd. | 0 | 0 |
| | | M3- Alcit Pvt. Ltd | 0 | 0 |
| González-Pérez *et al* (2019)[29] | Spain | Extract 1: Diater, | 1.21 | 4.22 |
| | | Extract 2: ALK-Abello | 11.95 | 9.12 |
| | | Extract 3: Leti | 26.25 | 20.49 |
| | | Extract 4: Stallergenes-Greer | 3.06 | 6.06 |
| | | Extract 5: Rox- all | 30.16 | 1.93 |
| | | Extract 6: Inmunotek | 4.64 | 2.23 |
| | | Extract 7: Probelte | 8.48 | 5.66 |
| | | Extract 8: Merck | 4.62 | 2.97 |
| | | Extract 9: Hal Allergy | 3.96 | 0.55 |

PUMCH: Peking Union Medical College Hospital.

PUMCH allergen extracts can directly diagnose *D. pteronyssinus* allergy. If 3 mm ≤MWD <3.25 mm, sIgE should be further detected to ensure the correct diagnosis. No typical clinical history and MWD <3 mm can exclude *D. pteronyssinus* allergy. In addition, Chauveau *et al*[27] reported that the combination of the SPT and sIgE increased the sensitivity of diagnoses of *D. pteronyssinus* allergy. It will be necessary to combine the clinical history, SPTs, and sIgE to diagnose *D. pteronyssinus* allergy in the future.

Compared with other *D. pteronyssinus* allergen extracts on the market used to perform SPTs, this product has certain advantages. First, the contents of the main allergen proteins in PUMCH allergen extracts were 2.8 μg/mL for Der p 1 and 2.39 μg/mL for Der p 2, which were higher than the protein contents reported in some other developing countries [Table 6]. Der p 1 and Der p 2 were the main allergen proteins in *D. pteronyssinus*.[30-33] According to several studies based on Indian *D. pteronyssinus* products,[28,34] the contained proteins of the extracts were low, even zero,[28] and the mean wheal sizes were smaller than the standard extracts from America.[34] Even in a study of extracts from European products, the useful protein concentrations varied from product to product (Der p1 1.21 to 30.16 μg/mL, Der p2 0.55 to 20.49 μg/mL).[29] Second, the diagnostic accuracy of the PUMCH allergen extracts was almost equivalent to that of other products on the market [Table 5] but had a larger sample. In a trial of only 95 outpatients in Guangzhou, China, the sensitivity and specificity of the SPT of the crude extract of *D. pteronyssinus* developed spontaneously were 80.60% and 96.40%, respectively, with the gold standard of sIgE.[10] In addition, a study[11] comparing the validity of Thai local and American imported *D. pteronyssinus* allergen extracts, including 84 patients, showed that the sensitivity of imported allergen extracts was 98.67% with 0% specificity. The sensitivity of local allergen extracts was 100% with 0% specificity. In this study, which included 910 participants, the sensitivity and specificity of the PUMCH allergen extracts were 72.03% and 90.85%, respectively, which provided evidence for the diagnostic accuracy of domestic *D. pteronyssinus* allergen extracts for a large sample.

The safety results of this study were concluded from the cases of 910 subjects who received SPTs of *D. pteronyssinus*, and none of them had adverse reactions.

SPTs may cause adverse reactions, such as local skin reactions, rhinitis symptoms, systemic skin symptoms, respiratory symptoms, and even anaphylactic shock.[35] In a retrospective study of skin trials from 1997 to 2010, among 907 patients who needed SPT, only 0.02% (6/907) needed epinephrine, and no deaths occurred.[36] In an SPT study involving 1029 patients in PUMCH, the incidence of adverse reactions was only 0.583% (6/1029).[37] No adverse events occurred in the 910 patients of this study, indicating that the pricking liquid has high safety.

In conclusion, the application of SPTs with PUMCH allergen extracts in the diagnosis of *D. pteronyssinus* allergy had high diagnostic accuracy and good safety. At present, there are few allergen extract options in China. The sample size of this study was large, and the clinical trial results of nearly a thousand samples were convincing. The standardized PUMCH allergen extract solution brought the SPT up to international standards and ensured accuracy and safety. This solution could be used as an important auxiliary method for clinical diagnosis in future applications.

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## Conflicts of interest

None.

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