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Predicting allergen immunotherapy efficacy based on early maintenance phase response in routine clinical practice

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ABSTRACT

Background: While allergen-specific immunotherapy (AIT) is acknowledged as an effective treatment, its efficacy varies, and consensus on predictive indicators for AIT responders remains elusive.

Objective: This study aimed to identify alternative parameters for predicting AIT responders based on clinical data collected in daily practice.

Method: We conducted a retrospective analysis of patients with house-dust-mite-driven asthma and/or rhinitis who completed 3 years of subcutaneous AIT (3y-AIT). We assessed the efficacy of AIT using the estimated daily symptom and medication score (edSMS) during different treatment periods, including up-dosing, maintenance I, II, and III phases. These scores were derived from detailed records of symptoms and medication use for AIT injections. A responder was defined as an individual with a reduction in edSMS of at least 30% from up-dosing to maintenance III phase ($\Delta edSMS_{U\text{-}M3}$).

Results: A cohort of 133 patients was analyzed, revealing a significant overall improvement in the disease condition after 3y-AIT. Responders demonstrated lower rates of polysensitization, daily tobacco smoke exposure, and milder pretreatment disease severity compared to non-responders ($p = 0.003$, $p = 0.001$, and $p = 0.019$, respectively). We observed 8 clinical response patterns among included subjects, but only a small group of patients (16/133, 12.03%) demonstrated consistent improvement throughout the 3y-AIT. Serum total immunoglobulin E (tIgE), specific immunoglobulin E (sIgE), sIgE/tIgE ratios, and edSMS during the up-dosing phase failed to differentiate the clinical response patterns or correlate with 3y-AIT efficacy. Notably, the reduction in edSMS from up-dosing phase to maintenance I phase ($\Delta edSMS_{U\text{-}M1}$) significantly associated with the 3y-AIT outcome ($r = 0.443$, $p < 0.001$). Receiver-operating characteristic curves indicated that $\Delta edSMS_{U\text{-}M1}$, with a cut-off of 18.40%, effectively predicted responders (AUC: 0.75, sensitivity: 76.20%, specificity: 76.70%).

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Conclusion: The individualized clinical responses to AIT may pose challenges in identifying predictors for treatment efficacy. Nonetheless, despite this complexity, our study highlights that the effectiveness observed in the early maintenance phase serves as a suitable predictor of 3y-AIT outcomes.

Keywords: House dust mite, Allergen immunotherapy, Asthma, Responders

INTRODUCTION

Allergen immunotherapy (AIT) stands as the only treatment for allergies capable of modifying the immune response, holding the potential to alter the natural history of allergic diseases such as allergic rhinitis and asthma.[1–3] In the realm of allergic asthma management, AIT has demonstrated its efficacy by significantly reducing allergic symptoms, minimizing medication requirements, and improving lung function.[4–6] Despite its proven effectiveness, it is essential to acknowledge that not all patients respond optimally to the treatment.

To address this challenge, the European Academy of Allergy and Clinical Immunology (EAACI) Immunotherapy Interest Group has conducted a comprehensive assessment of surrogate immunological and clinical biomarkers for AIT monitoring.[7] These biomarkers encompass immunoglobulin E (IgE), IgG-subclasses, serum inhibitory activity for IgE, basophil activation level, cytokines and chemokines, cellular markers, and *in vivo* biomarkers. However, a consensus on the most suitable parameter for predicting treatment responders, whether in clinical trials or routine practice, remain elusive. AIT remains underutilized in both adult and pediatric asthma populations, highlighting the need to identify and select patients most likely to benefit, thereby facilitating integration of AIT into clinical practice.[8]

It is crucial to recognize that the current surrogate biomarkers primarily originate from clinical trials designed to address specific research questions and contribute robust evidence to healthcare guidelines. However, participants in randomized controlled trials (RCTs) may not always accurately represent the broader spectrum of patients seen in primary care settings, as these trials often impose strict inclusion and exclusion criteria. Consequently, only a fraction of patients with asthma or allergic rhinitis seeking care in primary care and hospital outpatient clinics meet RCT eligibility criteria.[9,10] Currently, limited research focuses on identifying predictors of AIT effectiveness using daily practice data.

Moreover, RCTs typically rely on cross-sectional assessments, conducted at baseline, and at intervals of 1 year, 2 years, and 3 years into the treatment to evaluate AIT efficacy.[1,11,12] However, given the extended duration of AIT and the occurrence of unforeseen events such as common colds, influenza, or pneumonia, capable of exacerbating symptoms and necessitating increased medication dosages, a cross-sectional assessment may not accurately reflect the complex and evolving disease conditions.

In this study, we utilized the estimated daily symptoms and medication score (edSMS), derived from comprehensive evaluation of symptoms intensity and medication use in AIT injections, as the assessment tool to investigate predictors for AIT responders. This approach enabled us to comprehensively capture the precise disease condition at various treatment stages.

METHODS

Patients and intervention

We conducted a retrospective clinical study to gather detailed information on symptoms and medication use in patients who underwent house-dust-mite (HDM) AIT administered subcutaneously using standardized HDM allergen extracts with depot formulations (Alutard SQ ALK Denmark)[13] between 2012 and 2018 at the Department of Allergy and Clinical Immunology of the First Affiliated Hospital of Guangzhou Medical University.

The inclusion criteria were as follows: (1) a confirmed diagnosis of allergic asthma and/or rhinitis, fulfilling the diagnostic criteria of the

Allergic Rhinitis and its Impact on Asthma (ARIA) guideline for allergic rhinitis[14] and Global Initiative for Asthma (GINA) guideline for asthma;[15] (2) objective evidence of HDM allergy (defined as meeting all of the following criteria: a positive HDM skin test, elevated serum HDM-specific IgE [sIgE] levels, and a history of symptom exacerbation triggered by HDM exposure);[8,16,17] (3) completion of a three-year course of AIT (3y-AIT); and (4) possession of complete clinical data, encompassing demographic characteristics, clinical features, pre-treatment HDM sIgE, total IgE (tIgE), and comprehensive records of symptoms and medication use during AIT injections. Patients who did not complete 3y-AIT (in their up-dosing phase, 1 year or 2 year treatment period) or had incomplete records of symptoms and medication use during AIT injections, were excluded from the analysis. All patients received treatment in our clinic within the Department of Allergy and Clinical Immunology and were monitored for at least 30 minutes following each injection to prevent acute adverse events.

The AIT procedure adhered to the manufacturer's instructions,[4,18] employing 4 different vials (Nos.1-4) of standardized allergen extracts, with allergen concentrations increasing 10-fold from 100 to 10,000 SQ-U/mL. The up-dosing phase involved weekly injections, with volumes of 0.2, 0.4, and 0.8 mL in vials 1–3, and 0.1, 0.2, 0.4, 0.8, and 1.0 mL in the vial 4, ultimately reaching the maintenance dose of 100,000 SQ-U. Table 1 showed the detailed setting injection schedule of 3y-AIT.

The data included in this study were collected from routine clinical practice. Before undergoing AIT, all patients were thoroughly briefed on the AIT procedure and potential risks, and were required to provide written informed consent. This study was approved by the Ethics Review Board [IRB:2022–76] of the First Affiliated Hospital of Guangzhou Medical University.

Assessment of AIT effectiveness

In clinical practice, we recorded detailed symptoms and medication use of patients during AIT injections. The assessment begins after the first injection, with patients rating symptom intensity and reporting medication use during the interval between subsequent injections. For instance, prior to receiving the second injection, patients rate symptom intensity and report medication use during the interval between the first and the upcoming second injection. The general question posed to patients is: "Please rate your symptoms and report your medication use during the interval between the previous injection and the upcoming injection." During the study, there were typically 14 assessment records for the up-dosing phase and 7, 8, and 8 assessment records for maintenance phases I, II, and III, respectively. Table 1 provides detailed assessment timepoints throughout the 3y-AIT treatment.

The symptom assessment included both daytime and nighttime asthmatic symptoms, such as shortness of breath, wheezing, cough, and chest tightness. These symptoms were rated on a scale of 0–5 for daytime severity, and 0–4 for nocturnal occurrences. Both daytime and nighttime allergic symptoms (sneezing, nasal itching, eye itching, rhinorrhea, nasal congestion, watery eyes, rash, and urticaria) were rated separately on a scale from 0 to 2 for daytime and 0–2 for nighttime occurrences according to the severity and frequency of the symptoms in disturbing daily activities and sleep. A score of 0 indicated the absence of symptoms, 1 indicated mild symptoms that did not significantly impact daily activities and sleep, and 2 represented severe symptoms that affected daily activities and sleep.[19,20] Additionally, we meticulously documented asthma medication usage, considering the diversity in types and dosages among patients. The comprehensive scoring rule is outlined in eTable 1.

A series of assessment records between 2 injection intervals were used to calculate the estimated daily symptom score (edSS) and medication score (edMS) of various treatment periods. The edSS for the up-dosing phase, maintenance phases I, II, and III were denoted as $edSS_U$, $edSS_{M1}$, $edSS_{M2}$, and $edSS_{M3}$, respectively. Similarly, the edMS for the up-dosing phase, maintenance phases I, II, and III were denoted as $edMS_U$, $edMS_{M1}$, $edMS_{M2}$, and $edMS_{M3}$, respectively. The estimated daily Symptom Medication Score (edSMS) was derived by summing the edSS and edMS for each corresponding period, resulting in $edSMS_U$, $edSMS_{M1}$, $edSMS_{M2}$, and $edSMS_{M3}$.

AIT phases	Injection schedule	Injection sequence number	Vials	Volume (ml)	Concentration (SQ-U/ml)	Dosage (SQ-U)	edSMS assessment
Up-dosing phase	Week 1	1	1	0.2	100	20	Not applicable
	Week 2	2	1	0.4	100	40	☑
	Week 3	3	1	0.8	100	80	☑
	Week 4	4	2	0.2	1000	200	☑
	Week 5	5	2	0.4	1000	400	☑
	Week 6	6	2	0.8	1000	800	☑
	Week 7	7	3	0.2	10,000	2000	☑
	Week 8	8	3	0.4	10,000	4000	☑
	Week 9	9	3	0.8	10,000	8000	☑
	Week 10	10	4	0.1	100,000	10,000	☑
	Week 11	11	4	0.2	100,000	20,000	☑
	Week 12	12	4	0.4	100,000	40,000	☑
	Week 13	13	4	0.6	100,000	60,000	☑
	Week 14	14	4	0.8	100,000	80,000	☑
	Week 15	15	4	1.0	100,000	100,000	☑
Maintenance I phase	Week 17	16	4	1.0	100,000	100,000	☑
	Week 21	17	4	1.0	100,000	100,000	☑
	Week 27	18	4	1.0	100,000	100,000	☑
	Week 33	19	4	1.0	100,000	100,000	☑
	Week 39	20	4	1.0	100,000	100,000	☑
	Week 45	21	4	1.0	100,000	100,000	☑
	Week 51	22	4	1.0	100,000	100,000	☑
Maintenance II phase	Week 57	23	4	1.0	100,000	100,000	☑
	Week 63	24	4	1.0	100,000	100,000	☑
	Week 69	25	4	1.0	100,000	100,000	☑
	Week 75	26	4	1.0	100,000	100,000	☑
	Week 81	27	4	1.0	100,000	100,000	☑
	Week 87	28	4	1.0	100,000	100,000	☑
	Week 93	29	4	1.0	100,000	100,000	☑
	Week 99	30	4	1.0	100,000	100,000	☑

(continued)

AIT phases	Injection schedule	Injection sequence number	Vials	Volume (ml)	Concentration (SQ-U/ml)	Dosage (SQ-U)	edSMS assessment
Maintenance III phase	Week 105	31	4	1.0	100,000	100,000	☑
	Week 111	32	4	1.0	100,000	100,000	☑
	Week 117	33	4	1.0	100,000	100,000	☑
	Week 123	34	4	1.0	100,000	100,000	☑
	Week 129	35	4	1.0	100,000	100,000	☑
	Week 135	36	4	1.0	100,000	100,000	☑
	Week 141	37	4	1.0	100,000	100,000	☑
	Week 147	38	4	1.0	100,000	100,000	☑

Table 1. (Continued) Detailed injection schedule for 3-year AIT. *After reaching the maintenance dose, the first dose was administered every 2 weeks, the second dose every 4 weeks, and subsequent doses every 4–8 weeks as determined by the clinical doctor. In our center, the maintenance dose was typically administered every 6 weeks. Based on the injection schedule, the 3y-AIT contain 4 treatment periods, including up-dosing phase, mantaintence phase I, mantaintence phase II, and mantaintence phase III.The edSMS assessment begins after the first injection, with patients rating symptom intensity and reporting medication use during the interval between subsequent injections. For instance, prior to receiving the second injection, patients rate symptom intensity and report medication use during the interval between the first and the upcoming second injection. The general question posed to patients is: "Please rate your symptoms and report your medication use during the interval between the previous injection and the upcoming injection." During the study, there were typically 14 assessment records for the up-dosing phase and 7, 8, and 8 assessment records for maintenance phases I, II, and III, respectively. Abbreviations: edSMS: estimated symptoms and medication score*

Given the flexibility in injection schedules in real-world clinical practice, the intervals between injections can vary widely. To address this variability, we employ the Weighted Average Algorithm to compute the edSMS. This algorithm calculates the average of a set of values, assigning weights to each value based on its relative importance or frequency. Table 2 delineates the specific formulas utilized for computing the values of edSS, edMS, and edSMS across various phases of AIT.

Unlike RCTs, routine clinical practice typically does not incorporate a run-in period before AIT, resulting in a lack of pretreatment edSMS data. Consequently, in this study, the value of $edSMS_U$ was considered as the baseline indicator for 3y-AIT. A responder to AIT was defined as an individual who demonstrated a reduction in edSMS of at least 30% from up-dosing phase to mantainence phase III ($\Delta edSMS_{U\text{-}M3}$). The symbols $\Delta edSMS_{U\text{-}M1}$ and $\Delta edSMS_{U\text{-}M2}$ were used to denote the edSMS change rate from the up-dosing phase to maintenance phase I and maintenance phase II, respectively. Acknowledging that the symptom score and medication score do not carry equal weight, $\Delta edSMS_{U\text{-}M3}$ was computed as the average of the change rates in edSS ($\Delta edSS_{U\text{-}M3}$) and edMS ($\Delta edMS_{U\text{-}M3}$) from the up-dosing phase to maintenance phase III. Detailed formulas for calculating these change rates are provided in Table 2.

Allergen sensitization and pulmonary function

Prior to undergoing AIT, a blood sample was collected and processed. Serum tIgE and sIgE levels were measured using fluoroimmunoassay technique with ImmunoCAP, as per the manufacture's instructions (Phadia, Uppsala, Sweden). Atopic individuals were identified if they exhibited positive responses to at least 1 common aeroallergen, such as house dust mites, cats, dogs, grass pollen, tree pollen, or a mixture of molds. Pulmonary function testing was performed using a spirometer (MasterScreen PFT; Jaeger, CareFusion, Hoechberg, Germany) by trained personnel in accordance with the guidelines set forth by the American Thoracic Society/European Respiratory Society (ATS/ERS).[21]

Statistical analysis

Statistical analysis was performed utilizing the SPSS software package (version 22.0; IBM Corp,

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Item	Symbol	Formula	Description
Weighted average	$\overline{X}$	$\overline{X} = \frac{\sum_{i=1}^{n}(X_i \times W_i)}{\sum W_i}$	$\overline{X}$ represents the weighted average, X_i represents the value of the item, W_i represents the weight.
edSS Weighted average	$edSS_U$ $edSS_{M1}$ $edSS_{M2}$ $edSS_{M3}$	$edSS_{periods} = \frac{\sum_{i=1}^{n}(edSS_i \times d_i)}{\sum d_i}$	$edSS_{period}$ represents the estimated daily symptom score during different periods, including $edSS_U$, $edSS_{M1}$, $edSS_{M2}$, and $edSS_{M3}$. $edSS_i$ represents the value between previous and current injection. d_i represents the number of days between the 2 injections.
edMS Weighted average	$edMS_U$ $edMS_{M1}$ $edMS_{M2}$ $edMS_{M3}$	$edMS_{periods} = \frac{\sum_{i=1}^{n}(edMS_i \times d_i)}{\sum d_i}$	$edMS_{period}$ represents the estimated daily medication score during different periods, including $edMS_U$, $edMS_{M1}$, $edMS_{M2}$, and $edMS_{M3}$. $edMS_i$ represents the value between previous and current injection. d_i represents the number of days between the 2 injections.
edSMS Weighted average	$edSMS_U$ $edSMS_{M1}$ $edSMS_{M2}$ $edSMS_{M3}$	$edSMS_{periods} = \frac{\sum_{i=1}^{n}[(edSS_i + edMS_i) \times d_i]}{\sum d_i}$	$edMS_{period}$ represents the estimated daily symptoms and medication score during different periods, including $edMS_U$, $edMS_{M1}$, $edMS_{M2}$, and $edMS_{M3}$. $edMS_i$ represents the value of value between previous and current injection. d_i represents the number of days between the 2 injections.
edSS change rate	$\Delta edSS_{U\text{-}M1}$ $\Delta edSS_{U\text{-}M2}$ $\Delta edSS_{U\text{-}M3}$	$\Delta edSS_{u\text{-}m} = \frac{edSS_u - edSS_m}{edSS_u} \times 100\%$	$\Delta edSS_{u\text{-}m}$ represents the percentage change in edSS from up-dosing phase to maintenance phases, where u represents up-dosing phase and m represents specified maintenance phases.
edMS change rate	$\Delta edMS_{U\text{-}M1}$ $\Delta edMS_{U\text{-}M2}$ $\Delta edMS_{U\text{-}M3}$	$\Delta edMS_{u\text{-}m} = \frac{edMS_u - edMS_m}{edMS_u} \times 100\%$	$\Delta edMS_{u\text{-}m}$ represents the percentage change in edMS from up-dosing phase to maintenance phases, where u represents up-dosing phase and m represents specified maintenance phases.
edSMS change rate	$\Delta edSMS_{U\text{-}M1}$ $\Delta edSMS_{U\text{-}M2}$ $\Delta edSMS_{U\text{-}M3}$	$\Delta edSMS_{u\text{-}m} = \frac{\Delta edSS_{u-m} + \Delta edMS_{u-m}}{2}$	$\Delta edSMS_{u\text{-}m}$ represents the percentage change in edSMS from up-dosing phase to maintenance phases, where u represents up-dosing phase and m represents specified maintenance phases.

Table 2. Formulas used in the current study.

Armonk, NY). Continuous variables are presented as numbers (%), median (interquartile range), or mean (standard deviation). Normality testing was employed to determine whether the data adhered to a normal distribution. Comparisons of continuous endpoints between groups were calculated based on the variable normality assumptions using independent-sample t-tests or Mann-Whitney U tests, or ANOVA or Kruskal-Wallis tests. Categorical endpoints were analyzed using a $\chi 2$ test. Correlation analyses were conducted to evaluate the relationship either Pearson's correlation or Spearman's correlation, depending on the normality assumptions of the variables. Univariate and multivariate logistic regression analyses were employed to ascertain the factors associating with AIT responders. Covariates were included in the models based on statistical differences in the comparison between responders and non-responders. Receiver operating characteristic (ROC) curves were utilized to assess the predictive capability of clinical parameters for identifying responders to AIT. Statistical significance was defined as a p value of <0.05.

RESULTS

Overall efficacy of 3y-AIT

Among the 925 patients with asthma who underwent AIT in our department, 295 received 3y-AIT. A total of 630 patients were excluded from the study: 5 due to relocation, 26 due to severe systemic adverse reactions, 50 due to unsatisfactory treatment effects, 423 still undergoing up-dosing or in the 1–2 year period, and 126 with only allergic rhinitis. Of the 295 patients who received 3y-AIT, complete assessment data for edSMS were available for 133 asthmatic patients, while 162 patients were further excluded due to incomplete assessment data, preventing edSMS value determination for further analysis. The study flow chart is illustrated in Fig. 1.

There was no statistically differences in body mass index, age, allergic indices, and lung function between included and excluded subjects with a 3y-AIT, as detailed in Table 3. Overall, AIT demonstrated a significant improvement in disease conditions for asthmatic patients with 3y-AIT, as indicated by the

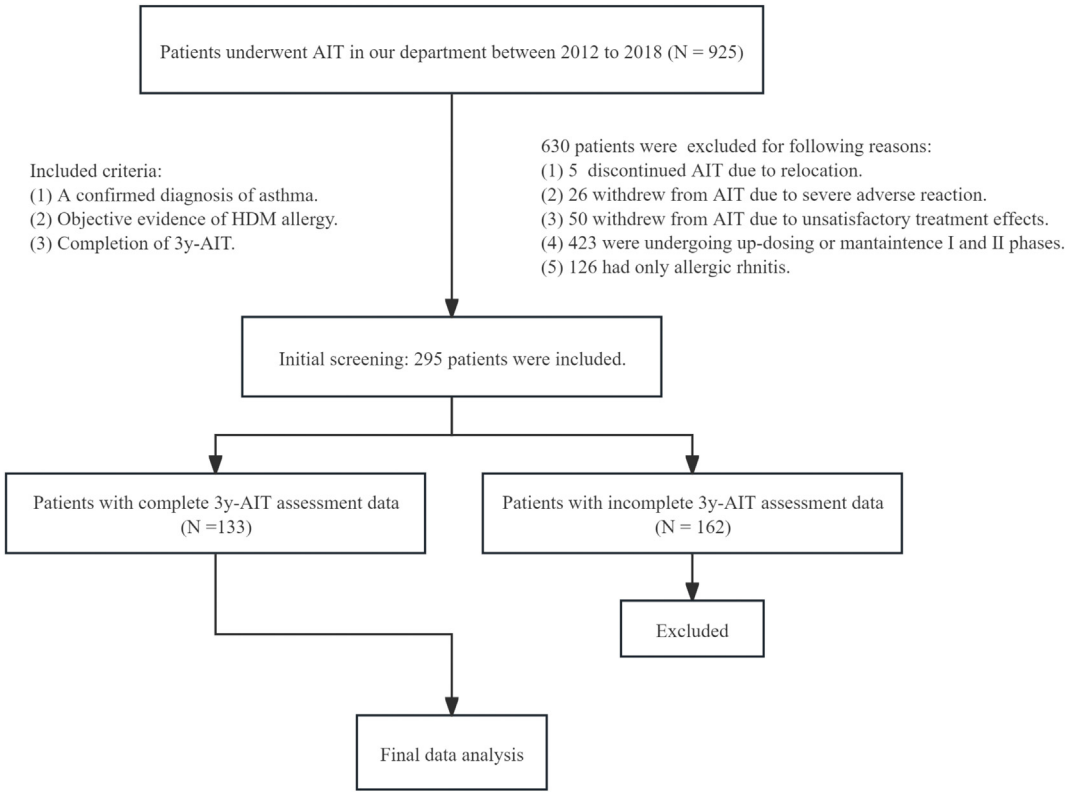

Fig. 1 The flow chart of current study.

Subjects' characteristics	Included subjects (N = 133)	Excluded subjects (N = 162)	P
Gender (male, %)[&]	43.00 (32.33)	88.00 (54.30)	<0.001
Body mass index[&]	19.56 (16.01,23.79)	18.69 (16.06,21.52)	0.633
Age (years)[&]	16.00 (10.50,32.50)	18.00 (11.00,23.00)	0.078
<18 years old (%)[#]	70.00 (52.63)	80.00 (49.38)	0.579
≥18 years old (%)[#]	63.00 (47.37)	82.00 (50.62)	
Living area (%)[#]			
Urban	116.00 (87.22)	133.00 (83.10)	0.329
Rural	17.00 (12.78)	27.00 (16.90)	
Allergic rhinitis (%)[#]	133.00 (100.00)	162.00 (100.00)	NA
Allergic state (%)[#]		N = 121	
Monosensitization	47.00 (35.34)	44.00 (36.36)	0.865
Polysensitization	86.00 (64.66)	77.00 (63.64)	
Serum total IgE (tIgE) (kU/L)[&]	357.44 (178.00,722.33)	337.00 (147.95,503.50) N = 98	0.748
Serum Der-*p* sIgE (kU/L)[#]		N = 119	
Level 0-2	6.00 (4.51)	4.00 (3.36)	0.934
Level 3	18.00 (13.53)	13.00 (10.92)	
Level 4	37.00 (27.82)	36.00 (30.25)	
Level 5	36.00 (27.07)	31.00 (26.05)	
Level 6	36.00 (27.07)	35.00 (29.41)	
Serum Der.*f* sIgE (kU/L)[#]		N = 108	
Level 0-2	6.00 (4.51)	9.00 (8.33)	0.181
Level 3	15.00 (11.28)	14.00 (12.96)	
Level 4	33.00 (24.81)	32.00 (29.63)	
Level 5	28.00 (21.05)	27.00 (25.00)	
Level 6	51.00 (38.35)	26.00 (24.07)	
Parameters of lung function[&]		N = 75	
FEV_1 (% predicted)	89.20 (78.60,98.53)	89.40 (78.20,100.40)	0.957
FVC (% predicted)	96.50 (87.70,105.00)	97.10 (88.50,104.30)	0.847
FEF_{25-75} (% predicted)	70.60 (52.60,85.20)	68.05 (52.38,84.18)	0.735

Table 3. Demographic and clinical characteristics of included and excluded subjects. *Data expressed as &median(interquartile range) or #percentage(%). The concentrations of Der-*p *sIgE and Der.*f *sIgE were not compared between the 2 groups because of numbers of sIgE values of excluded patients were exceed the upper limited of sIgE detection. The grade of sIgE was defined as follows: (1) Grade 0: <0.35 kU/L; (2) Grade 1: 0.35–0.69 kU/L; (3) Grade 2: 0.70–3.49 kU/L; (4) Grade 3: 3.50–17.49 kU/L; (5) Grade 4: 17.50–49.99 kU/L; (6) Grade 5: 50.00–100.00 kU/L; (7) Grade 6: >100.00 kU/L. P value was calculated from the chi-square test, independent-sample* t*-test, or Mann-Whitney* U *test. Abbreviations: FEV_1: forced expiratory flow in 1 s; FVC: forced vital capacity; FEF_{25-75}: forced expiratory flow between 25 and 75% of vital capacity; IgE: immunoglobulin E; Der-*p: Dermatophagoides pteronyssinus*; Der-*f: Dermatophagoides farinae

significant lower values of $edSMS_{M2}$ and $edSMS_{M3}$ compared to $edSMS_U$ ($p = 0.034$ and $p = 0.001$, respectively), as shown in eFig. 1.

Characteristics of AIT responders and non-responders

Using a criterion of at least 30% reduction of $\Delta edSMS_{U\text{-}M3}$, we identified 73 (54.89%) individuals as responders and 60 (45.11%) as non-responders to the 3y-AIT. There were no significant differences observed in demographic parameters, pretreatment allergic indices, and lung function between responders and non-responders. However, it is worth noting that responders exhibited fewer hospitalizations, lower usage of oral/intravenous medications, and less sick leave due to asthma exacerbation in the year preceding their AIT treatment. Additionally, they also had lower exposure to tobacco smoke from family members, a lower rate of polysensitization, and milder disease severity, as presented in Table 4. Moreover,

Characteristics	Responders (N = 73)	Non-responders (N = 60)	P
The demographic parameters			
Gender (male, %)[#]	20.00 (27.39)	23.00 (38.33)	0.180
Body mass index[&]	20.07 (17.46,23.99)	20.28 (15.14,23.82)	0.280
Age (years)[&]	16.00 (11.00,32.50)	18.00 (9.25,34.75)	0.600
Adolescent (%)[#]	37.00 (50.68)	33.00 (55.00)	0.620
Adult (%)[#]	36.00 (49.31)	27.00 (45.00)	
Living area (urban)[#]	65.00 (89.04)	51.00 (85.00)	0.487
The pretreatment clinical characteristics			
Exposure to tobacco smoke from family members (%)[#]	22.00 (30.13)	34.00 (56.67)	**0.001**
With self-reported food allergy (%)[#]	21.00 (28.76)	18.00 (30.00)	0.876
With medication allergy (%)[#]	22.00 (30.14)	14.00 (23.33)	0.380
With severe allergic reaction history (%)[#]	16.00 (21.92)	17.00 (28.33)	0.394
With family history of allergy (%)[#]	43.00 (58.90)	40.00 (66.67)	0.358
With allergic rhinitis (%)[#]	73.00 (100.00)	60.00 (100.00)	NA
With nasal polyps (%)[#]	5.00 (6.85)	2.00 (3.33)	0.457
With allergic dermatitis (%)[#]	30.00 (41.10)	25.00 (41.67)	0.947
The times of hospitalizations in the past year before AIT (%)[#]			
0	71.00 (97.26)	51.00 (85.00)	**0.032**
1	1.00 (1.37)	2.00 (3.33)	
> 1	1.00 (1.37)	7.00 (11.67)	
The times of emergency room visits in the past year before AIT (%)[#]			
0	63.00 (86.30)	52.00 (86.67)	0.557
1	5.00 (6.84)	2.00 (3.33)	
> 1	5.00 (6.84)	6.00 (1.00)	
The times of outpatient visits in the past year before AIT (%)[#]			
0	46.00 (63.01)	35.00 (58.33)	0.539
1	3.00 (4.10)	1.00 (1.67)	
> 1	24.00 (32.88)	24.00 (40.00)	
The times of taking oral/intravenous corticosteroid in the past year (%)[#]			
0	71 (97.26)	51.00 (85.00)	**0.029**
1	2 (2.74)	6.00 (5.00)	
> 1	0 (0.00)	3.00 (5.00)	
The times of sick leave because of asthma in the past year (%)[#]			
0	63.00 (86.30)	41.00 (76.67)	**0.010**
1	0.00 (0.00)	5.00 (0.00)	
> 1	10.00 (13.70)	14.00 (23.33)	

(continued)

Characteristics	Responders (N = 73)	Non-responders (N = 60)	P
Pretreatment allergic status			
tIgE(kU/L)[&]	372.00 (230.00,708.00)	334.65 (154.88,723.00)	0.971
Der-*p* sIgE(kU/L)[&]	64.00 (34.00,123.00)	61.85 (27.40,117.25)	0.579
Der-*f* sIgE(kU/L)[&]	74.00 (40.00,130.00)	88.45 (36.00,123.00)	0.848
Der-*p* sIgE/tIgE ratio[&]	0.17 (0.10,0.34)	0.18 (0.12,0.24)	0.782
Der-*p* plus Der-*f* sIgE/tIgE ratio[&]	0.36 (0.24,0.65)	0.38 (0.27,0.57)	0.823
Allergic state (%)[#]			
Monosensitization	34.00 (46.58)	13.00 (21.67)	**0.003**
Polysensitization	39.00 (53.42)	47.00 (78.33)	
Lung function			
FEV_1 (% predicted)[&]	89.20 (77.80,97.30)	89.15 (79.45,98.80)	0.771
FVC(% predicted)[&]	95.80 (87.40,105.00)	97.95 (89.78,104.60)	0.549
FEF_{25-75} (% predicted)[&]	71.00 (50.00.84.95)	69.55 (52.95,85.15)	0.988
Disease severity(%)			
Intermittent[#]	58.00 (79.45)	40.00 (66.67)	**0.019**
Mild[#]	14.00 (19.18)	11.00 (18.33)	
Moderate[#]	1.00 (1.37)	8.00 (13.33)	
Severe[#]	0.00 (0.00)	1.00 (1.67)	

Table 4. (Continued) The demographic and clinical characteristics of responders and non-responders to AIT. *Data expressed as &median(interquartile range) or #percentage(%). P value was calculated from the chi-square test, independent-sample t-test, or Mann-Whitney U test. Abbreviations: FEV_1: forced expiratory flow in 1 s; FVC: forced vital capacity; FEF_{25-75}: forced expiratory flow between 25 and 75% of vital capacity; IgE: immunoglobulin E; Der-p:* Dermatophagoides pteronyssinus; *Der-f:* Dermatophagoides farinae. *Bolded p-values indicate statistical significance.*

there was no discernible distinction in $edSMS_U$ and $edSMS_{M1}$ between responders and non-responders ($p = 0.086$ and $p = 0.299$, respectively). Conversely, responders exhibited a diminished value in $edSMS_{M2}$ and $edSMS_{M3}$ compared to non-responders ($p = 0.001$ and $p < 0.001$, respectively) (see eFig. 2). Notably, responders demonstrated higher $\Delta edSMS_{U\text{-}M1}$, $\Delta edSMS_{U\text{-}M2}$, and $\Delta edSMS_{U\text{-}M3}$ in comparison to non-responders (see eFig. 3).

Factors contributing to effectiveness of AIT

In our investigation, both univariate and multivariate analyses were conducted to identify the contributors to the effectiveness of AIT. Factors were selected based on differences between responders and non-responders. In the univariate analysis, a history of tobacco smoke exposure from family members was associated with reduced likelihood of being an AIT responder (OR = 0.330, 95CI % = 0.161–0.674, p = 0.002). Conversely, $\Delta edSMS_{U\text{-}M1}$ value showed a higher likelihood of response to AIT ($0 < \Delta edSMS_{U\text{-}M1} \leq 15\%$: OR = 7.167, 95CI% = 2.275–22.574, p = 0.001; $\Delta edSMS_{U\text{-}M1} > 15\%$: OR = 35.609, 95CI% = 12.345–102.713, $p < 0.001$). After adjusting for confounders, $\Delta edSMS_{U\text{-}M1}$ remained a significant independent predictor of response to AIT ($0 < \Delta edSMS_{U\text{-}M1} \leq 15\%$: adjusted-OR = 6.948, 95CI% = 2.188–22.059, adjusted-p = 0.001; $\Delta edSMS_{U\text{-}M1} > 15\%$: adjusted-OR = 31.232, 95CI % = 10.703–91.666, adjusted-p < 0.001) (**see** eTable 2).

Eight individual response patterns to 3y-AIT

Based on the values of $edSMS_U$, $edSMS_{M1}$, $edSMS_{M2}$, and $edSMS_{M3}$, we observed 8 distinct response patterns (Pattern I-VIII) to 3y-AIT in individuals (Fig. 2). Pattern VIII exhibited the highest responder rate (15/16, 93.75%), demonstrating consistent improvement throughout the 3y-AIT period. In contrast, Pattern I had the lowest responder rate (0.00%), indicating no discernible effect throughout the treatment. The remaining patterns showed varying degrees of fluctuating responses, with responder rates of 31.25% (5/16), 20.00% (3/15), 76.00% (19/25), 9.09% (1/11), 78.95% (15/19), and 65.21% (15/23) for Patterns II, III, IV, V, VI, and VII, respectively.In addition, the Pattern VIII group showed the highest level of *Dermatophagoides pteronyssinus* (Der-*p*) sIgE/tIgE ratio and Der-*p* plus *Dermatophagoides farinae* (Der-*f*) sIgE/tIgE ratio compared to other pattern groups ($p = 0.045$ and $p = 0.032$, respectively). However, we failed to differentiate the response patterns by other clinical parameters, including tIgE, sIgE, lung function, and disease severity (eTable 3).

Correlations between clinical parameters and AIT effectiveness

The heterogeneous response patterns observed in our study might pose a challenge when attempting to identify indicators for AIT effectiveness indicators. As expected**,** our analysis revealed no significant correlation between the efficacy of 3y-AIT and any of the included pretreatment allergic parameters, such as Der-*p* sIgE, Der-*f* sIgE, tIgE, Der-p sIgE/tIgE ratio, and Der-*p* plus Der-*f*/tIgE ratio. Additionally, there was no notable association found between $edSMS_u$ and the effectiveness of 3y-AIT. However, we found that the pretreatment Der-*p* sIgE/tIgE ratio and Der-*p* plus Der-*f*/tIgE ratio were correlated with $\Delta edSMS_{U\text{-}M1}$ ($r = -0.212$, $p = 0.018$ and $r = -0.197$, $p = 0.029$, respectively). Furthermore, a moderate positive association was observed between $\Delta edSMS_{U\text{-}M1}$ and $\Delta edSMS_{U\text{-}M2}$ ($r = 0.443$, $p < 0.001$), suggesting that the outcome of early maintenance phase might predict 3y-AIT effectiveness under heterogeneous response patterns (Table 5).

Predictors of AIT responders

To evaluate whether early improvements in maintenance phase may serve as an ideal predictor of the effectiveness of 3y-AIT, we generated ROC curves for clinical parameters aimed at predicting AIT responders. Our analysis revealed that $\Delta edSMS_{U\text{-}M1}$ had an AUC of 0.75 with cutoff of 18.40% (specificity: 76.70%, sensitivity: 72.60%). Considering the prolonged duration of AIT, early predication of treatment outcomes becomes of paramount importance for the practical application of AIT. Consequently, $\Delta edSMS_{U\text{-}M2}$ as a middle-phase parameter did not include into the analysis.These results are presented in Fig. 3.

DISCUSSION

In accordance with previous RCTs and retrospective real-world studies, we also observed significant improvements in disease conditions following 3y-AIT

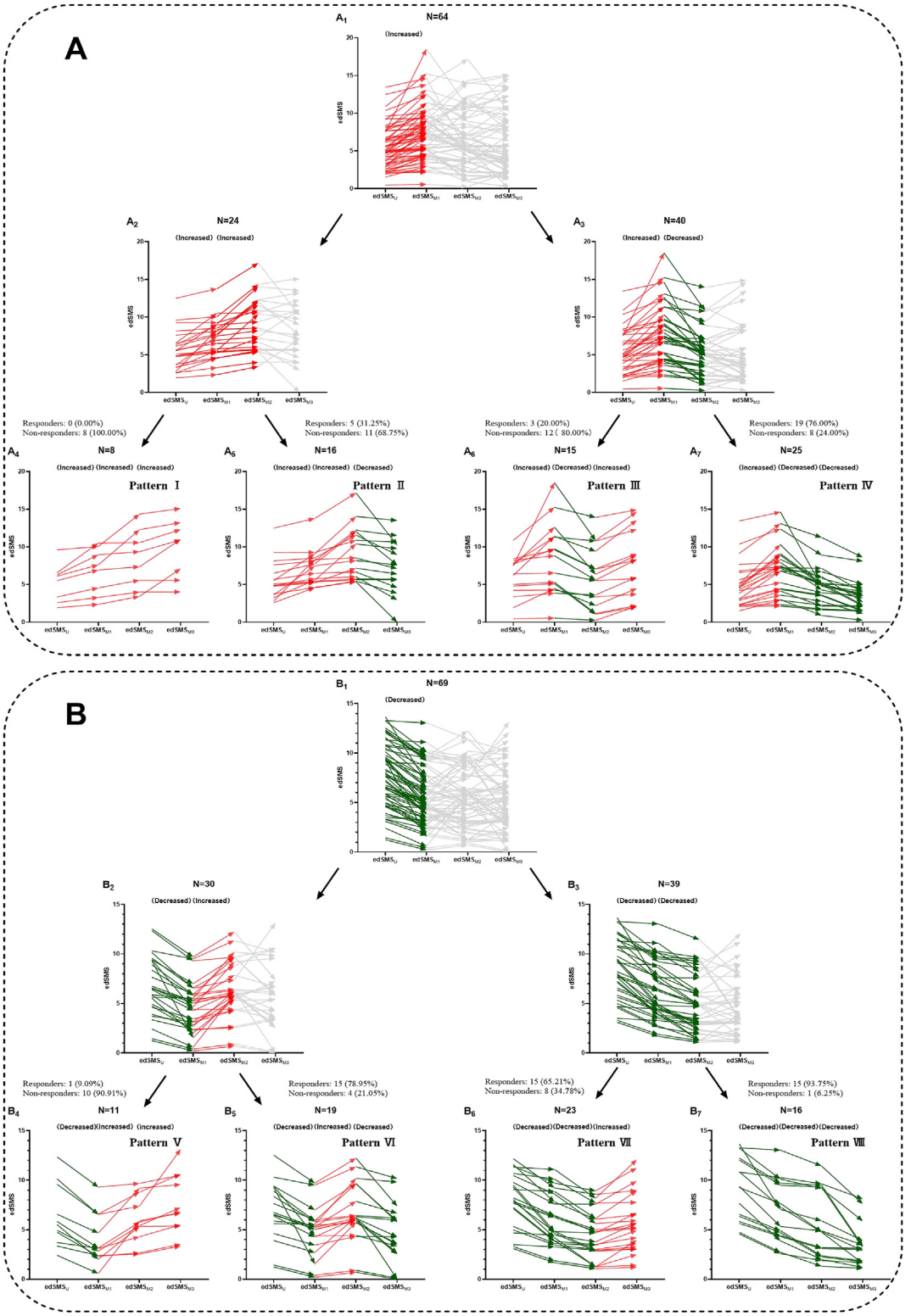

Fig. 2 Scatter plot of edSMS at different periods of AIT. (A) Scatter plots of edSMS for patients who exhibited improved edSMS during the maintenance I phase of AIT, showing 4 different effectiveness trends throughout the 3y-AIT period (A4-A7).(B) Scatter plots of edSMS for patients who exhibited decreased edSMS during the maintenance I phase of AIT, showing 4 different effectiveness trends throughout the 3-year AIT period (B4–B7).Abbreviations: $edSMS_{M1}$: estimated daily symptoms and medication score of maintenance I phase; $edSMS_{M2}$: estimated daily symptoms and medication score of maintenance II phase; $edSMS_{M3}$: estimated daily symptoms and medication score of maintenance III phase.

Factors	$\Delta edSMS_{U\text{-}M1}$ (%)		$\Delta edSMS_{U\text{-}M2}$ (%)		$\Delta edSMS_{U\text{-}M3}$ (%)	
	r	p	r	p	r	p
$edSMS_U$	−0.220	**0.011**	−0.175	**0.044**	−0.086	0.325
tIgE(kU/L)	0.038	0.675	−0.017	0.854	−0.058	0.522
Der-*p* sIgE(kU/L)	−0.153	0.082	0.021	0.809	−0.034	0.699
Der-*f* sIgE(kU/L)	−0.108	0.229	0.009	0.916	−0.047	0.603
Der-*p* sIgE/tIgE ratio	−0.212	**0.018**	0.027	0.768	0.007	0.940
Der-*p* plus Der-*f* sIgE/tIgE ratio	−0.197	**0.029**	0.024	0.788	0.026	0.774
Pretreatment FEV_1 (% predicted)	0.098	0.404	0.058	0.622	−0.031	0.791
Pretreatment FEF_{25-75} (% predicted)	0.019	0.875	−0.019	0.871	−0.021	0.858
$\Delta edSMS_{U\text{-}M1}$ (%)	-	-	0.463	**<0.001**	0.443	**<0.001**
$\Delta edSMS_{U\text{-}M2}$ (%)	-	-	-	-	0.681	**<0.001**

Table 5. The correlation between clinical parameters with effectiveness of AIT at different periods. *The correlation analysis was performed by using Spearman's correlation. Abbreviations: $edSMS_U$: estimated daily symptoms and medication score of up-dosing phase; IgE: immunoglobulin E; Der-p:* Dermatophagoides pteronyssinus*; Der-f:* Dermatophagoides farinae. *$\Delta edSMS_{U\text{-}M1}$: the change in edSMS from up-dosing phase to maintenance I phase; $\Delta edSMS_{U\text{-}M2}$: the change in edSMS from up-dosing phase to maintenance II phase; $\Delta edSMS_{U\text{-}M3}$: the reduction in edSMS from up-dosing phase to maintenance III phase. Bolded p-values indicate statistical significance.*

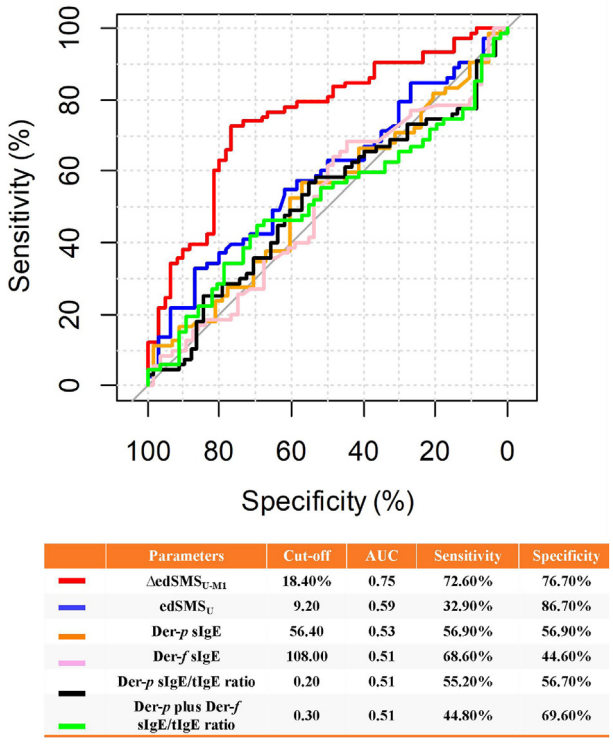

Fig. 3 Receiver operating characteristic curve (ROC) of clinical parameters to predict AIT responders. Abbreviations: $edSMS_U$: estimated daily symptoms and medication score of up-dosing phase; IgE: immunoglobulin E; Der-p: *Dermatophagoides pteronyssinus*; Der-f: *Dermatophagoides farinae*. $\Delta edSMS_{U\text{-}M1}$: the change in edSMS from up-dosing phase to maintenance I phase.

in our cohort. Responders were more likely to be monosensitized, less exposed to tobacco smoke from family members, and had milder disease severity compared to non-responders. Intriguingly, we identified 8 clinical response patterns of treatment efficacy over the 3-year course of AIT for individual patients. Despite none of the pretreatment clinical parameters, including Der-*p* sIgE, Der-*f* sIgE, total IgE (tIgE), Der-*p* sIgE/tIgE ratio, and Der-*p* plus Der-*f*/tIgE ratio, demonstrated significant correlations with AIT efficacy, the value of $\Delta edSMS_{U\text{-}M1}$, which represents the early effectiveness of allergen desensitization, exhibited valuable predictive capability for identifying responders. Our findings underscore the overall effectiveness of AIT while highlighting individualized treatment responses. Importantly, early responses in the maintenance phase appear to hold promise as potential predictors of 3y-AIT effectiveness.

In this study, the value of edSMS was derived from comprehensive records of AIT injections within a clinical practice setting. Traditionally, the assessment of AIT efficacy relies on cross-sectional evaluations, typically conducted at baseline, and then after 1 year, 2 years, and 3 years of treatment.[1,11,12] Through the analysis of edSMS data, we observed an overall improvement in symptom severity and reduced

medication use throughout the AIT course, consistent with previous research findings.[22,23] However, it seems that while a minority of patients experienced sustained improvement during the 3-year AIT period, the majority exhibited fluctuating efficacy patterns. This variability reflects the dynamic nature of asthma management, necessitating adaptable treatment approaches such as step-up and step-down strategies to maintain disease control. We were unable to distinguish these efficacy patterns using pretreatment clinical parameters. Thus, we hypothesize that this variability may be directly linked to daily disease management, including medication adjustments and individual factors. Personalized management of AIT, involving regular monitoring and timely medication adjustments, is crucial and may influence the transformation of efficacy patterns. However, reaching a consensus on a standardized approach for these adjustments in AIT remains an ongoing discussion.

According to the AIT guidelines,[8,17] patients with HDM-driven allergic asthma are recommended to initiate HDM AIT alongside their regular controlled treatment. However, treatment efficacy varies among individuals, highlighting the need to identify the most suitable candidates for AIT.[24] Our study found that AIT responders had a higher prevalence of monosensitization, better baseline disease conditions, and lower tobacco smoke exposure in their daily lives compared to non-responders. Although concerns persist regarding the impact of polysensitization on the efficacy of HDM AIT,[25,26] there is no solid evidence supporting differentiated treatment effectiveness between monosensitization and polysensitization.[17] Nevertheless, the potential influence of polysensitization on AIT assessment should not be overlooked, especially in assessment relying on subjective methods, such as visual analog scale and combined symptoms and medication score, particulary for patients with multi-allergen-driven asthma.[27] Extra exposure to other allergens might diminish the subjective assessment of AIT efficacy, warranting specific allergen challenges to confirm treatment effectiveness.

Furthermore, we observed that responders exhibited a better baseline disease status compared to non-responders. This highlights the importance of conducting a comprehensive assessment of pre-treatment disease status, which should include evaluating disease control, the frequency of exacerbation, and particularly medication adherence. In instances of inadequate adherence to medication, priority should be given to improving compliance. Additionally, environmental pollution is widely acknowledged for its detrimental effects on asthma development and progression.[28–30] Despite this recognition, the significance of incorporating personal and environmental measures to avoid smoking during long-term AIT management has been under emphasized. In addition to considering an individual's allergic history and functional immune response to allergen stimulation, daily exposure to tobacco smoke may also contribute to a decline in the efficacy of AIT. Our findings highlight the importance of maintaining a smoke-free living environment for the success of AIT. Therefore, we propose that factors such as the sensitization immune background, medication adherence, and daily environmental pollution exposure should be thoroughly evaluated in the context of AIT. This is particularly important when treatment outcomes are not satisfactory in the early phases.

Evaluating the effectiveness of AIT after 1 year of treatment is a recommended step in assessing the potential for AIT cessation.[8] However, there is no consensus on the standard defining effective treatment after 1 year AIT. In our study, we identified the improvement from the up-dosing phase to maintenance I, represented by $\Delta edSMS_{U\text{-}M1}$, as an early response indicator with substantial predictive capacity for the outcome of 3y-AIT. However, due to the lack of standardization among allergen extracts (composition, concentration, dosage schedule, and administration route), the cut-off value for determining early clinical response to AIT needs specification for each allergen product and cohort. Nevertheless, early response to AIT could serve as a "pilot test" for the three-year AIT regimen. A favorable early response indicates successful AIT management, effective allergen desensitization, and beneficial environmental interventions, collectively supporting the efficacy of the consecutive three-year treatment. This principle may apply broadly across various types of immunotherapy products.

Despite our aim to use edSMS values for more accurate reflection of disease conditions compared to cross-sectional assessments, implementing such

assessment in routine clinical practice can be challenging due to difficulties in obtaining complete detailed records of each AIT injection over the extended three-year or even longer for AIT period, the complexity of the calculation process, which may limit clinical application. However, telemedicine might offer a convenient solution to address these limitations.[31] In addition, the edSMS assessment method needs to be validated in other cohorts to support its reliability and practicality. Our ongoing multi-center studies might be able to address this limitation. Furthermore, our retrospective data did not allow for a direct comparison between period-based and symptom-based individualized adjusted management. Therefore, prospective studies are needed to offer guidance in establishing recommended approaches for guiding adjusted treatment.

In conclusion, AIT has exhibited a significant immunomodulatory effect in patients with asthma. However, individual responses vary, with a total of 8 clinical response patterns observed, highlighting the need for a personalized approach to AIT management. This comprehensive approach should encompass a thorough baseline assessment, continuous monitoring of disease status, individualized treatment modifications, and measures to mitigate exposure to environmental pollutants. While direct correlations between pretreatment clinical parameters and AIT outcomes were not established in our study, $\Delta edSMS_{U\text{-}M1}$ appears as a suitable indicator for predicting responders to 3-year AIT, despite the variability in treatment responses observed. These findings are particularly relevant for guiding decisions on whether to continue or discontinue AIT early in the evaluation process, thereby preventing prolonged AIT treatment burden for non-responders.

Abbreviations

AIT: allergen immunotherapy; RCTs: randomized controlled trials; HDM: house dust mite; edSS: estimated daily symptoms score; edMS: estimated daily medication score; edSMS: estimated daily symptoms and medication score; $edSMS_U$: estimated daily symptoms and medication score of up-dosing phase; $edSMS_{M1}$: estimated daily symptoms and medication score of maintenance I phase; $edSMS_{M2}$: estimated daily symptoms and medication score of maintenance II phase; $edSMS_{M3}$: estimated daily symptoms and medication score of maintenance III phase; $\Delta edSMS_{U\text{-}M1}$: the change rate of edSMS from up-dosing phase to maintenance I phase; $\Delta edSMS_{U\text{-}M2}$: the change rate of edSMS from up-dosing phase to maintenance II phase; $\Delta edSMS_{U\text{-}M3}$: the change rate of edSMS from up-dosing phase to maintenance III phase

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, J.L., upon reasonable request.

Author contributions

Data curation: RH, RBH, YBG, and LH. Formal analysis: RQ and JL. Funding acquisition: JL. Methodology: RQ, WYF, and XS. Project administration: RQ, WYF, RBH, LH, YBG and JL. Resources: JL. Validation: RQ, WYF, XS, and JL. Visualisation: RQ, RQ, WYF, and XS. Writing–original draft: RQ and JL. Writing–review and editing: RQ, WYF, XS, and JL.

Ethics statement

This study was approved by the Ethics Review Board [IRB:2022–76] of the First Affiliated Hospital of Guangzhou Medical University.

Submission declaration

All the authors have reviewed the manuscript and agreed to submit it by acknowledging the submission declaration.

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Declaration of competing interest

The authors declare that they have no relevant conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100986.

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REFERENCES

1. Dhami S, Kakourou A, Asamoah F, et al. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. *Allergy*. 2017;72(12):1825–1848.
2. Bieber T, Simon HU. Allergen-specific immunotherapy: current concepts and future directions. *Allergy*. 2011;66(6): 709–712.
3. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol*. 2007;119(4):780–791.
4. Wang H, Lin X, Hao C, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. *Allergy*. 2006;61(2):191–197.
5. Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. 2012;129(3):717–725.
6. Vogelberg C, Klimek L, Bruggenjurgen B, et al. Real-world evidence for the long-term effect of allergen immunotherapy: current status on database-derived European studies. *Allergy*. 2022;77(12):3584–3592.
7. Shamji MH, Kappen JH, Akdis M, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. *Allergy*. 2017;72(8):1156–1173.
8. Agache I, Lau S, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: house dust mite-driven allergic asthma. *Allergy*. 2019;74(5):855–873.
9. Costa DJ, Amouyal M, Lambert P, et al. How representative are clinical study patients with allergic rhinitis in primary care? *J Allergy Clin Immunol*. 2011;127(4):920–926.
10. Herland K, Akselsen JP, Skjonsberg OH, et al. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? *Respir Med*. 2005;99(1):11–19.
11. Di Lorenzo G, Mansueto P, Pacor ML, et al. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. *J Allergy Clin Immunol*. 2009;123(5): 1103–1110, 1110-1111.
12. Fortescue R, Kew KM, Leung M. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev*. 2020;9:CD11293.
13. Dong X, Huang N, Li W, et al. Systemic reactions to dust mite subcutaneous immunotherapy: a 3-year follow-up study. *Allergy Asthma Immunol Res*. 2016;8(5):421–427.
14. Brozek JL, Bousquet J, Agache I, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol*. 2017;140(4):950–958.
15. Global Initiative for Asthma. *Global strategy for asthma management and pre_x0002_vention*; 2021. Available at: www.ginasthma.org. Accessed December 10, 2021.
16. Li J, Kong W, Lin J, et al. [Chinese expert consensus on clinical practice of allergen specific immunotherapy]. *Zhonghua Jiehe He Huxi Zazhi*. 2012;(3):163–166 [Article in Chinese][J].
17. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136(3): 556–568.
18. Tabar AI, Arroabarren E, Echechipia S, et al. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol*. 2011;127(1):61–63, 57-63.
19. Wang H, Lin X, Hao C, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. *Allergy*. 2006;61(2):191–197.
20. Feng M, Zeng X, Su Q, et al. Allergen immunotherapy-induced immunoglobulin G4 reduces basophil activation in house dust mite-allergic asthma patients. *Front Cell Dev Biol*. 2020;8:30.
21. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–338.
22. Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2003;(4):CD1186.
23. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev*. 2010;(8):CD1186.
24. de Blay F, Gherasim A, Casale TB, et al. Which patients with asthma are most likely to benefit from allergen immunotherapy? *J Allergy Clin Immunol*. 2022;149(3):833–843.
25. Ciprandi G, Cadario G, Di Gioacchino GM, et al. Sublingual immunotherapy in children with allergic polysensitization. *Allergy Asthma Proc*. 2010;31(3):227–231.
26. Ciprandi G, Cirillo I. Monosensitization and polysensitization in allergic rhinitis. *Eur J Intern Med*. 2011;22(6):e75–e79.
27. Crocker DD, Kinyota S, Dumitru GG, et al. Effectiveness of home-based, multi-trigger, multicomponent interventions with an environmental focus for reducing asthma morbidity: a community guide systematic review. *Am J Prev Med*. 2011;41(2 Suppl 1):S5–S32.
28. Silvestri M, Franchi S, Pistorio A, et al. Smoke exposure, wheezing, and asthma development: a systematic review and meta-analysis in unselected birth cohorts. *Pediatr Pulmonol*. 2015;50(4):353–362.
29. Ribeiro SA, Furuyama T, Schenkman S, et al. Atopy, passive smoking, respiratory infections and asthma among children from kindergarten and elementary school. *Sao Paulo Med J*. 2002;120(4):109–112.
30. Pietinalho A, Pelkonen A, Rytila P. Linkage between smoking and asthma. *Allergy*. 2009;64(12):1722–1727.
31. Ekeland AG, Bowes A, Flottorp S. Effectiveness of telemedicine: a systematic review of reviews. *Int J Med Inf*. 2010;79(11):736–771.