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ORIGINAL RESEARCH

Comorbidity of Allergic Asthma and Rhinitis and High Allergen-Specific IgE are Risk Factors for Systemic Reactions to House Dust Mite Immunotherapy in Children

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Objective: To observe the adverse reactions during standardized dust mite allergen subcutaneous immunotherapy (SCIT) in children with allergic asthma (AA) and/or allergic rhinitis (AR), and to analyze the clinical characteristics and potential risk factors.

Methods: This single-center retrospective cohort study included 250 children with allergic diseases who received house dust mite (HDM) SCIT treatment at our hospital from July 2022 to July 2025. The participants were divided into a systemic reactions (SRs) group and a non-SRs group. Differences in baseline clinical data and laboratory indicators between the two groups were compared, and independent risk factors for SRs were analyzed using the generalized estimating equation (GEE) method.

Results: Among 250 children (9,244 injections), 114 (45.6%) experienced SRs, with an incidence of 3.47% per injection. SRs were predominantly characterized by immediate, mild grade I reactions, with only 2 cases of grade III reactions and no fatal or serious adverse events. The incidence of SRs during the maintenance period was higher than during the up-dosing period. Univariate analysis showed that the occurrence of SRs was associated with age 5–9 years, AR combined with AA, elevated total immunoglobulin E (IgE), and high Dermatophagoides pteronyssinus (Der.p) specific IgE (sIgE) levels ($P < 0.05$). Multivariate GEE analysis showed that AR +AA comorbidity (compared to AA alone, odds ratio [OR] = 2.219, 95% confidence interval [CI]: 1.061–4.638, P=0.034) and baseline Der.p.sIgE ≥ 17.5 IU/mL (OR = 2.233, 95% CI: 1.216–4.099, P=0.01) were independent risk factors for SRs.

Conclusion: HDM SCIT in children demonstrates a favorable safety profile, with SRs being predominantly mild and dose-dependent. The presence of AR+AA comorbidity (compared to AA alone) and a baseline Der.p.sIgE ≥ 17.5 IU/mL are key predictors of SR risk. These findings support pre-treatment risk stratification and suggest that children with these risk factors may benefit from a more individualized and monitored SCIT protocol to enhance safety.

Keywords: allergic asthma, allergic rhinitis, subcutaneous immunotherapy, house dust mite, adverse reactions, pediatrics

Introduction

Allergic diseases, including allergic asthma (AA) and allergic rhinitis (AR), can reduce patients' quality of life and impose a socioeconomic burden. In children, they may also affect their growth, development, and psychological state, and have become a global public health issue that cannot be ignored. Although current drug therapies can alleviate the symptoms of allergic diseases, they cannot alter the disease's immunopathological progression.

Allergen-specific immunotherapy (AIT), the only causal treatment that can alter the natural progression of allergic disease, such as house dust mite (HDM)-driven allergic asthma (AA) and allergic rhinitis (AR), plays an indispensable role in clinical practice.[1,2] In pediatric patients, achieving durable symptom control and potentially altering the atopic march is of paramount importance. Subcutaneous immunotherapy (SCIT), a well-established form of AIT, has demonstrated robust efficacy in children, significantly reducing symptom burden and medication needs.[1,3] However, the SCIT

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treatment course can last from 3 to 5 years, and allergic adverse reactions may occur. Among these, systemic reactions (SRs) are the primary concern, as they affect treatment safety, patient compliance, and completion rates.

Previous studies in adults and children have identified several potential risk factors for SRs during SCIT. These include uncontrolled asthma at baseline, high allergen dose or rapid dose escalation, high levels of specific immunoglobulin E (sIgE) or total IgE, younger age, large local reaction in previous injection, and the presence of multiple allergies.[4,5] In particular, asthma has been consistently reported as a major risk factor, and international guidelines recommend that asthma should be fully controlled before initiating SCIT.[6,7] Currently, the risk factors for SRs associated with HDM-SCIT in children remain poorly understood, particularly due to a lack of large-scale clinical data in the Chinese pediatric population. This lack of evidence-based guidance complicates pre-treatment counseling and individualized safety management for pediatric allergists. This study employed a single-center retrospective cohort design to systematically analyze the core characteristics of SRs in children undergoing HDM-SCIT. Specifically, it will examine the incidence, timing, severity, and associations with treatment stage and vaccine concentration. This study aimed to identify independent risk factors for SRs, to provide evidence-based guidance for risk stratification before SCIT in children, to reduce the risk of SRs, and to improve adherence to and completion of treatment in pediatric patients.

Materials and Methods

Patients

This study included 250 children aged 5–14 years with dust mite AR who underwent standardized SCIT at the Allergy Department outpatient clinic of Shanghai Children's Hospital between July 2022 and July 2025. They were clinically diagnosed with AA and/or AR, which may be accompanied by allergic diseases such as cough variant asthma (CVA) or atopic dermatitis (AD), or allergic conjunctivitis. They also met the following criteria: (1) serum HDM-sIgE≥Grade 2 (may coexist with dust mite-sIgE ≥ Grade 2). Dermatophagoides pteronyssinus (Der.p) must be the main allergen for patients with multiple allergies; (2) Patients who also have asthma must have good symptom control and stable lung function for at least 4 weeks before immunotherapy.[8] Maintenance asthma control medications may be continued; (3) exclude contraindications listed in the product label; and (4) inform the patient (or child's guardian) about the duration, cost, efficacy, and potential risks of allergen immunotherapy, and obtain signed informed consent. We collected information on patients' sociodemographic characteristics, allergic disease diagnoses, eosinophil counts and percentages, total IgE and Der.p.sIgE levels, fractional exhaled nitric oxide (FeNO), and lung function measurements. The study was reviewed and approved by the ethics committee of the Shanghai Children's Hospital (No: 2025R009-E01). Due to the retrospective nature of the study, the requirement for informed consent was waived. All patient data has been anonymized and kept confidential in accordance with the Declaration of Helsinki.

Subcutaneous Immunotherapy

SCIT uses a standardized house dust mite allergen extract (Alutard, ALK, Denmark) and is administered in two phases: an initial treatment phase (up-dosing period) and a maintenance treatment phase (dose maintenance period).[7,9] The up-dosing period involves weekly injections starting at 20 SQ-U, with gradual dose escalation over 15 weeks. After a one-week interval, the maintenance phase is initiated at week 17. Once the maximum tolerated dose is reached, injection intervals are progressively extended to 4–6 weeks for maintenance therapy, continuing until the treatment regimen is completed. To mitigate or prevent potential adverse reactions, patients are administered an oral antihistamine 30 minutes before each injection. Additionally, patients are monitored in the hospital for at least 30 minutes following each injection.

Record the delayed adverse reactions of the patient after the previous injection, as well as any adverse reactions occurring within 30 minutes after the current injection. Include the timing of the adverse reactions, primary symptoms and clinical signs, changes in PEF, and the corresponding treatment interventions implemented.

Classification and Treatment of Adverse Reactions

Adverse reactions can be classified into Local adverse reactions (LRs) and SRs based on their clinical manifestations.[10] Additionally, adverse reactions are further categorized temporally as immediate reactions, occurring within 30 minutes post-injection, and delayed reactions, which arise after 30 minutes.

LRs are adverse reactions that occur at the injection site, including redness, swelling, induration, pruritus, and necrosis. For LRs, the observation time after injection is extended to 45–60 minutes. Temporary treatment typically includes oral antihistamines and the application of ice packs to the injection site.

SRs are classified into five levels according to the grading system established by the European Society of Allergy and Clinical Immunology (EAACI) for SCIT.[11,12] Grade 0: Asymptomatic or symptoms unrelated to immunotherapy; Grade I: Mild SR, local urticaria, rhinitis or mild asthma (PEF decreased by<20% from baseline); Grade II: Moderate SR, occurring slowly (>15 minutes), with systemic urticaria and/or moderate asthma (PEF decreased by<40% from baseline); Grade III: Severe (non fatal) SR, occurring rapidly (<15 minutes), resulting in systemic urticaria, angioedema, or severe asthma (PEF decreased by>40% from baseline); Grade IV: Allergic shock, rapid onset of systemic itching, flushing, erythema, urticaria, wheezing (angioedema), asthma attacks, hypotensive shock, etc. Symptomatic treatment should be given to grade I and II SRs, including oral antihistamines and/or nebulized inhalation therapy, and observation time should be extended until symptoms are completely relieved; Grade III or above SRs should be immediately treated with emergency measures, followed by the use of adrenaline or glucocorticoids and observation in the hospital. Hospitalization should be considered if clinically indicated. The dosage for the next injection still needs to be adjusted.[7,10]

Statistical Methods

Data processing and statistical analysis were performed using SPSS version 27.0, and a P-value<0.05 was considered statistically significant. Categorical variables are presented as frequencies or percentages, and between-group comparisons are conducted using the chi-square test or Fisher's exact test. For categorical variables that do not conform to the chi-square test hypothesis, continuity correction or Fisher's exact test was applied. Continuous variables that conform to the normal distribution are described as mean ± standard deviation (M±SD), and intergroup comparisons are conducted using independent sample t-tests or analysis of variance; while those that do not conform to the normal distribution are described using the median and interquartile range, expressed as M (Q1, Q3), intergroup comparisons are conducted using the Mann–Whitney U-test or Kruskal–Wallis H-test.

Due to the correlation among repeated measurements generated from multiple SCIT injections received by each child in this study, generalized estimating equations (GEE) were used to analyze the independent risk factors for SRs, with a test level of α=0.05.[13]

Results

Demographics of Participants

As shown in Table 1, this study included 250 patients with dust mite AA/AR who received standardized SCIT, comprising 172 males (68.8%) and 78 females (31.2%). The age range was 5.03 to 14.88 years, with a median age of 8.18 years. 186 (74.4%) were aged 5–9 years, and 64 (25.6%) were aged 10 years or older. Regarding clinical diagnoses, 65 patients had AR alone (26.0%), 26 had AA alone (10.4%), and 159 had AA+AR (63.6%). Concerning allergen sensitization profiles, 119 patients (47.6%) tested positive for single HDM allergens, 30 (12.0%) for HDM mixed inhalant allergens, 62 (24.8%) for HDM mixed food allergens, and 39 (15.6%) for HDM mixed inhalant and food allergens.

Incidence and Severity of Adverse Reactions

As shown in Table 2, adverse responses occurred in 212 (84.8%) of the 250 children undergoing standardized SCIT. With 9,244 injections given overall (37 on average per patient). Among the 250 patients, 197 (78.8%) experienced LRs, and 114 (45.6%) experienced SRs at least once during the treatment course. By the number of injections, adverse reactions occurred 1453 times (15.72%), including 1407 immediate reactions (15.22%) and 46 delayed reactions (0.5%). LRs occurred 1177 times (12.73%), and SRs occurred 321 times (3.47%).

Table 1 Baseline Characteristics of Patients and Differences Between the Group with SRs and Non-SRs

	Overall Patients (n=250)	Patients with SRs (n=114)	Patients with Non-SRs (n=136)	*P*-value
Gender, n (%)				
Male	172 (68.8)	78 (54.9)	94 (66.2)	0.906
Female	78 (31.2)	36 (46.2)	42 (53.8)	
Age (years), n (%)				
5-9	186 (74.4)	92 (49.5)	94 (50.5)	0.037
>10	64 (25.6)	22 (34.4)	42 (65.6)	
Diagnosis, n (%)				
AA alone	26 (10.4)	8 (30.8)	18 (69.2)	0.038
AR alone	65 (26.0)	24 (36.9)	41 (63.1)	
AA+AR	159 (63.6)	82 (51.6)*	77 (48.4)	
Allergen, n (%)				
Single HDM	119 (47.6)	52 (43.7)	67 (56.3)	0.546
HDM mixed inhalant	30 (12.0)	11 (36.7)	19 (63.3)	
HDM mixed food	62 (24.8)	31 (50)	31 (50)	
HDM mixed inhalant and food	39 (15.6)	20 (51.3)	19 (48.7)	
Total IgE (IU/mL), M (Q1, Q3)	576.00 (293.00, 930.50)	631.50 (360.75, 1042.50)	485.50 (244.75, 866.25)	0.015
Der.p sIgE (IU/mL), M (Q1, Q3)	25.80 (10.26, 55.29)	28.08 (14.01, 61.16)	23.05 (7.91, 48.43)	0.049
Der.p.sIgE/total IgE ratio, M (Q1, Q3)	0.04 (0.02, 0.08)	0.04 (0.03, 0.08)	0.04 (0.02, 0.08)	0.743
EOS count (10^9/L), M (Q1, Q3)	0.44 (0.24, 0.62)	0.48 (0.28, 0.66)	0.40 (0.22, 0.60)	0.085
EOS ratio (%), M (Q1, Q3)	5.50 (3.10, 7.53)	5.60 (3.80, 8.58)	5.50 (3.00, 7.23)	0.312
FeNO (ppb), M (Q1, Q3)	16 (12, 26)	15 (12, 27)	17 (12, 25.75)	0.317

Notes: *P*-value was calculated from the Chi-square test, Fisher's exact test, Independent-sample *t*-test, or Mann–Whitney *U*-test.*Based on the chi-square test, the Bonferroni method was used for multiple comparisons. The AR+AA group showed statistically significant differences compared to the AR-alone and AA-alone groups.
Abbreviations: SRs, Systemic reactions; AA, allergic asthma; AR, allergic rhinitis; HDM, house dust mite; Der.p., Dermatophagoides pteronyssinus; IgE, immunoglobulin E; sIgE, specific immunoglobulin E; EOS, peripheral eosinophil; FeNO, fractional exhaled nitric oxide.

Table 2 SCIT-Related Adverse Reactions

	Adverse Responses	LRs	SRs
Patients, n (%)	212 (84.8)	197 (78.8)	114 (45.6)
Injections, n (%)	1453 (15.7)	1177 (12.7)	321 (3.47)
Time of occurrence of adverse reactions			
Immediate reaction, n (%)	1407 (15.2)	1137 (12.3)	315 (3.4)
Delayed reaction, n (%)	46 (0.5)	40 (0.4)	6 (0.06)
Phase of adverse reactions			
Initial treatment, n (%)	374 (4.0)	287 (3.1)	101 (1.1)
Maintenance treatment, n (%)	1079 (11.7)	890 (9.6)	220 (2.4)

Abbreviations: LRs, Local reactions; SRs, Systemic reactions.

Frequency and Severity of LRs and SRs by Allergen Extract Vial and Concentration

As shown in Table 3, LRs included 1168 (12.55%) mild cases and 17 (0.18%) moderate cases. SRs included 283 (3.06%) grade I, 36 (0.39%) grade II, and 2 (0.02%) grade III; no grade IV adverse reactions were observed.

SRs occurred 101 times (31.5%) during the up-dosing period, 220 times (68.5%) during the dose maintenance period; 315 (98.1%) were immediate reactions and 6 (1.9%) were delayed reactions. No SRs occurred when using vial No. 1 for injection, while the highest number of SRs occurred with vial No. 4 (307/321). SRs are more common at high-dose stages above 20,000 SQ-U, accounting for 94.1% (302/321). The proportion of grade I reactions at doses above 20,000

Table 3 Frequency and Severity of LRs and SRs by Allergen Extract Vial and Concentration

Vial no.	Concentration (SQ-U)	Total Injections (n)	Total LRs (n)	LRs (n)		Total SRs (n)	SRs (n)		
				Mild	Moderate		Grade I	Grade II	Grade III
1	20	301							
	40	304	2	2					
	80	310	3	3					
2	200	303	5	5					
	400	305	4	4		2	2		
	800	307	13	12	1	2	2		
3	2000	296	10	8	2	2	2		
	4000	310	9	8	1	4	3	1	
	8000	302	31	31		4	4		
4	10,000	327	23	23		5	4	1	
	20,000	383	26	25	1	14	13	1	
	30,000	22	1	1		7	5	2	
	40,000	459	63	63		34	28	6	
	50,000	78	15	15		14	13	1	
	60,000	893	136	136		71	63	7	1
	70,000	131	33	32	1	2	2		
	80,000	972	202	199	3	61	55	6	
	90,000	80	17	17		3	3		
	100 000	3161	584	576	8	96	84	11	1
Total injections (n)		9244	1177	1160	17	321	283	36	2
Total injections (%)			12.64	12.55	0.18	3.47	3.06	0.39	0.02
Up-dosing phase (n)		4573	287	280	7	101	89	12	0
Dose maintenance phase (n)		4671	890	880	10	220	194	24	2
Immediate (n)		1407	1137	1124	13	315	277	36	2
Delayed (n)		46	40	36	4	6	6	0	0

Abbreviations: LRs, local reactions; SRs, systemic reactions.

SQ-U was 94.0% (266/283) of the total grade I reactions, and the proportion of grade II reactions was 94.4% (34/36) of the total grade II reactions. Two grade III reactions occurred during the dose maintenance phase with 6,000 SQ-U and 100,000 SQ-U.

Clinical Manifestations and Management of SRs

Of the 321 SRs, 288 injections (89.7%) presented with respiratory symptoms and signs, including coughing, chest tightness, wheezing, bilateral pulmonary wheezes, pharyngeal pain, throat itching, and respiratory distress. 53 injections (16.5%) caused skin and mucosal symptoms, including generalized urticaria, skin flushing and itching, eye itching, lacrimation, conjunctival hyperemia and edema, nasal itching, rhinorrhea, and sneezing. Among them, 26 injections (8.1%) involved respiratory and skin symptoms. Two injections (0.6%) caused digestive symptoms, with one injection producing only vomiting, while the other injection simultaneously caused respiratory, skin, and digestive symptoms, including cough, rash, and abdominal pain.

LRs, Grade I, and Grade II SRs receive symptomatic treatment while being closely monitored until all symptoms have been resolved. Patients were given topical cold compresses if they had severe localized redness, edema, rash, or itching. Nebulized β-agonists were used to alleviate respiratory symptoms in grade I and II SRs. Oral second-generation antihistamines were administered to patients who presented with skin/mucosal symptoms such as urticaria, conjunctivitis, or rhinitis. Both Grade III SR cases immediately received supine oxygen therapy with continuous vital sign monitoring, established intravenous access, and nebulized β-agonists. After stabilization, the patients remained hospitalized until their

symptoms resolved. There are no patients who require the use of adrenaline. Patients who experience adverse reactions will have their dosage adjusted according to regulations during the next allergen injection.

Specifically, for the 13 patients who experienced SR three times in a row, we reduced the dose of allergen preparation for the next injection and adopted a "split injection" treatment method—divided into two equal doses injected in different parts, with a 30-minute interval between the two injections.

In this study, 12 patients voluntarily discontinued SCIT treatment after experiencing SRs. Two cases occurred during the dose escalation phase (0.2 mL in vial no. 3 and 0.6 mL in vial no. 3), while the remaining 10 cases occurred during the dose maintenance phase (1.0 mL in vial no. 4).

Characteristics of SRs

We compared patients who experienced SCIT-related SRs (n=114) with those who did not have SRs (n=136) (Table 1). The age range of patients with SRs is 5–14 years; the incidence of SRs in the 5–9 age group was significantly higher than in the 10–14 age group (49.5% vs 34.4%, P = 0.037). There was no statistically significant difference in the incidence of SRs between genders.

After Bonferroni correction, multiple comparisons showed that the incidence of SRs in the AR+AA group (51.6%) was significantly higher than that in the AR group alone (36.9%) and the AA group alone (30.8%) (P<0.05 after correction), but there was no significant difference between the AR group alone and the AA group alone. In addition, we found that the total IgE (P = 0.015) and Der.p.sIgE (P = 0.049) levels of SCIT-related SR patients were significantly higher than those of patients without SRs. However, no correlation was observed with Der.p.sIgE/total IgE ratio, eosinophil count, eosinophil proportion, or FeNO levels. The incidence of SRs in individuals with single allergen positivity (house dust mite and/or dust mite), dust mite combined with inhalation allergen positivity, dust mite combined with food allergen positivity, and dust mite combined with both inhalation and food allergen positivity were 43.7%, 36.7%, 50%, and 51.3%, respectively, with no statistically significant differences.

In the study, 240 patients completed baseline pulmonary function testing. We compared forced vital capacity (FVC), forced expiratory flow in 1 second (FEV1), FEV1/FVC, and maximal mid-expiratory flow at 25%-75% (MMEF25-75) between the group experiencing SCIT-related SRs and the group with non-SRs. We found no statistically significant differences (Table 4).

Factors Related to the Occurrence of SRs During SCIT

Due to missing data on baseline lung function testing in a small number of patients (n=10), the GEE analysis was based on 8814 injections from 240 patients. We classified variables, including gender, age, diagnosis, allergen type, total IgE, Der.p.sIgE, peripheral eosinophils (EOS), FeNO levels, and lung function parameters, all of which were incorporated into the GEE analysis. The results are shown in Table 5.

Regarding diagnostic type, patients with AA+AR have a significantly higher risk of developing SRs compared to those with pure AA, with an odds ratio (OR) of 2.22 (95% confidence interval [CI]: 1.06–4.64, p = 0.034). Compared to patients with pure AR, the risk of adverse reactions in AA+AR patients showed an increasing trend; however, this difference was not statistically significant (OR = 1.62, 95% CI: 0.92–2.85, p = 0.094).

Table 4 Pulmonary Function Parameters of 240 Study Subjects

Parameters of Lung Function	OverallPatients (n=240)	Patients with SRs (n=110)	Patients with non-SRs (n=130)	*P*-value
FVC (%predicted), M ± SD	102.33±12.66	103.75±13.29	101.14±12.03	0.112
FEV_1 (%predicted), M ± SD	104.32±12.65	105.11±12.58	103.63±12.77	0.354
FEV_1/FVC (%predicted), M (Q1, Q3)	101.25 (96.93, 107.55)	101.60 (97.05, 106.75)	102.95 (94.48, 108.05)	0.406
$MMEF_{25-75}$ (%predicted), M ± SD	87.74±20.41	86.25±19.10	88.96±21.52	0.317

Note: *P*-value was calculated from the Independent-sample *t*-test, or the Mann–Whitney *U*-test.
Abbreviations: SRs, systemic reactions; FVC, forced vital capacity; FEV_1, forced expiratory flow in 1 second; $MMEF_{25-75}$, maximal mid-expiratory flow at 25%-75%.

Table 5 GEE Analysis of Risk Factors for SRs in HDM-SCIT Treatment

Variables	P-value	OR (95% CI)
Age≥10 years old (5–9 years old)	0.083	0.619 (0.36–1.064)
Gender = female (male)	0.224	1.316 (0.845–2.049)
Diagnosis = AR+AA alone (AR)	0.094	1.621 (0.921–2.853)
Diagnosis = AR+AA alone (AA)	0.034	2.219 (1.061–4.638)
Allergen = multiple (single HDM)	0.855	0.961 (0.624–1.479)
Total IgE≥1000 IU/mL (<1000 IU/mL)	0.762	0.922 (0.546–1.558)
Der.p.sIgE≥17.5 IU/mL (<17.5 IU/mL)	0.01	2.233 (1.216–4.099)
Der.p.sIgE/total IgE ratio≥0.8 (<0.8)	0.232	0.583 (0.241–1.411)
EOS count≥3.5 $\times 10^9$/L (<3.5 $\times 10^9$/L)	0.328	1.268 (0.788–2.04)
EOS ratio≥3.5% (<3.5%)	0.601	0.857 (0.48–1.529)
FeNO>20ppb (≤20ppb)	0.196	0.748 (0.482–1.161)
FVC<80% (≥80%)	0.734	0.707 (0.095–5.243)
FEV_1<80% (≥80%)	0.581	1.814 (0.219–15.06)
FEV_1/FVC<92% (≥92%)	0.437	1.457 (0.564–3.765)
$MMEF_{25-75}$<65% (≥65%)	0.861	1.067 (0.517–2.202)

Note: *P*-value was calculated from the Generalized Estimation Equation (GEE).
Abbreviations: SRs, Systemic reactions; AA, allergic asthma; AR, allergic rhinitis; HDM, house dust mite; Der.p, Dermatophagoides pteronyssinus; IgE, immunoglobulin E; sIgE, specific immunoglobulin E; EOS, peripheral eosinophil; FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity; FEV_1, forced expiratory flow in 1 second; $MMEF^{25-75}$, maximal mid-expiratory flow at 25%-75%.

Regarding allergy characteristics, patients with Der.p.sIgE levels≥17.5 IU/mL had a significantly higher risk of SRs compared to those with Der.p.sIgE levels < 17.5 IU/mL (OR = 2.23, 95% CI: 1.22–4.10, $p = 0.010$). There was no significant difference in the risk of adverse reactions between patients with multiple allergies and those with single dust mite allergies ($p = 0.855$). There was no significant association between total IgE levels ≥ 1000 IU/mL, sIgE/total IgE ratios ≥ 0.8, multiple allergies, and systemic adverse reactions.

Regarding demographic characteristics, the risk of SR in patients over 10 years old may be lower than that in children aged 5–9 years, and the association is close to statistical significance (OR=0.619, 95% CI: 0.360–1.064, $P = 0.083$). Gender, EOS, FeNO, and lung function indicators do not significantly affect the risk of adverse reactions.

Discussion

SCIT is currently the only etiological treatment capable of altering the natural progression of allergic diseases.[2,12] It is recommended by both domestic and international guidelines as a first-line therapy for AA and AR mediated by HDM in children.[14,15] Adverse reactions during the treatment process remain a key issue limiting its safe application. This study included 250 children with allergic diseases undergoing HDM SCIT. The characteristics of SR occurrence, along with related clinical and laboratory factors, were systematically analyzed to provide an evidence-based basis for risk stratification, individualized treatment planning, and safety management of SCIT in children.

This study showed that the overall safety of pediatric HDM-SCIT treatment was favorable, with 45.6% of children experiencing SRs during the treatment process. The incidence of SRs based on injection was 3.47%, which falls within the reported range for pediatric SCIT treatments both domestically and internationally (0.1%–45.2% of children; 0.01%–5.6% per injection).[16–20] This further confirms the manageable safety profile of SCIT in children with allergic diseases. The relatively higher incidence of SRs in our study compared to some previous reports may be explained by: (1) our cohort included a high proportion of patients with AR+AA (63.6%) and elevated baseline sIgE levels (median 25.80 IU/mL), both independent risk factors; (2) meticulous recording of all mild immediate reactions, which may be under-reported elsewhere; and (3) high maintenance doses (>20,000 SQ-U) where 94.1% of SRs occurred.

Regarding the characteristics of SRs occurrence, over 98% of SRs in this study were immediate-type reactions, with only a very small proportion being delayed-type reactions. This finding aligns with the pathogenesis of IgE-mediated

type I hypersensitivity reactions: SRs are primarily caused by the cross-linking of exogenous allergens with sIgE bound to the surface of mast cells and eosinophils, which rapidly triggers cell degranulation and the release of inflammatory mediators such as histamine and leukotrienes, and the vast majority of reactions occur within 30 minutes after injection.[21,22] This result provides a critical basis for clinical safety management, indicating that standardized observation for 30 minutes following SCIT injection is essential for preventing and controlling SRs and avoiding serious adverse events. This protocol should be strictly implemented in clinical practice, and the observation time should not be arbitrarily shortened.

This study observed that SRs were more common in the dose maintenance phase (68.5%) and high concentration doses (>20000 SQ-U, 94.1%), with the majority of SRs (90.74%) occurring during the injection of vial 4. This result is fully consistent with the dose-dependent characteristics of allergen-induced allergic reactions. Continuous exposure to high concentrations of allergens during the maintenance period can more significantly activate sensitized immune cells in the body, thereby increasing the risk of adverse reactions. Previous studies have suggested that the risk of adverse reactions during the up-dosing period is higher;[23] this difference may be related to variations in sensitization levels, dose escalation regimens, and asthma symptom control level of the enrolled population. Our findings suggest that, in clinical practice, for children receiving high-concentration injections during SCIT maintenance—especially when reaching the target maintenance dose for the first time—it may be beneficial to strengthen risk assessment and monitoring for high-risk children, although these findings should be confirmed in larger, prospective studies. In our study, SRs were predominantly mild (grade I, 3.06% and moderate (grade II, 0.39%), with only two grade III reactions (0.02%) and no life-threatening grade IV reactions occurring. All SRs were promptly resolved completely, further confirming that the incidence of serious adverse reactions in pediatric HDM-SCIT is extremely low, indicating good clinical safety.

In the association analysis between baseline clinical features and SRs, univariate analysis in this study showed a higher incidence of SRs in children aged 5–9, but multivariate GEE analysis did not identify age as an independent risk factor for SRs. This finding suggests that young children may have relatively low tolerance to SCIT allergen stimulation due to their immature immune systems, but age itself is not an independent determinant of SRs, and its influence may be masked or mediated by other stronger factors, such as comorbidities and sIgE levels. These results are consistent with previous research.[24,25] Therefore, there is no need to restrict the use of SCIT solely based on young age in clinical practice, but it is necessary to strengthen monitoring and nursing during treatment in young children.

In terms of disease diagnosis, this study found that compared with children with simple AA, children with AA complicated with AR have a more than doubled risk of developing SRs (OR=2.22). Although there is an increasing risk compared to children with simple AR (OR=1.62), the difference did not reach statistical significance. This suggests that the presence of airway diseases (asthma) may be the core of comorbidities that increase risk, but the combined effects of upper and lower airway inflammation still need to be taken seriously. Additionally, multiple studies suggest that asthma is a key risk factor for SRs during SCIT.[7,19,21,23] Our results strongly support the recommendations in international guidelines stating that asthma symptoms should be fully controlled before initiating SCIT treatment, and treatment should only begin after achieving complete asthma control and stable lung function.[7]
This indicates that, in clinical practice, for children with AA+AR comorbidities, strict control of treatment initiation indications is necessary, and monitoring of airway inflammation and symptoms should be strengthened during the treatment process to reduce the risk of SRs.

Univariate analysis in this study showed that baseline total IgE and Der.p.sIgE levels were significantly elevated in children with SRs. Multivariate GEE analysis further confirmed that a baseline Der.p.sIgE level ≥ 17.5 IU/mL was an independent risk factor for SRs. SIgE is the core antibody mediating type I hypersensitivity reactions. High titers of sIgE can place mast cells and eosinophils in a highly sensitized state, making them more susceptible to degranulation under SCIT allergen stimulation, thereby triggering SRs.[26] This cut-off value (17.5 IU/mL) can be used as a clinical summary risk assessment tool to help identify children who require more careful dose escalation or enhanced monitoring. In clinical practice, for children with Der.p.sIgE levels ≥17.5 IU/mL and a diagnosis of AR+AA, physicians may consider a more gradual dose escalation schedule (eg., extending the up-dosing phase beyond 15 weeks) and a longer post-injection observation period, these suggestions are based on clinical experience and the observation that most SRs occurred at high concentrations, and that further studies are needed to determine optimal protocols.

At the initiation of SCIT treatment in the children enrolled in this study, asthma symptoms were well controlled, and baseline lung function was generally within the normal range. Therefore, no correlation was observed between lung function indicators and SRs.

A small number of patients (n=13) showed a continuous occurrence pattern of SRs, suggesting that for such patients, more aggressive dose adjustment strategies (such as staged injections) may be needed to maintain treatment.

This study has several limitations. First, it is a single-center retrospective study with a limited sample size, which may introduce selection bias. The findings need to be validated through prospective, multicenter studies with larger samples. Second, this study did not analyze potential confounding factors such as symptom control level, concomitant medications, intercurrent infections during the treatment course, and treatment adherence during pediatric patient management, which may have influenced the results. Thirdly, the study did not analyze trends in SR changes or dynamic alterations in immune indicators over long-term treatment. Further longitudinal follow-up studies are warranted to explore these aspects. Finally, the Der.p.sIgE cutoff of $\geq$ 17.5 IU/mL is based on the routine clinical Grade 3 threshold used in our center; although this is a widely applied standard, its predictive value for SRs may vary in other populations and requires further validation in independent, preferably multicenter, cohorts.

Conclusion

In summary, this study confirms that the overall safety of pediatric HDM SCIT treatment is good, with mild and immediate SRs being the most common type of adverse response, while severe reactions are rare. Comorbidity of AR and AA, as well as a baseline Der.p.sIgE level $\geq$ 17.5 IU/mL, are independent risk factors for SRs in children undergoing HDM SCIT. In clinical practice, for high-risk children with AR combined with AA and high Der.p.sIgE levels, it may be beneficial to strengthen risk assessment before the start of SCIT, consider closer monitoring and more cautious dose escalation plans, and require external validation in larger, prospective cohorts.

Data Sharing Statement

All data generated in the production of this manuscript will be freely available upon request.

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Disclosure

The authors declare no conflicts of interest in this work.

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