



Serum vitamin D₃ deficiency can affect the efficacy of sublingual immunotherapy in children with allergic rhinitis: a retrospective cohort study

Liang Li^{1#}, Xiaojian Cui^{2#}, Xinjie Zhang^{3,4#}, Lisheng Zheng², Xuyuan Sun¹, Cuihong Yang¹, Jianbo Shu^{3,4}, Guangping Liu¹

¹Department of Otolaryngology, Tianjin Children's Hospital, Tianjin University Children's Hospital, Tianjin, China; ²Department of Clinical Laboratory, Tianjin Children's Hospital, Tianjin University Children's Hospital, Tianjin, China; ³Tianjin Pediatric Research Institute, Tianjin Children's Hospital, Tianjin University Children's Hospital, Tianjin, China; ⁴Tianjin Key Laboratory of Birth Defects for Prevention and Treatment, Tianjin, China

Contributions: (I) Conception and design: L Li; (II) Administrative support: G Liu; (III) Provision of study materials or patients: X Sun, C Yang, L Zheng; (IV) Collection and assembly of data: L Li, X Cui, X Zhang; (V) Data analysis and interpretation: L Li, X Cui, X Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Prof. Liang Li. Department of Otolaryngology, Tianjin Children's Hospital, Tianjin University Children's Hospital, Tianjin, China. Email: lilang_729@163.com.

Background: Sublingual immunotherapy (SLIT) is effective and convenient for many allergic patients but it is still ineffective for many children with allergic rhinitis (AR). In previous studies, most of the patients with poor efficacy of SLIT used the method of individualized adjustment of drug dosage. Currently, there are few reports on the relationship between serum vitamin D₃ level and the efficacy of SLIT.

Methods: In this study, 153 patients with AR who received SLIT were selected as the study objects. All patients collected serum for vitamin D₃ test before treatment. The clinical characteristics of the patients were collected, and all patients were regularly followed up for at least 6 months. The improvement rates were assessed according to the combined symptom medication score (CSMS). A receiver operating characteristic (ROC) curve was drawn, and the optimal cut-off point was determined according to the Youden index. Univariate and multivariate logistic regression were used to analyze the relationship between serum vitamin D₃ and SLIT efficacy. The odds ratios (ORs) and 95% confidence intervals (CIs) were computed by logistic regression.

Results: Of 153 AR patients, 101 patients entered the final statistical analysis. According to CSMS, 29.7% of patients in low response (LR) group. The mean vitamin D₃ level was (20.42±7.48) ng/mL. The optimal cutoff point for vitamin D₃ was 22.25 ng/mL. Univariate logistic regression analysis of SLIT efficacy showed that whether the patient also had a food allergy ($P<0.001$) or asthma ($P=0.011$), whether they used acarid products ($P=0.002$), and whether vitamin D₃ is sufficient ($P=0.001$) were significantly related to the efficacy of SLIT. Multivariate logistic regression analysis showed that after adjusting for whether the patient also had asthma and whether they had used acarid products, whether the patient also had a food allergy (OR: 12.13, 95% CI: 3.57–41.18, $P<0.001$) and whether vitamin D₃ is sufficient (OR: 22.21, 95% CI: 4.04–122.30, $P<0.001$) were independent factors affecting the efficacy of SLIT.

Conclusions: Serum Vitamin D₃ deficiency can affect the efficacy of SLIT in children with AR. This study provided a new therapeutic approach for SLIT patients with poor efficacy.

Keywords: Children; allergic rhinitis (AR); sublingual immunotherapy (SLIT); vitamin D₃

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Introduction

Allergic rhinitis (AR) is a common atopic and chronic disease in childhood. Globally, between 10% and 40% of children suffer from AR, and its prevalence has increased markedly over the past two decades (1). Through etiological research, researchers have found that AR is a complex disease with multiple factors, mainly including genetic as well as environmental factors, such as air pollution, infection, diet, and nutritional status. In recent years, the relationship between vitamin D₃ and allergic diseases has attracted our attention and become the focus of several studies.

In allergy-mediated allergic diseases, allergen-specific immunotherapy (SIT) targets sensitized allergens and is the only treatment that can change the natural progression of the disease (2). Based on the method of allergen administration, allergen-SIT is classified into two types: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) (3). At present, numerous international studies on the efficacy and safety of SLIT in children with AR have been conducted. Patients with poor SLIT efficacy usually receive individual dose adjustments to further improve its efficacy but there are still some children with poor efficacy who cease SLIT treatment. The incidence of low response (LR) in SLIT treatment varies significantly among the reports of many studies. This study provides a new treatment idea for patients with poor efficacy of SLIT, and vitamin D₃ supplementation may become a powerful method to enhance the efficacy of SLIT in the future. The present study aimed to identify the independent factors affecting the efficacy of SLIT and provide new ideas

for improving the efficacy of SLIT in children with AR. We present the following article in accordance with the STARD reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1883/rc>).

Methods

Patients

In this study, 153 patients with AR who received SLIT with *Dermatophagoides farinae* (*D. farinae*) drops in the Otorhinolaryngology Department of Tianjin Children's Hospital from January 2020 to October 2021 were selected as the study objects. The patient's sex, age, serum vitamin D₃ levels, family history of allergic disease, food allergies, their caregiver's education level, asthma status, whether they had used acarid products, etc. were collected retrospectively. All patients included in this study recorded their visual simulation scores, symptom scores, medication scores, and quality of life scores to evaluate the efficacy of SLIT. The primary endpoint of this study was the efficacy of patients treated with SLIT, and the independent influencing factors affecting the efficacy of SLIT were analyzed.

The enrolled patients were required to fully meet the following conditions: (I) diagnosed with AR, with or without other allergic diseases; (II) 3–14 years old, male or female; (III) allergen detection results: dust mites were positive, closely related to clinical symptoms and were the main allergen; (IV) allergens could be avoided as much as possible during treatment; (V) willing to receive SLIT and able to comply with the program and receive follow-up. The exclusion criteria were as follows: (I) patients with infectious rhinitis; (II) patients who could not understand the purpose of this study and refused to cooperate with follow-up; (III) those with incomplete data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Tianjin Children's Hospital (No. KY2020-47) and informed consent was taken from all the patients' guardians.

Diagnostic criteria

The diagnostic criteria applied in this study are based on the Guidelines for the Diagnosis and Treatment of Allergic Rhinitis in Children (2022, revised edition) (4), which include the following typical symptoms of AR: watery nose, itching, stuffy nose, sneezing (note: two or more items

Highlight box

Key findings

- Serum vitamin D₃ deficiency can affect the efficacy of SLIT in children with allergic rhinitis.

What is known and what is new?

- SLIT is effective, tolerable, and convenient for many allergic patients but is still ineffective for many children with allergic rhinitis.
- To identify the independent factors influencing the efficacy of SLIT, this study analyzed the relationship between vitamin D₃ and SLIT efficacy.

What is the implication, and what should change now?

- The main question under investigation in this study is whether vitamin D₃ supplementation can improve the efficacy of SLIT.

Table 1 Dose schedule of *D. farinae* drops for children <14 years of age

Week(s)	Drug No.	Dose, mL						
		1 day	2 days	3 days	4 days	5 days	6 days	7 days
1	1	0.05	0.1	0.15	0.20	0.30	0.40	0.50
2	2	0.05	0.1	0.15	0.20	0.30	0.40	0.50
3	3	0.05	0.1	0.15	0.20	0.30	0.40	0.50
4	4	0.15	0.15	0.15	0.15	0.15	0.15	0.15
≥5	4	0.15	0.15	0.15	0.15	0.15	0.15	0.15

needed to be met, and had to last or accumulate for more than 1 hour every day). At the same time, the following were considered typical signs of AR: pale and edema of the nasal mucosa and watery secretion of the nasal cavity. Allergen detection was determined as follows: dust mite serum-specific immunoglobulin E (IgE) was positive.

Detection of serum allergen-specific immunoglobulin E (sIgE)

We collected 3 mL of venous blood to separate the serum for use and used the Fubok allergen detector and its allergen diagnostic reagent produced by Jiangsu Haooubo Biological Medicine Co., Ltd. (Suzhou, Jiangsu Province, China) to determine the specific IgE of the corresponding allergen in the serum. The system adopts the enzyme-linked immunostaining method to detect the serum-specific IgE content, which is a quantitative detection. Inhalation allergens include house dust mites, dust mites, mugwort, ragweed, cockroaches, cat epithelia, dog epithelia, house dust, *Alternaria*, and willow. Food allergens include peanut, egg, milk, cod, wheat flour, shrimp, soybean, crab, beef, and mutton.

Determination of 25 hydroxyvitamin D3 [25(OH)D₃] in serum

The content of 25-hydroxyvitamin D₃ [25(OH)D₃] in the serum was detected by high-performance liquid chromatography (tandem mass spectrometry). An isotopic internal standard was added to 10 microliter serum samples. The protein in samples was precipitated with anhydrous ethanol and the target chemicals were extracted using n-hexane. After extraction, the supernatants were evaporated to dryness under a stream of nitrogen. The residue underwent the derivation process and the derivatizing products were redissolved and

chromatographically separated and quantified by mass spectrometry. The liquid chromatographic column was InfinityLab Poroshell 120 EC-C18 (4.6 mm × 50 mm, 2.7 μm), C18 guard column (Phenomenex, USA). The LC-20AD liquid chromatography-API 3200MD triple quadrupole mass spectrometer (Shimadzu, AB Sciex, USA) with an automatic injector was used.

Medication method and dosage of SLIT

AR patients were treated by sublingual administration of *D. farinae* drops (Changdi, produced by Zhejiang Wowu Biotechnology Co., Ltd., China). SLIT with *D. farinae* drops can be divided into two stages: the increasing stage and the dose maintenance stage. Children under 14 years of age used No. 1–4, among which the No. 1–3 preparation was used in the incremental phase and No. 4 preparation was used in the maintenance phase. *Table 1* shows the dosage schedule of *D. farinae* drops for children. To administer the medication, it should be swallowed 1–3 minutes after it is under the tongue. If the number of drops is too large, it can be taken several times. Patients could eat and drink normally 5 minutes after taking the medicine. Concurrent with desensitization treatment, symptomatic drugs must be used together as needed to control symptoms. The drug regimen should follow Global Initiative for Asthma (GINA) and allergic rhinitis and its impact on asthma (ARIA), and the patient's condition should be evaluated regularly. When the patient's condition improves, symptomatic drugs can be used for degrading treatment.

Follow-up

The follow-up plan was divided into two methods: telephone and outpatient follow-up, and Internet APP and WeChat follow-up. In principle, telephone follow-

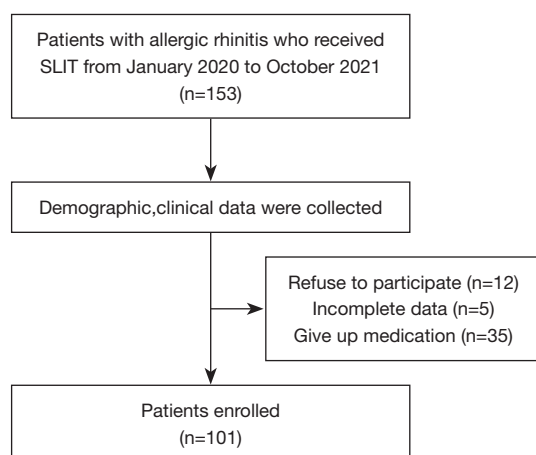


Figure 1 Study flow diagram. SLIT, sublingual immunotherapy.

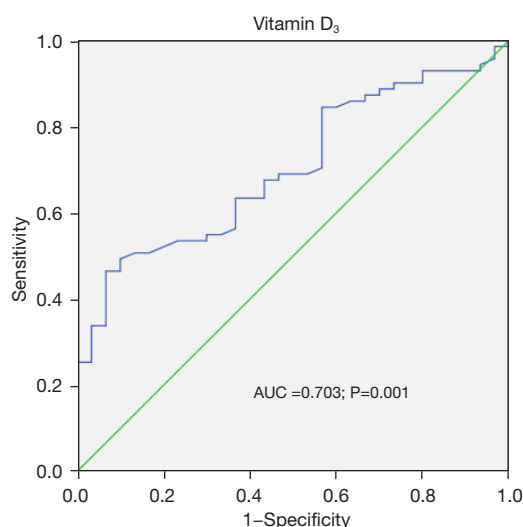


Figure 2 Receiver operating characteristic curve for vitamin D₃ predicting the efficacy of sublingual immunotherapy. AUC, area under the curve.

ups should be conducted once a month for the enrolled patients. The follow-up should include answering the patients' questions about sublingual medication, reminding them about the medication, and asking them about the use of symptomatic medication and their rhinitis symptoms. An outpatient follow-up visit should be conducted every 3 months. The follow-up content is the same as above, and the patient should be given a continuation of the prescription. Also, the latest knowledge about AR and precautions for SLIT should be popularized on the Internet APP. The symptom and medication questionnaire survey

were conducted through the Internet APP to follow up on the improvement of symptoms and medications of the children and monitor the adverse drug reactions to guide parents in their use of the drugs. A WeChat group should also be established, through which regular health lectures on AR can be given. We can also listen to the feedback of the children's parents, follow up on symptoms and medication, promote communication and interaction between families, and further enhance compliance.

Efficacy evaluation criteria

The patients were followed up after 6 months of treatment. According to the improvement rate of combined symptom medication score (CSMS), the patients were divided into high response (HR) and LR groups. Patients with CSMS improvement rates greater than 50% were defined as HR, while those with CSMS improvement rates between 20% and 50% were defined as LR (5).

Statistical analysis

A receiver operating characteristic (ROC) curve was drawn, the optimal cut-off point was determined according to the Youden index, and vitamin D₃ was converted into a classification variable. The Chi-square test was used to compare the categorical variables between groups. Univariate and multivariate logistic regression were performed to analyze the relationship between serum vitamin D₃ and the efficacy of SLIT. Statistically significant variables in univariate logistic regression analysis were included in multivariate regression analysis (using Enter method). Odds ratio (OR) value is used to measure the magnitude of the correlation effect. Two-tailed P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSSv26.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

A total of 153 patients were included in this study. Among them, 12 cases refused to participate in the study, 5 cases had incomplete data, and 35 cases ceased medication. The details are shown in Figure 1. The mean vitamin D₃ level of this patient cohort was (20.42±7.48) ng/mL. The optimal cutoff point for vitamin D₃ for the efficacy of SLIT (Figure 2) was determined according to Youden's index (cutoff value,

Table 2 Baseline clinical characteristics of the included patients

Characteristics	Total	Vitamin D ₃		P value
		≤22.25 ng/mL	>22.25 ng/mL	
Total, n (%)	101 (100.0)	66 (65.3)	35 (34.7)	
Sex, n (%)				0.629
Male	78 (77.2)	50 (75.8)	28 (80.0)	
Female	23 (22.8)	16 (24.2)	7 (20.0)	
Age, years, n (%)				0.524
≤6	39 (38.6)	24 (36.4)	15 (42.9)	
>6	62 (61.4)	42 (63.6)	20 (57.1)	
Family history of allergic disease, n (%)				0.341
No	26 (25.7)	15 (22.7)	11 (31.4)	
Yes	75 (74.3)	51 (77.3)	24 (68.6)	
Food allergy, n (%)				0.421
No	43 (42.6)	30 (45.5)	13 (37.1)	
Yes	58 (57.4)	36 (54.5)	22 (62.9)	
Education level of caregivers, n (%)				0.825
Higher education	39 (38.6)	26 (39.4)	13 (37.1)	
Not receiving higher education	62 (61.4)	40 (60.6)	22 (62.9)	
Follow-up mode, n (%)				0.938
Internet medical APP	64 (63.4)	42 (63.6)	22 (62.9)	
Traditional method	37 (36.6)	24 (36.4)	13 (37.1)	
Asthma, n (%)				0.361
No	61 (60.4)	42 (63.6)	19 (54.3)	
Yes	40 (39.6)	24 (36.4)	16 (45.7)	
Use of acarid products, n (%)				0.993
No	52 (51.5)	34 (51.5)	18 (51.4)	
Yes	49 (48.5)	32 (48.5)	17 (48.6)	
SLIT efficacy, n (%)				<0.001
High response	71 (70.3)	38 (57.6)	33 (94.3)	
Low response	30 (29.7)	28 (42.4)	2 (5.7)	

SLIT, sublingual immunotherapy.

22.25 ng/mL). Vitamin D₃ was then transformed into a classification variable according to this cutoff value (≤22.25, n=66; >22.25, n=35).

Table 2 shows the patients' baseline clinical characteristics according to vitamin D₃. The efficacy of SLIT among the different vitamin D₃ groups was statistically significant

(P<0.001). No significant differences existed between the vitamin D₃ groups in terms of the other clinical characteristics.

Finally, a total of 101 children with AR were included in this study. Among them, 78 cases (77.2%) were male, 39 cases (38.6%) were 3–6 years old, 75 cases (74.3%) had

Table 3 Logistic regression analysis of vitamin D₃ and the efficacy of SLIT

Variables	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Sex	1.26	0.44–3.59	0.67			
Age	0.47	0.18–1.20	0.11			
Family history of allergic disease	2.10	0.71–6.23	0.18			
Food allergy	10.95	3.88–30.90	<0.001	12.13	3.57–41.18	<0.001
Education level of caregivers	2.13	0.84–5.43	0.11			
Follow up mode	0.67	0.28–1.60	0.37			
Asthma	3.68	1.34–10.08	0.011	0.43	0.03–5.45	0.75
Use of acarid products	4.76	1.81–12.55	0.002	8.80	0.76–101.79	0.08
Whether vitamin D ₃ was sufficient	12.16	2.69–54.95	0.001	22.21	4.04–122.30	<0.001

SLIT, sublingual immunotherapy; OR, odds ratio; CI, confidence interval.

a family history of allergic diseases, 58 cases (57.4%) had food allergies, the main caregivers of 62 cases (61.4%) had no higher education, 64 cases (63.4%) had Internet APP follow-up, 40 cases (39.6%) had asthma, and 49 cases (48.5%) had acarid product use in their families. Also, 71 patients (70.3%) were classified into the HR group and 30 patients (29.7%) were in the LR group.

Logistic regression analysis

Univariate logistic regression analysis of the efficacy of SLIT (Table 3) showed that whether the patient also had food allergy ($P<0.001$) or asthma ($P=0.011$), whether they had used of acarid products ($P=0.002$), and whether vitamin D₃ is sufficient ($P=0.001$) were significantly related to the efficacy of SLIT, with statistically significant differences.

Subsequently, the above four variables were included in the multivariate analysis. Multivariate logistic regression analysis was performed to determine the independent factors influencing SLIT efficacy. Multivariate logistic regression analysis (Table 3) showed that after adjusting for whether the patient also had asthma and whether they had used acarid products, whether the patient also had a food allergy (OR: 12.13, 95% CI: 3.57–41.18, $P<0.001$) and whether vitamin D₃ is sufficient (OR: 22.21, 95% CI: 4.04–122.30, $P<0.001$) were independent factors affecting the efficacy of SLIT.

Discussion

SLIT can be used to treat allergic diseases. It is no longer

based on the failure of symptomatic drug treatment but is currently recommended as the initial first-line treatment for allergic respiratory diseases (6). SLIT is considered a disease improvement therapy that can prevent sensitization by new allergens and the progression of respiratory allergies (7). The first studies on the efficacy and safety of SLIT for children and adults with AR in China were published in 2007 and 2011 respectively (8,9). Therefore, as a disease improvement treatment scheme with good safety and tolerance, SLIT is currently recommended as the first-line treatment of AR in China (10). To guide and improve the effectiveness and safety of SLIT in clinical practice, the Chinese guidelines for SLIT of AR and asthma were published in 2019. These guidelines include the epidemiology, molecular mechanism, indications, and contraindications of SLIT, standardized allergen preparation, efficacy evaluation, and adverse event management of AR and asthma (11).

Sublingual administration of *D. farinae* drops improves the clinical symptoms of children with AR caused by dust mites and also enhances their immune function (12). Studies have confirmed the efficacy and safety of SLIT in children with AR coupled with single and multiple allergies and can achieve long-term efficacy (13–15). A study has shown that SLIT can effectively reduce the dose of inhaled corticosteroids (ICS) in adolescents with mild to moderate allergic asthma, with a good safety profile (16). Additionally, SLIT also improves disease severity and prevents new sensitization in children with an atopic dermatitis allergy to dust mites (17). Despite its good curative effect, SLIT still cannot improve the disease condition of some patients. For patients with poor SLIT

efficacy, individual dose adjustment is usually applied to further improve the efficacy (5); however, some children still have poor efficacy and cease SLIT treatment. Therefore, identifying the factors affecting the efficacy of SLIT is crucial.

Vitamin D₃ deficiency is positively correlated with the prevalence of allergy; A study has found that the OR remained significant after adjusting the model according to age, gender, race, smoking, drinking, and education (18). Vitamin D₃ deficiency is a risk factor for allergic diseases, especially in children (19). A study has shown that vitamin D₃ supplements can reduce the severity of atopic dermatitis and AR in children (20). Through animal experiments, some scholars have revealed that vitamin D₃ has a preventive and therapeutic effect on AR, which provides theoretical guidance for practical application (21). Comprehensive metabolomic analysis has demonstrated the links between vitamin D-related metabolites and the gut microbiome as well as immunosensitivity responses associated with childhood allergy (22). A systematic review and meta-analysis showed that vitamin D levels were not associated with the occurrence of AR but lower vitamin D levels were only associated with a higher prevalence of AR in children. Thus, there is insufficient evidence to support vitamin D supplementation to prevent AR.

However, doctors should consider assessing vitamin D deficiency in patients during AR treatment, especially in children (23). The incidence of vitamin D deficiency and insufficiency in Korean primary school students is very high. Low vitamin D levels are related to the recent symptoms of atopic dermatitis (AD) and AR (24). A study has shown that vitamin D deficiency is negatively related to mite-specific IgE levels, which may increase the susceptibility to early childhood allergies (including rhinitis and asthma) (25). A study has shown that adequate vitamin D levels are associated with a reduced risk of asthma attacks over a 3-year period (26). Compared with the healthy group, vitamin D deficiency was often observed in Egyptian children. A significant negative correlation was also identified between vitamin D levels and the severity of AR disease (27). Consistent with the above study, our study found that after adjusting for asthma and the use of acarid products, the adequacy of vitamin D₃ is an independent factor affecting the efficacy of SLIT. We also found that whether the patient also had a food allergy is an independent factor affecting the efficacy of SLIT. It may be that food allergies lead to dietary restrictions, which is related to the insufficient intake of vitamin D orally.

Chinese scholars have found that a certain proportion

of people of all ages in Hainan has vitamin D deficiency and insufficiency. Formal recommendation for vitamin D supplementation should be considered, especially in children over 7 years of age in autumn and winter (28). The common international classification of vitamin D nutritional status is as follows: vitamin D concentration less than 10 ng/mL is considered a severe deficiency; 10–25 ng/mL is considered a deficiency; 25–30 ng/mL is considered insufficiency; 30–100 ng/mL is considered normal; 100–150 ng/mL is considered excessive; and over 150 ng/mL is considered poisoning (29). The cutoff value of vitamin D₃ in this study was 22.25 ng/mL, which is basically consistent with the international reference standard and is convenient for clinical application. In the clinical application of SLIT for the treatment of AR in children, we should pay more attention to children with vitamin D deficiency. In future research, we will attempt to observe whether vitamin D supplementation can enhance the efficacy of SLIT in children with poor efficacy.

Jerzyńska *et al.* found that vitamin D 1,000 IU daily supplementation as a supplementary treatment of grass pollen allergy in children with pollen seasonal AR significantly reduced the symptom/drug score. They revealed the immunotherapeutic effect of vitamin D on AR in children (30). A study has found that vitamin D supplementation can enhance the efficacy of antihistamines in AR patients with vitamin D deficiency (31). Vitamin D₃ can also enhance the efficacy of SLIT by stimulating allergen-specific helper T cells (TH1) and regulatory T cells (Treg) (32). Although some studies have shown that vitamin D supplementation may play a role in the prevention of allergic diseases, other studies do not support this hypothesis. It is not possible to determine the effect of vitamin D on allergic diseases. Further research should focus on large, multicenter human studies to explore the dose of vitamin D supplementation at different stages of life and identify the key factors affecting efficacy.

This study has some limitations that should be considered. Due to the limited resources and number of patients, the small sample size may limit the generalizability of the results of this study to a larger population. In addition, the short follow-up period is another drawback, and we will extend the follow-up period in the future to enhance the reliability of our conclusions.

Conclusions

The present study found that whether vitamin D₃ is

sufficient is an independent factor affecting the efficacy of SLIT. Therefore, serum vitamin D₃ deficiency can affect the efficacy of SLIT in children with AR. This study provided a new therapeutic approach for SLIT patients with poor efficacy, and vitamin D₃ supplementation may be a powerful way to enhance SLIT efficacy in the future.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1883/rc>

Data Sharing Statement: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1883/dss>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Tianjin Children's Hospital (No. KY2020-47) and informed consent was taken from all the patients' guardians.

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