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Impact of COVID-19 on adverse reactions to subcutaneous specific immunotherapy in children:a retrospective cohort study

Jingjing Li[1,2†], Yanling Chen[1,2†], Hong Ye[1,2], Qiuyu Tang[1,2], Chengyi Wang[1,2], Qing Zhou[1,2], Ling Lin[1,2], Liyuan Jiang[1,2], Xiuling Peng[1,2], Huimin Zhang[1], Haibo Li[2*] and Lumin Chen[1,2*]

Abstract

Background COVID-19 is a new infectious disease. To investigate whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection increases the adverse reactions of subcutaneous specific immunotherapy (SCIT) in children.

Methods This study was conducted by collecting relevant data from children who underwent house dust mite SCIT from April 3, 2021, to March 18, 2023, including information on the time of COVID-19 infection, symptoms, and adverse reactions after each allergen injection. A mixed effects model was used to analyze the changes in adverse reactions before and after the COVID-19 infection.

Results Among the records of adverse reactions from 2658 injections in 123 children who underwent SCIT, the overall adverse reaction rate before COVID-19 infection was 39.8% and 30.0% after COVID-19 infection. Compared with pre-infection with COVID-19, the risks of overall adverse reactions, local adverse reactions, and systemic adverse reactions of immunotherapy after COVID-19 infection were reduced (odds ratio [OR] = 0.24, 0.31, and 0.28, all $P < 0.05$). Among the local adverse reactions, the incidence of the unvaccinated group was the highest (15.3% vs. 7.1%). The incidence of overall and local adverse reactions to SCIT decreased in 2-vaccinated COVID-19 recipients (OR = 0.29–0.31, $P < 0.05$).

Conclusions In children, SARS-CoV-2 infection does not increase the incidence of adverse reactions to SCIT. This finding can provide a basis for the implementation of allergen-specific immunotherapy (AIT) during the COVID-19 pandemic.

Keywords Adverse reactions, COVID-19, Children, SCIT

†Jingjing Li and Yanling Chen contributed equally to this work and should be considered co-first authors.

*Correspondence:
Haibo Li
haiboli89@163.com
Lumin Chen
clm2020@yeah.net
[1] Fujian Branch of Shanghai Children's Medical Center, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Children's Hospital, Fujian Maternity and Child Health Hospital, Fujian Medical University, Fuzhou 350001, China
[2] College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Maternity and Child Health Hospital, Fujian Medical University, Fuzhou 350001, China

Background

The new pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected in late 2019 and rapidly disseminated globally, leading to a pandemic. The World Health Organization (WHO) designated the Coronavirus illness 2019 (COVID-19) in February 2020 [1]. The COVID-19 pandemic has presented an unparalleled challenge to the global healthcare infrastructure. Although we have gradually entered a post-COVID-19 era after several years of struggle, this does not equate to the virus's eradication. As our understanding of the virus's characteristics and transmission patterns deepens, researchers are uncovering a potential link between viral infection and allergic disorders. Studies suggest that allergic individuals exhibit a reduced susceptibility to the novel coronavirus [2]. However, a new large-scale cohort study involving several countries reveals that the risk of allergic diseases persists and significantly increases even six months post-COVID-19 infection [3].

Allergic diseases, marked by their chronic and relapsing characteristics, have become a focal point for 21st-century health initiatives, with a notable and sustained increase in global prevalence each year [4–6]. The current approach to treating allergic diseases combines prevention with treatment, emphasizing the importance of allergen-specific immunotherapy (AIT) as the only method that can change the progression of allergies [7]. International guidelines recommend starting AIT early when the circumstances are appropriate [8–10]. AIT is a therapeutic approach where patients are repeatedly exposed to specific allergens over a period of 3–5 years, with the aim of modulating the aberrant type 2 immune response to induce immune tolerance [11]. Current evidence substantiates the safety and efficacy of AIT [12, 13], Subcutaneous specific immunotherapy (SCIT) and sublingual specific immunotherapy (SLIT) are the two principal modalities of AIT. The repeated administration of allergens, which is essential for these treatments, can lead to adverse reactions that may reduce the compliance of AIT. The high transmissibility and persistence of COVID-19 are likely to significantly hinder the implementation of AIT.

Even though COVID-19 was deemed to be no longer a "global public health emergency" by the WHO in May 2023, the virus has not disappeared, and its potential effects on humans remain unclear. Youngsters are a unique group. Will COVID-19 infection during the pandemic enhance the likelihood of treatment-related side effects for children with allergies who require SCIT for a minimum of three years? Should the course of therapy be discontinued due to the COVID-19 infection? There isn't currently a consensus on this matter. We conducted a retrospective cohort study to compare the adverse reactions to immunotherapy before and after infection with COVID-19 in children undergoing SCIT in our hospital, hoping to provide a basis for the implementation of SCIT during the COVID-19 epidemic.

Methods

Study design

This was a retrospective study. We enrolled children receiving mite SCIT in our hospital's desensitization treatment center from April 3, 2021, to March 18, 2023. The standardized house dust mite allergen vaccine selected for SCIT in this study was produced by ALK Company in Denmark, and we implemented the therapeutic dose schedule according to its instructions. Initially, we gradually increase the dosage by administering injections once a week, and during the maintenance phase, we commonly administer injections every 4–8 weeks, with a 6-week interval. Follow the instructions in the product manual to adjust to the delayed injection dosage (Supplementary Table 1).

Figure 1 illustrates the procedure of SCIT. Professionally trained allergist physicians and nurses follow a rigorous and standardized injection protocol throughout the SCIT course. We precede and follow each injection session with a thorough medical history review, physical examination, peak expiratory flow rate monitoring, and detailed documentation of each visit. Patients are observed for half an hour post-injection to ensure safety before they are discharged. Additionally, a WeChat follow-up group has been established to facilitate communication between medical staff and patients.

We adhered to the international guidelines set by the European Academy of Allergology and Clinical Immunology (EAACI) during the COVID-19 pandemic [14]. SARS-CoV-2 nucleic acid or antigen testing is conducted for each patient prior to injection. If the test results are positive, we postpone the injection until the clinical symptoms have completely resolved, the body temperature has stabilized for at least three consecutive days, and the antigen test has turned negative. The injection is resumed only after a physician's assessment and thorough communication with the patient and their family. Follow the product manual's instructions to adjust the delayed injection dosage (Supplementary Table 2).

The study was approved by the Ethics Committee of Fujian Children's Hospital. The ethics batch number was 2023ETKLR05098. All patients provided written informed consent signed by their guardians. We confirm that all methods were performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments or similar ethical standards.

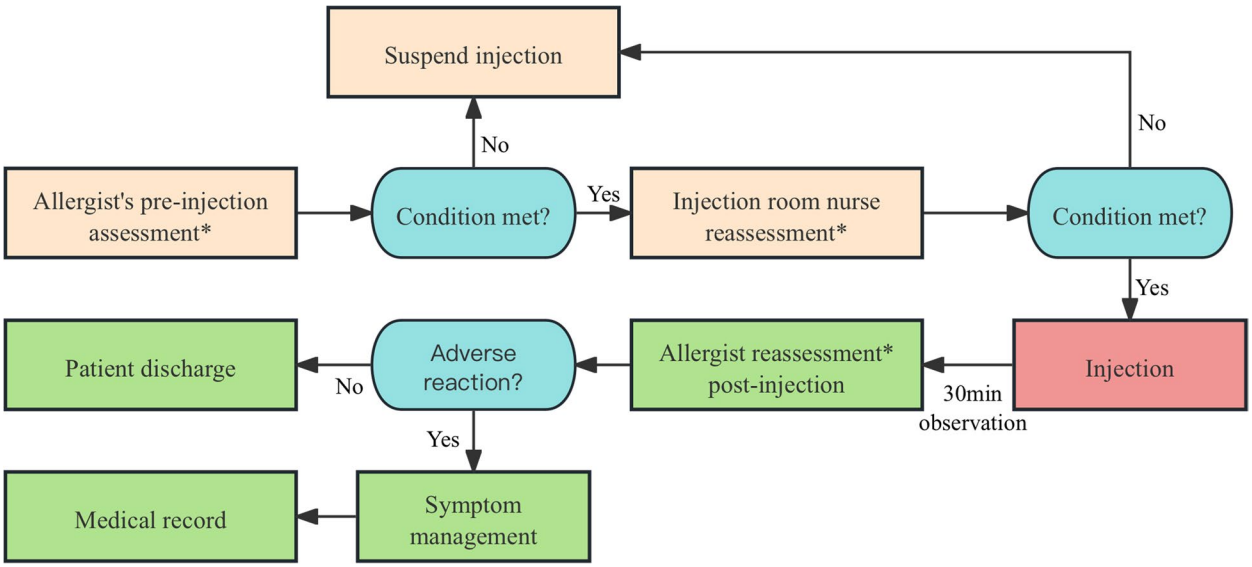

Fig. 1 Procedure of subcutaneous specific immunotherapy (SCIT). *The assessment includes: infection status (including COVID-19), allergic state, exercise status prior to injection, reaction to the last injection, pre- and post-injection peak expiratory flow (PEF) values, and lung auscultation findings

Study population

The study collected data from 142 patients who underwent mite SCIT in the Desensitization Center of Fujian Children's Hospital. According to the EAACI Allergen Immunotherapy User's Guide [15], 123 patients were included in the final analysis after the following inclusion and exclusion criteria were applied. Inclusion criteria: (1) children aged 4–16 years; (2) mite sIgE was positive (by the ImmunoCAP method), and mite was the main allergen; (3) confirmed allergic diseases, including allergic rhinitis (AR), allergic asthma (AA), allergic conjunctivitis (AC), atopic dermatitis (AD), etc.; (4) a pulmonary function test showed forced expiratory volume in 1 s (FEV1) ≥ 80% predicted. Exclusion criteria: (1) severe or uncontrolled asthma [FEV1 < 70% predicted]; (2) patients treated with β-blockers or angiotensin-converting enzyme inhibitors (ACEI); (3) patients with serious cardiovascular and cerebrovascular diseases, immune diseases (including autoimmune diseases and immunodeficiency diseases), malignant diseases, or chronic infectious diseases; (4) patients with severe mental illness, lack of compliance, or inability to understand the risks and limitations of treatment. (5) interruption of subcutaneous specific immunotherapy during the study; (6) patients receiving SCIT cluster immunotherapy. The inclusion and exclusion process is depicted by the flowchart in Supplementary Fig. 1.

Sample size and power analysis: Sample size and power were determined based on the "Time-Averaged Difference (Binary Data) Power Analysis" method. Sample sizes of 108 achieve 80% power to detect an odds ratio (OR) of 2.5 (assumed effect size of COVID-19 infections [binary independent variable] with adverse reactions to vaccination) in a design with 24 repeated measurements having a Compound Symmetry covariance structure when the proportion from the control group is 0.5, and the alpha level is 0.05.

Data collection

Patients need to visit the hospital on multiple occasions for injections, and we collect any missing information through a range of methods, including direct communication, phone calls, and WeChat messages, to ensure our data remains complete and precise. Furthermore, we use electronic medical records to keep patient data up-to-date, monitor their progress, and enhance collaboration among healthcare providers, all of which help to ensure holistic and high-standard patient care.

The following information was collected from each mite SCIT patient:

1) Primary disease diagnosis, age, gender, height, weight, and number of SARS-CoV-2 vaccinations;
2) The time of the SARS-CoV-2 infection;
3) The time of each injection, injection concentration, injection volume, and adverse reactions after injection were recorded.

Adverse reactions were divided into local adverse reactions (LRs) and systemic adverse reactions (SRs). Local

adverse reactions refer to the occurrence of local itching, redness, swelling, induration, necrosis, and other phenomena at the injection site. Systemic adverse reactions were classified into four grades according to the criteria of the EAACI [16].

Data analysis and statistics

Measurement data were expressed as Mean ± SD based on the normal distribution. Differences among groups were analyzed by Student t test or one-way Analysis of Variance (ANOVA). Qualitative data were described as n (percentages, %) and analyzed using Chi-square test or Fisher's exact test as indicated. Analysis of repeated measures data using a multivariate generalized linear mixed effect model for binomial (overall adverse reactions) and multinomial (local and system adverse reactions) responses, COVID-19 infections as the binary independent variable, and considering random (with intercept) and fixed effects for the time and number of measurements for each child. We chose these confounders on the basis of clinical interest, previous scientific literature. Covariates that have been known to affect the SCIT or be associated with COVID-19 were chosen a priori and adjusted in the mixed models. These included injection volume, concentration, gender, age, body mass index (BMI), number of COVID-19 vaccine injections, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, asthma, and cough variant asthma. The adjusted ORs (of fixed effect) with 95% confidence interval (CI) were reported, and the Wald test and likelihood ratio test were used for hypothesis testing. Moreover, E-values were calculated to assess the effect of unmeasured confounding.

All the analyses were performed with the statistical software packages R 4.2.2 (http://www.R-project.org, The R Foundation) and Free Statistics software versions 1.8 (FreeClinical, Beijing, China). The P-value reported was two-sided, and a value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics were presented in Table 1 and Supplementary Figs. 2–3. According to the exclusion criteria, 11 children who had discontinued treatment for various reasons and 8 children who had cluster treatment were excluded. A total of 123 children aged 4–16 years were finally included in the study, among whom 87 (70.8%) were boys. 108 patients were infected with SARS-CoV-2 (87.8% vs. 12.2%). The vast majority of COVID-19 cases were mild (87.0% vs.0.8%), with no severe cases, and 22% of COVID-19 cases were asymptomatic. The main clinical symptoms were fever and cough.

COVID-19 infection and allergy treatment according to the occurrence of adverse reactions

We analyzed desensitization treatment, COVID-19 vaccination, and infection according to the occurrence of adverse reactions in 2658 injection records (Table 2). Among the different adverse reaction groups, there were statistical differences in dose, drug concentration, number of COVID-19 vaccination injections, and COVID-19 infections ($P<0.05$). In the group with systemic adverse reactions, the highest rate of 1 ml doses (63.6% vs. 30.4% in no adverse reactions) and the highest rate of 1e+05 drugs concentrations (91.7% vs. 49% in no adverse reactions) were observed; in the group with local adverse reactions, the highest rate was in the group with no previous COVID-19 vaccination (15.3% vs. 7.1% in no adverse reactions), but the lowest rate occurred after infection with COVID-19 (7.3% vs. 12.2% in no adverse reactions).

The association between COVID-19 infections and adverse reactions

Table 3 shows the association between COVID-19 infections and adverse reactions. Using a mixed effect model to deal with the random effects of repeated measures for each child (2,658 injections recorded in 123 children), the results of the crude model analysis showed that relative to pre-infection with COVID-19, receiving immunotherapy after infection with COVID-19 showed a decreased risk of developing overall adverse reactions and LRs (OR = 0.55 and 0.67, $P<0.05$), but no statistically significant effect was found on the risk of developing SRs ($P>0.05$). After adjusting for potential confounders (volume, concentration, gender, age, BMI, number of COVID-19 vaccination injections, AD, AR, AC, AA, CVA), the risk of overall adverse reactions, LRs, and SRs were reduced after infection with COVID-19 (OR = 0.24, 0.31 and 0.28, respectively; all $P<0.05$).

In addition, a mixed effect model analysis also found that increased dose and drug concentration increased the risk of local and systemic adverse reactions (OR = 1.13–61.47, $P<0.05$), while previous vaccination with COVID-19 may have reduced the incidence of overall and local adverse reactions (OR = 0.29–0.31, $P<0.05$). See Supplementary Tables 3–4 for more information.

Additional and sensitivity analyses

Moreover, E-values were calculated to assess the effect of unmeasured confounding. We calculated an E-value of 5.91 with a lower 95% CI of 3.77 (Supplementary Fig. 4), which is a relatively strong effect size, suggesting that unmeasured confounding is unlikely to reverse the results of the current study.

Table 1 Baseline Characteristics of the study children

Variables	Total ($n=123$)	Boys ($n=87$)	Girls ($n=36$)	*P* value
Age, year	7.2 ± 2.3	7.2 ± 2.3	7.3 ± 2.6	0.958
Height, cm	129.4 ± 14.8	130.1 ± 14.8	127.7 ± 15.0	0.405
Weight, kg	29.6 ± 11.4	30.3 ± 11.7	27.8 ± 10.4	0.274
BMI, km/m^2	17.1 ± 3.5	17.4 ± 3.7	16.5 ± 3.0	0.237
Number of COVID-19 vaccination doses, n (%)				0.171
0	12 (9.8)	8 (9.2)	4 (11. 1)	
1	11 (8.9)	6 (6.9)	5 (13.9)	
2	95 (77.2)	71 (81.6)	24 (66.7)	
3	5 (4. 1)	2 (2.3)	3 (8.3)	
Atopic dermatitis(AD), n (%)				0.379
No	100 (81.3)	69 (79.3)	31 (86. 1)	
Yes	23 (18.7)	18 (20.7)	5 (13.9)	
Allergic rhinitis(AR), n (%)				0.67
No	6 (4.9)	5 (5.7)	1 (2.8)	
Yes	117 (95. 1)	82 (94.3)	35 (97.2)	
Allergic conjunctivitis(AC), n (%)				0.758
No	104 (84.6)	73 (83.9)	31 (86. 1)	
Yes	19 (15.4)	14 (16. 1)	5 (13.9)	
Allergic asthma(AA), n (%)				0.261
No	76 (61.8)	51 (58.6)	25 (69.4)	
Yes	47 (38.2)	36 (41.4)	11 (30.6)	
Cough variant asthma(CVA), n (%)				0.026
No	103 (83.7)	77 (88.5)	26 (72.2)	
Yes	20 (16.3)	10 (11.5)	10 (27.8)	
COVID-19 infection status				0.033
The uninfected	15 (12.2)	8 (9.2)	7 (19.4)	
Symptomatic	81 (65.8)	55 (63.2)	26 (72.2)	
Asymptomatic	27 (22.0)	24 (27.6)	3 (8.3)	
Duration of COVID-19 symptoms (days)				
	4.3 ± 3.3	4.1 ± 3.3	4.5 ± 3.4	0.546
Classification of COVID-19 severity				
Mild disease	107 (87.0)	79 (90.8)	28 (77.8)	
Moderate disease	1 (0.8)	0 (0.0)	1 (2.8)	
Clinical symptoms of COVID-19				< 0.001
Fever	74 (60.2)	52 (59.8)	22 (61. 1)	
Cough	44 (35.8)	30 (34.5)	14 (38.9)	
Nasal congestion	24 (19.5)	14 (16. 1)	10 (27.8)	
Sore throat	21 (17. 1)	15 (17.2)	6 (16.7)	
Runny nose	20 (16.3)	11 (12.6)	9 (25)	
Fatigue	13 (10.6)	10 (11.5)	3 (8.3)	
Headache	13 (10.6)	8 (9.2)	5 (13.9)	
Dizziness	12 (9.8)	8 (9.2)	4 (11. 1)	
Muscle soreness	9 (7.3)	7 (8.0)	2 (5.6)	
Hoarseness	3 (2.4)	3 (3.4)	0 (0.0)	
Changes in taste	3 (2.4)	1 (1. 1)	2 (5.6)	
Changes in smell	3 (2.4)	2 (2.3)	1 (2.8)	
Vomiting	3 (2.4)	1 (1. 1)	2 (5.6)	
Diarrhea	2 (1.6)	1 (1. 1)	1 (2.8)	
Wheezing	2 (1.6)	1 (1. 1)	1 (2.8)	
Chest distress	1 (0.8)	0 (0.0)	1 (2.8)	

Measurement data were expressed as Mean ± SD. Differences among groups were analyzed by Student t test or one-way ANOVA. Qualitative data were described as n (%) and analyzed using Chi-square test or Fisher's exact test

n in this table indicates the number of child

Table 2 COVID-19 infection and allergy treatment according to the occurrence of adverse reactions

Variables	Total($n=2658$)	Adverse reactions			*P* value
		None ($n=1628$)	LRs ($n=898$)	SRs ($n=132$)	
Volume of injection, n (%)					**< 0.001**
0.1	121 (4.6)	63 (3.9)	53 (5.9)	5 (3.8)	
0.2	482 (18. 1)	347 (21.3)	127 (14. 1)	8 (6. 1)	
0.4	480 (18. 1)	331 (20.3)	135 (15)	14 (10.6)	
0.6	119 (4.5)	62 (3.8)	48 (5.3)	9 (6.8)	
0.8	482 (18. 1)	330 (20.3)	140 (15.6)	12 (9. 1)	
1	974 (36.6)	495 (30.4)	395 (44)	84 (63.6)	
Concentration of injection, n (%)					**< 0.001**
100	363 (13.7)	320 (19.7)	43 (4.8)	0 (0)	
1000	361 (13.6)	269 (16.5)	91 (10. 1)	1 (0.8)	
10,000	362 (13.6)	241 (14.8)	111 (12.4)	10 (7.6)	
1e+05	1572 (59. 1)	798 (49)	653 (72.7)	121 (91.7)	
Number of COVID-19 vaccination doses, n (%)					**< 0.001**
0	260 (9.8)	115 (7. 1)	137 (15.3)	8 (6. 1)	
1	233 (8.8)	122 (7.5)	107 (11.9)	4 (3)	
2	2058 (77.4)	1330 (81.7)	611 (68)	117 (88.6)	
3	107 (4.0)	61 (3.7)	43 (4.8)	3 (2.3)	
COVID-19 infection status, n (%)					**< 0.001**
before	2375 (89.4)	1430 (87.8)	832 (92.7)	113 (85.6)	
after	283 (10.6)	198 (12.2)	66 (7.3)	19 (14.4)	

LRs Local adverse reactions, *SRs* Systemic adverse reactions

n in this table indicates the number of treatment injections

Table 3 Analysis of the association between COVID-19 infections and adverse reactions to vaccination based on a mixed effect model

Variable	No. of Adverse reactions, %	Crude		Adjusted[a]	
		OR (95%CI)	*P* value	OR (95%CI)	*P* value
Overall adverse reactions					
Before the COVID−19	945 (39.8)	Ref (1)		Ref (1)	
After the COVID−19	85 (30.0)	0.55 (0.32 ~ 0.95)	**0.031**	0.24 (0.14 ~ 0.43)	**< 0.001**
Local adverse reactions					
Before the COVID−19	832 (35)	Ref (1)		Ref (1)	
After the COVID−19	66 (23.3)	0.67 (0.48 ~ 0.95)	**0.024**	0.31 (0.2 ~ 0.46)	**< 0.001**
Systemic adverse reactions					
Before the COVID−19	113 (4.8)	Ref (1)		Ref (1)	
After the COVID−19	19 (6.7)	1.13 (0.61 ~ 2.09)	0.69	0.28 (0.13 ~ 0.64)	**0.003**

The models consider random effects for the time and frequency of vaccination for each child (2,658 injections recorded in 123 children), shown as fixed effects in the table

n in this table indicates the number of treatment injections

[a] Model adjusted injection volume, concentration, gender, age, BMI, number of COVID-19 vaccine injections, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, allergic asthma, cough variant asthma

Discussion

Since December 2019, the emergence of a novel coronavirus, marked by high contagiousness and the capacity to inflict multi-organ system damage, has led to tens of millions of fatalities [17], placing an immense strain on global physical and psychological well-being. Despite a downward trend in pathogenicity due to viral mutations, it suggests a long-term coexistence with the SARS-CoV-2 virus [18]. Chronic allergic diseases, with an ever-increasing global prevalence [4], can be positively

modulated by AIT, the singular etiological intervention that has the potential to alter their natural progression, with early initiation in children being particularly beneficial [15]. Nonetheless, the 3–5 year treatment duration of AIT faces considerable challenges due to the uncertainties and apprehensions linked to COVID-19 [19]. Following the easing of COVID-19 containment measures by the Chinese government in December 2022, there was a swift surge in infections across a broad population. Given this circumstance, our center has gathered a relatively comprehensive set of data, enabling us to analyze the impact of COVID-19 infection on the safety of AIT and assess any shifts in the rate of adverse reactions attributable to AIT.

Consistent with recommendations from international and national guidelines [14, 20], and considering the proven benefits of AIT for individuals with allergic diseases, the discontinuation of AIT during the COVID-19 pandemic is discouraged. In our pediatric practice, we pause AIT injections during the acute phase of the SARS-CoV-2 infection. We only resume AIT injections once all symptoms and signs have subsided, a rapid antigen test for COVID-19 returns negative, the patient's body temperature remains stable for at least three days, our medical team does a thorough evaluation, and the patient is fully informed. Our statistical analysis corroborates the prevailing research [21, 22], indicating that the majority of pediatric patients with COVID-19 in this study exhibited mild symptoms, with an absence of severe cases. Furthermore, our data show a link between the dosage of allergen administered and the incidence of adverse reactions to AIT, which is consistent with what is already known [23], confirming the reliability of our research results. Notably, our research unveils a counterintuitive reduction in the risk of adverse reactions, both local and systemic, following COVID-19 infection in SCIT-treated patients, a novel observation not previously reported in the literature.

The interaction between SARS-CoV-2 and allergic diseases is not well defined. Research indicates that atopic respiratory diseases might confer a protective effect against COVID-19, potentially due to type 2 cytokines reducing the expression of the SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2), on respiratory epithelial cells [24, 25]. Conversely, a recent multinational cohort study has identified a 20% increased risk of allergic diseases manifesting within 30 days post-COVID-19 infection compared to non-infected individuals, potentially due to etiologies such as T cell homeostasis disruption and cytokine storm phenomena [3]. Further investigation is warranted into the role of SARS-CoV-2 as either a protective or a risk factor in individuals with an atopic constitution.

The relationship between COVID-19 and AIT is still not fully understood. Larenas-Linnemann et al. suggest that AIT might lower the risk of severe COVID-19 in allergic patients. This might happen by encouraging a switch from type 2 T-helper (TH2) to TH1 cell immune response and raising levels of interleukin (IL)-10 and tumor-growth-factor-β (TGF-β) [26]. However, the effect of COVID-19 on AIT's safety is indeterminate. An EAACI online survey of 417 healthcare professionals indicated 75% continued AIT in the maintenance phase without early reports of intolerance [27]. Similarly, a German Society of Allergy and Clinical Immunology survey (DGAKI) reported no increase in adverse reactions [28], though these relied on web-based questionnaires and lacked empirical data. Our study, with comprehensive data collection and analysis, found a decreased risk of AIT adverse reactions after COVID-19 infection, a phenomenon that requires further study. Huang et al. note IL-10's key role in COVID-19's inflammatory response, with levels rising in line with disease severity [29]. AIT works by correcting the type 2 response, reducing type 2 follicular helper T cells (TFH2), and upregulating follicular regulatory T cells (TFR) to induce immune tolerance, promoting IL-10 secretion that drives the conversion of immunoglobulin E (IgE) to protective IgG4 antibodies [30–32]. We speculate that elevated IL-10 levels may foster immune tolerance with AIT, potentially attenuating adverse reactions. Nevertheless, the immunological pathways implicated in both COVID-19 and AIT are highly complex and interwoven. Further research within these areas remains to be explored by the broader academic community.

Our study further found that patients who received two doses of the COVID-19 vaccine had a lower risk of developing adverse reactions during the SCIT. The preventive role of vaccines against COVID-19 has been acknowledged [18]. The research conducted by the Yin Yao team demonstrates that, following the administration of two doses of the COVID-19 vaccine, patients with AR treated with AIT exhibit a reduction in TFH2 levels compared to those without AIT [33]. This reduction in TFH2, as previously reported [30], is correlated with the establishment of immune tolerance through AIT, potentially leading to a diminished adverse response. This may provide an explanation for the phenomena observed in this study. Our findings also offer evidence for the safety of vaccination for allergic patients undergoing AIT during the COVID-19 pandemic.

Our research was initiated following China's relaxation of COVID-19 restrictions, leading to a swift and extensive infection with a predominant coronavirus variant. According to data from the Chinese Center for Disease Control and Prevention, the main epidemic strains

of COVID-19 in mainland China starting in December 2022 were BA.5.2 (constituent ratio of 64.6%) and BF.7 (constituent ratio of 29.4%). The continuous mutation of the novel coronavirus and the potential impact of emerging variants on AIT's safety profile are uncharted territory. However, existing literature suggests that the Omicron variant has replaced prior strains, presenting with increased transmissibility and reduced virulence [34]. The virus's immune-evasive properties also suggest a decline in pathogenicity, hinting that the evolving nature of the coronavirus may not substantially alter its influence on AIT. Furthermore, despite ongoing viral mutations, current vaccines are still considered effective, affirming vaccination as a vital preventive strategy against the COVID-19 pandemic [35].

Given the ongoing nature of the pandemic, managing AIT is critical to maximizing safety and efficacy. The Allergic Rhinitis and its Impact of Asthma (ARIA) and EAACI offered guidance in 2020 [14], advising that the intervals between AIT injections might be extended if necessary without advocating for treatment discontinuation. Yet, global AIT implementation has been less than satisfactory, with a marked reduction in new SCIT prescriptions, increased treatment discontinuations, and waning patient adherence [19, 36, 37]. Conversely, SLIT, favored for its user-friendly administration and lower risk of adverse effects [8], is gaining traction among healthcare providers and patients. A retrospective study by Fabiana Furci in an Italian hospital revealed that SLIT did not cause COVID-19 adherence issues [38]. Shifting from a SCIT-centric to a SLIT-focused approach could be an emerging trend in AIT. Regardless of the chosen AIT method, we advise against discontinuation to maintain effective control of allergic diseases and improve the quality of life for individuals with allergies.

The existing body of literature mostly examines the influence of AIT on the severity of COVID-19 and the consequences of COVID-19 infection on the implementation of AIT and patient adherence. Our study pioneers the investigation into the nexus between COVID-19 infection and AIT-related adverse reactions within the pediatric population. We employed a mixed effect model to mitigate confounding factors and random effects, thereby enhancing the robustness of our findings. Nonetheless, our study encounters inherent limitations characteristic of retrospective research, where recall bias could potentially influence our results. We endeavored to curtail such bias through stringent researcher training to maintain data uniformity and by relying on contemporaneous electronic health records alongside multiple data measurements to ensure accuracy. Furthermore, some of the potential confounders (e.g., IgE, duration of SCIT before COVID-19 infection) were not assessed and adjusted for due to feasibility concerns and small sample sizes, which somewhat weakened the evidentiary strength. Beside, we must acknowledge the limitations of a single-center study with a limited observation timeframe. A cohort study has indicated that a subset of pediatric COVID-19 patients experience symptoms extending beyond 12 weeks [39], and research by Jiyeon Oh et al. identified a persistently elevated allergy risk of 1.61 even six months post-infection [3]. Given the ongoing evolution of SARS-CoV-2 variants and their possible long-term impacts, future research necessitates larger-scale, multicenter studies with longer follow-up periods to come to more solid conclusions.

Conclusions

With the advent of an enigmatic novel epidemic virus, the effects of COVID-19 on the safety of AIT, paramount for treating the underlying causes of allergic diseases, were indeterminate. Our study provides reassurance by showing that COVID-19 does not heighten the risk of adverse reactions associated with AIT, offering a basis for the continued application of AIT amidst the pandemic.

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCIT	Subcutaneous specific immunotherapy
SLIT	Sublingual specific immunotherapy
OR	Odds ratio
AIT	Allergen-specific immunotherapy
WHO	World Health Organization
COVID-19	Coronavirus illness 2019
EAACI	European Academy of Allergology and Clinical
AR	Allergic rhinitis
AA	Allergic asthma
AC	Allergic conjunctivitis
AD	Atopic dermatitis
CVA	Cough variant asthma
LRs	Local adverse reactions
SRs	Systemic adverse reactions
ANOVA	Analysis of Variance
BMI	Body mass index
CI	Confidence interval
DGAKI	German Society of Allergy and Clinical Immunology
ACE2	Angiotensin-converting enzyme 2
TH	T-helper
IL	Interleukin
TGF-β	Tumor-growth-factor-β
TFH	Follicular helper T cells
TFR	Follicular regulatory T cells
IgE	Immunoglobulin E
ARIA	Allergic Rhinitis and its Impact of Asthma

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
JL, YC: data collection and drafted the manuscript. LC: concept and design, revised the manuscript. HL: statistical analysis, data visualization and revised the manuscript. HY, QT, CW, QZ, LL, LJ, XP, HZ: data collection. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Fujian Children's Hospital. The ethics batch number was 2023ETKLR05098. All patients provided written informed consent signed by their guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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