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A retrospective cohort study on the association between allergic rhinitis, sublingual immunotherapy, and COVID-19 symptomatology

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The impacts of allergic rhinitis (AR) and allergen-specific sublingual immunotherapy (SLIT) on coronavirus disease 2019 (COVID-19) have not been fully understood. Therefore, the aim of this study was to investigate the effects of AR and SLIT on symptoms of COVID-19 within one month after Chinese authorities adjusted their COVID-19 response measures. The study enrolled 1368 participants, including 746 AR patients and 622 controls without allergic diseases. SLIT was administered to 122 infected AR patients (AR with SLIT group), while it was not administered to the other 483 infected AR patients (AR without SLIT group). Patients' outcomes were compared after propensity score matching (PSM). The data showed that AR played a dual role in COVID-19, acting as both a protective factor against respiratory symptoms and a risk factor increasing the likelihood of olfactory/gustatory dysfunctions and fever, compared to non-allergic individuals. Conversely, AR patients treated with SLIT presented a higher risk of respiratory symptoms but a lower risk of fever. SLIT did not influence the risk of olfactory/gustatory dysfunctions. Thus, respiratory symptoms should be considered when deciding whether to apply SLIT in AR patients with COVID-19. Additionally, the risk of fever should also be taken into account.

Keywords COVID-19, SARS-CoV-2, Allergic rhinitis, Respiratory symptoms, Olfaction disorders, Sublingual immunotherapy

Abbreviations

AA	Allergic asthma
ACE2	Angiotensin-converting enzyme 2
AD	Atopic dermatitis
AIT	Allergen immunotherapy
AR	Allergic rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BMI	Body mass index
Bregs	Regulatory B cells
CCL	C-C motif chemokine ligand
CI	Confidence intervals
CXCL	C-X-C motif chemokine ligand
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
Der f	*Dermatophagoides farinae*
FA	Food allergy

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IgE	Immunoglobulin E
IFN	Interferon
IL	Interleukin
OR	Odds ratios
PCR	Polymerase chain reaction
PSM	Propensity score matching
SARS-CoV-2	Severe acute respiratory syndrome virus 2
SCIT	Subcutaneous immunotherapy
SD	Standard deviation
SLIT	Sublingual immunotherapy
SPT	Skin prick tests
TGF-β	Transforming growth factor beta
Th2	Type 2 helper T cells
TNF-α	Tumor necrosis factor alpha
TMPRSS2	Transmembrane serine protease 2
Tregs	Regulatory T cells

The emergence of coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome virus 2 (SARS-CoV-2), has posed a huge challenge to public health systems worldwide. As of 29 January 2023, over 753 million confirmed cases and over 6.8 million deaths from COVID-19 have been reported globally[1]. Some underlying diseases or comorbidities, such as diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease (COPD), and others may impact the development of COVID-19 and the outcomes in patients[2].

Allergic rhinitis (AR) is a common disease that affects approximately 10–40% of the population worldwide, and is an underlying disease in many patients with COVID-19[3]. AR reduces quality-of-life and performance at work and school, and the avoidable costs from decreased work productivity attributable to AR are even higher than those attributable to asthma[3]. Since both AR and COVID-19 have such high prevalence worldwide, it is essential to identify the impact of AR on the development and symptoms of COVID-19. However, previous studies have reported conflicting findings. In particular, surveys in Korea[4] and China[5] suggested that AR increased the susceptibility to COVID-19 and severe clinical outcomes. On the contrary, Ren et al.[6] examined data from the UK Biobank and reported that AR decreased the risk of COVID-19, and hospitalization due to COVID-19, but had no impact on mortality. These discrepant results indicate the need to clarify this relationship.

COVID-19, caused by SARS-CoV-2, initiates infection via binding of the viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor on epithelial cells of the respiratory tract, with the help of transmembrane serine protease 2 (TMPRSS2) for S protein priming[7]. SARS-CoV-2 infection triggers a unique dysregulated inflammatory response characterized by low levels of type I and III interferons (IFNs) juxtaposed to elevated chemokines (including C–C motif chemokine ligand [CCL] 2, CCL8, C-X-C motif chemokine ligand [CXCL] 9, and CXCL16) and high expression of interleukin (IL)-6, which represents the defining and driving features of COVID-19 pathogenesis[8]. Severe COVID-19 is characterized by dysregulated immunity resulting in elevated levels of pro-inflammatory cytokines including IL-6, IL-8, and tumor necrosis factor alpha (TNF-α) at hospital admission, which serve as strong and independent predictors of patient survival[9].

The immunopathology of AR is characterized by a type 2 helper T (Th2)-skewed immune response, with elevated levels of cytokines such as IL-4, IL-5, and IL-13, which promote immunoglobulin E (IgE) production and eosinophilic inflammation[10]. This Th2-dominant milieu may downregulate the expression of the ACE2 receptor in airway epithelial cells, potentially altering susceptibility to SARS-CoV-2 infection[11,12]. However, in adults with asthma, an upregulation of other potential viral co-receptors, such as TMPRSS2, has been observed, which could facilitate viral entry and complicate the overall picture[13]. Allergic inflammation appears to influence SARS-CoV-2 infection primarily through modulation of viral entry receptor expression rather than by classical antiviral mechanisms. The clinical impact likely reflects a balance between Th2-mediated downregulation of ACE2 and upregulation of other facilitating receptors, underscoring the need for further mechanistic research.

Allergen immunotherapy (AIT) is the repeated administration of allergen extracts to individuals with allergic symptoms, and is regarded as the only potentially effective disease-modifying therapy for AR[14]. AIT alters the natural course of allergic diseases by restoring immune tolerance against allergens, characterized mainly by the generation of allergen-specific regulatory T cells (Tregs) and regulatory B cells (Bregs), increased production of anti-inflammatory mediators such as IL-10 and transforming growth factor beta (TGF-β), and reduced Th2 cytokine production[15,16]. In contrast, SARS-CoV-2 infection is associated with a reduction in Tregs[17], which may contribute to uncontrolled inflammation and worse clinical outcomes. By counteracting this Treg depletion and rebalancing immune responses, AIT could theoretically mitigate the hyperinflammatory state observed in COVID-19, thereby influencing symptom severity and disease progression. Additionally, such immunomodulation may reverse the Th2-associated downregulation of ACE2 and upregulation of other facilitating receptors, restore balanced antiviral IFN responses, and alter the intensity of inflammatory symptoms during SARS-CoV-2 infection. Sublingual immunotherapy (SLIT) is a form of AIT in which allergen drops, such as dust mite extract, are administered under the tongue. Therefore, we aspect immune tolerance induced by SLIT may influence COVID-19 outcomes. Zhang et al.[18] reported that AR patients who received SLIT had a reduced risk of developing COVID-19 symptoms after infection; however, the effect of the phase or duration of SLIT on the development of COVID-19 remains unknown[19].

The dominant variants of SARS-CoV-2 in China have transitioned from alpha, to beta, to delta, and to the less virulent Omicron, and the COVID-19 policies in China have adapted to these changes since 18 December 2022[20]. The policy was modified to allow infected individuals and their close contacts to receive home treatment

instead of being required to go to government-designated places for isolation and treatment until their nucleic acid tests of SARS-CoV-2 were negative. Afterward, the number of people infected with the Omicron variant increased significantly[21,22]. In this study, we retrospectively investigated the prevalence and symptoms of COVID-19 in different groups of AR patients and non-allergic individuals from China during a period when the Omicron variant was predominant.

Results

Study population

We enrolled a population of 1368 participants (48.5% females and 51.5% males), 1109 (81.1%) of whom had positive SARS-CoV-2 test results between 18 December 2022 and 18 January 2023. The average age was 21.3 ± 13.0 years in the entire AR group, and 28.1 ± 11.9 years in the non-allergic control group. Only 53 (3.9%) participants had a history of smoking and only 4 (0.3%) participants tested positive for SARS-CoV-2 before 18 December 2022. Moreover, 72 (5.3%) participants were not vaccinated, and 1286 (94.0%) received 2 to 4 doses of the COVID-19 vaccine. The entire AR group and the control group had significant differences in gender, age, body mass index (BMI), and concomitant allergic asthma (AA) (Supplementary Table 1). No enrolled outpatients were hospitalized or died during the study period.

Comparison of COVID-19 symptoms between AR without SLIT and control groups

By 18 January 2023, 504 (81.03%) participants in the non-allergic control group and 483 (80.5%) participants in the AR without SLIT group had SARS-CoV-2 infection ($p = 0.052$) (Supplementary Table 2). AR with SLIT patients were excluded from this analysis because immunotherapy could modify the course of disease due to its induction of immune tolerance, which decreases symptoms of AA and AR by altering B-cell memory[23]. There were significant differences in gender, age, BMI and concomitant AA between AR without SLIT and control groups (Supplementary Table 2). A propensity score matching (PSM) (1:1) was used to balance the gender, age, BMI, and concomitant AA between AR without SLIT and control groups (n = 335 for each group; Table 1). No significant differences in demographic and clinical characteristics were found between the two groups after a 1:1 PSM (Table 1). Next, we compared the post-infection symptoms of the control and AR without SLIT groups after PSM. The results showed that AR without SLIT group had a more than three-fold higher odds for fever (odds ratios [OR]: 3.03, 95% confidence intervals [CI]: 1.87–4.90; $p < 0.001$) and an 82.5% higher odds for olfactory and gustatory dysfunctions (OR: 1.83, 95% CI: 1.25–2.67; $p = 0.002$), but lower odds for fatigue (OR: 0.61, 95% CI: 0.44–0.83; $p = 0.002$), stuffy nose and rhinorrhea (OR: 0.60, 95% CI: 0.44–0.82; $p = 0.001$), pharyngalgia (OR: 0.72, 95% CI: 0.53–0.98; $p = 0.035$), and diarrhea (OR: 0.43, 95% CI: 0.26–0.70; $p = 0.001$). However, the two groups had no significant differences in myalgia (OR: 0.78, 95% CI: 0.57–1.06; $p = 0.116$), cough (OR: 0.82, 95% CI: 0.60–1.13; $p = 0.224$), or shortness of breath (OR: 0.28, 95% CI: 0.06–1.37; $p = 0.115$) (Fig. 1).

We also compared the persistence of symptoms beyond 7 days in the infected AR without SLIT group and the infected non-allergic control group to observe the persistence of the effect on the disease process. After PSM, the two groups had no significant differences in baseline characteristics. However, the infected AR without SLIT group had a lower risk of long-lasting fatigue (OR: 0.07, 95% CI: 0.02–0.30; $p < 0.001$) (Supplementary Table 3).

Characteristics	Total	AR without SLIT	Non-allergic controls	*p*-value
Subjects, N (%)	670 (100.0)	335 (50.0)	335 (50.0)	–
Gender, male, N (%)	324 (48.4)	165 (49.3)	159 (47.5)	0.643
Age, year, mean (SD)	26.83 (11.8)	26.5 (12.4)	27.2 (11.2)	0.445
BMI, mean (SD)	22.2 (3.1)	22.3 (3.1)	22.1 (3.0)	0.436
Vaccination, N (%)				0.825
Yes	649 (96.9)	325 (97.0)	324 (96.7)	
No	21 (3.1)	10 (3.0)	11 (3.3)	
Smoking history, N (%)				0.425
Yes	26 (3.9)	11 (3.3)	15 (4.5)	
No	644 (96.1)	324 (96.7)	320 (95.5)	
Asthma, N (%)				–
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
No	0 (0.0)	0 (0.0)	0 (0.0)	
SARS-CoV-2 infections during the study period, N (%)				1.000
First	670 (100.0)	335 (100.0)	335 (100.0)	
Second	0 (0.0)	0 (0.0)	0 (0.0)	
Third	0 (0.0)	0 (0.0)	0 (0.0)	

Table 1. Demographic and clinical characteristics of the SARS-CoV-2 infected AR without SLIT and non-allergic controls after propensity score matching. AR, allergic rhinitis; BMI, body mass index; SARS-CoV-2, severe acute respiratory syndrome virus 2; SD, standard deviation; SLIT, sublingual immunotherapy.

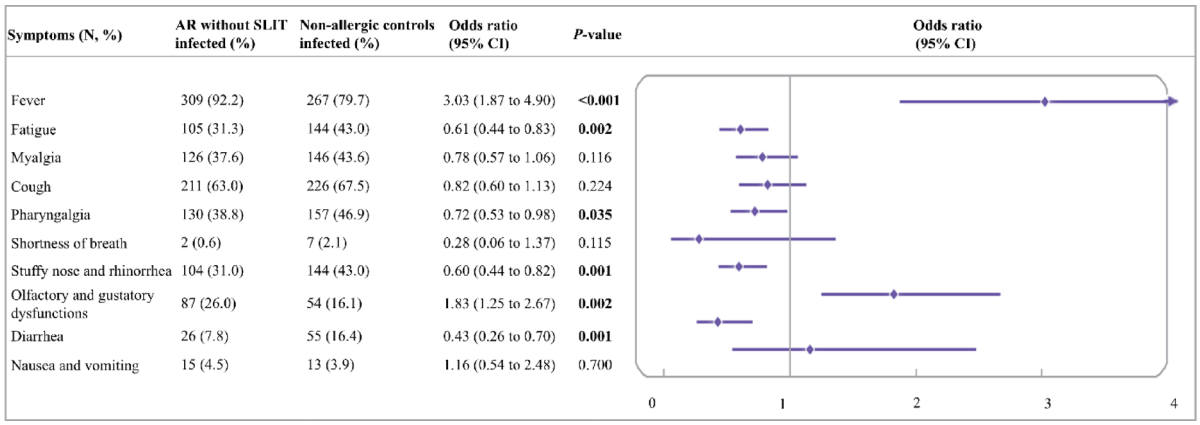

Fig. 1. Adjusted odds ratios for different COVID-19 symptoms in infected participants with AR without SLIT and in non-allergic controls with SARS-CoV-2 infection. AR, allergic rhinitis; COVID-19, coronavirus disease 2019; SARS-Cov-2, severe actue respiratory syndrome virus 2; SLIT, sublingual immunotherapy.

Characteristics	Total	AR with SLIT	AR without SLIT	*p*-value
Subjects, N (%)	605 (100.0)	122 (20.2)	483 (79.8)	–
Gender, male, N (%)	357 (59.0)	68 (55.7)	289 (59.4)	0.411
Age, year, mean (SD)	22.3 (12.6)	22 (10.4)	22 (13.1)	0.595
BMI, mean (SD)	21.3 (3.7)	21 (4.1)	21 (3.6)	0.623
Vaccination, N (%)				0.626
Yes	580 (0.5)	116 (95.1)	464 (96.1)	
No	25 (4.1)	6 (4.918)	19 (3.9)	
Smoking history, N (%)				0.852
Yes	18 (3.0)	4 (3.3)	14 (2.9)	
No	587 (97.0)	118 (96.7)	469 (97.1)	
Asthma, N (%)				0.090
Yes	31 (5.1)	10 (8.2)	21 (4.3)	
No	574 (94.9)	112 (91.8)	462 (95.7)	
SARS-CoV-2 infections during the study period, N (%)				0.569
First	602 (99.5)	121 (99.2)	481 (99.6)	
Second	3 (0.5)	1 (0.8)	2 (0.4)	
Third	0 (0.0)	0 (0.0)	0 (0.0)	

Table 2. Demographic and clinical characteristics of the SARS-Cov-2 infected AR with SLIT or AR without SLIT groups. AR, allergic rhinitis; BMI, body mass index; SARS-CoV-2, severe acute respiratory syndrome virus 2; SD, standard deviation; SLIT, sublingual immunotherapy.

Effects of SLIT for AR on COVID-19 symptoms

We then investigated whether the treatment of SLIT for AR affected COVID-19 symptoms by comparing COVID-19 symptoms between the AR with SLIT group and the AR without SLIT group. Both groups showed no significant differences in baseline characteristics, including gender, age, BMI, vaccination status, smoking history, asthma, and previous SARS-CoV-2 positivity (Table 2). During the study period, the positive rate of SARS-CoV-2 was 83.6% in the AR with SLIT group and 80.5% in the AR without SLIT group, without significant difference ($p = 0.397$). However, compared to the AR without SLIT group, the AR with SLIT group suffering from respiratory symptoms had a 61.7% higher odds for cough (OR: 1.62, 95% CI: 1.06–2.46; $p = 0.024$), a more than ten-fold higher odds for shortness of breath (OR: 10.28, 95% CI: 1.97–53.64; $p = 0.006$), and 99.7% higher odds for stuffy nose and rhinorrhea (OR: 2.00, 95% CI: 1.33–3.00; $p = 0.001$), but lower odds for fever (OR: 0.49, 95% CI: 0.27–0.90; $p = 0.021$), fatigue (OR: 0.28, 95% CI: 0.15–0.53; $p < 0.001$), and myalgia (OR: 0.36, 95% CI: 0.22–0.60; $p < 0.001$). Conversely, compared to the AR without SLIT group, the AR with SLIT group had tendencies for protection from olfactory and gustatory dysfunction (OR: 0.84, 95% CI: 0.51–1.38; $p = 0.486$), and risk tendency for pharyngalgia (OR: 1.00, 95% CI: 0.66–1.52; $p = 0.993$) (Fig. 2). The AR with SLIT group had a higher risk of stuffy and rhinorrhea lasting more than 7 days than AR without SLIT (OR: 8.60, 95% CI: 3.69–20.06; $p < 0.001$) (Supplementary Table 4). In addition, the dose of the vaccinations had no effect on the symptoms of COVID-19 no matter AR patients received SLIT or not (data not shown).

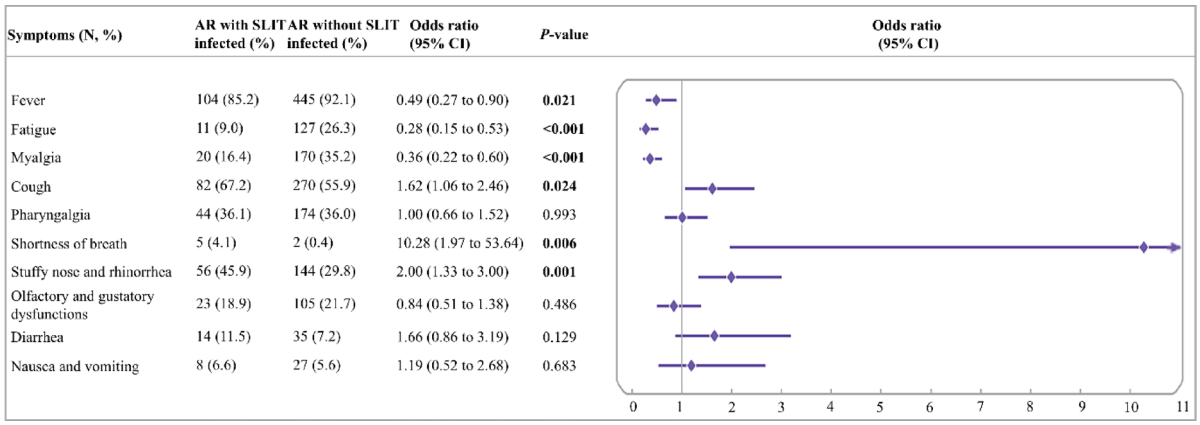

Fig. 2. Odds ratios for different COVID-19 symptoms in infected participants with AR who used SLIT and in infected participants with AR without SLIT. AR, allergic rhinitis; COVID-19, coronavirus disease 2019; SLIT, sublingual immunotherapy.

Effects of concomitant AA and multiple allergens on COVID-19 symptoms

No significant differences in COVID-19 symptoms showed between AR patients with and without AA (Supplementary Table 5). In addition, there were also no significant differences in COVID-19 symptoms between AR without SLIT patients with > 3 allergens and ≤ 3 allergens (Supplementary Table 6).

Discussion

Our findings further elucidated the effects of AR and SLIT on the risk of COVID-19 symptoms within one month of when Chinese authorities adjusted their COVID-19 response measures. We found that AR patients and non-allergic controls had similar susceptibility to SARS-CoV-2 infection. A previous study measuring genetic variations using Mendelian randomization[24] reached the same conclusions.

We found that significant demographic differences existed between the control group and AR patients, including age, BMI, and the prevalence of comorbidities such as AA (Supplementary Table 1). After PSM (1:1), no significant differences in these demographic and clinical characteristics were found between the two groups (Table 1). Although PSM was used to balance baseline characteristics between groups, several limitations should be considered. The exclusion of participants with multiple comorbidities may limit the generalizability of our findings. Additionally, while we matched on the presence of AA, we did not account for AA severity, which could potentially influence COVID-19 symptoms. Finally, the younger age of our AR cohort, even after matching, may have contributed to the observed differences in symptom presentation, as younger individuals generally experience milder COVID-19 symptoms[25,26]. Similarly, potential differences in BMI between groups could have influenced immune responses and symptom severity[27,28].

We found that AR without SLIT was a protective factor for respiratory symptoms, such as pharyngalgia, stuffy nose and rhinorrhea. AR patients receiving SLIT might be more vulnerable to respiratory symptoms, including cough, shortness of breath and stuffy nose and rhinorrhea. ACE2 activity, which is modulated by type 2 inflammatory factors, is a receptor expressed in most human respiratory cells, and is a well-defined receptor for the SARS-CoV-2 spike protein[11,29]. Jackson et al.[12] found that nasal allergens significantly reduced the level of ACE2 mRNA in nasal brush samples of AR patients and also in bronchial brush cells of patients with mild asthma, which was validated by the results from the ex vivo experiments involving primary airway epithelial cells[11]. Thus, the fewer ACE2 receptors in the airway epithelial cells of AR patients might be a reason for the milder respiratory symptoms of COVID-19 and the potentially effective disease-modifying immunotherapy may have reversed this protective factor for respiratory symptoms in AR. Conversely, Yang et al.[5] reported that the nasal symptoms of AR patients infected with SARS-CoV-2 were more severe than in those without AR. In their study, not all the self-reported AR patients provided positive allergen test results, and data on comorbidities, use of AIT, and details of vaccine status were also not reported. The lack of clinical information can be regarded as a major confounding factor, which may explain the discrepancies in results between previous clinical trials.

In our study, AR without SLIT patients with COVID-19 had a higher rate of fever and olfactory and gustatory dysfunctions than non-allergic controls, which is consistent with previous studies[30,31]. Some studies reported that some inflammatory cytokines play a crucial role in the pathogenesis of AR, as well as fever and anosmia. AR is characterized by type 2 inflammation. Nguyen et al.[32] reported that type 2 immune cytokines, such as IL-4 and IL-13, could alternatively activate macrophages to secret catecholamines and sustain adaptive thermogenesis during cold stress. Additionally, pro-inflammatory cytokines, such as IL-6, can act as a pyrogenic cytokines that function in two major phases of the febrile response: increasing the core temperature and acting as a downstream effector cytokine that coordinates the trafficking of lymphocytes to lymphoid organs[33].

Previous studies reported that SARS-CoV-2 infection can increase the level of IFNs in the olfactory epithelium[34–36]. These increases can downregulate odorant receptors in olfactory receptor neurons[37], which is a potential mechanism for olfactory dysfunction in patients with COVID-19[38]. Some other pro-inflammatory

cytokines, such as IL-6 and TNF-α, may also contribute to anosmia in AR[39–41]. However, the mechanism of anosmia in COVID-19 has not been fully explored.

AIT, which induces immune tolerance and modifies the skewed type-2 innate immune response, is the only disease-modifying treatment for AR[19]. Our results showed that the infected AR with SLIT group, had more severe respiratory tract symptoms (cough, shortness of breath, stuffy nose and rhinorrhea) than the infected AR without SLIT group. The benefits and risks of SLIT should be assessed to ensure the clinical efficacy and avoid the insidious events. However, Zhang et al.[18] recommended administration of SLIT after the onset of COVID-19 symptoms, since they found that use of SLIT was related to a decreased rate of post-infection symptoms. This contradictory result is most likely because their control group included non-AR patients who had no significant nasal symptoms for just one year. In contrast, our control subjects consisted of individuals who had never suffered from any allergic diseases.

SLIT exerts its immunomodulatory effects through multiple pathways that may differentially impact COVID-19 outcomes. First, SLIT increases the numbers of Tregs and Bregs[16], which may contribute to the observed reduction in fever and systemic symptoms such as fatigue and myalgia in our SLIT-treated group. These regulatory cells may modulate the production of pro-inflammatory cytokines such as IL-6, which acts as a pyrogenic cytokine that coordinates the febrile response[33]. Second, SLIT may reverse the protective effect of AR on respiratory symptoms by modulating ACE2 expression. As we previously noted, Jackson et al. found that nasal allergens significantly reduced the level of ACE2 mRNA in nasal brush samples from AR patients[12]. This reduction in ACE2, the primary receptor for SARS-CoV-2, may explain why our AR patients without SLIT had lower odds of respiratory symptoms. SLIT, by inducing immune tolerance and modifying the skewed type-2 innate immune response[16], may restore normal ACE2 expression levels, thereby increasing susceptibility to SARS-CoV-2 infection in the respiratory tract. Third, while SLIT did not significantly influence the risk of olfactory and gustatory dysfunctions in our study, we should consider the potential immune mechanisms underlying this observation. Olfactory dysfunction in COVID-19 has been associated with increased IFN levels in the olfactory microenvironment[42]. Additionally, pro-inflammatory cytokines such as IL-6 and TNF-α may contribute to anosmia in AR[39,43]. The lack of a significant effect of SLIT on olfactory/gustatory dysfunctions suggests that these particular immune pathways may not be substantially modified by SLIT treatment in our patient population.

Most of our participants in the study had mild or moderate COVID-19 symptoms. No patients presented with hypoxemia or acute respiratory distress syndrome[44], and no patients died or required hospitalization. AR and control groups in the study also had similar risks of symptoms for over 7 days, which was consistent with the findings of Yang et al.[5] It has been reported that AA was an independent and significant protective factor for SARS-CoV-2[6,45]. Concomitant AA was associated with worse clinical outcomes[4] and increased risk of hospitalization in patients with COVID-19[6]. In contrast, some studies reported that AR concomitant with AA reduced the risk of SARS-CoV-2 infection[45] and severe COVID-19[46]. Our study suggested that the concurrence with AA and the number of positive allergens in AR individuals had no impact on post-infection symptoms. We can suggest several reasons for these conflicting findings. First, previous studies did not conduct stratified analysis based on asthma endotypes. Asthma can be classified as IgE-mediated AA and non-atopic asthma (often triggered by viral upper respiratory tract infections or no apparent cause)[47]. Low ACE2 expression was not associated with non-atopic asthma[48]. Second, the sample size of AA participants in our study was small, and the impact of AA on the positive rates of SARS-CoV-2 and the symptoms of COVID-19 should be evaluated in a larger population. Third, a recent cohort study in Korea has observed that the incidence of new-onset asthma might be preventable by COVID-19 vaccination[49]. However, the vaccination rate was up to 95% in our study, which might play a role in reducing the symptoms of COVID-19.

Previous studies reported that polysensitized AR patients had more severe symptoms than mono-sensitized subjects[41]. Between AR without SLIT patients with positive allergens >3 and ≤ 3 allergens, our comparison indicated no significant differences in COVID-19 symptoms. AR symptoms are usually sustained by allergic inflammation, which is dependent on allergen exposure[50]. However, there was a lack of correlation between pollen concentration and COVID-19 epidemiological characteristics, which might be the reason that poly-allergens have no effect on virus epidemiology[51].

Our study has several strengths. We gathered data within one month after China adjusted its COVID-19 policies, and none participants had been infected with COVID-19 previously. We therefore collected data during a short period of time when the Omicron variant spread wide in order to obtain more real data for comparison of symptoms among the AR with SLIT patients, AR without SLIT patients, and non-allergic controls. All our AR participants were diagnosed with rhinitis symptoms and had positive allergen testing, and we did not diagnose AR upon self-reported symptoms only. Our study excluded participants with frequent underlying diseases, such as hypertension, diabetes, heart diseases, COPD, etc. We also recorded information on vaccination in detail.

Also, there are several shortcomings in the present study. First, our dataset did not include detailed information on post-infection medication use, including antibiotics, antipyretics, and COVID-19-specific treatments. As such medications may affect both symptom presentation and severity, the lack of these data should be considered a limitation of our analysis. Second, we minimized clinical confounders by PSM as possible, however, there might still be residual confounding factors due to unmeasured or incompletely measured covariates, such as the timing of the vaccinations and the use of vaccines in different types. Third, the retrospective nature of this study may have resulted in recollection or information bias, since all the symptoms were recalled by participants in one month. In addition, we collected symptom data for participants in the AR without SLIT group were obtained via telephone interviews rather than in-person consultations. While standardized procedures were implemented to reduce variability, the possibility of residual reporting bias cannot be excluded. The variability in SLIT adherence and potential selection biases may be potential bias for our study. Although all SLIT patients followed a standardized maintenance protocol with monitored adherence, individual variations

in self-administration could not be entirely excluded; however, such variability is unlikely to have materially affected the study outcomes. Although the severity of COVID-19 was not evaluated using a standardized clinical scoring system, all participants were non-hospitalized with mild to moderate disease, and symptom duration was used as a pragmatic surrogate indicator of disease severity. Finally, this study focused exclusively on SLIT due to its predominant use in China and cohort availability; subcutaneous immunotherapy (SCIT), although mechanistically distinct, was not evaluated. Future comparative studies of SLIT and SCIT are warranted to elucidate their respective impacts on COVID-19 symptoms.

In summary, we found that AR patients and non-allergic individuals had a similar susceptibility to SARS-CoV-2 infections. Compared to non-allergic individuals, AR patients were more susceptible to anosmia and ageusia, implying that once AR patients with COVID-19 exhibit olfactory and gustatory dysfunctions, early detection and interventions are needed to prevent disease progression and improve the prognosis. Furthermore, it is recommended that non-allergic individuals with COVID-19 receive timely airway management, as they are at higher risk for pharyngalgia and rhinorrhea.

It was noted that AR patients with SLIT who had COVID-19 were more susceptible to respiratory symptoms, but their incidence of fever was lower compared to AR patients without SLIT. However, whether AR patients received SLIT or not did not influence olfactory/gustatory dysfunctions. We recommend that clinicians carefully weigh these potential risks and benefits when considering SLIT continuation in AR patients during COVID-19 infection. Particularly, patients with pre-existing respiratory conditions may require closer monitoring if they continue SLIT during COVID-19, due to the substantially elevated risk of shortness of breath observed in our study. Conversely, the reduced systemic symptoms in SLIT-treated patients might indicate some protective effect against disease progression. These findings highlight the complex interplay between allergic inflammation, immunotherapy, and viral infections, and provide valuable insights for managing AR patients during the ongoing COVID-19 pandemic. Further prospective studies are warranted to confirm these observations and investigate the optimal management strategy for AR patients receiving SLIT who contract COVID-19.

Materials and methods

Study data and design

This cross-sectional study enrolled 746 AR patients and 622 non-allergic controls who had been treated in the Department of Otorhinolaryngology & Clinical Allergy Center, the First Affiliated Hospital with Nanjing Medical University, between 18 December 2022 and 18 January 2023. Among them, 605 AR patients and 504 non-allergic controls were infected with SARS-CoV-2. The medical history of AR with COVID-19 patients was also recorded. A total of 483 AR with COVID-19 patients were classified as AR without SLIT group, who used symptomatic drugs including intranasal corticosteroids, H1-antihistamines and/or leukotriene receptor antagonists, but not received any immunotherapy; 122 patients were classified as AR with SLIT group who received drug treatment as described above plus SLIT with standardized *Dermatophagoides farinae* (*Der f*) drops (Zhejiang Wolwo Biopharmaceutical Co., Ltd, Zhejiang, China). The whole treatment course of SLIT was recommended to last for 3–5 years, and all enrolled SLIT patients were in the maintenance phase during the study period, receiving the same daily dosage according to the manufacturer's protocol. Compliance was monitored during routine follow-up visits, and only patients who had continuously adhered to the regimen without interruption were included, ensuring protocol uniformity across participants. The symptoms of COVID-19 in the AR without SLIT group were collected by telephone interviews, and those in the AR with SLIT group were collected from medical records during visits for management of SLIT. Controls, mainly including patients' accompanying family members, medical workers and residents of surrounding communities, completed a survey on the Questionnaire Star, produced by Tencent (Shenzhen, China). Eligible controls were those who had no history of self-reported AR, asthma, food allergy (FA) and atopic dermatitis (AD). Follow-up survey questions would not appear until the participant answered "No", and the entire survey would continue to be completed. SARS-CoV-2 infection was identified based on patient self-reported positive results from either a polymerase chain reaction (PCR) test or a nucleic acid antigen test between 18 December 2022 and 18 January 2023. All tests were performed in certified clinical laboratories or authorized testing facilities in accordance with local public health guidelines. Asymptomatic cases were individuals who tested positive for SARS-CoV-2 by nucleic acid testing but reported no infection-related symptoms throughout the observation period. All participants completed questionnaires that collected information about age, gender, BMI, smoking history, number of vaccine doses, number of previous positive SARS-CoV-2 results, and the presence of COVID-19 related symptoms, including fever, fatigue, myalgia, cough, pharyngalgia, shortness of breath, stuffy nose and rhinorrhea, olfactory and gustatory dysfunctions, diarrhea, and nausea and vomiting. The complete questionnaire used in this survey has been provided in the supplementary materials (Supplementary Table 7).

This initial data collection was conducted from January 19 to January 29, 2023, after obtaining informed consent. The datasets used and/or analysed during the current study available from the corresponding author (L. Cheng at *chenglei@jsph.org.cn*) on reasonable request. Ethical approval for this study was granted by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (2023-SR-446) in accordance with the ethical standard of the Declaration of Helsinki.

Inclusion and exclusion criteria

The study participants were primarily young and middle-aged individuals whose mean age was 24.4 ± 13 years. COVID-19 was diagnosed according to established criteria[44] and all participants tested negative for SARS-CoV-2 before study entry. AR was diagnosed according to the Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA^{2}LEN, and AllerGen)[52] and the Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis[53]. This diagnosis was based on positive allergen skin prick tests (SPT) and rhinitis symptoms, including rhinorrhea, sneezing, nasal

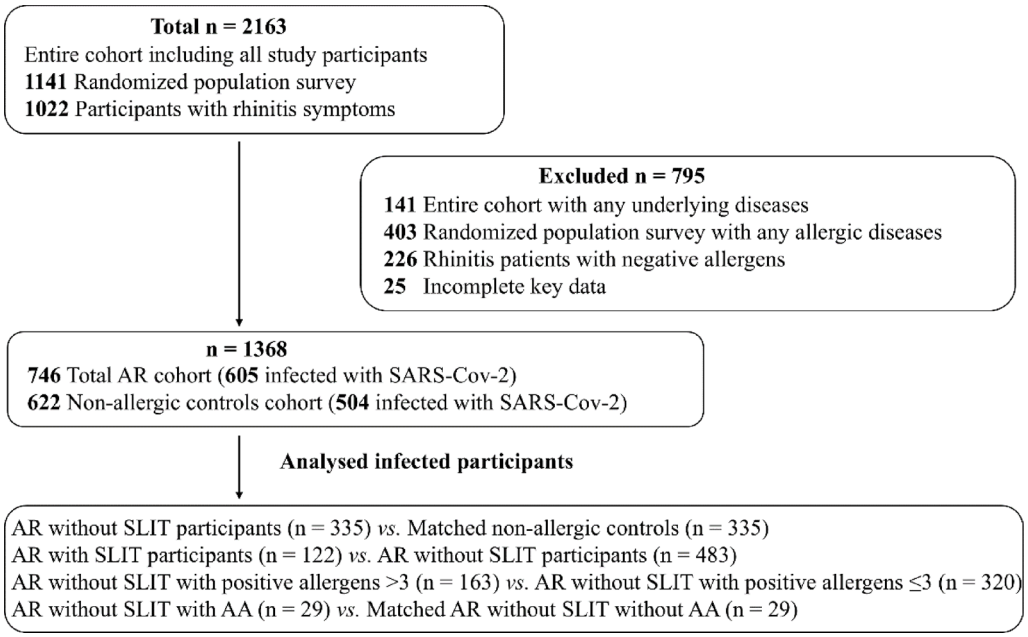

Fig. 3. Study participant flow diagram. AA, allergic asthma; AR, allergic rhinitis; AR with SLIT, AR patients received sublingual immunotherapy; AR without SLIT, AR patients without sublingual immunotherapy.

obstruction, and itch. A detailed list of allergens included in the SPT panel, based on the Min Xian Zhi® allergen panel (Guizhou Weike Technology Co., Ltd, Guizhou, China), has been provided in the supplementary materials (Supplementary Table 8). We reviewed a total of 1022 participants who had visited the Clinical Allergy Center of the First Affiliated Hospital with Nanjing Medical University with rhinitis symptoms within the past six months, without any age or sex limitations. We excluded 226 patients who had rhinitis symptoms with negative SPT. AR patients suffering from SARS-CoV-2 infection were recruited and further divided into an AR with SLIT group (n = 122) and an AR without SLIT group (n = 483) according to whether they received SLIT or not. The normal course of AIT consists of two phases (initiation and maintenance)[54], and all 122 enrolled AR with SLIT patients were in the maintenance treatment. In the control group, 403 participants who had any self-reported allergic diseases, including AR, AA, AD, or FA, were excluded. In addition, among the entire study cohort, 141 participants who had any underlying disease, such as hypertension, diabetes mellitus, hyperlipidemia, coronary heart disease, stroke, COPD, tuberculosis, malignant tumor, myocardial infarction, renal illness, hepatitis, or another underlying condition were excluded. A total of 25 other patients who did not complete questionnaires were also excluded (Fig. 3).

Statistical analysis

In the main analysis, a 1:1 PSM was used for comparisons. In this analysis, the completely adjusted model was performed to balance the baseline covariates of the two groups and reduce the effect of potential confounding variables. For visual presentation of the associations of different variables, model coefficients were transformed to OR. Continuous variables with normal distributions were presented as means ± standard deviation (SD). Categorical variables were presented as number (%). In hierarchical analyses, the entire AR cohort was divided into an AR concomitant with AA group, an AR alone group, a polysensitized AR group, and an AR with positive allergens ≤ 3 group. Continuous variables were compared between two groups with Student's *t* test or the Mann–Whitney *U* test. The χ^2 test or Fisher's exact test was used to analyze categorical variables. For each outcome, 95% CI and *p*-values were calculated, and a *p*-value below 0.05 was considered significant. Sample size was calculated using the formulas in the Online Repository. The design of the study achieved 80% power at a 2-sided significant level of 95%. All statistical analyses were conducted using R version 4.3.1.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author (L. Cheng at *chenglei@jsph.org.cn*) on reasonable request.

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Author contributions
Y.Y.Z., M.Z. and L.C. contributed to the design of the research. Y.Y.Z., M.Z., M.P.L., Y.B.C., L.J., Q.L. and Y.T. performed the data collection and analysis. Y.Y.Z. and M.Z. wrote the manuscript. L.C. and M.Z. contributed amendments to the manuscript and revised it critically. All authors participated in data interpretation, provided critical feedback, and approved the final manuscript for submission.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
Ethical approval for this study was granted by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University (2023-SR-446) in accordance with the ethical standard of the Declaration of Helsinki. All participants gave informed consent prior to the survey.

Additional information
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