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ORIGINAL RESEARCH

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Impact of the COVID-19 national lockdown in the allergic rhinitis symptoms in patients treated with immunotherapy at two allergy referral centers in Bogotá, Colombia

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Abstract

Background: Coronavirus disease-19 (COVID-19) "lockdowns" caused an abruptly restricted access to health care services such as immunotherapy for allergic rhinitis (AR) and led to higher exposure to indoor allergens. This study aimed to assess the impact of COVID-19 lockdowns on AR symptoms reported by the patients treated with immunotherapy who attended the Hospital Fundación Santa Fe de Bogotá and Unidad Médico Quirúrgica de Otorrinolaringología, Colombia.

Methods: Pre–post study that included patients with AR confirmed diagnosis (prick test), treated with immunotherapy before and after COVID-19 lockdowns on March–June 2020. Visual analog scales (VAS) and sociodemographic questionnaires were applied to assess AR symptoms (nasal obstruction, pruritus, rhinorrhea, and ocular symptoms) and their associated factors.

Results: A total of 318 participants were included, and their mean age was 18.9 years (SD: 12.8). The median number of immunotherapy doses applied before isolation was 11 (interquartile range [IQR]: 6–19), and the median number of immunotherapy doses missed during isolation was three doses (IQR: 2–3). Up to 38.4% of the AR patients reported that their symptoms got worse during lockdowns. A pre–post mean difference in the VAS score of 0.5 was found for nasal obstruction ($p = .01$), 0.7 for pruritus ($p < .001$), 0.7 points for rhinorrhea ($p < .001$), and 0.8 for ocular symptoms ($p < .001$). Factors associated with worsening of AR symptom scores were pet ownership, atopic dermatitis, lower educational level, and a low number of immunotherapy doses applied before lockdowns.

Conclusion: A large proportion of patients reported worsening of their AR symptoms, probably due to higher exposure to indoor AR allergens and interruption of immunotherapy during COVID-19 lockdowns.

KEYWORDS
allergic rhinitis, COVID-19, immunotherapy, lockdown, SARS-CoV2

1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has significantly disrupted Latin American health care systems.[1,2] Latin America is one of the regions with the highest rates of cases and mortality from coronavirus disease-19 (COVID-19).[3] Efforts to contain the spread of COVID-19 included isolation, movement restrictions, and national lockdowns, defined as large-scale physical distancing measures.[4] In Colombia, the first COVID-19 national lockdown was established between March and May 2020. Although lockdown restrictions were necessary to fight the pandemic, statistical models suggest that these restrictive measures mainly impacted patients with chronic diseases in low- and middle-income countries.[5,6] Thus, in patients with chronic diseases such as allergic rhinitis (AR) or asthma, lockdowns could lead to higher exposure to indoor allergens and the interruption of their specific allergen immunotherapy.[7]

Avoidance of indoor and outdoor allergens is considered the most effective primary preventive measure in patients with respiratory allergies.[8] Prior authors suggested a probable reduction of exposure to nasal irritants (i.e., pollen) in allergic populations located in polluted industrialized urban areas related to COVID-19 lockdowns.[9] However, the patients with AR could have a higher exposure to indoor allergens, such as dust mites or pet hair, and pollutants linked to human activities (i.e., tobacco, cooking smoke).[7,9,10] On the other hand, allergen-specific immunotherapy (SIT) is the only known treatment that changes the natural history of AR increasing patients' tolerance to allergen exposure and allowing a reduction in the pharmacological treatments.[11,12] In some countries, patients undergoing immunotherapy were forced to stop this treatment due to restrictions on nonessential health care.[7] Indeed, in tropical low-/middle-income countries like Colombia, immunotherapy was interrupted during a brief period, and a higher indoors allergen exposure to house dust mites (HDM) and pets could lead to worsening of AR symptoms in these patients.

Prior studies describe a high prevalence of allergic diseases in tropical countries due to geographical and environmental characteristics that prompt the existence of specific allergens.[13] Among the most frequent allergens in tropical countries are HDM (*Blomia tropicalis*, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farinae*), pet allergens (dog, cat, and others), and pollen (Gramineae, Cypress, etc.).[14] To date, no studies have described the probable association of lockdown, indoor allergen exposure, and changes in AR symptoms in any tropical country. Few studies have been performed worldwide, and real-world evidence is needed considering that due to new COVID-19 variants, new lockdowns could be likely to happen. This study aimed to assess the impact of COVID-19 lockdowns on AR clinical symptoms reported by the patients with confirmed AR diagnosis (prick test) who were treated with allergen-SIT at the Hospital Fundación Santa Fe de Bogotá (FSFB) and Unidad Médico Quirúrgica de Otorrinolaringología (UNIMEQ-ORL), Colombia.

2 | METHODS

2.1 | Study design

This was an observational, analytical, ambispective study conducted at two allergy referral centers: the FSFB and UNIMEQ-ORL, between March and May 2020. This study aimed to assess the changes in AR symptoms (nasal obstruction, pruritus, ocular symptoms, and rhinorrhea) during the COVID-19 lockdown in Colombia (March 24 and May 27, 2020). Parents or legal tutors of the patients aged under 14 years answered the written questionnaires, whereas the population aged 14 years or older received self-administered written questionnaires. The data collection of SIT and clinical information were extracted by trained researchers from the clinical records. The FSFB and UNIMEQ-ORL are both allergy and immunotherapy referral centers located in Bogotá, Colombia. Both institutions treat populations affiliated to health entities that provide health insurance packages to all socioeconomic-status populations. Ethics committee approval was received for this study from the ethics committee of the FSFB (CCEI-12403-2020) according to the Helsinki Declaration. Informed consent was obtained from all the participants and/or their legal tutors. No incentives were offered for study participation.

2.2 | Study population

The inclusion criteria were as follows: (a) patients aged 4–67 with a clinical diagnosis of AR performed by allergists and confirmed with skin prick test (SPT), (b) all the patients were treated with monthly depot allergen-SIT injections for at least 6 months which is considered as the maintenance phase for this type of SIT (the maintenance dose is reached the first day of immunotherapy),[15–18]and (c) these patients attended the allergy referral centers between March and May 2020. The exclusion criteria for this study were patients with severe systemic diseases and patients with any physical or mental disability that could limit the understanding of the questionnaires. The study population is located in Colombia, a low-/middle-income tropical country in

TABLE 1 Baseline clinical and sociodemographic characteristics of the study population

Variables	Total ($n = 318$)	
	n	%
Sex: Female/male	173/145	54.4/45.6
Age in years[a]	18.9 (12.8)	14.3 (10.1–25.1)
Age-group		
<18 years old	208	65.4
18 years old or more	110	34.6
Socioeconomic status		
Low-income levels	124	38.9
Medium-income levels	173	54.4
High-income levels	19	5.9
Educational level		
Preschool	16	5.0
Primary school	90	28.3
High school	127	39.9
University or technical degree	61	19.2
Postgraduate	24	7.6
Number of people in the household		
1–2	27	8. 5
3–4	193	60.7
5 or more	63	19.8
No data	35	11.0
Number of rooms in the household		
1–2	66	20.8
3–4	200	47.2
5 or more	17	5.3
No data	35	11.0
Overcrowding index[a]	1.32 (0.41)	1.33 (1–1.5)
Floor material in the household		
Tile, vinyl, tablet, brick, laminate	242	76.1
Parquet floor, polished wood,	53	16.7
coarse wood, or other vegetable	11	3.5
material	7	2.2
Cement, gravel	5	1.6
Rug		
No data		
Animal exposure during isolation		
Dogs	103	32.4
Cats	60	18.9
Other animals	22	6.9
Cigarette smoking of family members in the house		
Yes	27	8.5
Allergic rhinitis in comorbidity with		
Asthma	132	41.5
Atopic dermatitis	77	24.2
Asthma and atopic dermatitis	36	11.3
Number of immunotherapy doses applied before isolation[b]	11 (6–19)	
Number of monthly immunotherapy doses interrupted during isolation[b]	3 (2–3)	
Type of immunotherapy		
HDM—duo	147	46.2
HDM—trio	156	49.1
Grass/Gramineae	33	10.4
Dog	10	3.1
Cat	16	5.0
Pharmacotherapy during lockdown		
Nasal corticosteroid (mometasone/	66	20.8
fluticasone furoate)	63	19.8
Antihistamine	50	15.7
Antihistamines + nasal	11	3.5
corticosteroid	12	3.8
Antihistamines + nasal	116	36.5
corticosteroid + other medication		
Other medications		
Without treatment		

Abbreviations: HDM, House dust mites; IQR, interquartile range.
[a]Values reported as mean (SD) and median (IQR).
[b]Values reported in median (IQR).

Latin America. In the FSFB and UNIMEQ-ORL, patients are treated with monthly injections of pet-SIT, Gramineae-SIT, and two types of HDM-SIT: HDM duo that includes *D. pteronyssinus* and *D. farinae* allergen extracts (50%/50%), and HDM trio that includes *B. tropicalis*, *D. pteronyssinus*, and *D. farinae* (34%/33%/33%). These SIT extracts are an aluminum hydroxide–adsorbed depot allergen preparation produced by modification of the allergen by glutaraldehyde (glutaraldehyde polymerized). These characteristics preserve their capacity to be recognized by specific IgG and allow the administration of higher doses in a short period.[17,18] Due to this safety profile, this type of SIT can be administered using a rush schedule, reaching the maintenance dose on the 1st day of immunotherapy.[15–18] The treatment was performed with a rush-up dosing schedule with one injection of 0.5 ml per month, which is presented in a single vial at a concentration of 10,000 TU/ml.

2.3 | Assessment tools

Visual analog scales (VAS) scored from 0 (no symptoms) to 10 (severe symptoms) were applied to assess AR symptoms (nasal obstruction, pruritus, rhinorrhea, and ocular symptoms). VAS scores have outstanding reliability, good validity, moderate distribution-based responsiveness, and good anchor-based responsiveness compared to multi-item questionnaires.[19] Moreover, VAS scores are widely validated tools for the measurement of AR symptoms because they correlate well with the AR and its impact on asthma severity classification and with multi-item sino-nasal symptom scales such as the Sino-Nasal Outcome Test (SNOT-22).[20,21] Several treatment studies on AR have used VAS as an evaluation parameter for assessing

disease severity, monitoring the course of the disease, and for treatment decisions and disease burden.[20,21] VAS scores are applied on every SIT visit at our allergy centers as a follow-up tool to assess the course of the disease. The sociodemographic and clinical questionnaires including self-reported changes in AR symptoms were collected by trained researchers after the COVID-19 lockdown.

2.4 | Statistical analysis

Statistical analysis was performed using Stata 16MP software. About the descriptive analysis, absolute and relative frequencies were calculated for the qualitative variables. Measures of central tendency (average and median) were estimated for the quantitative variables. Standard deviation and interquartile range were assessed for the dispersion measures. A "change from baseline" measure of the VAS score was calculated using the differences between the baseline VAS score obtained before the lockdown and the VAS score after the lockdown. A bivariate and multivariable analysis between pre- and postmeasurement data of the symptom's VAS scores was analyzed by the paired samples Wilcoxon test. A robust cluster linear regression was carried out to assess the effect of lockdowns in the VAS score for each symptom: nasal obstruction, pruritus, ocular symptoms, and rhinorrhea. This effect was adjusted considering the clinical and demographic variables with clinical relevance or biological plausibility and those with a p value ≤ 0.2 in a Pearson/Spearman test or analysis of variance/Friedman test. Model assumptions were validated through a linearity test, an estimation of standardized residuals and leverage values, and a comparison between the crude and the adjusted models. Hypothesis testing to determine the level of statistical significance was performed using a 95% confidence interval and a p value < .05.

3 | RESULTS

A total of 318 individuals were included, with a mean age of 18.9 years (SD: 12.8), 55.1% ($n = 211$) were female, and 34.6% were aged over 18 years old. The baseline demographic and clinical characteristics of the study population are shown in Table 1. Up to 38.4% ($n = 122$) reported a family history of rhinitis, 11.3% ($n = 36$) of atopic dermatitis, and 9.8% ($n = 31$) of asthma. Overall, 38.4% ($n = 122$) of the participants reported that their symptoms got worse during the lockdown period. The percentage of missing data was 13%, but considering that this percentage was lower than 20%, the authors did not perform any statistical imputation of data.

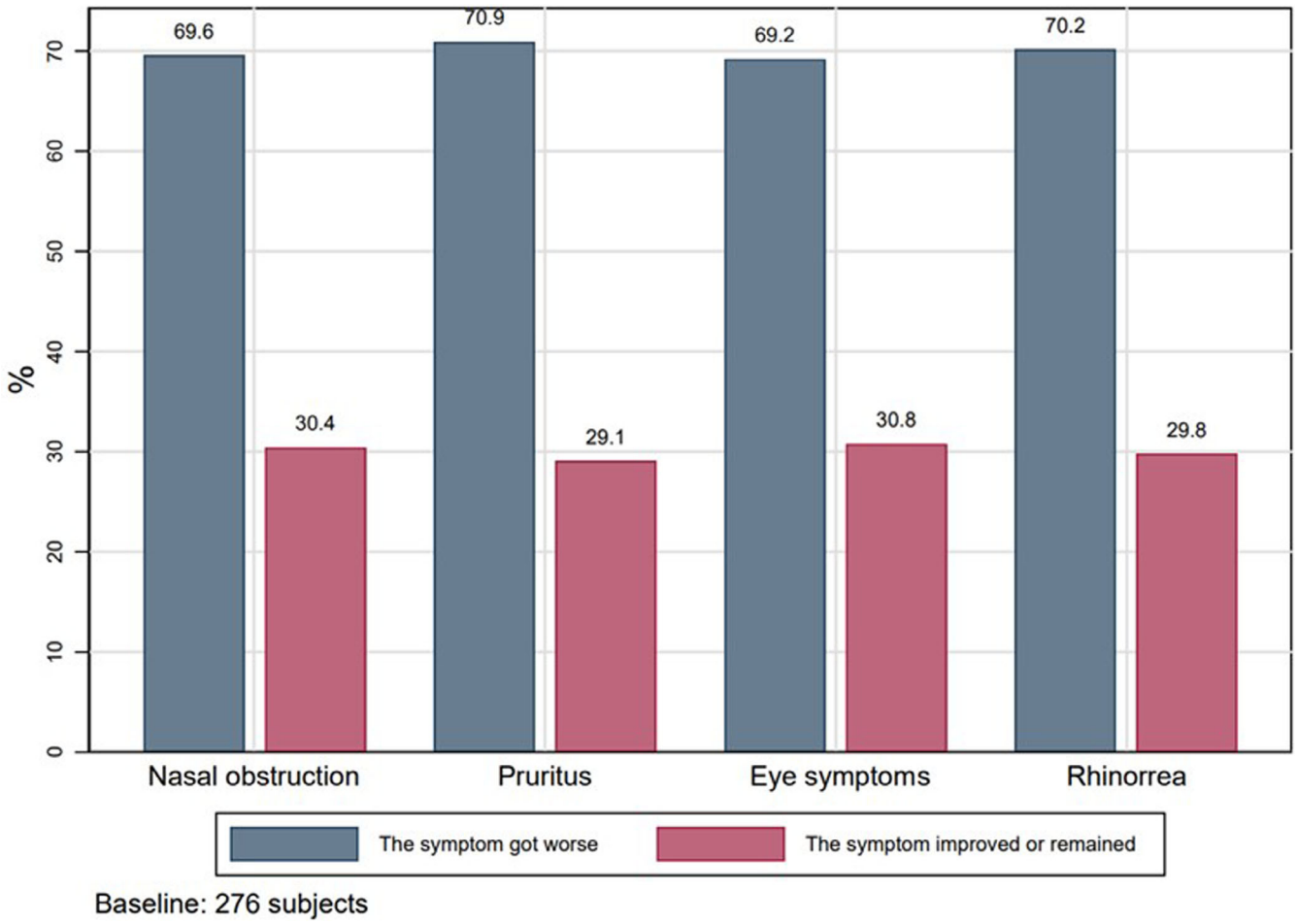

FIGURE 1 Changes in AR symptoms during the lockdown period reported by the patients. AR = Allergic rhinitis

3.1 | SPT, pharmacotherapy, and immunotherapy results

The median number of immunotherapy doses applied before isolation was 11 (interquartile range [IQR]: 6–19), and the median number of immunotherapy doses missed during isolation was 3 (IQR: 2–3). Table 1 shows the frequency of positive prick tests, type of immunotherapy, and pharmacotherapy in the study population. In terms of sensitization results obtained by SPT, the most frequent allergens were *D. farineae*, *D. pteronyssinus*, and *B. tropicalis* (84.6%, 84%, and 52.2%, respectively). Regarding animal allergens, the most frequent allergies were dog (22.6%) and cat (21.4%), whereas the most frequent pollen allergen was grass/Gramineae (18.2%). About the type of immunotherapy, up to 49.1%, 46.2%, and 10.4% of the study population were treated with HDM duo, HDM trio, and grass/Gramineae SIT. The frequency of pharmacotherapy in the patients was reported as follows: nasal corticosteroid 20.8%, antihistamines 19.8%, and antihistamines plus nasal corticosteroid 15.7%, respectively. Up to 116 participants (36.5%) were not treated with any pharmacological or biological treatment during the development of this study.

3.2 | Changes in AR symptoms and associated factors during lockdown

Figure 1 shows the changes in AR symptoms reported by the patients during the lockdown. The median of the VAS scores before and after lockdown for nasal obstruction, pruritus, rhinorrhea, and ocular symptoms are shown in Figure 2. The mean differences of these scores were 0.5 (SD: 2.9), 0.7 (SD: 3.1), 0.7 (SD: 2.8), and 0.8 (SD: 3.1), respectively. These changes in the scores were statistically significant.

Table 2 shows the multivariable and reduced analyses of the sociodemographic variables and treatment associated with VAS score symptoms. The reduced model showed a positive association between the final VAS score of nasal obstruction and the following variables: change from baseline in VAS score (coefficient [coef]: 0.6; 95% CI [0.3, 0.9]), presence of dogs in the house (coef: 0.8; 95% CI [0.10, 1.49]), presence of cats in the house (coef: 0.95; 95% CI [0.17, 1.73]), primary school education (coef: 2.63; 95% CI [1.52, 3.74]), high school education (coef: 1.78; 95% CI [0.67, 2.89]), university/technical education (coef: 1.72; 95% CI [0.21, 3.23]), treatment with HDM duo SIT (coef: 1.72; 95% CI [0.17, 3.26]), and HDM trio SIT (coef: 1.80; 95% CI [0.25, 3.35]). Conversely, the number of immunotherapy

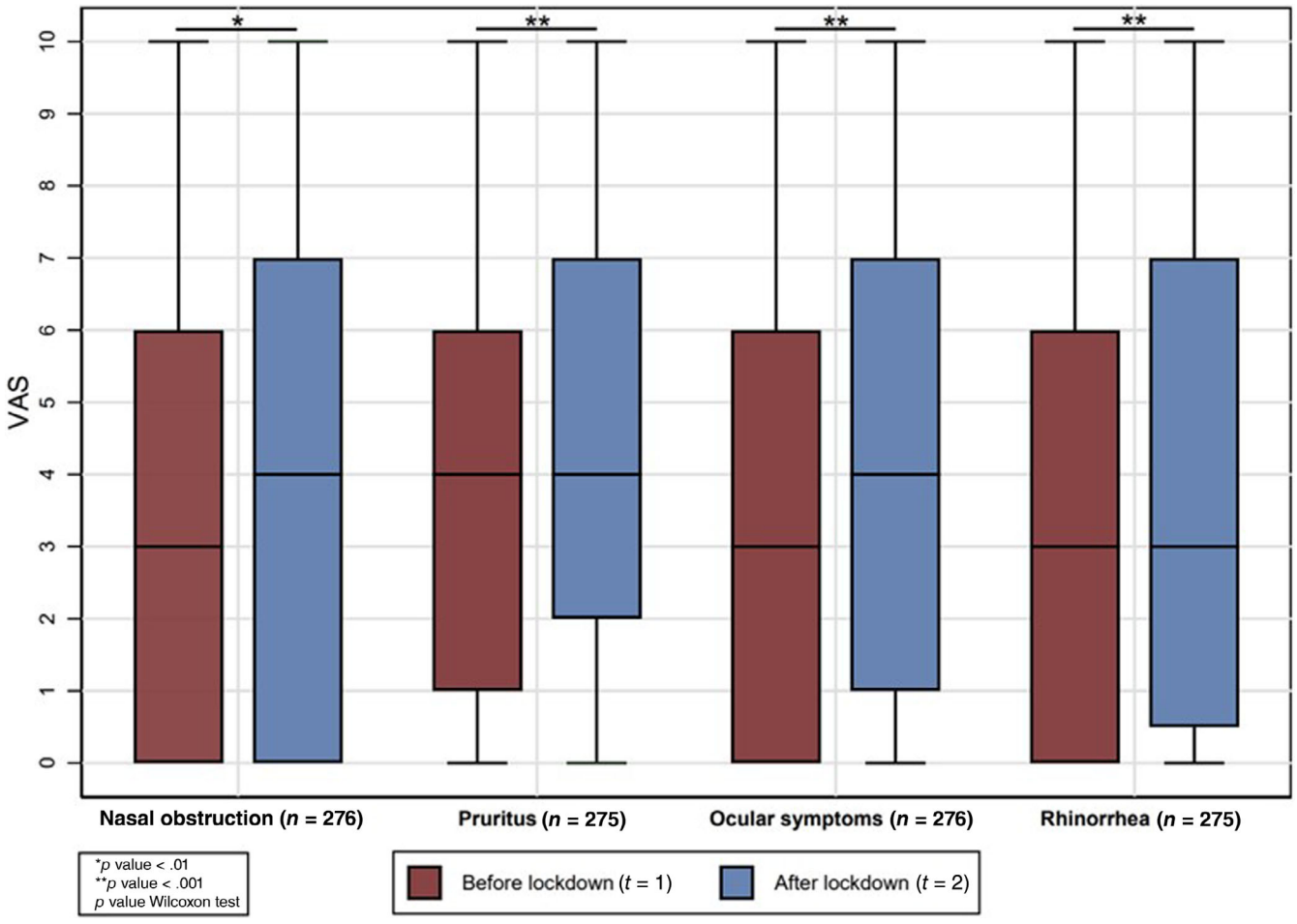

FIGURE 2 Assessment of VAS scores for AR symptoms before and after lockdown. AR = Allergic rhinitis; VAS, visual analog scales

TABLE 2 Factors associated with changes in VAS symptoms score (nasal obstruction, pruritus, ocular symptoms, and rhinorrhea)

	Nasal obstruction						Pruritus					
	Multivariable model			Reduced model[a]			Multivariable model			Reduced model[a]		
Variables	Coef	95% CI		Coef	95% CI		Coef	95% CI		Coef	95% CI	
Changes in VAS score symptoms												
After lockdown	0.59	0.23	0.95	**0.61**	**0.25**	**0.97**	0.71	0.34	1.09	**0.72**	**0.34**	**1.09**
Age-group												
18 years old or more	0.74	−0.36	1.84	0.60	−0.46	1.66	−0.15	−1.10	0.79	−0.38	−1.31	0.55
Sex												
Female	0.16	−0.54	0.87	—	—	—	0.74	0.09	1.39	**0.74**	**0.09**	**1.39**
Socioeconomic status												
Medium-income levels	−0.12	−0.85	0.61	−0.20	−0.89	0.49	0.16	−0.53	0.85	0.16	−0.54	0.85
High-income levels	0.96	−0.33	2.24	0.94	−0.24	2.12	0.69	−0.41	1.79	0.74	−0.31	1.79
Educational level												
Primary school	2.60	1.39	3.82	**2.63**	**1.52**	**3.74**	2.53	1.29	3.77	**2.46**	**1.25**	**3.68**
High school	1.75	0.57	2.94	**1.78**	**0.67**	**2.89**	2.03	0.76	3.30	**1.92**	**0.68**	**3.15**
University/technical	1.41	−0.18	3.01	**1.72**	**0.21**	**3.23**	2.07	0.43	3.71	**2.13**	**0.51**	**3.75**
Asthma												
Yes	−0.63	−1.35	0.08	−0.57	−1.24	0.11	−0.34	−1.04	0.36	−0.41	−1.10	0.28
Atopic dermatitis												
Yes	0.22	−0.58	1.03	**0.22**	**−0.52**	**0.96**	0.16	−0.65	0.97	0.11	−0.69	0.90
Presence of dog in house												
Yes	0.80	0.06	1.54	**0.80**	**0.10**	**1.49**	0.61	−0.13	1.36	0.63	−0.11	1.37
Presence of cat in house												
Yes	0.87	0.05	1.69	**0.95**	**0.17**	**1.73**	0.96	0.19	1.73	**0.93**	**0.16**	**1.69**
Positive skin prick tests for *D. farinae*												
Yes	−0.13	−1.17	0.91	—	—	—	0.29	−0.72	1.31	—	—	—
Positive skin prick tests for *D. pteronyssinus*												
Yes	0.28	−0.83	1.38	—	—	—	0.71	−0.21	1.63	—	—	—
Positive skin prick tests for *Blomia tropicalis*												
Yes	0.23	−0.71	1.17	—	—	—	−0.31	−1.10	0.47	—	—	—
Pharmacotherapy												
Nasal corticosteroids	0	Baseline		0	Baseline		0	Baseline		0	Baseline	
Antihistamines	−0.24	−1.35	0.88	−0.07	−1.14	0.99	−0.45	−1.47	0.57	−0.45	−1.45	0.56
Antihistamines + nasal corticosteroids	−0.28	−1.48	0.93	−0.29	−1.41	0.83	0.16	−0.97	1.30	0.15	−1.00	1.29
Antihistamines + nasal corticosteroid + other medication	2.08	0.06	4.10	1.60	−0.07	3.28	2.26	0.18	4.34	2.13	0.08	4.17
Without treatment	−0.03	−0.99	0.94	0.11	−0.85	1.06	−0.24	−1.15	0.68	−0.20	−1.12	0.71
Treatment with house dust mite duo-SIT?												
Yes	1.28	−0.83	3.40	**1.72**	**0.17**	**3.26**	0.78	−1.14	2.70	0.39	−0.27	1.04
Treatment with house dust mite trio-SIT?												
Yes	1.25	−1.01	3.51	**1.80**	**0.25**	**3.35**	0.64	−1.38	2.65	—	—	—
Treatment with grass/Gramineae-SIT?												
Yes	−0.52	−1.76	0.72	—	—	—	−0.12	−1.39	1.15	—	—	—
Number of immunotherapy doses applied before lockdown	−0.03	−0.07	0.01	**−0.04**	**−0.07**	**−0.001**	−0.04	−0.08	0.00	**−0.04**	**−0.07**	**−0.003**

TABLE 2 (Continued)

	Nasal obstruction						Pruritus					
	Multivariable model			Reduced model[a]			Multivariable model			Reduced model[a]		
Variables	**Coef**	**95% CI**		**Coef**	**95% CI**		**Coef**	**95% CI**		**Coef**	**95% CI**	
Number of immunotherapy doses interrupted in lockdown	−0.15	−0.45	0.15	—	—	—	−0.03	−0.26	0.21	—	—	—
Constant	0.84	−2.02	3.71	0.01	−1.93	1.95	0.90	−1.97	3.77	0.10	−2.62	2.83
Variables	Ocular symptoms						Rhinorrhea					
	Multivariable model			Reduced modela			Multivariable model			Reduced modela		
	Coef	95% CI		Coef	95% CI		Coef	95% CI		Coef	95% CI	
Changes in VAS score symptoms												
After lockdown	0.73	0.36	1.11	**0.72**	**0.36**	**1.09**	0.68	0.34	1.03	**0.68**	**0.34**	**1.02**
Age-group												
18 years old or more	−0.29	−1.38	0.80	—	—	—	0.71	−0.36	1.78	0.75	−0.29	1.79
Sex												
Female	0.23	−0.51	0.97	—	—	—	0.01	−0.69	0.71	—	—	—
Socioeconomic status												
Medium-income levels	0.29	−0.47	1.05	—	—	—	0.09	−0.65	0.84	—	—	—
High-income levels	0.64	−0.57	1.84	—	—	—	−0.20	−1.53	1.13	—	—	—
Educational level												
Primary school	**1.50**	**0.18**	**2.83**	—	—	—	1.61	0.38	2.83	**1.59**	**0.42**	**2.77**
High school	1.27	−0.12	2.66	—	—	—	2.05	0.79	3.31	**2.06**	**0.82**	**3.31**
University/technical	1.46	−0.31	3.22	—	—	—	1.67	−0.01	3.35	1.65	−0.02	3.32
Asthma												
Yes	−0.47	−1.26	0.31	−0.51	−1.29	0.26	−0.22	−0.98	0.54	—	—	—
Atopic dermatitis												
Yes	0.53	−0.38	1.45	—	—	—	−0.13	−0.95	0.70	—	—	—
Presence of dog in house												
Yes	0.56	−0.22	1.34	0.43	−0.32	1.17	0.91	0.12	1.69	**0.95**	**0.20**	**1.70**
Presence of cat in house												
Yes	1.30	0.48	2.13	**1.39**	**0.58**	**2.21**	0.52	−0.34	1.37	0.53	−0.31	1.36
Positive skin prick tests for *D. farinae*												
Yes	0.48	−0.64	1.60	0.62	−0.31	1.55	−0.19	−1.36	0.99	—	—	—
Positive skin prick tests for *D. pteronyssinus*												
Yes	−0.04	−1.14	1.05	—	—	—	0.28	−0.76	1.32	—	—	—
Positive skin prick tests for *Blomia tropicalis*												
Yes	0.17	−0.84	1.18	—	—	—	0.36	−0.54	1.26	—	—	—
Pharmacotherapy												
Nasal corticosteroids	0	Baseline		0	Baseline		0	Baseline		0	Baseline	
Antihistamines	−0.18	−1.39	1.02	−0.25	−1.39	0.89	−0.02	−1.15	1.11	0.10	−0.96	1.16
Antihistamines + nasal corticosteroids	0.60	-0.68	1.88	0.43	−0.79	1.66	−0.30	−1.55	0.96	−0.19	−1.35	0.96
Antihistamines + nasal corticosteroid + other medication	0.98	−1.22	3.19	0.54	−1.97	3.04	1.34	−1.63	4.32	1.37	−1.49	4.22
Without treatment	−0.52	−1.58	0.53	−0.71	−1.70	0.29	−0.31	−1.33	0.71	−0.22	−1.11	0.67
Treatment with house dust mite duo-SIT?												
Yes	0.45	−1.59	2.50	—	—	—	2.46	0.36	4.55	**2.73**	**1.17**	**4.28**

(Continues)

TABLE 2 (Continued)

	Nasal obstruction						Pruritus					
	Multivariable model			Reduced model[a]			Multivariable model			Reduced model[a]		
Variables	Coef	95% CI		Coef	95% CI		Coef	95% CI		Coef	95% CI	
Treatment with house dust mite trio-SIT?												
Yes	0.19	−1.91	2.29	—	—	—	1.68	−0.52	3.87	**2.21**	**0.66**	**3.76**
Treatment with grass/Gramineae-SIT?												
Yes	−0.76	−2.07	0.56	−0.94	−2.04	0.16	−0.29	−1.67	1.10	—	—	—
Number of immunotherapy doses applied before lockdown	−0.02	−0.06	0.02	—	—	—	−0.005	−0.05	0.04	−0.73	−1.60	0.145
Number of immunotherapy doses interrupted in lockdown	−0.05	−0.34	0.24	—	—	—	−0.04	−0.34	0.26	—	—	—
Constant	2.16	−0.76	5.07	3.79	2.06	5.53	0.17	−2.71	3.04	−0.36	−2.57	1.84

Note: Bolded numbers highlight the significant associations between the variables.
Abbreviations: Coef, Coefficient; *D. farinae*, *Dermatophagoides farinae*; *D. pteronyssinus*, *Dermatophagoides pteronyssinus*; SIT, specific immunotherapy; VAS, visual analog scales.
[a]The reduced model was based on the Furnival–Wilson leaps-and-bounds algorithm, linearity link test all models $p < .0001$.

doses applied before isolation (coef: −0.04; 95% CI [−0.07, −0.001]) was negatively associated with the VAS score for nasal obstruction.

In terms of VAS score for pruritus, the reduced model displayed a positive association for the following variables: change from baseline in VAS score (coef: 0.72; 95% CI [0.34, 1.09]), female (coef: 0.74; 95% CI [0.09, 1.39]), presence of cats in the house (coef: 0.93; 95% CI [0.16, 1.69]), and educational level in primary school (coef: 2.46; 95% CI [1.25, 3.68]), high school (coef: 1.92; 95% CI [0.68, 3.15]), and university/technical education (coef: 2.13; 95% CI [0.51, 3.75]). Meanwhile, a negative association was found between the number of immunotherapy doses applied before isolation (coef: −0.04; 95% CI [−0.07, −0.003]) and the VAS score for pruritus. Regarding the reduced model of the VAS score of ocular symptoms, positive associations were found for change from baseline in VAS score (coef: 0.72; 95% CI [0.36, 1.09]) and presence of a cat in the house (coef: 1.39; 95% CI [0.58, 2.21]).

Finally, the reduced model of VAS score of rhinorrhea exhibited positive associations for change from baseline in VAS score (coef: 0.68; 95% CI [0.34, 1.02]), presence of dog in house (coef: 0.95; 95% CI [0.20, 1.70]), and educational level in primary school (coef: 1.59; 95% CI [0.42, 2.77]), high school (coef: 2.06; 95% CI [0.82, 3.31]) along with treatment with HDM duo SIT (coef: 2.73; 95% CI: [1.17–4.28]) and HDM trio SIT (coef: 2.21; 95% CI [0.66, 3.76]). No collinearity problems were found in the models through the linearity and the goodness-of-fit tests. Overall, these assessments showed good models' specifications, and the residual outliers or leverage values did not disturb the models.

4 | DISCUSSION

Although lockdown measures were effective to fight COVID-19, our study population reported a significant worsening of their AR symptoms during the national lockdown, probably due to a higher indoors allergen exposure to HDM, and the interruption of SIT treatment.[22] Similarly, Gelardi et al. reported that quarantine at home for weeks increased the exposure to dust mites and lead to a significant worsening of nasal symptoms in Italian patients allergic to dust mites.[7] Conversely, in a similar study that included patients with pollen allergy, Geraldi et al. reported that these patients presented a significant reduction of allergy symptoms during the lockdown, probably due to lower allergen exposure.[23] All these authors highlight that an integrated strategy including environmental cleanup and therapeutic plans according to the international guidelines are required.[7] Nevertheless, none of these studies reported any information about the SIT treatment in allergic patients, and few studies assess the changes in AR symptoms in tropical environments that could lead to worsening of AR symptoms.

In terms of the VAS score symptoms in our study population, up to 38.4% of the AR patients reported that their ocular and nasal symptoms (i.e., pruritus, rhinorrhea) got worse during lockdowns, with statistically significant differences between the pre- and postmean scores ($p < .010$). Similarly, Geraldi et al. described statistically significant differences ($p < .05$) in clinical parameters such as "nasal obstruction," "runny nose," and "need to blow nose" using the SNOT-22.[7] In a Turkish children population with mild–moderate asthma, AR, and HDM sensitization, patients experienced reduced numbers of upper respiratory tract infections ($p = .008$) and reduced asthma exacerbations during lockdowns ($p < .001$) compared with the same period in the previous year.[10] And despite asthma control tests improved ($p < .001$) in this population, nasal symptoms were significantly worsened in HDM sensitized asthmatics with AR ($p < .001$).[10] Although none of the aforementioned studies included AR patients undergoing immunotherapy, all these results support a higher indoor allergen exposure to HDM during COVID-19 lockdowns. Thus, these results

and our findings support the hypothesis of a higher indoor exposure that could lead to worsening of allergy symptoms during lockdowns. However, considering that SARS-CoV-2 could cause similar symptoms to AR, patients could be more focused on these symptoms during this time and thus be more likely to report them. Besides, because patients were aware they were not getting their SIT shots, they might be more likely to perceive AR symptoms as more significant. All these factors should be considered for the interpretation of the results.

Regarding HDM sensitization in our population, the frequency of *B. tropicalis* sensitization was 52.2%, and this is a particularly important allergen in tropical countries. Prior studies in Mexico and Brazil described a frequency of *B. tropicalis* sensitization ranging from 12.1% to 52.7%, respectively, in atopic patients.[24,25] The frequency of *B. Tropicalis* was high compared to previous reports of atopic populations from temperate climate environments in high-income countries.[13,25] Earlier studies describe that mite species have geographical fluctuations depending on the humidity and proximity to the equatorial zone.[13] The diverse environmental conditions in Latin American tropical countries could account for these differences.[26] Furthermore, regarding pet allergens, our study showed a positive association between the final VAS score of nasal obstruction and the presence of dogs (coef: 0.80; 95% CI [0.10, 1.49]), and cats in the house (coef: 0.95; 95% CI [0.17, 1.73]). This association could also be related to higher exposure to indoors dog and cat allergens and is consistent with prior studies that highlight the importance of indoor avoidance measures for control of nasal symptoms in HDM-sensitized patients with AR.[7,10]

A positive association was also found between the final VAS score of AR symptoms (nasal obstruction and pruritus) and the educational levels of the population. Patients with a primary education level had a higher score on the VAS score compared with patients with a higher educational level. Similarly, prior authors reported that higher education was related to AR susceptibility in Asian populations.[27] This association could be related to a better perception of AR symptoms, easier access to pharmacological treatments in adult populations, a higher level of education about the importance of allergen avoidance, or even to differences in their domiciliary environment. Although several hypotheses could be speculated for such association, the effect of bias and cofounders could not be ruled out because this was not the main aim of this study. Thus, further studies are required to determine the associations between these factors.

In terms of immunotherapy treatment of AR in our population, we included patients who received at least 6 months of SIT injections and by the time of the study were receiving monthly injections. Prior authors stated that patients achieved a therapeutic response after a few doses with this type of depot allergen SIT.[17,18] Therefore, a median of 3 (2-3) interrupted doses of monthly SIT could lead to a significant immunologic impact which should be determined in future studies. As previously stated, patients undergoing immunotherapy were forced to stop their treatments due to restrictions on nonessential health care,[7] and in Colombia, immunotherapy was interrupted during March 24 and May 27, 2020. This scenario could have worsened AR symptoms and triggered chronic nasal obstruction which is very often responsible for the use of nasal decongestants.[28] Prior authors reported that the use of "systemic antihistamines" and "nasal decongestants" increased during the lockdowns ($p < .05$).[7] Up to 19.8% of our population reported the use of exclusive antihistamines during the lockdown, and 19.2% required antihistamines combined with additional medications. Thus, a total of 38.9% of the population required these medications to achieve the control of their symptoms, and around 36.5% ($n = 116$) remained without treatment during the lockdown periods. Despite no specific information about doses of medications was collected in this study, we highlight that no statistically significant association was found between the final VAS score of AR symptoms and the use of pharmacotherapy. Moreover, our patients have achieved a therapeutic response with SIT,[15–18] this scenario would explain why pharmacotherapy was not a statistically relevant variable in our findings.

Likewise, a negative association was found between the number of immunotherapy doses applied before isolation and the VAS score for nasal obstruction (coef: −0.04; 95% CI [−0.07, −0.001]). This supports the fact that allergen-SIT changes the natural history of AR.[12] Finally, about the pollen sensitivity, our results did not show statistically significant differences. These findings could be related to the small sample size of patients with pollen allergies in our study. Moreover, most tropical countries do not have seasons, and pollen sensitization is less frequent and less intense compared to mite allergens.[13] However, there is limited scientific literature about this native flora in tropical countries.[26,29] Despite these associations were not statistically significant, we found negative associations between AR symptoms and pollen in the multivariable model which could be clinically relevant. Geraldi et al. stated that less exposure to these outdoor allergens could lead to an improvement of AR symptoms.[23] Studies with a larger sample size of pollen-allergic populations and control populations with negative SPT are required to assess these probable associations.

Overall, these results highlight the urgent need for integrated strategies and guidelines focused on primary prevention in allergology, including environmental and therapeutic plans to prevent allergy exacerbations under pandemic conditions. We highlight that in patients with AR and asthma, preventive strategies that could reduce the likelihood of asthma exacerbations or sinus diseases include granting their SIT continuity, allergen-avoidance education, improvement of environmental controls, and adequate pharmacotherapy education. This scenario could also prevent the potential exposure to the agent of the pandemic and reduce the health care workers' burden due to these diseases. Long-term management, primary prevention, and control of AR by allergen avoidance measures, pharmacotherapy, and allergen-SIT are essential to reduce the symptoms and improve the quality of life in these patients.

Among the strengths of the study, we highlight that the questionnaires were developed by one otolaryngologist and two allergists with wide clinical experience, and the sociodemographic information was obtained by trained professionals to minimize measurement bias. Prior studies describe that VAS scores in AR do not show significant differences in terms of sensitivity and reproducibility from other

psychometric tests using categorical scales.[21] Moreover, there is extensive data on the clinically significant magnitude of these changes in the VAS scores for AR, and VAS have also been successfully used in real-life and observational studies.[21] Therefore, these statistically significant differences found in our study are also clinically significant. Moreover, the allergists of this study reviewed and classified all the information about pharmacotherapy and immunotherapy.

Regarding the limitations of the study, we highlight that the intensity of symptoms was assessed through self-reported questionnaires, and no objective tests were performed. Self-reported data can be strongly affected by reporter bias and overestimation of the true frequencies of the symptoms.[30] Moreover, reporter biases could be significant in a study of this type. About the environmental control measures in this study, we highlight that the allergists at both allergy centers provide education on allergen avoidance to all the patients with AR (i.e., avoidance of pets in the bedroom, rugs, and curtains, adequate ventilation of bedrooms). Attaching to the International Study of Asthma and Allergies in Childhood methodology, we obtained information about the floor material in the house because this is an important variable in allergic disease studies,[31] but no statistical association was found between AR symptoms and this variable. However, no additional environmental controls were applied in the study population which might have a significant effect on AR symptoms, and this is an important limitation of the study. Regarding pharmacotherapy, we stand out that this information was quite heterogenous for the study group. Despite specific doses of medications were prescribed by the allergists, we have no specific information about the changes in the pharmacotherapy, and there was not a standardized follow-up of changes in the doses of medications during this period. Moreover, pharmacotherapy was not correlated with the immunotherapy doses, and this variable can be a major factor in symptom scoring too. These issues should be considered as limitations of this study, and the results should be interpreted considering this scenario.

5 | CONCLUSION

A large proportion of patients reported worsening of their AR symptoms, probably due to higher exposure to indoor allergens (i.e., HDM and pets) and immunotherapy discontinuation during the COVID-19 lockdowns. Although this study was carried out in an extraordinary context, it stands out the importance of long-term management, primary prevention, and control of AR by allergen avoidance measures, pharmacotherapy, and allergen-SIT. Environmental factors appeared to play a critical role in the pathogenesis of AR, and immunotherapy remains the only treatment that changes the natural history of this disease.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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