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Allergic disorders and susceptibility to and severity of COVID-19: A nationwide cohort study

Jee Myung Yang, MD, PhD,[a]* Hyun Yong Koh, MD, PhD,[b]* Sung Yong Moon, BS,[c]* In Kyung Yoo, MD, PhD,[d] Eun Kyo Ha, MD,[e] Seulgi You, MD,[f] So Young Kim, MD, PhD,[g] Dong Keon Yon, MD,[h,i]‡ and Seung Won Lee, MD, PhD[c]

Seoul, Seongnam, and Suwon, Korea; and Boston, Mass

Background: There is inconclusive and controversial evidence of the association between allergic diseases and the risk of adverse clinical outcomes of coronavirus disease 2019 (COVID-19).

Objective: We sought to determine the association of allergic disorders with the likelihood of a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result and with clinical outcomes of COVID-19 (admission to intensive care unit, administration of invasive ventilation, and death).

Methods: A propensity-score–matched nationwide cohort study was performed in South Korea. Data obtained from the Health Insurance Review & Assessment Service of Korea from all adult patients (age, >20 years) who were tested for SARS-CoV-2 in South Korea between January 1, 2020, and May 15, 2020, were analyzed. The association of SARS-CoV-2 test positivity and allergic diseases in the entire cohort (n = 219,959) and the difference in clinical outcomes of COVID-19 were evaluated in patients with allergic diseases and SARS-CoV-2 positivity (n = 7,340).

Results: In the entire cohort, patients who underwent SARS-CoV-2 testing were evaluated to ascertain whether asthma and allergic rhinitis were associated with an increased likelihood of SARS-CoV-2 test positivity. After propensity score matching, we found that asthma and allergic rhinitis were associated with worse clinical outcomes of COVID-19 in patients with SARS-CoV-2 test positivity. Patients with nonallergic asthma had a greater risk of SARS-CoV-2 test positivity and worse clinical outcomes of COVID-19 than patients with allergic asthma.

Conclusions: In a Korean nationwide cohort, allergic rhinitis and asthma, especially nonallergic asthma, confers a greater risk of susceptibility to SARS-CoV-2 infection and severe clinical outcomes of COVID-19. (J Allergy Clin Immunol 2020;146:790-8.)

Key words: *COVID-19, asthma, allergic rhinitis, atopic dermatitis*

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, China, in December 2019 and has resulted in a rapidly spreading pandemic.[1,2] According to the World Health Organization reports issued in mid-May 2020, approximately 4 million COVID-19 cases have been officially confirmed, and more than a quarter of a million people have died.[3] With the rapid increase in the number of patients with COVID-19, the clinical progress, epidemiological facts, and prognosis of these patients continue to be swiftly revealed, and this could facilitate improved hospitalized management as well as prevention of COVID-19.[4] The spectrum of COVID-19 outcomes is related to underlying diseases or conditions that may potentially modify immunity, thereby aggravating the disease course.[5] For example, higher age (>65 years),[1,4] preexisting pulmonary disease,[5,6] chronic kidney disease,[7] diabetes mellitus,[6] hypertension,[5] cardiovascular disease,[8] obesity (body mass index > 30),[9] malignancy,[10] smoking,[11] and presumably immunocompromised status (eg, the use of anti-inflammatory biologics,[12] transplantation,[12] and chronic HIV infection)[13] are known to be possible epidemiologic risk factors for severe COVID-19.

Chronic allergic disease is associated with the tissue remodeling process, and persistent inflammation may weaken the patient's immune system to induce susceptibility to infection[14]; however, the association between allergic disease and severe clinical outcomes of COVID-19 has not been demonstrated and remains debatable (no association[15,16] or positive association[17,18]). In previous studies, asthma in patients with COVID-19 was found to be associated with severe clinical outcomes in analyses based on data from the UK Biobank[17] and Seattle,[18] but was not associated with severe clinical outcomes in Wuhan.[15,16] Asthma, atopic dermatitis, and allergic rhinitis contribute to the exacerbation of illnesses caused by common respiratory viruses,[19] with an increased risk of cutaneous and upper airway infections.[20] Moreover, impaired innate immunity, induced by the depletion of type 1 IFN, readily

From [a]the Department of Ophthalmology, Asan Medical Center, University of Ulsan College of Medicine, Seoul; [b]F.M. Kirby Neurobiology Center, Boston Children's Hospital, Harvard Medical School, Boston; [c]the Department of Data Science, Sejong University College of Software Convergence, Seoul; [d]the Department of Gastroenterology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam; [e]the Department of Pediatrics, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul; [f]the Department of Radiology, Ajou University Hospital, Ajou University School of Medicine, Suwon; [g]the Department of Otorhinolaryngology-Head & Neck Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam; [h]the Armed Force Medical Command, Republic of Korea Armed Forces, Seongnam; and [i]the Department of Pediatrics, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam.

*These authors contributed equally to this work.

‡Senior author.

This work was supported by the National Research Foundation of Korea grant funded by the Korean government (grant no. NRF2019R1G1A109977912). The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication June 6, 2020; revised August 7, 2020; accepted for publication August 7, 2020.

Available online August 15, 2020.

Corresponding author: Dong Keon Yon, MD, Armed Force Medical Command, Republic of Korea Armed Forces, 81 Saemaeul-ro 177, Seongnam, Gyeonggi-do 463-040, Korea. E-mail: yonkkang@gmail.com. Or: Seung Won Lee, MD, PhD, Department of Data Science, Sejong University College of Software Convergence, 209 Neungdong-ro, Gwangjin-gu, Seoul 05006, Korea. E-mail: swlsejong@sejong.ac.kr.

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0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2020.08.008

Abbreviations used
aOR: Adjusted odds ratio
COPD: Chronic obstructive pulmonary disease
COVID-19: Coronavirus disease 2019
ICD-10: *International Classification of Disease, Tenth revision*
ICU: Intensive care unit
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
SMD: Standardized mean difference

facilitates the spread of viruses or other pathogens.[21] However, Kimura et al[22] recently found that type 2 inflammatory cytokines, including IL-13, significantly modulate the expression of molecules that mediate SARS-CoV-2 host cell entry in asthma and atopic airway epithelial cells to induce angiotensin-converting enzyme 2 decrease and increase TMPRSS2 expression.[22] This implies a complex biological mechanism wherein an underlying asthmatic and atopic disease can affect the susceptibility to SARS-CoV-2 and pathogenesis of COVID-19, increasing the necessity for evidence of its clinical relevance. Therefore, the likelihood of a SARS-CoV-2 infection positivity rate and the severity of COVID-19 outcomes mediated by underlying allergic morbidities need to be determined.

We hypothesized that allergic comorbidity is associated with an increased likelihood of the risk of or clinical outcomes of COVID-19 (ie, death, admission to the intensive care unit [ICU], invasive ventilation, and length of hospital stay). This study aimed to ascertain an association of risk factors and COVID-19 illness severity, with a goal to improve the management of SARS-CoV-2 infection in patients with chronic allergic diseases. In a Korean nationally representative cohort of 219,959 participants who tested for SARS-CoV-2 in South Korea, we investigated the potential association of allergic disorders with the likelihood of SARS-CoV-2 test positivity. Furthermore, we examined the differences in COVID-19 clinical outcomes by allergic diseases among 7340 patients with confirmed SARS-CoV-2 infection.

METHODS

Data source

Data were obtained from a Korean national health insurance claims-based database. The government of the Republic of Korea decided to share the world's first deidentified COVID-19 nationwide patient data with domestic and international researchers. This large-scale cohort comprised all individuals who underwent SARS-CoV-2 testing in South Korea through services facilitated by the Health Insurance Review & Assessment Service of Korea, the Korea Centers for Disease Control and Prevention, and the Ministry of Health and Welfare, Republic of Korea. During the COVID-19 pandemic, the Korean government provided mandatory and free health insurance for all Korean patients with COVID-19.[23,24] Therefore, the data set analyzed in this study includes the records of personal data, health care records of inpatients and outpatients from the past 3 years (including health care visits, prescriptions, diagnoses, and procedures), pharmaceutical visits, COVID-19–related outcomes, and death records. The study protocol was approved by the Institutional Review Board of Sejong University (SJU-HR-E-2020-003). All patient-related records used in our study were anonymized to ensure confidentiality.

Study population

We identified all individuals older than 20 years who underwent SARS-CoV-2 testing in South Korea between January 1, 2020, and May 15, 2020, by medical or Korea Centers for Disease Control referral (excluding self-referral). The laboratory confirmation of SARS-CoV-2 infection was defined as a positive result on a real-time RT-PCR assay of nasal or pharyngeal swabs, in accordance with the World Health Organization guideline.[1] For each identified individual who underwent SARS-CoV-2 testing, the cohort entry data (individual index data) were the date of the first SARS-CoV-2 test. We combined the claims-based data from the national health insurance service between January 1, 2015, and May 15, 2020, and extracted information on age, sex, and region of residence from the insurance eligibility data. A history of diabetes mellitus (E10-14), ischemic heart disease (I20-25), cerebrovascular disease (I60-64, I69, and G45), chronic obstructive pulmonary disease (COPD; J43-J44, except J430), hypertension (I10-13 and I15), and chronic kidney disease (N18-19) was confirmed by the reporting of at least 2 claims within 1 year during this 3-year study period using the appropriate *International Classification of Disease, Tenth Revision* (*ICD-10*) code.[25] The Charlson comorbidity index score was calculated from the *ICD-10* codes by methods that were reported previously.[26] The use of systemic glucocorticoids within 180 days preceding cohort entry was also investigated and recorded.[27] The region of residence was classified as rural (ie, Gyeonggi, Gangwon, Gyeongsangbuk, Gyeongsangnam, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, and Jeju) or urban (eg, Seoul, Sejong, Busan, Incheon, Daegu, Gwangju, Daejeon, and Ulsan).[28,29] The final analysis data set comprised data from 219,959 individuals who underwent SARS-CoV-2 testing, and included 7,340 patients who tested positive for SARS-CoV-2.

Exposure

Asthma, allergic rhinitis, and atopic dermatitis were defined using the *ICD-10* code (asthma, J45 or J46; allergic rhinitis, J30.1, J30.2, J30.3, or J30.4; atopic dermatitis, L20) with at least 2 claims within 1 year during this 3-year study period.[25,30] The current allergic status was defined by the assignment of 2 or more claims using the appropriate *ICD-10* code from January 1, 2019, to May 20, 2020. Allergic asthma was defined as asthma with at least 1 additional allergic disorder (allergic rhinitis or atopic dermatitis), whereas nonallergic asthma was defined as asthma without any atopic disorder.[26]

Outcomes

The primary outcome of this study was a positive laboratory test result among all individuals who were tested for SARS-CoV-2. The secondary outcome was the length of hospital stay and the severe clinical outcomes of COVID-19,[5,31] which comprised ICU admission, administration of invasive ventilation, or death, of patients who tested positive for SARS-CoV-2.

Analysis overview

In this nationwide cohort study, the "exposure" comprised the development of allergic diseases; the "primary end point" was the positive laboratory test results for SARS-CoV-2 among all the individuals who underwent SARS-CoV-2 testing, and the "secondary end point" was the clinical outcome of patients with COVID-19 who tested positive for SARS-CoV-2.

Propensity score matching was performed to balance the baseline covariates of the 2 groups and to decrease the potential confounding factors from the predicted probability of (1) individuals with asthma versus individuals without asthma among all patients who underwent SARS-CoV-2 testing (n = 219,959); (2) individuals with allergic rhinitis versus individuals without allergic rhinitis among all patients who underwent SARS-CoV-2 testing; (3) individuals with atopic dermatitis versus individuals without atopic dermatitis among all patients who underwent SARS-CoV-2 testing; (4) individuals with asthma versus individuals without asthma among patients with confirmed COVID-19 (n = 7340); (5) individuals with allergic rhinitis versus individuals without allergic rhinitis asthma among patients with confirmed COVID-19; and (6) individuals with atopic dermatitis versus individuals without atopic dermatitis among patients with confirmed COVID-19. Furthermore, we performed 6 additional propensity score matching sets based on the current allergic status.

Each matching was undertaken in a 1:1 ratio using a "greedy nearest-neighbor" algorithm among all individuals who underwent SARS-CoV-2

TABLE I. Demographic and clinical characteristics of all patients tested for SARS-CoV-2 in a Korean nationwide cohort

Baseline characteristic	Entire cohort	Entire cohort		
		Patients who tested negative for SARS-CoV-2	Patients who tested positive for SARS-CoV-2	SMD
Total, n (%)	219,959	212,619 (96.7)	7340 (3.3)	
Age (y), mean ± SD	49.0 ± 19.9	49.5 ± 19.9	47.1 ± 19.0	0.124
Sex, n (%)				
Male	104,331 (47.4)	101,361 (47.7)	2,970 (40.5)	
Female	115,628 (52.6)	111,258 (52.3)	4,370 (59.5)	
Region of residence, n (%)				0.091
Rural	96,315 (43.8)	92,780 (43.6)	3,535 (48.2)	
Urban	123,644 (56.2)	119,839 (56.4)	3,805 (51.8)	
History of diabetes mellitus, n (%)	38,396 (17.5)	37,445 (17.6)	951 (13)	0.130
History of cardiovascular disease, n (%)	32,864 (14.9)	32,359 (15.2)	505 (6.9)	0.268
History of cerebrovascular disease, n (%)	22,134 (10.1)	21,676 (10.2)	458 (6.2)	0.144
History of COPD, n (%)	18,636 (8.5)	18,286 (8.6)	350 (4.8)	0.154
History of hypertension, n (%)	66,281 (30.1)	64,643 (30.4)	1,638 (22.3)	0.184
History of chronic kidney disease, n (%)	15,360 (7.0)	15,106 (7.1)	254 (3.5)	0.163
Charlson comorbidity index, n (%)				0.356
0	120,433 (54.8)	115,531 (54.3)	4,902 (66.8)	
1	25,938 (11.8)	25,129 (11.8)	809 (11.0)	
≥2	73,588 (33.5)	71,959 (33.9)	1,629 (22.2)	
Previous use of immunosuppressants, n (%)	3,922 (1.8)	3,873 (1.8)	49 (0.7)	0.104
Exposure				
Previous use of systemic glucocorticoids, n (%)	80,943 (36.8)	78,889 (37.1)	2,054 (28)	
Asthma, n (%)	32,845 (14.9)	32,120 (15.1)	725 (9.9)	
Current asthma, n (%)	27,638 (12.6)	27,080 (12.7)	558 (7.6)	
Allergic rhinitis, n (%)	138,743 (63.1)	134,533 (63.3)	4,210 (57.4)	
Current allergic rhinitis, n (%)	111,530 (50.7)	108,234 (51.0)	3,296 (44.9)	
Atopic dermatitis, n (%)	8,591 (3.9)	8,402 (4.0)	189 (2.6)	
Current atopic dermatitis, n (%)	6,840 (3.1)	6,704 (3.2)	136 (1.9)	

An SMD of <0.1 indicates no major imbalance.

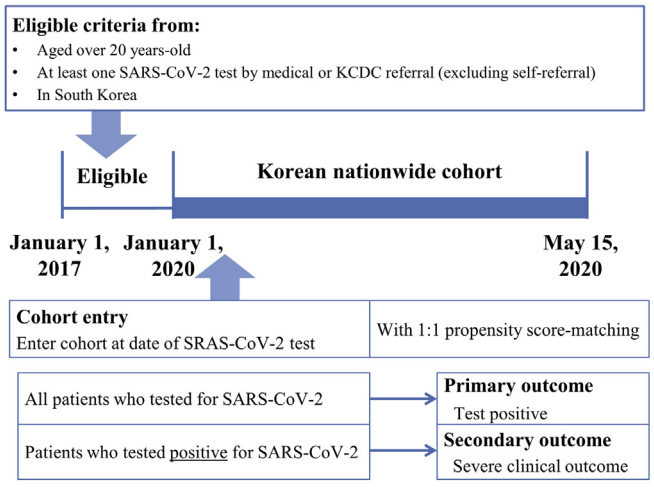

FIG 1. Flowchart depicting the study enrollment. *KCDC,* Korea Centers for Disease Control.

testing and among patients who tested positive for SARS-CoV-2 infection.[32] We used a logistic regression model adjusted for age; sex; region of residence; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, or chronic kidney disease; the Charlson comorbidity index; and use of immunosuppressants. The adequacy of matching was confirmed by comparing propensity score densities (see Figs E1-E12 in this article's Online Repository at www.jacionline.org) and standardized mean differences (SMD).[26]

Data were analyzed by using binary logistic regression or analysis of covariance models. The estimation of the adjusted odds ratios (aORs) with 95% CIs or the adjusted mean difference (with 95% CIs) was performed after adjusting for the following potential confounders to reduce the possibility of bias: age; sex; region of residence (urban or rural); history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, and chronic kidney disease; the Charlson comorbidity index (0, 1, and ≥2); previous use of systemic glucocorticoids and immunosuppressants; and allergic disorders (as relevant). Statistical analyses were performed in SAS version 9.4 (SAS Institute, Inc, Cary, NC). A 2-sided *P* value of less than .05 was considered statistically significant.

Statistical analysis

A primary analysis (a positive laboratory test result for COVID-19) using binary logistic regression, a secondary analysis (a severe clinical outcome of COVID-19) using binary logistic regression, and another secondary analysis (length of hospital stay) using analysis of covariance were conducted on the basis of presence of allergic diseases (asthma, allergic rhinitis, or atopic dermatitis). In addition, the following several analyses were undertaken: (1) we repeated the main analysis of the asthma phenotype (none vs allergic asthma vs nonallergic asthma), and (2) we redefined the cohort by using a stricter definition of "current allergic status."

Patient and public involvement

No patients were directly involved in designing the research question or in conducting the research. No patients were asked for advice on interpretation or writing up of the results. There are no plans to involve patients or the relevant patient community in the dissemination of study findings at this time.

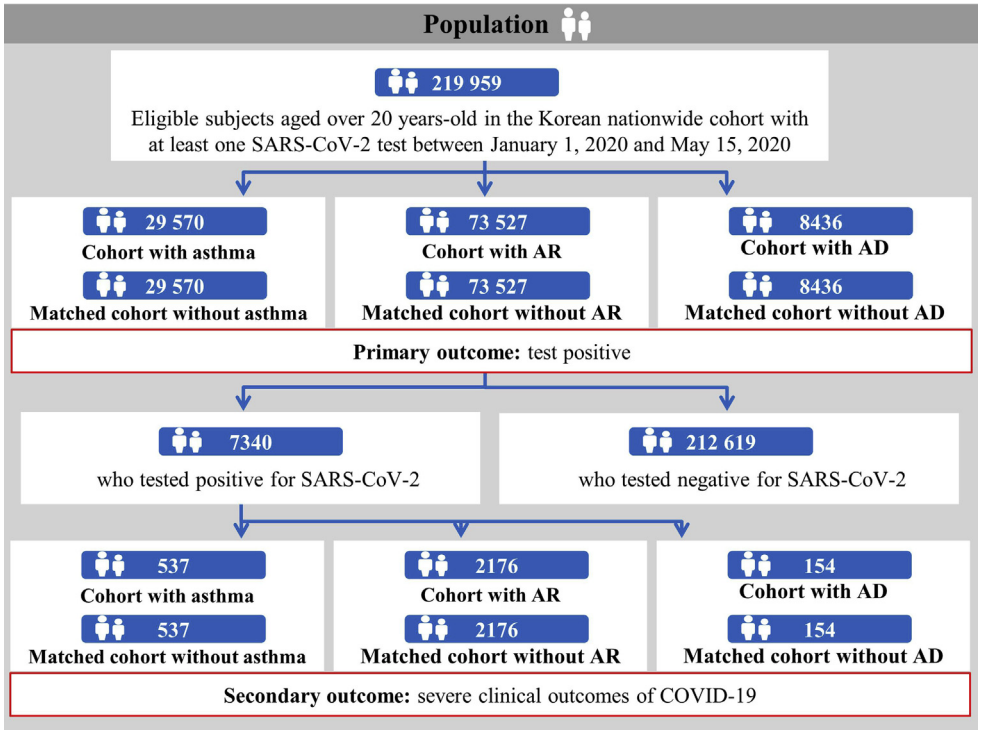

FIG 2. Disposition of patients in the Korean nationwide cohort. *AD*, Atopic dermatitis; *AR*, allergic rhinitis.

RESULTS

Descriptive overview

The demographic and clinical characteristics of a total of 219,959 patients (mean age ± SD, 49.0 ± 19.9 years; male [%], 104,331 [47.4%]) who underwent SARS-CoV-2 testing (Table I and Figs 1 and 2) were analyzed. In this study population, 32,845 patients (14.9%) were diagnosed with asthma, 138,743 patients (63.1%) with allergic rhinitis, and 8,591 (3.9%) with atopic dermatitis. Among the 7340 patients (mean age ± SD, 47.1 ± 19.0 years; male [%], 2970 [40.5%]) who tested positive for SARS-CoV-2, there were 725 (9.9%), 4210 (57.4%), and 136 (1.9%) patients with asthma, allergic rhinitis, and atopic dermatitis, respectively.

SARS-CoV-2 test positivity and allergic diseases

After propensity score matching among patients who were tested for SARS-CoV-2 (n = 219,959), there were no major imbalances in the baseline covariates evaluated by SMD between both groups (Table II; all SMDs < 0.1). Table II describes the ORs for the association of SARS-CoV-2 test positivity with allergic diseases among all patients who were tested for SARS-CoV-2. Among all the patients tested, the SARS-CoV-2 test positivity rate was 2.3% in patients with asthma, compared with 2.2% in those without asthma (aOR, 1.08; 95% CI, 1.01-1.17) and 3.3% in patients with allergic rhinitis compared with 2.8% in those without allergic rhinitis (aOR, 1.18; 95% CI, 1.11-1.25) (Table II and Fig 3). Analyses using a stricter definition of current allergic diseases also showed a significantly increased risk of SARS-CoV-2 test positivity (see Table E1 in this article's Online Repository at www.jacionline.org). Analysis of the effect of atopic status indicated that individuals with nonallergic asthma had a greater risk of SARS-CoV-2 test positivity (aOR, 1.34; 95% CI, 1.07-1.71) than those with allergic asthma (aOR, 1.06; 95% CI, 0.97-1.17) (Table IV).

Clinical outcomes in patients who tested positive for SARS-CoV-2

After propensity score matching among patients who tested positive for SARS-CoV-2 (n = 7340), there were no major imbalances in the baseline covariates evaluated by SMD between both groups (Table III; all SMDs < 0.1, except for a history of cerebrovascular disease and hypertension among patients without atopic dermatitis vs those with atopic dermatitis). Table III describes the ORs for the association of severe clinical outcomes of COVID-19 with allergic diseases among patients who tested positive for SARS-CoV-2; among these patients, the rates of severe clinical outcomes of COVID-19 were 6.9% and 4.5% in patients with and without asthma, respectively (aOR, 1.62; 95% CI, 1.01-2.67) and 4.7% and 3.7% in patients with and without allergic rhinitis, respectively (aOR, 1.27; 95% CI, 1.00-1.64, $P < .05$) (Table III and Fig 3). Furthermore, analyses using a stricter definition of current allergic diseases showed a significantly increased risk of severe outcomes of COVID-19 (see Table E2 in this article's Online Repository at www.jacionline.org). The analysis of the effect of atopic status indicated that individuals with nonallergic asthma had a greater risk for severe outcomes of COVID-19 (aOR, 4.09; 95% CI, 1.69-10.52) than those with allergic asthma (aOR, 1.40; 95% CI, 0.83-2.41) (Table IV).

To gain additional insights into the association between allergic diseases and the clinical outcomes of COVID-19, we conducted an analysis of the length of hospital stay (Table III). Patients with

TABLE II. 1:1 propensity-score–matched baseline characteristics, SARS-CoV-2 infection test results, and allergic diseases in all patients who underwent SARS-CoV-2 testing

	Patients who underwent SARS-CoV-2 test (total n = 219,959)								
	Asthma			Allergic rhinitis			Atopic dermatitis		
Characteristic	No	Yes	SMD	No	Yes	SMD	No	Yes	SMD
Total, n (%)	29,570	29,570		73,527	73,527		8,436	8,436	
Age (y), mean ± SD	57.7 ± 20.0	57.8 ± 20.0	0.005	49.7 ± 20.2	49.8 ± 20.0	0.007	52.7 ± 21.0	52.7 ± 21.4	0.002
Sex, n (%)			0.036			0.027			0.036
Male	12,595 (42.6)	13,126 (44.4)		36,797 (50.1)	37,779 (51.4)		3,783 (44.8)	3,936 (46.7)	
Female	16,975 (57.4)	16,444 (55.6)		36,730 (50.0)	35,748 (48.6)		4,653 (55.2)	4,500 (53.3)	
Region of residence, n (%)			0.011			0.164			0.004
Rural	12,670 (42.9)	12,830 (43.4)		32,243 (43.9)	38,227 (52.0)		3,353 (39.8)	3,368 (39.9)	
Urban	16,900 (57.2)	16,740 (56.6)		41,284 (56.2)	35,300 (48.0)		5,083 (60.3)	5,068 (60.1)	
History of diabetes mellitus, n (%)	8,128 (27.5)	8,175 (27.7)	0.004	11,987 (16.3)	13,146 (17.9)	0.042	2,225 (26.4)	2,200 (26.1)	0.007
History of cardiovascular disease, n (%)	7,724 (26.1)	7,928 (26.8)	0.017	10,050 (13.7)	12,208 (16.6)	0.083	2,006 (23.8)	2,048 (24.3)	0.013
History of cerebrovascular disease, n (%)	4,846 (16.4)	4,922 (16.7)	0.008	7,447 (10.1)	8,691 (11.8)	0.056	1,271 (15.1)	1,319 (15.6)	0.017
History of COPD, n (%)	6,641 (22.5)	6,791 (23.0)	0.014	3,203 (4.4)	4,531 (6.2)	0.069	1,330 (15.8)	1,342 (15.9)	0.004
History of hypertension, n (%)	13,616 (46.1)	13,474 (45.6)	0.010	21,987 (29.9)	22,974 (31.3)	0.029	3,457 (41.0)	3,404 (40.4)	0.013
History of chronic kidney disease, n (%)	2,896 (9.8)	3,205 (10.8)	0.037	4,723 (6.4)	5,823 (7.9)	0.060	1,014 (12.0)	1,095 (13.0)	0.032
Charlson comorbidity index, n (%)			0.010			0.078			0.012
0	10,774 (36.4)	10,523 (35.6)		42,096 (57.3)	39,524 (53.8)		3,419 (40.5)	3,472 (41.2)	
1	4,056 (13.7)	4,169 (14.1)		7,574 (10.3)	7,570 (10.3)		1,057 (12.5)	1,048 (12.4)	
≥2	14,740 (49.8)	14,878 (50.3)		23,857 (32.5)	26,433 (36.0)		3,960 (46.9)	3,916 (46.4)	
Previous use of immunosuppressants, n (%)	686 (2.3)	740 (2.5)	0.017	1,058 (1.4)	1,394 (1.9)	0.035	449 (5.3)	550 (6.5)	0.057
COVID-19, n (%)	640 (2.2)	683 (2.3)		2,044 (2.8)	2,415 (3.3)		209 (2.5)	189 (2.2)	
Minimally adjusted OR (95% CI)	Reference	**1.07 (1.00 - 1.15)***		Reference	**1.15 (1.09-1.22)***		Reference	0.90 (0.74-1.10)*	
Fully adjusted OR (95% CI)	Reference	**1.08 (1.01-1.17)†**		Reference	**1.18 (1.11-1.25)‡**		Reference	0.93 (0.76-1.13)§	

An SMD of <0.1 indicates no major imbalance. All SMD values were <0.1 in each propensity-score–matched cohort.
Numbers in boldface indicate significant differences ($P < .05$).
*Minimally adjusted: adjustment for age and sex.
†Fully adjusted: adjustment for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, chronic kidney disease, Charlson comorbidity index, use of immunosuppressants, use of systemic glucocorticoids, allergic rhinitis, and atopic dermatitis.
‡Fully adjusted: adjustment for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, chronic kidney disease, Charlson comorbidity index, use of immunosuppressants, use of systemic glucocorticoids, asthma, and atopic dermatitis.
§Fully adjusted: adjustment for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, chronic kidney disease, Charlson comorbidity index, use of immunosuppressants, use of systemic glucocorticoids, asthma, and allergic rhinitis.

allergic rhinitis were hospitalized for an average of 22.8 days, as compared with an average hospital stay of 21.8 days in patients without allergic rhinitis (adjusted mean difference, 0.71; 95% CI, 0.02-1.40). The mean length of hospital stay was 24.6 days and 22.1 days in patients with and without asthma (adjusted mean difference, 0.89; 95% CI, −0.25 to 2.3) and 22.3 days and 22.4 days in patients with and without atopic dermatitis (adjusted mean difference, −0.01; 95% CI, −2.07 to 2.04), respectively.

DISCUSSION

In a Korean nationwide cohort, we investigated the association between SARS-CoV-2 test positivity and allergic diseases among 219,959 patients who underwent SARS-CoV-2 testing. Moreover, we studied the association between the clinical outcomes of COVID-19 and allergic diseases among 7340 patients who tested positive for SARS-CoV-2. Asthma and allergic rhinitis were associated with an increased likelihood of SARS-CoV-2 test positivity and worse clinical outcomes (ie, death, ICU admission, and invasive ventilation). Allergic rhinitis was associated with longer hospital stay. Interestingly, patients with nonallergic asthma had a greater risk of SARS-CoV-2 test positivity and severe clinical outcomes of COVID-19 than those with allergic asthma.

COVID-19 was associated with several comorbidities, such as old age[1,4] and preexisting pulmonary disease[5,6]; however, studies of the association of COVID-19 and asthma are controversial, because previous studies have described either no association[15] or a positive association.[33,34] Moreover, previous studies on this topic were limited by their small sample of COVID-19–confirmed patients (n = 140,[15] n = 179,[33] or n = 23[34] vs n = 7340 in the

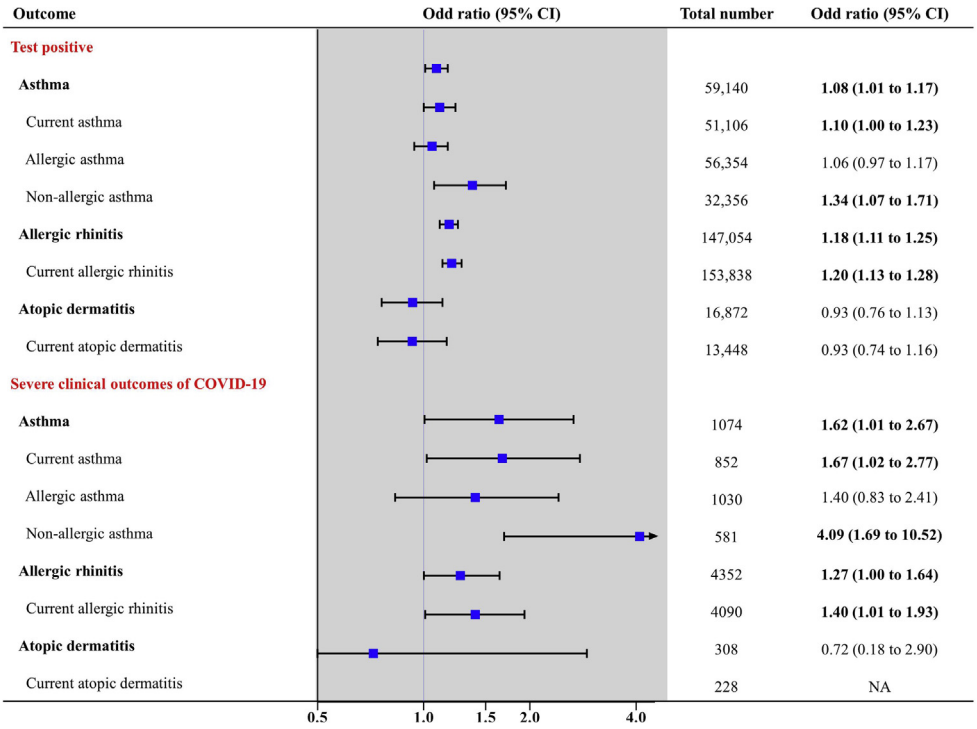

FIG 3. Association of allergic diseases with the results of SARS-CoV-2 test (primary outcome) among 291,959 patients, and the association of allergic diseases with clinical outcomes of COVID-19 (secondary outcome) among 7,340 patients who tested positive for SARS-CoV-2. The severe clinical outcomes of COVID-19 comprised admission to the ICU, invasive ventilation, or death. *NA*, Not applicable/available. The *x*-axis indicates a log-scale.

present study), making it difficult to reach a consistent conclusion regarding association (no association[15] or positive association[33,34]). For example, a previous study in Wuhan that was conducted early in the COVID-19 pandemic showed no COVID-19 risk association with an allergic history[15]; however, more recent epidemiological data indicate that asthma is a significant comorbidity related to COVID-19.[33] In addition, a cellular receptor of COVID-19, *angiotensin-converting enzyme 2*, is decreased,[34] whereas the expression of another entry molecule, *TMPRSS2*, is increased in the nasal and airway epithelial cells of children and adults with asthma and allergic rhinitis.[22] We hypothesized that the increased number of cases with adequate clinical information in combination with the precise study design of this research could clarify this inconsistency. No study has yet demonstrated a direct relationship between infectivity or clinical outcomes of COVID-19 and with a comprehensive set of allergic disorders (including asthma, allergic rhinitis, and atopic dermatitis) by using propensity score matching at a national level together with a subgroup analysis of asthma. This study highlights 2 important findings: (1) current or underlying asthma and allergic rhinitis were associated with a higher likelihood of SARS-CoV-2 test positivity and severe COVID-19 outcomes; and (2) individuals with nonallergic asthma were more likely to test positive and experience severe clinical outcomes of COVID-19.

Several possible pathophysiological mechanisms in the underlying allergic history could enhance the susceptibility to SARS-CoV-2 infection.[21] These respiratory viruses enter the bronchial epithelium of the upper and lower airway and provoke local inflammatory cascades that are characterized by neutrophil recruitment, T-lymphocyte trafficking, and activation of resident monocytes to induce a disruption of the bronchial defense system.[21] By inducing cytokines such as IL-25 and IL-33 in epithelial cells, the virus activates T_H2 pathways to cause eosinophilia, increased secretion of proinflammatory cytokines (ie, IL-4, IL-5, and IL-13), and enhanced mucin production, all of which eventually worsen the symptoms of asthma.[35] Moreover, patients with allergies have impaired secretion of innate IFNs, such as IFN-I and IFN-III, in mononuclear cells as well as in the epithelial cells of the airway, which increases their susceptibility to respiratory viral infection.[21] These IFNs are crucial for stimulating the expression of antiviral activity-related genes through a well-known Janus kinase/signal transducer and activator of transcription pathway in the bronchial epithelial cells and alveolar cells.[36] On the basis of these preliminary studies, we theorized that SARS-CoV-2 itself could potentially exacerbate allergy, which could, in turn, facilitate viral infection and lead to a devastating outcome of COVID-19. Although in the same category of allergic diseases, it is remarkable that atopic dermatitis does not show a potential association with the clinical outcomes of COVID-19, implying that changes in the local immunologic environment in the respiratory system, including the upper and lower respiratory tract, appear to be more important in the progression of infection than the systemic immunologic effects. The results of our nationwide cohort analysis clearly show that patients with respiratory allergic diseases are at a higher risk for worse clinical outcomes of COVID-19.

Interestingly, our data showed that patients with nonallergic asthma had a greater risk of SARS-CoV-2 test positivity and severe clinical outcomes of COVID-19 than those with allergic asthma. These results are in line with those from a previous

TABLE III. 1:1 propensity-score–matched baseline characteristics, severe clinical outcomes of COVID-19, and length of stay for patients and allergic diseases among patients with laboratory-confirmed SARS-CoV-2 infection

	Patients who tested positive for SARS-CoV-2 (total n = 7340)								
	Asthma			Allergic rhinitis			Atopic dermatitis		
Characteristic	No	Yes	SMD	No	Yes	SMD	No	Yes	SMD
Total, n (%)	537	537		2176	2176		154	154	
Age (y), mean ± SD	50.6 ± 18.35	51.1 ± 18.0	0.029	44.1 ± 18.6	45.0 ± 18.2	0.046	43.5 ± 18.8	44.7 ± 19.7	0.063
Sex, n (%)			0.062			0.012			0.040
Male	168 (31.3)	184 (34.3)		849 (39.0)	862 (39.6)		67 (43.5)	64 (41.6)	
Female	369 (68.7)	353 (65.7)		1327 (61.0)	1314 (60.4)		87 (56.5)	90 (58.4)	
Region of residence, n (%)			0.004			0.029			0.065
Rural	238 (44.3)	239 (44.5)		1081 (49.7)	1050 (48.3)		79 (51.3)	84 (54.6)	
Urban	299 (55.7)	298 (55.5)		1095 (50.3)	1126 (51.8)		75 (48.7)	70 (45.5)	
History of diabetes mellitus, n (%)	92 (17.1)	98 (18.3)	0.030	178 (8.2)	180 (8.3)	0.003	15 (9.7)	17 (11.0)	0.038
History of cardiovascular disease, n (%)	47 (8.8)	48 (8.9)	0.006	80 (3.7)	69 (3.2)	0.020	7 (4.6)	10 (6.5)	0.072
History of cerebrovascular disease, n (%)	34 (6.3)	47 (8.8)	0.086	102 (4.7)	105 (4.8)	0.006	2 (1.3)	8 (5.2)	0.167
History of COPD, n (%)	19 (3.5)	24 (4.5)	0.029	25 (1.2)	24 (1.1)	0.002	5 (3.3)	7 (4.6)	0.048
History of hypertension, n (%)	133 (24.8)	149 (27.8)	0.067	367 (16.9)	364 (16.7)	0.003	27 (17.5)	34 (22.1)	0.106
History of chronic kidney disease, n (%)	18 (3.4)	26 (4.8)	0.067	38 (1.8)	46 (2.1)	0.020	6 (3.9)	4 (2.6)	0.064
Charlson comorbidity index, n (%)			0.093			0.052			0.019
0	321 (59.8)	290 (54.0)		1681 (77.3)	1536 (70.6)		113 (73.4)	107 (69.5)	
1	69 (12.9)	78 (14.5)		182 (8.4)	295 (13.6)		17 (11.0)	20 (13.0)	
≥2	147 (27.4)	169 (31.5)		313 (14.4)	345 (15.9)		24 (15.6)	27 (17.5)	
Previous use of immunosuppressants, n (%)	4 (0.7)	2 (0.4)	0.048	9 (0.4)	10 (0.5)	0.006	0 (0.0)	1 (0.7)	0.062
Severe clinical outcomes of COVID-19, n (%)	24 (4.5)	37 (6.9)		81(3.7)	103 (4.7)		5(3.3)	7(4.6)	
Minimally adjusted OR (95% CI)	Reference	1.56 (0.95 to 2.62)*		Reference	**1.29 (1.02 to 1.66)***		Reference	1.16 (0.34 to 4.15)*	
Fully adjusted OR (95% CI)	Reference	**1.62 (1.01 to 2.67)†**		Reference	**1.27 (1.00 to 1.64)‡**		Reference	0.72 (0.18 to 2.90)§	
Length of stay for patients in hospital (d), mean ± SD	22.1 ± 14.1	24.6 ± 17.0		21.8 ± 14.3	22.8 ± 14.5		22.4 ± 14.4	22.3 ± 14.6	
Fully adjusted mean difference (95% CI)	Reference	0.89 (−0.25 to 2.03)†		Reference	**0.71 (0.02 to 1.40)‡**		Reference	−0.01 (−2.07 to 2.04)§	

An SMD of <0.1 indicates no major imbalance. All SMD values were <0.1 in each propensity-score–matched cohort, except history of cerebrovascular disease and hypertension among patients without atopic dermatitis vs those with atopic dermatitis.

Numbers in boldface indicate significant differences ($P < .05$).

*Minimally adjusted: adjustment for age and sex.

†Fully adjusted: adjustment for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, chronic kidney disease, Charlson comorbidity index, use of immunosuppressants, use of systemic glucocorticoids, allergic rhinitis, and atopic dermatitis.

‡Fully adjusted: adjustment for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, chronic kidney disease, Charlson comorbidity index, use of immunosuppressants, use of systemic glucocorticoids, asthma, and atopic dermatitis.

§Fully adjusted: adjustment for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, chronic kidney disease, Charlson comorbidity index, use of immunosuppressants, use of systemic glucocorticoids, asthma, and allergic rhinitis.

study.[17] Compared with allergic asthma, nonallergic asthma involves the activation of neutrophils and mast cells, which drives the immune response toward a T_H1 response.[37] Because the immunologic profile of patients with COVID-19 is polarized toward a classic T_H1 response, patients with nonallergic asthma might manifest an aggravated T_H1 immune response. Thus, they are predisposed to severe clinical outcomes of COVID-19.[38] Given these potential associations, patients with nonallergic asthma should be aware of the severe clinical outcomes of COVID-19, and careful monitoring of inflammatory status in this population should be emphasized.

This study has several limitations. First, the most important limitation is that the diagnosis of asthma, atopic dermatitis, and allergic rhinitis was defined by *ICD* codes, which may be inaccurate when compared with the diagnosis obtained from a review of a questionnaire. However, many previous studies have used claims-based definitions of allergic diseases similarly as in our study,[25,30] and have demonstrated good reliability. Because we have not interpreted the allergic status of the patients on the basis of their medical records, comprising laboratory data (eg, IgE levels), our results should be interpreted with caution and should be validated in studies that involve the analysis of laboratory data.

TABLE IV. Propensity-score–matched subgroup analyses for the association of SARS-CoV-2 test positivity with asthma phenotypes among all patients who underwent SARS-CoV-2 testing and clinical outcomes or length of hospital stay with asthma phenotypes among patients with laboratory-confirmed SARS-CoV-2 infection

Exposure	Event	Event number/total number (%)	Fully adjusted OR* (95% CI)
Patients who underwent SARS-CoV-2 test			
None	COVID-19	640/29,570 (2.2)	Reference
Allergic asthma		603/26,784 (2.3)	1.06 (0.97 to 1.17)
Nonallergic asthma		80/2,786 (2.9)	**1.34 (1.07 to 1.71)**
Patients who tested positive for SARS-CoV-2			
None	Severe clinical outcomes of COVID-19	24/537 (4.5)	Reference
Allergic asthma		30/493 (6.1)	1.40 (0.83 to 2.41)
Nonallergic asthma		7/44 (15.9)	**4.09 (1.69 to 10.52)**
Exposure	**Event**	**Duration (d), crude mean ± SD**	**Adjusted mean difference* (95% CI)**
Patients who tested positive for SARS-CoV-2			
None	Length of stay for patients in hospital	22.1 ± 14.1	Reference
Allergic asthma		24.1 ± 16.5	0.60 (−1.79 to 0.58)
Nonallergic asthma		29.3 ± 21.4	**3.91 (0.40 to 7.42)**

Numbers in boldface indicate significant differences ($P < .05$).
*Fully adjusted: adjustment for age, sex, region of residence, history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, chronic kidney disease, Charlson comorbidity index, use of immunosuppressants, use of systemic glucocorticoids, allergic rhinitis, and atopic dermatitis.

To overcome this limitation, we have adopted a novel "allergic asthma" concept, which could represent partially the severity of an allergic reaction.[17,28] Second, despite the sufficient amount of pediatric data (number of COVID-19–confirmed patients = 611), the association between pediatric allergic diseases and clinical outcomes of COVID-19 could not be analyzed because none of the children had any of the 3 specified composite end points (admission to ICU, administration of invasive ventilation, or death). Although we investigated the relationship between allergic status and length of hospital stay, the association was inconclusive (data not shown). Further large-scale international cohort studies in pediatric patients with COVID-19 with diverse medical outcomes are needed to clarify this issue. Third, because our data were claims-based, information on smoking was unavailable. The Health Insurance Review & Assessment Service of Korea, Korea Centers for Disease Control and Prevention, and the Ministry of Health and Welfare, Republic of Korea exclude information on smoking because of the governmental policy for protecting the personal information of patients. To compensate for this issue, we adjusted the patient's history of COPD, a well-known smoking-related disease.[26,39] Fourth, because of the urgent global situation, the COVID-19–related data provided by the Korean government involve short-term data (<3.5 years) of the patient's history for quick claim processing. More clinical studies involving longer follow-up data are required to provide more information and to validate the association between allergic diseases and COVID-19. Finally, because our database involves patients who underwent the SARS-CoV-2 test, systemic factors might differ in comparison to those of the general population. Despite this potential prevalence-induced bias, our study involved a large population-based cohort with propensity score matching to ensure that our results were highly credible.

In spite of these limitations, to our knowledge, this is the first large-scale study to investigate the association of the risk of COVID-19 with allergic diseases in all Korean patients who were tested for SARS-CoV-2 by using data from a Korean nationwide cohort. The strength of our cohort study was the large sample size (219,959 patients). Thus, our study provides strong evidence that the development of respiratory allergic diseases is associated with an increased risk of subsequent COVID-19 and/or worse clinical outcomes of COVID-19.

Conclusions

Asthma and allergic rhinitis were associated with an increased likelihood of SARS-CoV-2 test positivity and worse clinical outcomes of COVID-19 in a Korean nationwide cohort. Especially, patients with nonallergic asthma had a greater risk of SARS-CoV-2 test positivity and severe clinical outcomes of COVID-19 than those with allergic asthma. Thus, our findings provide an improved understanding of the relationship between the pathogenesis of COVID-19 and respiratory allergic diseases and suggest that clinicians should be aware of the greater risk of susceptibility to, and severity of, COVID-19 that is conferred by respiratory allergic diseases, especially nonallergic asthma, during the COVID-19 pandemic.

We appreciate health care professionals dedicated to treating patients with COVID-19 in Korea, and the Ministry of Health and Welfare and the Health Insurance Review & Assessment Service of Korea for sharing invaluable national health insurance claims data in a prompt manner.

Clinical implications: Our findings suggest that clinicians should be aware of the greater risk of SARS-CoV-2 infection and severe clinical outcomes of COVID-19 among patients with allergic rhinitis and asthma, especially nonallergic asthma.

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