Original Article

Estimating COVID-19 Infection and Severity Risks in Patients with Chronic Rhinosinusitis: A Korean Nationwide Cohort Study

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What is already known about this topic? Chronic rhinosinusitis (CRS) is one of the most common upper airway inflammatory diseases and may be associated with epithelial barrier dysfunction, bacterial colonization, exaggerated immune response, and specific antibody deficiency. Basic studies suggest that CRS may increase coronavirus disease susceptibility or severity; however, the potential association of CRS with coronavirus disease 2019 (COVID-19) susceptibility or severity has not been demonstrated.

What does this article add to our knowledge? In our large-scale, population-based nationwide cohort in South Korea, CRS was associated with an increased risk for severe acute respiratory syndrome coronavirus 2 infection and severe COVID-19. In particular, among patients with CRS, prior intranasal corticosteroid use, the absence of nasal polyps, or nonatopic type were associated with a greater risk for severe acute respiratory syndrome coronavirus 2 infection, and severe COVID-19 outcomes.

How does this study impact current management guidelines? Taken together, our findings suggest that clinicians should be cautious in assessing the prognosis and determining care for patients with CRS amid the COVID-19 pandemic.

BACKGROUND: Basic studies suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can affect chronic rhinosinusitis (CRS), but there is unclear real-world evidence regarding the association of underlying CRS with the risk for SARS-CoV-2 infection and severe coronavirus disease 19 (COVID-19).
OBJECTIVE: We aimed to determine whether CRS is associated with increased risk for SARS-CoV-2 infection and severe COVID-19.
METHODS: Altogether, 219,959 adult patients who tested for SARS-CoV-2 in South Korea from January 1 to May 15, 2020 (excluding self-referral) were identified in this nested case-control study with propensity score matching. Data on SARS-CoV-2 test results and COVID-19 worsened outcomes (ie, the need for oxygen therapy, intensive care, or mechanical ventilation, and death) were obtained from the Health Insurance Review and Assessment Service of Korea.
RESULTS: In this matched cohort, 380 of 12,217 patients with CRS (3.1%) tested positive for SARS-CoV-2 infection, compared with 310 patients without CRS (2.5%; adjusted odds ratio = 1.22; 95% confidence interval, 1.04-1.42). Moreover, 60 of 286 COVID-19 patients with CRS (21.0%) had severe COVID-19 outcomes, compared with 38 without CRS (13.3%; adjusted odds ratio = 1.71; 95% confidence interval, 1.09-2.71). Subgroup analysis identified that CRS patients with an absence

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Abbreviations used
ACE2- Angiotensin converting enzyme II
aOR- Adjusted odds ratio
CI- Confidence interval
COVID-19- Coronavirus disease 2019
CRS- Chronic rhinosinusitis
CRSsNP- Chronic rhinosinusitis without nasal polyp
CRSwNP- Chronic rhinosinusitis with nasal polyp
ICD-10- International Classification of Disease, 10th revision
IFN- Interferon
KCDC- Korea Centers for Disease Control and Prevention
SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2
SMD- Standardized mean difference
TMPRSS2- Transmembrane serine protease 2

of nasal polyps, prior intranasal corticosteroid use, or nonatopic type had a greater risk for SARS-CoV-2 infection and severe COVID-19 outcomes.
CONCLUSIONS: In patients with CRS, prior intranasal corticosteroid use, the absence of nasal polyps, or nonatopic type was associated with increased risk for SARS-CoV-2 infection and severe COVID-19 in the Korean nationwide cohort. Clinicians should be cautious in determining prognosis and care for patients with CRS amid the COVID-19 pandemic. **© 2021 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2021;■:■-■)**

Key words: *Severe acute respiratory syndrome 2; COVID-19; Chronic rhinosinusitis; Nasal polyp; Intranasal corticosteroids*

INTRODUCTION

A global pandemic of coronavirus disease 2019 (COVID-19) began in December 2019, when the pathogen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Wuhan, China.[1-3] Severe acute respiratory syndrome coronavirus 2 invades host cells by binding its spike proteins to receptor-angiotensin converting enzyme II (ACE2)[3] and by their priming and fusion with the cell membrane by host transmembrane serine protease 2 (TMPRSS2).[4] In addition to the different expression levels or affinities of viral entry factors, host immunity functions could influence the infectivity or severity of COVID-19.[4] Thus, asthma,[2] allergic rhinitis,[2] chronic obstructive pulmonary disease,[5,6] and immune-compromised status[7] have been reported to be potentially associated with increased susceptibility to or severity of COVID-19.

In addition to the lower airway, COVID-19 has been suggested to have a high impact on the upper airway.[8] The viral load of SARS-CoV-2 was found to be higher in nasal swabs than in throat swabs in both symptomatic and asymptomatic patients.[9] Furthermore, in healthy human tissues, higher expression levels of viral entry-associated genes ACE2 and TMPRSS2 were observed in nasal epithelial cells than in lower respiratory tract, corneal, and intestinal epithelial cells.[10,11] In the respiratory tract, a gradient was found in ACE2 expression and SARS-CoV-2 infection levels from the nose to the distal pulmonary epithelium, which suggests that SARS-CoV-2 affinity to the respiratory epithelium combined with inhalation-related viral spreading could explain the pathogenesis of COVID-19.[12]

Chronic rhinosinusitis (CRS) is one of the most common upper airway inflammatory diseases and could be associated with epithelial barrier dysfunction, bacterial colonization, exaggerated immune response, and specific antibody deficiency.[13,14] Owing to the upper airway inflammatory condition, epithelial barrier dysfunction, and high expression levels of viral entry genes, CRS may increase COVID-19 susceptibility or severity. Previous preliminary studies were equivocal,[11,15] and the potential association of CRS with COVID-19 susceptibility or severity has not yet been clarified.

In this nested case-control study in a Korean nationwide cohort, we investigated the potential association of CRS with SARS-CoV-2 infection (SARS-CoV-2 positive test result) and COVID-19 severity (COVID-19 worsened outcomes; including oxygen therapy, intensive care unit admission, use of mechanical ventilation, or death).

METHODS

The data were obtained from the Korea Centers for Disease Control and Prevention (KCDC), the Health Insurance Review and Assessment Service of Korea, and the Ministry of Health and Welfare in South Korea. As previously described, the nationwide cohort[2,3,16,17] had the following characteristics: (1) the Korean government provided a complimentary medical service for all COVID-19 patients; (2) the data consisted of health insurance claims over the previous 3.5 years (January 1, 2017 to May 15, 2020) of all patients who were tested for SARS-CoV-2 through KCDC or medical referrals (excluding self-referral); and (3) this health insurance claim-based cohort was kept anonymous to guarantee the confidentiality of COVID-19 infection status.

The study protocol was approved by the Institutional Review Board of Sejong University (SJU-HR-E-2020-003). The requirement for written consent was waived by the ethics committee because of urgent medical needs to be met amid the COVID-19 pandemic.

Study population

All adults (aged $\geq$20 years) who were tested for SARS-CoV-2 in South Korea from January 1, 2020 to May 15, 2020 (total n = 219,959, excluding self-referral) were enrolled. The observation period was from January 1, 2017 to May 15, 2020, and the individual index date was defined as the date of the first SARS-CoV-2 test. The medical history was defined using International Classification of Disease 10th revision (ICD-10) codes and at least two inpatient or outpatient claims within 1 year, as previously described.[2,3] The Charlson comorbidity index score was calculated, and the region of residence was classified as rural or urban, as previously described.[2,3,18,19] The use of medications was defined based on medications taken within 6 months before the individual index date.[2,3]

Exposure

We defined CRS using the ICD-10 code (J32) with at least two claims within 1 year and the use of head and neck computed tomography. We defined CRS with nasal polyp (CRSwNP) using ICD-10 codes J32 plus J33, and CRS without nasal polyp (CRSsNP) using ICD-10 code J32 alone.[20] Atopic CRS was defined as CRS with another allergic disease (asthma, atopic dermatitis, or allergic rhinitis), and nonatopic CRS as CRS with no other allergic disease.[2,21,22]

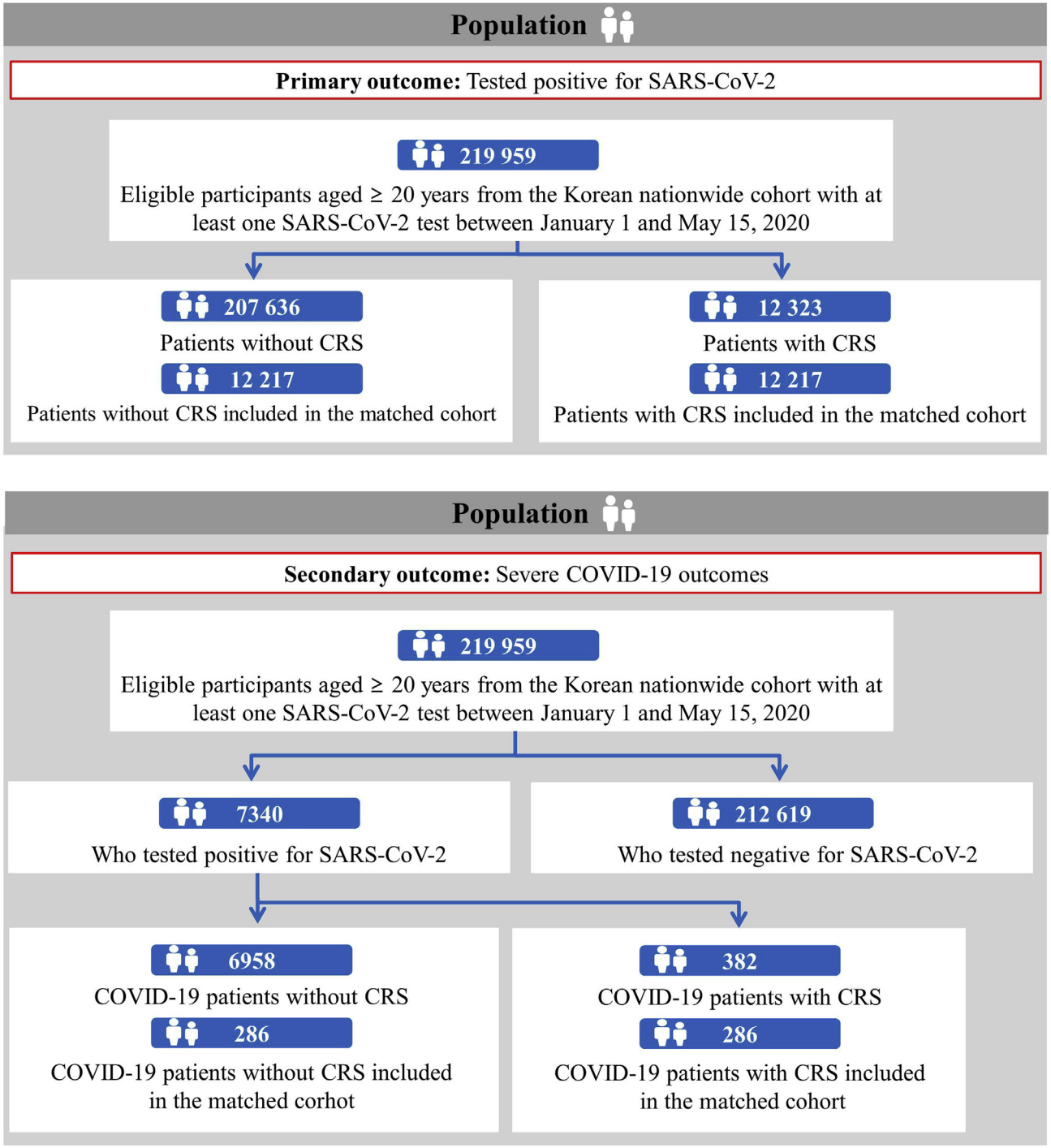

FIGURE 1. Participant flowchart. *COVID-19*, coronavirus disease; *CRS*, chronic rhinosinusitis; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

Outcomes

The primary outcome was a positive SARS-CoV-2 test result (laboratory-confirmed COVID-19) from real-time reverse transcription-polymerase chain reaction assays of pharyngeal or nasal swabs performed according to the guidelines of the World Health Organization and KCDC.[1-3] Secondary outcomes were severe COVID-19 outcomes, including the requirement of oxygen therapy, intensive care unit admission, use of mechanical ventilation, or death.[3]

Statistical analysis

In the nationwide cohort, preexisting CRS was defined as the exposure; a positive SARS-CoV-2 test result or severe COVID-19 outcomes were defined as the outcomes. We performed the

TABLE I. Baseline characteristics of all patients who underwent severe acute respiratory syndrome coronavirus 2 testing and those with laboratory-confirmed coronavirus disease 2019 in a Korean nationwide cohort

	All patients who underwent severe acute respiratory syndrome coronavirus 2 testing			Patients with laboratory-confirmed coronavirus disease 2019		
Characteristic	Total	Without CRS	With CRS	Total	Without CRS	With CRS
Total, n (%)	219,959 (100.0)	207,636 (94.4)	12,323 (5.6)	7340 (100.0)	6958 (94.8)	382 (5.2)
Age, y (SD)	49.0 (19.9)	49.1 (19.9)	55.0 (19.6)	47.1 (19.0)	46.7 (19.0)	56.1 (17.1)
Sex, n (%)						
Male	104,331 (47.4)	98,444 (47.4)	5887 (47.8)	2970 (40.5)	2818 (40.5)	152 (39.8)
Female	115,628 (52.6)	109,192 (52.6)	6436 (52.2)	4370 (59.5)	4140 (59.5)	230 (60.2)
Region of residence, n (%)						
Rural	96,315 (43.8)	91,252 (44.0)	5063 (41.1)	3535 (48.2)	3388 (48.7)	147 (38.5)
Urban	123,644 (56.2)	116,384 (56.1)	7260 (58.9)	3805 (51.8)	3570 (51.3)	235 (61.5)
History of diabetes mellitus, n (%)	38,396 (17.5)	34,715 (16.7)	3681 (29.9)	951 (13.0)	845 (12.1)	106 (27.7)
History of cardiovascular disease, n (%)	32,864 (14.9)	29,268 (14.1)	3596 (29.2)	505 (6.9)	433 (6.2)	72 (18.8)
History of cerebrovascular disease, n (%)	22,134 (10.1)	19,307 (9.3)	2827 (22.9)	458 (6.2)	381 (5.5)	77 (20.2)
History of chronic obstructive pulmonary disease, n (%)	18,636 (8.5)	16,157 (7.8)	2479 (20.1)	350 (4.8)	280 (4.0)	70 (18.3)
History of hypertension, n (%)	66,281 (30.1)	60,710 (29.2)	5571 (45.2)	1638 (22.3)	1501 (21.6)	137 (35.9)
History of chronic kidney disease, n (%)	15,360 (7.0)	13,762 (6.6)	1598 (13.0)	254 (3.5)	223 (3.2)	31 (8.1)
History of nasal polyp, n (%)	3069 (1.4)	1985 (1.0)	1084 (8.8)	60 (0.8)	32 (0.5)	28 (7.3)
Charlson comorbidity index, n (%)						
0	120,433 (54.8)	116,627 (56.2)	3806 (30.9)	4902 (66.8)	4758 (68.4)	144 (37.7)
1	25,938 (11.8)	24,165 (11.6)	1773 (14.4)	809 (11.0)	754 (10.8)	55 (14.4)
≥2	73,588 (33.5)	66,844 (32.2)	6744 (54.7)	1629 (22.2)	1446 (20.8)	183 (47.9)
Current use of medication, n (%)						
Aspirin	15,706 (7.1)	14,320 (6.9)	1386 (11.3)	310 (4.2)	272 (3.9)	38 (9.9)
Metformin	19,252 (8.8)	17,820 (8.6)	1432 (11.6)	550 (7.5)	496 (7.1)	54 (14.1)
Statin	41,011 (18.6)	37,482 (18.1)	3529 (28.6)	1078 (14.7)	949 (13.6)	129 (33.8)
Systemic corticosteroids	80,943 (36.8)	74,303 (35.8)	6640 (53.9)	2054 (28.0)	1876 (27.0)	178 (46.6)
Intranasal corticosteroids	10,384 (4.7)	8164 (3.9)	2220 (18.0)	263 (3.6)	187 (2.7)	76 (19.9)

CRS, chronic rhinosinusitis.

exposure propensity score matching method. Therefore, we used a 1:1 ratio greedy nearest-neighbor matching on the logit of the propensity score with the calipers less than 0.001 to balance the covariates of age (continuous); sex; region of residence (urban and rural); a history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, or chronic kidney disease; Charlson comorbidity index (0, 1, and ≥2); and use of medication (aspirin, metformin, or statin). We used two rounds of propensity score matching between patients without CRS versus patients with CRS: (1) among all patients who were tested for SARS-CoV-2 (n = 219,959) and (2) among patients with COVID-19 (n = 7340). We confirmed the adequacy of the propensity score matching as assessed by the propensity score densities (see Figures E1 and E2 in this article's Online Repository at www.jaci-inpractice.org) and standardized mean differences (SMDs).[2,21-23]

Main analysis

Data were analyzed using Firth's bias-reduced logistic regression to reduce the small sample bias and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) in each matched cohort, after adjusting for age; sex; region of residence; a history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, or nasal polyp; Charlson comorbidity index; and the use of medication (systemic or intranasal corticosteroids, aspirin, metformin, or statin). We performed several sensitivity analyses, applying stratification by nasal polyp (CRSwNP or CRSsNP), atopic phenotype (atopic CRS or nonatopic CRS), and prior intranasal corticosteroid use (CRS treated with or without intranasal corticosteroids). Statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc, Cary, NC) and R software (version 3.1.1, R Foundation, Vienna, Austria).[17] A two-tailed P value less than .05 was considered statistically significant.

RESULTS

Full unmatched cohort

In the entire study population (n = 219,959), we identified 207,636 patients without CRS (94.4%) and 12,323 with CRS (5.6%) (Figure 1). Among 7340 patients with laboratory-confirmed COVID-19, there were 6958 without CRS (94.8%) and 382 with CRS (5.2%). The positivity rate of the SARS-CoV-2 test was 3.3% (7340 of 219,959) in the entire study population, 2.3% in patients without CRS (6958 of 207,636), and 3.1% in patients with CRS (382 of 12,323).

Matched cohort

Table I reports the baseline characteristics of all patients tested for SARS-CoV-2 and all COVID-19 patients stratified by CRS. In the matched cohort (n = 24,434), baseline covariates were balanced between patients with and without CRS (Table II and Figure 2) (all SMDs <0.05). Patients with CRS had a 22%

TABLE II. One-to-one propensity score−matched baseline characteristics and adjusted ORs (95% confidence intervals) for association of severe acute respiratory syndrome coronavirus 2 test positivity with CRS among all patients who had severe acute respiratory syndrome coronavirus 2 testing

Characteristic	Without CRS	With CRS	SMD*
Total, n (%)	12,217	12,217	
Age, y (SD)	55.5 (19.8)	54.9 (19.6)	0.030
Sex, n (%)			<0.001
Male	5848 (47.9)	5847 (47.9)	
Female	6369 (52.1)	6370 (52.1)	
Region of residence, n (%)			0.006
Rural	4996 (40.9)	5031 (41.2)	
Urban	7221 (59.1)	7186 (58.8)	
History of diabetes mellitus, n (%)	3636 (29.8)	3600 (29.5)	0.007
History of cardiovascular disease, n (%)	3549 (29.1)	3504 (28.7)	0.009
History of cerebrovascular disease, n (%)	2673 (21.9)	2730 (22.4)	0.013
History of chronic obstructive pulmonary disease, n (%)	2412 (19.7)	2375 (19.4)	0.009
History of hypertension, n (%)	5565 (45.6)	5484 (44.9)	0.014
History of chronic kidney disease, n (%)	1532 (12.5)	1546 (12.7)	0.004
Charlson comorbidity index, n (%)			0.009
0	3793 (31.1)	3806 (31.2)	
1	1701 (13.9)	1772 (14.5)	
≥2	6723 (55.0)	6639 (54.4)	
Current use of medication, n (%)			
Aspirin	1209 (9.9)	1358 (11.1)	0.042
Metformin	1390 (11.4)	1414 (11.6)	0.007
Statin	3461 (28.3)	3466 (28.4)	<0.001
Coronavirus disease 2019, n (%)	310 (2.5)	380 (3.1)	
Minimally adjusted OR† (95% CI)	1.0 (reference)	**1.24 (1.06-1.43)**	
Fully adjusted OR‡ (95% CI)	1.0 (reference)	**1.22 (1.04-1.42)**	

CRS, chronic rhinosinusitis; *SMD*, standardized mean difference; *OR*, odds ratio.
Bolded data indicate significant differences in the regression model ($P < .05$).
*An SMD less than 0.1 indicates no major imbalance. All SMD values were less than 0.05 in the propensity score−matched cohort.
†Minimally adjusted for age and sex.
‡Fully adjusted for age; sex; region of residence; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, or nasal polyp; Charlson comorbidity index; and previous use of medication (systemic or intranasal corticosteroids, aspirin, metformin, or statin).

greater risk for SARS-CoV-2 infection after fully adjusting for confounding factors compared with patients without CRS (3.1% vs 2.5%; fully aOR = 1.22; 95% CI, 1.04-1.42). The stratification analysis found that patients with CRS had a 61% greater risk for severe COVID-19 compared with those without CRS (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) (0.7% vs 0.4%; fully aOR = 1.61; 95% CI, 1.12-2.29).

Next, patients with confirmed COVID-19 were matched for all baseline covariates between those with and without CRS (Table III and Figure 2) (all SMDs <0.1), except for a history of chronic obstructive pulmonary disease (SMD = 0.100). Patients with CRS had a 71% greater risk for severe COVID-19 outcomes after fully adjusting for confounding factors compared with patients without CRS (21.0% vs 13.3%; fully aOR = 1.09; 95% CI, 1.09-2.71).

Propensity score-matched subgroup analysis

Table IV reports the subgroup analysis of the effect of nasal polyps, intranasal corticosteroid use, and atopic status. Patients with CRSwNP did not experience a greater risk for SARS-CoV-2 infection (fully aOR = 1.01; 95% CI, 0.67-1.51) and severe COVID-19 outcomes (fully aOR = 1.34; 95% CI, 0.40-4.20) compared with patients without CRS. Patients with CRSsNP had a greater risk for SARS-CoV-2 infection (fully aOR = 1.24; 95% CI, 1.06-1.44) and severe COVID-19 outcomes (fully aOR = 1.75; 95% CI, 1.10-2.75) compared with patients without CRS.

Chronic rhinosinusitis patients treated with intranasal corticosteroids had a greater risk for SARS-CoV2 infection (aOR = 1.32; 95% CI 1.03-1.73) and severe COVID-19 outcomes (fully aOR = 2.24; 95% CI, 1.16-4.20) compared with CRS patients treated without intranasal corticosteroids (SARS-CoV-2 infection fully aOR = 1.19; 95% CI, 1.01-1.40; severe COVID-19 outcomes fully aOR = 1.55; 95% CI, 0.95-2.50). Patients with nonatopic CRS had a greater risk for SARS-CoV2 infection (aOR = 1.34; 95% CI 1.05-1.70) and severe COVID-19 outcomes (fully aOR = 2.27; 95% CI, 1.14-4.36) compared with patients with atopic CRS (SARS-CoV-2 infection fully aOR = 1.20; 95% CI, 1.00-1.41; $P < .05$; severe COVID-19 outcomes fully aOR = 1.56; 95% CI, 0.97-2.51).

DISCUSSION

We investigated the risk for COVID-19 susceptibility and severity in patients with CRS in a large-scale, population-based

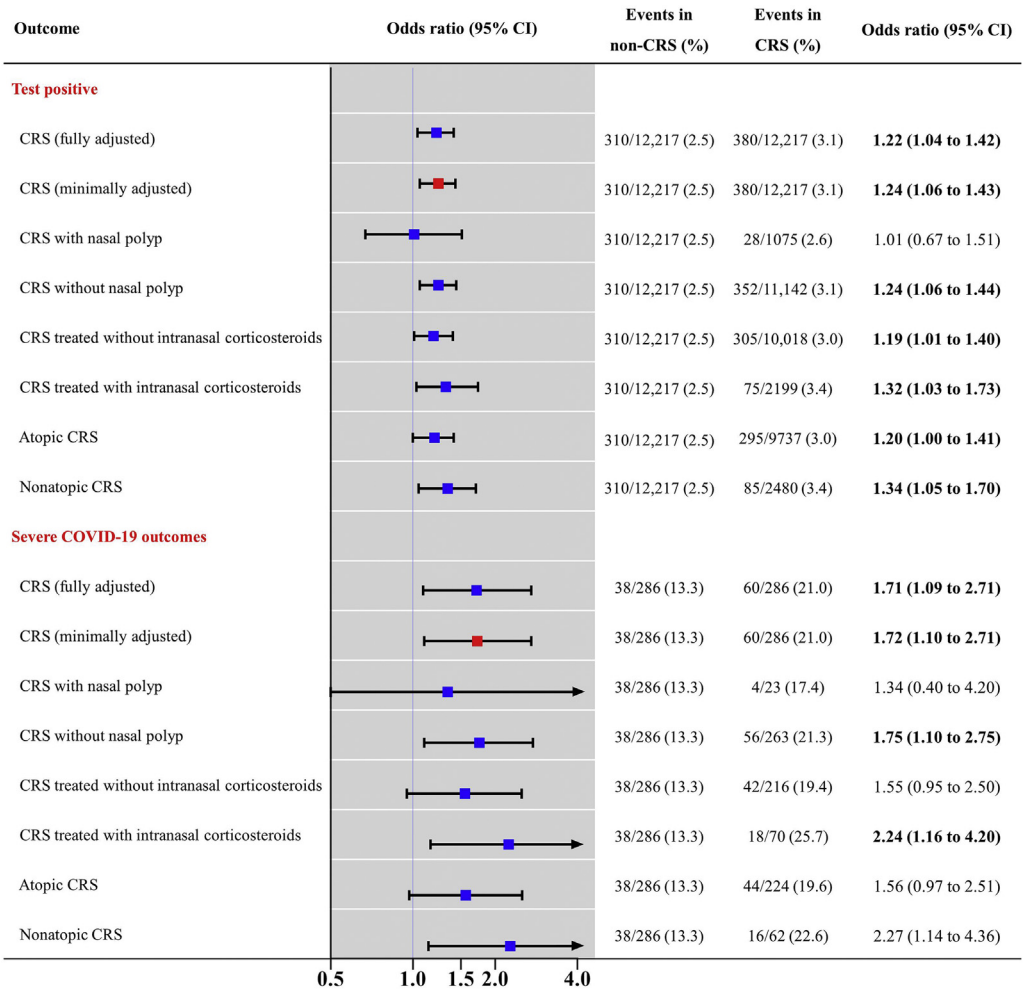

FIGURE 2. Propensity score-matched association of chronic rhinosinusitis (CRS) with coronavirus disease 19 (COVID-19) susceptibility and severity. Firth's bias-reduced logistic regression analysis ORs with 95% CIs are presented. Severe COVID-19 outcomes were the need for oxygen therapy, admission to the intensive care unit, invasive ventilation, or death. The x-axis indicates a log-scale; red dots indicate minimal adjustment and blue dots indicate full adjustment. *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *OR*, odds ratio; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

nationwide cohort in South Korea (n = 219,959). Patients with CRS had an increased risk for COVID-19 susceptibility and severity compared with people without CRS (Figure 3). In particular, CRSsNP, CRS treated with intranasal corticosteroids, and nonatopic CRS conferred a greater risk for SARS-CoV-2 infection and COVID-19 severity, although the event numbers were small.

Possible explanations of main results

To the authors' knowledge, this is the first real-world study to investigate potential associations between a diagnosis of CRS and the risks for SARS-CoV-2 infection and severe COVID-19. Previously, CRS was reported to increase the risks for pneumonia, sepsis, and mortality.[24,25] Those studies suggested that CRS could provide bacterial or viral reservoirs and reduce nitric oxide production in the sinus, implying impaired local host defense and increased susceptibility to secondary infection.[24,25] It is known that CRS is associated with immune dysfunction, such as epithelial barrier dysfunction[13,26] and specific antibody deficiency,[14] which may contribute to increased COVID-19 infectivity and severity.

The increased infectivity to SARS-CoV-2 and severity of COVID-19 observed in patients with CRS might be explained by several plausible mechanisms. First, the impairment of sinonasal epithelial barrier functions could increase the exposure of patients with CRS to viral pathogens and their invasion. The mucociliary clearance of viral pathogens might be impeded in CRS patients. Sinonasal epithelial cells in CRS patients have been shown to exhibit morphologic and functional changes in basal cell proliferation, goblet cell hyperplasia, and the loss of ciliated cells.[27] Second, patients whose CRS is caused by a viral infection may be more susceptible to viral coinfection, in particular with SARS-CoV-2. In a previous study,[28] CRS patients showed a 2.9 times higher rate of viral infection in nasal lavage fluids and nasal mucosa compared with patients without CRS, and approximately 21.6% of patients with CRS showed coronavirus infection.

TABLE III. One-to-one propensity score–matched baseline characteristics and adjusted ORs (95% confidence intervals) for association of severe coronavirus disease 2019 with CRS among patients with laboratory-confirmed coronavirus disease 2019

Characteristic	Without CRS	With CRS	SMD*
Total, n (%)	286	286	
Age, y (SD)	54.7 (16.5)	55.7 (16.4)	0.061
Sex, n (%)			0.058
Male	92 (32.2)	100 (35.0)	
Female	194 (67.8)	186 (65.0)	
Region of residence, n (%)			0.014
Rural	122 (42.7)	124 (43.4)	
Urban	164 (57.3)	162 (56.6)	
History of diabetes mellitus, n (%)	63 (22.0)	63 (22.0)	<0.001
History of cardiovascular disease, n (%)	26 (9.1)	23 (8.0)	0.039
History of cerebrovascular disease, n (%)	25 (8.7)	23 (8.0)	0.025
History of COPD, n (%)	14 (4.9)	21 (7.3)	0.100
History of hypertension, n (%)	89 (31.1)	89 (31.1)	<0.001
History of chronic kidney disease, n (%)	13 (4.5)	17 (5.9)	0.063
Charlson comorbidity index, n (%)			0.038
0	138 (48.3)	133 (46.5)	
1	44 (15.4)	47 (16.4)	
≥2	104 (36.4)	106 (37.1)	
Current use of medication, n (%)			
Aspirin	22 (7.7)	18 (6.3)	0.049
Metformin	25 (8.7)	29 (10.1)	0.048
Statin	64 (22.4)	66 (23.1)	0.017
Severe outcomes of coronavirus disease 2019†, n (%)	38 (13.3)	60 (21.0)	
Minimally adjusted OR‡ (95% CI)	1.0 (Reference)	**1.72 (1.10-2.71)**	
Fully adjusted OR§ (95% CI)	1.0 (Reference)	**1.71 (1.09-2.71)**	

COPD, chronic obstructive pulmonary disease; *CRS*, chronic rhinosinusitis; *OR*, odds ratio; *SMD*, standardized mean difference.
Bolded data indicate significant differences in the regression model ($P < .05$).
*An SMD less than 0.1 indicates no major imbalance. All SMD values were less than 0.1 in the propensity score–matched cohort, except a history of COPD.
†Severe outcomes of coronavirus disease 2019 were the need for oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.
‡Minimally adjusted for age and sex.
§Fully adjusted for age; sex; region of residence; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, chronic kidney disease, or nasal polyp; Charlson comorbidity index; and previous use of medication (systemic or intranasal corticosteroids, aspirin, metformin, or statin).

Third, the high expression levels of ACE2 and TMPRSS2 in the sinonasal cavity might have a role in the viral entry and transmission of SARS-CoV-2.[10,12,29] The sinonasal cavity and the nasal epithelium are two regions with the highest ACE2 protein expression within the human respiratory tract.[10,12,29] Therefore, viral retention in the sinonasal cavity caused by CRS could accelerate the intracellular entry of SARS-CoV-2 by binding the viral receptor to ACE2 and its cofactor to TMPRSS2. Fourth, local inflammatory responses in patients with CRS could modulate susceptibility to COVID-19. Impaired antiviral innate immune responses in sinonasal epithelial cells occur in CRS patients during inflammation.[30] Sinonasal inflammatory responses can increase the expression of proinflammatory cytokines such as interferon (IFN) in CRS patients,[31] which in turn can upregulate the expression of ACE2.[32] Thus, local inflammation with increased IFN in CRS patients could induce ACE2-mediated SARS-CoV2 infection.[32] Consistent with local inflammation in CRS that possibly contributes to the development of COVID-19, an inhibitor of interleukin-4 and interleukin-13 (dupilumab) has been reported potentially to alleviate the severity of COVID-19.[33,34] Altogether, the combined effects of impaired barrier functions, viral coinfection, increased expression of viral entry-associated factors, and local inflammatory response might contribute to the increased susceptibility to SARS-CoV-2 infection and severity of COVID-19 observed in CRS patients.

In our subgroup analysis, patients with CRSsNP or nonatopic CRS showed a higher rate of infection with SARS-CoV-2 and increased severity of COVID-19 compared with patients with CRSwNP or atopic CRS. Patients with CRSwNP or nonatopic CRS may prominently exhibit type 2 immune responses with downregulation of IFNs, which in turn might downregulate ACE2 expression.[8] An *in vivo* study of asthmatic rats with type 2 immune responses, which were given an ACE2 activator, demonstrated decreased expression of ACE2 together with the alleviation of altered airway responsiveness, eosinophilia, and inflammatory changes.[35,36] Consistent with this observation, our previous real-world study[2] suggested a greater risk for a positive SARS-CoV-2 test and severe COVID-19 in patients with nonallergic asthma compared with patients with allergic asthma. Furthermore, a recent study[37] found that asthmatic patients with preexisting eosinophilia had a protective association from COVID-19–associated admission and mortality. Altogether, these studies suggest that a prominent type 2 immune response caused by nasal polyps may contribute to lower SARS-CoV-2 infectivity and COVID-19 severity compared with CRSsNP.

TABLE IV. Propensity score–matched subgroup analyses for association of risk for positive SARS-CoV-2 test result with CRS by nasal polyp, prior intranasal corticosteroid use, and atopic phenotype among all patients who underwent SARS-CoV-2 testing, and for association of risk for COVID-19 worse outcomes with CRS by nasal polyp, prior intranasal corticosteroid use, and atopic phenotype among patients with laboratory-confirmed COVID-19

	Patients who underwent SARS-CoV-2 testing (propensity score–matched n = 24,434)		Patients with laboratory-confirmed SARS-CoV-2 infection (propensity score–matched n = 572)	
	COVID-19		Severe outcomes of COVID-19*	
Exposure	Event number/total n (%)	Fully adjusted OR† (95% confidence interval)	Event number/total n (%)	Fully adjusted OR† (95% confidence interval)
By nasal polyps				
None	310/12,217 (2.5)	1.0 (reference)	38/286 (13.3)	1.0 (reference)
CRS with nasal polyp	28/1075 (2.6)	1.01 (0.67-1.51)	4/23 (17.4)	1.34 (0.40-4.20)
CRS without nasal polyp	352/11,142 (3.1)	**1.24 (1.06-1.44)**	56/263 (21.3)	**1.75 (1.10-2.75)**
By use of intranasal corticosteroids				
None	310/12,217 (2.5)	1.0 (reference)	38/286 (13.3)	1.0 (reference)
CRS treated without intranasal corticosteroids	305/10,018 (3.0)	**1.19 (1.01-1.40)**	42/216 (19.4)	1.55 (0.95-2.50)
CRS treated with intranasal corticosteroids	75/2199 (3.4)	**1.32 (1.03-1.73)**	18/70 (25.7)	**2.24 (1.16-4.20)**
By atopic status				
None	310/12,217 (2.5)	1.0 (reference)	38/286 (13.3)	1.0 (reference)
Atopic CRS	295/9737 (3.0)	**1.20 (1.00-1.41)**	44/224 (19.6)	1.56 (0.97-2.51)
Nonatopic CRS	85/2480 (3.4)	**1.34 (1.05-1.70)**	16/62 (22.6)	**2.27 (1.14-4.36)**

COVID-19, coronavirus disease 2019; *CRS*, chronic rhinosinusitis; *OR*, odds ratio; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.
Bolded data indicate significant differences in the regression model ($P < .05$).
*Severe outcomes of COVID-19 were the need for oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.
†Fully adjusted for age; sex; region of residence; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, or chronic kidney disease or nasal polyp; Charlson comorbidity index; and previous use of medication (systemic or intranasal corticosteroids, aspirin, metformin, or statin).

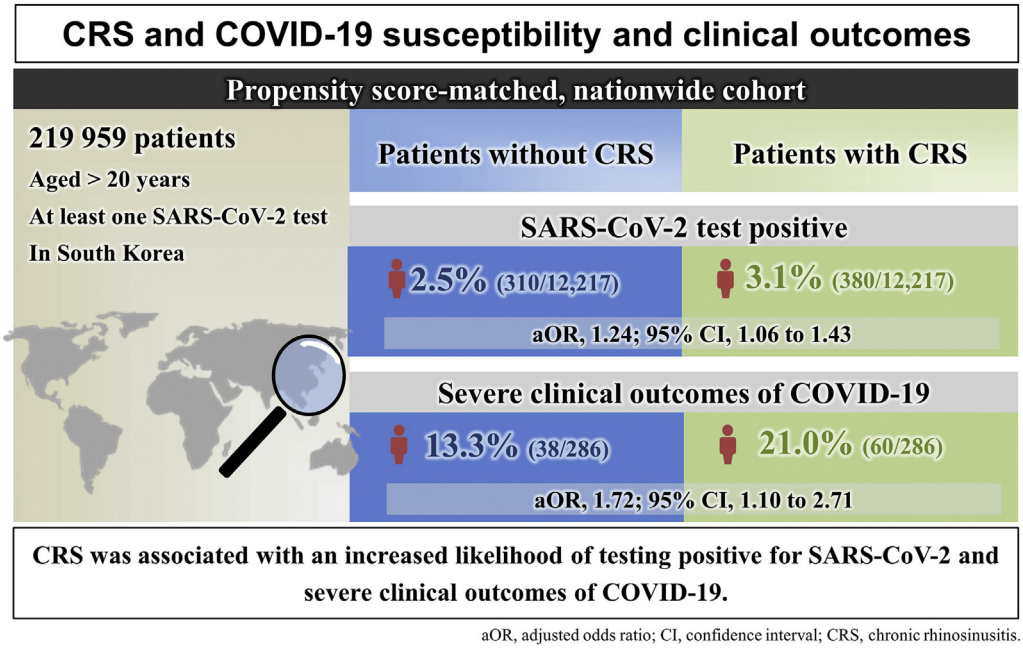

FIGURE 3. Graphical abstract. *aOR*, adjusted odds ratio; *CI*, confidence interval; *COVID-19*, coronavirus disease 19; *CRS*, chronic rhinosinusitis; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

Interestingly, we found that prior use of nasal corticosteroids increased the risk for SARS-CoV-2 infection and the severity of COVID-19. Recent *in vitro* and *in vivo* studies[38] suggest that inhaled corticosteroids may have beneficial or detrimental contributions to the altered susceptibility or severity of COVID-19. Because it is difficult to distinguish between the direct effect of

using intranasal corticosteroids and more severe CRS requiring intranasal corticosteroids, the clinical significance of the current intranasal corticosteroid results is not clear.

Limitations and strengths

Several limitations should be considered when interpreting these results, mainly owing to a lack of sufficient information about the study population. In particular, CRS endotypes could not be differentiated because the current study used health insurance claims-based data with ICD-10 codes and lacked laboratory findings and biomarkers. Furthermore, the history of endoscopic sinus surgery was not considered. Because of the heterogeneous types, varying severity, and an inaccurate claims-based definition of CRS in this cohort, this study might have underestimated the relation between CRS and the infectivity of SARS-CoV-2 or severity of COVID-19. The classification of CRS patients according to the atopic status was based on the ICD-10 codes; thus, misdiagnosed cases or untreated cases may have been excluded in this study. Furthermore, ethnic differences in atopic CRS could explain the conflicting results regarding the association of atopic CRS with COVID-19.[39] The relatively small study population of atopic patients and that of patients with nasal polyps limited the statistical power in this study. Furthermore, although we adjusted for comorbidities, including chronic obstructive pulmonary disease, other confounding factors such as smoking could exist.[40] Second, CRS-related confounders might affect our main results. Although we used a large-scale nationwide cohort and a sophisticated matching technique to reduce bias, anosmia associated with CRS can cause more frequent SARS-CoV-2 testing, which may increase the selection bias.[41] Also, CRS can cause sinonasal symptoms, which may make wearing masks less tolerable during the COVID-19 pandemic. Finally, the study population was limited to Koreans, and the association of CRS with the infectivity of SARS-CoV-2 or the severity of COVID-19 could reveal differences in other ethnic groups.[42] In particular, type 2/atopic/eosinophilic nasal polyps are less common in Asians.[39] The infectivity or severity of COVID-19 in CRS may not show a significant difference in Western countries owing to this geographic and ethnic difference in CRS endotypes.

Despite these limitations, this large-scale, population-based, nationwide cohort study evaluated the potential relation between CRS and SARS-CoV-2 infection and COVID-19 severity. We used a large sample and representative population (n = 219,959), sophisticated statistical techniques to identify accurate predictors of an outcome (propensity score matching to reduce potential confounders and selection bias and Firth bias correction to decrease the small sample bias), and a strict CRS definition (ICD code claims supported by head and neck computed tomography). During the current COVID-19 pandemic, this study provides evidence that CRS is potentially associated with SARS-CoV-2 infectivity and COVID-19 severity.

Conclusions

Chronic rhinosinusitis was associated with an increased risk for SARS-CoV-2 infection and severe COVID-19 in this large-scale, population-based nationwide cohort in South Korea. In particular, CRSsNP, CRS treated with intranasal corticosteroids, or nonatopic CRS was associated with a greater risk for SARS-CoV-2 infection and severe COVID-19 outcomes. Taken together, our findings suggest that clinicians should be cautious in assessing the prognosis and determining care for patients with CRS amid the COVID-19 pandemic.

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TABLE E1. Propensity score–matched subgroup analyses for association of risk for positive severe acute respiratory syndrome coronavirus 2 test results with chronic rhinosinusitis by COVID-19 outcome among all patients who underwent severe acute respiratory syndrome coronavirus 2 test (propensity score–matched n = 24,434)

Event	Variable	None	CRS
COVID-19	Event n/total n (%)	310/12,217 (2.5)	380/12,217 (3.1)
	Fully adjusted OR‡ (95% CI)	1.0 (reference)	**1.22 (1.04-1.42)**
Severe outcomes of COVID-19*	Event n/total n (%)	50/12,217 (0.4)	82/12,217 (0.7)
	Fully adjusted OR‡ (95% CI)	1.0 (reference)	**1.61 (1.12-2.29)**
Nonsevere outcomes of COVID-19†	Event n/total n (%)	260/12,217 (2.1)	298/12,217 (2.4)
	Fully adjusted OR‡ (95% CI)	1.0 (reference)	1.13 (0.95-1.32)

CI, confidence interval; *COVID-19*, coronavirus disease 2019; *OR*, odds ratio.
Bolded data indicate significant differences in the regression model ($P < .05$).
*Severe outcomes of COVID-19 were the need for oxygen therapy, admission to the intensive care unit, invasive ventilation, or death.
†Nonsevere outcomes of COVID-19 included COVID-19 patients, excluding severe COVID-19 patients.
‡Fully adjusted for age; sex; region of residence; history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, or nasal polyp; Charlson comorbidity index; and previous use of medication (aspirin, metformin, or statin, systemic corticosteroids, or intranasal corticosteroids).

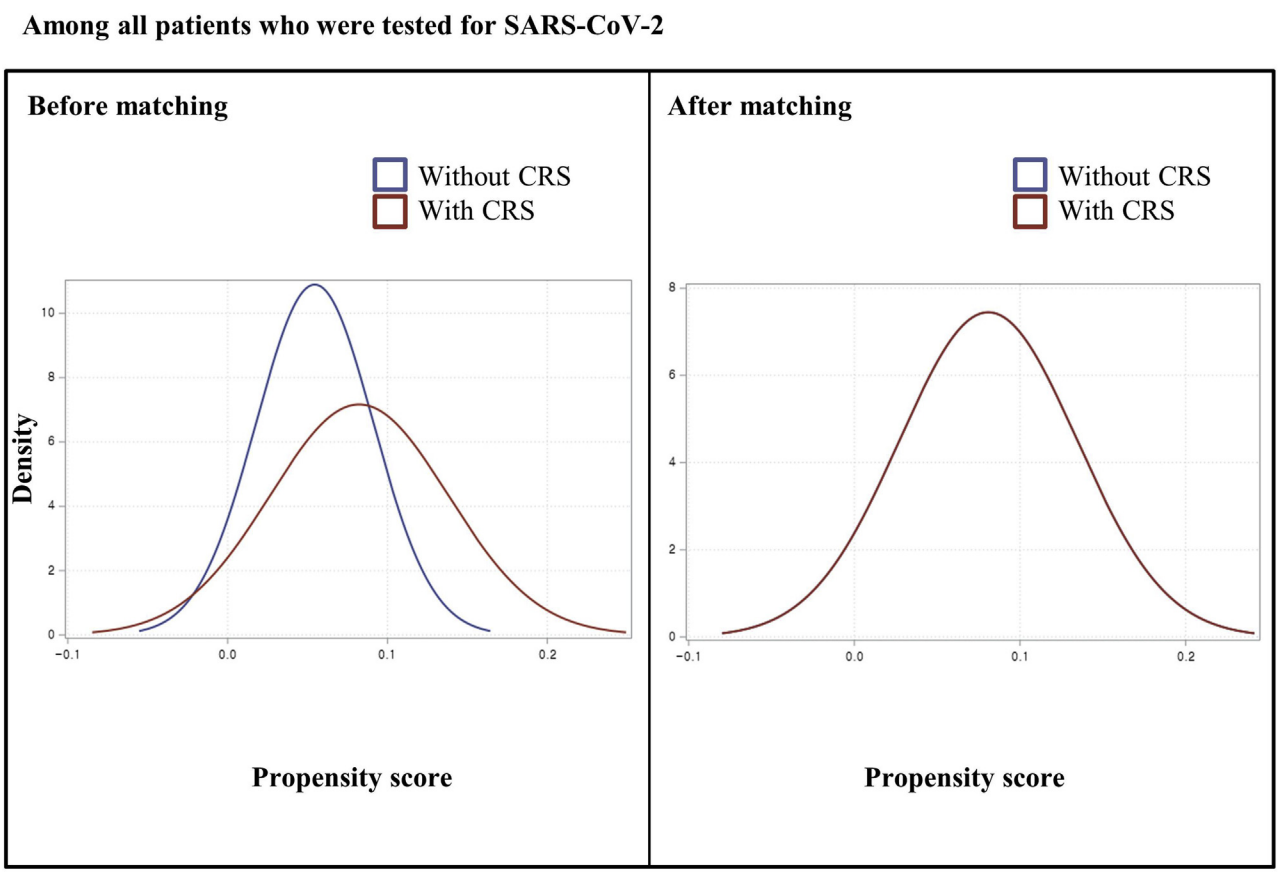

FIGURE E1. Density of propensity scores before and after matching among patients who received severe acute respiratory syndrome coronavirus 2 testing. *CRS*, chronic rhinosinusitis.

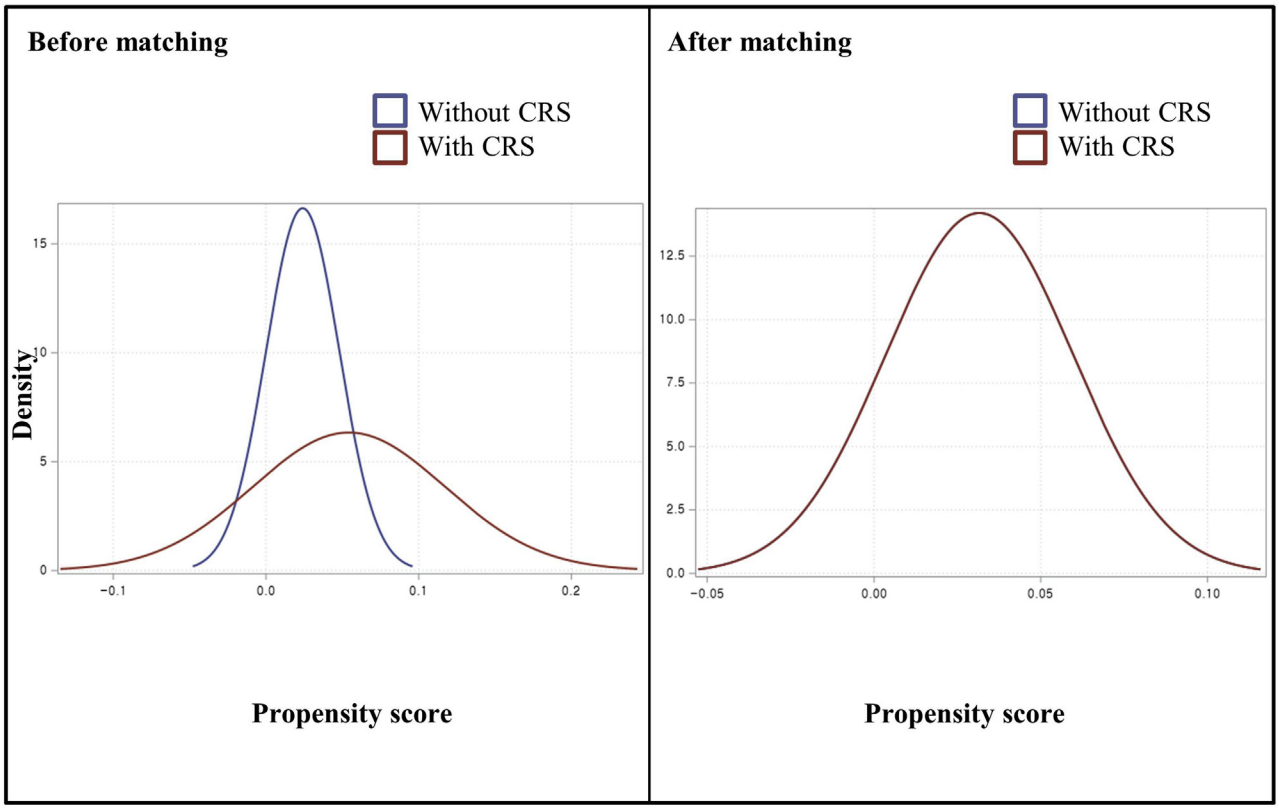

FIGURE E2. Density of propensity scores before and after matching among coronavirus 19 patients. *CRS*, chronic rhinosinusitis.