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# The characterization of chronic rhinosinusitis in hospitalized patients with COVID-19

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**Clinical Implications** 

• The prevalence of chronic rhinosinusitis (CRS) in hospitalized patients with coronavirus disease 2019 (COVID-19) in our cohort from Wuhan, China, was 6.1%, which is close to the CRS prevalence in the general population in China (8%). CRS comorbidity was not associated with the risk of developing severe illness of COVID-19.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a primary acute respiratory disease, which can lead to severe acute respiratory syndrome (ARDS), multiple organ dysfunction, and even death. Therefore, identifying risk and protective factors for COVID-19 is critical to developing efficient intervention and prevention strategies.

As a gateway of the respiratory tract, the physiological and pathological conditions in the nasal cavity may significantly influence the development of lower airway diseases. Chronic rhinosinusitis (CRS) is one of the most common nasal inflammatory disorders, affecting 5% to 12% of adult populations.<sup>1</sup> Nevertheless, the influence of CRS on COVID-19 remains largely unknown. Several studies reported low frequencies (0%-3%) of CRS comorbidity in patients with COVID-19.<sup>2,3</sup> However, these studies were based on the analysis of medical records of patients with COVID-19, which may underestimate the real incidence of CRS comorbidity because of incomplete records under actual emergency. More importantly, whether CRS comorbidity is associated with the disease severity of COVID-19 remains unclear.

Here we retrospectively analyzed 1172 patients with COVID-19 who were discharged from Tongji Hospital, Wuhan, China, from January 27, 2020, to March 10, 2020, and completed telephone follow-up within 1 month after discharge. The diagnosis was confirmed by the positive result of the real-time reverse-transcriptase-polymerase-chain-reaction assay for SARS-CoV-2 of throat or nasopharyngeal swab specimens. Information of patients with COVID-19 on demographic characteristics, laboratory findings, treatments, and complications was obtained with data collection forms extracted from electronic medical records. Comorbidities including CRS were determined based on patients' self-report on admission, and the accuracy of the records of comorbidities was checked by experienced physicians during follow-up. The severity of COVID-19 on admission and in-hospital

complications were determined according to the relevant guidelines.<sup>4</sup> The results of laboratory tests performed shortly after admission were used for analysis. To avoid the influence of confounding variables, multivariate logistic regression analysis and propensity score matching (PSM) of patients with CRS and without CRS were performed. More information regarding subjects and methods is provided in this article's Online Repository at www.jaci-inpractice.org. This study was approved by the Ethics Committee of Tongji Hospital.

A total of 72 (6.1%) patients reported physician-diagnosed CRS. Age and smoking status were comparable between COVID-19 patients with and without CRS, whereas COVID-19 patients with CRS tended to be male predominant than those without CRS (59.7% vs 48.5%; P = .07) (Table I). COVID-19 patients with CRS had a higher frequency of concomitant asthma (6.9% vs 2.2%; P = .01) (Table I). There were no significant differences regarding other major comorbidities including hypertension, diabetes, malignancy, and chronic obstructive pulmonary disease between COVID-19 patients with and without CRS (Table I). Although COVID-19 patients with CRS tended to more frequently suffer from fever than those without CRS (87.5% vs 78.0%; P = .07) (Table E1, available in this article's Online Repository at www.jaciinpractice.org), there was no difference in the frequency of fever between patients with and without CRS after adjusting for confounding factors including age, gender, smoking status, and comorbidities. No significant differences in other major symptoms including cough, shortness of breath, and diarrhea were observed between patients with CRS and without CRS before and after adjusting for confounding factors (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). In addition, there was no significant difference in most laboratory test results including blood neutrophil, lymphocyte, and eosinophil counts, and the levels of D-D dimer, IL-6, and IL-10. The difference in cardiac troponin I and IL-8 levels between patients with and without CRS disappeared after adjusting for confounding factors (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Moreover, we did not find significant differences in the proportions of severe cases on admission, complications including ARDS and in-hospital treatments including mechanical ventilation and glucocorticoids, and hospitalization days between patients with and without CRS before and after adjusting for confounding factors (Table II and Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

PSM analysis was further performed. Age, gender, smoking status, and all comorbidities were selected for PSM (Table I). We were able to match 72 COVID-19 patients without CRS to 72 patients with CRS at a ratio of 1:1 (Table I). All symptoms and laboratory test results were comparable between COVID-19 patients with and without CRS after PSM (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Importantly, again, we did not find significant differences in severe cases on admission, complications, in-hospital treatments, and hospitalization days between patients with and without CRS by PSM analysis (Table II and Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

TABLE I.	Demographics	and	comorbidities	for	COVID-	19	patients	with	and	without	CRS	before	and	after	propensity	score	matchin	g
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		Unmatched	Matched (1:1)*				
Demographics and comorbidities	Without CRS	With CRS	P value	Without CRS	With CRS	P value	
Subject, N (%)	1100 (93.9)	72 (6.1)	_	72 (50.0)	72 (50.0)	_	
Gender, male, N (%)	534 (48.5)	43 (59.7)	.07	45 (62.5)	43 (59.7)	.73	
Age (y)	61 (48, 68.75)	60.5 (46.25, 68)	.60	59.5 (46, 68)	60.5 (46.25, 68)	.93	
Smoking, N (%)	80 (7.3)	5 (6.9)	.92	5 (6.9)	5 (6.9)	.99	
Any comorbidity, N (%)							
Hypertension	350 (31.8)	22 (30.6)	.82	21 (29.2)	22 (30.6)	.86	
Diabetes	148 (13.5)	14 (19.4)	.15	12 (16.7)	14 (19.4)	.66	
Cardiovascular disease	102 (9.3)	6 (8.3)	.79	5 (6.9)	6 (8.3)	.75	
Cerebrovascular disease	21 (1.9)	2 (2.8)	.61	1 (1.4)	2 (2.8)	.56	
Malignancy	18 (1.6)	1 (1.4)	.87	1 (1.4)	1 (1.4)	.99	
Chronic kidney disease	22 (2.0)	2 (2.8)	.65	2 (2.8)	2 (2.8)	.99	
Chronic liver disease	16 (1.5)	1 (1.4)	.96	1 (1.4)	1 (1.4)	.99	
AR	105 (9.6)	10 (13.9)	.23	10 (13.9)	10 (13.9)	.99	
Asthma	24 (2.2)	5 (6.9)	.01	5 (6.9)	5 (6.9)	.99	
COPD	10 (0.9)	0 (0)	.42	0 (0)	0 (0)	_	

AR, Allergic rhinitis; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRS, chronic rhinosinusitis.

Data are presented as medians and interquartile range for continuous variables and numbers with percentage for categorical variables.

A Mann-Whitney U 2-tailed test was used for between-group comparison. For categorical variables, the  $\chi^2$  or Fisher's exact test was applied to compare the difference in proportions between groups when appropriate.

Bold indicates statistical significance (P < .05).

\*Age, gender, smoking status, and comorbidities (hypertension, diabetes, cardiovascular disease, cerebrovascular diseases, malignancy, chronic liver diseases, chronic kidney diseases, allergic rhinitis, asthma, and chronic obstructive pulmonary disease) were selected for propensity score matching.

TABLE II.	Complications and	treatments of C	COVID-19	patients with an	d without CRS	S before and af	ter propensity	score matching
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		Unm	Matched $(1:1)^{\dagger}$				
Complications and treatments	Without CRS $N = 1100$	With CRS $N = 72$	<i>P</i> value	Adjusted <i>P</i> value*	Without CRS $N = 72$	With CRS $N = 72$	<i>P</i> value
Complications, N (%)							
Acute liver injury	74 (6.7)	5 (6.9)	.81	.43	6 (8.3)	5 (6.9)	.75
ARDS	66 (6.0)	4 (5.6)	.88	.79	4 (5.6)	4 (5.6)	.99
Acute kidney injury	61 (5.5)	2 (2.8)	.42	.24	4 (5.6)	2 (2.8)	.40
Acute myocardial injury	29 (2.6)	2 (2.8)	.72	.88	1 (1.4)	2 (2.8)	.56
Shock	7 (0.6)	2 (2.8)	.10	.17	0 (0)	2 (2.8)	.15
In-hospital treatments, N (%)							
Antiviral treatment	1027 (93.4)	65 (90.3)	.31	.30	68 (94.4)	65 (90.3)	.35
Antibiotic treatment	799 (72.6)	51 (70.8)	.73	.55	49 (68.1)	51 (70.8)	.72
Oxygen supplementation	871 (79.2)	58 (80.6)	.78	.79	57 (79.2)	58 (80.6)	.84
Mechanical ventilation	43 (3.9)	2 (2.8)	.62	.61	2 (2.8)	2 (2.8)	.99
Glucocorticoid therapy	281 (25.5)	14 (19.4)	.25	.15	16 (22.2)	14 (19.4)	.68
Intravenous immunoglobulin therapy	177 (16.1)	12 (16.7)	.90	.94	14 (19.4)	12 (16.7)	.66

ARDS, Acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRS, chronic rhinosinusitis.

Data are presented as numbers with percentage for categorical variables.

The  $\chi^2$  or Fisher's exact test was applied to compare the difference in proportions between groups.

\*In adjusted logistic regression analysis, adjusted variables included age, gender, smoking, and comorbidities (hypertension, diabetes, cardiovascular disease, cerebrovascular diseases, malignancy, chronic liver diseases, chronic kidney diseases, allergic rhinitis, asthma, and chronic obstructive pulmonary disease).

†Age, gender, smoking status, and comorbidities were selected for propensity score matching. Please see Table I.

In this study, to reduce the bias caused by potentially incomplete medical records on admission, we rechecked the records of comorbidities with patients by telephone follow-up. This may be the reason that the CRS prevalence (6.1%) in our COVID-19 cohort was higher than those previously reported in China and Europe (0%-3%),<sup>2,3</sup> which is close to the CRS prevalence in the general population in China (8%).<sup>5</sup> It suggests that CRS comorbidity may not increase the susceptibility to

COVID-19. Very recently, Chhiba et al<sup>6</sup> reported that patients with rhinosinusitis showed a lower risk of hospitalization for COVID-19 than those without rhinosinusitis. The prevalence of rhinosinusitis in their study was 13.3%; however, they did not differentiate acute and chronic rhinosinusitis.<sup>6</sup> Moreover, the indicator, hospitalization, may not fully reflect the severity of COVID-19. In this study, we found that neutrophil and lymphocyte counts and serum levels of D-D dimer and IL-6, which have been identified as markers of COVID-19 severity,<sup>7,8</sup> were comparable between COVID-19 patients with and without CRS. More importantly, there was no association of CRS comorbidity with disease severity on admission, mechanical ventilation, ARDS, and hospitalization days in COVID-19 patients, suggesting that CRS may not modify the disease expression of COVID-19 either.

Our report has several potential limitations. First, self-reported comorbidities might lead to the potential misestimation of the prevalence. Second, to confirm the comorbidities, we did telephone follow-up. We did not include fatal cases in this report, because it was difficult to confirm those patients' comorbidities. However, we tried to confirm the records of CRS comorbidity in 15 deceased patients with COVID-19 admitted at the same period with their close relatives, and found that the incidence of CRS comorbidity in those fatal cases (1 of 15, 6.7%) was comparable with that in the discharged cohort (6.1%). Third, the information on medication use before admission is lacking. Fourth, CRS can be subtyped into CRS with and without nasal polyps. Nevertheless, the information of subtypes of CRS was lacking in the majority of patients. It was therefore not possible to determine whether CRS with versus without nasal polyps has different associations with COVID-19. Fifth, the asymptomatic patients and patients with mild symptoms who were not admitted to hospital were not included in this study. Studies on these outpatients with COVID-19 would be helpful to get a complete picture of the association between CRS and COVID-19. Sixth, compared with that in the western countries (5%-10%), the prevalence of aspirin-exacerbated respiratory disease (AERD) in Chinese patients with CRS is very low (0.57%).<sup>9</sup> No AERD was reported in our cohort. We were therefore unable to explore the association between AERD and COVID-19 patients with and without CRS.

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H. Wang performed data analysis and prepared the manuscript. J. Song collected clinical data and performed data analysis. L. Pan, Y. Yao, Y.-K. Deng, Z.-C. Wang, B. Liao, J. Ma, and C. He participated in clinical data collection. Z. Liu and M. Zeng designed the study, interpreted data, and prepared the manuscript.

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<sup>2213-2198</sup> 

### **ONLINE REPOSITORY**

## METHODS

# Patients, data collection, and tissue samples

A total of 1172 etiologically confirmed patients with coronavirus disease 2019 (COVID-19), who were discharged from Tongji Hospital, the largest designated hospital to treat patients with COVID-19 in Wuhan, China, from January 27, 2020, to March 10, 2020, and completed the telephone follow-up in 1 month after discharge, were retrospectively enrolled for the study of characteristics of COVID-19. The diagnosis of COVID-19 was based on the guidance for diagnosis and management of COVID-19 released by the World Health Organization. The diagnosis was confirmed by the positive result of the real-time reverse-transcriptase-polymerase-chain-reaction assay for severe acute respiratory syndrome coronavirus 2 of throat or nasopharyngeal swab specimens. Patients with COVID-19 were classified into severe or nonsevere type on admission according to the American Thoracic Society guidelines for community-acquired pneumonia. Patients who met 1 major criterion or at least 3 minor criteria were defined as severe type: major criteria: (1) septic shock with need for vasopressors; (2) respiratory failure requiring mechanical ventilation; and minor criteria: (1) respiratory rate  $\geq$ 30 breaths/min; (2) PaO<sub>2</sub>/FiO<sub>2</sub> ratio  $\leq$ 250; (3) multilobar infiltrates; (4) confusion/disorientation; (5) uremia (blood urea nitrogen level  $\geq 20 \text{ mg/dL}$ ); (6) leukopenia (white blood cell count <4000 cells/µL); (7) thrombocytopenia (platelet count <100,000/µL); (8) hypothermia (core temperature  $< 36^{\circ}$ C); and (9) hypotension requiring aggressive fluid resuscitation.

Information of patients with COVID-19 on demographic characteristics, laboratory findings, treatments, and complications was obtained with data collection forms extracted from electronic medical records. Laboratory measurements including routine blood, blood biochemistry, coagulation function, and infection biomarkers were performed. Patients' medical records were reviewed and analyzed by a well-trained team of physicians in Tongji Hospital. Comorbidities including chronic rhinosinusitis (CRS) were determined based on patients' selfreport on admission, and the accuracy of the records of comorbidities was checked by experienced physicians during follow-up. The results of laboratory tests performed shortly after admission were used for analysis of the difference between patients with CRS and without CRS.

This study was approved by the Ethics Committee of Tongji Hospital.

### **Complication definition of COVID-19**

Acute liver injury was defined as jaundice with a total bilirubin level of  $\geq$ 3 mg/dL and an acute increase in alanine aminotransferase of at least 2 times the upper limit of the normal range. Acute respiratory distress syndrome was defined as PaO<sub>2</sub>/FiO<sub>2</sub>  $\leq$ 300 mm Hg according to the Berlin Definition. Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes Guideline with an abrupt decrease in kidney function and an increase in serum Cr to  $\geq$ 1.5 times baseline. Acute myocardial injury was defined as an elevated serum cardiac troponin value above the 99th percentile upper reference limit. Shock was defined as systolic arterial pressure <80 mm Hg and pulse pressure <30 mm Hg.

#### Statistical analysis

For continuous variables, data are expressed as medians and interquartile ranges, and a Mann-Whitney U 2-tailed test was used for between-group comparison. For categorical variables, the  $\chi^2$  or Fisher's exact test was applied to compare the difference in proportions between groups when appropriate. Multivariate logistic regression was used to adjust the confounding factors in comparison between different groups. The variables potentially confounding the association between CRS comorbidity and the clinical characteristics of COVID-19 were further addressed using the propensity score-matching method. Exact matching with a caliper size of 0.05 was applied for all matching pairs according to the propensity scores. Significance was accepted at a *P* value less than .05. Statistical analyses were performed by using an IBM SPSS 22.0 package (SPSS Inc., Chicago, IL). TABLE E1. Clinical characteristics and lab test results of COVID-19 patients with and without CRS before and after propensity score matching

		Unmatched	Matched (1:1) <sup>†</sup>					
Characteristics	Without CRS	With CRS	<i>P</i> value	Adjusted <i>P</i> value*	Without CRS	With CRS	<i>P</i> value	
Subject, N (%)	1100 (93.9)	72 (6.1)	_	_	72 (50.0)	72 (50.0)	_	
Systemic signs and symptoms, N (%)								
Fever	858 (78.0)	63 (87.5)	.07	.12	56 (77.8)	63 (87.5)	.12	
Cough	725 (65.9)	42 (58.3)	.19	.23	51 (70.8)	42 (58.3)	.12	
Shortness of breath	469 (42.6)	26 (36.1)	.28	.20	31 (43.1)	26 (36.1)	.39	
Fatigue	268 (24.4)	17 (23.6)	.89	.95	17 (23.6)	17 (23.6)	.99	
Anorexia	258 (23.5)	16 (22.2)	.81	.86	10 (13.9)	16 (22.2)	.19	
Diarrhea	195 (17.7)	11 (15.3)	.60	.61	11 (15.3)	11 (15.3)	.99	
Myalgia	166 (15.1)	6 (8.3)	.11	.16	10 (13.9)	6 (8.3)	.29	
Nausea and vomiting	80 (7.3)	5 (6.9)	.92	.95	2 (2.8)	5 (6.9)	.25	
Headache	82 (7.5)	5 (6.9)	.87	.90	6 (8.3)	5 (6.9)	.75	
Dizziness	48 (4.4)	4 (5.6)	.63	.99	7 (9.7)	4 (5.6)	.35	
Severe COVID-19 cases, N (%)	191 (17.4)	8 (11.1)	.17	.18	12 (16.7)	8 (11.1)	.34	
Duration of hospitalization (d)	19 (14, 23)	18 (15, 23)	.90	.92	18 (12, 21.5)	18 (15, 23)	.29	
Leucocytes count ( $\times 10^9$ /L)	5.5 (4.4, 6.9)	5.6 (3.9, 7.3)	.94	.76	5.6 (4.4, 6.7)	5.6 (3.9, 7.3)	.82	
Neutrophil count ( $\times 10^{9}/L$ )	3.7 (2.7, 5.2)	4.0 (2.7, 5.4)	.77	.54	3.5 (2.6, 5.1)	4.0 (2.7, 5.4)	.53	
Lymphocyte count ( $\times 10^{9}/L$ )	1.2 (0.9, 1.6)	1.3 (0.9, 1.5)	.42	.70	1.3 (1.0, 1.5)	1.3 (0.9, 1.5)	.68	
Eosinophil count ( $\times 10^{9}/L$ )	0.04 (0.01, 0.1)	0.06 (0.02, 0.12)	.06	.12	0.04 (0, 0.08)	0.06 (0.02,0.12)	.06	
Alanine aminotransferase (U/L)	24 (15, 41)	27 (16, 48)	.30	.16	25.5 (16, 39.5)	27 (16, 48)	.46	
Aspartate aminotransferase (U/L)	24 (18, 35)	26 (19, 35)	.20	.28	28 (18, 35)	26 (19, 35)	.73	
Albumin (g/L)	35.9 (32.6, 39.7)	37.3 (33.2, 41.1)	.09	.06	36.1 (32, 40.6)	37.3 (33.2, 41.1)	.32	
Creatinine (µmol/L)	67 (56, 81)	68 (57, 83)	.74	.38	74 (61, 86)	68 (57, 83)	.25	
Urea (µmol/L)	4.2 (3.3, 5.3)	4.3 (3.6, 5.3)	.60	.50	3.8 (3.1, 5.1)	4.3 (3.6, 5.3)	.13	
Cardiac troponin I (pg/mL)	3.3 (1.9, 7.4)	2.3 (1.9, 5.0)	.04	.48	3.1 (1.9, 7.4)	2.3 (1.9, 5.0)	.24	
Procalcitonin (ng/mL)	0.05 (0.03, 0.08)	0.05 (0.03, 0.06)	.48	.09	0.05 (0.04, 0.09)	0.05 (0.03, 0.06)	.17	
Ferritin (µg/mL)	528.2 (311.5, 871.5)	440.3 (257.0, 825)	.25	.05	584.7 (295.4,1123.4)	440.3 (257, 825)	.33	
Erythrocyte sedimentation (mm/H)	30 (14, 58)	23.5 (8, 56)	.20	.30	25 (11, 64.5)	23.5 (8, 56)	.65	
D-D dimers (µg/mL)	0.63 (0.33, 1.36)	0.51 (0.22, 1.2)	.20	.48	0.59 (0.28, 1.38)	0.51 (0.22, 1.2)	.44	
Fibrin (g/L)	4.6 (3.6, 5.8)	4.0 (3.4, 5.8)	.11	.16	4.8 (3.6, 5.7)	4.0 (3.4, 5.8)	.10	
IL-6 (pg/mL)	4.7 (2.0, 16.6)	3.4 (1.7, 10.6)	.06	.06	5.5 (2.2, 22.8)	3.4 (1.7, 10.6)	.07	
IL-8 (pg/mL)	9.5 (5.5, 17.6)	8.2 (5.0, 12.2)	.04	.68	9.7 (5.4, 18.1)	8.2 (5.0, 12.2)	.14	
IL-10 (pg/mL)	5 (5, 5)	5 (5, 5)	.33	.53	5 (5, 5)	5 (5, 5)	.39	

COVID-19, Coronavirus disease 2019; CRS, chronic rhinosinusitis.

Data are presented as medians and interquartile range for continuous variables and numbers with percentage for categorical variables.

A Mann-Whitney U 2-tailed test was used for between-group comparison. For categorical variables, the  $\chi^2$  or Fisher's exact test was applied to compare the difference in proportions between groups when appropriate.

Bold indicates statistical significance (P < .05).

\*In adjusted logistic regression analysis, adjusted variables included age, gender, smoking, and comorbidities (hypertension, diabetes, cardiovascular disease, cerebrovascular diseases, malignancy, chronic liver diseases, chronic kidney diseases, allergic rhinitis, asthma, and chronic obstructive pulmonary disease).

†Age, gender, smoking status, and comorbidities were selected for propensity score matching. Please see Table I.