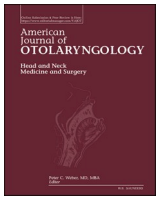
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

American Journal of Otolaryngology–Head and Neck Medicine and Surgery 43 (2022) 103469

Contents lists available at ScienceDirect

American Journal of Otolaryngology–Head and Neck Medicine and Surgery

journal homepage: www.elsevier.com/locate/amjoto



Chronic rhinosinusitis is associated with increased risk of COVID-19 hospitalization☆

Firas Sbeih [a], Jorge Gutierrez [b], George Saieed [b], Mohamad R. Chaaban [a,*]

[a] Head and Neck Institute, Cleveland Clinic, Cleveland, OH, United States of America
[b] Case Western Reserve University School of Medicine, United States of America

ARTICLE INFO

Keywords:
COVID-19
Chronic rhinosinusitis
SARS-CoV-2
Hospitalization
Pneumonia

ABSTRACT

Objective: The rationale of the study was to examine the association between chronic rhinosinusitis (CRS) and COVID-19 hospitalization.
Study design: Retrospective cohort study.
Setting: Cleveland Clinic hospital inpatient and outpatient.
Methods: A retrospective chart review of patients that were tested for COVID-19 at Cleveland Clinic. The study took place between March 8, 2020 and May 15, 2020.
Results: From a total of 23,282 Patients that underwent SARS-CoV-2 testing, 996 COVID-19 negative and 998 COVID-19 positive patients were included in the analysis. COVID-19 positive patients with chronic rhinosinusitis (CRS) were at higher risk for hospitalization compared to patients without CRS (39.2% vs 25.7%, $p = 0.0486$). There was no significant difference between the two groups in relation to ICU admission, mechanical ventilation, and death, After adjustment for covariates, our multivariate analysis showed that patients with chronic rhinosinusitis (CRS) were approximately 3.46 (OR = 3.19, 95% CI (1.12–10.68)) times more likely to be hospitalized compared to patients that have no CRS.
Conclusion: Our results demonstrated that patients with chronic rhinosinusitis are associated with higher risk of COVID-19 hospitalization, albeit no increased risk of mortality.

1. Introduction

Since the declaration of the coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in March 2020, the disease has spread rapidly throughout the world [1]. COVID-19 has a highly variable presentation from asymptomatic disease to severe acute respiratory distress and death. SARS-CoV-2 is a contagious virulent organism with an incubation period of 2 to 14 days with asymptomatic patients capable of transmitting the infection. The nasal and oral cavities are believed to be the most common portals of entry for the virus prior to its propagation into the lungs where the major comorbidities of the virus arise. Early reports regarding symptoms from China were mostly related to cough, fever, and fatigue, with symptoms of upper respiratory symptoms such as rhinorrhea, sore throat, and nasal congestion reported as very uncommon [2–6]. Early systematic reviews also reported symptoms of fever in 83.3%, cough 60.3%, and fatigue in 38% with no reports on impaired sense of smell or taste in these studies [6,7]. It was not until April 23rd 2020 that the CDC (Centers for Disease Control and Prevention) has updated the symptoms to include "new loss of taste or smell" to the full list of COVID-19 symptoms [8]. Impaired sense of smell has been one of the early identified symptoms of COVID-19 as has been reported in multiple countries across the globe [9–32]. There a wide variation in the reported loss of sense of smell with reported incidence as low as 5.1% and as large as 85.6% [33,34]. This symptom is more commonly reported in mild to moderate COVID-19 and much less in severe COVID-19 [34].

In addition to the variable presentation of patients infected with COVID-19, one of the most important and puzzling issues is related to the ability to identify high risk patients that further go on and develop severe to critical COVID-19 requiring hospitalization, intensive care unit (ICU) admission, and mechanical ventilation. Determining inter-

☆ Study was approved by Cleveland Clinic's Institutional Review Board (IRB).

* Corresponding author at: Rhinology, Sinus and Skull Base Surgery, Head and Neck Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, United States of America.
E-mail address: mchaaban@gmail.com (M.R. Chaaban).

https://doi.org/10.1016/j.amjoto.2022.103469
Received 30 March 2022;
Available online 9 April 2022

individual variation in disease severity has several implications including determining high risk patients and vaccine allocation. There are several known risk factors that have been linked to severe COVID-19 including advanced age and several comorbidities including chronic obstructive pulmonary disease (COPD), diabetes mellitus, hypertension, and obesity [35,36]. Additionally, COPD was also found to be associated with increased health care utilization (hospitalization) but not in-hospital mortality [36]. Despite the clear evidence of viral replication and increased receptors in the nasal cavity, no studies have examined the role of upper airway comorbidities such as the presence or absence of chronic rhinosinusitis as it affects health care utilization and disease severity in patients with COVID-19.

Our study assesses the relationship between chronic rhinosinusitis and clinical outcomes with COVID-19 infection using the Cleveland Clinic COVID-19 registry.

2. Methods

2.1. Cleveland clinic registry

The Cleveland Clinic Foundation (CCF) COVID-19 registry was used in this study [37]. The registry collects information on symptomatic patients presenting for COVID-19 testing. The variables that are collected by a dedicated research team include demographics, laboratory testing for COVID-19, symptoms, comorbidities, hospitalization data, medications, and mortality. The details regarding the characteristics of the registry were published previously [38–42]. Data was extracted from EHR (EpicR, Epic Systems Corporation, Wisconsin, USA) using an experienced research team using a predefined process [43].

Following Cleveland Clinic's Institutional Review Board (IRB), data on patients' demographics, symptoms, COVID-19 status, comorbidities, and outcomes (hospitalization, ICU admission, and mortality) were extracted from the CCF COVID-19 registry. Data extraction was performed manually by a trained research team streamlining all research projects at CCF using the COVID-19 registry. Additional variables were manually collected from the patient's electronic health records (EHR) including data on the presence or absence of impaired sense of smell, loss of taste, chronic rhinosinusitis, and history of adenoidectomy or tonsillectomy. Following the diagnosis of COVID-19, patients were enrolled in a home monitoring program that involved reporting their symptoms over a 14-day period by a registered nurse or through an app.

2.2. Participants

Data was collected on all patients that were tested for COVID-19 at CCF from March 8, 2020 until May 15, 2020. The registry started collecting data on symptomatic patients starting March 8, 2020. After April 15th 2020, the registry stopped collecting data on COVID-19 negative patients. We excluded patients younger than 18 years old. For the analyses, we randomly collected patients from a total of 23,282 patients to include 1000 COVID-19 positive patients, and 1000 COVID-19 negative patients. A random number was assigned to each patient in Excel using the RAND function. Rows were then sorted in ascending order of the number previously generated, and the first 1000 patients were selected for inclusion. This process was repeated for adults who tested negative for COVID-19. Data collected included demographics, COVID-19 testing results, symptoms, comorbidities, health care utilization, imaging, medications, ICU admission, mechanical ventilation, and mortality.

2.3. Statistical analysis

Descriptive statistics were presented as numbers and percentage for categorical variables with mean and standard deviation for continuous variables. Chi-square test was applied for group comparisons on categorical data, and the Fisher exact test was applied for data with an expected value <5. Group comparisons on continuous data, the Wilcoxon 2-sample test were used. Multivariate logistic regression models were applied for patient symptoms, demographic characteristics, and comorbidities that were significant from our bivariate analysis. Statistical analysis was performed using SAS JMP Pro statistical software (version 15.1; SAS Institute Inc., Cary, North Carolina).

3. Results

3.1. Demographics

Patient demographic information (age, gender, race), symptoms, smoking history, and comorbidities are reported in Table 1. Patients with unmatching medical record numbers were excluded from the analysis with a remaining 996 COVID-19 negative and 998 COVID-19 positive patients included in the analysis. Overall, the demographics varied considerably between the COVID-19 positive and negative groups. The COVID-19 positive group was significantly older (mean 51.69 ± 0.59 vs 54.50 ± 0.6, $p = 0.0009$), and had a significantly greater percentage of Black patients (27.35% vs 19.26%, $p < 0.0001$). The COVID-19 negative group had significantly more smokers and comorbidities such as asthma, COPD, coronary artery disease, and heart failure.

3.2. Symptoms

Compared to the COVID-19 negative group, the COVID-19 positive group reported significantly more symptoms of cough (83.22% vs 72.26%, $p < 0.0001$), fever (62.53% vs 49.33%, $p < 0.0001$), fatigue (53.82% vs 43.15%, $p < 0.0001$), loss of appetite (30.94% vs 13.87%, $p < 0.0001$), loss of taste (21.59% vs 2.21%, $p < 0.0001$), impaired sense of smell (18.69% vs 1.81%, $p < 0.0001$), and diarrhea (28.67% vs

Table 1
Demographics and characteristics of patients undergoing SARS-CoV-2 testing.

	COVID-19 negative	COVID-19 positive	P-value
N	996	998	
Demographics			
Age (in years) (SD)	51.69 ± 0.59	54.50 ± 0.60	**0.0009**
Female sex (%)	611 (61.28%)	519 (52.00%)	**<0.0001**
BMI (kg/m^2) (SD)	30.51 ± 0.35	29.78 ± 0.44	0.57
Race (%)			
White	661 (66.30%)	575 (57.62%)	**<0.0001**
Black	192 (19.26%)	273 (27.35%)	**<0.0001**
Symptoms			
Cough	594 (72.26%)	714 (83.22%)	**<0.0001**
Fever	367 (49.33%)	529 (62.53%)	**<0.0001**
Fatigue	230 (43.15%)	352 (53.82%)	**0.0003**
Shortness of breath	376 (54.18%)	392 (48.10%)	**0.0185**
Diarrhea	133 (23.09%)	203 (28.67%)	**0.0236**
Loss of appetite	62 (13.87%)	186 (30.94%)	**<0.0001**
Vomiting	56 (10.24%)	47 (6.83%)	**0.0379**
Impaired sense of smell	18 (1.81%)	186 (18.69%)	**<0.0001**
Sore throat	262 (26.36%)	225 (22.59%)	0.0537
Nasal congestion	238 (23.94%)	247 (24.80%)	0.68
Rhinorrhea	172 (17.30%)	145 (14.56%)	0.098
Loss of taste	22 (2.21%)	215 (21.59%)	**<0.0001**
Comorbidities			
Smoking	420 (47.89%)	326 (40.70%)	**0.0032**
COPD (emphysema)	84 (11.41%)	58 (7.31%)	**0.0062**
Asthma	221 (28.44%)	147 (18.19%)	**<0.0001**
Diabetes	202(25.96%)	206 (25.46%)	0.863
Hypertension	416 (51.23%)	429 (52.00%)	0.7668
Coronary artery disease	138 (18.25%)	112 (14.11%)	**0.0265**
Heart failure	115 (15.33%)	96 (12.09%)	0.0644
Cancer	149 (18.60%)	117 (14.18%)	**0.0188**
Immunosuppressive treatment	115 (14.67%)	86 (10.45%)	**0.0127**
Chronic rhinosinusitis	70 (7.05%)	52 (5.22%)	0.0932
Sinus surgery	17 (1.71%)	17 (1.71%)	1

Bolded text signifies P-values that are statistically significant.

23.09%, $p = 0.024$). On the other hand, COVID-19 patients reported significantly more vomiting (10.24% vs 6.83%, $p = 0.38$), and shortness of breath (54.18% vs 48.10%, $p = 0.019$), compared to COVID-19 positive group. The difference in symptoms of sore throat, nasal congestion, and rhinorrhea did not reach statistical significance between the two groups. Among COVID-19 positive patients, the most common symptoms experienced were cough (83.22%), fever (62.53%), fatigue (53.82%), and shortness of breath (48.10%).

The most common reported comorbidities in the COVID-19 positive group included hypertension (52.00%), diabetes (25.46%), and asthma (18.19%). Chronic rhinosinusitis (CRS) was noted in 5.22% of COVID-19 positive patients. The demographic and clinical characteristics of COVID-19 positive patients with and without CRS are included in Table 2. There was no statistically significant difference in age and race between the COVID-19 positive patients with and without CRS. In terms of symptoms, COVID-19 positive patients with CRS experienced more rhinorrhea (25.5% vs 14.1%, $p = 0.041$) compared to patients without CRS. The difference in other symptoms between the COVID-19 positive patients with CRS and without CRS did not reach statistical significance. COVID-19 positive patients with CRS were at higher risk for hospitalization compared to patients without CRS (38.46% vs 25.82%, $p = 0.036$). However, there was no significant difference between the two groups in relation to ICU admission, mechanical ventilation, and death (Table 2).

The demographic and clinical characteristics of COVID-19 positive patients with and without impaired sense of smell are included in Table 3. The group that experienced impaired sense of smell was significantly younger than the group that did not experience impaired sense of smell (45.0 ± 1.07 vs 56.8 ± 0.68, $p < 0.0001$). There was no significant difference between the two groups in race. In terms of symptoms, patients that had impaired sense of smell reported significantly more upper respiratory symptoms of nasal congestion, rhinorrhea, and loss of taste ($p < 0.0001$). In addition, this subset of patients with impaired sense of smell had significantly lower comorbidities including hypertension, heart failure, and coronary artery disease ($p < 0.0001$). COVID-19 positive patients with impaired sense of smell were significantly less hospitalized (13.97% vs 29.29%, $p < 0.0001$), and there were no deaths in this group (0.00% vs 5.49%, $p = 0.0223$).

Regarding need for hospitalization in the COVID-19 positive group (Table 4), patients who were hospitalized reported significantly more shortness of breath (71.68% vs 38.70%, $p < 0.0001$) and fatigue (67.01% vs 47.97%, $p < 0.0001$). COVID-19 positive patients who did not require hospitalization reported significantly more upper respiratory symptoms including impaired sense of smell (21.57% vs 9.73%, $p < 0.0001$), sore throat (24.48% vs 17.90%, $p = 0.0304$), and loss of taste (23.08% vs 16.73%, $p = 0.0336$). In terms of comorbidities, hospitalized COVID-19 positive patients were more likely to have hypertension (73.17% vs 43.01%, $p < 0.0001$), diabetes (42.45% vs 18.51%, $p < 0.0001$), heart failure (25.32% vs 6.45%, $p < 0.0001$), coronary artery disease (24.05% vs 9.76%, $p < 0.0001$), asthma (22.36% vs 16.25%, $p = 0.0440$), cancer (21.22% vs 11.17%, $p = 0.0003$), COPD (12.82% vs 4.77%, $p = 0.0002$), history of tonsillectomy and/or adenoidectomy (20.70% vs 14.31%, $p = 0.0219$), and chronic rhinosinusitis (7.81% vs 4.35%, $p = 0.0486$).

Table 2
Demographics and characteristics of COVID-positive patients with and without chronic rhinosinusitis.

	No chronic rhinosinusitis	Chronic rhinosinusitis	P-value
N	942	52	
Demographics			
Age (in years) (SD)	54.36 ± 0.62	58.14 ± 2.27	0.107
Female sex (%)	481 (51.06%)	35 (67.31%)	0.084
BMI	29.86 ± 0.46	28.74 ± 1.81	0.558
Race (%)			
White	542 (57.54%)	32 (61.54%)	0.665
Black	256 (27.18%)	16 (30.77%)	0.631
Symptoms			
Cough	673 (83.50%)	38 (80.85%)	0.686
Fever	499 (62.77%)	19 (41.30%)	0.639
Fatigue	330 (53.66%)	20 (55.56%)	0.865
Shortness of breath	370 (48.30%)	20 (44.44%)	0.647
Diarrhea	192 (28.96%)	11 (26.19%)	0.861
Loss of appetite	177 (31.49%)	8 (24.24%)	0.382
Vomiting	45 (6.97%)	2 (5.13%)	1
Sore throat	211 (22.40%)	13 (25.00%)	0.613
Impaired sense of smell	171 (18.17%)	15 (28.85%)	0.055
Nasal congestion	229 (24.31%)	18 (34.62%)	0.100
Rhinorrhea	132 (14.01%)	13 (25.00%)	**0.041**
Loss of taste	198 (21.02%)	17 (32.69%)	**0.046**
Comorbidities			
Smoking	299 (40.08%)	25 (50.00%)	0.1822
COPD (emphysema)	49 (6.63%)	9 (17.65%)	**0.0087**
Asthma	130 (17.22%)	17 (33.33%)	**0.00076**
Diabetes	191 (25.23%)	15 (30.00%)	0.503
Hypertension	399 (51.68%)	30 (58.82%)	0.386
Coronary artery disease	100 (13.48%)	12 (24.00%)	0.056
Heart failure	89 (11.99%)	7 (14.00%)	0.654
Cancer	110 (14.21%)	7 (14.29%)	1
Immunosuppressive treatment	70 (9.07%)	16 (32.65%)	**<0.0001**
Sinus surgery	4 (0.42%)	14 (25.49%)	**<0.0001**
Outcome			
Hospitalized	237 (25.82%)	20 (38.46%)	**0.0355**
Mechanical ventilation	53 (50.48%)	4 (28.57%)	0.1587
ICU admission	84 (35.59%)	4 (20.00%)	0.22
Death	24 (4.60%)	1 (2.94%)	1

Bolded text signifies P-values that are statistically significant.

Table 3
Demographics and characteristics of patients with and without impaired sense of smell in COVID-19 positive patients.

	No impaired sense of smell	Impaired sense of smell	P-value
N	807	186	
Demographics			
Age (in years) (SD)	56.81 ± 0.68	45.02 ± 1.07	**<0.0001**
Female sex (%)	388 (48.08%)	127 (68.28%)	**<0.0001**
BMI (kg/m^2) (SD)	29.40 ± 0.49	31.33 ± 1.07	0.096
Race (%)			
White	469 (58.12%)	104 (55.91%)	0.62
Black	211 (26.15%)	61 (32.80%))	0.069
Symptoms			
Cough	560 (83.04%)	150 (84.27%)	0.82
Fever	423 (63.61%)	102 (59.29%)	0.22
Fatigue	278 (53.88%)	72 (53.33%)	0.92
Shortness of breath	327 (51.01%)	63 (37.28%)	**0.0018**
Diarrhea	150 (27.42%)	53 (33.76%)	0.13
Loss of appetite	140 (30.30%)	45 (33.83%)	0.46
Vomiting	35 (6.57%)	12 (7.95%)	0.58
Sore throat	169 (20.94%)	55 (29.57%)	**0.015**
Nasal congestion	170 (21.01%)	76 (40.86%)	**<0.0001**
Rhinorrhea	98 (12.11%)	47 (25.27%)	**<0.0001**
Loss of taste	49 (6.06%)	166 (89.25%)	**<0.0001**
Comorbidities			
Smoking	265 (41.47%)	61 (38.61%)	0.53
COPD (emphysema)	55 (8.63%)	3 (1.97%)	**0.0029**
Asthma	111 (17.16%)	36 (22.78%)	0.11
Diabetes	181 (27.76%)	25 (16.23%)	**0.0028**
Hypertension	377 (56.78%)	52 (32.91%)	**<0.0001**
Coronary artery disease	108 (16.90%)	4 (2.63%)	**<0.0001**
Heart failure	95 (14.87%)	1 (0.66%)	**<0.0001**
Cancer	104 (15.73%)	13 (8.07%)	**0.012**
Immunosuppressive treatment	71 (10.71%)	15 (9.55%)	0.77
Chronic sinusitis	37 (4.58%)	15 (8.06%)	0.066
Sinus surgery	15 (1.86%)	2 (1.08%)	0.75
Outcome			
Hospitalized	232 (29.37%)	25 (13.97%)	**<0.0001**
Mechanical ventilation	53 (49.07%)	4 (36.36%)	0.53
ICU admission	80 (34.48%)	8 (32.00%)	1
Death	25 (5.49%)	0 (0.00%)	**0.022**

Bolded text signifies P-values that are statistically significant.

Table 4
Demographics and clinical characteristics of hospitalized and non-hospitalized COVID-19 positive patients.

	Not hospitalized	Hospitalized	P-value
N	715	257	
Demographics			
Age (in years) (SD)	50.67 ± 0.70	65.30 ± 0.96	**<0.0001**
Female sex (%)	435 (60.67%)	159 (61.39%)	0.39
BMI (kg/m^2) (SD)	29.41 ± 0.55	30.41 ± 0.74	0.32
Race (%)			
White	417 (58.32%)	146(56.81%)	0.71
Black	170 (23.78%)	95 (36.96%)	**<0.0001**
Symptoms			
Cough	508 (84.53%)	186 (79.83%)	0.12
Fever	382 (65.08%)	135 (56.96%)	**0.029**
Fatigue	212 (47.86%)	131 (66.84%)	**<0.0001**
Shortness of breath	219 (38.49%)	162 (72.00%)	**<0.0001**
Diarrhea	132 (27.39%)	66 (31.88%)	0.23
Loss of appetite	120 (28.85%)	63 (37.95%)	**0.037**
Vomiting	27 (5.78%)	18 (8.87%)	0.18
Impaired sense of smell	154 (21.63%)	25 (9.73%)	**<0.0001**
Sore throat	174 (24.40%)	46 (22.68%)	**0.037**
Nasal congestion	186 (26.09%)	55 (21.40%)	0.15
Rhinorrhea	112 (15.71%)	31 (12.06%)	0.18
Loss of taste	165 (23.08%)	43 (16.73%)	**0.0334**
Comorbidities			
Smoking	194 (36.06%)	123 (50.00%)	**0.0001**
COPD (emphysema)	26 (4.77%)	30 (12.88%)	**0.0002**
Asthma	90 (16.25%)	53 (22.46%)	**0.043**
Diabetes	102 (18.51%)	104 (42.39%)	**<0.0001**
Hypertension	243 (43.01%)	179 (73.36%)	**<0.0001**
Coronary artery disease	53 (9.76%)	57 (24.42%)	**<0.0001**
Heart Failure	35 (6.45%)	60 (25.32%)	**<0.0001**
Cancer	63 (11.17%)	52 (21.32%)	**0.0003**
Immunosuppressive treatment	53 (9.36%)	32 (13.33%)	0.10
Chronic rhinosinusitis	32 (4.49%)	20 (7.78%)	0.052
Sinus surgery	9 (1.26%)	8 (3.11%)	0.091

Bolded text signifies P-values that are statistically significant.

We also performed a multivariate logistic regression analysis predicting need for hospitalization adjusting for covariates that were shown to significantly correlate with impaired sense of smell including age, upper respiratory symptoms, lower respiratory symptoms, and comorbidities (Table 5). When adjusting for covariates, patients that reported shortness of breath were 4.34 (OR = 4.34, 95%CI (2.45–7.70), $p < 0.0001$) times more likely to be hospitalized compared to patients that had no shortness of breath. Patients with chronic rhinosinusitis were 3.46 (OR = 3.46, 95% CI (1.12–10.68)) times more likely to be hospitalized compared to patients that have no chronic rhinosinusitis. Patients that had impaired sense of smell were 0.28 (95% CI, 0.09–0.86) times less likely to be hospitalized compared to patients that did not have impaired sense of smell.

Table 5
Multivariate analysis of the factors predicting hospitalization.

Variable	Odds ratio	95% confidence interval		P-value
Age	0.95	0.93	0.97	**<0.0001**
Race: Black	2.33	1.23	4.41	**0.0092**
Fever	0.69	0.38	1.27	0.24
Fatigue	2.72	1.45	5.09	**0.0018**
Sore throat	0.57	0.29	1.09	0.090
Shortness of breath	4.34	2.45	7.70	**<0.0001**
Impaired sense of smell	0.28	0.09	0.86	**0.026**
Loss of taste	0.45	0.16	1.27	0.13
Loss of appetite	1.18	0.61	2.26	0.62
Smoking	1.30	0.74	2.29	0.36
COPD/emphysema	0.70	0.20	2.45	0.58
Asthma	1.07	0.53	2.13	0.85
Diabetes	2.00	1.05	3.82	**0.034**
Heart failure	4.57	1.53	13.60	**0.0064**
Chronic rhinosinusitis	3.46	1.12	10.68	**0.030**
Cancer	1.11	0.49	2.50	0.80
Hypertension	1.15	0.60	2.22	0.67
Coronary artery disease	1.56	0.63	3.89	0.34

Bolded text signifies P-values that are statistically significant.

4. Discussion

Using our CCF COVID-19 registry, we found that chronic rhinosinusitis (CRS) patients have an increased risk for hospitalization when compared to patients without CRS. Since the nasal and oral cavities are gateways for entry of the virus into the body, it is not surprising that upper airway pathologies may play a role in COVID-19 clinical outcomes. There are seven coronaviruses that cause infections in humans apart from SARS-CoV-2 [44]. Research has shown that the primary site of entry of coronaviruses depend on the type, with MERS-CoV infecting type II pneumocytes, SARS-CoV involving the lungs and SARS-CoV-2 infecting the nose and throat [45]. It is thought that goblet and ciliated cells are the targets that the virus infects [46] with nasal epithelial cells displaying the highest expression for ACE-2 receptors in the respiratory tree. The mechanism of entry into the host is through the interaction between its spike protein S1 and the host angiotensin-converting enzyme 2 (ACE2) receptor [47]. Transmembrane protease serine 2 (TMPRSS2) which is expressed in the host cells also plays a pivotal role in pathogenesis as it cleaves the viral S glycoprotein causing activation of viral particles [48]. In addition to nasal epithelial cells, recent studies have shown that ACE2 and TMPRSS2 are expressed by sustentacular and basal cells of the olfactory epithelium and are not expressed by olfactory sensory neurons [49] suggesting that olfactory impairment is related to the damage of the supporting cells rather than neurons.

CRS is among the most common chronic diseases in the world, affecting about 15% of the U.S. population [50]. The formal criteria for diagnosis includes the presence of 2 or more of the following cardinal symptoms for 12 weeks: nasal obstruction, nasal discharge, facial pressure or hyposmia; and objective evidence of inflammation/purulence from the paranasal sinuses on computed tomography (CT) or nasal endoscopy [51]. All patients diagnosed with CRS in this study were diagnosed by an otolaryngologist adhering to the aforementioned diagnostic criteria. Histologically, CRS differs based on whether the inflammation is eosinophilic versus neutrophilic [52]. In terms of symptoms, COVID-19 positive CRS patients experienced more rhinorrhea (25.5% vs 14.01%, $p = 0.041$) compared to patients without CRS. Interestingly, impaired sense of smell as a major cardinal symptom of CRS was not found to be differentially different between CRS and non CRS COVID positive patients.

The increased risk for hospitalization in CRS patients with COVID-19 was not associated with increased ICU admission risk, mechanical ventilation, or mortality. The risk of hospitalization associated with CRS was demonstrated even when controlling for known comorbidities. Our multivariate logistic regression model predicting need for hospitalization showed that CRS patients are 3.46 (95% CI, 1.11–10.68) times more likely to be hospitalized compared to patients that have no CRS. Studies on the link of CRS to COVID-19 severity are limited and the findings have been mixed in nature. Wang et al. reported that CRS was not associated with severe COVID-19 infection, but their study excluded deceased patients with CRS that may have represented patients with severe COVID-19 infection [53]. Conversely, Lee et al. performed a national study in South Korea which demonstrated that CRS increased the risk of COVID-19 infection and severity of illness [54]. Patients with chronic sinusitis without nasal polyps were noted to be at increased risk [54].

Our observed increased risk of COVID-19 hospitalization could be explained by the variation in receptor densities in the nasal epithelium of CRS patients or the use of steroids as part of the standard treatment of this disease. The first line treatment of CRS is intranasal corticosteroids; however, it is unlikely that the use of intranasal corticosteroids affected the outcome of our COVID-19 patients. In a study on COVID-19 positive patients with COPD, inhaled corticosteroid use was found to be

protective against hospitalization of COVID-19 infections [36]. Our observed worse outcomes in CRS patients are more likely to be explained by potential differences in ACE2 receptor densities in CRS patients. Several studies have found that patients with non-eosinophilic CRS had increased ACE2 and TMPRSS2 expression compared to eosinophilic CRS patients [55,56]. Another study looked at the effect of eosinophilic vs neutrophilic inflammatory histopathological profile on COVID-19 in asthmatics. Patients with the neutrophilic asthma phenotype were found to be at higher risk for COVID-19 infection compared to the eosinophilic counterpart [57]. Due to the nature of our study, we were not able to determine the histopathological phenotype of our CRS patients and future studies are needed to determine the effect of the CRS inflammatory profile on COVID-19 infectivity and severity.

Our study has several limitations. First, it was conducted at the beginning of the COVID-19 pandemic in the U.S. There was less awareness for testing at that time particularly among the younger patients which may present milder forms of COVD-19. Hence, we believe that impaired sense of smell is underreported in our study. Second, we were not able to divide CRS into eosinophilic vs neutrophilic endotypes. Third, our study was retrospective in nature and we were not able to collect data on the use of intranasal steroids given their over the counter use. Fourth, our study included Cleveland Clinic patients in Northeast Ohio and Southeast Florida population, which limits the generalizability of our results.

5. Conclusion

Chronic rhinosinusitis is associated with increased risk of hospitalization due to COVID-19. Future studies are needed to examine the mechanistic bases and examine the relationship in a prospective fashion.

Author contributions

Firas Sbeih: Data collection, analysis, and initial draft.
Jorge Gutierrez: Data collection, analysis and initial draft.
George Saieed: Data collection, analysis, and initial draft.
Mohamad R. Chaaban: Design, analysis, initial draft and revise manuscript.

Declaration of competing interest

Dr. Mohamad Chaaban is a member of the Optinose advisory board. All other authors have no financial or other conflicts of interest to disclose.

References

[1] Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020 Mar 13;7(1):11.
[2] Hofmann M, Kleine-Weber H, Schroeder S, et al. SARSCoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(271–280):6.
[3] Palasca O, Santos A, Stolte C, Gorodkin J, Jensen LJ. TISSUES 2.0: an integrative web resource on mammalian tissue expression. Database (Oxford) 2018:bay028. 2018.
[4] Muus C, Luecken MD, Eraslan G, et al. Integrated analyses of single-cell atlases reveal age, gender, and smoking status associations with cell type-specific expression of mediators of SARS-CoV-2 viral entry and highlights inflammatory programs in putative target cells. Bioinformatics 2020. https://doi.org/10.1101/2020.04.19.049254 8.
[5] Chen R, Wang K, Yu J, Chen Z, Wen C, Xu Z. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. Neuroscience 2020. https://doi.org/10.1101/2020.04.07.030650 9.
[6] Qi J, Zhou Y, Hua J, et al. The scRNA-seq expression profiling of the receptor ACE2 and the cellular protease TMPRSS2 reveals human organs susceptible to COVID-19 infection. Bioinformatics 2020. https://doi.org/10.1101/2020.04.16.045690.
[7] Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005;202:415–24.
[8] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Nerosci 2020;11:995–8.
[9] Lipner SR. Retrospective analysis of smell and taste disturbances associated with dermatological medications reported to the United States Food and Drug Administration and relevance to COVID-19 infections. J Am Acad Dermatol Aug, 2020;83(2):682–4.
[10] JM Abalo-Lojo JM Pouso-Diz F Gonzalez . Taste and smell dysfunction in COVID-19 patients. Ann Otol Rhinol Laryngol.
[11] Aggarwal S, Garcia-Telles N, Aggarwal G, et al. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): early report from the United States. Diagnosis (Berlin, Germany) 2020;7:91–6.
[12] Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. published online Eur J Neurol April 23, 2020;27(9):1738–41.
[13] Carignan A, Valiquette L, Grenier C, et al. Anosmia and dysgeusia associated with SARS-CoV-2 infection: an age-matched case-control study. published online CMAJ May 29, 2020;192(26):702–7.
[14] Coelho DH, Kons ZA, Costanzo RM, et al. Subjective changes in smell and taste during the COVID-19 pandemic: a national survey—preliminary results. published online Otolaryngol Head Neck Surg May 20, 2020;163(2):302–6.
[15] Gautier JF, Ravussin Y. A new symptom of COVID-19: loss of taste and smell. Obesity (Silver Spring, MD) 2020;28:848.
[16] Gilani S, Roditi R, Naraghi M. COVID-19 and anosmia in Tehran,Iran. Med Hypotheses 2020;141:109757.
[17] Hopkins C, Surda P, Whitehead E, et al. Early recovery following new onset anosmia during the COVID-19 pandemic: an observational cohort study. J Otolaryngol Head Neck Surg 2020;49:26.
[18] Kim GU, Kim MJ, Ra SH, et al. Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19 [published online May 4, 2020]. Clin Microbiol Infect. 14. Klopfenstein T, Kadiane-Oussou NJ, Toko L, et al. Features of anosmia in COVID-19. published online Med Malad Infect April 20, 2020;26(7): 948.
[19] Lao WP, Imam SA, Nguyen SA. Anosmia, hyposmia, and dysgeusia as indicators for positive SARS-CoV-2 infection. published online World J Otorhinolaryngol Head Neck Surg April 22, 2020;6(1):22–5.
[20] Lechner M, Chandrasekharan D, Jumani K, et al. Anosmia as a presenting symptom of SARS-CoV-2 infection in healthcare workers: a systematic review of the literature, case series, and recommendations for clinical assessment and management. published online Rhinology May 10, 2020;58(4):394–9.
[21] Lee Y, Min P, Lee S, et al. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J Korean Med Sci 2020;35:e174.
[22] Lehrich BM, Goshtasbi K, Raad RA, et al. Aggregate prevalence of chemosensory and sinonasal dysfunction in SARSCoV-2 and related coronaviruses. published online Otolaryngol Head Neck Surg May 20, 2020;163(1):156–61.
[23] Liguori C, Pierantozzi M, Spanetta M, et al. Subjective neurological symptoms frequently occur in patients with SARSCoV2 infection [published online May 18, 2020]. Brain Behav Immun. 20. Liu JY, Chen TJ, Hwang SJ. Analysis of imported cases of COVID-19 in Taiwan: a nationwide study. published online Int J Environ Res Public Health May 14, 2020;88:11–6.
[24] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. published online JAMA Neurol April 11, 2020;77(6):683–90.
[25] Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. published online Nat Med May 13, 2020; 11. Ibekwe et al.
[26] Merza MA, Haleem Al Mezori AA, Mohammed HM, et al. COVID-19 outbreak in Iraqi Kurdistan: the first report characterizing epidemiological, clinical, laboratory, and radiological findings of the disease. Diabetes Metab Syndr 2020;14:547–54.
[27] Moein ST, Hashemian SMR, Mansourafshar B, et al. Smell dysfunction: a biomarker for COVID-19. Int Forum Allergy Rhinol April 18, 2020;10(8):944–50.
[28] Roland LT, Gurrola II JG, Loftus II PA, et al. Smell and taste symptom-based predictive model for COVID-19 diagnosis [published online May 5, 2020]. Int Forum Allergy Rhinol. 26. Speth MM, Singer-Cornelius T, Obere M, et al. Olfactory dysfunction and sinonasal symptomatology in COVID-19: prevalence, severity, timing, and associated characteristics. Otolaryngol Head Neck Surg May 20, 2020; 10(7):832–8.
[29] Spinato G, Fabbris C, Polesel J, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. JAMA. 2020;323:2089-2090. 28. Tong JY, Wong A, Zhu D, et al. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. published online Otolaryngol Head Neck Surg May 6, 2020;323(20):2089–90.
[30] Vaira LA, Salzano G, Deiana G, et al. Anosmia and ageusia: common findings in COVID-19 patients. published online Laryngoscope April 3, 2020;130(7):1787.
[31] Vetter P, Vu DL, L'Huillier AG, et al. Clinical features of Covid-19. published online BMJ 2020;369:m1470.
[32] Zayet S, Klopfenstein T, Mercier J, et al. Contribution of anosmia and dysgeusia for diagnostic of COVID-19 in outpatients. Infection May 16, 2020;49(2):361–5.
[33] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:1–9. https://doi.org/10.1001/jamaneurol.2020.1127.
[34] Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020. https://doi.org/10.1007/s00405-020-05965-1.

[35] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. PMID: 32077115 Allergy 2020;75:1730–41. Doi:// 10.11.11/all.14238.
[36] Attaway AA, Zein J, Hatipoğlu US. SARS-CoV-2 infection in the COPD population is associated with increased healthcare utilization: an analysis of Cleveland clinic's COVID-19 registry. EClinicalMedicine. 2020 Sep;26:100515. https://doi.org/10.1016/j.eclinm.2020.100515. Epub 2020 Aug 26.
[37] Medina M, Babiuch C, Card M, Gavrilescu R, Zafirau W, Boose E, et al. Home monitoring for COVID-19. Cleve Clin J Med 2020. https://doi.org/10.3949/ccjm.87a.ccc028 [published online ahead of print, 2020 Jun 11].
[38] Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. JAMA: J Am Med Assoc 2020. https://doi.org/10.1001/jama.2020.4326. Epub 2020/03/20PubMed PMID:32191259PubMed Central PMCID: PMCPMC7082763.
[39] Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. COVID19 in critically ill patients in the Seattle region - case series. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2004500. Epub 2020/04/01PubMed PMID:32227758PubMed Central PMCID: PMCPMC7143164.
[40] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2002032. Epub 2020/02/29PubMed PMID:32109013.
[41] Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 2020. https://doi.org/10.7326/M20-0504. Epub 2020/03/ 10PubMed PMID:32150748.
[42] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in china: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA 2020. https://doi.org/10.1001/jama.2020.2648. Epub 2020/02/25PubMed PMID: 32091533.
[43] Milinovich A, Kattan MW. Extracting and utilizing electronic health data from fpic for research. Ann Transl Med 2018;6(3):42. https://doi.org/10.21037/atm.2018.01.13. Epub 2020/02/29PubMed PMID:32109013.
[44] Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L. Nervous system involvement after infection with COVID-19 and other coronaviruses. published online Brain Behav Immun Mar 30, 2020. https://doi.org/10.1016/j.bbi.2020.03.031.
[45] Rockx B, Kuiken T, Herfst S, Bestebroer T, Lamers MM, Oude Munnink BB. Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model. Science 2020;368:1012–5. https://doi.org/10.1126/science.abb7314.
[46] Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM. Position paper on olfactory dysfunction. Rhinol Suppl 2017;54:1–30.
[47] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Nerosci 2020;11:995–8.
[48] Mollica V, Rizzo A, Massari F. The pivotal role of TMPRSS2 in coronavirus disease 2019 and prostate cancer. Future Oncol 2020 Sep;16(27):2029–33. https://doi.org/10.2217/fon-2020-0571.
[49] D Brann , # 1, T Tsukahara C Weinreb M Lipovsek K Van den Berge B Gong R Chance et al Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia.
[50] Wullianallur R, Raghupathi V. An empirical study of chronic diseases in the United States: a visual analytics approach to public health. Int J Environ Res Public Health 2018 Mar;15(3):431.
[51] Sci Adv 2020 Jul 31;6(31):eabc5801. https://doi.org/10.1126/sciadv.abc5801. Epub 2020 Jul 24. 51. Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. International forum of allergy & rhinology. 2016 Feb;6 Suppl 1: S22-209.
[52] Shah SA, Ishinaga H, Takeuchi K. Pathogenesis of eosinophilic chronic rhinosinusitis. J Inflamm (Lond) 2016 Apr;6(13):11. https://doi.org/10.1186/s12950-016-0121-8.
[53] Wang H, Song J, Pan L, Yao Y, Deng YK, Wang ZC, et al. The characterization of chronic rhinosinusitis in hospitalized patients with COVID-19. J Allergy Clin Immunol Pract Nov-Dec 2020;8(10):3597–3599.e2. https://doi.org/10.1016/j.jaip.2020.09.013. Epub 2020 Sep 24.
[54] Lee SW, Kim SY, Moon SY, Yang JM, Ha EK, Jee HM, Shin JI, Cho SH, Yon DK, Suh DI. Estimating COVID-19 infection and severity risks in patients with chronic rhinosinusitis: a Korean nationwide cohort study. J Allergy Clin Immunol Pract 2021 Jun;9(6):2262–2271.e2.
[55] Sharif-Askari FS, Saheb N, Askarii S, Goel S, Fakhri S, Al-Muhsen S. Are patients with chronic rhinosinusitis with nasal polyps at a decreased risk of COVID-19 infection? Int Forum Allergy Rhinol 2020 Oct;10(10):1182–5. https://doi.org/10.1002/alr.22672. Epub 2020 Aug 19.
[56] Hong SN, Kim JK, Kim JA, Cha H, Kim JY, Lim HS, Eun KM, Kim DW. Viral stimulation modulates endotype-related ACE2 expression in eosinophilic chronic rhinosinusitis. Rhinology 2021 Oct 1;59(5):460–9.
[57] Ramakrishnan RK, Heialy S, Hamid Q. Implications of preexisting asthma on COVID-19 pathogenesis. Am J Physiol Lung Cell Mol Physiol 2021 May 1;320(5): L880–91. https://doi.org/10.1152/ajplung.00547.2020.