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

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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-
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 7.14%, p < 0.0001).

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

| Comorbidities | 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/m²) (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  |
| Shortness of breath | 18 (18.81%) | 186 (18.69%) | <0.0001 |
| Sore throat   | 262 (26.36%) | 225 (25.59%) | 0.5537  |
| 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 |
| Smoking       |                  |                  |         |
| Smoking (pack-year) | 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 (51.22%) | 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 (18.80%) | 117 (14.18%) | 0.0188  |
| Immunosuppressive treatment | 115 (14.67%) | 86 (10.45%) | 0.0127  |

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%, \( p = 0.0486 \).
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.

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
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.

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