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【 ORIGINAL ARTICLE 】

The Clinical Significance of Otolaryngology Manifestations in COVID-19 Pneumonia: A Single-center Retrospective Cohort Study

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Abstract:

Objective Although the absence of a runny nose and sore throat, both ear-nose-throat (ENT) symptoms, suggests community-acquired pneumonia (CAP), the association between ENT symptoms and coronavirus disease 2019 (COVID-19) pneumonia remains unclear. We therefore investigated the association between ENT symptoms and COVID-19 pneumonia.

Methods We retrospectively recruited consecutive confirmed COVID-19 inpatients with and without pneumonia admitted to a single institution from April 1, 2020, to July 31, 2021. After a descriptive analysis, we implemented univariable and multivariable regression analyses to assess the association between ENT symptoms and COVID-19 pneumonia.

Results The present study included 385 patients. Pneumonia patients exhibited lower rates of positive runny nose and sore throat than non-pneumonia patients. Univariable analyses found mean odds ratios of 0.59 and 0.61 and 95% confidence intervals (CIs) of 0.30-1.16 and 0.32-1.17 for runny nose and sore throat, respectively, and multivariable analyses found mean odds ratios of 0.73 and 0.70 and 95% CIs of 0.34-1.56 and 0.34-1.46, respectively.

Conclusion Our study found no statistically significant association between ENT symptoms and COVID-19 pneumonia. Clinicians should be aware that, unlike CAP, there is no correlation between ENT symptoms and pneumonia among patients with COVID-19, so it is necessary to consider the possibility of pneumonia even in the presence of ENT symptoms.

Key words: COVID-19, sore throat, runny nose, pneumonia

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Introduction

The global coronavirus disease 2019 (COVID-19) pandemic is expected to produce an increasing number of patients with disease severity ranging from asymptomatic to critical, highlighting the importance of efficiently detecting COVID-19 pneumonia, which may lead to respiratory failure and other poor outcomes. The medical history and physical examination findings are the mainstays for a respiratory disease diagnosis. In the pre-COVID-19 era, the absence of a runny nose suggested community-acquired pneumonia (CAP) among at-risk patients. In the early 1980s, Diehr's predictive model of pneumonia suggested that the absence of a runny nose supported a diagnosis of pneumonia among patients with acute cough (1). More recently, Groeneveld et al. (2019) reported a low likelihood of CAP suggested by the presence of a runny nose in the field of primary care (2). Despite the recent flurry of studies on COVID-19, whether or not otolaryngology manifestations, including a runny nose and sore throat, are correlated with pneumonia among COVID-19 patients remains unclear.

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While many clinicians believe that CAP typically involves bacterial infections, which tend to cause more localized symptoms than viral infections and are less appropriate for a comparison with COVID-19 pneumonia, there is evidence that CAP pathogens are often viral. Jain et al. (2015) studied CAP requiring hospitalization in the United States between 2010 and 2012, reporting that viral pathogens alone was a more common finding than bacterial pathogens alone among patients with detected pathogens (22% and 11%, respectively), although the specific pathogen was undetected in 62.5% of cases (3). This suggests that ear-nose-throat (ENT) symptoms in CAP are often caused by viral pathogens, thus suggesting the potential applicability of CAP diagnostic guidelines for COVID-19 patients.

As of February 2022, several studies have been conducted on the relationship between COVID-19 and ENT symptoms. A decreased sense of smell was the earliest reported ENT symptom of COVID-19, suggesting its complex influence on ENT symptoms (4, 5). However, El-Anwar et al. reviewed ENT symptoms in COVID-19, finding that a runny nose was less common than fever and other symptoms (6). Most previous studies have been limited to the area of otolaryngology, focusing on ENT symptoms and taste and smell disorders. To our knowledge, no studies have investigated whether or not ENT symptoms are correlated with disorders beyond the scope of otolaryngology, such as pneumonia, among COVID-19 patients.

This study explored whether or not the presence of a runny nose and sore throat are factors suggestive of COVID-19 pneumonia among COVID-19 patients. Furthermore, given the future vast amount of COVID-19 patients, assessing the clinical utility of a runny nose and sore throat on pneumonia among COVID-19 patients is expected to contribute to diagnosing COVID-19 pneumonia more efficiently.

Materials and Methods

This study was a retrospective COVID-19 cohort study. All participants were retrospectively recruited from among inpatients at Sapporo Hokushin Hospital, Japan. We recruited the patients consecutively to avoid selection bias. Participant data were compiled from the hospital's internal records and data submitted to the national COVID-19 registry (COVID-19 REGISTRY JAPAN; https://covid-registry.ncgm.go.jp/) maintained by the National Center for Global Health and Medicine, Japan. In the present study, registry data were included only from the single center where participants were admitted.

The COVID-19 status was confirmed by reverse transition polymerase chain reaction (RT-PCR) for infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) of the genus Betacoronavirus. Patients hospitalized with COVID-19 were consecutively recruited from April 1, 2020, to July 31, 2021. Registry data covered April 1, 2020, to March 31, 2021. The research hospital's internal cohort data extends beyond the registry data and covers the whole duration from April 1, 2020, to July 31, 2021. Our study was reported according to the STROBE criteria (Supplementary Material) (7).

Data collection

We collected the following data: patient characteristics including age, sex, body mass index (BMI), and medical history; laboratory data; imaging data, including chest X-ray and computed tomography; clinical symptoms, including runny nose and sore throat; and clinical outcomes, including death and transfer to other institutions. All data were obtained from patient hospital charts. The study data were collected and managed using Research Electronic Data Capture (REDCap) a secure, web-based data capture application hosted at the JCRAC data center of the National Center for Global Health and Medicine.

Inclusion and exclusion criteria

Inclusion criteria were age ≥20 years old, a diagnosis of COVID-19 confirmed by positive RT-PCR, and admission to the research hospital. Exclusion criteria were death or transfer out of the hospital due to acute exacerbation or intubation within 24 h of admission; COVID-19 developed after admission for other reasons; and lack of chest imaging.

Definitions

COVID-19 pneumonia was defined as the presence of COVID-19 confirmed by positive RT-PCR and lung infiltrates found on chest CT, including ground-glass opacity, consolidation, air bronchogram, reticulations, nodules, and halo sign, considering the various patterns of COVID-19 pneumonia previously reported (8, 9).

Ethical considerations

This study was approved by the ethics review board of the research hospital where the study was conducted. Patient consent was obtained using an opt-out method.

Statistical analyses

We described baseline characteristics using standard descriptive statistics: median, first quartile and third quantile for continuous variables, and percentages for categorical variables.

We used a chi-square test to assess the proportion of ENT symptoms between the pneumonia and non-pneumonia groups. Next, we implemented logistic regression, setting the presence of pneumonia as the primary outcome. A univariable regression analysis was performed with runny nose and sore throat as the objective variables. Next, a multivariable regression analysis was performed after adjusting for variables affecting pneumonia and otolaryngology symptoms. We chose the variables based on clinical experience. Statistical significance was defined as $p<0.05$ for a two-tailed test. Sample size was calculated using the 10 events per variable (EPV) rule (10). We planned to use 5 or more variables, requiring the recruitment of at least 50 non-

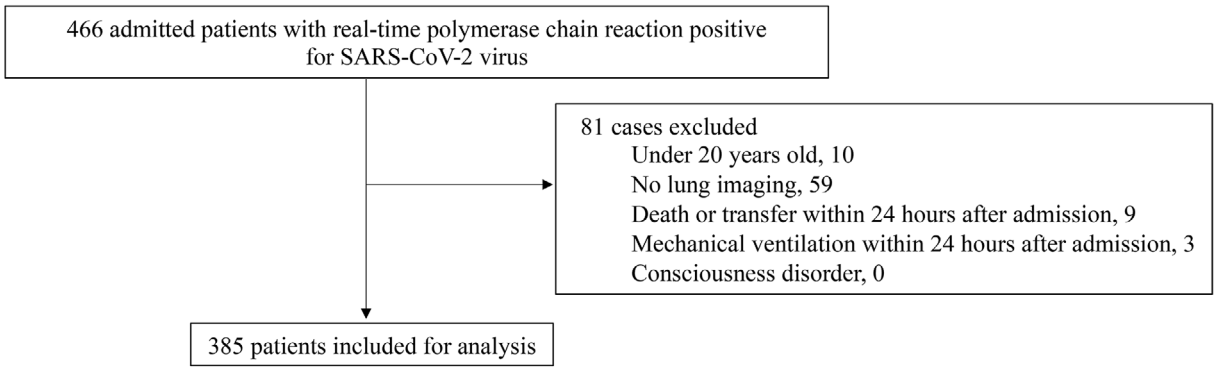

Figure. **Study flow chart of our study.**

pneumonia patients. As a sensitivity analysis of the multivariable regressions, we implemented robust Poisson regression instead of logistic regression because log binominal regression is feasible when the proportion of the lesser event is high (11, 12). Statistical analyses were performed using the R [R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.] and STATA software programs (Release 15; StataCorp, College Station, USA).

Results

In the present study, 466 adult patients were identified as candidates based on positive RT-PCR findings for SARS-CoV-2 virus. We excluded 10 patients under 20 years old, 9 who were transferred within 24 h after admission, 3 who needed mechanical ventilation immediately after admission, and 59 lacking chest CT images. As a result, 385 study participants were eligible for the analysis (Figure).

A summary of the patient characteristics and the number of patients missing data for each variable are presented in Table 1. There were 6 (1.6%) patients who died while hospitalized. The majority of participants were women (83.1%). The median body temperature was just below 37.0°C. Oxygen therapy was provided to more than one third of all participants (34.5%). Compared with the non-pneumonia group, pneumonia patients had a numerically higher median age, a higher median BMI, more frequently received oxygen therapy, and had a higher median white blood cell (WBC) count and serum lactate dehydrogenase (LDH) level. Regarding ENT symptoms, the non-pneumonia group had lower proportions of positive sore throat and runny nose, with p values of 0.123 and 0.134, respectively.

The results of our univariable and multivariable regression analyses are summarized in Tables 2 and 3. Univariable regression analyses for all ENT symptoms (runny nose, sore throat, taste disorder, and smell disorder) produced odds ratios with 95% confidence intervals (CIs) that crossed 1.0, thus failing to show statistically significant differences. However, the age, sex, BMI, WBC count, creatinine level, and Charlson Comorbidity Index (CCI) had p values below 0.05. On multivariable regression analyses after adjusting for the age, sex, BMI, and WBC count, the mean odds ratios of a runny nose and sore throat increased toward 1.0, and the p values also increased, again failing to show statistical significance. The p values for other variables (age, sex, BMI, WBC count) were all close to 0.05. Both old age and high BMI had odds ratios above 1.0. Regarding the sensitivity analysis, robust Poisson regression of a runny nose and sore throat produced a 0.95 incidence rate ratio (IRR), 95% CI of 0.86-1.05, and p value of 0.337 and 0.96 IRR, 95% CI of 0.87-1.05, and p value of 0.365, respectively.

Discussion

In the present study, neither a sore throat nor runny nose showed statistically significance in the multivariable analyses. Our results suggest that a sore throat and runny nose in COVID-19 patients are not useful factors to consider for a diagnosis of COVID-19 pneumonia. Compared with CAP, it may be more challenging to predict the presence of pneumonia among COVID-19 patients based on ENT symptoms. These results imply that COVID-19 pneumonia should not be assessed based on the presence or absence of these ENT symptoms but rather by evaluating a broader range of clinical information, such as the medical history, contact history with COVID-19 patients, vital signs, physical examination findings, laboratory tests, and chest X-ray images, particularly when CT is unavailable.

There may be some reasons why ENT symptoms do not lead to a definitive COVID-19 pneumonia diagnosis, despite their usefulness in diagnosing CAP. Importantly, COVID-19 can cause a wider variety of symptoms and affect a broader range of organs than other viruses that cause pneumonia, which may limit the diagnostic utility of a particular subset of negative clinical symptoms. In line with the developing understanding of COVID-19 pathophysiology, there are some reports explaining its multiorgan effects. COVID-19 has been reported to predominantly infect lung epithelial cells, alveolar macrophages, nasal goblet cells, vascular endothelium, and ileal cells (13). The angiotensin converting enzyme 2 (ACE2) receptor acts as a SARS-CoV-2 virus entry receptor (14). Since ACE2 receptors are widely ex-

Table 1. Patients' Characteristics and Symptoms in the Study.

	Pneumonia (n=339)	Non-pneumonia (n=46)	Total (n=385)
Age, years, median [IQR]	55.0 [45.5, 71.0]	43.5 [26.0, 68.3]	55.0 [44.0, 71.0]
Sex, number (%)			
Female	276 (81.4%)	44 (95.7%)	320 (83.1%)
Body mass index, median [IQR]	24.1 [20.9, 27.7]	21.9 [19.8, 24.4]	23.7 [20.8, 27.3]
Missing	25 (7.4%)	2 (4.3%)	27 (7.0%)
Systolic blood pressure (mmHg), median [IQR]	118 [107, 133]	118 [108, 129]	118 [107, 133]
Heart rate (per minute), median [IQR]	85.0 [75.0, 96.0]	77.0 [69.3, 86.0]	85.0 [74.0, 95.0]
Body temperature (Celsius), median [IQR]	37.0 [36.5, 37.7]	36.6 [36.3, 37.1]	36.9 [36.5, 37.6]
SpO_2 (%), median [IQR]	97.0 [96.0, 98.0]	98.0 [97.3, 99.0]	97.0 [96.0, 98.0]
Oxygen therapy, numbers (%)	133 (39.2%)	0 (0%)	133 (34.5%)
Current smoker, numbers (%)	41 (12.1%)	8 (17.4%)	49 (12.7%)
Missing	126 (37.2%)	8 (17.4%)	134 (34.8%)
White blood cells (per liter), median [IQR]	4,780 [3,770, 6,100]	3,920 [3,240, 4,610]	4,630 [3,710, 6,030]
Missing	3 (0.9%)	4 (8.7%)	7 (1.8%)
Lymphocyte, median [IQR]	920 [682, 1,240]	1,070 [825, 1,580]	932 [703, 1,280]
Missing	3 (0.9%)	4 (8.7%)	7 (1.8%)
LDH U/Ll, median [IQR]	265 [207, 346]	178 [152, 208]	254 [190, 329]
Missing	3 (0.9%)	4 (8.7%)	7 (1.8%)
Cre mg/dL, median [IQR]	0.650 [0.560, 0.800]	0.620 [0.533, 0.668]	0.650 [0.560, 0.788]
Missing	3 (0.9%)	4 (8.7%)	7 (1.8%)
Charlson Comorbidity Index, median [IQR]	0 [0, 1.00]	0 [0, 1.00]	0 [0, 1.00]
Hospital death, number (%)	6 (1.8%)	0 (0%)	6 (1.6%)
Symptom			
Sore throat, numbers (%)			
Negative	256 (75.5%)	30 (65.2%)	286 (74.3%)
Positive	83 (24.5%)	16 (34.8%)	99 (25.7%)
Runny nose, numbers (%)			
Negative	268 (79.1%)	31 (67.4%)	299 (77.7%)
Positive	71 (20.9%)	14 (30.4%)	85 (22.1%)
Missing	0 (0%)	1 (2.2%)	1 (0.3%)
Taste disorder, numbers (%)			
Negative	284 (83.8%)	37 (80.4%)	321 (83.4%)
Positive	55 (16.2%)	9 (19.6%)	64 (16.6%)
Smell disorder, numbers (%)			
Negative	297 (87.6%)	37 (80.4%)	334 (86.8%)
Positive	42 (12.4%)	9 (19.6%)	51 (13.2%)

IQR: interquartile range

Table 2. Univariable Regression Analysis Results.

Univariable analysis	Odds ratio	Standard error	Lower 95% CI	Higher 95% CI	p value
Runny nose	0.587	0.204	0.296	1.162	0.126
Sore throat	0.608	0.203	0.316	1.171	0.137
Taste disorder	0.796	0.318	0.364	1.743	0.569
Smell disorder	0.581	0.236	0.262	1.290	0.182
Age, years	1.032	0.010	1.013	1.051	0.001
Sex	5.022	3.698	1.186	21.264	0.028
Body mass index	1.109	0.043	1.028	1.196	0.007
While blood cells, 10^9/L	1.354	0.150	1.091	1.682	0.006
Creatinine, mg/dL	6.880	7.131	0.902	52.456	0.063
Charlson Comorbidity Index	1.115	0.181	0.811	1.531	0.503

CI: confidence interval

Table 3. Multivariable Regression Analysis Results.

	Odds ratio	Standard error	Lower 95% CI	Higher 95% CI	p value
Model 1					
Runny nose	0.725	0.283	0.337	1.559	0.410
Age, year	1.019	0.010	0.998	1.039	0.070
Sex	8.300	8.615	1.085	63.471	0.041
Body mass index	1.081	0.043	1.000	1.168	0.049
While blood cells, 10^9/L	1.235	0.143	0.983	1.550	0.070
Model 2					
Sore throat	0.700	0.261	0.337	1.456	0.340
Age, year	1.022	0.010	1.002	1.041	0.030
Sex	9.527	9.843	1.257	72.174	0.029
Body mass index	1.078	0.042	0.998	1.165	0.056
While blood cells, 10^9/L	1.236	0.142	0.986	1.550	0.066

CI: confidence interval

pressed in a range of tissues, such as nasal mucosa, bronchus, lung, stomach, heart, kidney, and ileum, these organs may be susceptible to infection by the virus (13, 15, 16). This is thought to explain the wide variety of COVID-19 symptoms, which include respiratory and cardiac symptoms as well as renal failure, diarrhea, and vomiting (13, 14). This range of symptoms is in contrast to the more localized symptoms typical of CAP, which may be why ENT symptoms have diagnostic value in CAP but not in COVID-19. Our results provide clinical evidence of the multiorgan effects of COVID-19 and underscore its dissimilarity with the viral pathogens of CAP.

We believe that our study's strengths allow for useful inferences, despite the limited number of cases included. As a patient cohort, we consecutively recruited all eligible patients. We chose the variables for the analysis based on clinical experience, and the outcomes of the univariable and multivariable analyses were in line with clinical practice. The sample size was determined following the EPV rule, considering the number of variables to be investigated (10). If the results of the multivariable analysis had shifted in the direction of significance for any ENT symptom variable, it could have suggested the possibility of finding a significant correlation in a future study with more participants. However, because the results of our multivariable analysis tended toward the null after adjustment, our findings do not suggest the likelihood of detecting a significant difference in the future. Conversely, on comparing the outcomes of univariable and multivariable regression, the odds ratios of variables other than ENT symptoms were generally consistent with clinical reports: elevated age, BMI and WBC odds ratios were all above 1.0. The mean odds ratios of ENT symptoms also matched clinical perspective, meaning that only an elevated age, BMI, and WBC count are potential indicators of pneumonia. Finally, our results are consistent with reports that physical examinations have decreased reliability in COVID-19 (17).

Several limitations associated with the present study warrant mention. First, it is a retrospective study, and many candidates were excluded due to a lack of chest imaging. Next, while we defined COVID-19 pneumonia as findings of abnormal lung infiltrates on CT in patients with confirmed SARS-CoV-2 infection, there is the possibility that some patients with bacterial pathogens were included. Furthermore, our participants' data did not include the vaccination status or SARS-CoV-2 variant information. The vaccination status and SARS-CoV-2 variant may have affected the result, so we wish we had had access to individual patients' SARS-CoV-2 variant information for further consideration.

Conclusion

The present study found no association between the absence of ENT symptoms, such as a runny nose and sore throat, and pneumonia among COVID-19 patients. Our study thus reinforces the importance of careful aggregation of a range of clinical symptoms for a COVID-19 pneumonia diagnosis.

The Japan Community Health-Care Organization Sapporo Hokushin Hospital ethics committee approved this research.

The authors state that they have no Conflict of Interest (COI).

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