Original Article

Sinonasal manifestations and dynamic profile of RT-PCR results for SARS-CoV-2 in COVID-19 patients

Xiaoqing Jia[1#], Shan Shao[2,3#], Hong Ren[4], Yuan Xu[5], Jinming Zhao[2], Yan Zhao[6], Yue Wang[2], Shiping Bao[3], Junping Yan[1], Xiangdong Wang[2,6], Luo Zhang[2,6]

[1]Department of Respiration, Third Hospital of Baotou City, Baotou, China; [2]Department of Otorhinolaryngology Head and Neck Surgery, Beijing Tongren Hospital, Key Laboratory of Otorhinolaryngology-Head & Neck Surgery Ministry of Education, Capital Medical University, Beijing, China; [3]Department of Otolaryngology Head and Neck Surgery, Beijing Youan Hospital, Capital Medical University, Beijing, China; [4]Department of Infection, Third Hospital of Baotou City, Baotou, China; [5]Departments of Oncology, Community Health Sciences, and Surgery, Cumming School of Medicine, and The Center for Health Informatics, University of Calgary, Calgary, Canada; [6]Beijing Institute of Otolaryngology, Beijing Key Laboratory of Nasal Diseases, Beijing, China

Contributions: (I) Conception and design: L Zhang, X Wang, S Shao, X Jia; (II) Administrative support: J Yan, Y Zhao, Y Wang, S Bao; (III) Provision of study materials or patients: X Jia, H Ren; (IV) Collection and assembly of data: X Jia, S Shao, H Ren; (V) Data analysis and interpretation: S Shao, X Wang, J Zhao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Luo Zhang, MD, PhD. Beijing Key Laboratory of Nasal Diseases, Beijing Institute of Otolaryngology, No. 17, Hougou Hutong, Dong Cheng District, Beijing 100005, China. Email: dr.luozhang@139.com; Xiangdong Wang, MD, PhD. Beijing Institute of Otolaryngology, No. 17, Hougou Hutong, Dong Cheng District, Beijing 100005, China. Email: entwxd@vip.sina.com; Junping Yan, MD, BS. Department of Respiration, Third Hospital of Baotou City, Kang-Fu Street, Donghe District, Baotou, Inner Mongolia, China. Email: btsyyyjp@163.com.

Background: Sinonasal symptoms were usually reported to appear initially, yielding the symptoms important for the early detection of coronavirus disease 2019 (COVID-19). This study was conducted retrospectively to investigate the detailed sinonasal manifestations and dynamic profile of real-time reverse transcription polymerase chain reaction (RT-PCR) results for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in COVID-19 patients longitudinally.

Methods: This retrospective study included 11 consecutive patients. The prevalence, timing and severity of sinonasal manifestations were analyzed. Oropharyngeal, nasal, sputum and stool specimens were collected to detect RT-PCR for SARS-CoV-2 over COVID-19 period.

Results: Among the 11 patients, 6 (54.5%) were female, and the median age was 51 (IQR, 36–62) years. Seven patients (63.6%) experienced sinonasal symptoms, with 6 (54.5%) exhibiting sinonasal symptoms on the onset day. Seven patients (63.6%) demonstrated nasal obstruction, 5 (45.5%) had rhinorrhea, and 4 (36.4%) exhibited olfactory dysfunction. All six patients with sinonasal symptoms on the onset day had non-severe infections. Most patients (85.7%) with sinonasal symptoms had non-severe infections. Sinonasal symptoms commonly appeared early. The positive RT-PCR rate for SARS-CoV-2 in various specimens was highest in the first week (73.3%), then gradually decreased over the disease course, but 3 patients (27.3%) had experienced a long-lasting fluctuated positive RT-PCR results since 29 days of illness in both groups, especially for two patients with airway comorbidities.

Conclusions: Sinonasal symptoms were more prevalent in patients with mild or moderate COVID-19 and usually appeared early. In addition, regular nucleic acid testing for SARS-CoV-2 should be considered for COVID-19 patients with certain airway comorbidities.

Keywords: Coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); sinonasal manifestations; dynamics profile; reverse transcription polymerase chain reaction (RT-PCR)

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Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first described in December 2019 in Wuhan, China (1-3). At present, the disease has rapidly spread to more than 200 counties across the world (4). Several studies have reported that COVID-19 can not only infect the lower respiratory tract with symptoms of fever, dry cough and dyspnea but also cause multiple systemic infections (5-10). In the literature, the rate of sinonasal symptoms among COVID-19 patients is highly inconsistent. Initial studies of COVID-19 reported a low prevalence of sinonasal symptoms, ranging from 4–8% (1,4,11). In contrast, other studies from Australia and America reported much higher prevalence of sinonasal symptoms among COVID-19 patients (12,13). Moreover, it has become apparent that some sinonasal symptoms appear early and may be considered a potential predictor of COVID-19 (14).

However, to our knowledge, the clinical manifestation of sinonasal symptoms in COVID-19 remains incompletely characterized. The aim of the present study was to characterize the prevalence, timing, and severity of sinonasal symptoms, as well as the dynamic profile of real-time reverse transcription polymerase chain reaction (RT-PCR) results for SARS-CoV-2, in a longitudinal fashion.

We present the following article in accordance with the MDAR checklist and the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-2493).

Methods

Patient population

This was a retrospective, observational study in which 11 consecutive patients with COVID-19 were recruited from January 22 to March 18, 2020 at Third Hospital of Baotou City (Inner Mongolia, China). All enrolled patients were confirmed to be diagnosed with COVID-19 according to China's "pneumonia diagnosis and treatment program of novel coronavirus infection (trial version 6)" (15). The next follow-up date was April 1,2020. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committees of Beijing Tongren Hospital and Third Hospital of Baotou City (No.: 2020-0413 and 2020-002, respectively) and informed consent was taken from all individual participants.

Data sources

The clinical symptoms and RT-PCR results for SARS-CoV-2 were extracted from electronic medical records. The diagnosis of a history of chronic rhinosinusitis (CRS) and allergic rhinitis (AR) were based on the current recommendations (16,17). Data on sinonasal symptoms included the start and end times of each symptom and worst symptom severity during COVID-19. Individual patient-assessed symptoms were assessed at their most severe level by a visual analog scale (VAS), which ranged from 0 (not troublesome) to 10 (worst thinkable), with total scores of 0 to 3 indicating the presence of mild symptoms, 3 to 7 indicating moderate symptoms, and 7 to 10 indicating severe symptoms (18). The diagnosis of sinonasal manifestations mainly depended on the subjective symptoms of the patients and the available examinations. Any missing or uncertain records were collected and clarified with the involved patients over the phone, on an online form or in the patient's room. According to China's "pneumonia diagnosis and treatment program of novel coronavirus infection (trial version 6)" (15), the severity of COVID-19 was divided into mild, moderate, severe and critical at its worst during the disease course. Mild disease of COVID-19 referred to mild clinical symptoms and no signs of pneumonia on imaging and moderate state referred to having fever, respiratory symptoms, and imaging showing pneumonia. For adults, severe state must meet any of the following: (I) shortness of breath occurred, respiratory rate was greater than or equal to 30 times/min; (II) at rest, the oxygen saturation was less than or equal to 93%; (III) arterial partial pressure of oxygen/inhaled oxygen concentration was less than or equal to 300 millimeters of mercury. Critical state of COVID-19 must meet any of the following: (I) respiratory failure occurred and required mechanical ventilation; (II) shock occurred; (III) combined with other organ failure, intensive care unit monitoring and treatment was required. The RT-PCR results of SARS-CoV-2 were collected and analyzed from the patients' nasal and oropharyngeal swabs, sputum,

and urine and stool specimens over time. The primers and probes of RT-PCR detection kit for specific detection of SARS-CoV-2 were selected from regions of Open Reading Frame 1ab (ORF1ab) and nucleocapsid (NP) gene of SARS-CoV-2 genome according to the manufacturer's protocol (Jiangsu Shuoshi Biotechnology Co., Ltd.). When two targets (ORF1ab, NP) tested positive by specific RT-PCR, the case would be considered to be laboratory confirmed. A cycle threshold value (Ct-value) less than 37 was defined as a positive test, and a Ct-value of 40 or more was defined as a negative test. A medium load, defined as a Ct-value of 37 to 40, required confirmation by retesting.

Statistical analysis

The SPSS statistical software (version 22.0) was used for all statistical analyses (SPSS, Inc., Chicago, IL, USA). Continuous variables are directly expressed as the mean, median and interquartile range (IQR) values. Comparisons of numerical variables between groups were conducted using the Mann-Whitney U test. Categorical variables are presented as frequencies (%) and were compared using the χ^2 test or Fisher's exact test between groups. All tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

Demographic and Epidemiologic characteristics of COVID-19 patients

A total of 11 hospitalized patients with confirmed SARS-CoV-2 infections were included in the analysis. Their demographic and clinical characteristics are shown in *Table 1*. Two family clusters are shown in *Figure 1*.

Prevalence, timing and severity of sinonasal symptoms in COVID-19 patients

At baseline, two patients who had accompanied with seasonal AR had no sinonasal symptoms. One patient who had a combined history of AR and CRS, had a stable mild self-reported sinonasal symptoms at baseline but the severity of sinonasal symptoms was aggravated during the period of COVID-19. The other patients had no sinonasal symptoms at baseline. In addition, none of them had a history of previous sinonasal surgeries prior to the onset of COVID-19.

The spectrum of the main symptoms is shown in *Figure 2*. Seven (63.6%) patients presented with sinonasal manifestations, and the most common sinonasal symptoms during the entire disease course were nasal obstruction [7 (63.6%)], rhinorrhea and olfactory dysfunction [5 (45.5%)]. Six patients (54.5%) presented sinonasal manifestations on the day of onset, and nasal obstruction [6 (54.5%)] was the most common symptom, followed by rhinorrhea [5 (45.5%)] and olfactory dysfunction [4 (36.4%)]. All six patients with sinonasal symptoms on the day of onset had non-severe infections, with mild infections in 66.7% of these patients and moderate infections in 33.3%. The majority of patients with any sinonasal symptoms mainly had non-severe infections, with mild infection in 57.1% of these patients, moderate infection in 28.6% and critical infection in 14.3%. The prevalence of isolated anosmia amongst the study population was 9.09%.

The timing of main symptoms of these patients is shown in *Figure 3*. Sinonasal symptoms including nasal obstruction, rhinorrhea and olfactory dysfunction, as well as cough and fever commonly appeared early, while other symptoms, such as phlegm, short of breath and sore throat, often appeared late. The median time from the onset of illness to nasal obstruction or olfactory dysfunction was 0 (IQR, 0–4) days. The patients with rhinorrhea presented this symptom on the day of onset. The four-week recovery rates from sinonasal symptoms were 85.7% for nasal obstruction, 80% for rhinorrhea and 66.7% for olfactory dysfunction. We further found that case #3, who had a history of AR and CRS, had a longer recovery time (over 40 days) from nasal obstruction, rhinorrhea and olfactory dysfunction. Notably, case #8, who experienced olfactory and subsequent gustatory dysfunction during COVID-19, still has not recovered to the pre-disease level and developed a distorted taste of certain flavors.

Figure 4 shows the worst reported severity of sinonasal symptoms during the course of COVID-19. All patients with nasal obstruction reported moderate severity, and 80% reported moderate rhinorrhea and a moderately decreased sense of smell. Twenty percent of patients who experienced rhinorrhea reported mild rhinorrhea, while 20% of patients who experienced olfactory dysfunction reported severe olfactory dysfunction.

Dynamic profile of SARS-CoV-2 detected by RT-PCR over the course of COVID-19

The total number of SARS-CoV-2 RT-PCR results for

Table 1 Demographic and clinical characteristics in COVID-19 patients with or without sinonasal symptoms

Characteristic	Total (N=11)	With sinonasal symptoms on the onset day (N=6)	Without sinonasal symptoms on the onset day (N=5)	P value*	With any† sinonasal symptoms (N=7)	Without any sinonasal symptoms (N=4)	P value**
Age, median (IQR), y	51 [36–62]	40 [21–53]	62 [54–66.5]	NA	44 [22–59]	59.5 [52.5–66.5]	NA
Female sex, No. (%)	6 (54.5)	4 (66.7)	2 (40.0)	0.567	4 (57.1)	2 (50.0)	1.000
Smoking history, No. (%)	2 (18.2)	1 (16.7)	1 (20.0)	1.000	2 (28.6)	0 (0.0)	NA
Comorbidities, No. (%)							
Allergic rhinitis	3 (27.3)	3 (50)	0 (0.0)	NA	3 (42.9)	0 (0.0)	NA
CRS	1 (9.1)	1 (16.7)	0 (0.0)	NA	1 (14.3)	0 (0.0)	NA
Atopic dermatitis	1 (9.1)	1 (16.7)	0 (0.0)	NA	1 (14.3)	0 (0.0)	NA
Drug hypersensitivity	1 (9.1)	1 (16.7)	0 (0.0)	NA	1 (14.3)	0 (0.0)	NA
Hypertension, No. (%)	5 (45.5)	2 (33.3)	3 (60.0)	0.567	2 (28.6)	3 (75.0)	0.242
Diabetes	2 (18.2)	0 (0.0)	2 (40.0)	NA	0 (0.0)	2 (50.0)	NA
Coronary heart disease	1 (9.1)	0 (0.0)	1 (20.0)	NA	0 (0.0)	1 (25.0)	NA
COPD	2 (18.2)	1 (16.7)	1 (20.0)	1.000	1 (14.3)	1 (25.0)	1.000
Disease severity, No. (%)				NA			NA
Mild	4 (36.4)	4 (66.7)	0 (0.0)		4 (57.1)	0 (0.0)	
Moderate	3 (27.3)	2 (33.3)	0 (0.0)		2 (28.6)	1 (25.0)	
Severe	1 (9.1)	0 (0.0)	1 (20.0)		0 (0.0)	1 (25.0)	
Critical	3 (27.3)	0 (0.0)	3 (60.0)		1 (14.3)	2 (50.0)	

†, any indicates having sinonasal symptoms at any time during the disease course; *, P values indicate differences between patients with sinonasal and without sinonasal symptoms at the onset day of COVID-19, and P values less than 0.05 were considered statistically significant; **, P values indicate differences between patients with any sinonasal symptoms and those without sinonasal symptoms during COVID-19, and P values less than 0.05 were considered statistically significant. CRS, chronic rhinosinusitis; COPD, chronic obstructive pulmonary disease; NA, not applicable; IQR, interquartile range.

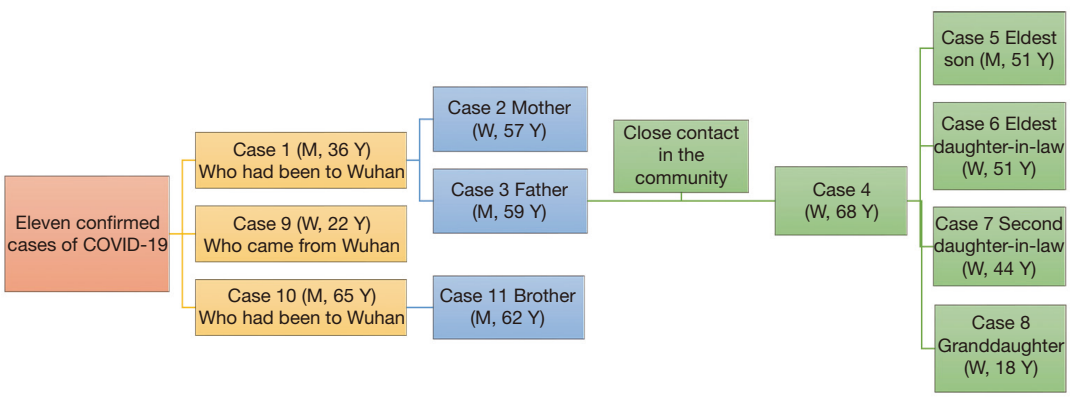

Figure 1 The epidemiologic characteristics of eleven COVID-19 patients in Baotou, Inner Mongolia, China. M, men; W, women; Y, year.

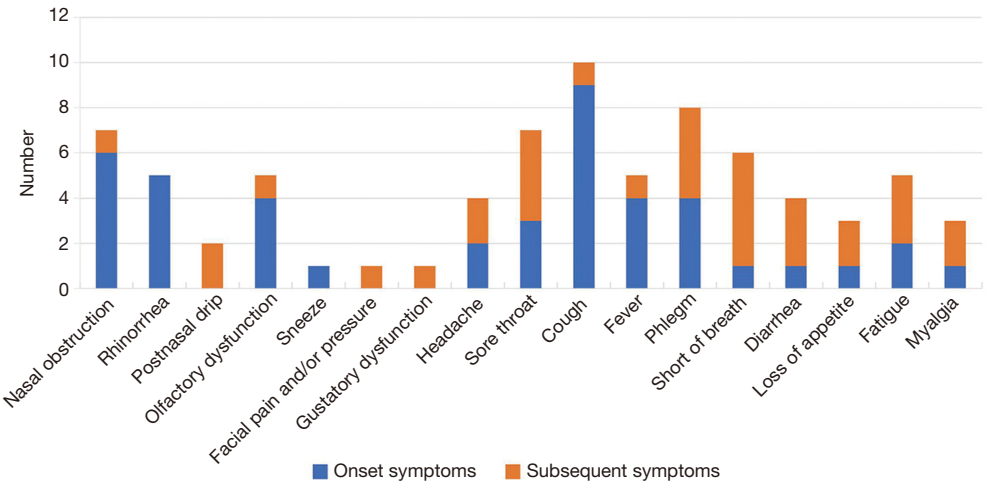

Figure 2 Distribution of onset times and subsequent symptoms in 11 patients with COVID-19.

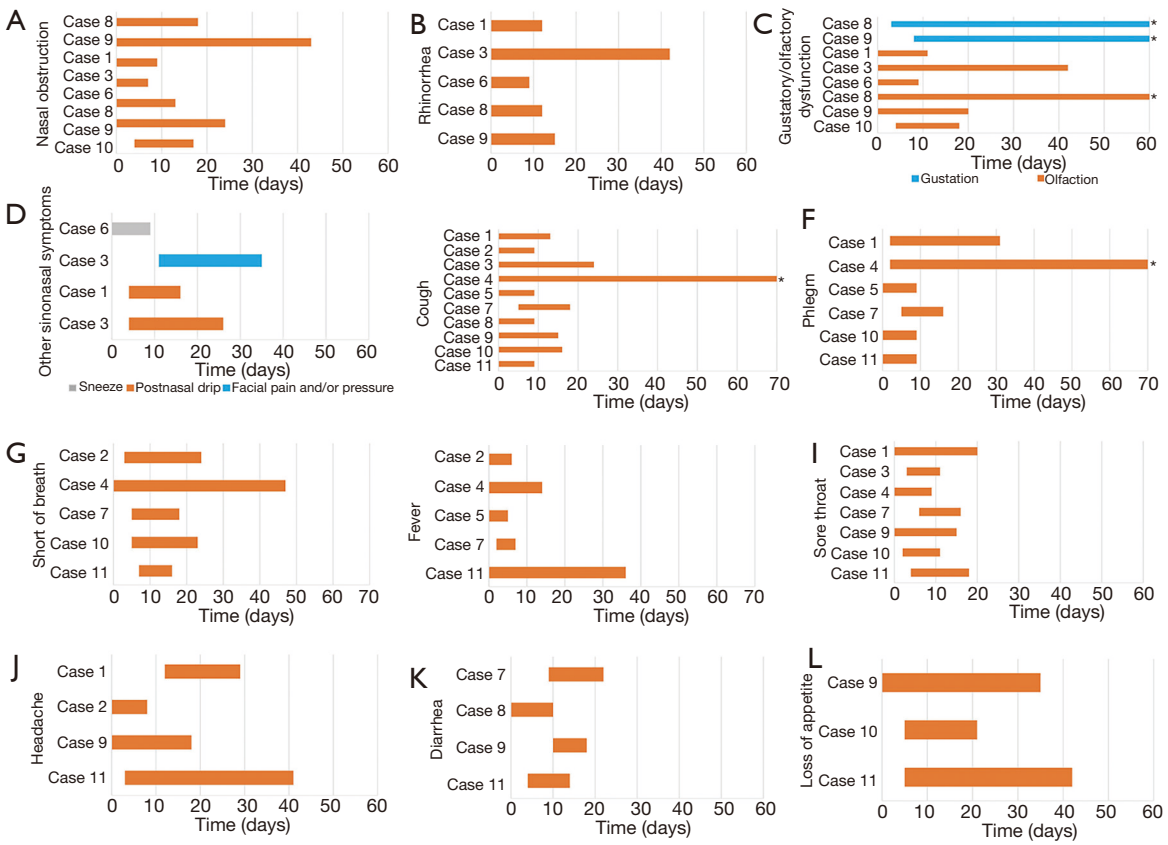

Figure 3 Timing profile of sinonasal symptoms in COVID-19 patients. (A) Timing profile of nasal obstruction; (B) timing profile of rhinorrhea; (C) timing profile of gustatory and olfactory dysfunction; (D) timing profile of other sinonasal symptoms; (E) timing profile of cough; (F) timing profile of phlegm; (G) timing profile of short of breath; (H) timing profile of fever; (I) timing profile of sore throat; (J) timing profile of headache; (K) timing profile of diarrhea; (L) timing profile of loss of appetite. * Indicates that the symptoms had not recovered to a pre-disease level as of the data collection deadline.

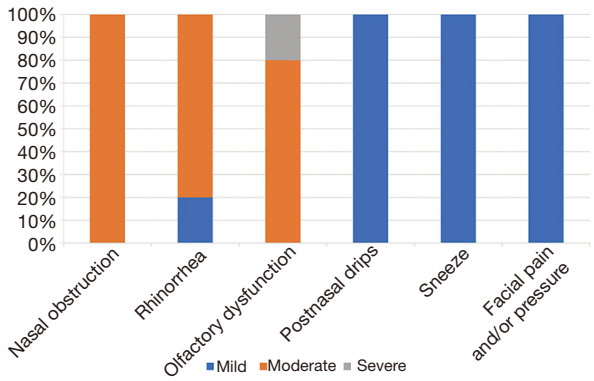

Figure 4 Self-reported severity rating of the main sinonasal symptoms in patients with COVID-19.

the 11 patients was 365 (average of 33 tests per patient). The RT-PCR results of urine samples were all negative during the course of COVID-19. The RT-PCR results of the various biological samples from the 11 patients over a seven-week period, starting from the onset of symptoms, are presented in *Table 2*. Because the patients without any sinonasal symptoms were transferred to the intensive care unit in another hospital for further treatment, some RT-PCR results for SARS-CoV-2 were not available. The overall rate of positive RT-PCR results from all specimens during the entire period was highest in the first week [11/15 (73.3%)] and then gradually decreased over time. However, 3 patients (27.3%) had experienced a long-lasting fluctuated positive RT-PCR results since 29 d.a.o in both groups, especially for the two patients with airway comorbidities (case #4 had a comorbidity of COPD and case #3 had a combined history of AR, CRS and dermatitis).

Compared to patients without sinonasal symptoms, patients with sinonasal symptoms presented a higher rate of positive RT-PCR results from all specimens collected 15–21 d.a.o (25% *vs.* 10%, P<0.001). However, the rate of positive RT-PCR results from all specimens collected 29–56 d.a.o. was lower in patients with sinonasal symptoms than in patients without sinonasal symptoms.

The current guidelines suggest that two consecutive negative RT-PCR test results are a criterion for discharge. According to the local policy, all patients meeting the discharge criteria were discharged and then transferred to another isolation ward in the same hospital for centralized isolation until two consecutive RT-PCR tests were negative every 2 weeks after discharge. Regarding the fluctuating positive RT-PCR results from sputum samples, case #4 was still in the hospital for further management as of our data collection deadline.

Discussion

According to the local anti-epidemic policy in Inner Mongolia, all patients should receive necessary follow-up in a centralized isolation department. Therefore, we had sufficient time to understand the dynamic changes of these patients in a longitudinal manner. To the best of our knowledge, this is the first report to detail the sinonasal manifestations and dynamic RT-PCR changes of SARS-CoV-2 in patients with COVID-19.

In our study, we found that sinonasal symptoms attributed to COVID-19 were more than 50%, which is in contrast to the findings of a previous study conducted in China (1,5,11). However, the reported prevalence of sinonasal symptoms was higher in Australia, USA and Europe, ranging from 30–50% (11,13,19,20). We analyzed the different prevalences of sinonasal symptoms, which may be partly attributed to the different disease statuses of COVID-19 patients, different levels of attention paid to nonspecific sinonasal complaints by patients and physicians, the diversity of angiotensin-converting enzyme 2 (ACE2) expression patterns, mutations of the virus, the differences in affinity of some viruses to certain tissues and individuals and environmental or seasonal factors (19,21,22). Another finding was that patients with sinonasal symptoms were more likely to have mild or moderate disease than patients without sinonasal symptoms. Sinonasal symptoms of COVID-19 may be related to disease severity. However, this hypothesis needs further investigation. Of note, case #4 in our study presented with isolated sinonasal symptoms, without any other symptoms during the course of COVID-19, suggesting that some individuals could be hidden carriers of SARS-CoV-2, as they do not meet the current criteria for a diagnosis of COVID-19; this may support the role of otolaryngologists as first-line physicians for some COVID-19 patients.

We then explored the timing profile of sinonasal symptoms attributed to COVID-19. We found that the majority of sinonasal symptoms appeared early, which was consistent with a previous study (14). In addition, patients had a relatively poor recovery rate from olfactory and gustatory dysfunction. Hence, sinonasal symptoms may appear early and should be cared for by physicians and patients, making the symptoms important for the early

Table 2 Dynamic profiles of qRT-PCR for SARS-CoV-2 in COVID-19 patients with and without overall sinonasal symptoms

Positive rate (n/N, %)	Total	With any† sinonasal symptoms	Without any sinonasal symptoms	P value*
0–7 d.a.o	11/15 (73.3)	7/8 (87.5)	4/7 (57.1)	0.282
Throat	9/11 (81.8)	6/6 (100.0)	3/5 (60.0)	0.182
Nasal	NA	NA	NA	NA
Sputum	1/2 (50.0)	0/1 (0)	1/1 (100.0)	NA
Stool	1/2 (50.0)	1/1 (100.0)	0/1 (0)	NA
8–14 d.a.o	7/14 (50.0)	6/10 (60.0)	1/4 (25.0)	1.000
Throat	3/6 (50.0)	2/4 (50.0)	1/2 (50.0)	1.000
Nasal	0/2 (0)	0/1 (0)	0/1 (0)	NA
Sputum	0/1 (0)	0/1 (0)	NA	NA
Stool	4/5 (80.0)	4/4 (100.0)	0/1 (0)	NA
15–21 d.a.o	9/42 (21.4)	8/32 (25.0)	1/10 (10.0)	<0.001
Throat	3/13 (23.1)	3/10 (30.0)	0/3 (0)	0.528
Nasal	2/9 (22.2)	2/7 (28.6)	0/2 (0)	1.000
Sputum	1/8 (12.5)	1/6 (16.7)	0/2 (0)	NA
Stool	3/12 (25.0)	2/9 (22.2)	1/3 (33.3)	0.250
22–28 d.a.o	6/31 (19.4)	6/31 (19.4)	NA	NA
Throat	1/8 (12.5)	1/8 (12.5)	NA	NA
Nasal	0/8 (0)	0/8 (0)	NA	NA
Sputum	2/6 (33.3)	2/6 (33.3)	NA	NA
Stool	3/9 (33.3)	3/9 (33.3)	NA	NA
29–42 d.a.o	16/108 (14.8)	8/69 (11.6)	8/39 (20.5)	<0.001
Throat	1/28 (3.6)	0/18 (0)	1/10 (10.0)	0.357
Nasal	4/27 (14.8)	3/18 (16.7)	1/9 (11.1)	1.000
Sputum	5/24 (20.8)	2/14 (14.3)	3/10 (30.0)	NA
Stool	6/29 (20.7)	3/19 (15.8)	3/10 (30.0)	NA
43–56 d.a.o	11/105 (10.5)	4/68 (5.9)	7/37 (18.9)	<0.001
Throat	2/27 (7.4)	0/17 (0)	2/10 (20.0)	0.128
Nasal	6/28 (21.4)	3/19 (15.8)	3/9 (33.3)	0.352
Sputum	3/25 (12.0)	1/16 (6.3)	2/9 (22.2)	NA
Stool	0/25 (0)	0/16 (0)	0/9 (0)	NA
≥57 d.a.o	2/43 (4.7)	0/29 (0)	2/14 (14.3)	NA
Throat	0/13 (0)	0/9 (0)	0/4 (0)	NA
Nasal	0/9 (0)	0/6 (0)	0/3 (0)	NA
Sputum	2/12 (16.7)	0/7 (0)	2/5 (40.0)	NA
Stool	0/9 (0)	0/7 (0)	0/2 (0)	NA

†, any indicated having sinonasal symptoms at any time during the disease course; *, P values indicate differences between patients with any sinonasal symptoms and those without sinonasal symptoms during COVID-19, and P values less than 0.05 were considered statistically significant. D.a.o, days after onset; NA, not applicable.

detection of this disease, and some sinonasal symptoms may be long lasting, causing symptoms that require aggressive treatment.

We also analyzed the dynamic profile of RT-PCR results for SARS-CoV-2 in various biological specimens over the course of COVID-19. Our study confirmed the findings of prior studies that the rate of positive RT-PCR results in all specimens is highest in the first week (23). Patients with sinonasal symptoms seemed to have a relatively different rate of positive RT-PCR results for SARS-CoV-2 in all specimens over the course of testing, but this needs further study. Only 2 patients (18.2%) showed at least one positive result for SARS-CoV-2 in nasal specimens, and this rate seemed unrelated to the occurrence of sinonasal symptoms. The positive rate of patients with sinonasal symptoms who exhibiting at least one positive result for nasal specimens was lower than that of patients without sinonasal symptoms (14.3% *vs.* 25%). Additionally, patients with underlying airway comorbidities seemingly presented with prolonged corresponding symptoms and had long-lasting positive RT-PCR results for SARS-CoV-2. However, these hypotheses still need further investigation in a larger population. The "re-positive" nucleic acid tests after discharge were attributed to intermittent virus excretion, an insufficient drug treatment regimen and false-negative RT-PCR test results due to differences in the sources of the collected samples, the method of sample collection, antiviral drugs or hormones administered, sample transportation, test methods and sensitivity of nucleic acid test kits (24-26). Although traces of SARS-CoV-2 detected by RT-PCR were not necessarily correlated with the ability of transmission, a longer observation period should be considered for certain groups of COVID-19 patients (25,27,28).

The results of our study should be interpreted within the constraints of its limitations. This study is limited by the small sample size and retrospective method. We also acknowledge that our study design relied heavily on adequate patient recall and reports. However, previous studies of recall bias suggest that the recall of disease-specific symptoms, in particular those related to noteworthy events (such as COVID-19), is generally reliable, particularly for short periods. In addition, we should improve the accuracy of the detection protocol, master the sampling method and regularly collect various biological specimens within the same period. Further research is required to investigate the relationship of RT-PCR results and symptom onset and overall symptoms on a large scale. Therefore, a prospective study with strict inclusion criteria and more clinicopathological measurements on a large scale are needed to validate these findings.

In conclusion, since COVID-19 is new and the pathogenesis is much complicated, as of yet, there remain more questions than answers. In our study, sinonasal symptoms were more prevalent in patients with mild or moderate COVID-19 and usually appeared at the beginning of the disease course. The rate of patients who presented positive RT-PCR results for SARS-CoV-2 in nasal specimens seemed unrelated to the incidence of sinonasal symptoms. Regular nucleic acid testing for SARS-CoV-2 should be considered for COVID-19 patients with certain airway comorbidities.

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Footnote

Reporting Checklist: The authors have completed the MDAR checklist and the STROBE checklist. Available at http://dx.doi.org/10.21037/apm-20-2493

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-20-2493

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2493). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committees of Beijing Tongren Hospital and Third Hospital of Baotou City (No.: 2020-0413 and 2020-002,

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