RESEARCH ARTICLE

The clinical course of smell and taste loss in COVID-19 hospitalized patients

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Abstract

Background: Recent studies have demonstrated an association between a new onset of smell or taste loss and COVID-19. We investigated the prevalence of smell and/or taste loss and the clinical characteristics and recovery in a comprehensive cohort of consecutive patients treated by two COVID-19 reference hospitals and evaluated late persistence of hyposmia.

Methods: A retrospective observational questionnaire study was conducted. All consecutive RT-PCR diagnosed patients who had been hospitalized in March-April 2020 in the COVID-19 care wards were contacted, excluding patients with cognitive disorders and severe deconditioning. The patients responded to a survey about the loss of smell and taste, nasal blockage, and rhinorrhea, rated the symptoms' severity from 0 to 4, and reported the recovery of smell and taste with time. Demographic and clinical characteristics were recorded.

Results: We contacted 117 patients. Ninety responded to the questionnaire; 38.9 % of them reported olfactory and 36.66 % gustatory disorders during their disease. Smell loss prior to other symptoms was reported by 42.86 %, and severe hyposmia/anosmia by 74.28 % of the hyposmic. Among the non-ICU treated patients, 43.75 % reported hyposmia. Only 8.89 % had nasal blockage, and 6.66 % rhinorrhea. Most of the patients (85.71 %) recovered their sense of smell in 3-61 days (median: 17; IQR: 24), but 8.57 % had persistent hyposmia. For one out of four, the olfactory loss lasted longer than a month.

Conclusion: Smell and taste loss are highly prevalent and early symptoms in hospitalized COVID-19 patients. The great majority recover their smell, but nearly one out of ten have not recovered in two months. HIPPOKRATIA 2020, 24(2): 66-71.

Keywords: Olfactory dysfunction, COVID-19, loss of smell, anosmia, loss of taste, post-viral

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Introduction

Since the coronavirus disease 2019 (COVID-19) pandemic outbreak, many studies demonstrated an association between a new onset of smell or taste loss and COVID-19[1-3]. The World Health Organization has included the loss of smell or taste as a symptom of COVID-19. Many researchers have suggested that sudden anosmia is a potential screening symptom that might contribute to the decision to test suspected cases or guide quarantine instructions. The reported prevalence of sudden loss of smell in patients positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2+)[1-5] ranges from 5.1 % to 85.6 %. Such a wide range of reported prevalence rates does not allow estimation of the value of anosmia as a screening symptom and dictates the need for studies with standardized patient recruitment that validates their results. Several studies reported a lower prevalence of anosmia in moderate/severe cases of COVID-19 compared to asymptomatic SARS-CoV-2+ patients and mild cases[6]. Initial reports vary regarding the duration of acute loss of smell or taste in COVID-19 patients[7-10], and this may be partly due to different study methods and time periods that the patients were evaluated. Another important finding of the first studies is that, although olfactory dysfunction could occur at any time during the infection, anosmia was the first symptom in a significant proportion of the patients[2,7,11]. Our study aimed to investigate the prevalence of smell and/or taste loss, the clinical characteristics and resolution of symptoms in a comprehensive cohort of consecutive patients treated by two COVID-19 reference hospitals and evaluate late persistence of olfactory loss.

Methods

The institutional review board of two COVID-19-Reference University Hospitals in Northern Greece approved the study (Scientific Board of AHEPA University Hospital, Thessaloniki, decision: SB10/347/8.5.2020, Scientific Board of University Hospital of Alexandroupolis, decision: SB8/9/18065/12.06.2020/25 .06.2020). The study was performed in accordance with the ethical standards of the institutional review boards and with the 1964 Helsinki declaration and its later amendments. All patients had been diagnosed via a reverse transcription-polymerase chain reaction (RT-PCR). All consecutive SARS-CoV-2+ patients who had been hospitalized in March and April 2020 in the COVID-19 care wards were contacted with telephone calls. All participants provided verbal consent during the interviews. Three call attempts were made. Patients who were not reachable or reported that they did not recall the relevant period events were excluded. Cognitive disorders and olfactory or/and gustatory disorders before COVID-19 were also exclusion criteria. We did not collect data for the deceased patients.

Study Design

A retrospective observational telephone survey study was conducted on hospitalized patients diagnosed with COVID-19. The survey was answered once by the patients. The patients were telephoned and asked to complete a survey related to taste and smell impairment. The survey included four questions: "During your COVID-19 illness: 1. Did you experience loss/impairment of smell? 2. Did you experience loss/impairment of taste? 3. Did you experience nasal congestion/obstruction? 4. Did you experience rhinorrhea?" The patients were asked to rate every symptom's severity on a Likert scale from 0 to 4. They were also asked to answer the following questions: "When did you first notice the loss of smell?" (Before diagnosis - At the same time with other symptoms - After diagnosis). "Did the loss/impairment of smell resolve, and when?" The survey also included the questions: "Are you smoking?" (Yes - No - Ex-smoker - Electronic). "Do you have a history of allergic rhinitis?" "Do you have a history of chronic rhinosinusitis?" Demographic characteristics (sex and age) and comorbidities were recorded from the medical records.

Statistical analysis

Descriptive analysis was applied to demographic and clinical characteristics. For continuous variables, mean values and standard deviation or median and interquartile range (IQR), and for categorical variables, counts and percentages are presented. All variables were checked for normality (Kolmogorov-Smirnov). Non-parametric tests were used where appropriate for comparisons. Relative frequencies of smell and taste loss between groups were compared with the chi-squared test and hyposmia duration with the Mann-Whitney U test. The threshold for statistical significance was set at $p < 0.05$. The IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses.

Results

We contacted 117 patients. Four patients declined to participate, 23 were not reachable, and 90 responded to the questionnaire. One patient had a history of hyposmia. All patients were Caucasian, and 53 (58.9 %) were men. The patients' age ranged from 19 to 89 years (mean: 55.8 ± 17.3). The median time from the disease onset to the patient's interview for the survey was 61 days (IQR: 7). The patients' demographic and clinical characteristics are presented in Table 1.

Thirty-five patients (38.9 %) reported experiencing loss of smell during their disease, 74.28 % of whom (26/35) reported severe hyposmia/anosmia. Fifteen out of 35 patients with hyposmia (42.86 %) experienced smell loss prior to and 11 (31.43 %) after other COVID-19 symptoms/diagnosis. Excluding intensive care unit (ICU) treated patients (n =10), none of whom reported hyposmia, 43.75 % of the patients reported a loss of smell. Thirty-three patients (36.66 %) reported experiencing taste loss, which was severe for 69.7 %. Thirty patients (33.33 %) reported olfactory and gustatory disorders, five patients reported isolated smell loss, and three isolated taste loss. Only eight patients (8.89 %) had nasal blockage, which was mild/moderate, and six (6.66 %) had moderate rhinorrhea.

Most patients (30/35; 85.71 %) recovered their sense of smell in 3-61 days. Two patients did not report recovery time. Three (8.57 %) had persistent hyposmia. Median recovery time was 17 days (IQR: 24), [mean: 18.27 ± 12.83]. In two weeks, 40 % of the patients had olfactory recovery and in a month, 74.29 %. Olfactory recovery time is presented in Figure 1. Comparing percentages of smell loss, taste loss, and hyposmia duration time between groups of varying disease severity (moderate, severe, critical)[12], and sexes showed no statistically significant differences (Table 2). We did not perform a subgroup analysis for smoking, allergy, and chronic rhinosinusitis because the numbers were small. The subgroup of patients who developed smell loss included four smokers (4/35; 11.42 %), and the group without chemosensory loss included seven smokers (7/55; 12.73%). Seven patients reported a history of allergic rhinitis (five among the subgroup of patients who developed smell loss and two among the patients without chemosensory loss). The five patients with a history of allergic rhinitis reported hyposmia resolution in a period ranging from five to 33 days. Only three patients reported a history of chronic rhinosinusitis (one of them developed smell loss).

Discussion

Our study investigated hospitalized patients, representative of the general affected population in our country, according to the reported statistics by the National Public Health Organization[13]. This was a comprehensive cohort of consecutive patients treated in two COVID-19

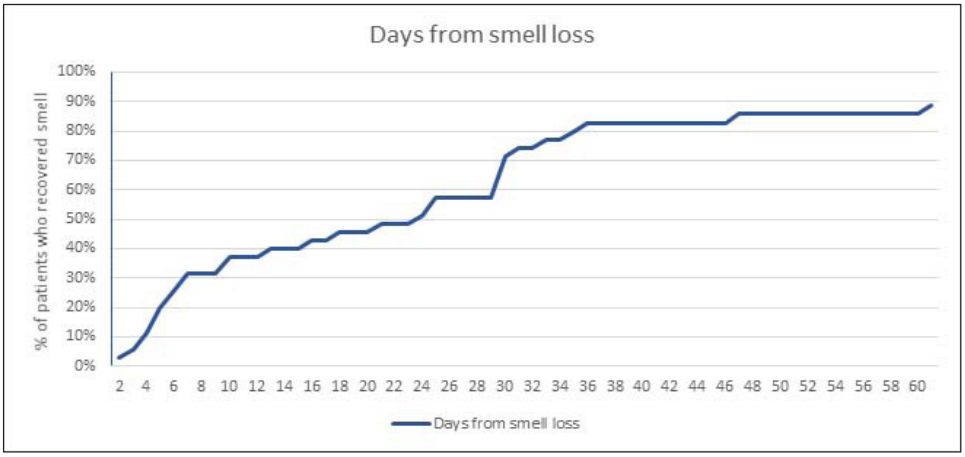

Figure 1: Line graph showing the percentage of olfactory recovery over time regarding a cohort of 90 consecutive patients hospitalized for confirmed COVID-19 during March-April 2020 in two reference hospitals in Northern Greece.

Table 1: Demographic and clinical characteristics of the 90 patients hospitalized for confirmed COVID-19.

	Patients n =90
Age (years)	
≤39	19 (21.11)
40-49	12 (13.33)
50-59	22 (24.44)
60-69	14 (15.55)
70-79	13 (14.44)
≥80	10 (11.11)
Sex	
Male	53 (58.9)
Female	37 (41.1)
Smoking	
Yes	11 (12.22)
No	66 (73.33)
Previously	11 (12.22)
Electronic	2 (2.22)
Allergic rhinitis	7 (7.77)
Chronic rhinosinusitis	3 (3.33)
Comorbidities	
No medical history	38 (42.22)
Hypertension	25 (27.77)
Diabetes	12 (13.33)
Dyslipidemia	3 (3.33)
Obesity	3 (3.33)
Hypothyroidism	3 (3.33)
Olfactory dysfunction	35 (38.88)
Gustatory dysfunction	33 (36.66)
Olfactory and gustatory dysfunction	30 (33.33)
Onset of hyposmia	
Before other symptoms	15 (42.86)
After other symptoms	11 (31.43)
Nasal blockage	8 (8.89)
Rhinorrhea	6 (6.66)
Covid-19 severity	
Mild-Moderate	45 (50)
Severe	35 (38.88)
ICU-treated	10 (11.11)

Values are given as number of patients and percentage in brackets, ICU: intensive care unit

reference hospitals. The reported sudden olfactory loss was 38.9 %. The vast majority of the patients reported loss of both smell and taste, and small percentages reported only loss of smell or taste. Nasal blockage and rhinorrhea affected less than one in ten. Our results are in agreement with most other cross-sectional and case-controlled studies reporting anosmia prevalence at 31-55 %[14-16]. The discrepancies in the reported prevalence in some studies could be due to varying study methods and possible patient selection bias[2]. The first observational study from China found that only 5.1 % of the patients suffered smell and taste loss[4], and a study of a big cohort of European patients reported anosmia prevalence at 85.6 %[7]. The possibility of different disease phenotypes in different populations has been discussed, but other explanations are also possible. The case series study in China was conducted when COVID-19 was a newly recognized disease, and the local health system was struggling to provide care for the seriously ill. Some underreporting of hyposmia can be anticipated under the circumstances. All subsequent studies reporting on Asian populations rated hyposmia between 22.7 % and 32 %[10,17,18]. In the study by Lechien et al[7], participants' recruitment method is not described, and it is possible that, due to mass press coverage of COVID-19-related anosmia and big numbers of affected health personnel, the cohort has not been representative of the general COVID-19 patients' population. Interestingly, the two biggest studies, an epidemiological study in Iceland[19] (1,044 patients) and a prospective study of 3,191 patients in South Korea[8], reported anosmia's prevalence to be 11.5 % and 15.3 %, respectively. The five meta-analyses on COVID-19 related smell loss published to date report the estimated prevalence of olfactory dysfunction from 41 % to 61 % and the estimated prevalence of taste dysfunction from 38.2 % to 49 %. A meta-analysis of 104 studies by von Bartheld et al[20] (38,198 patients) examined ethnicity and found it a significant variable. Caucasians had an estimated prevalence of chemosensory dysfunctions at 54.8 % and Asians at

Table 2: Comparison of smell loss, taste loss, and hyposmia duration between groups of varying disease severity, and sexes (for total 80 patients excluding ten ICU-treated patients).

	Smell loss	p[a]	Taste loss	p[a]	Hyposmia duration	p[b]
Disease severity						
Severe (n =35)	17 (48.6)	0.443	15 (42.)	0.797	24 (44)	0.053
Mild-Moderate (n =45)	18 (40)		18 (40)		7 (20)	
Sex						
Male (n =45)	18 (40)	0.443	17 (37.8)	0.474	17 (20)	0.485
Female (n =35)	17 (48.6)		16 (45.7)		7 (26)	

For smell and taste loss, values are given as number of patients and percentage in brackets, and for hyposmia duration (days) as median and interquartile range in brackets, ICU: intensive care unit n: number of patients; statistical test used, [a]: chi-squared test, [b]: Mann-Whitney U test. ICU-treated participants were not in essence representative of all ICU-admitted patients: we present comparison of mild-moderate to severe disease. Comparison of mild-moderate/severe/critical disease groups also not statistically significant.

17.7 %. A wide range of reported prevalence was noted in studies performed in all different geographical areas (Continent and country with most published studies): Asia: 5.1-66.7 % (China: 5.1-66.7 %); America: 6-81.9 % (USA: 6-67.5 %); Europe: 3.2-85.6 % (Germany: 19-74 %). These variations indicate that methodological issues are to be taken into account, and certainly not all studies reporting on COVID-19 related anosmia have been designed to measure the prevalence in the COVID-19 affected population.

No statistically significant difference in the prevalence of olfactory and gustatory disorders was noted between moderate and severe disease in hospitalized patients. Previous studies indicated a greater prevalence in outpatients compared to severe COVID-19[6]. It has been postulated that anosmia may be a biomarker of the magnitude of the host's response to SARS-CoV-2 infection[6]. Initial magnetic resonance imaging (MRI) findings demonstrated highly localized inflammation of the olfactory cleft[21], and recently, olfactory cleft mucosal thickening was observed in nearly one in four hospitalized COVID-19 patients who had a head computed tomography scan[22]. Bilateral transient olfactory bulbs edema[23] and MRI findings compatible with viral brain invasion in a cortical region associated with olfaction[24] have also been reported in Covid-19-related anosmia. Given that very little is known about the nervous system involvement, anosmia may indeed be a biomarker of the magnitude of the response to infection or/and patients with severe COVID-19 may be influenced by the presence of more severe symptoms such as respiratory distress and show decreased awareness of chemosensory dysfunction. Interestingly none among a small cohort of ICU-treated patients analyzed in our study reported olfactory or gustatory disorders. We need, though, to acknowledge that the non-ICU-treated patients were representative of all consecutive patients treated in COVID-19 wards. On the contrary, among the patients needing ICU admission, about half did not survive, and a significant proportion of the survivors were excluded from the study because they were still suffering from serious deconditioning at the time of the study. Therefore, the ICU-treated participants were not, in essence, representative of all ICU-admitted patients.

During an ongoing pandemic, it is an important finding that many patients (43 %) experienced olfactory or gustatory dysfunction before other symptoms. Anosmia has been reported as an initial symptom at rates ranging from 4.5 % to 35.5 % and as the only symptom from 3 % to 8.6 %[2,25]. The interpretation of these findings should take into account the time that the studies were conducted, whether anosmia was a recognized COVID-19 symptom at that time, and the population studied (hospitalized patients, symptomatic cases, or SARS-CoV-2+ persons tested as asymptomatic contacts). The most interesting finding regarding the early onset of anosmia is that it was found to show a high specificity for detecting COVID-19 infection as a screening symptom[16,25,26].

The clinical course of COVID-19-related olfactory and gustatory loss is characterized by a quick recovery in the majority of patients. Most of our patients (85.71 %) recovered in 3-61 days, and 74.29 % had recovered within 31 days. However, the reported recovery time (median: 17 days) was not as short as reported in previous studies. Lee et al[8] reported a median recovery time of 7 days. Lechien et al[7] reported the short-term recovery to be 44 %, and 72.6 % of these patients recovered olfactory function within the first eight days. Beltrán-Corbellini et al[16] reported the mean duration of olfactory and gustatory disorders to be 7.5 days. Meini et al reported a complete and near-complete recovery in 83 % of the studied patients within a month from the hospital discharge[9]. A recent Brazilian study demonstrated that COVID-19-related hyposmia had a lower rate of full recovery and a longer duration (52.6 % recovery; median: 15 days) than hyposmia in COVID-19-negative patients (70.3 % recovery; median: 10 days) in a group of patients with a median follow-up 31 days (IQR: 10.5-39)[27]. Our study demonstrated that 8.57 % of the patients had persistent hyposmia.

Our study's strength is the inclusion of a comprehensive cohort of consecutive patients treated for confirmed COVID-19 during a given period by two reference hospitals, therefore limiting patient selection bias related to age, residence, health-care profession, and information about smell loss. Another strength is that our study evaluated

the olfactory and gustatory recovery in 61 days. There are limited published data on the short- and medium-term recovery of post-viral sudden olfactory dysfunction.

A limitation of our study is that the olfactory and gustatory dysfunction were not documented with olfactory and gustatory tests. Self-reporting was appropriate given the retrospective observational type of our study. Patients remaining hyposmic were invited to get standard olfactory testing and consultation. Olfactory questionnaires have been shown to be less reliable in comparison to objective tests. When smell was objectively tested and compared with the patients' reporting of subjective impressions, the percentage of subjects with dysfunction increased in most studies. However, the research on COVID-19 related hyposmia relies a lot on questionnaires due to the pandemic restrictions and the hyposmia's short duration. The largest meta-analysis that examined COVID-19 patient-reported hyposmia and olfactory testing measured an estimated prevalence of 68.7 % of hyposmic patients on objective testing versus 43.9 % on self-reporting[20]. The only prospective controlled published trial that objectively assessed with validated psychophysical tests the patients' complaints of smell and taste loss[28] reported a subjective loss in smell in 61 % of COVID-19 patients and a positive test for hyposmia in 54 %. Another limitation of the study is that reports about the onset and clinical course of olfactory and gustatory dysfunction are subjected to recall bias. Out of 104 studies included in the largest meta-analysis published to date, the majority are cross-sectional, retrospective observational studies, and therefore, recall bias may be present[20]. It has to be considered that in all these studies, data were collected during an unprecedented pandemic that disrupted the functioning of health systems and social life, and the most appropriate methods of data collection were applied, balancing recruitment bias, recall bias, and the research questions[20]. Recall has been shown to be good for distinctive disease symptoms over not-long time intervals[29]. Smell loss is a very distinct symptom, and the majority of our patients reported anosmia or severe hyposmia (26/35, 74.28 %). Intervening health events, reference to a calendar, and asking the patients to recall events at a certain order can improve recall[29]. During the pandemic, being hospitalized for COVID-19 is a cardinal health event. With all the uncertainty regarding knowledge about COVID-19 and the anxiety of whether the mild disease will turn to more severe or claim the patient's life, a reference to a calendar of events is strong, and a timeline exists regarding the disease resolution for hospitalized patients. Recall reliability can increase by using precise language, confirming that the patient is not psychologically or physically impaired, and ensuring that the patient has a clear sense of the time frame in question. Our study followed these recommendations. We developed a short survey appropriate for telephone use, asking with simple everyday language about smell and taste loss. Furthermore, we excluded from this study patients under rehabilitation for serious deconditioning after ICU discharge due to reports about long-standing serious deconditioning following critical care for COVID-19 and data unavailability regarding the appropriate time for acquiring reliable patient self-reports. We used an appropriate set of questions because we considered that the use of validated nasal questionnaires had several limitations during the pandemic since the quarantine, the social and psychological impact of the pandemic, and COVID-19 itself were deemed too strong influences to allow for valid estimates of the impact of anosmia to be accurately made via the questionnaires that include items not applicable to hospitalized COVID-19 patients.

Conclusions

Smell and taste loss are highly prevalent, and early symptoms in hospitalized COVID-19 patients. Although many patients recover quickly, for one out of four, the olfactory and gustatory loss lasts longer than a month, and nearly one out of ten have not recovered in two months.

Conflict of interest

The authors declare that there is no conflict of interest related to this paper.

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