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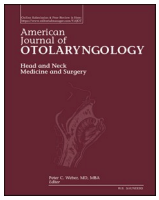

Predictors of smell recovery in a nationwide prospective cohort of patients with COVID-19

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ABSTRACT

Objective: To determine which factors (demographic, symptoms, comorbidities, and treatments) are associated with recovery of smell in patients with COVID-19 associated olfactory loss.
Study design: Prospective, longitudinal questionnaires.
Setting: National survey.
Methods: A longitudinal web-based nationwide survey of adults with COVID-19 associated smell and taste loss was launched April 10, 2020. After completing an initial entry survey, participants received detailed follow-up questionnaires 14 days, and 1, 3 and 6 months later.
Results: As of June 25, 2021, 798 participants met study inclusion criteria and completed 6-month questionnaires. Of demographic characteristics only age <40 years was positively associated with smell recovery ($p < .003$). Of symptoms, difficulty breathing was negatively associated with smell recovery ($p < .004$), and nasal congestion positively associated with smell recovery ($p < .03$). Of pre-existing comorbidities only previous head injury ($p < .017$) was negatively associated with smell recovery. None of the queried medications used to treat COVID were associated with better rates of smell recovery.
Conclusions: Age <40 and presence of nasal congestion at time of COVID-19 infection were predictive of improved rates of smell recovery, while difficulty breathing at time of COVID-19 infection, and prior head trauma predicted worsened rates of recovery. Further study will be required to identify potential mechanisms for the other observed associations. Such information can be used by clinicians to counsel patients suffering COVID-19 associated smell loss as to prognosis for recovery.

1. Introduction

The coronavirus pandemic (COVID-19) continues to ravage the world. At the writing of this manuscript, roughly 18 months after the first reports of COVID-19 began to emerge, over 200 million people worldwide have been infected, of whom over 4.2 million have lost their lives [1]. In that time the medical research community has scrambled to better understand this novel disease and its various and enigmatic presentations.

Some progress has been made in better characterizing one of COVID-19's most curious symptoms – loss of smell and taste. Today, loss of smell and taste has become well-recognized as one of the cardinal symptoms of infection. Over the past year and a half a flurry of academic activity has better characterized the phenomenon of COVID-associated smell and taste changes, yielding important advances in understanding the pathophysiology, epidemiology, and natural history of these deficits [2–6].

Chemosensory dysfunction is surprisingly common in patients with COVID-19, with two recent meta-analyses reporting a roughly 50% prevalence of olfactory loss [7,8]. As such, likely over 100 million (and growing) people have suffered from COVID-19 related olfactory dysfunction – millions of whom for which it will be a permanent deficit. Fortunately, reports from varied institutions around the world have demonstrated a relatively high rate of recovery of smell and taste loss

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[9–12]. Yet despite an overall recovery rate of roughly 80%, little to nothing is known about the factors that may influence such recovery. As even short term anosmia can have serious real-world consequences for both personal safety and quality of life, further investigation is warranted [13].

The aim of this study is to analyze data from a large, prospectively-collected nationwide cohort of subjects with chemosensory changes experienced during the COVID-19 pandemic in order to determine which factors, if any, are associated with recovery of smell function.

2. Methods

A web-based nationwide survey was conducted of adults ≥18 years of age who had either been diagnosed with COVID-19 or experienced a sudden change in smell and/or taste since January 2020. Recruitment began April 10, 2020 through online social media platforms, and participants received follow-up surveys 14 days, 1 month, 3 months, and 6 months after enrollment. Following consent, patient demographics, symptoms, comorbidities, testing status, treatment, and smell recovery status were collected and managed using REDCap electronic data capture tool [14,15]. Patients were asked to rate their sense of smell as "very good", "good", "poor", "very poor", or "absent" at the different timepoints, including prior to January 1, 2020 (considered as a pre-COVID-19 baseline). Within this questionnaire, there were multiple questions regarding demographics (age, race, sex, smoking history, body mass index, and blood type), symptomatology during COVID-19 (dyspnea, cough, fever, weakness/fatigue, myalgias, diarrhea, nasal congestion, runny nose, and headaches), pre-existing medical comorbidities (including diabetes, cardiovascular disease, seasonal allergies, chronic sinusitis, nasal polyposis, chronic respiratory diseases, neurologic disorders, or history of head trauma), and outpatient COVID-directed medication treatments.

Subjects were included in the study population if the following criteria were met: a) reported a change in sense of smell occurring after January 1, 2020; b) a pre-COVID-19 rating of sense of smell as "very good" or "good" prior to January 1, 2020; c) diagnosed with COVID-19 infection prior to the initial survey; and d) reported their worst sense of smell during suspected COVID-19 infection as "poor", "very poor" or "absent". Recovery was defined as a reply indicating a smell rating of "very good" or "good" at some time-point after initial smell loss.

All analyses were done using R statistical programming language (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized with means, standard deviations, and ranges, whereas categorical variables were summarized with frequencies and percentages. Simple logistic regression models were estimated to determine whether each predictor was significantly associated with recovery. Statistical significance was set a level of 0.05. This study was approved by Virginia Commonwealth University Institutional Review Board (HM20019186).

3. Results

As of June 25, 2021, 2864 individuals enrolled in the study. Over 98% of subjects rated their overall sense of smell as "good" or "very good" prior to January 1, 2020. 1231 met the current study inclusion criteria and were eligible to participate in the 6-month follow-up questionnaire, of whom 798 completed the survey (response rate of 64.8%).

Table 1 demonstrates the frequency and percentage of respondents who experienced recovery (back to "good" or "very good") from smell loss at each follow-up questionnaire timepoint, reaching 79.5% by the 6-month follow-up. The demographic variables are listed in Table 2. Of these, only age <40 was positively associated with smell recovery (83.2% vs. 74.5%, $p < .003$). Race, sex, smoking history, body mass index, and blood type were not predictors of recovery. Patient symptomology during COVID-19 infection is presented in Table 3. Of these symptoms, difficulty breathing was negatively associated with smell recovery (82.3% vs. 73.3%, $p < .004$), and nasal congestion positively associated with smell recovery (with 81.6% vs without: 74.9%, $p < .03$). The number of symptoms exhibited by each participant did not correlate with recovery status. "Pre-existing" self-reported medical comorbidities are presented in Table 4. Only a history of head injury (80.2% vs. 61.3%, $p < .017$) was negatively associated with smell. The total number of comorbidities was not associated with smell recovery. Table 5 lists the medications used by participants for treatment during their COVID-19 infection. Neither the number of medications used by each participant, nor use of any particular medication was correlated with recovery status.

Table 1
Sense of smell recovery rates at each survey timepoint.

	Number of survey respondents	n (%)
Baseline survey	1231	241 (19.58)
14 day survey	804	418 (51.99)
1 month survey	796	522 (65.58)
3 month survey	760	564 (74.21)
6 month survey	798	634 (79.45)

4. Discussion

Reported rates of recovery form COVID-19 associated olfactory loss vary, though most studies have found relatively high rates of return to normal or near normal function with most recovery occurring within the

Table 2
Sense of smell recovery by patient demographic characteristics.

		Overall N = 798	Recovered N = 634	Abnormal smell N = 164	p-Value
Age group	<40 years old	457 (57.3)	380 (83.2)	77 (16.8)	**.0029**
	>40 years old	341 (42.7)	254 (74.5)	87 (25.5)	
Race[a]	White	625 (78.5)	490 (78.4)	135 (21.6)	.1258
	Non-white	171 (21.5)	143 (83.6)	28 (16.4)	
Sex[b]	Female	643 (80.9)	505 (78.5)	138 (21.5)	.2244
	Male	152 (19.1)	126 (82.9)	26 (17.1)	
Smoking history	Never smoked	567 (71.1)	449 (79.2)	118 (20.8)	.6971
	Currently smoke	46 (5.8)	34 (73.9)	12 (26.1)	
	Quit after Jan 1, 2020	25 (3.1)	20 (80.0)	5 (20.0)	
	Quit before Jan 1, 2020	160 (20.1)	131 (81.9)	29 (18.1)	
BMI group[c]	Normal weight	304 (44.6)	248 (81.6)	56 (18.4)	.1558
	Overweight	182 (26.7)	135 (74.2)	47 (25.8)	
	Obese	196 (28.7)	153 (78.1)	43 (21.9)	
Blood type[d]	Type A	168 (41.2)	127 (75.6)	41 (24.4)	.1660
	Type B	45 (11.0)	36 (80.0)	9 (20.0)	
	Type AB	29 (7.1)	17 (58.6)	12 (41.4)	
	Type O	166 (40.7)	117 (70.5)	49 (29.5)	

[a] (2 missing).
[b] (3 missing).
[c] (116 missing).
[d] (390 missing).

Table 3
Sense of smell recovery and co-existing COVID symptoms.

		Overall N = 798	Recovered N = 634	Abnormal smell N = 164	p-Value
Number of symptoms	1	49 (6.1)	40 (81.6)	9 (18.4)	.9689
	2	68 (8.5)	55 (80.9)	13 (19.1)	
	3	108 (13.5)	86 (79.6)	22 (20.4)	
	4	106 (13.3)	83 (78.3)	23 (21.7)	
	5	125 (15.7)	103 (82.4)	22 (17.6)	
	6	139 (17.4)	110 (79.1)	29 (20.9)	
	7	101 (12.7)	78 (77.2)	23 (22.8)	
	8	74 (9.3)	59 (79.7)	15 (20.3)	
	9	28 (3.5)	20 (71.4)	8 (28.6)	
Difficulty breathing	No	543 (68.0)	447 (82.3)	96 (17.7)	**.0039**
	Yes	255 (32.0)	187 (73.3)	68 (26.7)	
Cough	No	327 (41.0)	257 (78.3)	70 (21.4)	.6188
	Yes	471 (59.0)	377 (80.0)	94 (20.0)	
Fever	No	431 (54.0)	339 (78.7)	92 (21.3)	.5469
	Yes	367 (46.0)	295 (80.4)	72 (19.6)	
Weakness or fatigue	No	173 (21.7)	144 (83.2)	29 (16.8)	.1559
	Yes	625 (78.3)	490 (78.4)	135 (21.6)	
Muscle aches	No	316 (39.6)	261 (82.6)	55 (17.4)	.0727
	Yes	482 (60.4)	373 (77.4)	109 (22.6)	
Diarrhea	No	491 (61.5)	391 (79.6)	100 (20.4)	.8703
	Yes	307 (38.5)	243 (79.2)	64 (20.8)	
Nasal congestion/ stuffy nose	No	259 (32.5)	194 (74.9)	65 (25.1)	**.0295**
	Yes	539 (67.5)	440 (81.6)	99 (18.4)	
Runny nose	No	504 (63.2)	400 (79.4)	104 (20.6)	.9390
	Yes	294 (36.8)	234 (79.6)	60 (20.4)	
Headache	No	195 (24.4)	160 (82.1)	35 (17.9)	.2953
	Yes	603 (75.6)	474 (78.6)	129 (21.4)	

first month of loss. Initial publications from Europe and Asia reported higher rates of recovery. A French study of PCR-tested patients showed 98% experiencing a complete subjective recovery within 28 days, with mean duration of anosmia near 9 days [16]. Workers in the United Kingdom repeated surveys 1 week after initial survey, revealing that 80% had experienced some recovery, while only 17% remained anosmic [9]. They also noted a "plateau" in recovery after approximately 3 weeks, with a 70% recovery rate for those with anosmia of 3 or more weeks duration. Similarly, a study from Korea using daily phone surveys of almost 500 newly diagnosed COVID-19 patients showed median duration of anosmia or ageusia of 7 days, and almost all recovering within 3 weeks [17]. By 1 month after loss, Reiter et al. demonstrated a 71.% recovery rate [10]. Only a handful of studies have followed recovery beyond one month. Four studies with the longest follow-up time were Otte et al. [18] with average follow-up of 57.9 days ± 1.4, Li et al. [19] at 62 days (range 25–95), Stavem [20] at 117 days (range 41–193) and Petersen et al. [21] at 125 days (45–215) with recovery rates were 54%, 89%, 88% and 84%, respectively. The current study reports only

Table 4
Sense of smell recovery and comorbidities at 6 month survey.

		Overall N = 798	Recovered N = 634	Abnormal smell N = 164	p-Value
Number of comorbidities	0	409 (51.3)	326 (797)	83 (20.3)	.9287
	1	269 (33.7)	212 (78.8)	57 (21.2)	
	2	92 (11.5)	75 (81.5)	17 (18.5)	
	3	22 (2.8)	16 (72.7)	6 (27.3)	
	4	5 (0.6)	4 (80.0)	1 (20.0)	
	5	1 (0.1)	1 (100.0)	0 (0.0)	
Diabetes	No	778 (97.5)	616 (79.2)	162 (20.8)	.1999
	Yes	20 (2.5)	18 (90.0)	2 (10.0)	
Cardiovascular disease	No	711 (89.1)	572 (80.5)	139 (19.5)	**.0537**
	Yes	87 (10.9)	62 (71.3)	25 (28.7)	
Seasonal allergies	No	508 (63.7)	396 (78.0)	112 (22.0)	.1631
	Yes	290 (36.3)	238 (82.1)	52 (17.9)	
Chronic sinus infection	No	766 (96.0)	607 (79.2)	159 (20.8)	.4675
	Yes	32 (4.0)	27 (84.4)	5 (15.6)	
Nasal polyps	No	793 (99.4)	629 (79.3)	164 (20.7)	.1286
	Yes	5 (0.6)	5 (100)	0 (0.0)	
Chronic respiratory disease	No	721 (90.4)	574 (79.6)	147 (20.4)	.7293
	Yes	77 (9.6)	60 (77.9)	17 (22.1)	
Neurological disease	No	796 (99.7)	632 (79.4)	164 (20.6)	.3371
	Yes	2 (0.3)	2 (100.0)	0 (0.0)	
Previous head injury	No	767 (96.1)	615 (80.2)	152 (19.8)	**.0181**
	Yes	31 (3.9)	19 (61.3)	12 (38.7)	

Table 5
Sense of smell recovery and medications.

		Overall N = 793	Recovered N = 629	Abnormal smell N = 164	p-Value
Number of medications taken	0	149 (18.8)	110 (73.8)	39 (26.2)	.2424
	1	422 (53.2)	345 (81.8)	77 (18.2)	
	2	184 (23.2)	146 (79.3)	38 (20.7)	
	3	37 (4.7)	27 (73.0)	10 (27.0)	
	4	1 (0.1)	1 (100.0)	0 (0.0)	
Tylenol	No	310 (39.1)	243 (78.4)	67 (21.6)	.6044
	Yes	483 (60.9)	386 (79.9)	97 (20.1)	
NSAIDs	No	483 (60.9)	380 (78.7)	103 (21.3)	.5753
	Yes	310 (39.1)	249 (80.3)	61 (19.7)	
Zithromax	No	703 (88.7)	556 (79.1)	147 (20.9)	.6526
	Yes	90 (11.3)	73 (81.1)	17 (18.9)	
Remdesivir	No	790 (99.6)	628 (79.5)	162 (20.5)	.0852
	Yes	3 (0.4)	1 (33.3)	2 (66.7)	
Hydroxychloroquine	No	778 (98.1)	620 (79.7)	158 (20.3)	.0855
	Yes	15 (1.9)	9 (60.0)	6 (40.0)	
Chloroquine	No	789 (99.5)	625 (79.2)	164 (20.8)	.1728
	Yes	4 (0.5)	4 (100.0)	0 (0.0)	

patients with a minimum of at least 6 months follow up, and reveals an overall recovery rate of 79.5%, consistent with earlier published reports. Our restricting inclusion criteria to subjects reporting worst sense of smell as "poor," "very poor," or "absent" – thus excluding subjects with more mild losses, may suggest why our rate of recovery was lower than some of the above prior reports.

Despite numerous reports describing rates of smell recovery, very little information exists regarding the factors associated with recovery vs. non-recovery. Few have investigated this phenomenon, and to date almost no clinical, epidemiological, or laboratory markers have been identified [22–25]. In their study of prospectively recruited patients from 3 European centers, Saussez and colleagues examined patterns of recovery among 288 patients within 60 days of onset of olfactory dysfunction [23]. In their analysis of both demographic and clinical (COVID-related symptoms) factors, the authors found no statistically significant markers of recovery. In addition they also found no association between recovery of smell function and viral load on nasopharyngeal swab testing or COVID-19 severity. Contrarily, Makaronidis et al. found in their study of 380 patients (270 female, 110 male) recruited online from a community-based cohort that men were more likely than women (72.8% vs. 51.4%) to fully recover their sense of smell [24]. Age, race, and smoking status were not associated with improved rates of recovery at 4 weeks. Both studies, though well done, are limited by relatively short follow up and smaller patient populations that may preclude adequate sub-statistical analysis. Petrocelli et al. presented what is likely the strongest evidence to date, finding age <50 (but no other demographic or symptom variables) associated with improved rates of recovery at 6-months in their study of 300 patients [25].

The current study of 789 patients, taken from a wide geographical distribution across the United States, includes patients with a minimum of 6 months since the onset of olfactory dysfunction and represents both the largest known series and that with the longest follow-up to date. Of the variables examined, factors positively associated with smell recovery were age <40 and nasal congestion. Factors negatively associated with smell recovery were difficulty breathing (during COVID) and a history of head trauma. Whereas the finding of younger age likely represents some sort of innate resiliency to injury and is corroborated by findings from previous studies, the other factors identified in this study warrant further examination.

It is likely that nasal congestion may be reflective of some patients experiencing "conductive" olfactory losses due to nasal congestion caused by their COVID-19 infection. A study of experimentally induced "common cold" after inoculation with coronavirus 229E indicated change in sense of smell correlated to the degree of nasal congestion as measured by acoustic rhinometry [26]. It is further interesting that other studies have revealed a rather low overall prevalence of nasal congestion with COVID-19 infection – on order of 4%,whereas congestion was reported in about two thirds of our respondents [27]. This may have led to both the observed association of congestion with recovery, as well a higher observed rate of recovery as comparted with other studies. Of particular interest are those factors negatively associated with smell recovery. It has been recognized that chemosensory loss is seen, perhaps counterintuitively, more commonly in more mild cases of COVID [28,29]. Whereas difficulty breathing may be a marker for those with more severe disease, in may also result in decrease nasal and retronasal airflow, thereby decreasing presentation of odorants to the nasal mucosa. Previous head injury as a predictor may lead credence to the "second hit" theory whereby neural injury is potentiated by earlier injury [30,31]. However, there is very little is known about this controversial subject in humans, with no known studies evaluating repeat head injury as a risk factor for loss of smell.

Some findings in the present study are corroborated by similar findings in the literature, while others are contradicted. Such discrepancies are likely due to differences in study populations, sample size, methodologies, geography, COVID-severity and total duration of follow up since onset of symptoms. What remains clear is that despite slight and incremental additions to the understanding of COVID-19-related olfactory made by this and other studies, it remains a poorly understood phenomenon. Much like COVID-19 itself, it is unclear if the disparate clinical presentations are attributable to inherent properties of the virus itself (or its variants), the severity of infection, innate biophysical properties of the hosts infected, or a combination of all.

Slightly more is known about the risk factors for some of the non-chemosensory long-term sequalae of COVID-19. Meta-analysis shows that 80% of individuals with a confirmed COVID-19 diagnosis continue to have at least one overall effect beyond two weeks following acute infection. For these so called "long-haulers" some clinical and patient-specific risk factors have been identified, with more invariably to be discovered over time. Among those confirmed by multiple studies are female sex, age over 70, and more than five symptoms during the first week of infection, which were all predictive of prolonged symptoms [32]. Why some of the studied variables seem to predict general recovery but not smell recovery is a target ripe for further investigation.

This study is not without limitations. Our study population shows a disproportionately high percentage of young and female subjects, which therefore may not represent a fair sampling of the nationwide population of COVID-19 sufferers. It is unclear if this is a result of the online social media solicitation used for subject recruitment differentially reaching these demographics, or reflects differing motivations to complete the surveys or ability to access the online survey. Likewise, limited numbers of non-white respondents precluded more detailed statistical analysis of the impact of race on recovery of olfactory function. The retrospective nature of such a longitudinal survey is prone to both selection and recall bias and patients with more severe, longer lasting or persistent symptoms may be more inclined to participate than those with lesser or no symptoms. Thus if those experiencing complete and rapid recovery of olfactory function may have been less inclined to respond to our initial survey, we would expect actual recovery rates to be higher than those observed in our cohort. Nonetheless, despite the lack of objective olfactory data, it has been well established that patient self-reports of olfactory dysfunction likely underestimate the true incidence of these deficits [33,34]. As of the writing of this manuscript, emergence of novel COVID-19 variants (e.g. delta, iota, etc.) are spreading rapidly both within and outside the United States. Precious little is known about the overall clinical phenotypes of these variants, and at this writing nothing on the potential disparate olfactory effects. At least for the near future and despite ongoing research by chemosensory groups across the world, it appears there are more questions than answers.

5. Conclusions

Olfactory loss is a common manifestation of COVID-19 infection. Fortunately, almost 80% of those afflicted recover smell function by 6 months after infection. Although little is currently known about what factors may portend a higher or lower likelihood of olfactory recovery. This study suggests recovery of function is positively associated with younger age patients and those with nasal congestion, and negatively associated with difficulty breathing, and previous head trauma. Despite relatively high rates of subjective olfactory recovery, healthcare providers should counsel their patients according to what factors may or may not influence that recovery.

Contributions

Conception: DHC, ERR, ZAK, RMC
Design: DHC, ERR, ZAK, RMC
Data Analysis: DHC, ERR, YS, SGB, RMC
Manuscript Drafting: DHC, ERR, SGB, ZAK, RMC
Final Approval: DHC, ERR, YS, SGB, ZAK, RMC

Declaration of competing interest

None.

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