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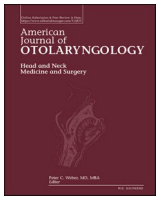

Recovery from Covid-19 smell loss: Two-years of follow up

Michael P. McWilliams [a], Daniel H. Coelho [a,b,*], Evan R. Reiter [a], Richard M. Costanzo [a,b]

[a] Department of Otolaryngology – Head & Neck Surgery, Virginia Commonwealth University School of Medicine, Richmond, VA, USA
[b] Department of Physiology & Biophysics, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

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ABSTRACT

Objective: To report long-term patterns of recovery and non-recovery in a large nationwide cohort of subjects with COVID-19 associated smell loss.
Study design: Prospectively, longitudinal questionnaires.
Setting: Web-based national survey.
Methods: A longitudinal survey of adults with COVID-19 and/or sudden change in smell or taste since January 1, 2020 was launched April 10, 2020. Participants were queried again in late May 2022 regarding recovery. Data from respondents with >2 years since loss were analyzed and compared to recovery status of those more recently effected.
Results: 1103 responded to the survey of whom 946 met inclusion criteria. Among the 267 respondents for whom at least 2 years of follow up was available, 38.2 % reported full recovery, 54.3 % partial, and 7.5 % no recovery. For the entire cohort (all with ≥3 months since smell loss), 38.7 % reported complete recovery, 51.0 % reported partial recovery (ranging from mild complaints to severe phantosmia or dysosmia), and 10.3 % reported no improvement at all. Complete recovery of smell function was significantly higher in those under 40 years old (45.6 % compared to 32.9 % in those over 40).
Conclusion: Although the vast majority of subjects who do recover do so within the first 3 months, long-term spontaneous recovery can occur. Rates of recovery do not seem to differ depending on when during the pandemic the loss first occurred.

1. Introduction

Since the early days of the COVID-19 pandemic olfactory loss was identified as a cardinal symptom of infection [1,2]. A recent systematic review found olfactory loss present in over 50 % of patients [3], and with worldwide COVID-19 cases nearing 550 million, an estimated two-to-three hundred million people have likely experienced loss of smell with its associated substantial impact on safety and quality of life [4,5]. The high prevalence of smell loss has sparked considerable clinical and laboratory investigation into the underlying pathophysiology and epidemiology of this phenomenon. Of particular interest to clinicians and patients have been information regarding prognosis, including rates and predictors of recovery. Fortunately many studies have found that a large majority of affected individuals (70–88 %) recover most olfactory function within 1–3 months [6], while a small minority (5 % to 8.6 %) report no recovery at all [7–10]. However, as the pandemic still rages over 2.5 years since initial reports from Wuhan, China, few studies to date have looked at recovery outcomes beyond 12 months, and none beyond 18 months. This study aims to report 2-year recovery data and recovery time-course from a large, prospectively collected nationwide cohort of subjects with chemosensory changes associated with COVID-19 infection.

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 [11,12]. An additional email questionnaire was sent to all

* Corresponding author at: Department of Otolaryngology – Head & Neck Surgery, PO Box 980146, Virginia Commonwealth University School of Medicine, Richmond, VA 23298-0146, USA.
E-mail address: daniel.coelho@vcuhealth.org (D.H. Coelho).

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participants on May 28, 2022 with a reminder 7 days later for those who had yet to complete the questionnaire. For the current follow up study, data were utilized with the following inclusion criteria: 1) positive Covid-19 test result before March 2022 (allowing a minimum of 3 months follow up), 2) loss of smell at the time of positive Covid-19 test. The follow up survey included questions about status of smell loss and recovery outcomes. Based on their answers, respondents were divided into groups: "complete recovery", "partial recovery", "no recovery at all". For those subjects who did not experience *complete* recovery, further questions were asked regarding the severity and character of their persistent olfactory dysfunction. Participants were further divided into 3 groups by time since loss of smell. Group A included all respondents with ≥3 months since smell loss (January 2020–February 2022), Group B included all respondents with ≥1 year since smell loss (January 2020–May 2021), and Group C included all respondents with ≥2 years since smell loss (January 2020–May 2020).

All analyses were performed using SPSS Statistics (version 28.0.1.0; IBM Corp, Armonk, NY). Continuous variables were summarized with means, standard deviations, and ranges, whereas categorical variables were summarized with frequencies and percentages. Chi-squared analysis was used to compare groups. Statistical significance was set a level of 0.05. This study was approved by Virginia Commonwealth University Institutional Review Board (HM20019186).

3. Results

3801 participants were invited. As of survey close (June 23, 2022) 1113 (29.3 %) participants responded of whom 946 (24.9 %) met both inclusion criteria. Mean participant age was 43.8 ± 13.9 with a range of 18–82. 79.6 % ($N = 753$) of our sample was female, 18.8 % ($N = 178$) was male, and 1.6 % ($N = 15$) elected to not answer or self-describe.

Fig. 1 shows the distribution of COVID-19 onset times over the course of subject recruitment. 83 % ($n = 786$) of cases in our study were from early stages of the pandemic (before March 2021) prior to the emergence of the alpha, delta, and omicron variants. 267 participants tested positive for COVID-19 prior to June 2020 and thus had at least 2 years post-COVID infection follow up.

Table 1 lists recovery outcomes for three groups. Among the 945 participants in Group A (one of the 946 did not answer all recovery questions), 38.7 % (366) reported complete recovery, 51.0 % (482) reported partial recovery, and 10.3 % (97) reported no recovery at all Among the 267 in Group C who had 2 or more years post-infection time to recover 38.2 % (102) report complete recovery, 54.3 % (145) report partial recovery, while 7.5 % (20) report no recovery at all.

Table 1
Recovery status by duration of loss group.

	Percentage (count)		
	Complete recovery	Partial recovery	No recovery at all
Group A ($N = 945$) ≥ 3 months since COVID	38.7 % (366)	51.0 % (482)	10.3 % (97)
Group B ($N = 809$) ≥ 1 year since COVID+	38.9 % (315)	51.4 % (416)	9.6 % (78)
Group C ($N = 267$) ≥ 2 years since COVID+	38.2 % (102)	54.3 % (145)	7.5 % (20)

The impact of age and sex on recovery from olfactory loss is presented in Table 2. Subjects under age 40 reported *complete* recovery at a higher rate (45.6 %) than those over 40 (32.9 %; $p = 0.001$). Further analysis revealed that participants over 40 were more likely to have no recovery at all compared to those under 40 (14.1 % vs. 5.1 %; p = 0.001). Males were significantly more likely to report *complete* recovery than females (46.1 % vs 36.7 %, $p = 0.021$). Men and women were equally likely to report no improvement at all (9.4 % vs 14.0 %, $p = 0.069$).

Fig. 2 shows the time course of recovery for the 363 participants who reported *complete* recovery of smell function (3 of 366 did not answer all recovery questions). 51.2 % recovered within 1 month, 70 % within 3 months, and 8.8 % took over 1 year to reach full recovery. Boldface denotes statistical significance.

For the 579 participants who did not report complete recovery, 64.9 % (376) of participants reported smell distortion, 38.9 % (225) reported smelling strong odors only, and 32.6 % (189) reported phantosmia.

Table 2
Analysis of failure to recover by age and gender.

		Percentage (count)		*P*-value
		Complete recovery	Partial or no recovery	
Age group (N = 920)	<40 years old (N = 410)	45.6 % (187)	54.4 % (233)	**0.001**
	>40 years old (N = 510)	32.9 % (168)	67.1 % (342)	
Sex (N = 930)	Female (N = 752)	36.7 % (276)	63.3 % (476)	**0.021**
	Male (N = 178)	46.1 % (82)	53.9 % (96)	

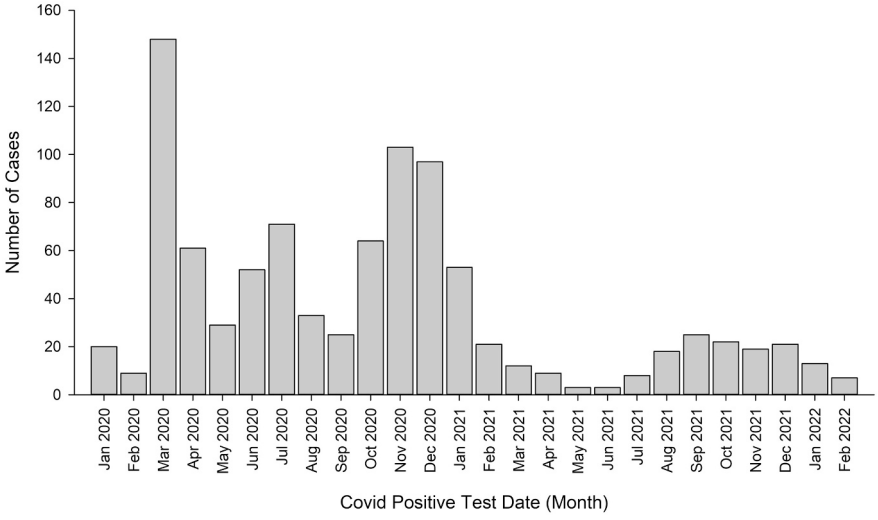

Fig. 1. Incidence of Covid-related smell loss, by month of onset.

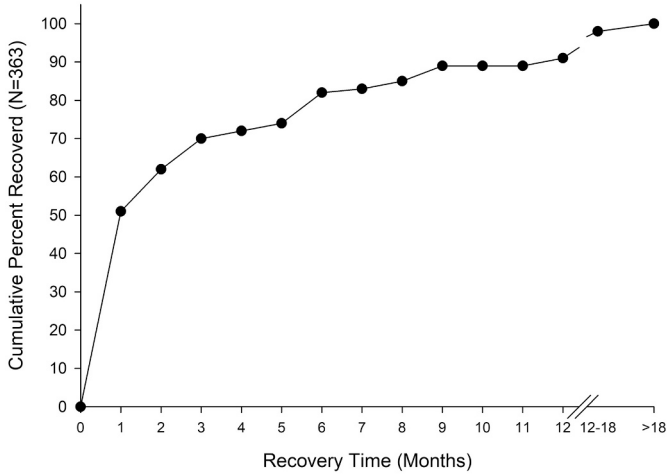

Fig. 2. Cumulative recovery for participants who report "Complete Recovery". (After 12 months, recovery time choices were "12–18 months" and ">18 months", separated by a break).

4. Discussion

At the writing of this manuscript, only a handful of papers have followed recovery from COVID-19 related olfactory loss up to or beyond one year. Yet, anecdotal evidence from the authors own experience suggests that, while rare, recovery of smell can occur a year or years later. Five studies with 1 year follow up and a single study with 18 month follow-up show that at their latest time-point, complete recovery rate ranges from 54 % to 86.9 %, with partial recovery ranging from 13.1 % to 46 % [7,9,13–16]. Additionally, four papers with recovery follow-up between 6 and 12 months - two using subjective, two using objective measures - show that between 5 % and 8.5 % of participants show no recovery at all at their latest timepoint [7–10].

The current study of nearly 1000 subjects, taken from a wide geographic distribution across the United States, represents one of the largest data series and the longest follow-up published to date. The main finding that at 2 years, 7.5 % of participants continue to have no smell improvement at all is in line with published reports. However, the finding that only 38.2 % report completely recovery is lower than most percentages reported in literature. This may be due to the more granular detail of olfactory dysfunction queried, and *any* persistent olfactory abnormality, no matter how minor, precluded subjects from being considered "completely recovered". As such, the partial recovery group includes individuals with widely disparate complaints in terms of both severity and character of dysfunction. 69 % of this group endorsed odor distortion, 39 % endorsed smelling strong smells only, and 33 % endorsed phantosmia. Several subjects in the partial recovery group submitted descriptions of their smell status indicating nearly normal olfactory function; one stated "I would estimate I have about 95% of my smell" while another wrote "Most of my normal smell has returned but burnt smells do not smell the same as they used to". One participant even stated "Everything is seemingly normal now except…the smell of coffee". Others in the same group, however, reported persistent substantially abnormal olfaction, such as one participant over 2 years after his initial loss reporting that their 'sense of smell is nowhere near as sensitive as it was prior to Covid' and another reporting that their sense of smell remains "much more muted" after infection. This variety of responses and smell status offers a possible explanation as to why our complete recovery numbers are lower than expected. Some subjects in the 'partial recovery' group might have selected complete recovery, if they hadn't had the opportunity to explain the very subtle residual abnormalities.

When looking at the distribution of recovery categorization among our groups divided by duration of follow-up, there is little if any difference between the entire cohort (Group A) when compared with those with 2 or more years duration since loss of smell (Group C). This would suggest that the 2 year group is likely an accurate representation of long term covid recovery percentages – and that across the population, closer to 7.5 % of people fail to recover, rather than the 10.3 % seen in the entire cohort. Interestingly, although recent evidence suggests olfactory dysfunction may be less prevalent as variants evolve, it would appear that recovery rates are not similarly improved over time [17].

Analysis of demographic variables showed that subjects with age <40 years old had a significantly higher rate of *complete* recovery and a significantly lower rate of reporting "no recovery at all" than those with age >40 years old. This is in keeping with Petrocelli et al.'s finding that patient age under 50 is associated with a higher rate of recovery, and our groups prior study showing that age <40 is positively associated with smell recovery [8,17]. This finding is likely explained by older individuals having less ability to withstand the olfactory insult associated with COVID-19 infection. Our data showed that men report a complete recovery at higher rate than women (46.1 % vs 36.7 %, $p = 0.021$). Interestingly, pre-COVID Sorokowski et al. published a 2019 meta-analysis showing that women outperformed men in nearly every aspect of olfaction [18]. As such, women in our sample may be more aware of residual smell abnormalities and more likely to place themselves in the partial recovery group than males. Mean age of the men and women who selected "complete recovery" was analyzed to ensure that age was not causing this effect, and no significant difference was found (men: 40.9 ± 14.9 vs women: 41.3 ± 13.0) There was no difference in rates of reporting "no recovery at all" between men and women, a finding corroborated by both our prior study and Saussez et al.'s 2021 study [17,19].

Many publications have shown that the majority of those who recover olfactory function, do so quickly [20–23], and the finding that most (51.2 %) recovered in 1 month and 70 % of those who recover do so in the first 3 months is in-line with these other studies. However, as is seen in Fig. 1, recovery can continue to occur beyond 12, 18, and 24 months. The data showing that 8.8 % of people who recovered did so >1 year after infection, provides evidence that there is still a possibility – though improbable– of recovery after one year. Given the paucity of therapeutic options for those with smell loss, even the glimmer of hope can have substantial impact on patient wellbeing.

This study is not without limitations. This study has a much larger percentage of female respondents than males and may represent a biased sampling of those who suffered from COVID related olfactory dysfunction in the US. 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. Additionally, this survey was susceptible to both selection and recall bias. Subjects with more severe or persistent symptoms might be more likely to respond than subjects who recovered completely months or years prior to entering the survey. This could play a theoretical role in explaining the current study's lower than expected rates of complete recovery. However, analysis of groups that include those more recently infected with COVID (Groups A and B) compared with those infected over 2 years ago (Group C) demonstrates no substantial differences in the breakdown of recovery/non-recovery – suggesting that any contribution of selection bias, if any, is likely minimal. Nonetheless, the current study provides clinically significant information about the persistence of COVID-19 related olfactory dysfunction and the recovery time course for those who are fortunate enough to recover completely.

5. Conclusion

This study presents the first report of olfactory recovery in large cohort of patients with COVID-19 related olfactory dysfunction up to 29 months following loss. Our data suggests that after 2 years, while 7.5 % percent continued to report no recovery, most (93.5 %) reported some

recovery – either complete recovery (38.2 %) or partially recovery (54.3 %). Nonetheless, a large percentage of respondents in this cohort had persistent symptoms, even 2 years after their initial loss. Although the vast majority of participants who do recover do so within the first 3 months, delayed recovery can occur but is relatively rare. Rates of recovery do not seem to differ depending on when during the pandemic the loss first occurred.

Declaration of competing interest

None.

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Author responsibilities (authorship was determined using ICMJE recommendations)

MPM: Data acquisition, analysis, drafting, final approval.

DHC: Conception, design, analysis, interpretation, drafting, final approval.

ERR: Conception, design, analysis, interpretation, drafting, final approval.

RMC: Conception, design, analysis interpretation, drafting, final approval.

In consideration of the American Journal of Otolaryngology's reviewing and editing my submission, we the author(s) undersigned transfers, assigns and otherwise conveys all copyright ownership to Elsevier Inc. in the event that such work is published in the American Journal of Otolaryngology.

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