

## LETTERS TO THE EDITOR

## RESEARCH

# Age and subtle cognitive impairment are associated with long-term olfactory dysfunction after COVID-19 infection

## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic, has been widely associated with extra-pulmonary manifestations, including a broad range of neurological symptoms.<sup>1</sup>

Olfactory and taste disorders have been consistently reported as common nonrespiratory symptoms of SARS-CoV-2 infection, although the persistence of neurosensory dysfunctions is still a theme of debate.<sup>2</sup> Age and premorbid health status might play a major role in modulating the vulnerability to long-term olfactory recovery after SARS-CoV-2 infection. Indeed, the prevalence of olfactory dysfunction increases in normal aging but has also been associated with several age-related neurodegenerative conditions.<sup>3</sup>

In this study, we thus evaluated the prevalence and predictors of olfactory dysfunction in a consecutive series of patients hospitalized for COVID-19 and its potential association with features or symptoms suggestive for long-term neurological involvement.

## RESULTS

A total of 168 patients hospitalized for mild to moderate COVID-19 were evaluated at 6 months after discharge. Of these, 106 patients were assessed in presence through a standardized assessment. Five patients (5.7%) were excluded from the study for allergic rhinitis, resulting in a final dataset of 101 patients.

The Sniffin' Sticks test<sup>4</sup> identified 50 patients with an abnormal score  $\leq 8$ , including 11 patients with severe (score  $< 4$ ) hyposmia (4/11 of them reported subjective olfactory dysfunction) (Table 1). Patients with subjective hyposmia exhibited lower Sniffin' Sticks total score ( $5.3 \pm 3.5$  vs.  $8.1 \pm 2.4$ ,  $p = 0.012$ ) but three of them exhibited normal scores. Conversely, patients with long-term subjective hyposmia exhibited similar Sniffin' Sticks total scores

compared to subjects without complaints ( $7.8 \pm 2.5$  vs.  $7.8 \pm 2.8$ , respectively,  $p = 0.70$ ). Hyposmia and hypogeusia reported during hospitalization did not predict long-term objective hyposmia (odds ratio [OR] 1.1; 95% confidence interval [CI] 0.75–1.7) or subjective hyposmia (OR 1.03; 95% CI 0.70–1.5,  $p = 0.52$ ).

Compared to patients with normal olfactory function, those with objective hyposmia were older ( $68.2 \pm 11.3$  vs.  $58.2 \pm 12.1$  years,  $p < 0.001$ ) but exhibited similar comorbidity score at admission and during hospitalization and did not differ for duration of hospitalization, oxygen therapy, and severity of COVID-19 (OR 1.5; 95% CI 0.83–2.7,  $p = 0.10$ ). Age was confirmed as the only predictor of long-term objective hyposmia in logistic regression analyses (Wald 6.4,  $\exp[B] = 0.09$ ,  $p = 0.01$ ); subjects older than 65 years exhibited a 1.86 increased risk of hyposmia (95% CI 1.19–2.9) and subjects older than 75 years of 2.67 (95% CI 1.10–6.5).

No difference of either self-reported neurological symptoms at the neuro-checklist or objective neurological signs was documented between patients with normal olfactory function and hyposmia (Table S1). Patients with hyposmia exhibited lower MoCA (Montreal Cognitive Assessment) total score ( $23.2 \pm 3.4$  vs.  $25.7 \pm 2.5$ ) compared to subjects with normal olfactory function in logistic regression analyses adjusted for age, sex, and educational levels (Wald 5.8,  $\exp[B] = 1.2$ ,  $p = 0.01$ ).

## DISCUSSION

The prevalence of objective hyposmia in our cohort of hospitalized patients was 50%, definitively higher compared to prevalence of hyposmia in the general population in the sixth decade of age.<sup>5</sup> This prevalence fits well with recent reports adopting sniffing sticks in independent cohorts of SARS-CoV-2 patients.<sup>6</sup>

Older age was the most important factor associated with long-term hyposmia as patients older than 75 years of age were at three-fold risk of long-term hyposmia compared to younger subjects. Conversely, we failed to find an association between olfactory dysfunction and the severity of COVID-19,

**TABLE 1** Demographic and clinical characteristics between previous COVID-19 patients with and without persistent olfactory dysfunction

	<b>Total (n = 101)</b>	<b>Normal olfactory function (n = 51)</b>	<b>Hyposmia or anosmia (n = 50)</b>	<b>p-Value<sup>a</sup></b>
Demographic and clinical characteristics				
Age, years	63.62 ± 12.9	58.20 ± 12.1	68.24 ± 11.3	<0.001
Sex, female	28 (27.7%)	17 (33.3%)	11 (22.0%)	0.186
Total days of hospitalization	12.36 ± 10.5	11.14 ± 8.5	12.98 ± 11.7	0.374
BCRSS	0.92 ± 0.90	1.02 ± 0.99	0.82 ± 0.80	0.649
Low-flow oxygen therapy needed	68 (67.3%)	33 (64.7%)	35 (70.0%)	0.830
Noninvasive ventilation	13 (12.9%)	6 (11.8%)	7 (14.0%)	0.796
Orotracheal intubation	2 (1.98%)	1 (1.96%)	1 (2.0%)	0.747
CIRS comorbidity index prehospitalization	1.35 ± 0.25	1.35 ± 0.20	1.40 ± 0.21	0.08
CIRS comorbidity index during hospitalization	1.76 ± 0.28	1.71 ± 0.24	1.81 ± 0.31	0.10
Subjective hyposmia at follow-up	11 (10.89%)	3 (5.9%)	8 (16.0%)	0.2
Subjective hypogeusia/dysgeusia at follow-up	17 (16.8%)	9 (17.6%)	8 (16.0%)	0.795
MoCA at follow-up	24.4 ± 3.2	25.7 ± 2.5	23.2 ± 3.4	<0.001

Abbreviations: BCRSS, Brescia-COVID Respiratory Severity Scale; CIRS, Cumulative Illness Rating Scale; COVID-19, coronavirus disease 2019; MoCA, Montreal Cognitive Assessment.

<sup>a</sup>p-Values were calculated by *t*-test or Fisher's exact test, as appropriate.

thus supporting the claim that hyposmia is independent from the degree of respiratory involvement.<sup>7</sup> Our study went also further, by showing an association between long-term hyposmia and cognitive impairment, after controlling for age, gender, and education. These findings corroborate the well-known association between subtle cognitive deficits and olfactory dysfunction in the older subjects.<sup>8</sup> Although the mechanisms underlying long-term central nervous system impact of SARS-CoV-2 are still unclear,<sup>9,10</sup> these preliminary results seem to suggest that older subjects with subtle cognitive deficits are a “vulnerable” population with a higher risk of long-term olfactory dysfunction.

We acknowledge that this study entails different limitations. First, we limited the observation to patients presenting with mild to moderate COVID-19; second, patients were evaluated only for orthonasal olfaction, whereas taste disorders were not assessed. Furthermore, no data about preexisting objective hyposmia or cognitive deficits were available, although we accurately excluded subjects with premorbid cognitive impairment or subjective hyposmia from the analyses.

Despite these limitations, the study underlined the high prevalence of objective hyposmia 6 months after COVID and identified age and subtle cognitive deficits as factors strongly associated with long-term olfactory dysfunction. Further studies evaluating the nature and progression of cognitive changes and olfactory function would be necessary over time.

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## CONFLICT OF INTEREST


All authors have no conflict of interest regarding the research related to the manuscript.


## AUTHOR CONTRIBUTIONS

Conception and design of the study: Viviana Cristillo, Andrea Pilotto, and Alessandro Padovani. Acquisition and analysis of data: Viviana Cristillo, Andrea Pilotto, Stefano Cotti Piccinelli, Nicola Zoppi, Giulio Bonzi, Stefano Gipponi, Davide Sattin, Silvia Schiavolin, Alberto Raggi, Michela Bezzi, Matilde Leonardi, and Alessandro Padovani. Drafting the manuscript and figures: Viviana Cristillo, Andrea Pilotto, and Alessandro Padovani.

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The study was not financially supported.

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## Association of COVID-19 vaccination prioritization and hospitalization among older Washingtonians

### INTRODUCTION

In experimental conditions, all Food and Drug Administration-approved vaccines have demonstrated vaccine-related reductions in COVID-19 hospitalizations.<sup>1,2</sup> While the literature is rapidly evolving, several observational studies have evaluated the efficacy of COVID-19 vaccination on particular populations. Studies of healthcare workers in Jerusalem,<sup>3</sup> Italy,<sup>4</sup> and the United States found reduced COVID-19 infection rates soon (generally within 1–2 weeks)<sup>5</sup> following vaccination. National observational studies of the general population in Scotland<sup>6</sup> and Israel<sup>7</sup> found lower rates of symptomatic infection, hospitalization, and death soon (withing 2–3 weeks) following vaccination.

Starting January 18, 2021, Washington prioritized Washingtonians aged 65 and older (65+) for COVID-19 vaccination.<sup>8</sup> We sought to explore whether reduced COVID-

19 hospitalizations could be discerned in real-world conditions following vaccination prioritization for that population. To do this, we used historical trends of Washington State COVID-19 hospitalizations for the 65+ and other age groups to generate estimates of COVID-19 hospitalization in the 65+ years age group had prioritization not occurred, and compared these estimates with actual hospitalization in the first 6 weeks following prioritization.

### METHODS

We analyzed 16,511 Washington Department of Health COVID-19 hospitalizations that occurred between March 1, 2020 and March 1, 2021.