OLFACTORY PERFORMANCE IN POST MILD-TO-MODERATE ACUTE COVID-19 ACROSS 2 YEARS

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BACKGROUND

Existing longitudinal studies (n=6) of olfaction performance post acute COVID-19 have a maximum follow-up of 6-month, lack demographic corrections, use non-standard tests, and have not concurrently tested cognition. Although olfactory dysfunction appears to improve within two months of symptom onset, 4/6 longitudinal studies show that persistent olfactory impairment (up to 60%). Lastly, only two studies used objective olfaction tests included biomarkers.

METHODS

- ***Study design:*** Prospective observational study
- ***Participants***: PCR-confirmed COVID-19 patients in the prospective ADAPT cohort (Sydney, Australia) were assessed across 18 acute symptoms and hospitalization status: 40% mild, 50% moderate, 10% severe/hospitalized – none deceased). **See also Table 1.**

Table 1: Demographic, Clinical Characteristics by Acute Disease Severity at the 2-month initial visit

	Full sample n=178		Mild n=66		Moderate n=90		Severe n=22		
	n	%	n	%	n	%	n	%	p
Sex (% Female)	74	41.6%	29	43.9%	40	44.4%	5	22.7%	.16
English-Speaking Background	149	83.7%	57	86.4%	75	83.3%	17	77.3%	.73
Comorbidities	72	40.4%	21	31.8%	36	40%	15	68.2%	.01
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*p*
Age (Years)	46.4	15	47.2	16	43.1	13	57	15	.001
Education (Years)	15.2	2.7	15.4	2.6	15.1	2.6	15.1	3.3	.68
Total Lung Capacity	97.1	12.3	98.4	11.2	99.3	10.9	86.9	14.9	.02
Diffusing capacity of the lungs for carbon monoxide	90.7	15.8	94.3	13.8	90.8	12.7	82.3	25	.39

- ***Procedures and timeline***: Blood samples were taken 2 (N=178), 4 (N=148) and 12-month (N=117) post diagnosis. **The NIH Odor Identification Test, OIT** and the Cogstate brief cognitive battery were performed. 57 also had an olfaction test at 24-month.
- ***Outcomes***: The OIT raw data were transformed into demographically-corrected T-scores. OIT's attrition was completely random and only initial age (40±15 versus 47±15) differed between patients lost to follow-up and those in the study at 24-month. We tested **peripheral neurobiomarkers (NFL, GFAP, S100B, GM-CSF) and immune markers (Interleukin-IL panel: 1-β, 1R-alpha, 4, 5, 6, 8, 10, 12p40, 12p70, 13, and MCP-1, TNF-alpha and INF-beta),** analyzed as Log transformed and elevated/normal range using published references. Our previous analyses had shown no relationship with the kynurenine pathway, but an association of impaired olfaction and impaired cognition at 2-month only.
- ***Statistics***: Linear mixed effect regressions with time effect (months) tested olfaction trajectories (random subject effect) and its association with the biomarkers (main and time interaction).

Post acute mild to moderate COVID-19 is associated with a declining olfactory performance up to 2-yr post diagnosis especially when initially impaired. Olfactory performance decline may be mediated by upregulated immune parameters which are distinct from those driving cognitive changes.

RESULTS

- At 2 months post diagnosis 30% had impaired olfaction and those who had acute severe disease were more likely to be impaired (p=.009; Fig. 1).
- 21%, 31% and 37% had impaired olfaction at 4, 12 and 24-months. Olfactory performance decline over time (p<.0001), which was dependent on the initial performance (Fig 3).
- Neurobiomarkers were within the normal range. IFN-beta, IL-1Ra, IL-13 and TNF-alpha increased across time, p<.03-p<.0005.
- TNF-alpha and IFN-beta showed a time covariance with poorer olfaction performance.

Fig 1. % Impaired Olfaction (T-score <40) by Acute disease severity at 2-month post diagnosis

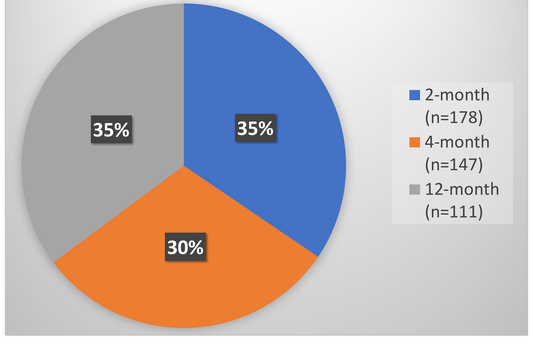


Fig 2. % Impaired Olfaction (T-score <40) by across the 2-year study

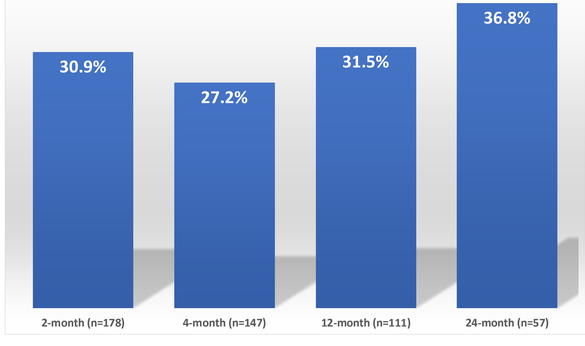


Fig 3: Trajectory of olfactory performance by initial visit impairment status

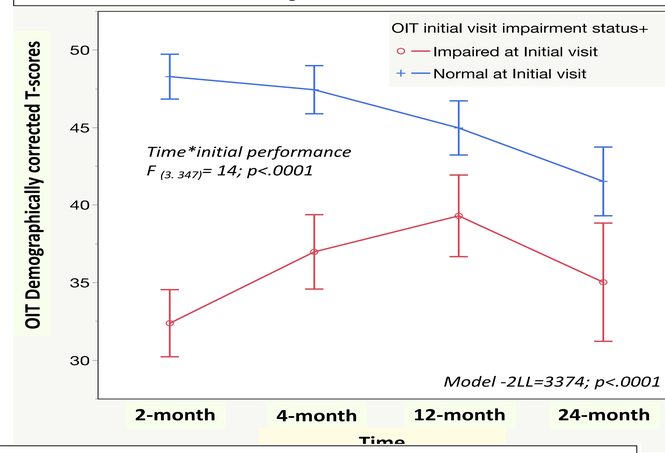
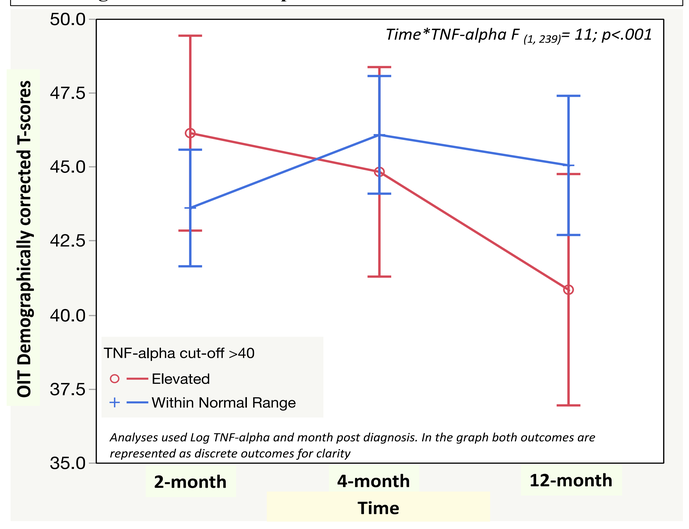


Fig 4: Elevated TNF-alpha covaries with olfaction difficulties



CONCLUSIONS

Persistent olfaction impairment is a concern months after the initial infection. While we corrected for attrition in our data analyses, 24-month data warrant replication in larger samples. Our data support that neurocovid is *not* a single neuropathogenetic entity.

ADDITIONAL KEY INFORMATION

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