Alterations in smell or taste – Classic COVID-19?

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Dear Editor,

There are increased reports of loss of smell (anosmia) and taste (ageusia) in patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causing coronavirus disease 2019 (COVID-19), in particular in the setting of mild disease. The data to date has been presented predominantly from post-diagnosis surveys or retrospective cohort series[1-5]. The pathogenesis is postulated to be due to invasion of the olfactory neuroepithilium and olfactory bulb, seen previously in other coronaviruses, due to the high expression of angiotension-converting enzyme (the receptor which allows virus cellular entry) present in the respiratory system[1, 6]. Luers and colleagues described from a retrospective adult cohort of confirmed SARS-CoV-2 from Germany (n = 72) that 74% of patients reported anosmia and 69% ageusia [7]. Spinato *et al*. prior to this also described from a retrospective cohort study of COVID-19 patients interviewed 5-6 days post diagnosis that 64.4% reported alternations in taste or smell[1]. However, both these studies suffer from the absence of a control group and significant limitation of recall and selection bias. Further, both fail to answer the question if anosmia and ageusia are in fact more frequent in COVID-19 patients than those with other upper respiratory tract infections.

To address the identified deficiencies of current data presented we utilized a prospectively collected dataset from patients assessed at our institution's COVID-19 screening clinic (Melbourne, Australia) between 1 April to 22 April 2020 (Data collection, see **eMethods**) to determine if anosmia and/or ageusia were more frequent in patients with confirmed SARS-CoV-2 infection.

1788 patients underwent clinical evaluation; we identified that 40 (2.2%) of patients reported both anosmia and ageusia, with 3.1% (56) for anosmia alone and 4.1% (74) for ageusia alone. Similar proportions were seen in the subgroup of 1236 patients who subsequently underwent SARS-CoV-2 testing (**eTable 1**). The distribution of symptom prevalence over time is displayed in **eFigure 1**. In those who underwent SARS-CoV-2 testing, anosmia or ageusia were more frequently reported in females and in those reporting more symptoms (**eTable1**). Of those who reported anosmia or ageusia, 9.3% tested positive for COVID-19 (positive predictive value), while the negative predictive value was 98.5%. Ansomia and/or ageusia were more common in COVID-19 positive than negative (39.3%

vs 8.9%, p <0.001), and were more common when examined in isolation: anosmia (25% vs 5%, p <0.001) or ageusia (25% vs 6%, p = 0.002) (**Table 1**). After adjusting for confounders, both anosmia and ageusia were independently associated with SARS-CoV-2 infection, e**Table 2**.

Whilst supporting the observations made by Leuers[7] and Spinato[1], our data also highlights a significantly lower prevalence of symptoms in a comparative outpatient COVID-19 population (39.3% [AUS] versus 64.4% [US] versus 68% [Germany]) when prospective data is used. Also, we demonstrate similar olfactory symptoms in the control group (SARS-CoV-2 negative). It is important for clinicians to realize that ansomia and ageusia are likely to be commonly reported symptoms in other upper respiratory tract infections, when appropriately asked (8.9% of our COVID-19 test negative group)[3, 8]. From data available, anosmia and/or ageusia whilst associated with COVID-19 should not yet be considered pathognomonic for the disease. Larger prospective population studies are required to validate these findings, as we collectively search for key clinical predictors of COVID-19 that can aid clinical decision making.

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Conflicts of interest – Nil

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Table 1 – Baseline demographics of patients assessed for COVID-19 screening clinic that underwent SARS-CoV-2 testing.

Variable		Overall	Not detected	Detected	p-value
N		1236	1208	28	
Age, years, median (IQR)		42 (31, 56)	42 (31, 56)	55 (46, 63.5)	<0.001
Sex - male		427 (34.5%)	413 (34.2%)	14 (50.0%)	0.11
Not indigenous		1153 (93.3%)	1127 (93.3%)	26 (92.9%)	0.21
Comorbidities					
	Cardiovascular disease	62 (5.0%)	60 (5.0%)	2 (7.1%)	0.65
	Diabetes	50 (4.0%)	50 (4.1%)	0 (0.0%)	0.62
	Hypertension	146 (11.8%)	140 (11.6%)	6 (21.4%)	0.13
	Smoking	100 (8.1%)	100 (8.3%)	0 (0.0%)	0.16
	Chronic renal or liver disease	14 (1.1%)	14 (1.2%)	0 (0.0%)	1.00
	Immunosuppressed	62 (5.0%)	61 (5.0%)	1 (3.6%)	1.00
	Chronic respiratory disease	146 (11.8%)	144 (11.9%)	2 (7.1%)	0.76
Overseas health facility exposure		34 (2.8%)	33 (2.7%)	1 (3.6%)	0.70
Australian health facility exposure		157 (12.7%)	155 (12.8%)	2 (7.1%)	<0.001
Contact with confirmed COVID-19 patient		132 (10.7%)	117 (9.7%)	15 (53.6%)	<0.001
Overseas travel		29 (2.3%)	29 (2.4%)	0 (0.0%)	1.00
Number of symptoms					0.13
	0	33 (2.7%)	31 (2.6%)	2 (7.1%)	
	1	120 (9.7%)	120 (9.9%)	0 (0.0%)	
	2	223 (18.0%)	220 (18.2%)	3 (10.7%)	
	3	272 (22.0%)	266 (22.0%)	6 (21.4%)	
	4 or more	588 (47.6%)	571 (47.2%)	17 (60.7%)	
Symptoms					
	Anosmia (with or without ageusia)	69 (5.6%)	62 (5.1%)	7 (25.0%)	<0.001
	Ageusia (with or without anosmia)	76 (6.1%)	69 (5.7%)	7 (25.0%)	0.001
	Anosmia or ageusia	118 (9.5%)	107 (8.9%)	11 (39.3%)	<0.001
	Anosmia and ageusia	27 (2.2%)	24 (2.0%)	3 (10.7%)	0.021
	Any fever	477 (38.6%)	463 (38.3%)	14 (50.0%)	0.24
	Fever > 38 C	114 (9.2%)	108 (8.9%)	6 (21.4%)	0.038
	Fever subjective	384 (31.1%)	375 (31.0%)	9 (32.1%)	1.00
	Shortness of breath	412 (33.3%)	401 (33.2%)	11 (39.3%)	0.54
	Sore throat	806 (65.2%)	792 (65.6%)	14 (50.0%)	0.11
	Sinusitis	4 (0.3%)	4 (0.3%)	0 (0.0%)	1.00
	Cough	808 (65.4%)	787 (65.1%)	21 (75.0%)	0.32
	Chest pain	37 (3.0%)	37 (3.1%)	0 (0.0%)	1.00
	Coryza	629 (50.9%)	618 (51.2%)	11 (39.3%)	0.25
	Diarrhoea	193 (15.6%)	185 (15.3%)	8 (28.6%)	0.065
	Other GI symptoms	24 (1.9%)	24 (2.0%)	0 (0.0%)	1.00

	Malaise/myalgia/arthralgia	584 (47.2%)	569 (47.1%)	15 (53.6%)	0.57
	Headache	159 (12.9%)	153 (12.7%)	6 (21.4%)	0.16
SPO2, median (IQR)		98 (97, 99)	98 (97, 99)	98 (96, 99)	0.24
Temperature Tympanic, median (IQR)		36.7 (36.4, 36.9)	36.7 (36.4, 36.9)	36.7 (36.3, 37.1)	0.43
Systolic Blood Pressure, median (IQR)		133 (121, 147)	133 (121, 147.5)	128.5 (119.5, 145.5)	0.54
Diastolic Blood Pressure, median (IQR)		80 (74, 87)	80 (74, 87.5)	82 (75.5, 85.5)	0.71
Respiratory Rate, median (IQR)		18 (17, 19)	18 (17, 19)	18 (17, 20)	0.22
Pulse Rate, median (IQR)		84 (74, 96)	84 (74, 96)	85 (73.5, 98)	0.79