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Chemosensory assessment and impact on quality of life in neurosensorial cluster of the post COVID 19 syndrome

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COVID-19 pandemic brought chemosensory impairment to the forefront of medicine, revealing gaps in the knowledge of pathophysiological mechanisms, true prevalence and preventive/therapeutic alternatives. This is a sub-study of the ORCHESTRA cohort focusing on post-COVID-19 chemosensory symptoms. Risk factors for neurosensorial cluster of post-COVID-19 syndrome (NSc-PCS) were assessed through multivariable analysis. Psychophysical validated tests were applied on a sub-population of 50 patients. Qualitative chemosensory symptoms as well as nasal and oral chemesthesis were evaluated through anamnestic interview and the quality of life through the SF-36 questionnaire. Chemosensory symptoms evolution and olfactory training's outcome were assessed through phone-call interviews. Out of 1187 patients (female, N = 630), 550 (47%) presented NSc-PCS, with a lower risk for older age and monoclonal antibodies treatment, and a higher risk in females ($p < 0.001$). Out of the 50 patients evaluated with psychophysical tests, 66% showed smell reduction with a qualitative alteration in 50% of hyposmic and 35% of normosmic patients. Hypogeusia was present in 14 (28%) of the patients assessed, with 56% showing a qualitative alteration; 53% of normogeusic patients presented qualitative disorders. NSc-PCS has a complex, fluctuating, multifaceted presentation. Quantifying and characterizing COVID-19-related chemosensory impairment is key to understand underlying mechanisms and to develop preventive and therapeutic treatment.

Keywords Chemosensory impairment, Post-COVID syndrome, SARS-CoV-2 long-term sequelae

Abbreviations

AUROC	Area under the ROC curve
BAU	Binding antibody units
BMI	Body mass index
CI	Confidence interval
COVID-19	COronaVIrus Disease 19
HIV	Human immunodeficiency virus
ICU	Intensive care unit
NRS	Numeric rating scale
NSc-PCS	Neurosensorial cluster of post-COVID-19 syndrome
OR	Odds ratio
PAC	Psychophysical assessment of chemosensory impairment
PCS	Post-COVID-19 syndrome

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QoL	Quality of life
RBD	Receptor-binding domain
REDCap	Electronic data capture tool (Research Electronic Data CAPpture)
SD	Standard deviation
SF-36	36-Item Short Form Survey
SRC	Self-reported chemosensory impairment
SSET	Sniffin' Sticks Extended Test
TDI	Threshold (T), discrimination (D) and identification (I)
TST	Taste Strips Test
VoCs	Variants of concern

The COVID-19 pandemic brought taste and smell impairment to the forefront of medicine, revealing considerable gaps in the knowledge of underlying pathophysiological mechanisms. Olfactory and gustatory dysfunction are reported in more than half of the infected individuals during the first wave of COVID-19, often as the first, and sometimes as the sole presentation of the acute disease[1]. Accordingly, some authors proposed that chemosensory symptoms could be used as early predictors of SARS-CoV-2 spread in the population[2–4]. More recently, smell dysfunction showed two to tenfold lower prevalence among Omicron-infected patients compared to those with other variant of concerns (VoCs), mostly Delta[5] and persistence after the resolution of the acute phase in a considerable proportion of individuals[6–12]. Furthermore, sustained smell loss at 12 months is suggested to be permanent[13], while an improvement in olfactory function has been observed after olfactory training[14].

Patients reporting an olfactory and/or gustatory impairment may experience poor appetite and malnutrition. Furthermore, people with anosmia or ageusia are at an increased risk to accidentally consuming spoiled or rancid foods or being unaware when they are breathing toxic, polluted or smoke-filled air. Hence, olfactory and gustatory evaluation by means of validated tests is essential to correctly identify patients with such impairments[15]. Currently, chemosensory dysfunction is detected both through self-reported methods (including interviews, surveys, and electronic health records) and through validated psychophysical assessment[16–18].

As a sub-study of the ORCHESTRA (connecting European cohorts to increase common and effective response to SARS-CoV-2 pandemic) Project[12,19], aiming at tackling the Coronavirus pandemic to establish an international large-scale-cohort to generate rigorous evidence in the field of prevention and treatment of SARS-CoV-2 infection, the present study offers a comprehensive evaluation of the neurosensorial cluster of post-COVID-19 syndrome (NSc-PCS) across the different stages of COVID-19 disease, including a comparison between self-reporting and psychophysical tests, the characteristics and determinants of chemosensory impairment, the outcome of the olfactory training, and the impact on quality of life (QoL) through the 36-Item Short Form Survey (SF-36) questionnaire.

Results

The cohort included 1187 patients (630, 53% female) diagnosed with a SARS-CoV-2 infection between February 2020 and April 2022 (Fig. 1, Table 1).

Of these, 47% (550) reported smell/taste dysfunction at any time point (NSc-PCS). Persistent symptoms were observed in 7%, while 22 experienced fluctuating symptoms. Over 50% have reported a recovery from smell and taste impairments within 4- and 5-months, respectively. By month 14, reporting recovery rates decreased, with ~ 1% in smell and 2% in taste improvements until month 21 (Supplement, Fig. 1). For ~ 5% patients chemosensory impairment started after the infection.

Patients with NSc-PCS exhibit significantly lower anti-SARS-CoV-2 (RBD) (1243.35 vs 4921.72 BAU; $p < 0.001$) and neutralization antibodies titers (12.57 vs 26.65 BAU; $p < 0.001$) compared to patients without PCS, with no relevant differences in laboratory parameters. QoL differences were non-significant, except for lower vitality subscale in NSc-PCS (52.21 vs 55.09, $p = 0.011$) (Supplement, Figs. 2, 3, 4).

Determinants of self-reported neurosensorial impairment during the acute phase and follow up

Chemosensory impairment prevalence was higher during the July-December 2020, and the lower in early 2022, when Omicron VoC was predominant (Fig. 2). Acute smell and taste impairments were strongly positively associated (Matthews coefficient 0.81; $p < 0.001$). Multivariable risk factors models for chemosensory symptoms during the acute infection included significant variables from the bivariable analysis (Supplement, Figs. 5, 6). Models yielded AUROC values of 0.81 and 0.82 for smell and taste, respectively. The risk of smell and taste dysfunction during acute COVID-19 was higher for females (smell OR: 3.36; taste: OR: 2.42; $p < 0.001$) and second wave (OR: 3.83; taste: OR: 3.23; $p < 0.001$). The probability of smell impairment decreased with age (OR: 0.41; $p = 0.014$), while that of taste impairment was lower for breakthrough infection (OR: 0.44; $p = 0.039$) (Table 2).

Two multivariable models identified risk factors for NSc-PCS. The first highlighted that smell and taste impairment during the acute phase were significant predictors (smell OR: 16.05, $p < 0.001$; taste OR: 3.67, $p = 0.003$) (Table 3). Older age was associated with a lower NSc-PCS risk, while monoclonal antibodies, hospitalization, and VoCs during the third wave reduced olfactory dysfunction risk in the follow-up. The second set of models (both AUROC > 0.80), excluding acute chemosensory symptoms, confirmed age ($p < 0.001$, both for smell and taste) and monoclonal antibodies (smell: $p = 0.025$; taste: $p = 0.022$) to be associated with a lower risk for NSc-PCS, while females had a higher probability to develop chemosensory sequelae (smell: $p < 0.001$; taste: $p = 0.043$) (Table 4).

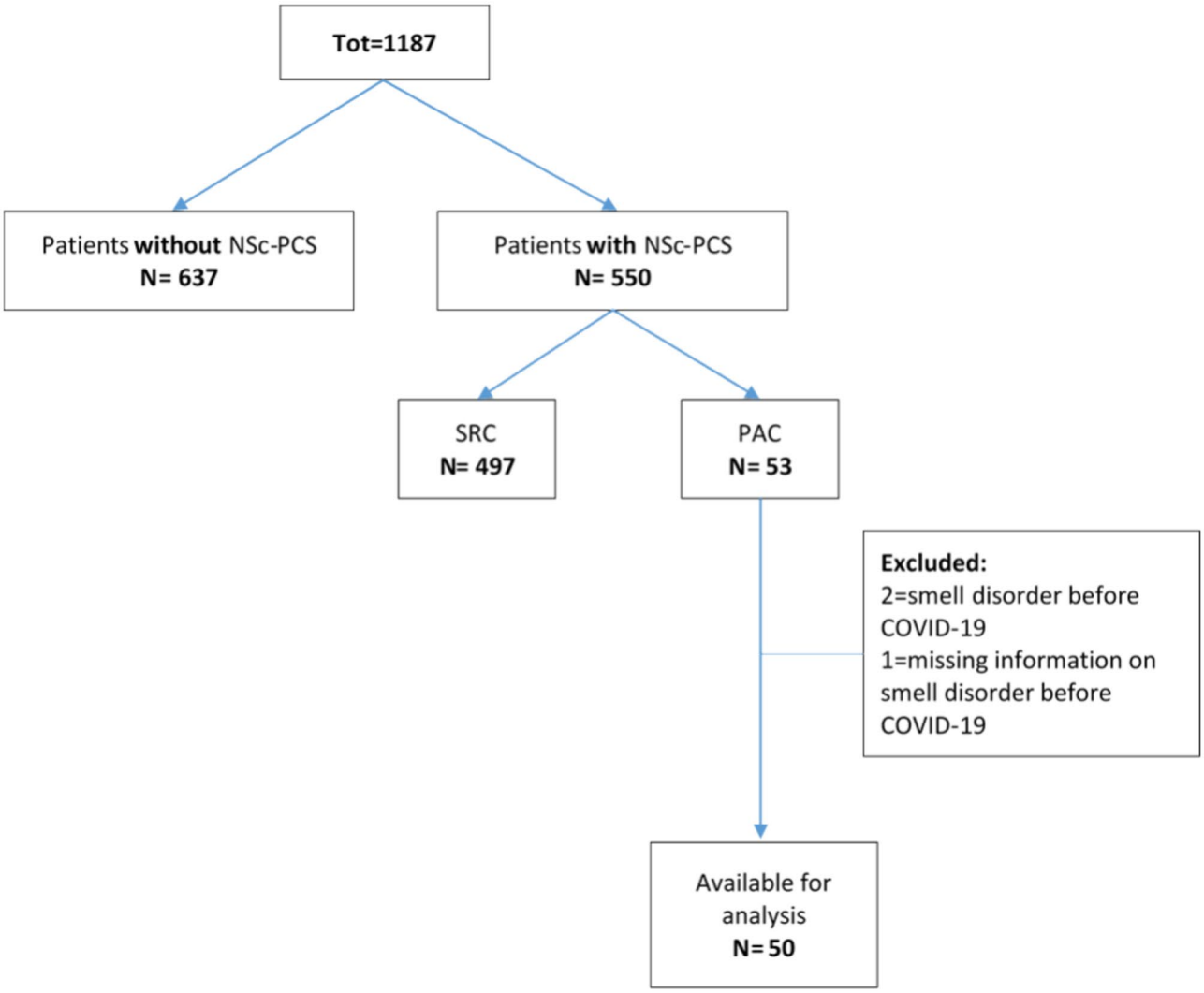

Fig. 1. Flow chart of the study. NSc-PCS: neurosensorial cluster of post-COVID syndrome, including smell and/or taste impairment; SRC: Self-Reported Chemosensory impairment group; PAC: Psychophysical Assessment of Chemosensory impairment group.

Comparison between patients with psychophysical assessment of chemosensory impairment (PAC, N = 50) and patients who self-reported chemosensory impairment (SRC N = 497)

PAC patients were mostly female (36, 71%), and younger than the SRC (PAC: 45.3 ± 16.81, SRC: 52.48 ± 14.28; $p = 0.002$), with no significant differences in demographic and epidemiological features (Table 1). More PAC patients were infected during the second ($p = 0.004$) and fewer during the first waves ($p = 0.003$) compared to SRC. Smell impairment was equally reported during the acute infection but more prevalent in the PAC during follow up ($p < 0.001$ for each of all time points). Taste impairment was similar between PAC and SRC during acute infection and the first three months, but PAC showed higher prevalence in the follow up ($p < 0.001$ for 6-, 12-, and 18-months follow up) (Table 1). PAC patients exhibited a slower resolution of smell and taste impairments compared to SRC. The time between the acute phase and psychophysical assessment varied from 105 to 705 days (average 415 ± 149 days), and difference between the assessment and the follow-up phone-call ranged from 130 to 473 days (average 318 ± 98 days) (Supplement, Fig. 7).

Characteristics of smell and taste function in PAC (N = 50)

Three patients, two with a pre-existing smell disorder, and one with information missing, were removed, resulting in a dataset of 50 patients (Fig. 1). Of these, 96% experienced smell impairment during the acute infection and 98% at the chemosensory evaluation. A lower rate of self-reported smell impairment was detected at the phone-call interview compared to the chemosensory evaluation (74% vs 98%; $p < 0.001$).

The mean TDI score was 24.1 (SD: 7.51). A quantitative smell deficit, predominantly hyposmia, was detected in 33 (66%) patients. Among patients with smell impairment, half had a qualitative disorder, mostly parosmia and consistently unpleasant. Thirty-five percent of normosmic patients presented either parosmia or phantosmia. At the phone-call interview, 36 (73%) patients still reported smell impairment, with 23% reporting a qualitative

	Patients without NSc-PCS (N = 637)	Patients with NSc-PCS (N = 550)		
		SRC (N = 497)	PAC (N = 50)	SRC vs PAC
Demographics				
Age	59.65 ± 14.14	52.48 ± 14.28	45.3 ± 16.81	**0.002**
BMI	29.15 ± 5.44	27.46 ± 5.15	26.27 ± 3.2	0.740
Female	293 (46.0%)	301 (60.56%)	36 (70.59%)	0.176
Current smoker	44 (7.72%)	45 (23.94%)	9 (50.0%)	**0.02**
Breakthrough infection	87 (13.66%)	42 (8.48%)	1 (1.96%)	0.165
Hospital admission	238 (37.36%)	151 (30.38%)	9 (17.65%)	0.074
ICU admission	72 (11.3%)	32 (6.44%)	4 (7.84%)	0.764
Vaccinated before acute infection	215 (33.86%)	121 (24.35%)	11 (20.75%)	0.36
Pregnancy	1 (0.35%)	3 (1.03%)	1 (2.78%)	0.76
Diabetes	73 (11.48%)	30 (6.1%)	2 (3.77%)	0.76
HIV	2 (0.31%)	1 (0.2%)	0 (0.0%)	1.000
Transplant patient	10 (1.57%)	3 (0.6%)	0 (0.0%)	1.000
Autoinflammatory disease	35 (5.49%)	31 (6.24%)	1 (1.89%)	0.349
Cardiovascular disease	315 (49.61%)	169 (34.42%)	15 (28.3%)	0.446
Chronic liver disease	17 (2.68%)	11 (2.24%)	1 (1.89%)	1.000
Chronic kidney disease	28 (4.5%)	10 (2.06%)	1 (1.96%)	1.000
COVID-19 complications				
Pulmonary	13 (2.04%)	9 (1.81%)	1 (1.89%)	1.000
Cardiac	26 (4.08%)	10 (2.01%)	1 (1.89%)	1.000
Embolic	16 (2.51%)	8 (1.61%)	1 (1.89%)	0.601
Neurological	3 (0.47%)	2 (0.4%)	0 (0.0%)	1.000
Renal	13 (2.04%)	6 (1.21%)	1 (1.89%)	0.510
Gastrointestinal	11 (1.73%)	4 (0.8%)	1 (1.89%)	0.399
Any COVID-19 complication	64 (10.05%)	32 (6.44%)	4 (7.55%)	0.768
Therapy during acute phase				
Corticosteroids	211 (36.01%)	177 (37.74%)	12 (23.08%)	**0.047**
Antivirals	104 (16.69%)	80 (16.39%)	1 (1.92%)	**0.003**
Immunomodulators	21 (3.42%)	20 (4.11%)	0 (0.0%)	0.242
Chloroquine	3 (0.47%)	2 (0.4%)	0 (0.0%)	1.000
Hydroxychloroquine	71 (11.15%)	64 (12.88%)	0 (0.0%)	**0.002**
Azithromycin	36 (5.65%)	46 (9.26%)	2 (3.77%)	0.301
Ivermectin	1 (0.16%)	1 (0.2%)	0 (0.0%)	1.000
Colchicin	3 (0.47%)	0 (0.0%)	0 (0.0%)	1.000
Monoclonal antibodies	262 (42.12%)	109 (22.2%)	4 (7.55%)	**0.012**
Anticoagulants	193 (31.08%)	131 (26.68%)	9 (17.31%)	0.182
Self-reported smell impairment				
Acute		417 (85.63%)	50 (94.34%)	0.091
Month 3		35 (23.65%)	8 (72.73%)	< **0.001**
Month 6		64 (21.4%)	28 (87.5%)	< **0.001**
Month 12		47 (15.36%)	36 (75.0%)	< **0.001**
Month 18		32 (12.4%)	32 (80.0%)	< **0.001**
Acute		417 (85.63%)	50 (94.34%)	0.091
Self-reported taste impairment				
Acute		424 (87.42%)	47 (88.68%)	1.000
Month 3		25 (32.05%)	5 (55.56%)	0.265
Month 6		61 (36.97%)	27 (84.38%)	< **0.001**
Month 12		47 (27.33%)	35 (79.55%)	< **0.001**
Month 18		26 (10.04%)	27 (67.5%)	< **0.001**
Waves				
1st wave	92 (14.44%)	77 (15.49%)	1 (1.89%)	**0.003**
2nd wave	97 (15.23%)	144 (28.97%)	25 (47.17%)	**0.004**
3rd wave	271 (42.54%)	165 (33.2%)	21 (39.62%)	0.362
4th wave	154 (24.18%)	101 (20.32%)	6 (11.32%)	0.066

Continued

	Patients without NSc-PCS (N = 637)	Patients with NSc-PCS (N = 550)		
		SRC (N = 497)	PAC (N = 50)	SRC vs PAC
Symptoms during acute infection				
Fatigue	369 (59.9%)	373 (77.87%)	31 (59.62%)	**0.006**
Dyspnoea	227 (36.97%)	209 (43.63%)	12 (23.53%)	**0.007**
Myalgia	217 (35.57%)	252 (5239%)	23 (44.23%)	0.307
Arthralgia	167 (27.24%)	215 (45.07%)	19 (36.54%)	0.303
Headache	152 (24.92%)	229 (47.61%)	20 (38.46%)	0.243
Memory loss	35 (5.72%)	41 (8.51%)	4 (7.69%)	1.000
Cough	325 (52.25%)	289 (59.59%)	18 (34.62%)	**0.001**

Table 1. Demographic characteristics in the UNIVR Orchestra cohort: comparison between patients not reporting chemosensory impairment (patients without NSc-PCS, N = 637) and patients with chemosensory impairment (patients with NSc-PCS, N = 550), either only self-reported (SRC, N = 497) or detected through a psychophysical assessment (PAC, N = 50). NSc-PCS: neurosensorial cluster of post-COVID-19 syndrome; SRC: self-reported chemosensory impairment; PAC: psychophysical assessment of chemosensory impairment; BMI: body mass index; ICU: intensive care unit; HIV: human immunodeficiency virus; COVID-19: COronaVIrus Disease 19. Significant values are in bold.

disorder. Despite 82% of patients engaging in the olfactory training, and half of them completing the protocol, 75% continued to report smell impairment (Fig. 3, Table 5).

No patient reported taste impairment pre-COVID-19, while most experienced it during acute infection (45, 90%) and at the neurosensorial evaluation (38, 76%). At the phone-call interview, a lower proportion reported taste impairment (53% vs 76%; $p = 0.012$). The mean TST score was 11.6 (SD: 2.81). Most patients were normogeusic (36, 72%), with the remaining (14, 28%) presenting with hypogeusia. No cases of ageusia emerged. Over half of the patients showed a qualitative alteration (28, 56%), mostly parageusia, always described as unpleasant. More than half (19, 53%) of TST normogeusic patients reported at least one qualitative disorder. During the phone-call interview, 26 (53%) patients still reported taste impairment, especially parageusia with unpleasant valence (14, 29%). Among hypogeusic patients some showed reduced scores for single taste qualities (i.e. sweet, sour, salty, bitter) (Fig. 3, Table 5).

Deficit in nasal chemesthesis, was reported especially at the acute phase, and in 6 (12%) patients persisted until the chemosensory evaluation. 26 (52%) patients reported nasal congestion during acute infection, which was negatively associated with chemesthesis (Cohen's − 0.27; $p = 0.077$). Considerably less patients reported deficit in oral compared to nasal chemesthesis at the acute infection (28% vs 76%), while these proportions were similar at the chemosensory evaluation (10% and 12%, respectively) (Table 5).

A combined smell and taste quantitative impairment occurred in 11 (22%) patients, while 14 (28%) had normal function for both smell and taste (Supplement, Fig. 8). A majority (28, 56%) reported impairments in both smell and taste. Among these, 20% experienced persistent taste but fluctuating smell impairment, whereas four patients (8%) reported a fluctuating smell with persistent taste impairments, and in eight patients (16%), both were fluctuating.

The proportion of patients reporting smell and taste impairments decreased between the chemosensory evaluation and the phone-call interview. Parosmia showed a stable decreasing trend ($p = 0.100$), while phantosmia increased ($p = 0.013$). The prevalence of parageusia decreased significantly ($p < 0.001$), while for phantogeusia the decrease was not significant ($p = 0.152$). Parosmia and phantosmia were positively associated at the acute phase (Cohen's 0.42; $p = 0.01$) and during the phone-call (Cohen's 0.42; $p = 0.005$). Phantosmia at the acute phase and chemosensory evaluation were positively associated (Cohen's 0.46; $p = 0.005$).

Among patients with normal psychophysical assessment, the proportion of patients with qualitative taste was higher compared to qualitative smell disturbances (53% vs 35%). When examining chemosensory patterns, disregarding temporal aspects and considering reports at any time during follow-up, the two most prevalent patterns consisted of: (a) self-reported smell and taste impairments without any qualitative alterations and normal SSET and TST results; and (b) quantitative impairment (either hyposmia or functional anosmia) together with parosmia and parageusia (Supplement, Table 1). Only parosmia and parageusia at any time showed an agreement (Cohen's: 0.52; $p < 0.001$).

TDI scores were significantly lower in women (22.85 ± 7.36 vs 27.15 ± 6.97; $p = 0.050$), and 20–40 age group (22.4 ± 6.92 vs 27.24 ± 7.52; $p = 0.013$). Patients hospitalized during the acute infection presented higher TDI scores (25.26 ± 7.58 vs 19.06 ± 4.49; $p = 0.015$). Conversely, TST scores were higher in women (12.11 ± 2.73 vs 10.4 ± 2.63; $p = 0.030$). Arthralgia (10.22 ± 3.14 vs 12.29 ± 2.26; $p = 0.025$) and taste impairment during the acute infection (11.33 ± 2.83 vs 14.0 ± 0.89; $p = 0.033$) were associated with lower TST scores (Supplement, Tables 2, 3).

SF-36 QoL assessment conducted close to the chemosensory evaluation (63 ± 50 days), was available for 46 patients. Patients experiencing phantosmia during follow-up showed a decrease in the physical functioning (50.72 vs 57.03; $p = 0.022$), role limitations due to physical health (47.05 vs 56.85; $p = 0.018$), and social functioning (43.20 vs 56.85; $p = 0.002$) scales. Patients reporting phantogeusia presented a significant reduction in the summary physical score (48.99 vs 58.18; $p = 0.05$), and role limitations due to physical health scales (32.37 vs 56.85; $p = 0.012$) (Supplement, Figs. 9–12).

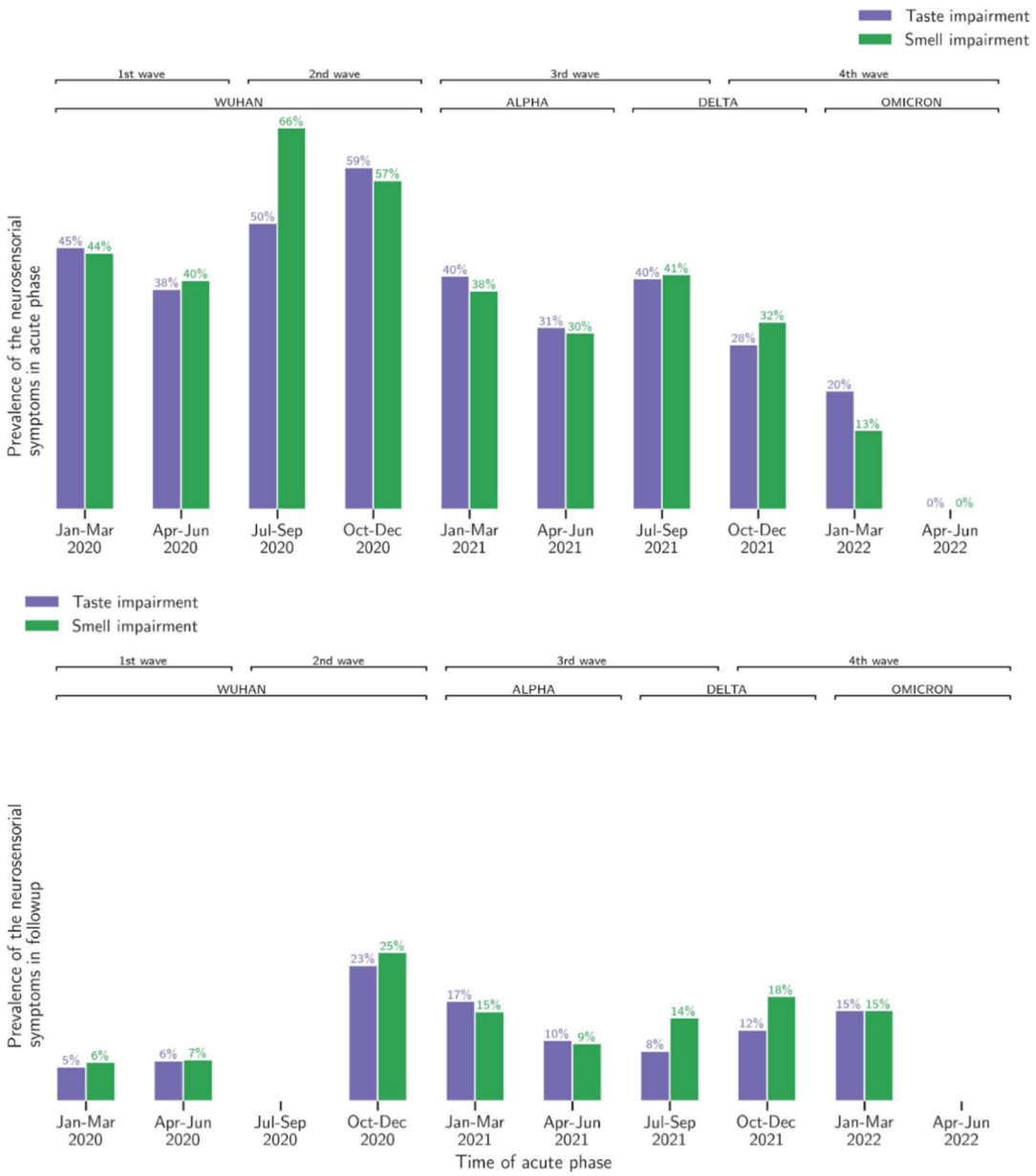

Fig. 2. Prevalence of self-reported chemosensory symptoms in the acute phase (top panel) and at the follow-up (bottom panel), by the time of the acute phase and annotated with the waves and variants dominating in Europe, based on the Nextstrain prevalence data. Only groups with at least 10 patients are shown.

Discussion

This study offers a comprehensive analysis of chemosensory impairment across the acute and lingering stages of COVID-19 disease. We analyzed the risk factors for acute smell/taste impairment, and for developing NCs-PCS. We also assessed the differences in the levels of serological and biochemical markers of the patients, and the impact on the quality of life. A subset of patients with NSc-PCS underwent a detailed chemosensory evaluation through the collection of qualitative smell and taste disorders and by means of validated psychophysical tests including for smell, besides identification, also discrimination and thresholds assessment. Overall, we confirmed the high prevalence of chemosensory impairment reported in literature[20,21], as almost half of the patients reported a smell/taste dysfunction at any time point, and the possible persistence of symptoms up to 18 months. In a large proportion of patients, we observed a fluctuating trend over time of chemosensory symptoms. This may contribute to inaccurate prevalence estimates of NSc-PCS and undermine the reliability of cross-sectional studies.

Consistently with previously published data[12], patients with NSc-PCS did not present an overall reduction in QoL at SF-36 questionnaire. However, an impact of some qualitative disorders on different SF-36 domains was observed, thus suggesting that qualitative alteration might influence specific aspects of QoL. Further research is warranted to enable a better measurement of the effect of the different types of chemosensory impairment on QoL.

	Smell impairment at acute AUROC: 0.81 N = 1059, 413 positive				Taste impairment at acute AUROC: 0.82 N = 1061, 421 positive			
Variable	**OR**	**CI_low**	**CI_high**	***p*-value**	**OR**	**CI_low**	**CI_high**	***p*-value**
Age	0.41	0.2	0.84	**0.014**	0.92	0.44	1.93	0.82
Breakthrough infection	0.58	0.27	1.21	0.148	0.44	0.2	0.96	**0.039**
Diabetes	0.58	0.28	1.2	0.144				
Vaccination before COVID-19	0.93	0.54	1.6	0.803	0.89	0.51	1.55	0.688
Cardiovascular disease	1.09	0.69	1.73	0.71	0.83	0.51	1.34	0.443
Female	3.36	2.26	4.99	**< 0.001**	2.42	1.61	3.63	**< 0.001**
2nd wave	3.83	2.15	6.82	**< 0.001**	6.77	3.23	14.2	**< 0.001**
4th wave					0.94	0.54	1.64	0.821

Table 2. Results of the multivariable models for a binary outcome of experiencing smell (left) and taste (right) impairments during the acute phase. AUROC: area under the roc curve; OR: odd ratio; CI: confidence interval; COVID-19: COronaVIrus Disease 19. Significant values are in bold.

	Smell impairment at follow-up AUROC: 0.96 N = 982, 126 positive				Taste impairment at follow-up AUROC: 0.88 N = 989, 118 positive			
Name	**OR**	**CI_low**	**CI_high**	***p*-value**	**OR**	**CI_low**	**CI_high**	***p*-value**
Age	0.03	0.01	0.12	**< 0.001**	0.01	0.0	0.03	**< 0.001**
3rd wave	0.27	0.13	0.54	**< 0.001**				
Hospitalization	0.31	0.14	0.67	**0.003**				
Monoclonal antibodies	0.41	0.19	0.9	**0.027**	0.53	0.27	1.01	0.054
Headache during acute COVID-19	0.55	0.3	1.02	0.059	0.8	0.46	1.37	0.417
2nd wave	0.63	0.3	1.34	0.231	1.46	0.78	2.75	0.237
Cardiovascular disease	0.75	0.38	1.48	0.412				
Taste impairment during acute COVID-19	1.1	0.43	2.77	0.845	3.67	1.58	8.55	**0.003**
Female	1.14	0.61	2.14	0.679	0.97	0.57	1.65	0.902
Nasal congestion during acute COVID-19	1.34	0.65	2.78	0.427	1.38	0.72	2.66	0.33
Smell impairment during acute COVID-19	16.06	6.07	42.52	**< 0.001**	1.81	0.78	4.22	0.167

Table 3. Results of the multivariable logistic regression models for a binary outcome of experiencing smell and taste impairments during any time of the follow up (months 3 to 18). AUROC: area under the roc curve; OR: odd ratio; CI: confidence interval; COVID-19: COronaVIrus Disease 19. Significant values are in bold.

	Smell impairment at follow-up AUROC: 0.84 N = 1066, 134 positive				Taste impairment at follow-up AUROC: 0.83 N = 1077, 127 positive			
Name	**OR**	**CI_low**	**CI_high**	***p*-value**	**OR**	**CI_low**	**CI_high**	***p*-value**
Age	0.08	0.03	0.25	**< 0.001**	0.04	0.01	0.11	**< 0.001**
3rd wave	0.35	0.19	0.64	**< 0.001**				
Hospitalization	0.4	0.12	1.26	0.118	0.45	0.22	0.92	**0.029**
Monoclonal antibodies	0.45	0.23	0.9	**0.025**	0.45	0.22	0.89	**0.022**
Corticosteroids	0.89	0.48	1.63	0.696	1.33	0.72	2.46	0.358
Oxygen therapy	1.11	0.31	3.96	0.872				
Cardiovascular disease	1.17	0.64	2.14	0.607				
2nd wave	1.42	0.74	2.73	0.296	2.19	1.23	3.92	**0.008**
Female	2.31	1.4	3.81	**< 0.001**	1.63	1.02	2.63	**0.043**

Table 4. Results of the multivariable logistic regression models for a binary outcome of experiencing smell and taste impairments during any time of the follow up (months 3 to 18). For these models the acute-phase symptoms were not used. AUROC: area under the roc curve; OR: odd ratio; CI: confidence interval. Significant values are in bold.

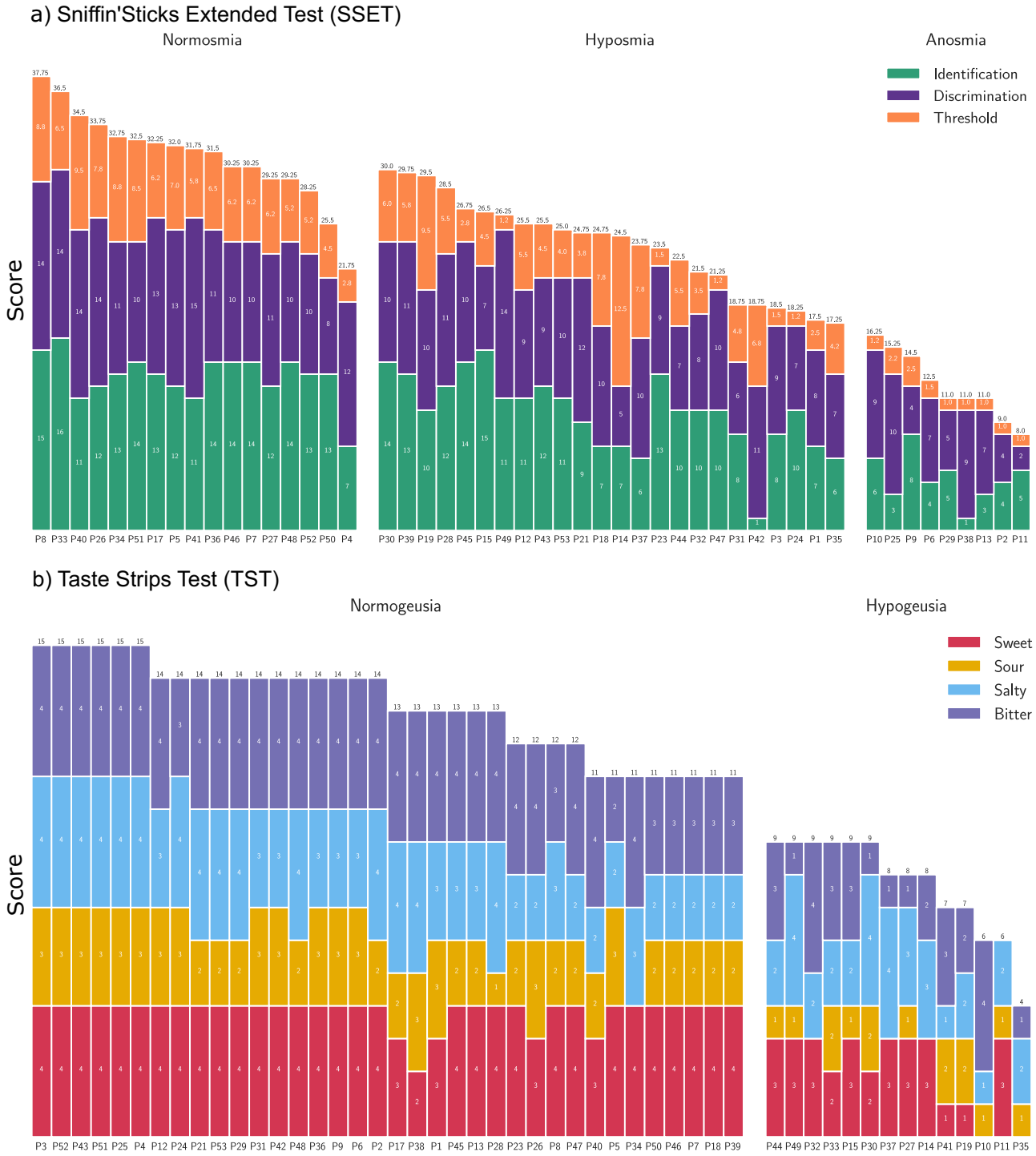

Fig. 3. Composite scores for SSET (top panel) and TST (lower panel). Each bar corresponds to a single patient. Colours correspond to the measurements of score composites. Each plot is divided into sections according with the cut offs defining normogeusia and hypogeusia for gustatory function and normosmia, hyposmia and anosmia for olfactory function. Each bar is annotated with the summary score. As the SSET cut-off was adjusted by age (see "Methods") the plot is not strictly monotonous.

In our cohort, being female and VoCs circulating during the second wave of the pandemic (when Delta variant was the dominating strain) were independently associated with a higher probability of acute chemosensory impairment. Conversely, older age was associated with a lower occurrence. Older age and early treatment for SARS-CoV-2 were confirmed to be associated with a lower occurrence of lingering chemosensory symptoms, while females were at higher risk of NSc-PCS. Pre-existing clinical conditions and COVID-19 severity did not show to increase the risk of long-lasting chemosensory impairment. These findings suggest that NSc-PCS is probably not driven by previous clinical conditions or by age, that patients with long-lasting smell/taste dysfunction

Chemosensory features	Acute infection	Chemosensory evaluation	Phone-call interview
Olfactory impairment			
Smell impairment reported	48 (96.0%)	49 (98.0%)	36 (73.5%)
Parosmia	10 (20.0%)	23 (47.9%)	18 (36.7%)
Phantosmia	9 (18.0%)	9 (18.0%)	17 (34.7%)
Parosmia and Phantosmia	5 (10.0%)	6 (12.5%)	11 (22.4%)
Parosmia or Phantosmia	14 (28.0%)	26 (53.1%)	24 (49.0%)
SSET assessment			
Anosmia	NA	9 (18.0%)	NA
Hyposmia	NA	24 (48.0%)	NA
Normosmia	NA	17 (34.0%)	NA
Patients with normosmia experiencing qualitative disorders			
Parosmia	NA	6 (6/17, 35.3%)	NA
Phantosmia	NA	2 (2/17, 11.8%)	NA
Parosmia and Phantosmia	NA	2 (2/17, 11.8%)	NA
Parosmia or Phantosmia	NA	6 (6/17, 35.3%)	NA
Gustatory impairment			
Taste impairment reported	45 (90.0%)	38 (76.0%)	26 (53.1%)
Parageusia	9 (18.4%)	25 (50.0%)	14 (28.6%)
Phantogeusia	5 (10.2%)	8 (16.3%)	5 (10.2%)
Parageusia and Phantogeusia	2 (4.2%)	5 (10.2%)	2 (4.1%)
Parageusia or Phantogeusia	12 (25.0%)	28 (56.0%)	17 (34.7%)
Sweet taste impairment	NA	27 (54.0%)	21 (42.0%)
Bitter taste impairment	NA	23 (46.0%)	21 (42.0%)
Salty taste impairment	NA	30 (60.0%)	23 (46.0%)
Sour taste impairment	NA	24 (48.0%)	22 (44.0%)
Umami taste impairment	NA	10 (23.8%)	8 (20.5%)
TST assessment			
Hypogeusia	NA	14 (28.0%)	NA
Normogeusia	NA	36 (72.0%)	NA
Sweet taste impairment	NA	2 (4.0%)	NA
Bitter taste impairment	NA	8 (16.0%)	NA
Salty taste impairment	NA	2 (4.0%)	NA
Sour taste impairment	NA	5 (10.0%)	NA
Patients with normogeusia experiencing qualitative disorders			
Parageusia	NA	18 (18/36, 50.0%)	NA
Phantogeusia	NA	3 (3/36, 8.0%)	NA
Parageusia and phantogeusia	NA	2 (2/36, 5.6%)	NA
Parageusia or phantogeusia	NA	19 (19/36, 52.8%)	NA
Sweet taste impairment	NA	0 (0.0%)	NA
Bitter taste impairment	NA	0 (0.0%)	NA
Salty taste impairment	NA	0 (0.0%)	NA
Sour taste impairment	NA	0 (0.0%)	NA
Umami taste impairment	NA	6 (6/36, 16.7%)	NA
Nasal chemesthesis			
Nasal chemesthesis deficit reported	38 (76.0%)	6 (12.0%)	NA
Air flux	8 (16.0%)	0 (0.0%)	NA
Air temperature	9 (18.0%)	1 (2.0%)	NA
Spicy food	18 (36.0%)	6 (12.0%)	NA
Nasal congestion	26 (52.0%)	0 (0.0%)	NA
Oral chemesthesis			
Oral chemesthesis deficit reported	14 (28.0%)	5 (10.0%)	NA
Food temperature	0 (0.0%)	0 (0.0%)	NA
Food texture	0 (0.0%)	0 (0.0%)	NA
Spicy food	14 (28.0%)	4 (8.0%)	NA
Fizzy drinks	1 (2.0%)	1 (2.0%)	NA

Continued

Chemosensory features	Acute infection	Chemosensory evaluation	Phone-call interview
Olfactory training information, at phone-call interview			
Patients involved in olfactory training	NA	40 (81.6%)	NA
Patients who completed olfactory training	NA	NA	20 (20/40, 50%)
Smell impairment reported	NA	NA	15 (15/20, 75%)
Parosmia	NA	NA	11 (11/20, 55%)
Phantosmia	NA	NA	8 (8/20, 40%)
Parosmia and Phantosmia	NA	NA	6 (6/20, 30%)

Table 5. Chemosensory features of the PAC (Psychophysical Assessment of Chemosensory impairment) cohort (N = 50) at the three timepoints: acute infection, neurosensorial evaluation, phone-call interview. SSET: Sniffin' Sticks Extended Test; TST: Taste Strips Test.

are more often young and otherwise healthy individuals and, ultimately, that COVID-19 severity does not influence the probability to develop chemosensory impairment. As is recognized, older age is a risk factor for smell and taste reduction. In our cohort, its negative association with chemosensory impairment suggests that the underlying mechanisms for NSc-PCS are different from those responsible for age-dependent smell/taste deterioration.

Females elicit a stronger humoral and cellular immune response compared to men, probably due to sex hormones and genetic factors[22], and local inflammation is reported to have a central role in the pathophysiological pathway leading to smell impairment[15]. Results from the present study and prior evidence[12,20] encourage further research to investigate the impact of early therapy for SARS-CoV-2 on acute and chronic chemosensory symptoms. Moreover, the effects of other therapies (i.e. corticosteroids or antivirals) in reducing acute inflammation and preventing PCS deserve to be explored through randomized clinical trials.

As published previously[12], data from this sub-study do not show that vaccination before infection has an impact on the prevalence of acute and long-lasting chemosensory symptoms. However, patients with NSc-PCS exhibit lower anti-RBD and neutralizing antibody titer compared to patients without PCS. In literature, the role of vaccination in preventing chemosensory symptoms is controversial. In a cross-sectional study, post-vaccination infections were less likely associated with loss of taste or smell[23], while, in another study, chemosensory dysfunctions were observed both in unvaccinated and fully vaccinated individuals[24]. As per the antibody decay, evidence on the association of a particular serological trend with the occurrence of long-term consequences are inconclusive, adding this aspect to the long list of issues to be addressed.

NSc-PCS has a complex, fluctuating multifaceted presentation. A qualitative disorder was diagnosed in more than one third of normosmic patients self-reporting a smell impairment and in more than half of the normogeusic individuals. This contributes to inaccurate prevalence estimates of NSc-PCS and confirms that patients often fail in distinguishing between quantitative and qualitative disorders, as well as between smell and taste impairment[25]. Direct (taste receptor cell injury) or indirect infection mechanisms through inflammatory cytokines, as well as the implication of the signalling pathway or impaired taste bud cells renewal, were suggested to be involved in determining gustatory impairment[26–29]. Our results underline the need to adopt validated tests to fully quantify and characterize COVID-19-associated chemosensory impairments[30].

At the phone-call interview, half of the patients who completed the training reported persisting smell impairment. The outcome of olfactory training was not assessed through psychophysical tests, hence patients reporting persisting dysfunction may have qualitative rather than quantitative impairment. The effectiveness of olfactory training is probably depending on training duration and aetiology of chemosensory impairment[31], hence the outcome in patients with COVID-related smell dysfunction needs to be assessed in large cohort studies[32].

This study has several limitations. Firstly, patients evaluated with psychophysical assessment may not be fully representative of the entire patient population. Patients experiencing long-lasting symptoms were probably more motivated to undergo further assessments, while, for the same reason, those asymptomatic were not assessed, thus we could not assess the accuracy of SSET and TST. Additionally, the timing of psychophysical assessment was not standardized. Therefore, this makes it hard to draw definitive conclusions.

However, most of the evidence available in literature presents self-reported data. COVID-19 is probably the first worldwide pandemic being characterised by such an extensive and accurate sharing of symptoms, supported by social media and telecommunication systems[3]. Self-reported symptoms can help collecting information but, in some cases, fail in giving an exhaustive picture of the problem. COVID-related olfactory and gustatory disturbances are often referred to as a mere reduction of the ability to perceive odours and tastes. However, the shades of different types of chemosensory impairments can vary considerably, and more detailed evaluations would be useful to better understand the problem. Validated tests were available well before COVID-19 but have been rarely used during the pandemic because they are time-consuming and could not be administered during acute infection and quarantine. In such circumstances, on-line questionnaires or phone-call interviews are more feasible, but subjective reports alone fail to measure the true prevalence of chemosensory impairment and to describe its diversity and complexity.

A very recent work by Sharetts et al. reported a nationwide post-Covid-19 study conducted in the US applying direct validated and self-administered taste and smell identification tests[33]. The mean time between Covid-19 onset and quantitative assessment was 395 days and they found no quantitative taste deficit while in one-third of

individuals some smell loss was revealed, pointing out that smell loss could be the reason for taste complaint. A detailed focus on the long-term qualitative disorders is also meaningful especially for taste, considering that we found a qualitative disorder in more than half of the normogeusic individuals. Indeed, the detailed mechanism of COVID-19 dysgeusia remains unknown and taste qualitative disorders are independent symptoms that need to be discussed separately[34,35]. Therefore, there is still a particular need for well-designed long-term studies analysing the determinants and risk factors for post-COVID-19 chemosensory impairment, combined with the quantitative assessment and detailed qualitative description of its characteristics[36].

We believe that this report, even if including a limited number of psychophysical evaluations, is of utmost importance to stress the utility of combining validated tests with self-reported symptoms in the context of post-COVID-19-related smell and taste dysfunction. This approach could fill existing gaps in NSc-PCS knowledge and may contribute to better understand post-infective chemosensory impairment.

Methods

Design of the study, definitions and population

This prospective monocentric cohort included patients with previous laboratory-confirmed SARS-CoV-2 infection enrolled at the University Hospital of Verona, within the ORCHESTRA long-term sequelae study, after a written informed consent was collected. As a sub-study, the present paper focuses on chemosensory evaluation through direct tests in patients diagnosed with NSc-PCS, as defined in the previously published study[12] and Supplement. To estimate differences according to the methodology of detection of chemosensory impairment, two groups were identified: one including patients with self-reported chemosensory impairment (SRC) without any further evaluation, and the second including patients who underwent the chemosensory evaluation with a psychophysical assessment (PAC) (Fig. 1).

In addition to the time-points foreseen by the study protocol[12], the dates of symptoms onset and end were extrapolated to account for exact duration of symptoms and recovery rates. A chemosensory evaluation, including an anamnestic interview and psychophysical validated tests, was conducted at the Neurology Unit of the University Hospital of Verona by qualified research staff. A subsequent follow up was performed through a phone-call interview.

To account for VoCs-related differences in chemosensory impairment[5], the epidemiological wave recorded in Italy at the time of acute infection was specified according to Nextstrain SARS-CoV-2 resources website for Europe[37] (Supplement, Definition).

The QoL was assessed through SF-36 questionnaire physical and mental component scores according to the study protocol[12]. Since the questionnaire was administered at different time points, the closest evaluation to the chemosensory assessment was selected.

Data were collected and managed using REDCap electronic data capture tool (Research Electronic Data CAPpture). The study was registered on ClinicalTrials.gov (CT registration number: NCT05097677) and the protocol is available at the ORCHESTRA website[19]. All investigations were carried out in accordance with the Helsinki Declaration and its later amendments. The protocol was approved by the Ethical Committee of the University Hospital of Verona (ORCHESTRA project-Prot. n. 3199CESC).

Chemosensory evaluation

Exclusion criteria for chemosensory evaluation were conditions known to affect smell and/or taste (e.g., recent traumatic event, otolaryngology disorders, stroke, neurodegenerative diseases). Qualitative disorders were assessed for both olfaction (i.e., phantosmia/parosmia) and taste (i.e. phantogeusia/parageusia). Intensity of perceptions was recorded by means of a Numeric Rating Scale (NRS) scale (0–10). Information was collected for nasal and oral chemesthesis too (i.e. nasal and oral trigeminal somatosensation, Table 5). The Sniffin' Sticks Extended Test (SSET, Burghart, Germany) was applied for evaluating smell dysfunction. This is a validated olfactory test consisting of odour dispensing pens, forced choice paradigm based, including three subtests assessing odour threshold (T), discrimination (D) and identification (I), respectively. The sum of results obtained in each test defines the "TDI score", indicating the olfactory performance *status* of the subject. The score was interpreted according to scores adjusted for age, according to literature[31,38]: between 11 and 20 years the cut-off was 28.5, 21–30: 30.75, 31–40: 30.5, 41–50: 28.15, 51–60: 27.25, 61–70: 24.88, 71–80: 19.2 and > = 81: 13.

An olfactory training was proposed to patients with smell impairment[17,39–41].

Gustatory impairment was assessed through the Taste Strips Test (TST, Burghart, Germany), using filter paper strips impregnated with the four taste qualities in four different concentrations (sweet: 0.4, 0.2, 0.1, 0.05 g/ml sucrose; sour: 0.3, 0.165, 0.09, 0.05 g/ml citric acid; salty: 0.25, 0.1, 0.04, 0.016 g/ml sodium chloride; bitter: 0.006, 0.0024, 0.0009, 0.0004 g/ml quinine hydrochloride). Paper strips were placed on the tongue and patients were asked to close the mouth and move each strip on the tongue to check a whole gustatory sensitivity. Then the patient was asked to choose from a list of four tastes (sweet, sour, salty, bitter). The patient is required to rinse the mouth with water before each strip test. One point is assigned to each correct answer; normogeusia is defined for $TST \geq 9$, while $TST < 9$ indicates hypogeusia. Complete ageusia is diagnosed in case of no sensation to the highest concentrations of all the four taste solutions. Taste strips qualities do not include umami taste, which has been found to be poorly conceptualised in European countries[42].

Statistical analysis

Proportions and Fisher's test were used for categorical variables. Median, quartiles and Kruskall Wallis tests were used for ordinal variables. A bivariable analysis of factors associated with acute and long-term self-reported chemosensory impairment was carried out. Odds ratios (OR) with 95% confidence interval (CI) and two-sided Fisher's exact test's p-value estimation corrected for multiple testing (Bonferroni correction) were computed

with scipy (v.1.10) and statsmodels (v. 0.14.0)[43]. Variables significantly associated with the outcomes (corrected $p <= 0.05$) were selected to compute the multivariable Generalized Linear Model with Binomial linking function. The negative class of the dataset was under-sampled with the Neighbourhood Cleaning Rule[44]. The fitting of the models was assessed by evaluating the discrimination power and generalizability of the area under the roc curve (AUROC). No missing data imputation was performed; hence only full data-vectors were used for the multivariable models. Time to event analysis and log-rank test for comparing symptoms duration between patients with self-reported chemosensory alteration was performed with STATA v.17. Concordance between self-reported chemosensory impairment and the results of psychophysical tests was assessed by computing Cohen-Kappa coefficients, and possible causes of discordance were investigated. Visualisations were carried out in Python3.11 using matplotlib package v. 3.7.1.

For laboratory values and SF-36 results, the Mann–Whitney test was applied for comparison of the distributions between patients with NSc-PCS and patients without PCS. For biochemistry assessment, outliers (datapoints falling outside the 1.5 interquartile range) were removed.

Data availability

Data were collected and managed using REDCap electronic data capture tool (Research Electronic Data CAPpture). The study was registered on ClinicalTrials.gov (CT registration number: NCT05097677) and the protocol is available at the ORCHESTRA website.

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References

1. Gary, J. B. et al. Qualitative olfactory dysfunction and COVID-19: An evidence-based review with recommendations for the clinician. *Am. J. Rhinol. Allergy.* **37**(1), 95–101. https://doi.org/10.1177/19458924221120117 (2023) (**Epub 2022 Aug 11**).
2. Pierron, D. et al. Smell and taste changes are early indicators of the COVID-19 pandemic and political decision effectiveness. *Nat. Commun.* **11**(1), 5152. https://doi.org/10.1038/s41467-020-18963-y (2020).
3. Rocke, J., Hopkins, C., Philpott, C. & Kumar, N. Is loss of sense of smell a diagnostic marker in COVID-19: A systematic review and meta-analysis. *Clin. Otolaryngol.* **45**(6), 914–922. https://doi.org/10.1111/coa.13620 (2020) (**Epub 2020 Sep 16**).
4. Esmaeili, M. et al. Olfactory and gustatory dysfunction in 2019 novel coronavirus: An updated systematic review and meta-analysis. *Int. J. Prev. Med.* **12**, 170. https://doi.org/10.4103/ijpvm.IJPVM_484_20 (2021).
5. von Bartheld, C. S. & Wang, L. Prevalence of olfactory dysfunction with the omicron variant of SARS-CoV-2: A systematic review and meta-analysis. *Cells.* **12**(3), 430. https://doi.org/10.3390/cells12030430 (2023).
6. Spinato, G. et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA.* **323**(20), 2089–2090. https://doi.org/10.1001/jama.2020.6771 (2020).
7. Cecchini, M. P. et al. Persistent chemosensory dysfunction in a young patient with mild COVID-19 with partial recovery 15 months after the onset. *Neurol. Sci.* **43**(1), 99–104. https://doi.org/10.1007/s10072-021-05635-y (2022) (**Epub 2021 Oct 2**).
8. Honda, H. et al. Prolonged symptoms after COVID-19 in Japan: A nationwide survey of the symptoms and their impact on patients' quality of life. *Am. J. Med.* https://doi.org/10.1016/j.amjmed.2023.04.040 (2023) (**Epub ahead of print**).
9. Tsuchiya, H. COVID-19 oral sequelae: Persistent gustatory and saliva secretory dysfunctions after recovery from COVID-19. *Med. Princ. Pract.* https://doi.org/10.1159/000531373 (2023) (**Epub ahead of print**).
10. Boscolo-Rizzo, P. et al. Evolution of altered sense of smell or taste in patients with mildly symptomatic COVID-19. *JAMA Otolaryngol. Head Neck Surg.* **146**(8), 729–732. https://doi.org/10.1001/jamaoto.2020.1379 (2020).
11. Vaira, L. A. et al. Prevalence of persistent olfactory disorders in patients with COVID-19: A psychophysical case-control study with 1-year follow-up. *Otolaryngol. Head Neck Surg.* **167**(1), 183–186. https://doi.org/10.1177/01945998211061511 (2022) (**Epub 2021 Nov 23**).
12. Gentilotti, E. et al. Clinical phenotypes and quality of life to define post-COVID-19 syndrome: A cluster analysis of the multinational, prospective ORCHESTRA cohort. *EClinicalMedicine.* **62**, 102107. https://doi.org/10.1016/j.eclinm.2023.102107 (2023).
13. Mendes Paranhos, A. C. et al. Sociodemographic characteristics and comorbidities of patients with long COVID and persistent olfactory dysfunction. *JAMA Netw. Open.* **5**(9), e2230637. https://doi.org/10.1001/jamanetworkopen.2022.30637 (2022).
14. Asvapoositkul, V. et al. Therapeutic options of post-COVID-19 related olfactory dysfunction: A systematic review and meta-analysis. *Rhinology.* **61**(1), 2–11. https://doi.org/10.4193/Rhin22.221 (2023).
15. Whitcroft, K. L. & Hummel, T. Clinical diagnosis and current management strategies for olfactory dysfunction: A review. *JAMA Otolaryngol. Head Neck Surg.* **145**(9), 846–853. https://doi.org/10.1001/jamaoto.2019.1728 (2019).
16. Hannum, M. E. et al. Taste loss as a distinct symptom of COVID-19: A systematic review and meta-analysis. *Chem. Senses.* **47**, 001. https://doi.org/10.1093/chemse/bjac001 (2022).
17. Hummel, T., Kobal, G., Gudziol, H. & Mackay-Sim, A. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: An upgrade based on a group of more than 3,000 subjects. *Eur. Arch. Otorhinolaryngol.* **264**(3), 237–243. https://doi.org/10.1007/s00405-006-0173-0 (2007) (**Epub 2006 Sep 23**).
18. Landis, B. N. et al. "Taste Strips"—a rapid, lateralized, gustatory bedside identification test based on impregnated filter papers. *J. Neurol.* **256**(2), 242–248. https://doi.org/10.1007/s00415-009-0088-y (2009) (**Epub 2009 Feb 7**).
19. Follow-up of COVID-19 long term sequelae study protocol. Prospective multinational cohort study on characteristics and determinants of post-COVID-19 long-term sequelae. https://orchestra-cohort.eu/protocols (Accessed 3 Aug 2023)
20. Liu, M. F. et al. Incidence and prognosis of olfactory and gustatory dysfunctions related to infection of SARS-CoV-2 Omicron strain: A national multi-center survey of 35 566 population. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* **58**(6), 579–588. https://doi.org/10.3760/cma.j.cn115330-20230316-00117 (2023).
21. WHO. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 (Accessed 3 Aug 2023)
22. Lipoldová, M. & Demant, P. Gene-specific sex effects on susceptibility to infectious diseases. *Front. Immunol.* **12**, 712688 (2021).
23. Hara, M. et al. Comparison of self-reported symptoms in COVID-19 patients who had or had not previously received COVID-19 mRNA vaccination. *Hum. Vaccin. Immunother.* **19**(2), 2226575. https://doi.org/10.1080/21645515.2023.22 (2023).
24. Vaira, L. A. et al. New onset of smell and taste loss are common findings also in patients with symptomatic COVID-19 after complete vaccination. *Laryngoscope.* **132**(2), 419–421. https://doi.org/10.1002/lary.29964 (2022) (**Epub 2021 Nov 26**).

25. Le Bon, S. D. et al. Making scents of loss of taste in COVID-19: Is self-reported loss of taste due to olfactory dysfunction? A prospective study using psychophysical testing. *Int. Forum Allergy Rhinol.* **11**(10), 1504–1507. https://doi.org/10.1002/alr.22815 (2021) (**Epub 2021 May 19**).
26. Cooper, K. W. et al. COVID-19 and the chemical senses: Supporting players take center stage. *Neuron.* **107**(2), 219–233. https://doi.org/10.1016/j.neuron.2020.06.032 (2020) (**Epub 2020 Jul 1**).
27. Manganotti, P. et al. Clinical neurophysiology and cerebrospinal liquor analysis to detect Guillain-Barré syndrome and polyneuritis cranialis in COVID-19 patients: A case series. *J. Med. Virol.* **93**(2), 766–774. https://doi.org/10.1002/jmv.26289 (2021) (**Epub 2020 Jul 27**).
28. Meunier, N., Briand, L., Jacquin-Piques, A., Brondel, L. & Pénicaud, L. COVID 19-induced smell and taste impairments: Putative impact on physiology. *Front. Physiol.* **11**, 625110. https://doi.org/10.3389/fphys.2020.625110 (2021).
29. Tsukahara, T., Brann, D. H. & Datta, S. R. Mechanisms of SARS-CoV-2-associated anosmia. *Physiol. Rev.* **103**(4), 2759–2766. https://doi.org/10.1152/physrev.00012.2023 (2023) (**Epub 2023 Jun 21**).
30. Hintschich, C. A. et al. Psychophysical tests reveal impaired olfaction but preserved gustation in COVID-19 patients. *Int. Forum Allergy Rhinol.* **10**(9), 1105–1107. https://doi.org/10.1002/alr.22655 (2020) (**Epub 2020 Jul 21**).
31. Oleszkiewicz, A., Schriever, V. A., Croy, I., Hähner, A. & Hummel, T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. *Eur. Arch. Otorhinolaryngol.* **276**(3), 719–728. https://doi.org/10.1007/s00405-018-5248-1 (2019) (**Epub 2018 Dec 15**).
32. Hummel, T. et al. Effects of olfactory training in patients with olfactory loss. *Laryngoscope.* **119**(3), 496–499. https://doi.org/10.1002/lary.20101 (2009).
33. Sharetts, R., Moein, S. T., Khan, R. & Doty, R. L. Long-term taste and smell outcomes after COVID-19. *JAMA Netw. Open.* **7**(4), e247818. https://doi.org/10.1001/jamanetworkopen.2024.7818 (2024).
34. Ghods, K. & Alaee, A. Olfactory and taste disorders in patients suffering from Covid-19, a review from the literature. *J. Dent. Shiraz Univ. Med. Sci.* **23**(1), 1–6 (2022).
35. Wang, J., Liu, R., Ma, H. & Zhang, W. The pathogenesis of Covid-19-related taste disorder and treatments. *Crit. Rev. Oral Biol. Med.* **102**(11), 1191–1198 (2023).
36. Boesveldt, S., Postma, E. M., Boek, W., Kamalski, D. M. A. & van Dijk, B. Longitudinal follow-up of taste function and trigeminal perception in COVID-19 patients with olfactory dysfunction—The COVORTS study. *Clin. Nutr. Open Sci.* **55**, 249–262 (2024).
37. Nextstrain SARS-CoV-2 resources. https://nextstrain.org/sars-cov-2/ (Accessed 3 Aug 2023)
38. Kobal, G. et al. Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. *Eur. Arch. Otorhinolaryngol.* **257**(4), 205–211. https://doi.org/10.1007/s004050050223 (2000).
39. Hopkins, C. et al. Management of new onset loss of Journal Pre-proof 47 sense of smell during the COVID-19 pandemic—BRS Consensus Guidelines. *Clin. Otolaryngol.* **46**(1), 16–22. https://doi.org/10.1111/COA.13636 (2021).
40. Huart, C. et al. Systemic corticosteroids in coronavirus disease 2019 (COVID-19)-related smell dysfunction: An international view. *Int. Forum Allergy Rhinol.* **11**(7), 1041–1046. https://doi.org/10.1002/ALR.22788 (2021).
41. Pieniak, M., Oleszkiewicz, A., Avaro, V., Calegari, F. & Hummel, T. Olfactory training—Thirteen years of research reviewed. *Neurosci. Biobehav. Rev.* **141**, 104853. https://doi.org/10.1016/j.neubiorev.2022.104853 (2022) (**Epub 2022 Sep 5**).
42. Cecchini, M. P. et al. A cross-cultural survey of umami familiarity in European countries. *Food Qual. Preference* **74**, 172–178
43. Seabold, S. & Perktold, J. statsmodels: Econometric and statistical modeling with python. In *Proceedings of the 9th Python in Science Conference* (2010).
44. Laurikkala, J. Improving identification of difficult small classes by balancing class distribution. In *Artificial Intelligence in Medicine. AIME 2001. Lecture Notes in Computer Science*, (eds Quaglini, S. et al.) Vol 2101. https://doi.org/10.1007/3-540-48229-6_9 (Springer, 2001).

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Author contributions

E.G., M.P.C. and A.G. conceived the study. E.G. and A.G. wrote the first draft of the manuscript. E.G. was responsible for enrolling and visiting the patients, performed the data collection and management, reviewed the literature and contributed to the statistical plan. A.G. contributed to the data management and data analysis, and performed the visualization. M.P.C. performed the chemosensory evaluation and contributed to the writing of the manuscript. M.Mirandola contributed to the statistical analysis. M.Meroi was responsible for the data entry of neurosensorial evaluation data; P.D.N. visited the patients at the post-COVID ambulatory and contributed to the draft of the manuscript. A.S. was responsible for recalling the patients and performed a structured telephone interview. C.K.D.T. reviewed the literature. S.K.S. supervised was laboratory studies. G.Z. and S.M. supervised the chemosensory evaluation and reviewed the manuscript and E.T. directed the project, supervised the design of the study and data analysis and reviewed the manuscript. All authors discussed the results and commented on the manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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