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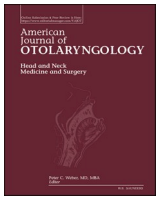

Relationship between disease severity and serum IL-6 levels in COVID-19 anosmia

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ABSTRACT

Background: An association between IL-6 levels and cytokine storm syndrome in COVID-19 patients has been suggested. Cases with higher IL-6 levels have more rapid progression and a higher complication rate. On the other hand, COVID-19 cases with anosmia have a milder course of the disease.

Objective: We aimed to investigate whether there is a relationship between serum IL-6 levels and presence of anosmia in COVID-19 patients.

Methods: Patients with a confirmed diagnosis of COVID-19 based on laboratory (PCR) were stratified into two groups based on presence of olfactory dysfunction (OD). In all cases with and without anosmia; psychophysical test (Sniffin' Sticks test) and a survey on olfactory symptoms were obtained. Threshold (t) – discrimination (d) – identification (i), and total (TDI) scores reflecting olfactory function were calculated. Clinical symptoms, serum IL-6 levels, other laboratory parameters, and chest computed tomography (CT) findings were recorded.

Results: A total of 59 patients were included, comprising 23 patients with anosmia and 36 patients without OD based on TDI scores. Patients with anosmia (41.39 ± 15.04) were significantly younger compared to cases without anosmia (52.19 ± 18.50). There was no significant difference between the groups in terms of comorbidities, smoking history, and symptoms including nasal congestion and rhinorrhea. Although serum IL-6 levels of all patients were above normal values (7 pg/mL), patients with anosmia had significantly lower serum IL-6 levels (16.72 ± 14.28 pg/mL) compared to patients without OD (60.95 ± 89.33 pg/mL) ($p = 0.026$).

Conclusion: Patients with COVID-19 related anosmia tend to have significantly lower serum levels of IL-6 compared to patients without OD, and the lower IL-6 levels is related to milder course of the disease. With the effect of low cytokine storm and IL-6 level, it may be said that anosmic cases have a milder disease in COVID-19.

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1. Introduction

Patients with COVID-19 mainly present with cough and fever and may have parenchymal changes on chest computed tomography (CT). Anosmia (loss of smell) and dysgeusia (altered sensation of taste) have been reported in 33–80% of patients with COVID-19 [1,2]. Anosmia/hyposmia and dysgeusia are reported to be associated with other upper respiratory tract infections with a rate of 11–40%, mainly due to nasal congestion and secretions [3,4] The main differences between COVID-19 related anosmia and anosmia seen in other upper respiratory tract infections are sudden onset irrespective of presence of nasal congestion/obstruction and possible correlation with neurological symptoms in COVID-19 disease [5–8].

Exact pathophysiology of anosmia in COVID-19 infection has not been firmly established. Angiotensin-2 (ACE2) receptors have been identified as a cellular receptor for SARS-CoV-2, which are highly expressed in olfactory mucosa. A plausible mechanism is direct extension through the nasal mucosa with direct neuropathic damage in olfactory filia and olfactory bulb [9,10]. Neurotropism with involvement of olfactory nuclei has been proposed as an additional mechanism for anosmia/hyposmia [11]. This neurotropism can also result in brainstem involvement which might be responsible for the respiratory distress [11,12]. Another potential route of spread may involve initial uptake at alveoli through ACE2 receptors, followed by hematogenous spread and intracranial involvement due to blood brain barrier disruption [5,13].

Anosmia/hyposmia can be the initial and only symptom of COVID-19 infections, and usually show improvement over a 1–2-week period without treatment in majority of cases [8,14,15]. COVID-19 anosmia is usually seen in younger age group with female predominance, patients have milder symptoms with some cases being asymptomatic [16]. In this aspect, anosmia is an important symptom for suspecting COVID-19 disease and appropriate patient triage and isolation.

IL-6 is an important pro-inflammatory cytokine and has been associated with more rapid disease progression and a higher complication rate in COVID-19 cases. Accumulated evidence so far has demonstrated cytokine storm syndrome is associated more severe disease and complications [17]. On the other hand, COVID-19 anosmia cases have milder disease. Based on these observations, we aimed to investigate the relationship between IL-6 levels and presence of COVID-19 related anosmia. Secondary aim of the study was to assess the clinical and radiological prognosis in cases with COVID-19 related anosmia.

2. Material and methods

2.1. Study population

Institutional review board approval and informed consent were obtained from Acıbadem University (2020-12/26). This was a retrospective study including patients with a confirmed diagnosis of COVID-19 based on laboratory (PCR) and radiological (CT) features between March and June 2020. Laboratory and radiological data obtained at initial admission to the hospital within the first week of symptoms onset were reviewed. Patients with a serum IL-6 available were included in the study. Subsequently, patients were contacted by phone and olfactory symptoms were reviewed using a questionnaire. Patients were stratified into two groups based on olfactory symptoms: Group 1: cases with no OD during the course of COVID-19 infection, and Group 2: cases with OD during the course of COVID-19 infection.

All patients included in the study had serum IL-6 levels at the time of admission to the hospital. These first values were included in the calculation since control laboratory parameters were not examined in cases with mild clinical course. In cases with severe clinical course, IL-6 levels, which were higher on laboratory control within an average of 10 ± 6 days compared to the clinical course, were included in the calculation.

Pediatric and pregnant patients, patients with history of head trauma, preexisting smell and taste alterations for any other reason, allergic rhinitis and chronic rhinosinusitis based on clinical history and CT findings were excluded.

Table 1
Demographic features and clinical symptoms based on presence of anosmia and dysgeusia.

		Total (n = 59)	Group-1 Without anosmia (n = 36)	Group-2 With anosmia (n = 23)	p
Age	Min–max (median)	21–89 (45)	21–89 (53.5)	21–75 (39)	[a]*0.022**
	Mean ± SD	47.98 ± 17.90	52.19 ± 18.50	41.39 ± 15.04	
Sex	Female	24 (40.7)	14 (38.9)	10 (43.5)	[b]*0.726*
	Male	35 (59.3)	22 (61.1)	13 (56.5)	
Comorbidities		18 (30.5)	11 (30.6)	7 (30.4)	[b]*0.992*
Smoking history		7 (11.9)	5 (13.9)	2 (8.7)	[c]*0.694*
Fever		33 (55.9)	17 (47.2)	16 (69.6)	[b]*0.092*
Cough		20 (33.9)	10 (27.8)	10 (43.5)	[b]*0.214*
Dsypnea		5 (8.5)	2 (5.6)	3 (13.0)	[c]*0.369*
Myalgia		17 (28.8)	4 (11.1)	13 (56.5)	[b]*0.001***
Fatigue		4 (6.8)	3 (8.3)	1 (4.3)	[c]*1.000*
Headache		6 (10.2)	0 (0.0)	6 (26.1)	[c]*0.002***
Sore throat		5 (8.5)	2 (5.6)	3 (13.0)	[c]*0.369*
Nasal congestion		2 (3.4)	0 (0.0)	2 (8.7)	[c]*0.148*
Rhinorrhea		1 (1.7)	0 (0.0)	1 (4.3)	[c]*0.390*
Abdominal pain		5 (8.5)	4 (11.1)	1 (4.3)	[c]*0.639*
Diarrhea		1 (1.7)	1 (2.8)	0 (0.0)	[c]*1.000*

[a] Student-*t*-test.
[b] Pearson Chi-Square test.
[c] Fisher's Exact test.
* $p < 0.05$.
** $p < 0.01$.

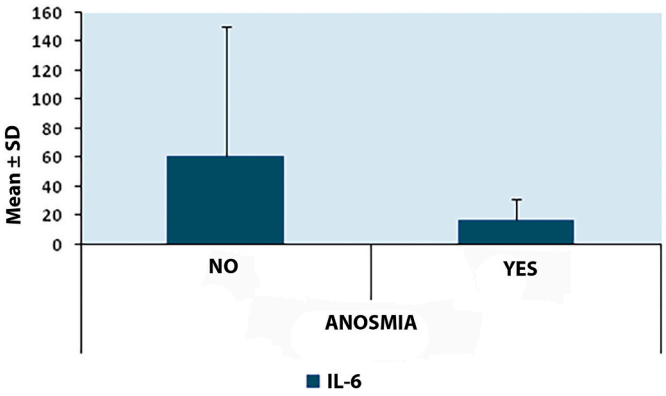

Fig. 1. Distribution of IL-6 levels based on presence of olfactory dysfunction.

2.2. Clinical and laboratory findings

Symptoms (fever, cough, dyspnea, headache, nasal congestion, rhinorrhea), serum IL-6 levels and other laboratory parameters (hemoglobin, complete blood count, C-reactive protein (CRP), D-dimer, ferritin, fibrinogen, lactic acid dehydrogenase (LDH) levels) were recorded. Comorbidities, smoking and contact history were reviewed.

2.3. CT examination and Image analysis

All patients underwent chest CT scans with Siemens Somatom Sensation-Syngo CT device using a low-dose non-contrasted CT protocol. Patients were scanned in supine position during deep inspiration. All

Table 2
Distribution of threshold, discrimination, identification and total TDI scores according to the Sniffin' Stick test and the relationship between these values and the IL-6 level.

		Olfactory dysfunction			
		Threshold	Discrimination	Identification	TDI
Sniffin' Stick test	Min–max (median)	1–3.25 (2)	0–3 (2)	0–4 (2)	1–10.25 (6.75)
	Mean ± SD	1.91 ± 0.95	1.48 ± 1.38	1.65 ± 1.58	5.04 ± 3.75
IL-6	n	23	23	23	23
	r	0.028	−0.110	0.011	−0.011
	p	0.899	0.618	0.958	0.961

r = Spearman's correlation coefficient.

images were evaluated by a single radiologist with 20 years of experience in chest CT.

Chest CT findings were reviewed for extent of parenchymal involvement and categorized based on quartiles as 1: <25%, 2: 25–50%, 3: 50–75%, 4: >75%. Dominant infiltration pattern (ground-glass, crazy-paving, consolidation) and distribution of parenchymal involvement (unilateral/bilateral involvement, lower/upper lobe predominance, diffuse/peripheral/central/mixed) were reviewed. Additionally, changes at follow-up chest CT scans were assessed. Radiological evaluation was done based on the Radiological Society of North America (RSNA) Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19, as of April 2020 [18].

2.4. Psychophysical test

The odor test was done using the Sniffin' Stick test battery (Burghart Messtechnik, Germany). This test was performed to all patients included in the study after conversion of PCR results to negative.

Sniffin' Stick test has 3 components: odor threshold (t), odor discrimination (d) and odor identification (i). TDI is a composite score representing the sum of these 3 scores. TDI score can be 48 points as the sum of maximum 16 points that can be taken from each subtest. TDI score is considered normosmic if ≥30.5, hyposmic if between 16.5 and 30.5, functionally anosmic if <16.5 [19]. The applicability of "Sniffin' Sticks" test for target population has been previously validated [20].

2.5. Survey

All patients were contacted via phone for a survey related to anosmia symptoms. This survey focused on subjective scaling of anosmia severity, duration and change over time. Additionally, relation of OD to other clinical symptoms like headache, nasal congestion, diarrhea, abdominal pain was questioned. All surveys were done after patients showed complete clinical improvement. A sample of the questionnaire can be found as a supplementary file.

2.6. Statistical analysis

All statistical analysis was performed with NCSS (Number Cruncher Statistical System, 2007, Kaysville, Utah, USA). Descriptive statistics were expressed as number and percentage for categorical variables and as mean, standard deviation, median, minimum, and maximum for numerical variables. Shapiro-Wilk test was used to determine whether the data showed normal distribution. Student-*t*-test and Mann-Whitney *U* test were used for parametric and nonparametric data, respectively. For categorical variables, chi-square, Fisher's exact and Fisher-Freeman-Halton exact-tests were used. Spearman test was used for correlation. Receiver operating curves were plotted for IL-6 levels based on presence of anosmia and best cut-off value was determined. p value <0.05 was considered as statistically significant.

Table 3
Laboratory parameters based on presence of anosmia and dysgeusia.

Total (n = 59)		Group-1 Without anosmia (n = 36)	Group-2 With anosmia (n = 23)	p
IL-6 (pg/mL)	2–292 (16.6)	2.5–292 (20.8)	2–48.94 (11.3)	[b]*0.026**
<7 pg/mL	43.71 ± 73.25	60.95 ± 89.33	16.72 ± 14.28	
Leukocyte count (10^3/μL)	2.8–14,366 (6.11)	2.8–14,366 (8.87)	3.53–16.64 (5.43)	[b]*0.010**
4.06–10.6 × 10^3/μL	320.07 ± 2116.99	633.8 ± 2993.52	6.34 ± 3.27	
Neutrophil (%)	9.8–93.3 (65.8)	9.8–93.3 (66.05)	30.1–84.9 (65.8)	[a]*0.727*
%40–%70	64.47 ± 15.76	65.27 ± 18.28	63.63 ± 12.99	
Lymphocyte (%)	4–85 (22.3)	4–85 (20.45)	6.9–61.3 (23.8)	[b]*0.371*
%20–%50	24.3 ± 14.99	23.62 ± 17.2	25.02 ± 12.62	
Neutrophil (count) (10^3/μL)	1.45–81.7 (3.72)	1.74–16.1 (4.56)	1.45–81.7 (3.36)	[b]*0.187*
1.9–7 × 10^3/μL	6.61 ± 11.7	5.68 ± 3.7	7.59 ± 16.42	
Lymphocyte (count) (10^3/μL)	0.5–30.4 (1.34)	0.5–30.4 (1.42)	0.6–2.94 (1.34)	[b]*0.482*
1.3–3.76 × 10^3/μL	2.1 ± 4.27	2.74 ± 5.94	1.42 ± 0.61	
Thrombocyte (10^3/μL)	93–443 (190)	121–443 (207.5)	93–377 (179.5)	[b]*0.141*
150–439 × 10^3/μL	214.76 ± 85.33	229.63 ± 92.49	198.55 ± 75.54	
CRP (mg/dL)	0.03–19.73 (1.08)	0.04–19.73 (1.98)	0.03–9.98 (0.94)	[b]*0.167*
<0.5 mg/dL	2.63 ± 3.63	3.37 ± 4.39	1.87 ± 2.49	
D-dimer (μg/mL)	0.17–5.36 (0.38)	0.19–2.42 (0.58)	0.17–5.36 (0.28)	[b]*0.097*
0–0.55 mg/L	0.76 ± 0.95	0.76 ± 0.63	0.75 ± 1.19	
LDH (IU/L)	97–742 (199.5)	97–742 (259)	147–445 (190)	[b]*0.205*
85–227 IU/L	240.32 ± 129.94	281.08 ± 167.7	205 ± 74.69	
Ferritin (ng/mL)	7–1237 (176)	14–1237 (193)	7–812 (143)	[b]*0.733*
22–322 ng/mL	241.65 ± 238.68	264.09 ± 278.3	219.22 ± 194.99	
Fibrinogen (mg/dL)	0.05–804 (392)	392–680 (460)	0.05–804 (351)	[b]*0.007***
150–400 mg/dL	409.57 ± 164.99	489.13 ± 104.2	367.14 ± 178.33	
Hemoglobin (g/dL)	9.3–15.7 (13.8)	9.3–15.7 (13.7)	11.3–15.4 (14.1)	[b]*0.798*
13.5–17 g/dL	13.39 ± 1.56	13.28 ± 1.78	13.51 ± 1.33	

Data is presented as min–max (median) and mean ± standard deviation.
[a] Student's *t*-test.
[b] Mann Whitney *U* test.
* $p < 0.05$.
** $p < 0.01$.

Table 4
Lymphocyte subsets based on presence of anosmia and dysgeusia.

		Total (n = 12)	Olfactory dysfunction absent (n = 5)	Olfactory dysfunction present (n = 7)	
Leukocyte count (CD4/CD8) (μL)	Min-Max (Median)	3000–13,590 (5375)	3000–13,590 (4650)	3850–6920 (5840)	[a]1.000
	Mean ± SD	5936.67 ± 2711.03	6652 ± 4188.36	5425.71 ± 1023.98	
Lymphocyte count (CD4/CD8) (μL)	Min-Max (Median)	920–10,830 (1505)	920–10,830 (1310)	1120–3030 (1700)	[a]0.935
	Mean ± SD	2328.33 ± 2733.99	3212 ± 4270.1	1697.14 ± 657.49	
CD4/CD8 ratio	Min-Max (Median)	0.87–4.62 (1.84)	1.42–4.02 (2.25)	0.87–4.62 (1.53)	[a]0.372
	Mean ± SD	2.2 ± 1.18	2.41 ± 0.97	2.06 ± 1.37	
CD3 (T Lymphocyte) %	Min-Max (Median)	0–80.7 (73.05)	0–73.1 (61.1)	45.1–80.7 (75)	[a]0.062
	Mean ± SD	58.5 ± 27.63	43.02 ± 36.11	69.56 ± 13.71	
CD3 (T Lymphocyte) count (μL)	Min-Max (Median)	518.7–2421 (1002.7)	526.2–1308.9 (855.6)	518.7–2421 (1256.3)	[a]0.372
	Mean ± SD	1080.96 ± 527.59	877.26 ± 289.53	1226.46 ± 628.61	
CD4 (T-Helper) %	Min-Max (Median)	4.6–63.1 (47.05)	4.6–51.3 (45.8)	28.3–63.1 (48.3)	[a]0.684
	Mean ± SD	43.45 ± 15.16	38.62 ± 19.48	46.9 ± 11.61	
CD4 (T-Helper) count (μL)	Min-Max (Median)	316.4–1463.49 (608.78)	421.36–918.45 (501.43)	316.4–1463.49 (771.8)	[a]0.372
	Mean ± SD	729.38 ± 344.56	599.45 ± 198.89	822.18 ± 408.87	
CD8 (T-Suppressor) %	Min-Max (Median)	3.3–43.1 (22.1)	3.3–22.4 (20.3)	13.7–43.1 (27.3)	[a]0.061
	Mean ± SD	22.78 ± 10.75	15.84 ± 8.3	27.74 ± 9.85	
CD8 (T-Suppressor) count (μL)	Min-Max (Median)	104.9–957.5 (329.65)	104.9–390.4 (294)	254.1–957.5 (385.5)	[a]0.123
	Mean ± SD	385.03 ± 213.63	277.8 ± 111.46	461.63 ± 242.81	

Data is presented as min–max (median) and mean ± standard deviation.
[a] Mann Whitney *U* test.

3. Results

A total of 59 patients were included in this study, with 36 patients in Group 1 (without OD) and 23 patients in Group 2 (with OD). The interval between symptoms onset and odor test was 28 ± 5 days in all patients. Mean TDI score in Group 1 was 37.28 ± 2.6 (33–42), indicating all patients were normosmic. Mean TDI score in Group 2 was 5.04 ± 3.75 (1–10.25), indicating all cases had functional anosmia. Group 1 patients had mean threshold (t) value of 10.94 ± 0.98, discrimination (d) of 13.4 ± 1.2, identification (i) of 13.2 ± 1.4, and the mean t value of Group 2 patients was 1.91 ± 0.95, d value 1.48 ± 1.38, i value 1.65 ± 1.58.

Cases with anosmia were younger (41.39 ± 15.04) compared to cases without OD (52.19 ± 18.50) with difference reaching statistical significance ($p = 0.022$). Both groups showed similar slight male predominance with similar male/female ratio. There was no significant difference between the groups in terms of comorbidities, smoking history, and symptoms including fever, cough, dyspnea, fatigue, nasal congestion, rhinorrhea and diarrhea ($p > 0.05$). However, headache and myalgia were significantly more prevalent in cases with anosmia. Table 1 presents more detailed information on demographic features and clinical symptoms.

Patients with anosmia had significantly lower serum IL-6 levels (16.72 ± 14.28 pg/mL) compared to patients without OD (60.95 ± 89.33 pg/mL) ($p = 0.026$) (Fig. 1) (Table 2). No significant difference was found between the two groups in CBC (lymphocyte, CD-3 lymphocyte and CD-4 lymphocyte), hemoglobin, CRP, D-dimer, ferritin and LDH levels ($p > 0.05$). Leukocyte and CD8-lymphocyte counts were significantly higher; fibrinogen levels were significantly lower in the anosmia group. In addition, PLT, CRP, LDH, ferritin levels were lower in the anosmia group (Tables 3–4).

Patients without OD had significantly higher percentage of parenchymal involvement compared to patients with anosmia ($p = 0.006$; $p < 0.01$). All anosmia cases had less than 25% parenchymal involvement. No significant difference was observed in dominant infiltration pattern and distribution of parenchymal involvement between the two groups. Anosmia cases had significantly lower rate of pleural effusion ($p = 0.017$; $p < 0.05$). On control chest CT, patients with anosmia had significantly lower rate of progression ($p = 0.016$; $p < 0.05$). Cases with anosmia showed regression of chest CT findings faster that patients without anosmia, however this difference did not reach a statistically significant level. Chest CT findings based on presence of anosmia are presented in Table 5.

Based on survey results in patients with COVID-19 related anosmia, mean odor discrimination score was 9.1 points prior to COVID-19, which decreased to a nadir of 2 points during COVID infection. Similarly, mean taste discrimination score was 9.3 points prior to COVID-19, which decreased to a nadir of 2.5 points during COVID infection. Mean interval to recovery of olfactory and taste dysfunction was 27.9 and 25 days, respectively.

Receiver operating curve (ROC) was plotted for IL-6 levels based on presence of anosmia. ROC curve had an area under curve (AUC) of 67%. (CI 0.533–0.812). Cut-off value for IL-6 to distinguish presence of anosmia was 11.3 pg/mL with sensitivity, specificity, positive predictive and negative predictive values of 52%, 75%, 57% and 71%, respectively.

There was no significant relationship between TDI scores and IL-6 levels in patients with anosmia ($p > 0.05$) (Fig. 2).

The important data of the study are arranged as a flowchart in Fig. 3.

4. Discussion

The results of this study showed that, although increased relative to normal serum IL-6 levels were detected in both groups, mean IL-6 levels were significantly higher in subjects without OD than in patients with anosmia. Additionally, chest CT findings were milder and more subtle in anosmia cases with a lower rate of progression and more rapid radiological recovery.

Chemokines and cytokines are responsible for the immune mediated response in COVID-19 disease similar to other infectious and inflammatory diseases. Uncontrolled inflammatory response, failure to establish anti-inflammatory balance and defective immune system can result in cytokine storm syndrome. The most important mediators of cytokine storm syndrome in COVID-19 disease are IL-6, IL-10 and TNFα [21]. IL-6 is a strong pro-inflammatory molecule and can induce other inflammatory cells and mediators resulting in lung parenchyma damage and dyspnea [22–25]. Meta-analysis and studies have shown that increased IL-6 levels in COVID-19 correlates with disease severity, complications, need for ICU admission and mortality [24,26–29]. Zhu et al. in a study investigating the relation between prognosis and inflammatory/immune parameters showed correlation between IL-6 levels and CRP, NLR, IL-10 and IFNγ levels. The authors suggested IL-6 level to be an independent risk factor for severe disease course and changes in IL-6 levels depending on stage of disease to be used as a marker for disease monitoring [30]. Chen et al. reported an IL-6 cut-off value of 55 pg/mL for severe disease course, whereas Aziz et al. reported a cut-off value of 80 pg/mL for mortality [29,31].

Previously COVID-19 related anosmia was suggested to be related with milder disease course [16]. One study showed that the percentage of anosmia was lower in hospitalized patients (26.9%) compared to non-

Table 5
Chest CT findings based on presence of anosmia.

		Total n = 59 (%)	Group-1 Without anosmia n = 36 (%)	Group-2 With anosmia n = 23 (%)	p
CT	Normal	8 (13.6)	6 (16.7)	2 (8.7)	[d]*0.468*
	Typical pattern	35 (59.3)	19 (52.8)	16 (69.6)	
	Atypical pattern	16 (27.1)	11 (30.6)	5 (21.7)	
Percentage of parenchymal involvement	1 (<%25)	40 (78.4)	19 (63.3)	21 (100.0)	[d]*0.006***
	2 (%25–50)	7 (13.7)	7 (23.3)	0 (0.0)	
	3 (%50–75)	3 (5.9)	3 (10.0)	0 (0.0)	
	4 (%75–100)	1 (2.0)	1 (3.3)	0 (0.0)	
Side	Unilateral	10 (19.6)	4 (13.3)	6 (28.6)	[c]*0.283*
	Bilateral	41 (80.4)	26 (86.7)	15 (71.4)	
Dominant infiltration pattern	Ground glass	30 (59.0)	16 (53.3)	14 (66.7)	[d]*0.263*
	Crazy-paving	16 (31.0)	12 (40.0)	4 (19.0)	
	Consolidation	5 (10.0)	2 (6.7)	3 (14.3)	
Dominant lober distribution	Lower lobe	35 (68.6)	17 (56.7)	18 (85.7)	[d]*0.085*
	Upper lobe	5 (9.8)	4 (13.3)	1 (4.8)	
	Diffuse	11 (21.6)	9 (30.0)	2 (9.5)	
Distribution	Basal/ peripheral	34 (68.6)	17 (56.7)	18 (85.7)	[d]*0.060*
	Central	3 (5.9)	2 (6.7)	1 (4.8)	
	Diffuse	13 (25.5)	11 (36.7)	2 (9.5)	
Largest lesion diameter	n	36	16	20	[b]*0.062*
	Min–max (median)	1–10 (3)	2–10 (4)	1–8 (3)	
	Mean ± SD	4.00 ± 2.22	4.81 ± 2.54	3.35 ± 1.73	
Pleural effusion		8 (13.8)	8 (22.9)	0 (0.0)	[c]*0.017**
Progression on control CT		16 (55.2)	14 (73.7)	2 (20.0)	[a]*0.016**
Interval (days) to regression on chest CT	n	10	5	5	[b]*0.207*
	Min–max (median)	15–60 (32.5)	25–60 (35)	15–50 (20)	
	Mean ± SD	34.00 ± ± 15.78	40.00 ± 14.58	28.00 ± 16.05	

[a] Pearson Chi-Square test.
[b] Mann Whitney *U* test.
[c] Fisher's Exact test.
[d] Fisher Freeman Halton test.
* $p < 0.05$.
** $p < 0.01$.

hospitalized patients (66.7%) [32]. In a study with 3191 COVID-19 positive cases who had mild disease, 15.3% of cases had anosmia and/or dysgesuia. [16]. Leichen et al., in a study focusing on 417 cases with mild and moderate disease course showed that OD was present in 88% of cases and in 11.8% of cases hyposmia was the initial presenting symptom [8]. A similar study by Kaye et al. including 237 cases showed that anosmia was present in 73% of cases during disease course, with 26.6% of cases presenting with anosmia initially [15]. In our study, 34% of cases had anosmia and/or dysgesuia during disease course and in 14.8% of cases these were the initial presenting symptoms. All cases with anosmia in our study were evaluated objectively with psychophysical olfactory test. Majority of COVID-19 anosmia studies in the literature have been performed just with survey without obtaining psychophysical olfactory tests due to droplet precautions and risk of contamination. However as shown by Lechien et al. in a study using Sniffin' Sticks test in 86 patients, 33 patients (38%) that had hyposmia symptoms were normosmic on odor test, and 78.8% of cases with anosmia had hyposmia on odor test [33]. In this regard, due to subjectivity of patient symptoms, an objective psychophysical olfactory test is important to obtain, and this point is a major strength of our study compared to the rest of COVID-19 literature.

OD in inflammatory and infectious diseases might be related to intense inflammatory response in nasal mucosa and subsequent epithelial injury. This might be the pathogenesis of OD in post-infectious olfactory loss, chronic rhinosinusitis, neurodegenerative diseases and age-related OD [25,33]. Direct olfactory epithelial tissue biopsy in COVID-19 related anosmia, showed elevated proinflammatory cytokine levels such as TNF-α, IL-1β. TNF- α level in COVID-19 related anosmia compared to control group, suggesting that direct inflammation in olfactory epithelium might play a role in COVID-19 related anosmia [34,35]. Henkin et al. assessed the IL-6 levels in plasma, saliva, and nasal mucosa in hyposmia patients with different etiologies. IL-6 levels in all fluids, especially in the nasal mucosa, were higher in hyposmic cases compared to the control group [36]. Similarly, in our study, systemic serum IL-6 levels were found above normal levels in anosmic cases, however IL-6 levels did not reach a level as high as seen in cytokine storm syndrome. We did not obtain nasal-olfactory biopsies due to risk of exposure, and did not show a direct relation between inflammatory markers in olfactory epithelium and OD. To the best of our knowledge, there is no study investigating IL-6 levels in nasal mucosa or olfactory epithelium in COVID-19 anosmia. This association between nasal mucosal IL-6 levels and COVID-19 anosmia could be investigated in further studies separately or in combination with systemic IL-6 levels. We think that there is a more severe nasal cytokine storm in COVID-19 anosmia which leads to mucosal, epithelial and receptor damage mediated via proinflammatory cytokines. In this regard, cases who could summon a response to the virus at olfactory epithelium level would have a milder systemic disease but suffer from OD. We propose that olfactory epithelium is the initial site of inoculation and first line of defense against the virus.

Major limitation of our study is limited number of cases due to single-center nature of the study. A second major limitation is that laboratory markers and radiological evaluations were obtained at different time points of disease stage which incorporates heterogeneity to the study population.

In conclusion, our study supports the observations that patients with COVID-19 anosmia have milder disease course as demonstrated by clinical, laboratory and imaging findings. COVID-19 anosmia cases had lower IL-6 levels compared to COVID-19 patients without olfactory dysfunction which might be an underlying mechanism for the difference in clinical course. Further studies to assess the relationship between other cytokines responsible for cytokine storm syndrome and anosmia are needed to better define the underlying etiologies and prediction of prognosis.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

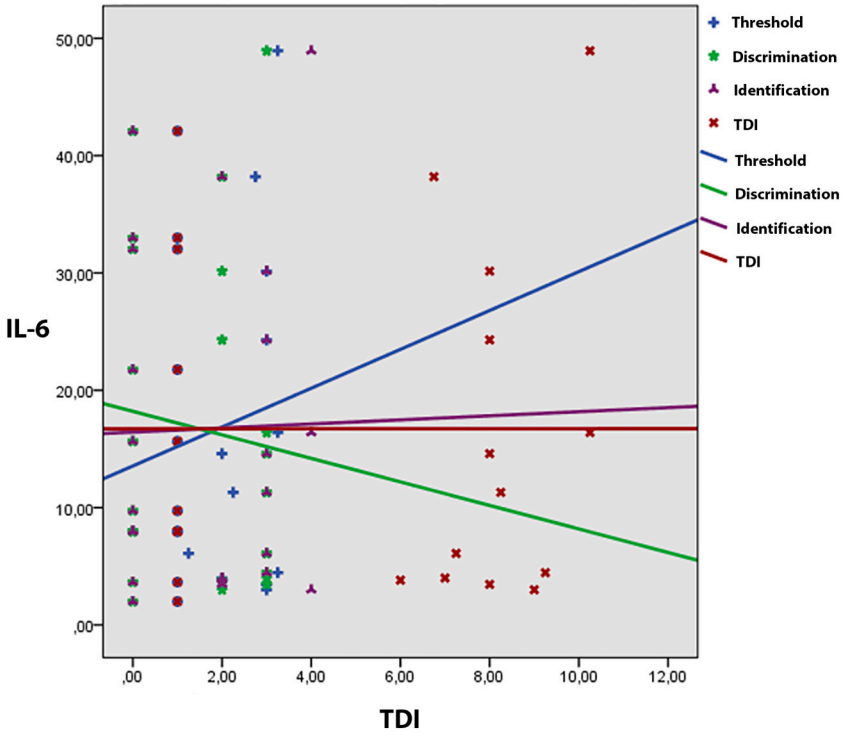

Fig. 2. Distribution of threshold, discrimination, identification, total TDI scores and IL-6 levels in patients with olfactory dysfunction.

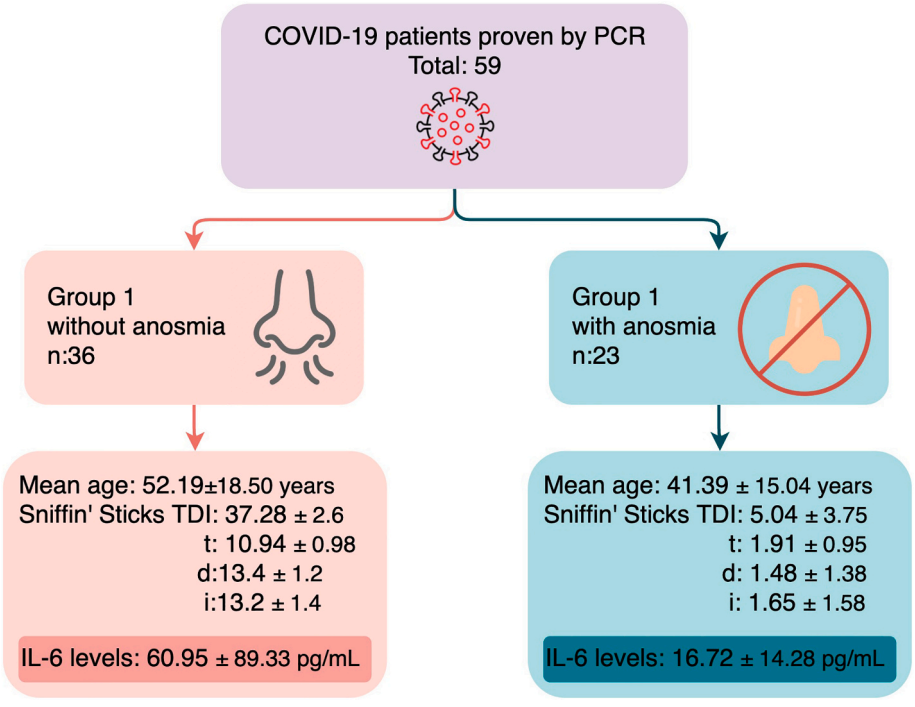

Fig. 3. A flowchart summarizing the data of the study.

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This paper is dedicated to the memory of our intensive care unit colleague Dr. Taner Ljama, who recently passed away during the COVID-19 pandemic.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjoto.2020.102796.

References

[1] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061–9. https://doi.org/10.1001/jama.2020.1585.
[2] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020;77:1–9. https://doi.org/10.1001/jamaneurol.2020.1127.
[3] Daher VB, Soares Oliveira DS, Daher Júnior MF, et al. Anosmia: a marker of infection by the new corona virus. Respir Med Case Rep 2020;31:101129. https://doi.org/10.1016/j.rmcr.2020.101129.
[4] Welge-Lüssen A, Wolfensberger M. Olfactory disorders following upper respiratory tract infections. Adv Otorhinolaryngol 2006;63:125–32. https://doi.org/10.1159/000093758.
[5] Han AY, Mukdad L, Long JL, Lopez IA. Anosmia in COVID-19: mechanisms and significance. Chem Senses 2020. https://doi.org/10.1093/chemse/bjaa040. Epub ahead of print 17 Jun.
[6] Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol 2020;10:806–13. https://doi.org/10.1002/alr.22579.
[7] Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. Clin Infect Dis 2020;71:889–90. https://doi.org/10.1093/cid/ciaa330.
[8] Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020;277:2251–61. https://doi.org/10.1007/s00405-020-05965-1.
[9] Bertram S, Heurich A, Lavender H, et al. Influenza and SARS-coronavirus activating proteases TMPRSS2 and HAT are expressed at multiple sites in human respiratory and gastrointestinal tracts. PLoS One 2012;7:e35876. https://doi.org/10.1371/journal.pone.0035876.
[10] Brann DTT, Weinreb C, Logan D, et al. Non-neural exporessio of SARSCoV- 2 entry genes in the olfactory epithelium suggests mechanisms of underlying anosmia. BioRxiv 2020. https://doi.org/10.1101/2020.03.25.009084. Epub ahead of print 28 Mar.
[11] Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. J Virol 2018;92:e00404–18. https://doi.org/10.1128/JVI.00404-18.
[12] Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol 2008;82:7264–75. https://doi.org/10.1128/JVI.00737-08.
[13] Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203:631–7. https://doi.org/10.1002/path.1570.
[14] Duncan HJ, Seiden AM. Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection. Arch Otolaryngol Head Neck Surg 1995;121:1183–7. https://doi.org/10.1001/archotol.1995.01890100087015.
[15] Kaye R, Chang CWD, Kazahaya K, Brereton J, Denneny 3rd JC. COVID-19 anosmia reporting tool: initial findings. Otolaryngol Head Neck Surg 2020;163:132–4. https://doi.org/10.1177/0194599820922992.
[16] Hopkins C, Surda P, Whitehead E, Kumar BN. Early recovery following new onset anosmia during the COVID-19 pandemic - an observational cohort study. J Otolaryngol Head Neck Surg 2020;49:26. https://doi.org/10.1186/s40463-020-00423-8.
[17] Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med 2020;8:e46–7. https://doi.org/10.1016/S2213-2600(20)30216-2.
[18] Simpson S, Kay FU, Abbara S, et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - secondary publication. J Thorac Imaging 2020;35:219–27. https://doi.org/10.1097/RTI.0000000000000524.
[19] Kobal G, Klimek L, Wolfensberger M, 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 2000;257:205–11. https://doi.org/10.1007/s004050050223.
[20] Tekeli H, Altundağ A, Salihoğlu M, Cayönü M, Kendirli MT. The applicability of the "sniffin' sticks" olfactory test in a Turkish population. Med Sci Monit 2013;19:1221–6. https://doi.org/10.12659/MSM.889838.
[21] Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front Immunol 2020;11:827. https://doi.org/10.3389/fimmu.2020.00827.
[22] Gupta KK, Khan MA, Singh SK. Constitutive inflammatory cytokine storm: a major threat to human health. J Interferon Cytokine Res 2020;40:19–23. https://doi.org/10.1089/jir.2019.0085.
[23] Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy 2016;8:959–70. https://doi.org/10.2217/imt-2016-0020.
[24] Ulhaq ZS, Soraya GV. Interleukin-6 as a potential biomarker of COVID-19 progression. Med Mal Infect 2020;50:382–3. https://doi.org/10.1016/j.medmal.2020.04.002.
[25] Wang H, Luo S, Shen Y, et al. Multiple enzyme release, inflammation storm and hypercoagulability are prominent indicators for disease progression in COVID-19: a multi-centered, correlation study with CT imaging score. SSRN 2020. https://doi.org/10.2139/ssrn.3544837. Epub ahead of print 22 Feb.
[26] Wan S, Yi Q, Fan S, et al. Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients. Br J Haematol 2020;189:428–37. https://doi.org/10.1111/bjh.16659.
[27] Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020;71:762–8. https://doi.org/10.1093/cid/ciaa248.
[28] Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa449. Epub ahead of print 17 Apr.
[29] Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. J Med Virol 2020. https://doi.org/10.1002/jmv.25948. Epub ahead of print 28 Apr.
[30] Zhu Z, Cai T, Fan L, et al. Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019. Int J Infect Dis 2020;95:332–9. https://doi.org/10.1016/j.ijid.2020.04.041.
[31] Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study [published correction appears in BMJ. 2020 Mar 31;368:m1295]. BMJ 2020;m1091:368. https://doi.org/10.1136/bmj.m1091.
[32] Loss of taste, smell might signal less-severe case of COVID-19. www.uspharmacist.com/article/loss-of-taste-smell-might-signal-lesssevere-case-of-covid19. [Accessed 8 September 2020].
[33] Lechien JR, Cabaraux P, Chiesa-Estomba CM, et al. Objective olfactory evaluation of self-reported loss of smell in a case series of 86 COVID-19 patients. Head Neck 2020;42:1583–90. https://doi.org/10.1002/hed.26279.
[34] Chidambaram S, Goh EL. The link between cytokine levels and loss of olfaction in chronic rhinosinusitis. JAMA Otolaryngol Head Neck Surg 2017;143:195. https://doi.org/10.1001/jamaoto.2016.2424.
[35] Torabi A, Mohammadbagheri E, Akbari Dilmaghani N, et al. Proinflammatory cytokines in the olfactory mucosa result in COVID-19 induced anosmia. ACS Chem Nerosci 2020;11:1909–13. https://doi.org/10.1021/acschemneuro.0c00249.
[36] Henkin RI, Schmidt L, Velicu I. Interleukin 6 in hyposmia. JAMA Otolaryngol Head Neck Surg 2013;139:728–34. https://doi.org/10.1001/jamaoto.2013.3392.