Original Article

Olfactory and Gustatory Dysfunctions as Prognostic Factors in Patients with the SARS-CoV-2 Virus

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Abstract

Background: Coronavirus disease 2019 (COVID-19) neurologic symptoms such as anosmia and ageusia are considered the most challenging issues for patients in the first steps of viral infection. Herein, we aimed to investigate the olfactory and gustatory dysfunction and their association with prognostic factors in patients with COVID-19.

Materials and Methods: The current retrospective study was performed on patients admitted to a hospital with a definite diagnosis of COVID-19 between March and November 2020. Based on the study criteria, information of 150 eligible participants (89 males and 61 females) was collected entirely. The olfactory and gustatory symptoms, including anosmia, hyposmia, ageusia, and dysgeusia, were assessed, and five main COVID-19 prognostic factors, including the level of D-dimer, C-reactive protein (CRP), lymphocyte count (LC), lactic acid dehydrogenase (LDH) and COVID-19 related lung involvement was measured.

Results: Among all patients, 102 (68%) participants were treated entirely, and 48 (32%) died. All prognostic factors, including CRP, LDH, LC, D-dimer, and lung involvement, were significantly higher in death cases compared to treated patients. We found that 97 (64.7%) patients experienced at least one olfactory or gustatory dysfunction. The level of CRP, LC, D-dimer, and lung involvement showed a better prognosis among patients with at least one sensory dysfunction. Moreover, a better outcome was observed in patients with sensory dysfunction.

Conclusion: It can be concluded the evaluation of CRP, LDH, D-dimer, and LC, together with the HRCT scan score, contributes to a better prognosis in COVID-19 patients with sensory dysfunction.

Keywords: COVID-19, Prognosis, Olfactory, Gustatory Dysfunction, HRCT

Please cite this article as:
Haghighi M, Hatami H, Asadi E, Ebadi SS, Soleimantabar H, Shadkam A, et al. Olfactory and Gustatory Dysfunctions as Prognostic Factors in Patients with the SARS-CoV-2 Virus. J Cell Mol Anesth. 2022;7(4):213-9. DOI: https://doi.org/10.22037/jcma.v7i3.38157

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Introduction

In December 2019, a novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was primarily detected in Hubei Province, China, and subsequently spread worldwide (1). Before an outbreak began in Wuhan, the virus and disease were completely obscure, but the rapid spread of the virus worldwide has raised increasing concerns. It is estimated that COVID-19 affects more than 220 countries worldwide (2). The most common reported symptoms in patients with COVID-19 are fever, dry cough, shortness of breath, myalgia, headache, and diarrhea (3). According to the World Health Organization (WHO), most of the infected patients have experienced respiratory illnesses ranging from mild to moderate and recovered without any specific medical intervention (4).

Otolaryngologic symptoms such as sore throat, cough, rhinorrhea, and nasal congestion were also prevalent among infected patients (3-5). Nasal airway blockage or sensory network deficits, impaired by a viral infection, can cause smell dysfunction. In acute viral infections, the most prevalent symptoms are hyposmia, dysosmia, and dysgeusia. Gustatory and olfactory systems are strongly associated with smell dysfunction and would gradually experience gustatory impairments (6). Loss of smell (anosmia) and taste (ageusia) were the most common olfactory and gustatory impairments, which can even happen before the main signs of COVID-19 (5, 6).

Smell loss can be an appropriate preventive strategy in asymptomatic people to inhibit viral transmission at the early stages of disease (7). Accordingly, finding an association between these symptoms, laboratory findings, and prognostic factors can lead to faster therapeutic measures in such patients. Therefore, we aimed to investigate a link between olfactory and gustatory dysfunctions and laboratory outcomes in hospitalized COVID-19 patients referred to a hospital in Tehran, Iran.

Methods

Settings and Ethical Statements: The present study is a retrospective investigation conducted between September 2020 and January 2021 in a teaching and referral hospital in Tehran, Iran.

Ethical considerations: All participants' identities and information remained confidential. Moreover, the present study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (SBMU) under reference number (IR.SBMU.PHNS.REC.1399.185).

Patients and Methods: The current study was retrospectively performed on patients admitted to the hospital with a definite diagnosis of COVID-19 from March to November 2020. All admitted patients above 18 years old with a definite diagnosis of COVID -19 approved by real-time reverse transcription polymerase chain reaction test were eligible to participate in the study. The hospital admission criteria of the present study were based on the Iranian diagnostic and therapeutic protocol for COVID-19. The admission criteria were as follows: 1) Respiratory rate>30, 2) partial pressure of Oxygen (PO2) <93%, and 3) The presence of pulmonary infiltrates in chest X-ray or high-resolution computed tomography (HRCT) scan. All patients who had any comorbidities including malignancies, high blood pressure, diabetes mellitus, rheumatoid arthritis, chronic respiratory disease, cardiovascular accident, immune system disorders, chronic kidney disease, utilization of any immune suppressor medications, and BMI>40, were considered as a high-risk group and excluded from the study. In addition, pregnant and lactating women were not allowed to participate in this study. Finally, data were collected from documented HISs by trained general practitioners.

Variables and Outcomes Measurement: Patients' anthropometric and sociodemographic characteristics, including gender, age, weight, and height, were extracted from their medical records. The olfactory and gustatory symptoms, including anosmia, hyposmia, ageusia, and dysgeusia, were also collected from archived electronic medical records. In the case of a lack of data, the information was obtained by telephone contact by trained general practitioners. We considered hyposmia and anosmia as olfactory impairment, ageusia, and dysgeusia as gustatory dysfunctions. Four main COVID-19 prognostic factors, including the level

of D-dimer, c-reactive protein (CRP), lymphocyte count (LC), and lactic acid dehydrogenase (LDH), were extracted from documented laboratory records (8). HRCT scan in the lung was measured to evaluate COVID-19 severity and progression (9). A semiquantitative scoring system was used to estimate the percentage of pulmonary involvement in HRCT scans. Based on this system, every five lobes of the lung were visually scored in a range of 0-5, where 0 is lack of any involvement, 1 is less than 5% involvement, 2 is 5-25% involvement, 3 is 25-50% involvement, 4 is 50-75% involvement, and 5 is more than 75% involvement. Then the total scores were calculated using the sum of lobar scores.

Data analysis: The SPSS version 26 was considered a statistical analysis calculator, and the significance level was set at 0.05. The dichotomous variables are presented as counts and percentages, and normal, non-normal, and continuous variables are presented as mean (standard deviation [SD]) and median (interquartile range [IQR]), respectively. The normality was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Analysis between the group was performed using Pearson's χ^2 and independent sample t-test for dichotomous and continuous variables, respectively.

Results

Sociodemographic Characteristics: Among all patients admitted to the hospital from March 2020 to November 2020 with a positive test for COVID-19, 178 patients met the study criteria. Finally, 28 participants were excluded from the study due to a lack of data, and information from 150 patients was completely collected (84.2 %). The study flowchart is shown in detail in Figure 1. Among all patients, 89 (59.3%) participants were male, and 61 (40.7%) were female. The mean (SD) age was 56.7 (12.9), ranging from 23 to 88 years old. No significant difference was observed between the mean (SD) age among males, 57.4 (12.6), and females, 55.7 (13.4) patients.

The mean (SD) BMI was 24.8 (2.2) kg/m2 which no significant difference was observed among male and female patients: 24.7 (2.2) kg/m^2 versus 25.0 (2.0) kg/m^2, p=0.3. Altogether 102 (68%) patients were completely treated and discharged from the hospital, and 48 (32%) patients died from SARS-CoV-2 infection. The mean (SD) recovery time was 10.1 (2.2) days ranging from 2 to 31 days. Among all dead patients, 32 (66.7%) were male, and 16 (33.3%) were female. No significant difference was seen in the outcomes between genders. Nevertheless, the need for ICU admission was significantly higher in male than female participants (p=0.01). The sociodemographic characteristics of participants and outcomes are shown in detail in Table 1.

Prognostic factors and HRCT scan scores: All evaluated biochemical markers, including CRP, LDH, D-dimer, and LC, showed predictive features in the present study. The mean (SD) CRP level in patients who were treated completely was significantly higher than in dead patients: 191.5 (22.1) mg/L versus 82.4 (12.7) mg/L, p<0.001. Moreover, the mean (SD) CRP

Table 1: Primers design.

Variables Mean (SD)		Gender		P-value
		Male (n=89)	Female (n=61)	
Age		57.4 (12.6)	55.7 (13.4)	0.42
BMI		24.7 (2.2)	25.0 (2.0)	0.31
Admitted to ICU	Yes (%)	51 (58.9)	23 (31.1)	0.01*
	No (%)	38 (50.0)	38 (50.0)	
Outcome	Dead (%)	32 (66.7)	16 (33.3)	0.21
	Live (%)	57 (55.9)	45 (44.1)	

*P<0.05

Table 2: Prognostic factors and outcomes among study participants.

Variables Mean (SD)	ICU admission		P-value	Outcome		P-value
	Yes (n=74)	No (n=76)		Dead (n=48)	Live (n=102)	
Lymphocyte (numb/µl)	674.4 (71.7)	1166.8 (115.1)	<0.01*	595.4 (82.2)	1078.5 (103.3)	<0.001*
CRP (mg/l)	160.5 (28.6)	75.2 (11.9)	<0.001*	82.4 (12.7)	191.5 (22.1)	<0.001*
D-dimer (ng/ml)	2771.7 (541.3)	673.7 (149.9)	<0.001*	3397.2 (640.2)	914.1 (180.0)	<0.001*
LDH (U/l)	1035.5 (102.4)	631.0 (86.0)	<0.001*	1146.0 (275.1)	682.1(166.7)	<0.001*
CT score	17.5 (2.7)	7.5 (2.1)	<0.001*	18.2 (3.1)	7.2 (1.3)	<0.001*

*P<0.05

Table 3: The association of prognostic factors and outcome of participants with vitamin D level.

Variables Mean (SD)		Sensory Dysfunction		P-Value
		Yes (n=97)	No (n=53)	
Lymphocyte (numb/µl)		1138.2 (321.8)	789.3 (142.2)	0.01*
CRP (mg/l)		65.3 (12.9)	84.1 (10.1)	0.03*
D-dimer (ng/ml)		736.9 (104.4)	1089.3 (277.1)	<0.001*
LDH (U/l)		689.7 (97.9)	791.2 (141.1)	0.08
CT score		16.2 (4.2)	9.4 (2.6)	<0.001*
ICU admission	Yes (%)	30 (40.5)	44 (59.5)	<0.001*
	No (%)	53 (69.7)	23 (30.3)	
Outcome	Dead (%)	21 (43.7)	27 (56.2)	<0.001*
	Live (%)	76 (74.5%)	26 (25.5)	

*P<0.05

level of participants who needed to be in ICU was significantly higher than non-ICU patients: 160.5 (28.6) mg/L versus 75.2 (11.9), p<0.001. Likewise, LDH and D-dimer levels of dead or ICU-add patients were significantly higher than live or non-ICU patients (p<0.05). The mean (SD) LC of live (1078.5 (103.3) numb/µl) and non-ICU (1166.8 (115.1) numb/µl) patients were significantly higher than dead (595.4 (82.2) numb/µl) and ICU-add (674.4 (71.7) numb/µl) cases, respectively (p<0.001).

Among all 150 participants, lung involvement was detected in 139 (92.7%) patients in the HRCT scan, and only 11 patients (7.3%) did not have any lung involvement. The mean (SD) total HRCT scan score was 10.7 (1.2), and no significant difference was detected in the involvement of lung lobes. The ground glass opacity (GGO) pattern was the dominant pattern among all detected patterns in the HRCT scan, so 112 (80.6%) patients had a GGO pattern. In comparison, 19 (13.7%) and 8 (5.7%) patients had GGO-consolidation and consolidation patterns, respectively. The mean (SD) total HRCT scan score in dead cases (18.2 (3.1)) or ICU admitted patients (17.5 (2.7)) was significantly higher than live (7.2 (1.3)) or non-ICU (7.5 (2.1)) patients (p<0.001). All patients with lung involvement showed a GGO-consolidation pattern with worse outcomes (p<0.05). However, no significant difference was seen in the outcome of patients with GGO and

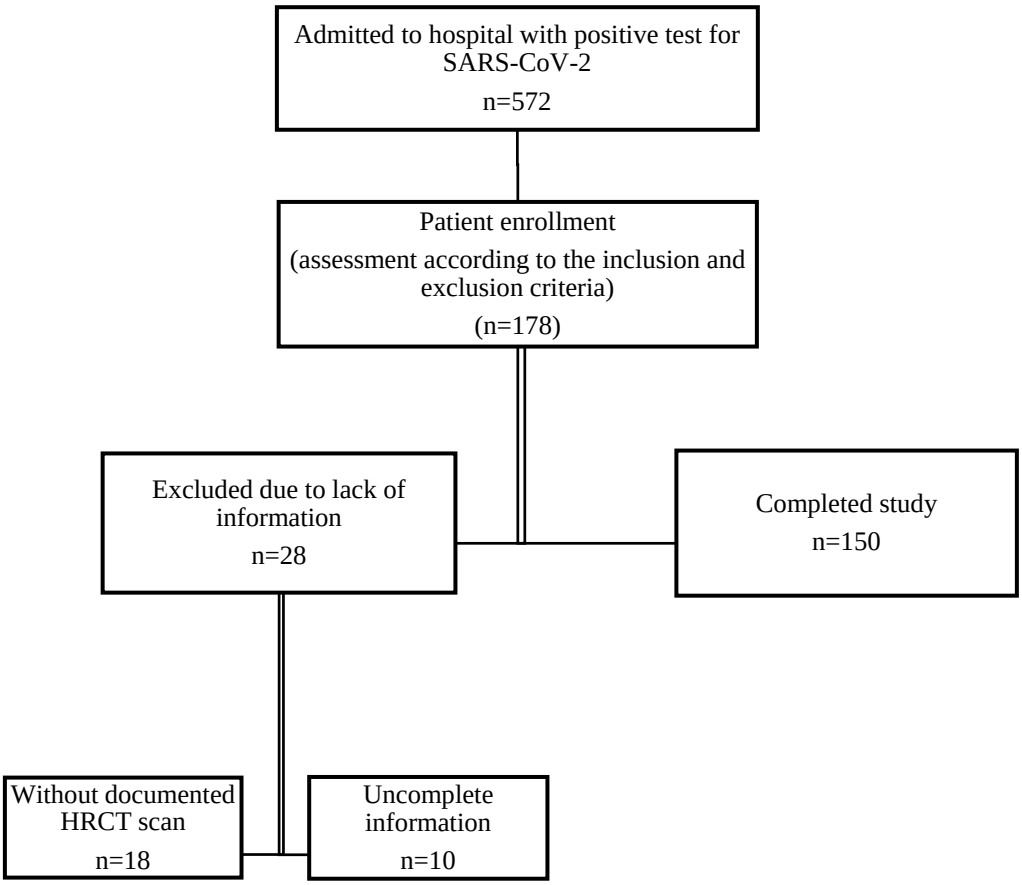

Figure 1. The study flowchart.

consolidation patterns. The association between prognostic factors and clinical outcome is shown in detail in Table 2.

Prognosis in patients with olfactory and gustatory dysfunction: Among all 150 participants, 97 (64.7%) patients had at least olfactory or gustatory dysfunction, and 53 (35.3%) patients reported no problem with their olfactory or gustatory sensation. A total of 51 (52.6%) patients reported both olfactory and gustatory dysfunction. Dysfunction in both olfactory and gustatory sensation was the dominant pattern in sensory dysfunction. In comparison, 31 (31.9%) and 16 (16.5%) patients had only olfactory or gustatory dysfunction. Generally, the patients with at least one sensory dysfunction showed a better prognosis than the other participants. Among all 102 treated patients, 76 (74.5%) participants had at least olfactory or gustatory dysfunction, while 21 (43.7%) dead patients were reported with severe sensory dysfunction ($p<0.05$).

On the other hand, the evaluation of prognostic factors, including CRP, D-dimer, and LC, showed a better prognosis among patients with sensory dysfunction. The mean (SD) CRP level among patients with sensory dysfunction was significantly lower compared to other patients: 65.3 (12.9) mg/L versus 84.1 (10.1) mg/L, $p=0.03$. However, no significant difference was observed in the LDH level of patients with or without sensory dysfunction. A significantly higher HRCT scan score, another prognostic factor, was also revealed in patients with sensory dysfunction compared to other patients. There was no significant difference in prognosis among different patterns of sensory dysfunction. The association between prognosis and sensory dysfunction is shown in detail in Table 3.

Discussion

Herein, we found that CRP, LDH, and D-dimer levels were significantly elevated compared to completely treated patients in both ICU-admitted and death cases. Moreover, treated and non-ICU patients showed substantially higher LC levels than finally dead subjects and ICU patients. Accordingly, it can be deduced that evaluation of the four mentioned factors contributes to a much better prognosis in infected patients. In line with our results, Jiacheng et al. found that CRP, B-type natriuretic peptide (BNP), D-dimer, and baseline neutrophil-to-lymphocyte ratio (NLR) is helpful prognostic biomarkers for the early diagnosis of infection (10). Hong et al. also revealed that elevated levels of inflammatory mediators such as CRP, LDH, and IL-6, together with D-dimer and platelet count, can be helpful to diagnostic markers for early stages of infection. Therefore, they can be the most appropriate prognostic biomarkers in patients with COVID-19 (11).

More than 90% of patients had lung involvement, and a GGO pattern was observed in approximately 80% of patients. In addition, there was a significant difference between the patients with the GGO-consolidation pattern and other patients with lung involvement. The GGO-consolidation pattern showed worse outcomes. Other studies have detected the prognostic factors related to a higher risk of COVID-19 infection mortality (9, 12).

Our results showed that 64.7% of patients experienced olfactory or gustatory dysfunction, and a better prognosis was found in patients with at least one sensory dysfunction. Olfactory or gustatory dysfunction was significantly higher in treated patients. The results illustrated that evaluating prognostic factors, including CRP, D-dimer, and LC, improved prognosis among patients with sensory dysfunction. HRCT scan as another prognostic factor also revealed significantly higher scores in patients with sensory dysfunction.

In line with our results, another study found that the prevalence of anosmia in non-critically ill patients is significantly higher. Compared to the ICU-admitted patients, they also reported more olfactory dysfunction in hospitalized patients (13). Evidence showed the association between olfactory and gustatory impairments and COVID-19 (14). Luers et al. illustrated that two-thirds of confirmed COVID-19 patients in Europe showed olfactory and gustatory dysfunction (15). Mehraeen et al. reported that one of the main and early clinical symptoms of COVID-19 infection is anosmia which happens suddenly (5). Isolated sudden onset anosmia (ISOA) was also reported in a confirmed COVID-19 case that showed no other clinical presentations such as respiratory disturbances. Loss of smell or taste functions is assumed to be originated from nasal congestion and rhinorrhea, which inhibit reaching the sensory input to neurons carrying olfaction and gustation (16). Another hypothesis is that the olfactory bulbs probably contribute to the infection entry into the brain. The nasal neuroepithelium, covered by sustentacular cells, has ACE-2 and TMPRSS-2 receptors contributing to the infection entry. Loss of olfaction subsequently affects gustatory dysfunction. However, the plausible mechanism has not been fully understood yet (17).

The olfactory and gustatory dysfunction association with prognostic factors has been reported, even though the precise pathogenesis in COVID-19 patients has remained unclear. It is well-established that followed by the viral infection, cytokine storm would increase in the body. Degeneration of olfactory neurons, as a result of overproduction of such inflammatory responses, happens. The immune system in the olfactory mucosa (OM) will be impaired, resulting in the loss of smell function (18).

Talavera et al. represented that in approximately 60% and 80% of patients, anosmia was respectively present from the first day and first five days of COVID-19. They mentioned that laboratory parameters such as elevated levels of CRP and IL-6 are the most significant abnormalities in patients with anosmia, which was related to fewer comorbidities and less disability. Consistent with our results, they also concluded that olfactory dysfunction is linked to a less mortality rate (19). Elevated levels of inflammatory responses were also reported by Sanli et al. illustrating that although there is an association between olfactory disorder and high levels of IL-6 in all patients, serum IL-6 levels were significantly higher in patients without the olfactory disorder (20). However, our findings showed that inflammatory factors and olfactory and gustatory disorders provide a better

prognosis in patients with mild COVID-19.

Conclusion

The current study showed an association between olfactory or gustatory dysfunction and viral infection in patients diagnosed with COVID-19. Also, a better prognosis can be expected in patients with at least one sensory dysfunction. Olfactory or gustatory dysfunction was significantly higher in those who were treated. In addition, evaluation of CRP, D-dimer, and LC together with HRCT scan score contributes to a better prognosis in patients with sensory dysfunction.

Acknowledgment

The authors thank the Departments of Medicine and Anesthesiology & Critical Care, Shahid Beheshti University of Medical Sciences, for their facilities and technical assistance. This study was funded by the Clinical Research Development Center, Imam Hossein A.S. Hospital, SBMU, Tehran, Iran.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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