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The relationship between anosmia and ageusia with biochemical markers, severity, and duration of the disease in patients with COVID-19

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ABSTRACT

Introduction: Due to the increasing prevalence of COVID-19 and its effects on the sense of taste and smell, we analyzed Blood electrolyte levels and biomarkers in COVID-19 patients who have a sign of anosmia and ageusia in Zanjan, Iran, and its relationship with biochemical blood indicators.

Materials and Methods: The retrospective study included all hospitalized patients with confirmed COVID-19. We registered laboratory parameters. A questionnaire that validity and reliability have already been confirmed was used to assess anosmia and ageusia. Statistical analysis was evaluated using a bivariate Bayesian logistic regression in the binomial distribution.

Results: A total of 450 COVID-19 patients completed the study (221 females). The mean age of the patients was 56.36±17.34 years. 31.8% and 24.9% of patients reported anosmia and ageusia. There was no significant relationship between anosmia and ageusia with age, gender, place of hospitalization, marriage status, duration of hospitalization, and CT scan ($p<0.05$). The Male's platelet was 18.72 lower than the female's ($p=0.002$). Male's C-reactive protein was 4.96 units higher than female ($p=0.002$). In hospitalized persons for less than four days and people under 39 years of age, CRP levels were lower ($P=0.001$, $P=0.019$ respectively). The Levels of lactate dehydrogenase in patients with anosmia were 51.72 units less than in patients without anosmia ($p=0.010$).

Conclusion: These results suggest that anosmia and ageusia are prevalent symptoms in Iranian COVID-19 patients. More information on serum biomarkers would help us to establish a greater degree of accuracy on this matter.

Keywords: COVID-19; Anosmia; Ageusia; C-reactive protein; Lactate dehydrogenase.

Introduction

Coronavirus, SARS-CoV-2, is a highly contagious disease first identified in East Asian countries in December 2019 in china, that quickly became a worldwide epidemic [1,2]. COVID-19 has a commune period of approximately 14 days, with an average time of 4.5 days from exposure to symptoms onset [3,4].

Some clinical symptoms of COVID-19 have been introduced as nonspecific, understanding the common symptoms of this illness is very important. Prevalent symptoms include fever (83-99%), cough (59-82%), fatigue (44-70%) and myalgia (11-35%), dyspnea (31-40%), and anorexia (40-84%) [5-7]. Other related symptoms that have been reported include diarrhea, headache, confusion, chest pain, sore throat, and vomiting [5,6]. Also, other symptoms attract more attention as some possible indicators of this disease, such as olfactory and gustatory dysfunctions [8,9].

Anosmia (loss of smell), and ageusia (loss of taste), have also been reported as well-known symptoms related to a wide range of viral infections [10,11]. Some possible mechanisms may explain the pathogenesis effect of SARS-CoV-2 infection on taste and olfactory disorders. A mice model indicated a trans neural penetration of SARS-CoV-2 through the olfactory bulb [12]. Furthermore, SARS-CoV-2 used angiotensin-converting enzyme 2 (ACE2) receptor to bind and penetrate the cell, which is widely expressed on the epithelial cells of the mucosal of oral activity [13].

The Centers for Disease Control and Prevention (CDC) recently added "new loss of taste or smell" as a potential early symptom to its list [14]. Agyeman et al. found that 41% and 38% of diagnostic patients with COVID-19 have olfactory or taste disorders [9]. Bagheri et al. indicated that 48.23% of patients with COVID-19, reported anosmia/hyposmia [15]. The recovery time for Anosmia and dysgeusia in most patients with COVID-19 approximately 7 days, while another viral infection is usually from a few weeks to several months [16]. Patients under 40 years recover from the olfactory problem more quickly than patients over 40 years [16].

Although a few studies have mentioned this issue [17-25], more clinical studies are needed to confirm these findings. On the other hand, due to the epidemic and pathogenesis of COVID-19, early screening of patients with acute anosmia and ageusia can help in the early diagnosis of patients infected with COVID-19. On the other hand, few studies showed an association between OGD disorder with some blood and serum indicators [26-28]. Understanding this association and evaluating the electrolytes and biochemical parameters can help patients with this disorder. To the best of our knowledge, this study aimed to investigate the prevalence of taste and smell disorders in Zanjan, Iran, and its relationship with blood biochemical indicators.

Materials and Methods

Study design and participants

This study protocol was approved by the Medical Ethical Committee of Baqiyatallah University of Medical Sciences (approval number IR.BMSU.REC.1399.079). This retrospective study was conducted based on the medical records of Vali-Asr patients who diagnosed with COVID-19 in Zanjan, Iran in the year 2020. Due to the limitation of inpatient centers and the lack of significant differences in terms of variables, Vali-Asr Hospital was selected as the sampling location.

Due to the 30% prevalence of anosmia in patients with COVID-19 in the study by Russell et al [20], The calculation of the sample size was based on an alpha level of 0.05 and a power of 95%, the minimum number of participants required for the present study was estimated at 450 people. The samples were selected by a systematic random sample method based on the patient registration system. Patients were enrolled who were previously hospitalized based on laboratory-confirmed COVID-19 and had a definite result. After explaining the objectives and method for patients considering the inclusion and exclusion criteria, the informed consent was obtained from recovered patients and was entitled to withdraw from the study at any time. Pregnant women, and children (<18 years) were excluded. All patient information remained confidential.

Covid-19 disease diagnosis

We used Nasal and/or pharyngeal swabs, presented typical chest CT, and RT-PCR assay for COVID-19 pneumonia diagnosis [29].

Eligibility Criteria

We included all consecutive patients that had the following criteria. 1) had an approved COVID-19 disease, 2) were hospitalized. They were excluded if their clinical record is incomplete, or if they were hospitalized before the outbreak of COVID-19 due to another illness.

Data collection

Retrospective data including demographic features, clinical variables, laboratory findings, exposure history, clinical presentation, chest CT images, comorbidities, the severity of COVID-19, and treatment were collected from electronic medical records. Biochemical laboratory included as following: WBC; white blood cell, HB; hemoglobin, Plat; Platelets, Lyme; lymphocyte Na, K, Ca, P, BS; blood sugar, ALK; Alkaline phospha-

tase, liver enzymes, Alb; BUN; blood Urea Nitrogen Cr; creatinine, D-dimer, Myoglobin, CPR; C-Reactive Protein, LDH; Lactate dehydrogenase, PRL; prolactin, ESR; Erythrocyte sedimentation rate and vitamin D. A questionnaire that validity and reliability have already been confirmed was used to assess anosmia and ageusia [30]. To determine anosmia and ageusia, a 3-item questionnaire was used. The answer to each question was scored from 1 to 7 so that a score of 1 was assigned to "very poor" and a score of 7 to "excellent". Also, data related to the severity of the disease and length of stay in the hospital were collected by using the information in the patient file. The severity of the disease was confirmed by physicians and according to the CT-SCAN and SpO2 and Respiratory Rate. All data independently were checked by two physicians (FZ and ZL). Definition of anosmia and ageusia [31]. Anosmia is defined as a temporary or permanent loss of the ability to detect one or more odors. Ageusia is defined as loss of sense of taste.

Statistical Analysis

In the present study, IBM-SPSS statistical software version 26 was used for analyzing the data. quantitative variables were reported as mean and standard deviations (SD or median and interquartile range) and qualitative variables were reported as numbers (percent). Chi-Square test and multivariate regression analysis were used to relations between variables. The variable selection method was used to design the final model. We assessed all the analyzes by 95% confidence intervals (CI). The significance level was determined at $p < 0.05$.

Results

In this study, 450 patients who recovered from CVID-19 were evaluated and analyzed. The mean age of the patients was 56.36±17.34 years. of 450 patients recovered 229 (50.9%) were male and 221 (49.1%) were female. 258 (57.3%) of patients were hospitalized between 5 and 10 days. 431 (95.8%) were hospitalized in the ward. Hydroxychloroquine was prescribed to 95.8% of patients and 99.3% of patients had Ground glass opacity. The most age group affected by COVID-19 disease was 61≥years 191 (42.4%) the prevalence rates of ageusia and anosmia were 24.9%, 31.8%, characteristics of COVID-19 patients showed in Table 1. The results showed that 163 (71.2%) were male and 144 (65.2) females without anosmia, 180 (78.6%) were male and 158 (71.5%) females without agnosia. Patients were hospitalized inward without anosmia 278 (67.3%) and without ageusia 312 (75.5%). In the age group of 40 to 60 years, 117 [68] had without anosmia, 135 (78.5) had without ageusia and patients 61 years old or over 136 (71.2%) had without anosmia, 143 (74.9%) had without ageusia. Patients with Ground glass opacity had 306 (68.5%) without anosmia, and 336 (75.2%) had without ageusia. Patients hospitalized between 10-5 days 171 (66.3%) without anosmia, 191 (74%) without ageusia, and 87 (33.7%) anosmia and 67(26%) had ageusia. There was no significant relationship between anosmia and ageusia with age, gender, place of hospitalization, marriage status, duration of hospitalization, and CT-scan (Table 2).

Male's PLT was 18.72 lower than females. Male's CRP was 4.96 units higher than female. Levels of CRP patients were hospitalized less than 4 days and between 10-5 days, 11.94 and 7.36, respectively, units less than patients hospitalized more than 11 days. Also, the levels of CRP patients were 39≤ years 7.22 units less than patients 61≥ years. The Levels of LDH in patients with anosmia were 51.72 units less than patients without anosmia. Levels of lymphocytes male were 2.55 units less than in female (Table 3).

Table 1. Characteristics of COVID-19 patients.

Characteristic	*Frequency*	*Percent*
Gender		
Male	*229*	*50.9*
Famale	*221*	*49.1*
Place of hospitalization		
ICU	*33*	*7.3*
Ward	*413*	*91.8*
Region		
Urban	*373*	*82.9*
Rural	*77*	*17.1*

Characteristic	Frequency	Percent
Marriage status		
Single	*25*	*5.6*
Married	*425*	*94.4*
Avg		
19-39 years	*87*	*19.3*
40-60 years	*172*	*38.2*
≤61years	*191*	*42.4*
Duration of hospitalization		
4 day or less	*117*	*26*
5-10 day	*258*	*57.3*
11 day or more	*74*	*16.4*
Treatment		
Antibiotics	*250*	*55.6*
Hydroxychloroquine	*431*	*95.8*
Atazanavir-Ritonavir	*234*	*52*
CT-scan		
Ground glass opacity	*447*	*99.3*
Other	*3*	*0.7*
Anosmia-Ageusia		
With anosmia	*143*	*31.8*
without anosmia	*307*	*68.2*
With ageusia	*112*	*24.9*
Without ageusia	*338*	*75.1*

Table 2. The relationship between characteristics of COVID-19 patients with anosmia and ageusia.

Characteristics	Anosmia			Ageusia		
	with anosmia n (٪)	without anosmia n (٪)		with anosmia n (٪)	without anosmia n (٪)	
Gender						
Male	*66 (28.8)*	*163 (71.2)*		*49 (21.4)*	*180 (78.6)*	
Famale	*77 (34.8)*	*144 (65.2)*		*63 (28.5)*	*158 (71.5)*	
p-value[a]		*0.170*			*0.081*	
Place of hospitalization						
ICU	*8 (24.2)*	*25 (75.8)*		*11 (33.3)*	*22 (66.7)*	
Ward	*135 (32.7)*	*278 (67.3)*		*101 (24.5)*	*312 (75.5)*	
p-value[a]		*0.317*			*0.258*	
Marriage status						
Single	*10 (40)*	*15 (60)*		*9 (36)*	*16 (64)*	
Married	*133 (31.3)*	*292 (68.7)*		*103 (24.2)*	*322 (75.8)*	
p-value[a]		*0.364*			*0.186*	
Avg						
19-39 years	*33(37.9)*	*54(62.1)*		*27(31)*	*60(69)*	

Characteristics	Anosmia			Ageusia		
	with anosmia n (%)	without anosmia n (%)		with anosmia n (%)	without anosmia n (%)	
40-60 years	55 (32)	117 (68)		37 (21.5)	135 (78.5)	
≤61years	55 (28.8)	136 (71.2)		48 (25.1)	143 (74.9)	
p-value	0.316			0.245		
Duration of hospitalization						
4 day or less	35 (29.9)	82 (70.1)		25 (21.4)	92 (78.6)	
5-10 day	87 (33.7)	171 (66.3)		67 (26)	191 (74)	
11 day or more	21 (28.4)	53 (71.6)		20 (27)	54 (73)	
p-value	0.598			0.572		
CT-scan						
Ground glass opacity	141 (31.5)	306 (68.5)		111 (24.8)	336(75.2)	
Other	2 (66.7)	1(33.3)		1 (33.3)	2(66.7)	
p-value[b]	0.238			1		

a. Based on Pearson Chi -Square test.
b. Fisher's Exact Test.

Table 3. Multivariate regression analysis for determining the relationship between biochemical indicators with Anosmia and Ageusia.

	WBC				PLT				CRP				LDH				LMY			
Variable levels	β	Confidence interval (95%)		P-value	β	Confidence interval (95%)		P-value	β	Confidence interval (95%)		P-value	β	Confidence interval (95%)		P-value	β	Confidence interval (95%)		P-value
		Upper	Lower			Upper	Lower			Upper	Lower			Upper	Lower			Upper	Lower	
With anosmia	-0.45	0.11	-1.01	0.116	4.58	17.45	-8.27	0.484	-1.98	2.65	-6.63	0.400	-51.72	-12.30	-91.15	0.010	1.72	3.57	-0.14	0.070
Without anosmia	1	.	.	.	1	.	.		1	.	.	.	1	.	.	.	1	.	.	0
With ageusia	-0.53	0.55	-0.66	0.865	9.47	23.37	-4.41	0.181	-2.84	2.16	-7.85	0.264	-0.53	42.04	-43.12	0.980	-0.41	1.60	-2.41	0.690
Without ageusia	1	.	.	.	1	.	.	.	1	.	.	0	1	.	.	.	1	.	.	.
4 days or less	-0.73	0.11	-1.57	0.088	-7.37	11.86	-26.61	0.452	-11.94	-5.01	-18.88	0.001	-20.54	38.42	-79.52	0.494	2.54	5.31	-.24	0.074
5-10 day	-0.66	0.07	-1.39	0.077	-.28	16.45	-17.01	0.973	-7.36	-1.32	-13.39	0.017	28.36	79.66	-22.92	0.278	.75	3.17	-1.65	0.538
11 days or more	1	.	.	.	1	.	.	.	1	.	.	.	1	.	.	.	1	.	.	.
Male	-0.12	0.39	-0.63	0.648	-18.72	-6.945	-30.509	0.002	4.96	9.20	.71	0.022	2.62	38.73	-33.48	0.886	-2.55	-0.85	-4.26	0.003

Variable levels	WBC				PLT				CRP				LDH				LMY			
	β	Confidence interval (95%)		P-value	β	Confidence interval (95%)		P-value	β	Confidence interval (95%)		P-value	β	Confidence interval (95%)		P-value	β	Confidence interval (95%)		P-value
		Upper	Lower			Upper	Lower			Upper	Lower			Upper	Lower			Upper	Lower	
female	0[a]	.	.	.	0[a]	.	.	.	0[a]	.	.	.	0[a]	.	.	.	0[a]	.	.	.
19-39 years	0.08	0.81	-0.65	0.825	12.83	29.61	-3.95	0.134	-7.22	-1.17	-13.27	0.019	-47.50	3.94	-98.94	0.070	2.07	4.49	-0.35	0.094
40-60 years	-0.34	0.24	-0.93	0.247	-8.22	5.17	-21.62	0.228	-0.04	4.78	-4.87	0.985	-26.88	14.18	-67.96	0.199	0.11	2.04	-1.82	0.911
≤61 years	1	.	.	.	1	.	.	.	1	.	.	.	1	.	.	.	1	.	.	.

1. Reference

WBC: White Blood Cell, PLT: Platelets, CRP: c-Reactive Protein LDH: Lactate Dehydrogenase, LMY: Lymphocyte.

Discussion

In this study, we demonstrated a significant prevalence of olfactory and taste dysfunction among 450 patients with COVID-19. About 31.8% of patients reported anosmia and 24.9% ageusia. Acute anosmia is usually caused by a viral infection or trauma [32]. Studies show different estimates of the prevalence of anosmia or ageusia. Lee DY showed that anosmia or dysgeusia was more than a third of patients [16]. Hopkins showed that anosmia reports ranged from 34% to 68% of COVID-19 patients [33]. In the study of Sheng et al anosmia was reported about 33.6% and/or dysgeusia 28.6% [34]. Lee et al reported approximately 15% of patients had anosmia and/or dysgeusia in the early stage of COVID-19 [18]. Tong et al. showed that 52.7% of the patients with COVID-19 had anosmia and 43.9% of the patients had dysgeusia [35]. Biadsee found that anosmia and dysgeusia were 38.3% and 32.8% respectively [36]. Da Costa et al examined that 60.7% and 56.4% had anosmia and dysgeusia, respectively [37].

Anosmia was present in half of the European COVID-19 patients and was often associated with dysgeusia [38]. It seems different viral layers and levels of ACE2 expression in different ethnic populations are responsible for differences in the prevalence of anosmia and dysgeusia [39]. Anosmia and dysgeusia are common signs of the disease, especially in the early stages. The effect of sex differences on COVID-19 outcomes can be attributed to differences in the expression of the angiotensin-converting enzyme (ACE2 [40]. On the other hand, Kalinke showed that men were substantially less affected than women by olfactory dysfunction [41]. According to our results, there was no difference in male and female anosmia. This also accords with our earlier observations, which showed that there is no difference between men and women in terms of the amount of SARS-CoV-2 damage to the olfactory system [42]. According to the study by Han et al. higher levels of cytokine storm are related to more severe disease development [43]. We examined that the levels of CRP were higher in men. As Qin et al showed that males with severe COVID-19 reportedly have a higher CRP concentration compared with females [44]. Another study showed that C-reactive protein (CRP) greater than 15 mg/L provides a marker of disease severity [45] and tended to be a good predictor of adverse consequences [46,47]. We showed that people who were hospitalized for a shorter duration had lower CRP levels than those who were hospitalized for a long duration. In our study, people less than 39 years had lower CRP levels. CRP levels are associated with the level of inflammation [48]. Charlmes showed that patients with severe pneumonia had a high level of CRP [49]. Recent studies have shown the systemic inflammation called "cytokine storm" in patients with COVID-19 [50,51]. Inflammatory molecules can induce inflammatory cells and other mediators resulting in lung parenchyma damage and dyspnea [52]. Inflammation of the olfactory system has also been reported in other viral diseases [11]. Anosmia may be due to a severe inflammatory response in the nasal mucosa and epithelial damage [53]. Our study showed that both lymphocytes and platelets were lower in men with COVID-19 than in women. Lymphocytes are the first responders to viral agents, for example, SARS-CoV-2, and are related to COVID-19 severity [54]. Studies show that in severe disease, male lymphocytes are consistently reduced and lymphocytes are decreased [44,55].

Liu found that lymphopenia, elevated neutrophil, lactate dehydrogenase (LDH), and C-reactive protein (CRP) are all related to severe cases. Also, he observed that the time of hospitalization in COVID-19 patients with lymphopenia was extended [56]. During recovery, the patients with substantially elevated platelets had longer total hospitalization days, and the patients with higher platelets during recovery had longer total days of hospitalization [57]. In predicting mortality in COVID-19 patients, the mean platelet volume can be used as an auxiliary measure [58].

The relationship is not well known between olfactory dysfunction and lymphocytes. Decreased lymphocyte mitogenesis and lymphocyte count have been seen in olfactory bulbectomized mice [59]. Our analysis shows that in a patient with anosmia, LDH levels were lower. An independent risk factor for the seriousness of COVID-19 disease was the elevated LDH level [60] and high levels of CRP and LDH need serious care [61]. Li et al found that elevated serum levels of D-Dimers and LDH are known to be a risk factor in younger patients [62]. Wu et al. illustrated that there are major variations between the non-extreme and severe classes in LDH levels [63]. Anosmia was independently associated with lower mortality [64] and also is common in patients with mild COVID-19 [18,34]. It can be seen that anosmic patients have a milder COVID-19 disease at low cytokine storm and IL-6 levels [65]. Serum LDH reduction can also predict a favorable response to COVID-19 infection therapy [66]. We first examined the association between serum LDH levels and anosmia in COVID-19 patients. In further studies, the relationship between LDH levels and COVID-19 anosmia may be investigated alone or in combination with systemic LDH levels. There are still many unanswered questions about anosmia and blood biomarkers and their relationship.

To explain the details and elucidate the mechanisms underlying the development of these symptoms, Future epidemiological, clinical, and basic science studies are needed in a large population. One of the strengths of our study was using a standard questionnaire. This study has several limitations. First, this is a study conducted on a population of hospitalized patients. It is better to consider the high sample size and other hospitals from different regions for further studies. Second, we did not determine the severity and period or characteristics of anosmia and ageusia. Third, they may not be able to explain the symptoms of patients with serious symptoms.

Conclusion

Taken together, these results suggest that Olfactory and gustatory disorders are prevalent symptoms in Iranian COVID-19 patients. More information on serum biomarkers would help us to establish a greater degree of accuracy on this matter.

Acknowledgment

This study was approved by the Medical Ethical Committee of Baqiyatallah University of Medical Sciences (approval number IR.BMSU.REC.1399.079). We would also like to express our appreciation to all those participating in this study for their sincere cooperation.

Conflict of Interest

There is no conflict of interest to declare.

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