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The Impact of Age and Gender and Their Association with Chemosensory Dysfunction, in Hospitalized and Self-Quarantine Patients with Covid-19 Infection, in Epirus, Greece

Athina ZARACHI[a], Vasileios PEZOULAS[b], Orestis MILIONIS[c], Aikaterini N. LIANOU[a], Eleutherios KLOURAS[c], Ioannis KOMNOS[a], Dimitrios FOTIADIS[b], Ioannis KASTANIOUDAKIS[a], Charalampos MILIONIS[c], Angelos LIONTOS[c]

[a]Department of Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

[b]Unit of Medical Technology and Intelligent Information Systems, Departement of Materials Science and Engineering, University of Ioannina, Ioannina, Greece

[c]Faculty of Medicine, Department of Internal Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

ABSTRACT

Objectives: *Background: Olfactory and gustatory dysfunction that relates with the infection from severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) has already improved. The relation between chemosensory dysfunction and age and gender in covid-19 positive patients is the main objective of the present study.*

Methods: *We used a questionnaire to select information about medical history, patient demographics and reported symptoms during infection. Three hundred covid-19 positive patients, who underwent a RT-PCR test in the University Hospital of Ioannina, Grecce, were included in this study; 150 of them recovered at home and the remaining 150 were admitted to hospital. Statistical analysis based on IBM-SPSS Statistics 26.0 was done.*

Results: *The total sample included 300 patients, of which 106 females and 194 males. There was a statistically significant difference between the subgroup of patients aged 21-25, 61-65 and 71-75 with loss of smell, that of hospitalized patients aged 41-45 with loss of smell and the subgroup of those aged 31-35 and 71-75 with loss of taste.*

Address for correspondence:
Athina Zarachi
Postal address: Stavros Niarchos Avenue, 451 10, Ioannina, Greece
Tel.: +30 6979007589; email: athinazarachi@gmail.com

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Conclusion: *There is a significant association between chemosensory dysfunction and younger age groups. Olfactory and gustatory dysfunction appears more frequently in women than men. Male gender relates with disease severity.*

Keywords: COVID-19, chemosensory dysfunction, age, gender, sex, loss of smell, loss of taste.

INTRODUCTION

Chemosensory dysfunction seems to be a strong cause of loss of smell and loss of taste symptoms in the early stages of SARS-CoV-2 infection. Invasion of the central nervous system (CNS) along the olfactory pathway as well as the role of the angiotensin converting enzyme 2 (ACE2) receptor had been proven for the SARS-CoV-2 infection (1-14).

Ethnicity, genetics, male gender, older age as well as disease severity relate with decreased smell and taste dysfunction (15-18). The impact of sex and age on COVID-19 outcomes had already been investigated in many studies before. Advanced age and male gender are more markedly associated with worse prognosis of disease. Furthermore, the prevalence of smoking and chronic diseases is higher in men than women. Moreover, the immunological profile in men is wicker that women. Nicotine can possibly affect the putative virus receptor (ECA2) and destroy lung epithelial cells, which may contribute to worse prognosis of respiratory viral infections (19-24).

Therefore, the aim of this study was to assess the relation between the loss of smell and/or taste and participants' age and sex, in a cohort of mixed, hospitalized and self-quarantine COVID-19 positive patients who were examined in Epirus, Greece. ❑

MATERIALS AND METHODS

Participants

The present research is a prospective observational cohort study. The total sample included 300 patients aged 16 to 90 years, both men and women, who referred to either the Emergency Department (ED) of Infectious Diseases or the Outpatient Clinic screening for SARS-CoV-2 infection. All participants had a positive reverse transcription-polymerase chain reaction (RT-PCR) test result. After undergoing the RT-PCR test, all of them were examined and followed up at the University Hospital of Ioannina, Greece, between November 2020 and May 2021. The study population was divided into two equal groups. The first one included 150 patients whose symptoms and disease severity did not require hospitalization; they had mild to moderate disease and recovered at home. The remaining 150 patients had severe disease and were hospitalized in the Infectious Diseases Unit (IDU) of the University General Hospital of Ioannina, Greece. The purpose of this division was to analyze and compare the results of every subgroup both separately and in the total sample.

We used specific inclusion criteria and selected only individuals with the following common characteristics: adults aged 16 or over and ≤ 90 years, and COVID-19 positive patients who underwent the RT-PCR test at the University Hospital of Ioannina, Greece. We also used specific exclusion criteria. Taking into account the factors that potentially influence olfactory and taste function, we excluded every participant who either had previous sinus surgery, underwent head and neck radiation therapy, suffered from allergic rhinitis or chronic rhino sinusitis, or had a history of head injury (25-35).

Data collection

Data were collected during the early stage of SARS-CoV-2 infection using a questionnaire. For this purpose, one of the formal investigators participating in the study contacted 150 COVID-19 positive patients recovering at home, who offered the requested information by telephone, email or in person, following the safety measures provided by National Organization of Public Health of Greece. The remaining 150 patients who were hospitalized in the IDU of the University General Hospital of Ioannina were examined in person by one of the investigators officially participating in the study. Patient demographics, including name, age, height, weight, sex and contact details were recorded. Medical history, comorbidities, smoking and alcohol habits were

also recorded. After answering questions related to these issues, every patient had to report their associated symptoms experienced during the infection as per the following list: fever, cough, headache, symptoms of pharyngitis, dyspnea, fatigue, muscle aches, runny nose, nasal congestion, loss of smell, and loss of taste.

The questionnaire was completed by the examinee after every patient had received information regarding the study purpose and had provided a written consent form.

The present study was approved by the research ethic committee and the scientific council of the University General Hospital of Ioannina, Greece.

Statistical analysis

The statistical analysis approach regarding the categorical data was performed using the χ^2 (chi-square) test or Fisher's exact test in the case where at least one frequency in the contingency table was smaller than 5. As far as numerical data are concerned (*i.e.*, age), either the Mann–Whitney test or t-test was applied upon evaluation of the normality of each distribution using the Shapiro-Wilk normality test.

We analyzed the percentage of male and female participants. Mean values and percentages were measured for the total sample, the subgroup of hospitalized patients and the subgroup of self-quarantine patients. We also analyzed the percentage of men and women with chemosensory dysfunction, for the total sample, subgroup of hospitalized patients and subgroup of self-quarantine patients.

We also analyzed the mean percentage of age for the total sample, subgroup of hospitalized patients and subgroup of self-quarantine patients.

We analyzed the percentages of OGD among male and female patients in every subgroup and the total sample.

We divided the total age range of 16–90 years into 15 groups: age 16-20, age 21-25, age 26-30, age 31-35, age 36-40, age 41-45, age 46-50, age 51-55, age 56-60, age 61-65, age 65-7, age 71-75, age 76-80, age 81-85, and age 86-90.

We did a statistical analysis and compared every group with the following characteristics: with loss of smell, without loss of smell, with loss of taste, without loss of taste.

All features were analyzed for the total sample, the subgroup of hospitalized patients and subgroup of self-quarantine patients.

We used odds ratios (OR) to measure the association between our outcomes (36-39). ❑

RESULTS

Three hundred patients, comprising 106 females (35,33%) and 194 males (64,67%), participated in the study.

The analysis of mean percentages of men and women in the two subgroups showed that in the subgroup of hospitalized patients, 60% were men and 40% women, while in the subgroup of patients who recovered at home, 69,33% were men and 30,67% women (Table 1).

In the total sample, the analysis of gender-based percentages of olfactory dysfunction revealed that loss of smell was experienced by 66 (22%) women and 105 (35%) men, with the percentage of loss of smell being 62.26% in female participants and 54.1% in male ones. In hospitalized patients, loss of smell occurred in 32 (21.3%) women and 38 (25.3%) men, with the percentage of loss of smell being 53.3% in the female population and 42.2% in the male one. In the subgroup of patients who recovered at home, loss of smell appeared in 34 (22.6%) women and 67 (44.6%) men. In self-quarantine patients, the percentage of loss of smell was 73.9% in the female population and 46.4% in the male one (Table 1).

In the total sample, the analysis of gender-based percentages of taste dysfunction revealed that loss of taste occurred in 59 (19.6%) women and 96 (32%) men, with the percentage of loss of taste being 55.6% in the female population and 49.48% in the male one. In hospitalized patients, loss of taste appeared in 30 (20%) women and 40 (26.6%) men, with the percentage of loss of taste being 50% in the female population and 44,4% in the male one. In the subgroup of patients who recovered at home, loss of taste appeared in 29 (19.3%) women and 56 (37.3%) men. In self-quarantine patients, the percentage of loss of taste was 63% in the female population and 53.8% in the male one (Table 1).

Subsequently, participants' mean age was 45.98 (SD ±18.41) years old (y.o.) in the total sample, 57.35 (SD ±14,02) y.o. in hospitalized

	Total sample (n=300)%	Hospitalized (n=150)%	Self-quarantine (150)%
Male	64,67	60	69,33
Male with loss of smell	35	25,3	22,6
Loss of smell in male	54,1	42,2	46,4
Male with loss of taste	32	26,6	37,3
Loss of taste in male	49,48	44,4	53,8
Female	35,33	40	30,67
Female with loss of smell	22	21,3	44,6
Loss of smell in female	62,26	53,3	73,9
Female with loss of taste	19,6	20	19,3
Loss of taste in female	55,6	50	63

TABLE 1. Mean percentages of male and female population, percentages of males and females with loss of smell and loss of taste, and percentage of loss of smell and taste in genders – data from the total sample, subgroup of hospitalized patients and subgroup of self-quarantine patients

	Total sample (n=300)	Hospitalized (n=150)	Self-quarantine (n=150)
Mean age (years old), mean (SD)	45,98 (±18,41)	57,35(±14,02)	34,84 (±15)

TABLE 2. Mean age in the total sample, subgroup of hospitalized patients and subgroup of self-quarantine patients associated with standard deviation (mean ± SD)

patients and 34.84 (SD=±15) y.o. in self- quarantine ones (Table 2).

The 15 age subgroups, with or without the characteristics (loss of smell and loss of taste), were subjected to statistical analysis. In the total sample, there was a statistically significant difference between the subgroup of patients aged 21-25 with loss of smell (42 patients) and that of patients aged 21-25 without loss of smell (16 patients) ($p = 0.013^{**} < 0.05$). There were higher odds of association with exposure and outcome (OR 2.299418605) (Table 3).

In the total sample, there was also a statistically significant difference between the subgroup of patients aged 61-65 with loss of smell (eight patients) and that of patients aged 61-65 without loss of smell (15 patients) ($p = 0.043^{**} < 0.05$). There were lower odds of association with exposure and outcome (OR 0.373006135) (Table 3).

In the total sample, we observed a statistically significant difference between the subgroup of patients aged 71-75 with loss of smell (four patients) and that of patients aged 71-75 without loss of smell (10 patients) ($p = 0.049^{**} < 0.05$). There were lower odds of association with exposure and outcome (OR=0,28502994) (Table 3).

In the subgroup of hospitalized patients there was a statistically significant difference between

Age subgroups	Loss of smell-(yes)	Loss of smell-(no)	Loss of taste-(yes)	Loss of taste-(no)
age16-20	7	2	6	3
age21-25	42	16	31	27
age26-30	17	11	14	14
age31-35	6	0	6	0
age36-40	13	9	14	8
age41-45	15	6	14	7
age46-50	14	9	12	11
age51-55	18	10	18	10
age56-60	15	20	15	20
age61-65	8	15	9	14
age66-70	7	11	7	11
age71-75	4	10	3	11
age76-80	4	4	4	4
age81-85	0	1	0	1
age86-90	1	4	1	4

TABLE 3. Number of patients with or without loss of smell/taste between the different age groups in the total sample

Age subgroups	Loss of smell-(yes)	Loss of smell-(no)	Loss of taste-(yes)	Loss of taste-(no)
age16-20	0	0	0	0
age21-25	3	3	3	3
age26-30	1	2	1	2
age31-35	2	0	2	0
age36-40	4	5	6	3
age41-45	5	0	3	2
age46-50	9	8	7	10
age51-55	11	7	12	6
age56-60	12	17	11	18
age61-65	8	13	9	12
age66-70	6	9	7	8
age71-75	4	10	3	11
age76-80	4	2	4	2
age81-85	0	1	0	1
age86-90	1	2	1	2

TABLE 4. Number of patients with or without loss of smell/taste between the different age groups in hospitalized patients

the subgroup of patients aged 41-55 with loss of smell (five patients) and that of patients aged 41-45 without loss of smell (0 patients) ($p = 0.02^{**} < 0.05$) (Table 4).

Age subgroups	Loss of smell-(yes)	Loss of smell-(no)	Loss of taste-(yes)	Loss of taste-(no)
age16-20	7	2	6	3
age21-25	39	13	28	24
age26-30	16	9	13	12
age31-35	4	0	4	0
age36-40	9	4	8	5
age41-45	10	6	11	5
age46-50	5	1	5	1
age51-55	7	3	6	4
age56-60	3	3	4	2
age61-65	0	2	0	2
age66-70	1	2	0	3
age71-75	0	0	0	0
age76-80	0	2	0	2
age81-85	0	0	0	0
age86-90	0	2	0	2

TABLE 5. Number of patients with or without loss of smell/taste between the different age groups in home-quarantine patients

There was no statistically significant difference between any of the subgroups of patients who recovered at home (Table 4).

We further describe the outcomes regarding the loss of taste.

In the total sample, there was a statistically significant difference between the subgroup of patients aged 31-35 with loss of taste (six patients) and that of patients aged 31-35 without loss of taste (0 patients) ($p = 0.03^{**} < 0.05$) (Table 3). Also, there was a statistically significant difference between the subgroup of patients aged 71-75 with loss of taste (three patients) and that of patients aged 71-75 without loss of taste (11 patients) ($p = 0.027^{**} < 0.05$). There were lower odds of association with exposure and outcome (OR 0.240430622), (Table 4).

Among hospitalized patients there was no statistically significant difference between the subgroup of patients in any age subgroup (Table 4).

Finally, among patients who recovered at home there was also a statistically significant difference between the subgroup of patients in any age subgroup (Table 5). ❑

DISCUSSION

Our data confirm the impact of sex and age in SARS-CoV-2 infection in our population of patients with COVD-19 in Epirus, Greece, and represent the first of its kind dataset from the region. Our findings showed that the percentage of infected men was higher than women in both the total sample and two subgroups. Gender is a risk factor for higher severity and mortality in patients with COVID-19 and there is increasing evidence that coronavirus disease produces more severe symptoms and higher mortality among men than women. This is probably associated with the fact men have a shorter life expectancy than women. Furthermore, the disproportionate death ratio in men may be explained by the occurrence of comorbidities (*i.e.*, hypertension, diabetes, and chronic lung disease), higher smoking and alcohol use, and occupational exposure. It has also been shown that men had higher levels of circulating ACE2 than women. Finally, women are more likely to follow hand hygiene practices and seek preventive care than men. Takehiro Takahashi and his collaborators investigated whether the immune responses against severe acute respiratory syndrome coronavirus differed between sexes and whether such differences correlated with the sex difference in the disease course of COVID-19. They found that male patients had higher plasma levels of innate immune cytokines and female had more robust T cell activation their counterparts during SARS-CoV-2 infection. They also noticed that a poor T cell response was associated with worse disease outcome in male patients (40-45). Moreover, we noticed a higher percentage of

loss of smell and taste in the female population than male population, which is in accordance with the results of other researchers, who reported that women were significantly more affected by chemosensory dysfunctions than men (46-50).

Both clinical features and epidemiological data of patients with COVID-19 have been recently reported (51-55). Furthermore, data on prognostic factors of COVID-19 have been described in many prior studies, which estimated that older patients (≥65 years old) were more likely to have a severe form of SARS-CoV-2 infection (55-57). Several mechanisms and risk factors contribute to the higher risk of infection in the elderly. Firstly, the high expression of the receptor for SARS-CoV-2 spike protein, angiotensin-converting enzyme-2 (ACE-2) is associated with aging. Secondly, immune changes and dysregulation, also known to occur as a result of aging, can contribute to a cytokine attack, which is estimated to be one of the main indicators of disease severity. Furthermore, decrement in growth hormone as well as oxidative stress and mitochondrial dysfunction in both pneumocytes and immune cells contribute to the severity of infection. Physical activity and nutrition are compromised in the elderly, and these are important factors in SARS-CoV-2 infection. Finally, comorbidities that are associated with aging, including cardiovascular disease, diabetes and hypertension, are risk factors for disease severity in older patients (58-65).

Our results provide support to these previous studies. The highest mean age was seen in the subgroups of hospitalized patients and the lowest mean age in that of patients who recovered at home. So, older age was associated with disease severity and need of hospitalization in our population of COVID-19 positive patients in Epirus, Greece.

Except the impact of older age in COVID-19 severity, we tried to investigate the association between chemosensory dysfunction and specific age-groups. So, we noticed that, in the total sample of subjects with SARS-CoV-2 infection, the loss of smell affected only the 21-25 age group, but not the older age groups of 61-65 and 71-75 years; also, the 31-35 age group was affected by the loss of taste, while the older five-year group of 71-75 was associated with the absence of gustatory dysfunction. Given that OGDs occurred in proportionally younger subjects and increasing age was associated with lower prevalence of OGDs, as previously reported by many other researchers, we came to similar conclusions in our population-based study. The significant association between the 41-45 age group and loss of smell in hospitalized patients is probably related to the overall elevated average age in this subgroup of patients (66, 67).

There are probably some limitations is this study. We did not differentiate and sub-classify the loss of smell and taste to various degrees, as for example Carrillo-Larco and Altez-Fernandez did in their study (68), so we are not able to justify the effect of gender and age in the severity of chemosensory dysfunction. Furthermore, there are no data for disease progression, so we are not able to define the severity of disease. The only factor to determine severity is the need for hospitalization.

In conclusion, our data collected from a West Greek population confirm the commonality of chemosensory dysfunction in COVID-19 and the impact of age and gender in OGDs. ❑

CONCLUSION

The aim of this study was to investigate the impact of age and gender in SARS-CoV-2 infection and their relation to chemosensory dysfunction through an analysis of data collected from hospitalized and self-quarantine COVID-19 positive patients in Epirus, Greece. The findings of our data analysis support those reported by previous studies. We concluded that, as in other populations, there is a significant association between chemosensory dysfunction and younger age in SARS-CoV-2 infection. Olfactory and gustatory dysfunctions occur more frequently in women than men, while male gender relates with disease severity and need for hospitalization. ❑

Conflicts of interest: none declared.

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can be a useful tool for preparedness with accurate human movement data (17).

Currently, vector-borne illnesses remain mostly unnoticed, causing sickness primarily among the impoverished. Fever is the most frequent symptom of zika, dengue, malaria, and COVID-19, making a proper diagnosis for either illness difficult at the moment (18, 19). Encouragement and information for early fever screening should be made available to both rural and urban populations. Monsoons tend to facilitate the spread of Aedes aegypti, which is the main vector for most of the vector-borne infections in India. Solid wastes to be eliminated then and there to prevent the breeding of the mosquitoes. At the home, neighborhood, and institutional levels, vector management should involve larval surveillance, biological, and chemical control. Surveillance and source reduction operations for Aedes larvae should be conducted in airports, seaports, and rural and urban civic wards. When suspecting the sickness, a travel history should be considered. The usage of insect repellent as a preventive strategy to decrease mosquito bites must be maintained among the people living in areas endemic to vector-borne diseases (20). ❑

CONCLUSION

With better preparedness, the threat of climate change on vector-borne diseases may be negated. Designing and strengthening an intervention strategy for environmental sanitation, regular cleaning of living house, and keeping personal hygiene shall be considered. Risk assessment is crucial to optimize surveillance, preventative measures (vector control), and resource allocation (medical supplies). ❑

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