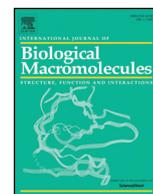




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COVID-19 as a worldwide selective event and bitter taste receptor polymorphisms: An ecological correlational study

Shima Parsa^a, Vahid Mogharab^b, Mohsen Ebrahimi^c, Sayyed Reza Ahmadi^c, Behzad Shahi^d, Neema John Mehramiz^e, Mahdi Foroughian^c, Mohammad Zarenezhad^f, Navid Kalani^g, Mohammad Hashem Abdi^h, Farshid Javdani^a, Pouyan Keshavarz^a, Naser Hatami^{a,*}

^a Student Research Committee, Jahrom University of Medical Sciences, Jahrom, Iran

^b Department of Pediatrics, Jahrom University of Medical Science, Jahrom, Iran

^c Department of Emergency Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

^d Department of Emergency Medicine, Faculty of Medicine, Zahedan University of Medical Sciences, Zahedan, Iran

^e Department of Psychiatry & Neurology, Banner University Medical Center, Tucson, AZ, USA

^f Iranian Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran

^g Research Center for Social Determinants of Health, Jahrom University of Medical Sciences, Jahrom, Iran

^h Medical Surgical Nursing, Jahrom University of Medical Sciences, Jahrom, Iran

ARTICLE INFO

Article history:

Received 29 October 2020

Received in revised form 18 January 2021

Accepted 8 February 2021

Available online 11 February 2021

Keywords:

COVID-19

Polymorphism

TAS2R38 gene

Mortality

ABSTRACT

Background: Given the observed olfactory and gustatory dysfunctions in patients with COVID-19 and recent findings on taste receptors possible important activities in the immune system, we elected to estimate the correlation between COVID-19 mortality and polymorphism of a particular type of bitter taste receptor gene called TAS2R38, in a worldwide epidemiological point of view.

Methods: Pooled rate of each of the rs713598, rs1726866, rs10246939, and PAV/AVI polymorphisms of the TAS2R38 gene was obtained in different countries using a systematic review methodology and its relationship with the mortality of COVID-19. Data were analyzed by the comprehensive meta-analysis software and SPSS.

Results: There was only a significant reverse Pearson correlation in death counts and PAV/AVI ratio, $p = 0.047$, $r = -0.503$. Also, a significant reverse correlation of PAV/AVI ratio and death rate was seen, $r = -0.572$, $p = 0.021$. rs10246939 ratio had a significant positive correlation with death rate, $r = 0.851$, $p = 0.031$. Further analysis was not significant. Our results showed that the higher presence of PAV allele than AVI, and a higher rate of G allele than A in rs10246939 polymorphism in a country, could be associated with lower COVID-19 mortality. While assessing all three polymorphisms showed a huge diversity worldwide.

Conclusion: Due to extraoral activities of bitter taste receptor genes, especially in mucosal immunity, this gene seems to be a good candidate for future studies on COVID-19 pathophysiology. Also, the high worldwide diversity of TAS2R38 genes polymorphism and its possible association with mortality raises concerns about the efficiency of vaccine projects in different ethnicities.

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1. Introduction

The human body function facing difficult conditions such as diseases is largely being modified by two main factors of genetics and environmental factors. The human genome, inherited from previous generations, is one of the most important determinants of the body's response to conditions such as infectious diseases. During the process of modern human evolution out of Africa, various human communities have been expanded around the planet with worldwide genetic variations [1]. In recent years, genetic mapping of human genome genes

has attracted the attention of many researchers [2]. Genetic studies and comparisons of different communities have led to the identification of genes that show the evolutionary history of humans, to the extent that some of these genes are referred to as evolution signatures [3]. In an evolutionary view, when a particular selective event contributing to natural selection is distributed over multiple populations, the same widespread families of genes within populations that are acquired from the same parent will respond similarly in all populations. Recognizing these common selective events may recognize significant genomic characteristics of humans in recent global history [3].

The world is currently experiencing the most tangible pandemic of the century due to a virus called n-SARS-CoV, which could be assumed as a very good sample of a global selective event. Coronavirus 2019

* Corresponding author.

E-mail address: avazhatami@gmail.com (N. Hatami).

disease (COVID-19) is spreading rapidly around the world and is responsible for many deaths worldwide. COVID-19 patients may show mild to severe clinical manifestations of pneumonia.

However, the disease has had a variety of manifestations including cough, body aches, headaches, anosmia, etc. There is currently no definitive or effective treatment for COVID-19 [4]. In our previous study, we showed that in a study of 48,758 people of different ethnicities, polymorphism of a specific type of gene in the Renin-angiotensin system called ACE I was associated with a better improvement ratio of COVID-19 patients in each country [5]. Olfactory and gustatory dysfunctions have also been observed in patients with COVID-19 [6]. Some researchers have suggested a possible link between the Olfactory and gustatory genes and COVID-19 disease [7]. Taste receptors, especially G protein-coupled receptors, which detect different tastes, respond to a wide range of food stimuli [8]. Some of these taste receptors are involved not only in sense but also in immunity and inflammatory processes. Bitter Taste Receptors (TAS2Rs) are a group of taste receptors that in addition to their role in the gustatory system, also have very important activities in the immune system [9]. From the same group, the bitter taste receptor T2R38 is expressed in ciliated cells of the human upper airways [10], where the new coronavirus appears to replicate [11]. T2R38 also regulates the innate defense settings of the human upper respiratory tract by producing nitric oxide (NO), which stimulates mucus secretion and has direct immunological effects [12]. Besides, common polymorphisms of the TAS2R38 gene, based on taste sensitivity to phenylthiocarbamide (PTC), a bitter molecule stimulant, make significant differences in susceptibility of the upper respiratory tract to respiratory infection [13]. Therefore, it is very likely that genetic changes in the TAS2R38 function may cause individual differences in how airway cells act against infectious agents [14]. So in the present study, the TAS2R38 gene was chosen as a suitable factor for mapping its differences in the genome of people around the world. T2R38 is encoded by the TAS2R38 gene, which has two common polymorphisms in different populations around the world. The functional form of the receptor contains proline, alanine, and valine (PAV), while the non-functional form of the receptor contains alanine, valine, and isoleucine (AVI). Therefore, the active haplotype in this field is called PAV and the inactive haplotype is called AVI. Various other polymorphisms have also been suggested for this gene. The TAS2R38 gene is encoded by three non-synonymous coding SNPs (rs713598 - G145C, Ala49Pro; rs1726866 - T785C, Val262Ala; rs10246939 - A886G, Ile296Val) [15].

The present study sought to investigate the possible relationship between genetic differences in bitterness receptors in different communities against COVID-19. Comparison of epidemiological data on the occurrence of Covid-19 disease in different ethnicities can provide a scientific basis for future research to implement protocols related to the treatment and vaccination of COVID-19.

2. Methods

2.1. COVID-19 data

The COVID-19 death rate in each country was retrieved from the WHO Coronavirus Disease Dashboard [<https://covid19.who.int/WHO-COVID-19-global-data.csv>]. WHO database has provided statistics of positive cases and death cases in a monthly manner. The mortality rate on the 31 August of 2020 was very low in lots of countries, so many countries were excluded. The countries with available studies reporting TAS2R38 polymorphism included in our study.

2.2. TAS2R38 polymorphism

Preferred Reporting Items for Systematic Studies and Meta-Analysis (PRISMA) statement was considered for collecting studies that had reported the TAS2R38 polymorphisms. Our search strategy was querying through ISI, PubMed, Scopus, and Google Scholar databases with

keywords of as TAS2R38 gene, Polymorphism, rs713598, rs1726866, rs10246939, and PAV/AVI from the from eternity to 2020. At the step of title checking, 654 studies were detected. 96 duplicated studies were excluded. Checking the abstracts, 255 irrelevant studies were excluded. Evaluating the full-text of studies, studies not having a proper methodology of polymorphism assessment, having a sample size of patients with genetic disorders, and not reporting the number of subjects, were excluded. In the end, 22 articles were included in our study.

2.3. Static analysis

The collected data of death rate and polymorphisms rate were analyzed using the Comprehensive Meta-Analysis (CMA) software version 2 based on the random-effects model. The I^2 index was utilized to detect heterogeneity in studies. Since the I^2 index of the combined polymorphisms ratio was 99, 98, 87, 100% percent for rs713598, rs1726866, rs10246939, and PAV/AVI random effect model was used and the inverse method was applied for variance and weight estimation for each study. Grouping was done based on the country. Meta-regression of the COVID-19 mortality rate with polymorphisms ratio was conducted using CMA. There was no evidence of study bias based on egger's test ($p > 0.05$).

3. Results

In the present study, 21 studies reporting different types of TAS2R38 gene polymorphisms in healthy individuals were included in the study (Table 1). These studies reported data on 19,997 people living in 22 different countries.

Studies examined four different types of TAS2R38 gene polymorphisms, including rs713598, rs1726866, rs10246939, and PAV/AVI. To calculate the overall ratio of alleles in different polymorphisms, the random-effect model was used to cumulatively calculate the ratio of alleles for each subgroup (country). In the study of rs713598 polymorphism, data from 10 countries; in rs1726866 assessment, data from 6 countries; in rs10246939 assessment, 6 countries and in the PAV/AVI polymorphism assessment, 16 countries were studied. The results are shown in Table 2.

Data on the prevalence and mortality of COVID-19 in different countries were extracted from the WHO website. As shown in Fig. 1, the disease has spread to most parts of the world, with the highest mortality rates (brown colored) in the USA, Brazil, various parts of Europe, and Asian countries such as India, Japan, and Iran, and so on. The ratio of allele's distribution for different polymorphisms is shown in Fig. 1. The interpretation of geographical differences of polymorphisms was difficult due to wide changes between different countries. But the data was not available in other parts of the world.

Then correlation of the calculated point estimate for the polymorphism rate of each country with reported cases and deaths of COVID-19 was estimated. There was only a significant reverse Pearson correlation in death counts and PAV/AVI ratio, $p = 0.047$, $r = -0.503$ (Fig. 2.a). Also, a significant reverse correlation of PAV/AVI ratio and death rate was seen, $r = -0.572$, $p = 0.021$ (Fig. 2.b). rs10246939 ratio had a significant positive correlation with death rate, $r = 0.851$, $p = 0.031$ (Fig. 2.c). Further analysis was not significant.

4. Discussion

Variation in the disease spreads in different regions can be attributed to a large number of genetic, cultural, and environmental influences, which has led researchers to investigate the possible link between genetic factors and susceptibility to COVID-19. Anosmia has been reported as a manifestation of COVID-19 and other coronavirus infections of SARS and MERS [38].

Surprisingly it is not accompanied by nasal obstruction or other symptoms of rhinitis. Therefore, this is probably due to the direct

Table 1
Frequent study of different types of TAS2R38 gene polymorphisms in healthy individuals.

Study	Country	n	rs713598		rs1726866		rs10246939		PAV	AVI
			G	C	T	C	A	G		
Vinuthalakshmi K [16]	India	100	144	56	124	74	114	84	74	114
Carrai M [22]	Czech	576	619	533	663	481	640	540	449	569
Carrai M [22]	German	679	795	563	569	801	739	633	–	–
Choi JH [17]	Korea	3567	–	–	–	–	2942	4192	–	–
Schembre SM [18]	Native Hawaiians	236	–	–	–	–	–	–	298	148
Schembre SM [18]	Japanese Americans	383	–	–	–	–	–	–	423	343
Choi JH [19]	Korea	1361	–	–	–	–	–	–	1576	1122
Adappa ND [20]	USA	70	–	–	–	–	–	–	50	90
Yamaki M [21]	Japanese	79	–	–	–	–	–	–	222	150
Barragán R [23]	Spain	949	1137	761	–	–	–	–	–	–
Sandell M [24]	Finland	1860	2443	1277	2331	1389	2331	1389	1693	3135
Perna S [25]	Italy	118	129	107	–	–	–	–	–	–
Deshaware S [27]	India	393	545	241	533	253	520	266	238	520
Hayes JE [28]	USA	198	–	–	–	–	–	–	175	179
Shen Y [26]	UK	136	–	–	–	–	–	–	118	154
Ooi SX [29]	Malaysia	100	122	78	–	–	–	–	–	–
Khataan NH [30]	Canada	911	971	851	–	–	–	–	–	–
Melis M [31]	Italy	192	–	–	–	–	–	–	348	366
Sandell MA [32]	Spain	23	–	–	–	–	–	–	22	22
Sandell MA [32]	Finland	22	–	–	–	–	–	–	21	23
Sandell MA [32]	UK	35	–	–	–	–	–	–	38	32
Lambert JD [33]	UK	6250	–	–	–	–	–	–	374	512
Robino A [34]	Georgia	116	–	–	–	–	–	–	282	127
Robino A [34]	Armenia	47	–	–	–	–	–	–	95	41
Robino A [34]	Azerbaijan	91	–	–	–	–	–	–	198	87
Robino A [34]	Uzbekistan	57	–	–	–	–	–	–	127	56
Robino A [34]	Kazakhstan	80	–	–	–	–	–	–	174	76
Robino A [34]	Tajikistan	105	–	–	–	–	–	–	227	98
Wang K [35]	china	673	–	–	–	–	–	–	–	–
Gorovic N [36]	Denmark	490	627	353	590	392	586	390	327	559
Siasi E [37]	Iran	100	–	–	76	124	–	–	–	–

damage of the virus to the olfactory and taste receptors [39]. Our study examined the genetic basis of this issue by looking at a gene involved in the olfactory and taste systems, at a worldwide perspective. Our results showed that the higher presence of PAV allele than AVI, and a higher rate of G allele than A in rs10246939 polymorphism in a country, could be associated with lower COVID-19 mortality. So far, no study has examined the relationship between these genetic factors and COVID-19 at the epidemiological level. However, some studies provide laboratory evidence to support this hypothesis. Innate airway immunity

Table 2
Polymorphisms of TAS2R38 gene in different countries.

Country	n	rs713598	rs1726866	rs10246939	PAV/AVI
		G/C	T/C	A/G	
Canada	911	1.141011	–	–	–
China	673	2.167059	–	–	–
Czech	576	1.161351	1.378378	1.185185	0.789104
Denmark	490	1.776204	–	–	–
Finland	1860	1.913078	1.678186	1.678186	0.542749
German	679	1.412078	0.710362	1.167457	–
Denmark	491	–	1.505102	1.502564	0.584973
Italy	118	1.205607	–	–	0.95082
Malaysia	100	1.564103	–	–	–
Spain	949	1.494087	–	–	1
India	492	2.319865	2.009174	1.811429	0.492114
Iran	100	–	0.612903	–	–
Korea	3567	–	–	0.701813	1.404635
Japan	79	–	–	–	1.48
USA	198	–	–	–	1.254197
UK	6421	–	–	–	0.75
Georgia	116	–	–	–	2.220472
Armenia	47	–	–	–	2.317073
Azerbaijan	91	–	–	–	2.275862
Uzbekistan	57	–	–	–	2.267857
Kazakhstan	80	–	–	–	2.289474
Tajikistan	105	–	–	–	2.316327

depends on the efficient and timely detection of bacteria and viruses by the airway mucosa [40]. Deshpande et al. showed the presence of bitter taste receptors in the human lung and broncho dilation associated with their stimulation [41].

Shah et al. stated that TAS2R expression in the human airway epithelial cells. Also they find that bitter compounds increase intracellular Ca²⁺ concentration and stimulate ciliary beat frequency. Ciliated cells of the airways help to clear mucus and toxic chemicals from the airways. Viral infections and cigarette smoke have also been shown to damage these cilia and can interfere with the defense mechanism [42]. Recent data suggest that a specific TAS2R (TAS2R38) is involved in the innate immune defense of the upper airways, and changes in this gene contribute to individual differences in susceptibility to respiratory infection [13]. Airway T2R expression was first studied in human bronchial ciliated epithelial cells, where they amplify calcium signals that increase the frequency of ciliary beats [43].

In the lung, T2Rs may be very important in the sinus cavity, which is at the forefront of the respiratory defenses, and are in contact with large volumes and types of pathogenic microbes. Host and pathogen interactions occur continuously with each breath, and when the nasal line of defense is destroyed, bacterial infections are likely to cause lower airway infections or exacerbate airway disease [44].

Immune system components also contribute to the regeneration of damaged tissues by stem cells, which could be important in COVID-19 recovery, especially in taste and loss recovery. Stem cells are also present in the oral cavity. Immune system responses to SARS-CoV-2 may also get started from the oral cavity. Research has shown that important molecules for SARS-CoV-2 infection are plentiful throughout the oral cavity [45]. The SARS-CoV-2 receptor, ACE2, and TMPRSS2 that facilitate entry of the SARS-CoV-2 into the human cells were defined as factors of SARS-CoV-2 infection. ACE2 and TMPRSS2 expression were detected in the dorsal part of the tongue, gingiva, saliva, and tongue coating cells from taste buds [46]. The main concern is that the SARS-CoV-2 specifically influences smell perception by

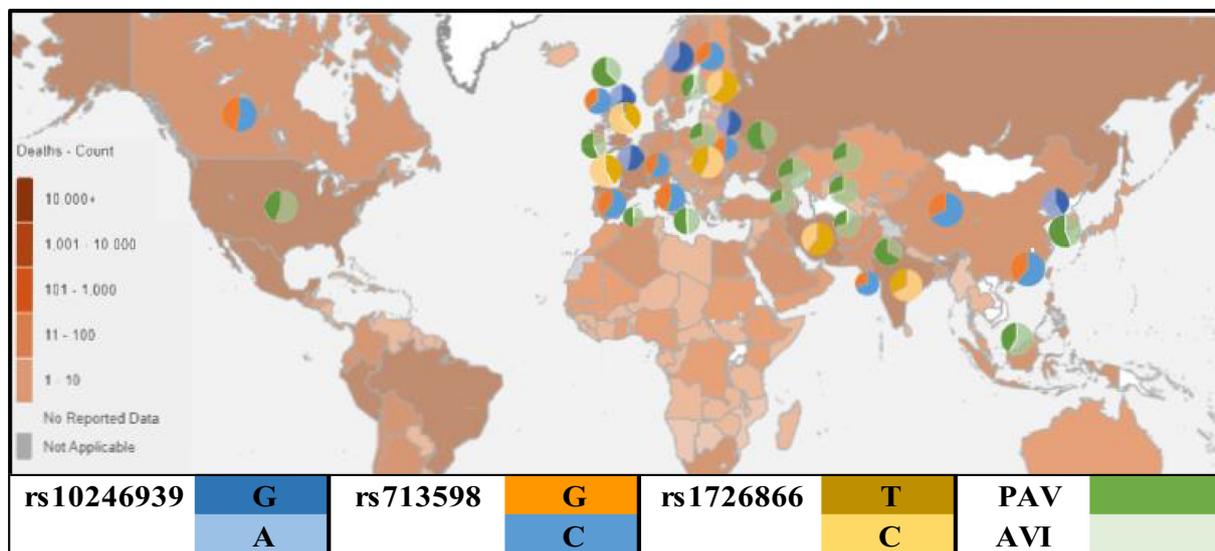


Fig. 1. Image of the Earth based on the COVID-19 mortality rate from the WHO website (<https://covid19.who.int/explorer>).

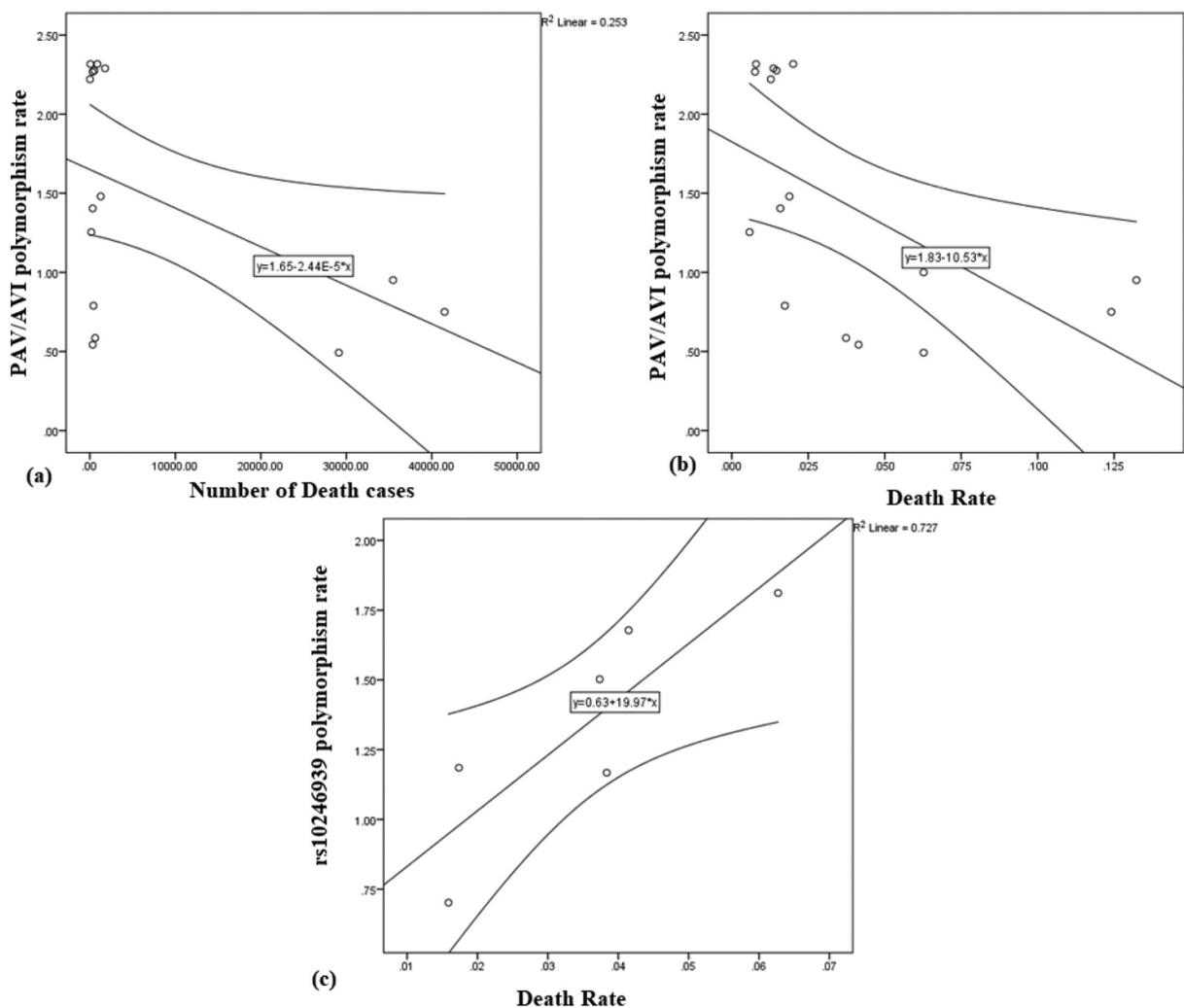


Fig. 2. Correlation of the PAV/AVI polymorphism rate and death cases of each country (a); PAV/AVI polymorphism rate vs. death rate (b); rs10246939 polymorphism rate and death rate (c).

contaminating olfactory sensory neurons or passively via disrupting linked cells. Chou et al. described the olfactory epithelium and olfactory bulb cells expressing SARS-CoV-2 cell entry molecules. In COVID-19 patients, non-neuronal forms of cells contribute to anosmia and associated defects of smell sensation. Sustentacular and oral stem cells are probably direct targets of SARS-CoV-2 in the human oral cavity [47]. Oral-derived stem cells are known to have a contribution to injured tissue regeneration and local immunomodulation [48]. Rather than immune responses as being in the first line of the virus confrontation, these stem cells may also be a good candidate for cell therapy due to regenerative potential [49]. Various clinical studies have previously been conducted on mesenchymal stromal/stem cells as a potential therapy for COVID-19. Treatment options for COVID-19 are not completely provided, but stem cell therapies have already shown efficiency in treating inflammatory responses in patients with COVID-19 [50]. Unless the stem cells of the oral cavity are not severely impaired, the olfactory system may have the substantial regenerative ability, contributing to spontaneous odor perception recovery [51]; So, stem cell therapies can be queried for smell and taste perception loss treatment in COVID-19. It is possible to provide a specific technique to recognize signaling pathways that trigger the stimulation and neurogenesis of olfactory stem cells and thus utilize the intrinsic ability of the olfactory resident stem cells for recovery [52]. Novel biotechnology advancements could help us and should be taken to account as our available choices for the COVID-19 researches. Bioimpedance is a technique that is used to detect inflammatory tissues in the oral cavity [53,54]. Also, some researchers have used it to detect inflammatory processes in airways, by analyzing extracellular bioelectrical conductivity [55]. The taste sensation is a bioelectrical process at the level of the taste receptors [56]. Interestingly, human tongue-recorded bio-electrical impulses were shown to be related to the TAS2R38 PAV-AVI genotypes [57]. So, we think that bio-electrical analysis could help in researches which are going to be conducted on the gustatory recovery of COVID-19 [58].

Renin-angiotensin system (RAS) is an important regulator of body fluids and sodium homeostasis. Angiotensin II (AngII) is an important active product of RAS. The RAS system appears to alter individuals' sensitivity to taste through the AngII receptor type 1 (AT1), which is expressed in taste cells. However, the molecular mechanisms involved in these changes have not been identified [59].

On the other hand, the RAS system is involved in modulating the activity of taste cells. Expression of the ACE-2 gene, the major route of new coronavirus entry into cells, in taste cells provides a possible explanation for taste disorders in patients with COVID-19. That is, SARS-CoV-2 may enter taste cells via ACE-2: as a result, the normal function of these sensory cells is disrupted, leading to a change or loss of taste perception [60].

On the other hand, one of the most important interpretations of our current study and previous study on ACE I polymorphism's correlation with epidemiological aspects of the COVID-19 is raising cautions about the possible effect of huge ethnic differences of communities on the COVID-19 vaccine's efficiency that are going to be available worldwide. Also, there is the possibility of bitter taste receptors' effect on cellular immunity against COVID-19. A study stated that Tas2Rs genes are also being expressed in white blood cells and upregulation of TAS2Rs in human white blood cells is seen in patients with severe refractory asthma [61]. Tran et al. have shown the higher expression of T2R38 in resting and activated human lymphocytes [62]. Identification of bitter receptors role in response to n-SARS-Cov may help to get new therapeutic targets for stimulating mucociliary clearance [12] as a major defect in the elderly making them susceptible to severe COVID-19 [60]. As one of the agonists of TAS2Rs, caffeine is a very good candidate for future studies in this field [63].

4.1. Limitations

However, this study deals with various known and unknown factors affecting global mortality of COVID-19, including demographic

characteristics such as patient sex, age, underlying diseases, and different methods for treating patients in different countries.

An important limitation of studies such as our study that examines correlational relationships is the impossibility of confidence to the investigated relationship as a causal relationship. Understanding whether there is a real causal relationship or whether these relationships occur for a variety of mediating reasons requires further study. Because the human taste system is greatly affected by genetic polymorphisms; these genetic changes may be associated with a change in a person's lifestyle. T2R38 gene polymorphisms have been important predictors of behaviors such as alcohol or smoking [64]. Also, concerning other types of genes involved in taste perception, genetic variation in taste receptors has been associated with differences in food salinity perception, which has affected a person's risk of developing hypertension [65]. Blood pressure is also one of the main risk factors for mortality in COVID-19. These countless potential relationships can all exist. Therefore, it is necessary to determine the exact mechanisms in the transmission of T2R38 signals in response to COVID-19 in more detail.

5. Conclusion

Extraoral functions of bitter taste receptor genes, especially in mucosal immunity, suggest it a good candidate for future studies seeking to understand the pathophysiology of COVID-19. Our study showed a high diversity of TAS2R38 genes polymorphism in various parts of the world and its possible assassination with the mortality rate that raises concerns about the efficiency of vaccine projects in different ethnicities. Also, this study suggests further attention to bitter taste receptors and underlying pathways as a potential approach to help COVID-19 patients' improvement.

Ethics approval and consent to participate

There is no human subject participating in this study.

Consent for publication

Not applicable.

Availability of data and material

All data would be available in the manuscript.

Funding

None.

CRediT authorship contribution statement

Shima Parsa: Conceptualization, Methodology, Data curation, Resources, Investigation, Writing - Original draft, Supervision. **Vahid Mogharab:** Data curation, Investigation, Resources, Writing - Original draft. **Mohsen Ebrahimi:** Conceptualization, Writing - Original draft, Data curation. **Sayyed Reza Ahmadi:** Writing - Review & editing, Data curation, Methodology, Supervision. **Behzad Shahi:** Data curation, Resources. **Neema John Mehrmiz:** Supervision, Investigation. **Mahdi Foroughian:** Investigation, Data curation. **Mohammad Zarenezhad:** Data curation, Writing - Original draft. **Navid Kalani:** Writing - Original draft, Writing - Review & editing, Investigation. **Mohammad Hashem Abdi:** Investigation. **Farshid Javdani:** Investigation. **Pouyan Keshavarz:** Data curation, Resources, Methodology, Writing - Original draft. **Naser Hatami:** Conceptualization, Methodology, Data curation, Writing - Original draft, Writing - Review & editing, Supervision.

Declaration of competing interest

None.

Acknowledgements

We would like to thank the Clinical Research Development Unit of Peymanieh Educational and Research and Therapeutic Center of Jahrom University of Medical Sciences for providing facilities for this work.

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