ORIGINAL ARTICLE

CONTENTS

Chemo-sensory loss and FUT2 gene in COVID-19 infected Iraqi dentists

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ABSTRACT

Aim: To find any association between specific ABO blood groups and *FUT2* secretory status and COVID-19 in a sample of Iraqi dentists.

Materials and Methods: For each participant, a questionnaire including demography, COVID-19 status, blood grouping, and RH factor, with chemo-sensitive symptoms was recorded. The saliva samples were collected and DNA was extracted from leukocytes. Sequencing of molecular detection of the *FUT2* gene by real-time PCR and the data was done, whilst drawing the phylogenetic tree.

Results: Out of 133, most of the dentists were female 61%, most were just under 35 years of age. The most participants in this study were predominantly with blood group O (40%), followed by B, A, and AB, with (90%) of them were RH+. All blood grouping and RH factor were high significantly associated with COVID-19 infection and its frequency ($p<0.001$). A significant association between smell dysfunction and infected blood group A and RH+ ($p=0.044, 0.038$) while taste dysfunction was negatively and significantly correlated with AB group ($r=-0.73$; $p=0.008$). The *FUT2* secretor showed a significant association with COVID-19 infection and frequency. The majority of COVID-19-infected participants experienced a significant loss of both smell and taste with fast recovery within 2 weeks.

Conclusions: The COVID-19 infection susceptibility and reinfection are associated with *FUT2* secretory status and greatly associated to olfactory and gustatory sense loss.

KEY WORDS: ABO system, COVID-19, non-secretor status

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INTRODUCTION

Susceptibility to COVID-19 is not so different from other infectious diseases [1]. The Oligosaccharide structures, unique to antigens, are formed through the action of glycosyltransferase enzymes, products of primary gene. The sugar molecules attach to the Oligosaccharide chain by enzymes. Antigens of blood groups, considered secondary *gene products, found on cell surface of RBCs, platelets, leukocytes, plasma proteins, specific tissues, and enzymes also are presented in body secretions, like saliva, gastric secretions, amniotic fluid, breast milk, seminal fluid, sweat and urine [2]. The ABO blood type system includes antigens A, B, and H. Individuals with blood type A could face a higher susceptibility to the infection than those with blood type O [3]. Pathogens may express antigens resembling the type A blood group. Types O and B produce antibodies against type A antigens, reducing their susceptibility. In contrast, types A or AB, lacking anti-A antibodies, might exhibit higher susceptibility to the pathogen due to the absence of this specific immune response [4]. Anti-A antibodies demonstrated the capability to hinder the interaction between spike protein and ACE2 [5]. The half-life of Von Willebrand factor and factor VIII is longer and higher concentrated in individuals with blood group A unlike other blood groups [6]. The enzyme called glucoside 2-alpha-L-fucosyltransferase 2 production are coded by Fucosyltransferase 2 (FUT2) gene. Which determines the ABO antigens secretor status [7]. The size of FUT2 gene 9,980 bases with a plus-strand orientation, is located on chromosome 19q13.33 and it comprises of two exons, with lengths of 118 and 2,995 base pairs, respectively, an intron of 6,865 base pairs separates them. The first exon serves as a non-translated coding region, while the 343 protein amino acids are coded in second exon [8-10]. Fucosyltransferase 2 'SE' is an Autosomal dominant pattern, secretor gene, 'whereas 'se' is the recessive form [11]. A population lacking ABH antigens in secretions is characterized by the presence of a non-functional (mutated) gene, non-functional secretor gene (FUT2) a non-secretor status, had only (FUT1) a single functional H gene, resulting in the expression

of H antigen only on the (RBCs) but absent in their secretions [12]. International Society of Blood Transfusion (ISBT) represented 29 null and weaker alleles identified for the FUT2 gene (ISBT 018). The se^{428} (Trp143stop) allele is a highly prevalent non-secretor allele among Caucasians. It is employed in genome study research that the (rs601338), or (G428A) was occurred due to mutations in the second exon of the FUT2 gene, the single nucleotide polymorphism (SNP) rs601338. It is a stop codon at 143 a.a position (Trp-Ter) more common in Iranians, and Africans beside Europeans [13]. Genetic diversity within FUT2 is estimated to be as ancient as three million years. At least 1.87 million years ago, the 428G>A mutation occurred [14]. Researchers have observed that this polymorphism plays a regulatory role in the innate immune response and to evaluate the continuation of the human race when facing pathogen outbreaks [15]. Additionally, it has indirect effects by modifying the microbiota or serving as a nutrient source for pathogens [16]. The epidemiological cause for linking ABO blood types, in addition to multiple clinical, developmental, and genetic factors all can be affected epithelial tissues' inheritance the secretor status and pathogens exposures [17] and carcinoma and ulcers. Non-secretors, particularly those with blood type A, are linked to lower levels of infections, caused by yeast (Candida) and Streptococcus or gastric bacterial overgrowth. Moreover, individuals who are non-secretors have a heightened susceptibility to Crohn's disease among other autoimmune disorders. Those patients with significant symptoms of respiratory illness and influenza A virus, rhinovirus, or respiratory syncytial virus were Secretors overrepresented patients [16]. A high expression of the secretor (H) antigen in postnatally alive newborns saliva and tracheal aspirates, was found [17]. The susceptibility associated with the FUT2 gene may have implications for vaccine development and study design (1). The study aims to find any association between specific ABO blood groups and *FUT2* secretor status and COVID-19 in a sample of Iraqi dentists.

AIM

Aim of this work was to find any association between specific ABO blood groups and *FUT2* secretory status and COVID-19 in a sample of Iraqi dentists.

MATERIALS AND METHODS

SAMPLE COLLECTION

According to STROBE guidelines for cross-sectional studies [18], this study was conducted on Iraqi dentists from Baghdad City working in primary health centers and private clinics. Sample collection was done from 9 March-21 September 2022 after acquiring the approval of the Ethics Committee for Research from the College of Dentistry, University of Baghdad, Baghdad, under protocol number 460722. A consent form was signed by each volunteer's participant before starting. A questionnaire for each participant was filled out by one examiner after being validated by experts, including demographic information, medical history, COVID-19 infection status, and vaccination date and type. The dentists were asked about the onset, duration, the ABO blood grouping, and eventual regression of the chemo-sensitive symptoms.

Exclusion criteria for these study participants including the exclusion criteria for CCCRC test for olfactory assessments:

- Prior surgical procedure or radiation therapy in mouth or nose.
- Already present manifestation of altered gustation or smell.
- Previous history of trauma in head.
- Allergic rhinitis, chronic rhinosinusitis.
- Psychiatric or neurological disorders or treatments.
- Dentists vaccinated by other than Pfizer or Astra-Zeneca.
- Dentists refused to continue this study and disagreed to give blood and saliva samples or not in contact with patients.

SALIVA COLLECTION

According to Garbieri et al. (2017), the saliva was collected and stored for DNA extraction (19), supplement A.

MOLECULAR DETECTION OF ALPHA (1,2) FUCOSYLTRANSFERASE (FUT2) GENE

DNA extraction from saliva: saliva in a polyethylene tube was used for DNA extraction procedure by Using Favor prep: genomic DNA mini kit; the kit is special for blood/cultured cells; (100 preps) for research use only cat.no: FABGK 100 lot no: CB 827122103 from Favorgen biotech corp. Taiwan (WWW.FAVORGEN.COM). The extracted DNA was determined by using Agarose gel Electrophoresis.

PRIMER DETECTION

The primer was detected and analyzed by the National Center for Biotechnology Information (blast.ncbi.nlm.nih.gov/blast.cgi) USA and primer 3 pulse bio-informatics (bio-informatics.nl/cgi-bin/primer3plus/primer3plus.cgi)

Table 1. Blood groups in total sample according to variables

Infected blood groups count	Frequency of infection			Association (Fisher's Exact)	Correlation Spearman
	one time	twice	> 2 times	P Value	P Value
O	19	11	7	<0.001	r=-0.81;<0.001
A	8	2	3	<0.001	r=-0.91;<0.001
B	14	6	2	<0.001	r=-0.90;<0.001
AB	3	4		0.001	r=-0.89;<0.001
TOTAL	44	23	12	<0.001	r=-0.88;<0.001
RH	40	21	10	<0.001	r=-0.88;<0.001
	Olfactory clinical dysfunction				
	Ansonia	hyposomnia		P Value	
		severe	Moderate	Mild	
O	3	19	11	5	0.47
A	1	4	6	2	0.044
B	3	7	8	4	0.16
AB		3	2	2	0.6
TOTAL	7	33	27	15	0.09
RH+	7	31	23	11	0.038
	Gustatory dysfunction				
	Agusia	Hypogeusia		P Value	
		Severe	Moderate	Mild	
O	0	7	11	15	0.21
A		3	0	8	0.27
B		3	6	9	0.53
AB			1	3	0.1
Total		13	18	35	0.013
RH+	0	11	17	31	0.07
Total RH	0	13	18	35	0.012
	loss of both sense				
	Both	Taste only	smell only		
O	17	2	4	0.001	r=0.3;0.03
A	6	3	2	0.003	0.71
B	14	0	2	0.001	r=0.33;0.036
AB	4	1	1	0.1	0.86
TOTAL	41	6	9	<0.001	r=0.21;0.015
RH+	35	6	8	<0.001	r=0.22;0.014
	Lasting to recovery/days				
	1-15	>15-30	>30		
O	15	2	6	0.008	r=-0.46;0.001
A	5	4	2	0.003	r=-0.63;0.002
B	9	5	2	0.002	0.29
AB	1	2	3	0.09	r=-0.67; 0.014
Total	30	13	13	<0.001	r=-0.4;<0.001
RH+	26	12	11	<0.001	r=-0.4; <0.001

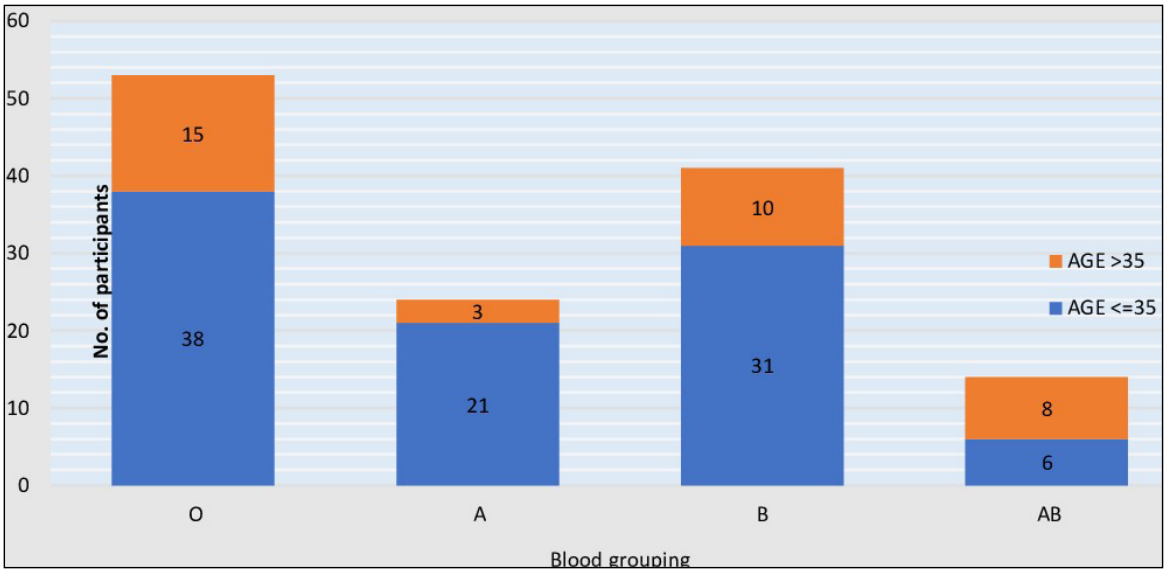

Fig. 1. Age and blood groups of the total sample.

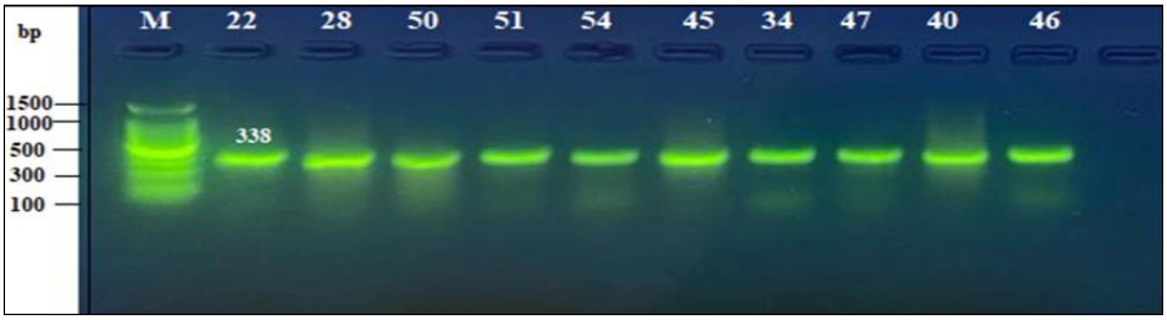

Fig. 2. The gel electrophoresis profile results of 338 bp of FUT2 partial gene band using 2 % Agarose stained with a red safe DNA dye and electrophoresed by 5vol/cm in TBE buffer lane M.DNA Marker 100 bp.

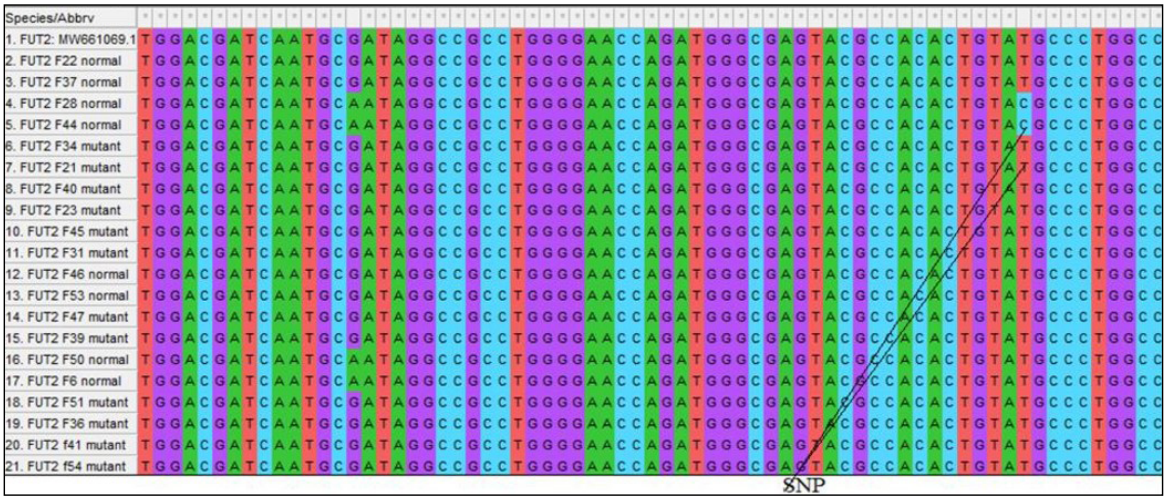

Fig. 3. The substitution (Transition) at 171A>G; and at 216C>T both non sense mutations.

DETECTION OF FUT2 GENE BY PCR

The procedure started by using a kit for the previous synthesis primers for FUT2 (rs601338) Foreword primer (F); Internal oligonucleotide (I); and Reverse primer (R). The kit's name Alpha AND, S.E.N.C. date 17/8/2022. (Synthesis number 696328; name of oligonucleotide F428; sequence (5´ to 3´) od -269 nm).

SEQUENCING

The PCR products of the FUT2 gene for each sample were amplified using both primers forward, reverse. Subsequently, sequencing was done after sending amplified products to Korean company, 'Macro Gene'. Data

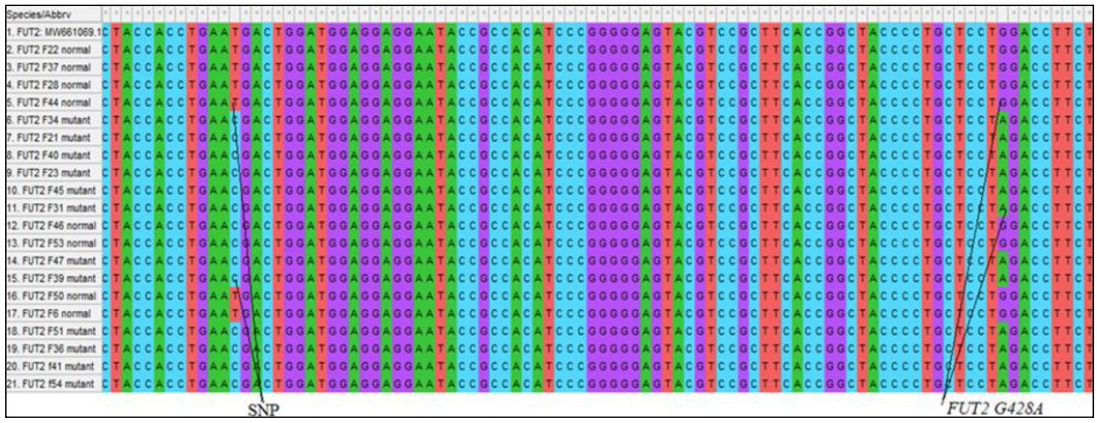

Fig. 4. Nucleotide sequence of sense flanking the partial FUT2 gene compared with the related identity to gene bank strains: MW661069.1 of FUT2 gene using the MEGAX program with non-sense transition at 357T>C.

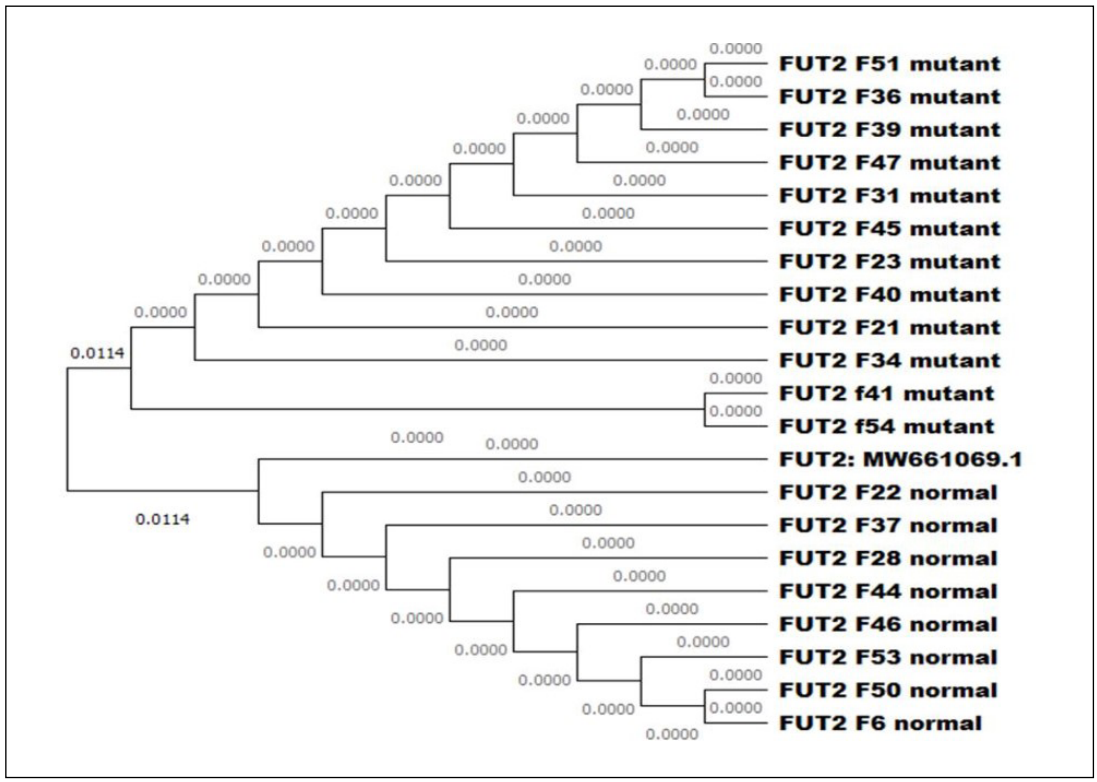

Fig. 5. The Maximum Likelihood method was used to infer the evolutionary tree of the flanking region of FUT2 G428A mutant. In the analysis, 21 nucleotide sequences were examined, comprising a total of 47 positions in the final dataset. MEGA X was used to perform the evolutionary analyses.

that sequenced underwent analysis using sequence analyzer software, specifically Finch software. Nucleotides were then subjected to BLAST (Basic Local Alignment Search Tool) analysis using specialized software to identify and compare sequence similarities (http://www.ncbi.nim.nih.gov). Using the 'MEGA 6.0 version' software, through 'UPGMA method' was employed to construct the phylogenetic tree.

STATISTICAL TESTS

Data was expressed using mean/standard deviation and frequency/percent according to the type of the variable. Normally distributed data the independent sample t test was used and for non-normally distributed data the Mann-Whitney U test was used to assess the difference between 2 continuous variables. Kruskal-Walli's test and ANOVA test were used alternatively to assess the difference between more than 2 independent continuous variables. Chi-square test and Fisher's exact test were used alternatively to assess the association between categorical variables. Correlation tests were used to assess the strength and direction of association between the studied variables. A significance level of 95% with a P-value was deemed significant in this analysis if equal to or less than 0.05.

Table 2. Nucleotide substitution in FUT2 partial gene located on chromosome 19 p13.3 isolated in Iraq.

No. of sample	Type of substitution	Location	Nucleotide	Range of Nucleotide	Sequence ID	Expect	Identification
12	Transition	272	G>A	1-285	OR453929	2.00E-138	99%
8	Transition	272	G>G	1-285	OR453928	4.00E-145	100%

Table 3. FUT2 gene association to COVID-19 infection status

Variable	Secretor	FUT2 GEN		P-Value
		Non- Secretor		
Infection	PCR +	7	5	0.053
	PCR -		7	
	NO PCR	1		
Clinical olfactory	Anosmia	1		r=0.2, p=0.048
	severe	3	4	
	moderate	2	6	
	mild	2	1	
Frequency of infection	Once	1	3	0.008*[1]
	Twice	5		
	>twice	1	2	
	None	1	6	
Loss of sense	Both	6	1	0.21
	Taste		1	
	Smell		1	
	none	2	9	
Recovery time	1-15 days	2	2	0.16
	>15-30 days	2		
	>30days	2		
	none	2	9	
Duration from last vaccine	0-6 Mon.	3	3	r=0.22, p=0.037
	>6-12 Mon.	4	5	
	>12Mon.	2	3	
	none			

*Significant value. [1] Fisher's Exact test. r Spearman correlation.

RESULTS

DEMOGRAPHICAL AND CLINICAL FINDINGS

Out of 133 Iraqi dentists were included in this study, (52; 39%) male and (81; 61%) female. The age range was 24-67 (years) and the age mean was 31.36 (±9.09 years). The samples were divided into two age groups equal and below 35 years old (97; 73%) and above 35 years old (36; 27%). The clinical features included systemic disease, participants suffered from systemic diseases were limited (24; 18%) and these systemic diseases were diabetes milieus, hypothyroidism, and anemia. A positive infection was found in 60% of our participants, 34% once, 17% twice, and 9% more than twice.

BLOOD GROUPING AND RH FACTOR

The predominant blood group among 133 participants was O+(46, 34.5%) followed by B+ (36, 27%), A+ (24, 18%), AB+ (14, 10.5%), O- shown in (8, 6%), B- (4, 3%) and AB- was only1 (1%) Using Fisher's Exact, a significant association was detected between blood groups and age (p =0.034).While no significant association was found between RH factor and both age and sex in the study groups, this could be shown in (Figure 1) as high infected blood grouping individuals were young age. All blood groups were highly associated and correlated negatively and significantly with both positive COVID-19 infection and its frequency of recurrent infection, beside of that infected group A and RH+ were associated significantly with olfactory

dysfunction (p=0.044; 0.038) respectively, whereas taste dysfunction was shown in both infected total blood and RH groups (0.013; 0.012) respectively. High negative significant correlation was reported between infected AB blood group and taste dysfunction (r=-0.73; 0.008). Both senses smell and taste loss were associated with infected blood groups O, A, B, RH+ (0.001, 0.008, 0.001, <0.001) respectively, while a positive significant weak correlation was detected between infected blood groups O, B, RH+ (r=0.3; 0.03, r=0.33; 0.036, r=0.22; 0.014) respectively. The recovery time was occurred faster within first 2weeks and significantly in infected group O, A, B, RH+ (0.008, 0.003, 0.002, 0.001) respectively whereas the negative significant correlation was found in infected groups O, A, AB, RH+ (Table 1, Fig. 1).

THE MOLECULAR DIAGNOSIS

Genomic DNA was extracted from all study sample saliva and gave perfect concentration (20-100 ng/µl) and purity (1.7-1.9), the extracted DNA was analyzed by gel electrophoresis and visualized under UV light as a clear band.

THE PCR REACTION FOR *FUT2* SECRETOR GENE

The amplification of the *FUT2* gene flanking region fragment with 338 bp showed a clear sharp band in the total sample when electrophoresis on 2% agarose gel, Fig. 3, Fig.2.

THE SEQUENCING

Sequencing was done for 20 samples selected randomly from whole sample groups. The mutation in allele G428A (at 272 of the sample sequences) appeared in 12 samples out of 20 selected samples and the associated nonsenses at 357 T→C (201 of sample sequence) the substitution occurred with no changes in the amine acid expressed Asparagine AAT(AAU)→AAC as AAT--AAU(RNA) as both AAU, AAC nitrogen bases expressed the same amine acid Asparagine so the mutation not sense; another substitution occurred on location 216 C→T (60 of sample sequence) the substitution occurred with no changes in the amine acid Tyrosine as both TAC (UAC)→TAT (UAU) both expressed the same a.a. And last one at 171 as A→G in nitrogen bases related to amine acid Alanine GCA→GCG as both GCA, GCG both related to same amine acid so no sense mutation associated, but both substitution mutations associated with a main mutation on G428A non-secreter gen samples than normal secreter samples, Fig. 3., Fig.4.

A PHYLOGENIC TREE

A phylogenic tree was drawn for the main mutation in this study, 12 mutants with and 8 normal with the bank gene standard sequence, (Fig. 5).

GENE BANK SUBMITTING AND ID

The non-secretor and secretor sequencing of this study selected samples was sends to gen bank and ID was sent from NCBI gen bank for two sequences, Table 2.

THE *FUT2* GENE ACCORDING TO OTHER VARIABLES

The normal secreter *FUT2* gene appeared in infected person more than non-infected one, although no significant association with infection was detected. There was a significant association between the secreter gene and frequency of infection with COVID-19 (Fisher Exact test=14.7, p =0.008), the normal secreter participant had more times of infection than non-secreter One, Table 3.

A low positive significant correlation exhibited between this gene and olfactory dysfunction (spearman correlation=0.2, p=0.048), and same correlation with last vaccine duration with secretor status (r=0.22, p=0.037), Table 3.

DISCUSSION

The distribution order of blood grouping ABO was (O>B>A>AB) and (RH+>RH-); the COVID-19 rate among patients in this study decreased in the order of (RH+, O, B, A, AB). Partially approximate with order showed by Ray (O> A>B>AB) [20]; different countries studies exhibited the same order of Ray, Saudi Arabia, United Arab Emirates (UAE), and USA [21]. Both COVID-19 infection and frequency were significantly associated with blood grouping and RH+ mostly in RH+ and blood group O than in other blood groups; no direct link between each specific blood group and COVID-19 infection was found; agreeing with Anderson [22]. Unlike a previous Iraqi study that associated blood group A and men's sex to COVID-19 susceptibility [23]; no such association was found, a lower sample size of this study if compared to previous could be the cause. Despite varying rates of ABO admitted persons, in different populations, blood groups A and O tend to be more

prevalent in those studies [23], while O and B, in contrast, were higher in this study population. More hazards and susceptibility was noted in group A, and more protection and asymptomatic in group O in previous studies [21]. Study group O, participants despite their high percentage of COVID-19 infection and frequency along with RH+, showed mild signs and symptoms/or no symptoms at all; which agreed with the Turkish study [24]. The oligosaccharides blood antigens act as receptors for coronaviruses, N-acetyl galactosamine is an extra sugar in group A. It is absent in group O making an expression of the virus more in group A [25]. Anti-A antibodies bind to COVID-19 S protein limiting its binding to ACE2 in epithelial cells, [26] decreasing initial infection, and delaying the spread of the virus, which is influenced by the titer of ABO iso-agglutinins and the incidence of blood group O [27]. Greater olfactory loss occurred in groups A and RH+. Besides, it is more prominent in group A blood group if compared to group O, when both had sense loss with frequent infection of COVID-19. The blood concentrations of ABO glycoproteins changing are affected by several factors like inflammation, endothelial function, and microvascular coagulation. The environmental factors and racial divergence may alter associations of certain blood groups with certain infections [28], and could explain, besides ABH gene polymorphisms, an increase in ACE1 levels associated with increases in the predisposition to cardiovascular problems and severe cases of COVID-19. Regarding the RH+ group, individuals exhibited a greater chance for a positive result for SARS-CoV-2, while individuals with Rh-negative (Rh–) blood group may experience a protective effect against severe illness caused by SARS-CoV-2. This could be explained by most of the population with RH+ grouping [29]. Taste dysfunction varied from mild to severe scoring, which showed in infected and recurrent RH+ and group O different levels of ACE between blood groups affected the lower risk or severe symptoms [30] and high expression of ACE2 in keratinized mucosa and taste bud [31]. The anosmia and ageusia were unnoticed among COVID-19 patients, unless an objective test was done, and it was not interpreted as a severe COVID-19 manifestation [32]. This agreed with this study. A lower level of ACE which converted angiotensin I to II, which is a recruited inflammation reaction, increasing blood pressure, makes group O with low risk of severe symptoms. The rs601338 (W154X) is identified as the most prevalent inactivating variant [33]. The rs601338 variant results in the expression of the FUT2 enzyme with significantly low activity, as a significant association was recorded between the COVID-19 infection and frequency with the secretor status than non-secretor ones agreed with the increased proportion of secretor antigens and infectious diseases especially virus. Histo-blood group antigens (HBGA), such as the H antigen, may play a role in mediating the attachment of pathogens, leading to infections [34]. Recognizing of cell attachment spike protein to A-type HBGA causes a higher vulnerability of secretors compared to non-secretors [35], while the non-secretor or carriers of FUT2 non-functional mutations are protected from infection [36]. Secreter participants showed more sense loss and a higher recovery rate than non-secreter ones. This is due to a modification of the innate immune by molecular mimicry. The complex glycan of (S) protein structure can support ABH epitopes [37]; and are extensively expressed in various tissues, respiratory and gastric mucosa, and endothelium, kidney, and heart tissues [38]. Prolonged diarrhea, vomiting, severe disease, and greater infection transmissibility were shown in secreters than non-secretors [39]. The proportion of FUT2 was considered during the study of the efficacy of the vaccine, so, Pfizer type of vaccine was significantly related to secreter status in participants who received 2 doses of Pfizer. The gap among studies could be accredited to sample sizes, ABO heterogeneity, genetic differences in viral strain, phenotypes variation in blood groups across countries, as well as genetic differences in *FUT2* mutation, which might influence the assortment of COVID-19 clinical phenotypes [40].

CONCLUSIONS

The frequent blood group varies according to the population that they take. The A-antigen and H antigen of ABO, HBGA groups are acting as receptors for coronavirus; this increased susceptibility and severity of infection and more dysfunction associated. On the other hand, the anti-A antibodies, RH- and non-secreter act as protectors from the infection.

ETHICAL APPROVAL

The Ethics Committee for Research from the College of Dentistry, University of Baghdad, Baghdad, under protocol number 460722

LIMITATIONS

The small sample size taken and the lack of control groups made the comparison difficult.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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