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ACE2 POLYMORPHISMS (RS6629110 AND RS2106806) AND SEVERITY OF COVID 19 DISEASE IN MOSUL POPULATION OF IRAQ

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ABSTRACT

Background: The biggest challenge that humanity has faced since 2019 is the spread of the Covid 19 pandemic worldwide. The researchers focused more on the mechanism by which the spike (S) protein of the virus binding with the ACE2 receptor and then enters the host. **Methodology**: In the current study, 124 individuals of COVID-19 patients were classified into three groups, Mild (N=39), Moderate (=40), and Sever (N=45) cases. We used an amplification refractory mutation system (ARMS-PCR) for ACE2 (rs6629110 and rs2106806) genotyping. **Results:** As the results show, there is no significant difference in the genotype distributions of ACE2 (rs6629110 and rs2106806). However, in over dominant models of ACE2 (rs6629110) CT genotype we indicate a relative increase in the value of the added ratio in moderate cases with OR 1.2879 (95%) CI = (0.5235 to 3.1683), $p < 0.5817$ and with OR 1.4006 (95%) CI = (0.5813 to 3.3743), $p < 0.4527$ in severe cases. Also, the codominant model in ACE2 rs2106806 (AA) genotype was observed a relative increase in the value of the added ratio in moderate cases with OR 1.9286 (95%) CI = (0.7020 to 5.2984), $p < 0.2028$ and with OR 2.4545 (95%) CI = (0.8940 to 6.7388), $p < 0.0814$ in severe cases**. Conclusions:** This study has found that generally an association between over dominant models of ACE2 (rs6629110) CT and increased symptoms of illness, but not significantly. Also findings the association between codominant models of ACE2 (rs2106806) AA and increased symptoms of illness, but not significantly. However, to prove the theory, we need more future studies with a larger number of volunteers, preferably from different populations. .

KEYWORDS: SARS-CoV-2; COVID-19; ACE2, single-nucleotide polymorphism; polymorphism; severity.

1. INTRODUCTION

Coronaviruses are a miscellaneous family of viruses that caused diseases in many animals, and they can cause mild to severe respiratory symptoms in humans.[1] Coronavirus disease 2019 (COVID-19) is an extremely intended, infectious illness causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which originated in Wuhan China at the end of 2019.[2] Globally**,** as of 4 April 2022, there have been 489,779,062 confirmed cases of COVID-19, including 6,152,095 deaths.[3]

SARS-CoV-2 is an enveloped single-stranded RNA virus with three structural protein ingredients comprised of S (spike), M (membrane), and (envelope) proteins.[4,5] The spike (S) protein has two subunits, S1 and S2.[6] The S1 subunit has a receptor-binding domain (RBD) that identifies and binds to the host receptor angiotensin-converting enzyme 2 (ACE2), while the S2 subunit plays a vital role in virus-cell membrane fusion.[7] It was suggested that increased susceptibility tissue susceptibility to SARS-CoV-2 infection may be associated with the expression of the target ACE2 receptor.[8]

The ACE2 gene is located on chromosome X at the Xp22 position. It contains 18 exons that appear a remarkable semblance in exons size and organization to those of the ACE gene.[9,10] Males are hemizygous (XY Chromosomes) while females have two XX chromosomes. In normal females because of X chromosome inactivation, are a natural mosaic

depending on the random process of X chromosome inactivation at early development stages.[11] The ACE2 gene sequence demonstrates a high degree of genetic heterogeneity and highly polymorphic, which explain the characteristics of gender, ethnic and geographical specific genetic diversity.[12] Based on a number of studies, Suryamohan et al. (2021) recorded 298 unique protein-altering variants via 256 genetic codons distributed throughout the 805 amino acids of the human ACE2.[13]

On the other hand, the population frequencies of ACE2 SNPs in several regions of the world showed that the population of North America, Southeast Asia, and China is the most susceptible to SARS-CoV-2, while the European population have the lowest frequencies of these SNPs, based on Chinese studies.[14] For example, rs6629110, localized in the *ACE2* intron, has the highest frequencies (AF) in the populations of Europe (0.997) and African (0.5699) and the lowest AF in the populations of Asian (0.046) and Latin American (0.321). However, in various populations, the genetic polymorphisms of ACE2 positively correlated with the susceptibility to infection of the SARS-CoV-2 in different populations remain mostly unclear. Therefore, the SNPs of ACE2 linked with increased risk for SARS-CoV-2 infection need to be more researched in various population.[15] This study was ongoing to recognize relevant SNPs (rs6629110 and rs2106806) of ACE2 in a group of human populations from Mosul/Iraq, which may be linked with an increased risk for covid 19 infection.

2. MATERIAL AND METHODS

2.1. Population and Study design

In the current study, target population was restricted from the city of Mosul / northern Iraq. Examination of 119 COVID-19 patients was made attributed to patients' clinical status as agreed by the World Health Organization.[16] and a positive result on RT-qPCR, in the accredited laboratories of the Iraqi Ministry of Health within the city of Mosul.

Depending on the symptoms, the study samples were divided into three groups: Mild (45 samples: 24 males and 21 females), moderate (40 samples: 23 males and 17 females), and severe symptoms (24 samples: 10 males and 14 females). Blood Samples from positive cases of COVID-19 were collected between November 2021 and February 2022. The ethical approvals for the current study were taken from local committees of the College of Science, University of Tikrit (No. 3/7/ 4615 in 1/11/2021), in agreement with the Declaration of Helsinki Principles. All volunteers signed a written informed consent before they were recruited and reported themselves to be from the Mosul population.

2.2. Genomic DNA Extraction

Genomic DNA was extracted from 200 µl of EDTA-whole blood using the protocol described previously.[17] DNA was assessed by agarose gel electrophoresis (1%). DNA purity and amount were measured in a Nanodrop 2000 spectrophotometer (Thermo Scientific, Waltham, MA, USA).

2.3. Genotyping of the ACE2

The polymorphism of ACE2 gene (rs6629110 and rs2106806) was done by amplification refractory mutation system (ARMS-PCR) PCR. The primers used in the current study were listed in Table 1. The PCR protocol for both ACE2 SNPs (rs6629110 and rs2106806) was carried out by initial denaturation step at 94˚C for 4 min; 35 cycles of denaturation step at 94˚C for 1 min, annealing steps at 56˚C for 30 sec, and elongation step at 72˚C for 45 min. Then final extension cycle at 72˚C for 5 min. Finally, the PCR product was assessed by electrophoresis in agarose gel (2%).

Table 1: Primers sequence, PCR product and annealing temperature for ACE2 gene polymorphisms.

Primer Sequence for rs6629110 OF10 GATAGCATTAGGAGATATACCTAACG OR10 GCAGTCTTGTCTTCATAACATTTT IF10 CTTGAACACTACCTCTAAGAGTATTAGAC IR10 TTTATATGTTTGTATCTTCACACTCAA	PCR Product	Annealing Temperature	Source
	Product size for C allele: 201 Product size for T allele: 251 Product size of two outer primers: 396	56 C	This study
Primer Sequence for rs2106806 OF06 CATTCCTGTCCTCTGTATCATTTT OR06 AAACCATGTGAATATCCTGTTCTC IF06 AAAGAATATGGTGGAAGAAAGGGG IR06 TAAAAAAAGAGCTTTCTCTTTTATT	Product size for G allele: 190 Product size for A allele: 129 Product size of two outer primers: 270	56 C	

2.4 Statistical analysis

Demographic age was tested for Mean ± SD distribution using standard division SD TEST and Excell 2016. The number of cases and percentages of the data were calculated and divided into totals in this study to confirm the presence of significant differences and statistical relationships using chi-square test. (IBM spss v25,UK) at a significant value of $p<0.05$.[18] The associations between ACE2- rs6629110 C > T, ACE2 rs2106806 G > A genotypes and computing the odds ratios (ORs), with 95% confidence intervals (CIs) to appraise the risk of COVID-19 patients.[19]

3. RESULTS

The demographic age and gender characteristics of the 119 individuals with COVID-19 illness are classified to three group, Mild (N=39), Moderate (=40) and Sever (N=45). Of 39 mild cases, 21 (53.85%) patients were equal to or less than 45 years and 18 (46.15%) were over 45 years of age. Of 40 moderate cases, 26 (65%) patients were equal to or less than 45 years and 14 (35%) were over 45 years of age. Of 45 sever cases, 21 (46.77%) patients were equal to or less than45 years and 23 (53.33%) were over 45 years of age (Figure 1). The mean age ± standard deviation (SD) of covid19 patients was 43.6 ±7.023 years in Mild cases (control group), while the mean age was higher among moderate (48.075 ±10.584 years), but the difference was not Significant (p= 0.145). Also, the difference was not Significant (p= 0.966), when compared between sever (43.2 ±7.084) and mild cases. (Figure 2).

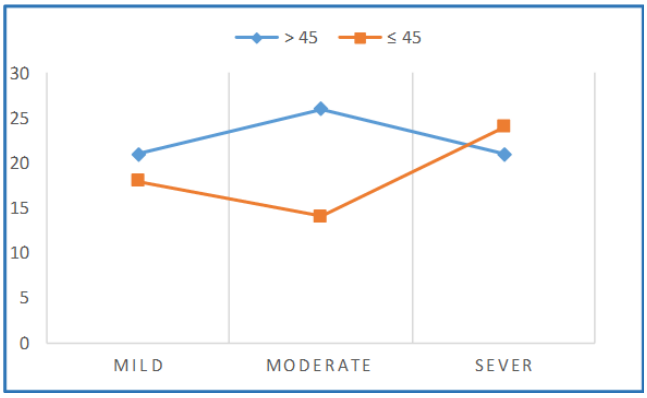

Figure 1: covid 19 cases distributed according to age group.

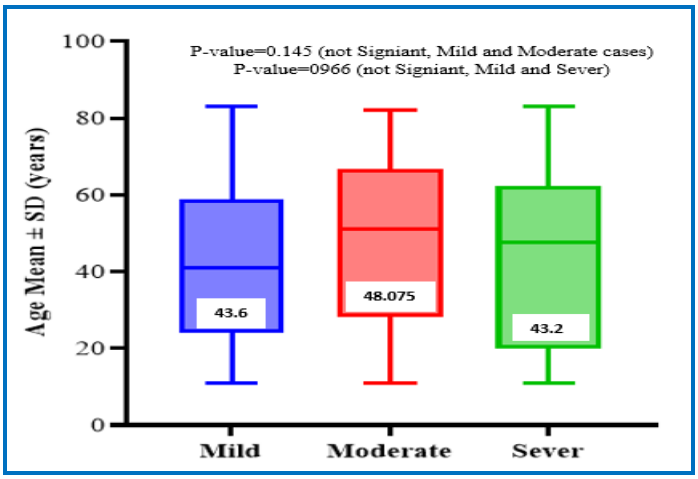

Figure 2: Box-plot presentation of Mean ± SD age among covid 19 cases distributed according to severity of disease.

Among 39 mild patients, 11 (28.17%) had T2DM, 19(48.7%) were having hypertension. Of 40 moderate cases, 19(47.5%) a having T2DM and 18(45%) were having hypertension. Of 45 sever cases, 15(33.3%) a had T2DM, 23(51.1%) a were having hypertension. but the difference was not Significant among cases group (Table 1).

Table 2: shows that relationship between the severity of COVID-19 Cases and the variables of diabetes and Hypertension in the three groups.

COVID-19 Cases	T2D		Hypertension	
	Yes (%)	No (%)	Yes (%)	No (%)
Mild control (N=45)	11(28.2%) a	28(71.8%)	19(48.7%) a	20(51.3)
Moderate (N=40)	19(47.5%) a	21(52.5%)	18(45%) a	22(55%)
Sever (N=39)	15(33.3%) a	30(66.7%)	23(51.1%) a	22(48.9)

No statistically significant relationship between the severity of COVID-19 Cases and the variables of diabetes □2(2)=3.447 and Hypertension □^{2}(2)=0.319 in the three groups at a significant value p<0.05.

One hundred and nine teen patient were genotyped. The results of the PCR products for *ACE2* rs662911 and *rs2106806* are represented in Fig. 3. In the rs662911, the PCR product size was 201 bp for wild allele (A) and 251 bp for polymorphic allele (C) (Fig. 3A). For rs2106806, the PCR product sizes of both alleles were 129 bp (A, polymorphic allele) and 190 bp (G, Wild allele), respectively (Fig. 3B).

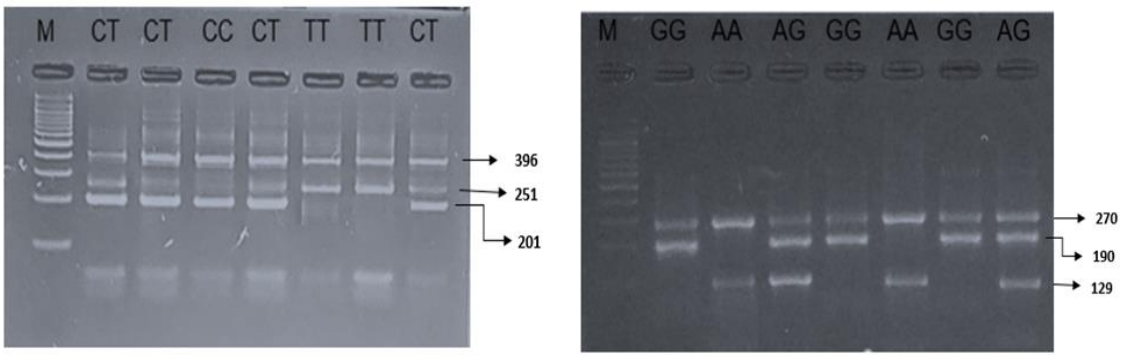

Figure 3. Agarose gel electrophoresis (1.5%) of polymerase chain reaction (PCR) product of tetra-primer Amplification refractory mutation system-PCR (T-ARMS-PCR) for the ACE2 gene,(A) rs662911and (B) rs2106806. M=DNA ladder (100 bp)

A multivariate analysis of odds ratio (OD) with 95% confidence intervals (CI) were calculated for each patients group to assessed the relationship between ACE2 (rs662911and rs2106806) polymorphism and the COVID-19 severity and the experimental data are presented in Table 3. No significance was recorded in all inheritance models. However, our results from ACE2-rs6629110 showed in the Over dominant model, the a value of the odds ratio in CT genotype is relatively high with OR=1.4006 (95%) CI (0.5813 to 3.3743) when comparing the mild and severe cases group, and with OR=1.2626 (95%) CI (0.4673 to 3.7183) when comparing between mild and moderate cases. Also in CT genotype, the Codominant model also observed an increase in the value of the odds ratio when comparing the mild and severe cases with OR=1.3182 (95%) CI (0.4673 to 3.7183), and with OR=1.2626 (95%) CI (0.4342 to 3.6714). Based Codominant model, our results from ACE2 (rs2106806) polymorphism was showing relatively high in the a value of the odds ratio between AA genotype vs GG genotype with OR=2.4545 (95%) CI (0.8940 to 6.7388) when comparing the mild and severe cases group and with OR=1.9286 (95%) CI (0.7020 to 5.2984) between AA genotype vs GG genotype when comparing the mild and moderate cases.(Table 3).

Table 3: Multivariate analysis of risk factors for COVID-19 severity with ACE2-(rs662911and rs2106806) genotypes.

Genotypes	**COVID-19 Cases**			**OR (95% CI)**	**p-Value**
rs6629110	**Mild control (N=45)**	**Moderate (N=40)**	**Sever (N=39)**		
Codominant					
CC	10	9	-	1 (ref.)	
		-	10		
CT	22	25		**1.2626(0.4342 to 3.6714)**	P = 0.6685
		--	29	**1.3182(0.4673 to 3.7183)**	P = 0.6016
TT	7	6	-	0.9524 (0.2315 to 3.9175)	P = 0.9461
		-	6	0.8571(0.2116 to 3.4726)	P = 0.829
Dominant					
CC	10	9	-	1 (ref.)	
		-	10		
CT+TT	29	31	-	1.1877(0.3227 to 3.3374)	P = 0.7441
			35	1.2069(0.4417 to 3.298)	P=0.7139
Recessive					
CC+CT	22	34	-	1 (ref.)	
		-	38		
TT	7	6	-	**0.5546(0.1645 to 1.8696)**	P = 0.3417
		-	6	**0.4962(0.1479 to 1.6646)**	P = 0.2565
Allele					
C	42	43	-	1 (ref.)	

		-	49		
T	36	37		1.0039(0.5370 to 1.8766)	P = 0.9903
		-	41	0.9762(0.5312 to 1.7939)	P = 0.9381
Over dominant					
CC+TT	17	15	-	1 (ref.)	
		-	16		
CT	22	25	-	**1.2879(0.5235 to 3.1683)**	P = 0.5817
		-	29	**1.4006(0.5813 to 3.3743)**	P = 0.4527
rs2106806					
Codominant					
GG	18	12	-	1 (ref.)	
		-	11		
AG	12	10	-	1.2500(0.4109 to 3.8028)	P = 0.6942
		-	13	**1.7727(0.5987 to 5.2489)**	P = 0.3013
AA	14	18	-	**1.9286(0.7020 to 5.2984)**	P = 0.2028
		-	21	**2.4545(0.8940 to 6.7388)**	P = 0.0814
Dominant					
GG	13	12	-	1 (ref.)	
		-	11		
AG+AA	26	28	-	1.1667(0.4517 to 3.0136)	P = 0.7502
		-	34	1.5455(0.5968 to 4.0024)	P = 0.3699
Recessive					
GG+AG	25	22	-	1 (ref.)	
			24		
AA	14	18		1.4610(0.5920 to 3.6058)	P = 0.4107
		-	21	1.5625(0.6493 to 3.7599)	P = 0.3192
Allele					
G	38	34	-	1 (ref.)	
		-	35		
A	40	46	-	1.2853(0.6863 to 2.4070)	P = 0.4330
		-	55	1.4929(0.8081 to 2.7579)	P = 0.2007
Over dominant					
GG+AA	27	30	-	1 (ref.)	
		-	32		
GA	12	10	-	**0.7500(0.2795 to 2.0128)**	P = 0.5679
		-	13	**0.9141(0.3581 to 2.3330)**	P = 0.8509

4. DISCUSSION

A range of different clinical symptoms were observed in patients with covid 19, from the absence of clinical symptoms completely to the serious clinical symptoms. In general, the symptoms can be divided into mild illness, moderate illness, and severe illness. However, clinical symptoms may overlap between the categories or my change occur in the patient's status over time.

Although the results of this study did not show any significant differences between the age and the severity of covid 19 disease. But also notice the age distribution of COVID-19 cases with severity symptoms was similar to worldwide data in which patients were above 45 years[20, 21] Instead of applying age thresholds, protection programs against covid 19 pandemic should consider the continuous increase in risk and spread of illness. There is a need for continuous, efficacy and quality research to estimate the evidence throughout the pandemic, as results may change depending on various circumstances.[22]

Our results about T2DM and severity of covid 19, notice the levels observed in this investigation are below those observed by.[23,24] Generally, the association between COVID-19 severity prevalence in adult patients with diabetes, race/ethnicity, social vulnerability, and socioeconomic status. The interrelation of these circumstances points to the need for a comprehensive, multifaceted way to address public health and chronic disease prevention.[25]

This study has been unable to demonstrate a significant difference between hypertension and the severity of covid 19. However, the findings of the current study do not support the previous researches.[26,27] To date, the accurate mechanism by which hypertension biases to negative outcomes in patients infected with COVID-19 is still unclear.[27,28] A comparison of the findings with those of other studies confirms, that there is until now no strong evidence that hypertension is linked to ACE inhibitors or outcomes of COVID-19, during the COVID-19 pandemic.[29,30] The use of these factors should be maintained for the Prevention and control of

hypertension, and they should not be stopped, at least on the basis of current evidence at this time.[29]

In our study, the ACE2 rs6629110 C > T gene polymorphism observed between COVID-19 cases was not statistically significant. But can also vary in volume odd ratio among different inheritance models. For example in over dominant model, ACE2-(CT) genotype was associated with increased COVID-19 severity between mild and moderate cases with OR 1.2879 (95%) CI = (0.5235 to 3.1683), p < 0.5817 and with OR 1.4006 (95%) CI = (0.5813 to 3.3743), p < 0.4527 between mild and sever cases. Also in codominant model, ACE2-(CT) genotype was linked with COVID-19 severity in moderate cases with an OR 1.2626 (95% CI) (0.4342 to 3.6714), p < 0.6685 and with an OR 1.3182 (95% CI) (0.4673 to 3.7183), p < 0.6016 in severity cases. The ACE2 rs2106806 G > A gene polymorphism observed between COVID-19 cases was not statistically significant. But in codominant model, ACE2-(AA) genotype was associated with increased COVID-19 severity between mild and moderate cases with OR 1.9286 (95%) CI = (0.7020 to 5.2984), p < 0.2028 and with OR 2.4545 (95%) CI = (0.8940 to 6.7388), p < 0.0814 between mild and severe cases. These results are in accord with recent study indicated that association between ACE2 polymorphism and COVID-19 severity in the codominant model.[31]

In addition, will need to be understand, Although ACE2 anchors onto the cell surface, it is not stable, and can leave the cell membrane, which is known as ACE2 shedding.[32] ACE2 shedding produces soluble ACE2 (sACE2), resulting in the lack of the membrane-bound form. Whether ACE2 shedding and increasing sACE2 are physiological or pathological has not been clearly elucidated.[33] Future studies on the current topic are therefore recommended.

5. CONCLUSIONS

Although there were no significant differences between the study groups, the current study concluded a limited association between severe cases and the average age over 45 years old. In addition, ACE2- rs6629110 (CT) genotype was a relative risk factor for increased severity of illness in both Over dominant and codominant models. While ACE2- rs2106806 (AA) genotype was a relative risk factor for increased severity of illness in codominant models. The limitations of the study include a relatively smaller sample size of 124 patients and the study population was limited to the city of Mosul only, so future studies on other populations must be verified before confirming the results obtained.

Author Contributions: **Adwaa F. Saleh**: Conceptualization, Methodology. Rafea **Z. Al-sugmiany:** Conceptualization, Supervision, and Investigation. **Maan H. Salih**: Supervision, Conceptualization, Methodology, data analysis, and Writing—Review and Editing. **All Authors** have Writing and agreement to the original manuscript.

Conflicts of Interest: no conflict of interest.

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