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Research Article

EXPLORATION OF THE EFFECT OF SNPS (ACE1/ACE2) IN THE VARIABILITY OF THE SEVERITY OF COVID-19 DISEASE IN HYPERTENSIVE PATIENTS

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ABSTRACT

Background: ACE2 has been identified as the entry receptor for coronaviruses into human cells, including SARS-COV-2 that causes COVID-19. Since hypertension is a leading comorbidity in non-survivors of COVID-19, we aimed to identify relevant SNPs of ACE1, ACE2 that may associated with increased risk for SARS-CoV-2/SARS-CoV infection and there susceptibility to increase the cardiovascular diseases in hypertensive patients. **Methods:** Literature was searched in PubMed, Science direct and Google Scholar to identify studies that had either assessed the SNPs of ACE2 gene with SARS-CoV-2/SARS-CoV infection or suggested the SNPs that could possibly regulate ACE2 expression in different human tissues. Then make a list of these SNPs of ACE1 and ACE2 considering as potential candidate for investigating the genetic effects in future studies. **Results:** In 11 studies analyzed and interpreted, we identified and analyzed 37 mutations that affect ACE1/ACE2 causing an imbalance of the renin agiotensin aldosterone system and modifying the severity of Covid-19 in patients with hypertension. From the studies done so far, we found that there are 20 mutations among the 37 identified that affect the receptors of the renin angiotensin aldosterone system that are directly related to the severity of Covid-19 since they all present P values<0.05. **Conclusion:** This is the first meta-analysis that gathers all the polymorphisms that affect the receptors of the renin angiotensin aldosterone system, causing an imbalance in the latter and also increasing the expression of this receptor as the main receptor of Covid-19 severity.

KEYWORDS: *Covid-19, SARS-COV2 Spike protein, ACE1/ACE2 polymorphism, hypertension, meta-analysis.*

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in China that causes coronavirus induced disease 19 (COVID-19).[1] COVID19 has confronted a major threat to human health globally and posed a serious risk to the public healthcare systems. This pandemic has resulted in 173 271 769 confirmed cases and 3 733 980 case deaths worldwide as of June 08, 2021.[2] The clinical spectrum of COVID-19 includes asymptomatic, mild symptom and severe acute respiratory distress syndrome (ARDS) with high mortality due to respiratory failure, stroke, thrombotic complications and multi organic failure.[3] Severity of COVID-19 patient increases with other comorbidities such as older age, diabetes, hypertension, and obesity.[4] However, many cases without these comorbidities also have severe lung disease or ARDS.[5] Thus, underlying pathophysiological mechanism of COVID-19 is not yet fully understood.

The entry of SARS-CoV-2 into host cells is facilitated by the binding of viral spike protein (S-protein) to the extracellular peptidase domain of angiotensin converting enzyme 2 (ACE2), followed by the s-protein priming through a particlular transmembrane serine protease 2 (TMPRSS2).[5] ACE2 converts angiotensin II to angiotensin 1–7 and prevent the effects of ACE1/angiotensin II axis. Angiotensin II can induce strong vasoconstriction, proinflammatory effects, and profibrotic effects, while angiotensin 1–7 exhibits antiproliferative, antiapoptotic, and mild vasodilating abilities and protect different cardiovascular effects such as anti–heart failure, anti-thrombosis, anti-myocardial hy-pertrophy, anti-fibrosis, anti-arrhythmia, anti-atherogenesis, and attenuating vascular dysfunction related to metabolic syndrome.[6] Therefore, the coexistence in the ACE1 and ACE2 genes of inherited predispositions or common genetic polymorphisms of these genes that affect their levels of mutual expression can lead to increased capillary

permeability, fibrosis, coagulation and apoptosis in the alveolar cells and accelerating lung damage.

Angiotensin-converting enzyme 2 (ACE2) encoded by the ACE2 gene has impacts on renin–angiotensin–aldosterone system (RAAS) and regulating cardiovascular effects. The ACE2 gene is highly polymorphic and many of the single nucleotide polymorphism (SNP) of this gene had been established as a risk factor for developing **cardiovascular diseases.**[7] Therefore, the variability and magnitude of ACE2 expression in different human tissues governed by the genetic variants of ACE2 might be of critical for the susceptibility, symptoms and outcome of SARS-CoV-2 infection. As evidenced elsewhere, some patients may have higher expression of ACE2 as found in recent single-cell RNA-sequencing (RNA-seq) analysis. After adjusting confounders, a very recent study elucidated that ACE2 gene expression in nasal epithelium was lowest in younger children and increased with age.[8] This reflects that unrevealed genetic polymorphisms of ACE2 might contribute this expression variability.

Despite all the efforts done by researchers, still there are no considerable studies focused on the effect of ACE1/ACE2 variants on different population's susceptibility to COVID-19.

This study was designed to identify relevant SNPs of ACE1, ACE2 that may associated with increased risk for SARS-CoV-2/SARS-CoV infection and there susceptibility to increase the cardiovascular diseases in hypertensive patients.

1- Viral entry mechanism of SARS-CoV 2

The mechanism for SARS-CoV 2 infection necessitates the binding of the virus to the membrane bound form of angiotensin-converting enzyme 2 (ACE2) receptor and internalization of the complex by the host cell (**Figure 1**). Apart from its role as a receptor for SARS-CoV 2, ACE2 is well-known for its role in hypertension ACE2 modulates blood pressure and maintains blood pressure homeostasis through negatively regulating the renin-angiotensin system (RAS).[9-10] ACE and its homolog ACE2 are two key enzymes involved in the synthesis of bioactive components of the RAS.[10] ACE2 exerts its functions through cleaving either angiotensin I (Ang I) or Ang II into the inactive peptides Ang (1–9) and Ang (1–7), respectively (**Figure 1**). Ang (1–9) gets further metabolized into Ang (1–7). Ang (1–7) is a vasodilator, hence ACE2 counteracts the vasoconstrictor effects of the ACE-Ang II axis. The mechanism by which ACE2 antagonizes the effects of Ang II is either by cleaving the precursor Ang I, which reduces Ang II synthesis in tissues, or by directly hydrolyzing Ang II and reducing its levels in plasma.

Both ACE and ACE2 are endothelium-bound carboxypeptidases that can be cleaved by different metalloproteases located on the cell surface and released in a soluble form. Contrary to ACE, which is widely expressed in many tissues and organs, ACE2 high expression is confined to the endothelial cells of the arteries, arterioles, and venules of the heart and kidney Therefore, ACE2 has been a potential therapeutic target in treating hypertension and cardiac dysfunctions and consequently hypertension.[9]

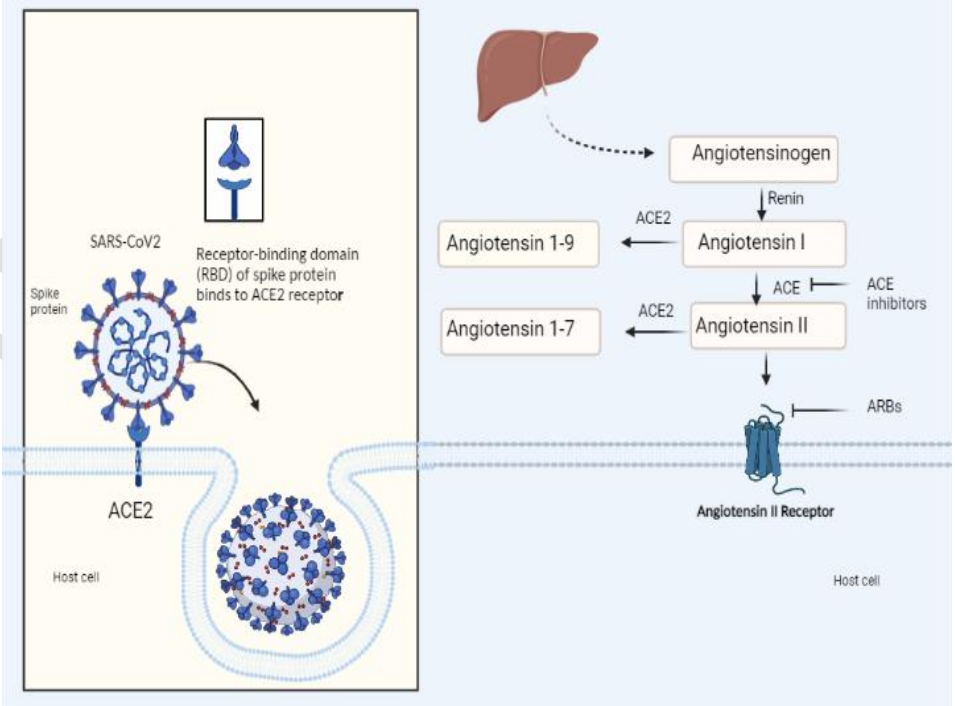

Fig 1: ACE2 in the Entry of SARS-CoV 2 into the Host Cell: Illustration of the two key arms in the renin-angiotensin system.

2- ACE2 : Localisation, Structure, Functions

The ACE2 gene codes for the angiotensin-converting enzyme 2 (ACE2) protein. The ACE2 gene span 39.98 kb of genomic DNA and contains 20 introns and 18 exons, is situated on chromosome X at position Xp22.[11] It encodes a type I cell-surface glycoprotein of about 100 kDa which contains a catalytic domain composed by 805 amino acids.[12] It is characterized by a N terminal signal peptide of 17 amino acids residues, a peptidase domain (PD) with its HEXXH zinc binding metalloprotease motif and a C-terminal transmembrane anchoring region.[13] Single nucleotide polymorphisms (SNPs) in ACE2 may result in modulation of RAS pathway and associated cardiovascular diseases.[14]

ACE2 belongs to the family of ACE members which have a wider tissues distribution. The juxtamembrane, transmembrane and cytoplasmic tail of ACE2 do not resemble ACE but these two proteins share the CLD region, a 220 amino-acid domain. Angiotensin converting enzymes (ACE) are zinc metallopeptidases. ACE, is a widely distributed protein of 170 kDa encoded by a 21 kb gene located on chromosome 17 (17q23).[15] That converts the inactive decapeptide, angiotensin (Ang) I to an active vasoconstrictor octapeptide Ang II [Asp-Arg-Val-Tyr-Ile-His-Pro-Phe] that controls the blood pressure.[16] And through inactivation of bradykinin vasodilatator.[17]

3- ACE2, ACE1, TMPRSS2 and COVID-19 disease

The incidence and severity of COVID-19 disease varies worldwide.[18] Initially, SARS-CoV-2 infection occurred in Asian countries, followed by Southern European countries, which experienced much higher morbidity and mortality rates.[19] SARS-CoV-2 infection transmission occurs mainly through respiratory droplets and direct contact with the virus.[20] The pathogenesis of SARS-CoV-2 infection might be influenced by host genetic factors ACE2 and AngII receptor type 2 gene, both are situated on the X-chromosome, TMPRSS2, pre-existing comorbidities, nonmodifiable factors like age and sex together. Thus many factors collectively determine the fate and prognosis of SARS-CoV-2 infection, also affecting the associated mortality. Basically, X-linked heterozygous alleles could act in favor of females by imparting a greater sexual dimorphism which might counteract viral infection, inhibiting local inflammation and thus protecting female from severe adverse outcomes of COVID-19. The incidence and progression of COVID-19 disease depends on the interaction between the virus-host. Multiple factors from host like genetic polymorphisms, gender, age, life style status and nutritional, physical status, neuroendocrine-immune regulation and ethnicity contribute while factors such as type of virus, mutations present within the virus, viral titer, viral load, and viability of the virus act as viral factor. COVID-19 disease showed a variation in symptoms, from mild or asymptomatic, influenza-like symptoms, severe pneumonia, acute respiratory distress and even death. Also a wide difference was observed in outcome of Novel Coronavirus (2019-nCoV) infection between males and females. This variation is expected to be multifactorial including genetics. Three strains of coronavirus, SARS-CoV-2, SARS-CoV and NL63 utilize the ACE2 receptor, a zinc metalloprotease. Evidence suggested that variations in host ACE2 sequences and viral spike protein both may affect the trans-species spread of viral infection. The transmembrane spike (S) glycoprotein of virus binds to the ACE2 making it essential for the invasion of the virus into the host cell, followed by attachment of the virus to the target cells. S- protein priming by TMPRSS2, therefore necessary for the correct maturation of these proteins that enter the cell through ACE2, allowing the bonding of viral and cellular membranes, resulting in virus entry and replication in the host cells.[23–37] As binding of SARS-CoV-2 with ACE2 is a prerequisite for the entry in the host cells, hence[21] the distribution and expression of ACE2 in target organ could be important determinant for the initiation of virus infection and its progression. Spike (S) proteins of virus gets recognized by the critical lysine 31 present on the ACE2 receptor. The residue 394 (glutamine) in the SARS-CoV-2 receptor-binding domain (RBD) binds with ACE2 receptor. Followed by TMPRSS2 facilitated adhesion of the virus with host cell membrane, thus allowing the virus entry into host cell cytosol and subsequent virus replication.[22] ACE I/D genotype occurs in different populations, which might impact the incidence of the SARS-CoV-2 infection. In European population, the deletion genotype DD of ACE1 was associated with SARS-CoV-2 infection.[23] In Europe and Southern Europe, the occurrence of D allele of ACE1 was higher as compared to Asian population.[24] This might be one of the reasons behind the higher incidences of morbidity and case fatality in Europeans as compared to Asians. However, frequency of D allele is low in India as compared to East Asian Chinese and Korean populations.[25] Higher frequency of I allele, as reported by the studies in different Indian population subgroups could be an explanation behind the lower incidence of SARS-CoV-2 infection in Indian population.[26] Report from China suggested that Asians neither have distinctive ACE2 genetic polymorphisms nor high level expressions of ACE2.[27] On the contrary, another study has denied any relationship between the human ACE2 variants and susceptibility to SARS-CoV-2 infection.[28] Genetic variants of ACE2 gene affect the interaction between host receptor and viral spike protein.[29] Significant variations in the levels of ACE2 expression in lung tissues of transcontinental human populations are reported but still the evidence is non-conclusive.[19] Hence looking for the abundance of ACE2 gene among different populations will be important. This could be one of the important area for research of genetic epidemiology, with an objective to explore the reason for differential spread and mortality of COVID-19 disease in different regions of the world. TMPRSS2 expression is crucial for spread of virus and pathogenesis. Genetic variation in this gene may modulate genetic predisposition to infection and virus clearance in the host. As TMPRSS2 is expressed significantly more in androgen sensitive tissues like prostate and testis, male gender seems to be more

vulnerable for acquisition of infection. This may be the cause of gender specific differential infection rates.[30] eQTLs is found in high number for TMPRSS2 of allele frequency of whom varies among the different populations. In East Asians, the TMPRSS2 allele is found in lower frequency.[30] Gender differences in case fatality and morbidity could also be explained by the presence of TMPRSS2 : ERG fusion protein in men specific diseases like prostate cancer and the effective regulation of TMPRSS2 by androgens. The expression of TMPRSS2 mRNA level in lung tissue of men is not different than that of women. However, there was a broad range variation in expression of mRNA levels among both genders.[31]

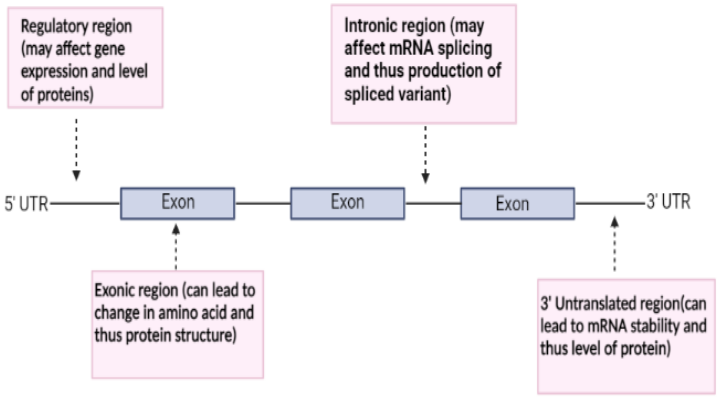

Fig 2: Role of polymorphism.

Methods

Literature was searched in **PubMed**, **Science direct** and **Google Scholar** to identify studies that had either assessed the SNPs of ACE2 gene with SARS-CoV-2/SARS-CoV infection or suggested the SNPs that could possibly regulate ACE2 expression in different human tissues. Then make a list of these SNPs of ACE1 and ACE2 considering as potential candidate for investigating the genetic effects in future studies.

1- Inclusion criteria

The inclusion criteria for the studies were as follows:
-Target population: patients with covid-19 and hypertension.
-Outcome measure: all SNPs that affect ACE1 and ACE2 in modifying the severity of Covid-19 in patients with hypertension.
Methodology: cohort studies, case-control studies, or retrospective/prospective studies.

2- Exclusion criteria

Exclusion criteria were :

- Unclear criteria or data
- incomplete or inaccessible articles
- Articles that did not investigate the variables being measured
- Reviews

3- The study selection process

Our database search yielded 920 publications after searching Pubmed and Google scholar and initial screening of titles and abstracts. Subsequently, 909 studies were excluded for failure to meet inclusion criteria, yielding 11 studies that met the criteria and were included in this meta-analysis for the association of SNPs affecting ACE1 and ACE2 with variability in covid-19 severity.

Figures 3 and 4 explain the process and steps involved in selecting the studies and conducting this meta-analysis.

Fig 3: ***Flow chart illustrating the steps involved in conducting the meta-analysis.***

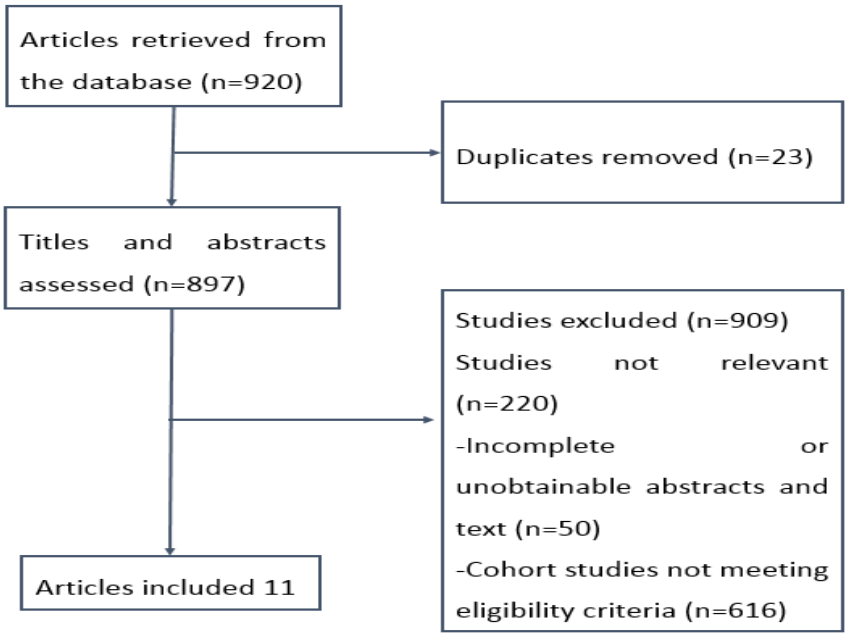

Fig 4: ***Flow work describing the systematic literature search and study selection process.***

RESULTS

11 studies were included in this meta-analysis. They were identified through database searches. All cohort, retrospective, observational, prospective studies on polymorphisms affecting ACE1 and ACE2 affecting the severity of Covid-19.

Table 1: ***ACE2 Polymorphisms Associated with the Risk of Hypertension and Covid-19 in Different Populations.***

Study	Author	Publication	Type of study	Publication date	Population	Nomber of patients	Median age	Sex (Men (%))
1	P. Hamet and al.,	[32]	Prospective cohort study	December 31, 2020	French, Canada	403	≥ 50 Years old	57.1%
2	J. Gómez and al.,	[33]	Prospective cohort study	June 12, 2020	Caucasian Individuals	204	70 Years old	61%
3	L. Wulandari and al.,	[34]	Prospective cohort study	29, mai 2021	Surabaya, Indonesia	95	≥ 50 Years old	63.2%
4	S. Rangaprasad and al.,	[35]	Prospective cohort study	24 August 2020	Europe, Africa, America	349	> 50 Years old	–
5	H. Lanjanian et al.,	[36]	bioinformatics simulation of 3D structures and docking (Cohort Study)	11, November, 2021	Iranian, African, American, East Asian, European, and South Asian and China	3304	–	–
6	C. Anastassopoulou and al.,	[37]	Cohorts (Meta-analysis)	2020	Italy Spanish	1980	≥ 50 Years old	50%
7	M. Calcagnile and al.,	[38]	bioinformatics simulation(in silico molecular docking)	2021	European, Italy people Wuhan, China South	131	–	–

					America			
8	C. Cafiero and al.,	[39]	Prospective cohort study	27 May 2021	Caucasian individuals	104	68 Years old	58%
9	J. Martínez-Sanz and al.,	[40]	Prospective cohort study	9 March 2021	Asian Individuals	67	58 Years old	56%
10	B. Möhlendick and al.,	[41]	Prospective cohort study	27 January 2021	German	550	60 Years old	58,7%
11	Sevim Karaka¸s and al.,	[42]	Prospective cohort study	March 14, 2021	European patients	155	70 Years old	60 %
12	L. Wooster and al.,	[43]	Prospective cohort study	June 22, 2020	Caucasian patients	62	62 Years old	56%

Table 2: ***Association the effect of SNPs in the variability of the severity of Covid-19 disease in HT patients.***

Study	Polymorphism ID	Gene & Choromo somal location	Localisation	P Value Hypertension	Associated severity to HT	P value Covid-19	Associated severity to Covid-19	Publications
1	rs2074192(T/C) rs233575 (A/G) rs4646142(C/G) rs2285666(T/C) rs1978124(T/A) rs2106809(C/T) rs2048683(T/A) rs4646156(A/C) rs879922(G/T) rs4240157(C/T) rs1514280(A/C)	ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2)	Intron 16 Intron 16 Intron 7 Intron 4 Intron 2 Intron 2 Intron 5 Intron 8 Intron 11 Intron 14 Intron 14	0.0270 0.0008 NS 0.0396 0.0490 0.0240 0.0019 0.0041 0.0018 0.0023 0.0023	High High - High High High High High High High High	0.0359 NS 0.0396 0.0396 NS NS NS NS NS NS NS	High _ High High _ _ _ _ _ _ _	[32]-[54]-[55] [32]-[56] [32] [32]-[33]-[57] [32] [32]-[42] [32]-[54] [32]-[54] [32] [32]-[54]-[56] [32]
2	rs4646994 (DD) rs4646994 (ID) rs4646994 (II) rs2285666(A/G)	ACE(17q23.3) ACE(17q23.3) ACE(17q23.3) ACE2 (Xp22.2)	Intron 16 Intron 16 Intron 16 Intron 3	0.020 NS NS 0,005	High _ _ High	0.049 NS NS 0.18	High _ _ No association	[33]-[42] [33]-[42] [33]-[42]
3	rs4646994 (I/D)	ACE(17q23.3)	Intron 16	< 0.001	High	NS	_	[35]
4	rs769062069 rs776995986	ACE2 (Xp22.2) ACE2 (Xp22.2)	_ _	NS NS	_ _	<0,01 <0,01	High High High	[36]
5	p.Arg514-Gly (A/G)	ACE2 (Xp22.2)	_	NS	_	0,003	High	[37],[58]
6	rs1244687367 rs1434130600 rs4646116 rs146676783 rs775273812 rs867318181	ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2)	N-terminal sequence of the mature protein	_	_	0.000005 _ 0.003971 0.000033 0.000006 _	High High High High High	[38]
7	rs2074192(C>T) rs1799752(ins-del)	ACE2 (Xp22.2) ACE1(17q23.3)	Intron 16 Intron 16	NS	_	P=0.001754 P>0.00001	High High	[39]
8	rs2106806 (A/G) rs6629110 (C/T)	ACE2 (Xp22.2) ACE2 (Xp22.2)	_	NS NS	_ _	P = 0.0165 P = 0.0289	High High	[40]

9	rs2285666 (G>A)	ACE2 (Xp22.2)	Intron3	P=0,02	High	P=0,02	High	[41]
10	rs2106809 rs2285666	ACE2 (Xp22.2) ACE2 (Xp22.2)	Intron 4 Intron 4	-	High High	- -	- -	[42]
11	rs4240157 (C/T) rs6632680 (A/C) rs1548474 (G/T) rs4830965 (A/G) rs1476524 (T/C)	ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2) ACE2 (Xp22.2)	- -	-	-	0,014 0,014 0,025 0,027 0,030	High High High High High	[43]

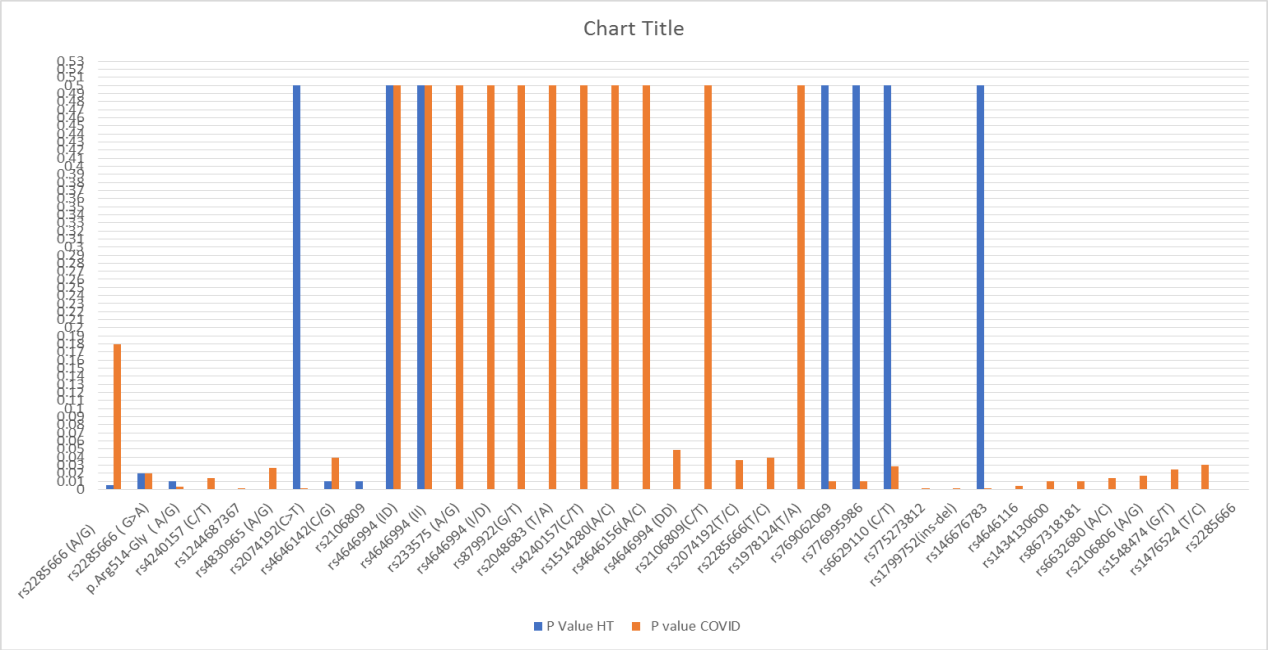

Fig 5: ***Association the effect of SNPs in the variability of the severity of Covid-19 disease in HT patients*.**

DISCUSSION

A total of 11 studies were included in this meta-analysis. The title, abstract, and full text of all papers that could be identified in the search database were analyzed and those reporting information on receptor (ACE1/ACE2) Single nucleotide Polymorphe (SNPs) and their variability in the severity of Covid-19 in hypertensive patients.

Table 1 : shows that the average age of the participants is between 50-70 years, the male sex is well dominant compared to the female sex (most mortality occurs in the elderly and is almost double in males (4.7%) compared to females (2.8%)[32]) and comorbidities are present in half of the patients, hypertension is the most common comorbidity, followed by diabetes, cardiovascular diseases and obesity, in fact comorbidities are associated with a higher risk of Covid-19.

This graph shows the frequency of association of SNPs polymorphisms affecting ACE1/ACE2 with the severity of Covid-19 in hypertensive patients. In 11 studies analyzed and interpreted, we identified and analyzed 37 mutations that affect ACE1/ACE2 causing an imbalance of the renin agiotensin aldosterone system and modifying the severity of Covid-19 in patients with hypertension.

From the studies done so far, we found that there are 20 mutations among the 37 identified that affect the receptors of the renin angiotensin aldosterone system that are directly related to the severity of Covid-19 since they all present P values<0.05: rs2285666 (G>A) P=0,02, p. Arg514-Gly (A/G) P=0,01, rs4240157(C/T) P=0,01, rs4830965 (A/G) P=0,02, rs2074192(C>T) P<0,01, rs4646142(C/G) P=0,04, rs2074192(T/C) P=0,03, rs2285666(T/C) P=0,04, rs769062069 P=0,01, rs776995986 P=0,01, rs6629110 (C/T) P=0,03, rs4646116 P<0,01, rs1434130600 P=0,01, rs867318181 P=0,01, rs6632680 (A/C) P=0,01, rs2106806 (A/G) P=0,01, rs1548474 (G/T) P=0,02, rs1476524 (T/C) P= 0,03, rs2285666 (G>A) Fig5.

Among them we find that 3 mutations (p. Arg514-Gly (A/G), rs4646142, rs2285666) that cause hypertension have present very significantly P values and are associated

with an increased severity of Covid-19 up to death and requiring intensive care and mechanical ventilation, the First variant whose P value is P=0,01) is significantly associated with severity of Covid-19 and hypertenstion, this variant was more likely to be associated with cardiovascular and pulmonary conditions by altering the angiotensinogen (AGT)-ACE2 interactions in the African/African-American population.[37] The second mutation (rs4646142 whose P value is P=0,04) was examined by other researchers to increase the affinity of ACE2 with the Spike protein and the third SNP was essentially correlated with hypertension. In addition, 8 mutations among them are significantly correlated with Covid-19 since they revealed P values always lower than 0.05, starting from the one that presents a very strong association to the one that are weakly associated respectively : rs4646116 P<0,01, rs1434130600 P=0,01, rs867318181 P=0,01, rs4240157(C/T) P=0,01, rs6632680 (A/C) P=0,01, rs2106806 (A/G) P=0,01, rs1548474 (G/T) P=0,02, rs1476524 (T/C) P= 0,03, rs4646994 (DD) P= 0,04 Fig5. The first three SNP were found in In the 6th study, the variants affecting ACE2 were identified using modelling and homology simulation methods. Indeed, two mutations were found in the Iranian population and these mutations decrease the affinity of ACE2 for its protein spike[38] and the last mutation(rs4646994 (DD)) was also strongly associated with the development of coron-virus severe cases (often requiring ventilation and intensive care). This same work suggested that the ACE-I/D and ACE II might influence COVID-19 severity, but the effect was dependent on the hypertensive status. This result requires further validation in other large cohorts.[33]

Two variants were associated with a 3- to a 4 fold greater risk of COVID19: rs6629110 and rs2106806. Because ACE2 is the target molecule of SARS-CoV-2 for cell entry, higher levels of ACE2 expression are expected to lead to higher levels of SARS-CoV-2 viremia. The Genotype-Tissue Expression (GTEx) database revealed that SNP rs6629110 was associated with greater expression of ACE2, although researchers were not able to confirm the link between variants in the ACE2 gene and COVID-19. The SNP rs2106806 was among those included in a recent study aimed at describing a transcription regulatory network within the ACE2 locus in the context of SARS-CoV-2 infection, but no correlation was found. Here, we show that the minor A allele within rs2106806 increases the risk of critical COVID-19. The allele frequency of the ACE2 SNP rs6629110 is much higher in East Asian than in European populations but its importance during SARS-CoV-2 infection remains unknown. This variant has been associated with high expression of ACE2 in tissues such as the tibial artery, but, to our knowledge, an association with increased expression of ACE2 inlung tissue has not been described so far and there is no association between the variant and expression of ACE2 in nasal epithelium. Hence, this is the first report linking the rs6629110 variant with COVID19 susceptibility. However, it requires external validation in other studies.[40]

In other study we found that there are 5 SNPs (rs4240157, rs6632680, rs1548474, rs4830965, rs1476524) that are strongly correlated with the severity of covid-19 in elderly patients older than 62 years who have arterial hypertension. These results provide preliminary evidence of a genetic link between the ACE2 genotype and COVID-19 disease severity and suggest that the ACE2 genotype may inform COVID-19 risk stratification and need for more intense therapy.[43]

Contrary to these results, 8 SNPs showed no association with Covid-19 since they have values greater than 0.05: rs233575 (A/G), rs4646994 (ID), rs2048683(T/A), rs4240157 (C/T), rs1514280(A/C), rs4646156(A/C), rs1978124(T/A), rs4646994 (II).

Multiple studies have reported on the prevalence of ACE I/D polymorphism, specifically the ID and DD polymorphism in increasing levels of ACE and Ang-II, which could in part influence susceptibility to underlying pathologies considered high risk for COVID-19 infections, progressive organ dysfunction and poor outcomes. Thus, presence of ID and DD polymorphism by itself is a potential underlying risk factor associated with severity and outcomes in individuals withpositive diagnosis of COVID-19 infection.[52]

CONCLUSION

Some specific genetic variations in the sequences of ACE1/ACE2 may affect the cell-entry efficiency of viruses, either by changing its expression levels or causing higher binding affinity for SARS-CoV-2.

This is the first meta-analysis that gathers all the polymorphisms that affect the receptors of the renin angiotensin aldosterone system, causing an imbalance in the latter and also increasing the expression of this receptor as the main receptor of Covid-19 severity.

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