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Polymorphisms in ACE, ACE2, AGTR1genes and severity of COVID-19 disease

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Abstract

The SARS-Cov-2 virus infects humans and causes a disease that is very variable and unpredictable in severity. A higher susceptibility to infection or exaggerated inflammatory response might be the result of frequent genetic single nucleotide polymorphisms (SNPs) in a population. SARS-CoV-2 needs the ACE2 protein to enter a cell, and ACE2 controls the renin-angiotensin system. So, ons het die verband tussen 8 SNPs from AGTR1, ACE2 and ACE genes en die ernst van die siekte veroorsaak deur SARS-Cov-2 virus ondersoek. 318 COVID-19 pasiënte (mans 62,6%), who were 59.6–17.3 years of age, were divided according to the severity of their symptoms. These were outpatients (n = 104, 32.7%), hospitalised on the wards (n = 73, 23.0%), ICU (n = 84, 26.4%), and deceased (n = 57, 17.9%). Data wat verband hou met mediese toestande soos diabetes, hypertension, obesity, longsiekte en cancer, is ingesamel om aanpassing te maak. Die genotipeverspreiding van agt gekies SNPs in verskillende sterktegroepe is ondersoek. **Results** Die erns van die siekte is gekorreleer met vier SNPs in ACE2. Daar is gevind dat rs2074192 en rs1978124 'n protector-effek getoon het, aangesien hulle 'n overdominant model van inheritance aangeneem het (G/A vs. GG-AA, OR = 0.32, 95% CI = 0.12–0.82; p = 0.016, en A/G vs. AA-GG, OR = 0.37, 95% CI = 0.14–0.96; p = 0.038). Daar is ook gevind dat rs2106809 en rs2285666 As verwag, het ouderdom (OR = 1,47), manlike geslag (OR = 1,98) en comorbiditeit (OR = 2,52) getoon. increased groter risiko van dood of ICU-opname in vergelyking met 'n minder ernstige outpatient prosedure. Multivariable navorsing het die impak van sekere genotypes (ACE2) op COVID19 se intensiteit getoon (OR: 0.31, OR: 0.37 vir RS2074192 en RS1978124, OR: 2.67, OR: 2.70 vir RS2106809 en RS2285666, respectively). In the hospitalised group for I/D SNP in ACE, there was no Hardy-Weinberg equilibrium (p <0.05), which may be related to the disease. Multivariable studies het geen verband getoon tussen COVID-19 siekte en verskillende AGTR1 SNPs nie, maar die A/A genotype vir rs5183 het getoon dat pasiente met comorbidities meer geneig is om hospitale te besoek. **Conclusions** Patients met COVID-19 wat 'n ernstige clinical course en sterftesyfers ervaar, is geassosieer met verskeie genetic variants in ACE2. Independently from other known markers like gender, age, and comorbidities, ACE2 common SNPs in the population might modulate COVID-19 infection severity.

Keywords: Polymorphisms in genes (ACE, ACE2, AGTR1), Covid-19

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تعدد الأشكال في الجينات(ACE، ACE2، AGTR1) وشدة مرض كوفيد-19

زيد محمد جاسم

الملخص

يصيب فيروس SARS-Cov-2 البشر ويسبب مرضًا شديد التنوع ولا يمكن التنبؤ به في شدته. قد تكون القابلية العالية للعدوى أو الاستجابة الالتهابية المبالغ فيها نتيجة لتعدد أشكال النوكليوتيدات المفردة الجينية المتكررة (SNPs) في مجتمع ما. يحتاج SARS-CoV-2 إلى بروتين ACE2 لدخول الخلية، ويتحكم ACE2 في نظام الرينين أنجيوتنسين. لذلك، تم دمج 8 SNPs من جينات AGTR1 وACE2 وACE، وهي أول مجموعة موثوقة من فيروس SARS-Cov-2.الطُرق : تم تقسيم 318 شخصًا من مرضى كوفيد-19 (62,6٪ للرجال)، الذين تتراوح أعمارهم بين 59.6 و17.3 عامًا، وفقًا لشدة أعراضهم. وكان هؤلاء المرضى الخارجيين (ن = 104، 32.7٪)، والمستشفيات في الأجنحة (ن = 73، 23.0٪)، وحدة العناية المركزة (ن = 84، 26.4٪)، والمتوفين (ن = 57، 17.9٪). البيانات التي تتحدث بها عن مرض السكري وارتفاع ضغط الدم والسمنة والسرطان والسرطان هي ingesamel om aanpassing te maak. إن التكاثر الوراثي للعديد من الـ SNPs في مجموعة متنوعة من الكائنات الحية أمر مطلوب.النتائج يتم مطابقة العناصر الأربعة مع العديد من SNPs في ACE2. يُظهر هذا rs2074192 و rs1978124 تأثيرًا وقائيًا، وهو نموذج سائد للهيكل في الميراث (G/A مقابل GG-AA، OR = 0.32، 95٪CI = 0.12–0.82 ؛ p = 0.016) en A/G =، AA-GG مقابل OR = 0.37، 95% CI = 0.14–0.96؛ p = 0.038). يبدو الأمر جيدًا كما هو موضح في rs2106809 وrs2285666، حيث أن الرائحة الكريهة (OR = 1,47)، والشيخوخة الذكورية (OR = 1,98) والمرض المصاحب com.getoon(OR = 2,52) . زيادة المخاطر الكبيرة لوحدة العناية المركزة في إجراء العيادات الخارجية. يتغذى متعدد المتغيرات على الأنماط الجينية الضارة (ACE2) بسبب كوفيد19 بشكل مكثف (نسبة الأرجحية: 0.31، أو: 0.37 من RS2074192 وRS1978124، أو: 2.67، أو: 2.70 من RS2106809 وRS2285666، على التوالي). في المجموعة التي تم إدخالها إلى المستشفى لإجراء I/D SNP في ACE، لم يكن هناك توازن هاردي-وينبرغ (P <0.05)، والذي قد يكون مرتبطًا بالمرض. دراسات متعددة المتغيرات لا تحتوي على عدوى كوفيد-19 متعددة الاستخدامات AGTR1 SNPs، ولكنها تحتوي على النمط الجيني A/A rs5183 الذي يعاني من أمراض مصاحبة أكثر شيوعًا في المستشفى الذي تطلبه، الاستنتاجات المرضى الذين أصيبوا بكوفيد-19 في دورة سريرية حقيقية ومتطورة، هي أكبر من المتغيرات الجينية المختلفة في ACE2. بشكل مستقل عن العلامات المعروفة الأخرى مثل الجنس والعمر والأمراض المصاحبة، قد تعدل ACE2 SNPs الشائعة في السكان من شدة الإصابة بـCOVID-19.

كلمات مفتاحية : الأشكال في الجينات(ACE، ACE2، AGTR1) ، كوفيد-19

Introduction

Certous patients contract the SARS-CoV-2 virus, which causes a severe and fatal infection; this is mostly, but not exclusively, in elderly people with significant preexisting conditions. One of the most reliable markers of mortality is hypertension [1, 2]. Angiotensin converting enzyme inhibitors or angiotensin II receptor blockers might help with the first phase of viral infection because SARS-CoV-2 needs the ACE2 protein to enter the cell membrane [3]. Daarbenewens is daar 'n verband tussen hypertensive patients se hoër risiko van komplikasies.

However, it is possible that these same medications might be beneficial during the inflammatory stage of the disease. Daar is bewyse dat veranderinge in die ekspressie van ACE, ACE2, en AGTR1 veroorsaak word deur langdurige behandeling met angiotensin system agentsis [3–5]. As 'n manier om die virale SARS-CoV-2 load in die pneumocytes te verminder, kan 'n mens probeer om dit in ander organe te keer deur ACE2 te blokker [6]. In teenstelling hiermee kan die inhibition van ACE2 in COVID-19 pasiënte wat reeds geïnfekteer is skadelik wees as gevolg van 'n afname in die produksie van angiotensin 1–7, wat bekend is vir sy anti-inflammatory en antifibrotic eienskappe via its receptor (MasR) [7–9]. The SARS-Cov-2 virus infects humans and causes a disease that is extremely variable in severity and unpredictable. Daar is individue wat heeltemal asimptomaties is, terwyl ander, na 'n reeks infeksies en inflammatoriese prosesse, begin simptome toon. gaan deur angs, mikrovaskulêre trombose en dood van meer as een organ [10]. There is a lot of unexplained variability, in spite of the prognostic factors that have been identified [11]. The presence susceptibility to infeksie, 'n hoër efficiency van viral replication, of 'n oormatige inflammatory response kan almal veroorsaak word deur die algemeen voorkomende polymorphic genetic variants in die populasie. [12], rs2074666) and AGTR1 (rs5183, rs5185, rs5186) genes could affect the likelihood of infection, the spread to different organs, and the degree of COVID-19 clinical presentations [13, 14]. Gevolglik was ons doelwit om die verbande tussen die polymorfismes van agt AGTR1, ACE2 en ACE gene en die erns van die siekte wat deur die SARS-Cov-2 virus veroorsaak, te ondersoek.

Methods

Research ethics considerations

The study was conducted in line with the principles of the 1975 Declaration of Helsinki and was approved by the Ethics and Scientific Committees of all the institutions participating in it. These institutions include Hospital Universitario Virgen de la Arrixaca, BIOBANC-MUR (Murcia), Biobank Hospital Universitario y POLITÉCNICO la Fe (Valencia), Biobank Hospital Universitario de A Coruña (A Coruña), Biobank Hospital Universitario Puerta de Hierro Majadahonda (Madrid), and Biobank Hospital Clínico San Carlos (Barcelona). Informeed written consent was verkry van elke pasiënt of hulle familielede.

Study subjects

In die studie was 318 COVID-19-proewe wat 'n positiewe polymerase chain reaction (PCR) toets ondergaan het om die SARS-Cov-2 virus te identifiseer. Die PCR-toets is uitgevoer met behulp van 'n Real Time Multiplex RT-PCR (Detection for 3 Genes) kit wat deur Shanghai ZJ Bio-Tech Co., Ltd. gemaak is. (BioRad) en

die Liferiver se CFX96 Touch Real-Time PCR Ontdekkingstelsel. Die pasiënte is in vier groepe verdeel: diegene wat herstel het, diegene wat op die wards was, diegene wat in die intensiewe sorgeenheid was, en diegene wat gesterf het as gevolg van 'n infeksie of sy komplikasies. Patiente is gekies op grond van hoeveel biobanks in elkeen van die vyf deelnemende centers beskikbaar was, met die doel om ten minste.

DNA is onttrek uit 400 µl of peripheral blood samples using the Maxwell1-16 Blood DNA Purification Kit (Promega). Die PCR protokol is gebruik om die I/D polymorphism in ACE te ondersoek. Dit het begin met 'n 5 minute denaturation by. PCR-reaksies is uitgevoer in 'n eindelike volume van 25 milliliter wat 2 milliliter van DNA bevat het, met behulp van 'n touchdown PCR protokol. Die eerste was denaturation vir vyf minute by 94 grade Celsius, gevolg deur tien touchdown cycles (met 'n 0.2 °C afname in annealing temperatuur elke cycle) en dertig standaard cycles: denaturation vir een minute by 94 grade Celsius, primer annealing vir 35 minute by 62 grade Celsius en primer extension vir 30 minute by 72 grade Celsius The final cycle was followed by an incubation period of five minutes at a primer extension temperature of 72 degrees Celsius. They were then sequenced and purified on a DNA 3500XL Genetic Analyzer from Applied Biosystems.

SNPs in genes of renin-angiotensin system included in the study Different SNPs

was gekies op grond van vorige navorsing waarin hulle geassosieer is met sterftesyfers in pneumonia of acute respiratory distress syndrome as gevolg van die I/D polymorphism in ACE [15, 16]. 'n Aantal SNPs in ACE2 is ondersoek as risikofaktore vir hypertension en hart failure; rs2106809, 'n belangrike predictor of the response to

Table 1. Different SNPs of renin-angiotensin system included in this study.

Chr	Gen	Locus	rs	Variant	Type	MAF (gnomAD)
X	ACE2	NG_012575	rs2074192	g.42403G>A	Intron	0.42428
			rs1978124	g.7130A>T	Intron	0.37498
			rs2106809	g.7132T>C	Intron	0.19141
			rs2285666	g.14845G>A	Intron	0.280049
3	AGTR1	NG_008468	rs5183	NG_008468.1:g.49227A>G NM_000685.4:c.1062A>G	Synonymous Variant	0.061514
			rs5185	NG_008468.1:g.49315T>G	3' UTR	0.026048
				NM_000685.4:c.*70 =		
			rs5186	NG_008468.1:g.49331A>C	3' UTR	0.227483
				NM_000685.4:c.*86 =		
17	ACE	NG_011648	rs4646994[a]	Intrón 16	Intron	[b] II 48.1%
			I/D 287 pb			ID 40.5%
						DD 11.5%

Daar is ook 'n verband tussen antihypertensive behandeling met ACE inhibitors [17] of rs2074192 and rs2106809 en die risiko van left ventricular hypertrophy [18]. Furthermore, rs2285666 SNP is onlangs gekoppel aan 'n laer COVID-19 infection and case-fatality rate in Indian communities [19]. AGTR1 se rs5186 (C) allele is gekoppel aan 'n groter waarskynlikheid om essential hypertension te ontwikkel [20, 21]. Gender en ouderdom kan ook die risiko van AGTR1 SNPs en hul rol in hypertension en verwante toestande beïnvloed [22]. The frequencies of the various SNPs from the renin-angiotensin system (RAS) that were included in this study are shown in Table 1.

Statistical and bioinformatics analysis

The two-test was used to evaluate the Hardy-Weinberg equilibrium (HWE). I/D polymorphism in ACE het nie HWE bereik nie, so dit is uit die navorsing verwyder. In die outpatientgroep was $p>0.05$. Because the ACE2 gene is on the X chromosome, SNPs from ACE2 males and females were studied separately. Genotypes van elke pasiënt is gebruik om alle frekwensies te bepaal. Genotypes se variasie in frequency distribution sowel as demographic kenmerke soos gender, age en comorbidities is ondersoek met behulp van 'n Pearson chi-square test of Fisher's exact probability (for categorical variables). Die krag van die vereniging is bepaal deur gebruik te maak van odds ratios (ORs) en 95 persent. vertroue intervalle (CI). SNPStats (https://www.snpstats.net/start.htm) is gebruik om elkeen van die sewe SNPs se individuele genetikamodelle te ondersoek, insluitend dominant, recessive, co-dominant, overdominant, en log additive inheritance models. Assumptions about the genetic effect vary from model to model. Additionally, the expectation maximization algorithm was used to determine haplotype frequencies for ACE2 and AGTR1 using SNPStats [25]. SPSS 23.0 (IBM, Chicago, USA) was gebruik vir statistiese analyses. Multivariable analyses wat age, gender en comorbidities van SNPs ingesluit het, is gebruik om die forest-plot te skep.As $p<0.05$, was the statistical tests considered significant. In silico program Mutation Taster is gebruik om die moontlike impak van elke SNP op die funksionele protein te ondersoek. [26].

Results

General characteristics of the study subjects

vertroue intervalle (CI). SNPStats (https://www.snpstats.net/start.htm) is gebruik om elkeen van die sewe SNPs se individuele genetikamodelle te ondersoek, insluitend dominant, recessive, co-dominant, overdominant, en log additive

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Prediction of functional impacts of SNPs on protein function and stability

In Intron 2, there are rs1978124 and rs2106809, and in Intron 3, there are rs2285666 and rs2074192. By gebruik van in silico software Mutation Taster [26], is 'n ontleding van these four SNPs in ACE2 gene uitgevoer om te bepaal hoe hulle die splicingproses beïnvloed. As gevolg hiervan het ACE2 function getoon dat rs2074192 'n groter donor site veroorsaak en dat 'n verandering in die eienskappe van die protein kan plaasvind. As gevolg hiervan het rs 1978124 en rs2285666 gelei tot die skepping van 'n nuwe donorspliceplek. Rs2106809 het geen potensiële impak op splicing getoon nie.

Table 2. Characteristics of each group of patients included in the study.

		Total (n = 318)	Outpatients (n = 104)	On the wards (n = 73)	Intensive Care Unit (n = 84)	Deceased (n = 57)	P value	Hospitalized[b] (n = 214)	P value	ICU + deceased (n = 141)	P valu
Age (mean ±SD)		59.6±17.3	52.7±17.5	60.1±16.4	57.6±13.5	74.6±14.0	<0.0001	63.1±16.2	<0.0001	64.6±16.0	<0.00
Gender[a]	Male	198 (62.3%)	59 (56.7%)	43 (58.9%)	65 (77.4%)	31 (54.4%)	0.007	139 (65.0%)	0.175	96 (68.6%)	0.080
	Female	119 (37.4%)	45 (43.3%)	30 (41.1%)	18 (21.4%)	26 (45.6%)		74 (34.6%)		44 (31.4%)	
Comorbidities		196 (63.6%)	48 (50.5%)	49 (67.1%)	52 (62.7%)	47 (82.5%)	0.001	148 (69.5%)	0.002	99 (70.7%)	0.002
Hypertension		105 (34.1%)	19 (20.4%)	31 (43.1%)	27 (32.5%)	28 (49.1%)	0.001	86 (40.4%)	<0.0001	55 (39.3%)	0.003
Diabetes		44 (14.3%)	4 (4.3%)	11 (15.3%)	17 (20.5%)	12 (21.1%)	0.005	40 (18.8%)	<0.0001	29 (20.7%)	<0.00
Obesity		40 (13.0%)	5 (5.4%)	19 (26.4%)	8 (9.6%)	8 (14.0%)	0.001	35 (16.4%)	0.006	16 (11.4%)	0.161
Chronic lung disease		27 (8.8%)	5 (5.4%)	10 (13.9%)	9 (10.8%)	3 (5.3%)	0.172	22 (10.3%)	0.191	12 (8.6%)	0.444
Cancer		29 (9.4%)	7 (7.5%)	8 (11.1%)	5 (6.0%)	9 (15.8%)	0.212	22 (10.4%)	0.528	14 (10.0%)	0.642

[a]n = 1 missing gender.
[b]Hospitalized = hospitalized on the wards + ICU + deceased patients. ICU: intensive care unit.

Daarbenewens kan die AGTR1 funksion deur RS5183, RS5185 en RS5186 SNPs beïnvloed word. Rs5185 en Rs5186 SNPs is in die 3'UTR gebied en lei tot twee nuwe donor splice sites en meer acceptor en donor splice sites, respectively. Rs5183 kom by die einde van die codifying area met geen aminoacid verandering en lei tot 'n groter acceptor splice site.

The association between ACE2 and AGTR1 SNPs and hospitalization risk

Volgens Table 3 en S2 Table, drie ACE2 SNPs, rs2074192, rs2106809, en rs2285666, was daar 'n verband tussen hospitalisering van vroue en hospitalisering. In die log-additive en recessive models of inheritance, rs2074192 het 'n protector-effekte getoon, aangesien rs2074192 in 'n overdominant model van inheritance gevind is [(OR = 2.12, 95% CI: 1.00–4.52; p = 0.0 Rs2074192 het 'n significante verband tussen die G/A genotype en 'n laer risiko van hospitalisering getoon (OR = 0.40, 95%CI: 0.17–0.92; p = 0.029). There was no evidence of a connection between the different AGTR1 SNPs and the COVID-19 patent setting (outpatient versus hospitalized) disease.

The association between ACE2 and AGTR1 SNPs and severity of the disease (outpatiens vs ICU+deceased)

Daar moet in ag geneem word dat, in die woorde van sommige pasiënte, die rede vir hospitalisering dalk nie net die ernst van die COVID-19-infeksie nie, maar eerder die verwachte "a priori" risiko van

Table3.GenotypeandallelefrequenciesofACE2andAGTR1SNPsinhospitalizedandnon-hospitalizedCOVID-19cases.

Locus	Model	Genotype	Outpatients (n = 104)	Hospitalized (n = 214)	Odds Ratio	p-value
ACE2 FEMALE (n = 119, adjusted by age + comorbidities)						
rs2074192	Overdominant	G/G-A/A	14 (31.1%)	41 (56.2%)	1.00	**0.029**
		G/A	31 (68.9%)	32 (43.8%)	0.40 (0.17–0.92)	
rs1978124	Overdominant	A/A-G/G	22 (48.9%)	45 (61.6%)	1.00	0.13
		A/G	23 (51.1%)	28 (38.4%)	0.53 (0.23–1.21)	
rs2106809	Log-additive				2.12 (1.00–4.52)	**0.039**
rs2285666	Recessive	G/G-G/A	43 (97.7%)	66 (89.2%)	1.00	**0.048**
		A/A	1 (2.3%)	8 (10.8%)	6.56 (0.71–60.20)	
ACE2 MALE (n = 190, adjusted by age + comorbidities)						
rs2074192	---	G/G	33 (64.7%)	87 (62.6%)	1.00	0.86
		A/A	18 (35.3%)	52 (37.4%)	1.06 (0.52–2.17)	
rs1978124	---	G/G	26 (51%)	74 (53.2%)	1.00	0.68
		A/A	25 (49%)	65 (46.8%)	0.87 (0.44–1.71)	
rs2106809	---	T/T	43 (84.3%)	103 (74.1%)	1.00	0.24
		C/C	8 (15.7%)	36 (25.9%)	1.68 (0.70–4.05)	
rs2285666	---	G/G	44 (86.3%)	108 (77.7%)	1.00	0.29
		A/A	7 (13.7%)	31 (22.3%)	1.62 (0.64–4.10)	
AGTR1 (n = 309, adjusted by age + gender + comorbidities)						
rs5183	Recessive	A/A-A/G	96 (100%)	212 (99.5%)	1.00	0.21
		G/G	0 (0%)	1 (0.5%)	NA (0.00-NA)	
rs5185	---	T/T	95 (99.0%)	210 (98.6%)	1.00	0.7
		T/G	1 (1%)	3 (1.4%)	1.59 (0.14–17.53)	
rs5186	Log-additive				0.72 (0.48–1.08)	0.12

In hierdie afdeling van die artikel presenteer ons genotype distributions van diverse SNPs in die groepe "outpatients" (n = 104) en "ICU + deceased" (n = 141). Table 2 toon die clinical characteristics of the two patients groups. In the combined ICU plus deceased group was the age and percentage of patients with comorbidities aansienlik higher. Die mees algemene was hypertension en diabetes. comorbidities wat verband hou met die risiko van admission to the ICU or death. In both the outpatient female group and the female group with higher disease severity, there was a relationship between the various ACE2 SNPs. Daar is vergelykings gemaak tussen (ICU + oorlede persoon) groter risiko van ICU-opname of dood gehad. Die AGTR1 SNP genotype distribution did not show any significant differences in disease severity between the different groups.

Interaction analysis with comorbidities

As verwag, het mense met comorbidities 'n groter kans om in die hospitalization group te wees. Maar die interaction analysis het getoon dat sekere genotypes die sterkte van hierdie verband beïnvloed het. In the more severe outpatient group, some genotypes in certain SNPs were more common (S4 Table). In females met rs2074192, 'n G/A genotype (OR = 0.13, 95% CI: 0.03–0.52, p = 0.019), het 'n SNP genotype Interaksienavorsing oor genotipes en comorbiditeite in ACE2 het getoon dat dit 'n beskermende faktor bied vir pasiënte sonder ander komplikasies (S4 Table). Vroue met 'n G/A genotype vir rs2074192 en comorbiditeit het egter 'n groter risiko gehad om hospitalisasie te ondergaan (OR = 1.27, 95% CI: 0.22–7.19, p <0.0001). As gevolg van 'n p-waarde van 0.0074, was these interactions between comorbidities and the genotype in rs2074192 of ACE2 more apparent among the female outpatients in comparison to the ICU + deceased group.

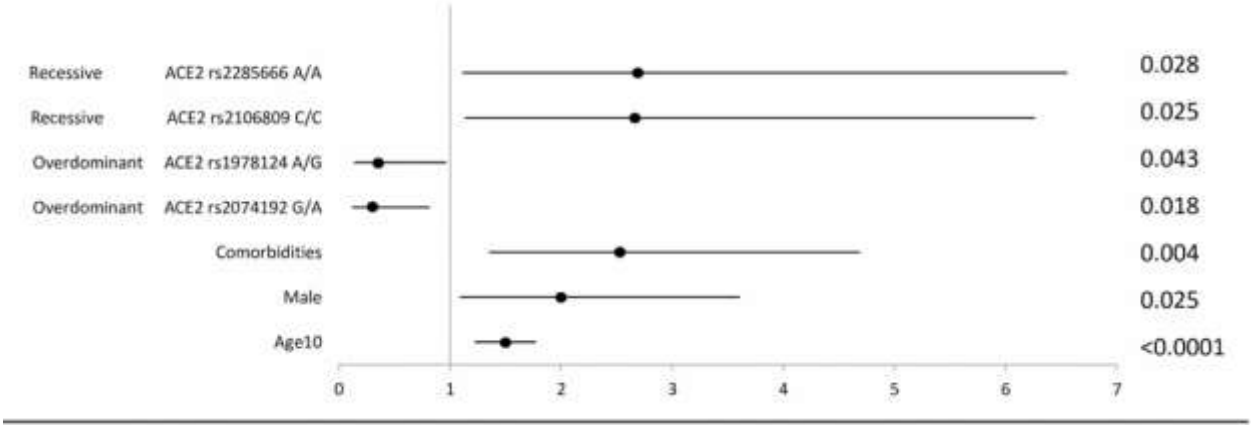

Fig 1. Forest plot of different covariates included in the association study of selected SNPs for estimation of OR of ICU+deceased vs outpatient individuals. The horizontal lines correspond to the study specific OR and 95% CI. Each of the

SNPs were included separately in different models with age(10), gender and comorbidities as covariates. Age(10) represents OR per 10 years increase.

Table4.GenotypeandallelefrequenciesofACE2andAGTR1SNPsinoutpatientsandICU+deceasedCOVID-19cases.

Locus	Model	Genotype	Outpatients (n = 104)	ICU+deceased (n = 141)	OR (95% CI)	P-value
ACE2 FEMALE (n = 88, adjusted by age + comorbidities)						
rs2074192	Overdominant	G/G-A/A	14 (31.8%)	26 (59.1%)	1.00	**0.016**
		G/A	30 (68.2%)	18 (40.9%)	0.32 (0.12–0.82)	
rs1978124	Overdominant	A/A-G/G	20 (46.5%)	30 (68.2%)	1.00	**0.038**
		A/G	23 (53.5%)	14 (31.8%)	0.37 (0.14–0.96)	
rs2106809	Recessive	T/T-T/C	42 (97.7%)	37 (84.1%)	1.00	**0.012**
		C/C	1 (2.3%)	7 (15.9%)	11.41 (1.12–115.91)	
rs2285666	Recessive	G/G-G/A	43 (97.7%)	37 (84.1%)	1.00	**0.0081**
		A/A	1 (2.3%)	7 (15.9%)	12.61 (1.26–125.87)	
ACE2 MALE (n = 147, adjusted by age + comorbidities)						
rs2074192	---	G/G	53 (64.7%)	63 (65.6%)	1.00	0.91
		A/A	18 (35.3%)	33 (34.4%)	0.96 (0.43–2.10)	
rs1978124	---	A/A	26 (51%)	50 (52.1%)	1.00	0.68
		G/G	25 (49%)	46 (47.9%)	0.86 (0.41–1.81)	
rs2106809	---	T/T	43 (84.3%)	70 (72.9%)	1.00	0.16
		C/C	8 (15.7%)	26 (27.1%)	1.93 (0.75–4.96)	
rs2285666	---	G/G	44 (86.3%)	73 (76%)	1.00	0.22
		A/A	7 (13.7%)	23 (24%)	1.82 (0.68–4.86)	
AGTR1 (n = 235, adjusted by age + gender + comorbidities)						
rs5183	---	A/A	87 (90.6%)	122 (87.8%)	1.00	0.67
		A/G	9 (9.4%)	17 (12.2%)	1.24 (0.46–3.32)	
rs5185	---	T/T	95 (99%)	138 (99.3%)	1.00	0.83
		T/G	1 (1.1%)	1 (0.7%)	0.71 (0.03–17.17)	
rs5186	Log-additive				0.73 (0.47–1.15)	0.17

Discussion

Volgens hierdie studie was daar 'n verband tussen swak resultate in COVID-19 disease en comorbidities, older age, and male gender [27]. Kouhpayeh HR et al. (2021) het getoon dat COVID-19-pasiënte met ernstige toestande meer geneig is om diabetes en hypertension te hê as mense sonder ernstige toestande [28]. In 'n poging om te vergelyk, is verskillende grade van severiteit geskep, wat wissel van outpatients, hospitalisasie, ICU-opnames en dood. As gevolg van polymorphisms in the ACE2 and AGTR1 genes, was daar interessante verbande tussen die ernst van die aandoening en die moontlikheid van clinical stratification. Die doel van ons studie was om te bepaal of algemene genetiese veranderinge in belangrike RAS-genes die uitkomste van COVID-19-infeksies beïnvloed. Ons studie het getoon dat 'n paar SNPs in ACE2 verband hou met COVID-19 siekte. Die genotype frekwensies van rs2074192 and rs1978124 SNPs waargeneem vir vroue wat heterozyg is, dui op 'n beskermende effek. Dit is belangrik om te noem dat ACE2 op die X-chromosome is, wat veroorsaak dat heterozygosity in mans onmoontlik is. As gevolg hiervan kan daar 'n verband tussen die swak resultate wat in mans gesien is, en SNPs in hul enkele kopie wees [29]. Furthermore, when the When the outpatient group and the group of higher severity (ICU + deceased) compared, was daar 'n korrelasie tussen die verskillende ACE2 SNPs en 'n groter risiko van hospitalisering (Table 3). ACE2 is betrokke by die balansering van die

stelsel. in wat malfunctioning met verskeie siektes geassosieer is [30]. Dit sluit hypertension, myocardial infarction, hartversaking, acute lung injury en diabetes mellitus in. Baie studies het getoon dat ACE2 polymorphisms sterk verband hou met hypertension in mense, veral in Chinese vroue met essential hypertension of metabolic syndrome [30]. As gevolg hiervan, saam met die biochemiese data, word ACE2 as 'n negatiewe RAS-regulator geïdentifiseer, wat beteken dat dit Angiotensin II afbreek om Angiotensin When the outpatient group and the group of higher severity (ICU + deceased) compared, was daar 'n korrelasie tussen die verskillende ACE2 SNPs en 'n groter risiko van hospitalisering (Table 3). ACE2 is betrokke by die balansering van die stelsel. in wat malfunctioning met verskeie siektes geassosieer is [30]. Dit sluit hypertension, myocardial infarction, hartversaking, acute lung injury en diabetes mellitus in. Baie studies het getoon dat ACE2 polymorphisms sterk verband hou met hypertension in mense, veral in Chinese vroue met essential hypertension of metabolic syndrome [30]. As gevolg hiervan, saam met die biochemiese data, word ACE2 as 'n negatiewe RAS-regulator geïdentifiseer, wat beteken dat dit Angiotensin II afbreek om Angiotensin verbind nie. and the COVID-19 clinical course on 155 patients [35]. In teenstelling hiermee het Srivastava et al. (2020) ontdek dat daar 'n verband was tussen Rs.2285666 en 'n afname in infeksie- en sterftekoerse in Indië [19]. Daar is ook gevind dat allele A van rs2285666 die splice site beïnvloed, wat serum ACE2 proteinvlakke verhoog [36]. Volgens ons resultate het ons navorsing 'n verband tussen hierdie variant en die intensiteit van COVID-19-simptome in vroue getoon (OR = 12.61, 95% CI: 1.26–125.87, p = 0.0081). AGTR1, wat op die chromosome is, kodeer die angiotensin type 1 receptor. 3 q24 Angiotensine II, 'n vasopressorhormoon, beheer groei en hiperplasia, vascular cell migration and the expression of pro-inflammatory genes. Dit ondersteun hoofsaaklik vasgespanne spiere deur AGTR1. It is noodsaaklik vir die handhawing van bloeddruk en cardiovascular homeostasis. As gevolg van 'n verskeidenheid pathological toestande, is daar bewyse van verhoogde tissuevlakke van Angiotensine II. Dit toon dat Angiotensine II 'n belangrike rol speel in die ontwikkeling van hypertension, kidney disease, en cardiovascular diseases, insluitend myocardial infarction en arteriosclerosis [37, 38]. Die resultate van ons studie het geen beduidende verskille in die SNP-frekwensies van AGTR1 genotypes getoon nie. Daar is ook geen verband gevind tussen die groep mense wat in die hospitaal was en die ernst van die siekte nie. Nevertheless, there were notable variations in A/A genotype frequencies in AGTR1 rs5183. in terme van die risiko van hospitalisering tussen die groepe met en sonder comorbidities. Dit dui daarop dat hypertension of diabetes in individue met 'n sekere genotipe die COVID-19-infeksie kan vererger.

Angiotensin II, die hoofeffektor van RAS, help met die begin en ontwikkeling van vaskulêre senescence, wat vaskulêre toestande met ouderdom veroorsaak [39]. Die AGTR1 receptor beheer die nadelige effek. Two SNPs (rs422858 and rs275653) in the AGTR1 promoter was linked to low protein levels and to very oldness, suggesting their role in aging and diseases associated with age. [40]. ACE I/D polymorphism [41], obesity [42], and hypertension have been linked to higher serum ACE levels. [43], 'n verhoogde waarskynlikheid van kardiovaskulêre siektes [44] en thrombophilia [45]; al hierdie kliniese simptome is geassosieer met 'n meer agressiewe COVID-19-infeksie.In die hospitaalgroep van ons studie het die I/D polymorphism in ACE nie HWE getoon nie. Dit kan die gevolg wees van die verband tussen die situasie en die individu se gesondheid.. Patiente met COVID-19 met 'n DD genotype in ACE het 'n groter waarskynlikheid om hospitalisasie te ondergaan (OR = 2.97, 95% CI: 1.23–7.17; $p<0.05$).Wanneer die vier groepe van elke ernst ondersoek is, was daar ook 'n merkwaardige verband tussen D/D-groepe en die oorlede groep. gevolglik [28]. Daar is ook bevind dat D/I polymorphism in ACE verband hou met ACE2 proteinvlakke in lung tissue. Dit dui daarop dat SARS-CoV-2 se aansteeklikheid kan verander [47].Ten spyte van die feit dat subgroepstudies getoon het dat daar 'n verband was tussen sekere polymorphisms in ACE en AGTR1 en severiteit, het multivariable studies geen konsistente resultate gebring nie. to definitively identify the function of ACE and AGTR1 polymorphisms in COVID-19

Conclusions

As 'n faktor van verdediging vir vroue, is heterozygosity van rs2074192 and rs1978124 SNPs in ACE2 gekoppel aan die erns van die siekte veroorsaak deur SARS-CoV-2. Daarteenoor is die C/C genotype van rs2106809 en die allele A van rs2285666 in ACE2 faktore van risiko in COVID-19-pasiënte. In patients met COVID-19 en comorbidities is daar 'n verband tussen die verskillende SNPs van ACE2 and rs5183 AGTR1.

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