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Original Article

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Renin-Angiotensin System Genes Polymorphisms in Patients With COVID-19 and Its Relation to Severe Cases of SARS-CoV-2 Infection

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Abstract

Background: Different variants of single nucleotide polymorphisms (SNPs) of angiotensinogen (AGT), angiotensin-converting enzyme type 1 (ACE1), and angiotensin II receptors type 1 (AGTR1) and 2 (AGTR2) genes determine different susceptibility to cardiovascular disease (CVD) and hypertension, which can be considered as risk factors for fatal outcomes among coronavirus disease 2019 (COVID-19) patients. The objective of our study was to assess the relation between the frequency of SNPs of the renin-angiotensin system (RAS) components, and the severity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Methods: The cross-sectional study included 100 patients with a laboratory-confirmed diagnosis of COVID-19 admitted to the hospital. Criteria for severe COVID-19 included respiratory rate (RR) > 30/min, blood oxygen saturation (SpO_2) ≤ 93%, signs of unstable hemodynamics with systolic blood pressure (SBP) < 90 and/or diastolic blood pressure (DBP) < 60 mm Hg. All patients were identified with alleles and genotypes of the polymorphic markers rs4762 of the AGT gene, rs1799752 of the ACE1 gene, rs5186 of the AGTR1 gene and rs1403543 of the AGTR2 gene using the polymerase chain reaction method in human DNA preparations on real-time CFX96C1000 Touch, Bio-Rad equipment (Syntol, Russia). Statistical analysis was performed in R v.4.2.

Results: Patients were divided into groups with severe (n = 44) and moderate COVID-19 (n = 56). For ACE1 rs1799752, a significant deviation from the population distribution was detected in both studied subgroups. A higher frequency of the C allele SNP rs5186 AGTR1 gene was detected in the group with severe disease. More frequent A/A genotype of SNP rs1403543 AGTR2 was detected among females with severe COVID-19. Haplotype analysis revealed more common DCG haplotype among patients with severe COVID-19. The odds ratio for severe COVID-19 in the presence of the DCG haplotype was 3.996 (95% confidential interval: 1.080 -14.791, P < 0.05).

Conclusions: Our data suggest that the SNP genes of the RAS components, may allow to identify groups of patients predisposed to a more severe course of COVID-19.

Keywords: COVID-19; SARS-CoV-2 infection; Single nucleotide polymorphisms; Angiotensinogen gene; Angiotensin-converting enzyme type 1 gene; Angiotensin II receptor type 1 gene; Angiotensin II receptor type 2 gene

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Introduction

Disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to the 2020 - 2022 coronavirus pandemic with high morbidity and mortality, introduction of total quarantine measures, social and economic collapse. Despite the official announcement by the World Health Organization of the end of the global pandemic, the morbidity of coronavirus disease 2019 (COVID-19) remains at a high level. The relation between the cardiovascular risk factors, cardiovascular diseases (CVDs), and all-cause in-hospital mortality in patients with COVID-19 is well established [1-3]. Thus, according to meta-analyses made by Dessie et al [4] and Degarege

et al [5], CVD, diabetes, and hypertension can be considered as risk factors for fatal outcomes among COVID-19 patients.

The relevance of the association between COVID-19 and CVDs might be explained by the pathogenesis of the coronavirus infection. The key factor for SARS-CoV-2 entering the cells is angiotensin-converting enzyme type 2 (ACE2) with participation of transmembrane serine proteases type II. ACE2 is a transmembrane protein involved in the breakdown of angiotensin II (1-8) to form angiotensin (1-7). It has the properties of a vasodilator and a functional angiotensin II antagonist [6]. A decrease in ACE2 activity due to various reasons leads to the activation of other components of the renin-angiotensin system (RAS) with all its pathologic consequences such as activation of inflammation, thrombogenic potential, and oxidative processes [6].

The genetic heterogeneity of RAS components is well known. Different variants of single nucleotide polymorphisms (SNPs) of angiotensinogen (AGT), angiotensin-converting enzyme type 1 (ACE1), and angiotensin II receptor types 1 and 2 (AGTR1 and AGTR2) genes determine different susceptibility to CVDs and hypertension. The most studied is I/D polymorphism in ACE1 rs1799752, for which a significant association with the prevalence and severity of the course of CVDs has been shown [7]. There are data on the association of T/T and C/T genotypes of the AGT rs4762 gene [8, 9], C/C and T/T genotypes of the AGTR1 rs5186 gene [10, 11] with hypertension and preeclampsia. There are a few studies of RAS gene polymorphism in symptomatic patients with COVID-19 [12, 13] and in COVID-19-related retinopathy [14].

This work aims to assess the relation between the frequency of SNPs of the AGT, ACE1 genes, and AGTR1 and AGTR2, and the severity of SARS-CoV-2 infection.

Materials and Methods

The cross-sectional study included 100 Caucasian patients who were treated at the University Clinical Hospital No. 4 of Sechenov University with a laboratory-confirmed diagnosis of COVID-19 from November 2021 to February 2022. Written informed consent was obtained from all patients voluntarily joined the study. Research protocol was approved by the Locale Ethical Committee of Sechenov University. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Inclusion criteria for the study were patient age > 18 years and informed consent for the study. Exclusion criteria: acute coronary syndrome, acute cerebrovascular accident, pulmonary embolism, severe liver or kidney pathology (glomerular filtration rate (GFR) < 15 mL/min/1.73 m^2), hyperkalemia > 5.0 mmol/L, severe anemia, cancer. Patients underwent standard laboratory and instrumental examinations [15]. All patients were symptomatic.

The data on the severity of SARS-CoV-2 infection were taken from the discharge summaries. The severity of the coronavirus infection was assessed in accordance with the temporary guidelines of the Russian Ministry of Health. Criteria for severe COVID-19 included respiratory rate (RR) > 30/min, blood oxygen saturation (SpO_2) ≤ 93%, signs of unstable hemodynamics with systolic blood pressure (SBP) < 90 and/or diastolic blood pressure (DBP) < 60 mm Hg [15], which meet international criteria for the severity of COVID-19 [16]. The extent of pulmonary impairment was evaluated based on the established categorization according to the results of multi-slice spiral computed tomography (CT) of the chest: CT0 denotes the nonexistence of inflammation foci and infiltrates; CT1 signifies the manifestation of viral pneumonia symptoms, encompassing up to a quarter of the pulmonary tissue; CT2 corresponds to the breadth of lung impairment ranging from 25% to 50%; CT3 relates to the pulmonary tissue damage spanning from 50% to 75%; CT4 represents injury to over 75% of the pulmonary tissue.

All patients (n = 100) were identified with alleles and genotypes of the polymorphic markers rs4762 of the AGT gene, rs1799752 of the ACE1 gene, rs5186 of the AGTR1 and rs1403543 of the AGTR2 using the polymerase chain reaction method in the real-time in human deoxyribonucleic acid (DNA) preparations. They were obtained from venous blood using allele-specific TagMan probes on real-time CFX96C1000 Touch, Bio-Rad equipment. To isolate DNA from the analyzed material, a set of reagents DNA-EXTRAN-1 (Syntol, Russia) was used. As a result, alleles C and T, genotypes C/C, T/T, C/T were identified for the rs4762 polymorphic marker of the AGT gene; alleles I and D, genotypes I/I, D/D, D/I were identified for the polymorphic marker rs1799752 of the ACE1 gene; alleles A and C, genotypes A/A, C/C, A/C were identified for the polymorphic marker rs5186 of the AGTR1 gene; alleles G and A, genotypes G/G, A/A, G/A were identified for the polymorphic marker rs1403543 of the AGTR2 gene.

Statistical analysis was performed in R v.4.2. For categorical data, the proportions and absolute values were determined. Comparative analysis of quantitative variables was carried out using the Mann-Whitney U test, categorical and qualitative features using Pearson's Chi-square criterion, if not applicable, Fisher's exact test was used. The odds ratio (OR) was calculated to assess the link between genotypes and COVID-19 severity. The frequencies of SNPs rs1799752, rs5186, and rs1403543 were compared with the population prevalence of these genomes and alleles obtained in the study by Kuznetsova et al, 2004 about the distribution of genetic variants of the RAS genes in the East Slavic population [17]. Allele frequencies of SNPs rs4762 were compared with their prevalence in the European population obtained from the open database 1000 Genomes Browsers (A Deep Catalog of Human Genetic Variation) [18, 19]. Genome association analysis was performed using the SNPassoc library [20] and haplo.stats library [21]. For genotypes, the significance of the Hardy-Weinberg equilibrium (HWE) was calculated. Statistics were calculated for the whole group, depending on the severity and gender. Haplotype analysis included the estimation of frequencies in the whole sample and by severity (moderate or severe). Scores and significance were adjusted for age and gender.

Results

According to the severity criteria of COVID-19 (RR, SpO_2 and

Table 1. Main Clinical and Demographic Characteristics of Patients With COVID-19

	Total group (n = 100)	Severe course (n = 44)	Moderate course (n = 56)	P value
Age, years	58.5 (50.5 - 69.0)	59.5 (49.5 - 70.0)	56.5 (51.5 - 68.0)	0.409
Male gender, n (%)	49 (49)	21 (47.7)	28 (50)	0.778
Smoking, n (%)	13 (13)	5 (11.4)	8 (14.3)	0.522
SBP, mm Hg	125 (120 - 134)	129.5 (120 - 134.5)	125 (120 - 132)	0.661
DBP, mm Hg	80 (74 - 84)	80 (74.5 - 85)	80 (75 - 84)	0.883
HR, beats/min	80 (75 - 88.5)	84 (78.5 - 90.0)	80.0 (74.0 - 88.0)	0.154
BMI, kg/m^2	28.74 (24.84 - 32.49)	30.04 (26.22 - 32.87)	27.66 (24.64 - 31.62)	0.129
RR, /min	22 (21 - 23.5)	23 (22 - 24)	22 (21 - 22)	0.0004
SpO_2, %	94 (92 - 96)	92 (91 - 93)	96 (95 - 97)	< 0.0001
Glucose, mmol/L	6.11 (5.69 - 6.7)	6.22 (5.81 - 7.05)	6.07 (5.55 - 6.48)	0.105
TG, mmol/L	1.62 (1.15 - 2.22)	1.71 (1.21 - 2.53)	1.61 (1.11 - 2.09)	0.316
LDL-C, mmol/L	2.94 (2.37 - 3.84)	2.80 (2.19 - 3.87)	3.03 (2.57 - 3.70)	0.282
GFR, mL/min/1.73 m^2	75.8 (64.5 - 84.6)	78.4 (62.95 - 86.1)	73.6 (65.0 - 82.5)	0.483
CRP, mg/L	19.8 (7.0 - 50.55)	32,6 (19.1 - 80.8)	11.7 (4.9 - 29.6)	< 0.0001
Ferritin, µg/L	363.0 (7.0 - 50.55)	468.5 (271.0 - 894.5)	268.0 (148.0 - 492.0)	0.0004
D-dimer, mg/L	0.4 (0.29 - 0.62)	0.46 (0.29 - 0.74)	0.36 (0.29 - 0.56)	0.148
CT-grade pulmonary injury, %	25 (15 - 35)	30 (25 - 45)	20 (15 - 30)	0.0001
Concomitant diseases, n (%)				
Hypertension	69 (69)	30 (68.2)	39 (69.6)	0.760
Dyslipidemia	49 (49)	24 (54.6)	25 (44.6)	0.158
Obesity	43 (43)	21 (47.7)	22 (39.3)	0.200
Diabetes	4 (4)	2 (4.5)	2 (3.6)	0.734
CHD	12 (12)	6 (13.6)	6 (10.7)	0.522
CKD (GFR < 60 mL/min/1.73 m^2)	16 (16)	9 (20.5)	7 (12.6)	0.133
CHF	11 (11)	4 (9.1)	7 (12.5)	0.367

P values for the group of severe vs. moderate COVID-19. CHD: coronary heart disease; CHF: chronic heart failure; CKD: chronic kidney disease; CRP: C-reactive protein; CT: computed tomography; DBP: diastolic blood pressure; GFR: glomerular filtration rate; HR: heart rate; LDL-C: low-density lipoprotein-cholesterol; RR: respiratory rate; SBP: systolic blood pressure; SpO_2: average value of oxygen saturation measured with a pulse oximeter; TG: triglycerides.

hemodynamic instability), patients were divided into groups with severe (44 people) and moderate coronavirus infection (56 people). The main clinical and demographic characteristics of the groups are given in Table 1. Age, gender, levels of SBP, DBP, and heart rate (HR) of the groups did not differ. There were substantial differences between RR and SpO_2, that were explained by the group selection criteria. Along with this, patients with severe COVID-19 had higher concentration of C-reactive protein (CRP), ferritin, D-dimer, and CT-grade of pulmonary injury. The analysis of concomitant pathology did not reveal any significant differences in the frequency of comorbidities. Half of the patients, included in the study, took antihypertensives. Thirty-three percent (33%) of the whole group received anti-RAS drugs (either ACE inhibitors or angiotensin II receptor blockers): 34.1% in group with severe COVID-19 vs. 32.1% in moderate severe COVID-19 (P = 0.764).

The distribution of various genotypes and alleles frequency of the studied genes in patients with severe and moderate COVID-19 is presented in Table 2. The subgroups revealed the equal distribution of genotypes and alleles of SNP AGT rs4762 without deviation from the HWE. For SNP ACE1 rs1799752, a significant deviation from the HWE was detected in both studied subgroups. A predominance of D alleles of ACE1 polymorphism rs1799752 was revealed compared to the population data (D-allele 52.9%, I-allele 47.1% [16]): $\chi^2 = 17.73$, $P < 0.001$ for severe COVID-19 and $\chi^2 = 25.69$, $P < 0.001$ for moderate COVID-19. Groups with severe and moderate disease did not differ significantly in allele frequency of ACE1 rs1799752. Significant differences in the distribution of alleles and genotypes depending on the severity of COVID-19 were for SNP rs5186 of the AGTR1 gene. A higher frequency of the C allele was detected in the group with severe disease. The AGTR2 rs1403543 gene is in the X chromosome, and therefore the distributions of genotypes and alleles of this SNP were analyzed separately in males and females. A significant deviation in the distribution of SNP rs1403543 from the HWE was

Table 2. Frequency Distribution of Genotypes and Alleles of Studied Polymorphisms in Patients With Severe and Moderate COVID-19

			Severe (N = 44)	Moderate (N = 56)	χ^2 value and P value
AGT rs4762	Genotypes, %	C/C	72.8	78.6	2.246 0.325
		C/T	22.7	19.6	
		T/T	4.5	1.8	
	Alleles, %	C	84.15	88.4	0.374 0.415
		T	15.85	11.6	
	HWE, P		0.277	0.544	
ACE1 rs1799752	Genotypes, %	I/I	11.4	7.1	1.259 0.533
		I/D	15.9	14.3	
		D/D	72.7	78.6	
	Alleles, %	I	19.35	14.25	0.581 0.341
		D	80.65	85.75	
	HWE, P		0.004	0.008	
AGTR1 rs5186	Genotypes, %	A/A	52.3	69.6	9.341 0.009
		A/C	36.4	26.8	
		C/C	11.4	3.6	
	Alleles, %	A	70.4	83.0	4.705 0.031
		C	29.6	17.0	
	HWE, P		0.468	0.642	
AGTR2 rs1403543 males	Alleles, %	G	47.6	57.7	2.007 0.157
		A	52.4	42.3	
	HWE, P		0.000	0.000	
AGTR2 rs1403543 females	Genotypes, %	G/G	26.1	23.3	10.570 0.006
		G/A	56.5	40.0	
		A/A	17.4	36.7	
	Alleles, %	G	54.35	43.3	2.654 0.104
		A	45.65	56.7	
	HWE, P		0.572	0.454	

ACE1: angiotensin-converting enzyme type 1; AGT: angiotensinogen; HWE: Hardy-Weinberg equilibrium.

revealed in a male subgroup with both severe and moderate disease. In the female group with different severity of COVID-19, there was a significant difference in the genotype frequencies of SNP rs1403543 (Table 2).

Haplotype distribution analysis was performed using rs1799752, rs5186, and rs1403543 SNPs that demonstrated deviations from HWE, population distribution, and/or intergroup differences. Thus, nine variants of haplotypes were formed, and their frequencies are presented in Table 3. The DCG haplotype was significantly more common among patients with severe COVID-19. The distribution of other haplotypes did not differ significantly between subgroups. The ICG haplotype was the rarest and was not detected in patients with severe COVID-19 in the examined cohort. The OR for severe COVID-19 in the presence of the DCG haplotype was 3.996 (95% confidence interval (CI): 1.080 - 14.791, $P < 0.05$).

Table 3. Haplotype Analysis Performed on ACE1 rs1799752, AGTR1 rs5186, and AGTR2 rs1403543 SNPs and Their Corresponding Frequencies in Moderate (N = 56) and Severe (N = 44) COVID-19

Haplotypes			Frequencies			P value
rs1799752	rs5186	rs1403543	Total	Moderate	Severe	
D	A	A	0.2712748	0.3190880	0.2054829	0.0750527
I	A	G	0.0347194	0.0417922	0.0255644	0.6474502
D	A	G	0.3910026	0.4057926	0.3753691	0.7787819
I	A	A	0.0780032	0.0636843	0.0981290	0.5735669
D	C	A	0.1034446	0.0977041	0.1155361	0.4660593
I	C	A	0.0472774	0.0284521	0.0694884	0.2323572
D	C	G	0.0692780	0.0345580	0.1104301	0.0495588
I	C	G	0.0050000	0.0089286	NA	NA

ACE1: angiotensin-converting enzyme type 1; AGT: angiotensinogen; SNPs: single nucleotide polymorphisms.

Discussion

We studied the SNP of AGT rs4762, ACE1 rs1799752, AGTR1 rs5186 and AGTR2 rs1403543 genes in a cohort of 100 patients hospitalized with confirmed COVID-19. To identify relation between the frequency of SNP and the severity of COVID-19, we have formed two groups, depending on the severity of the disease: 44 patients with severe and 56 patients with moderate COVID-19.

We have shown a significantly higher frequency of I/D, D/D genotypes and the D-allele of the ACE1 rs1799752 gene among patients hospitalized with COVID-19 compared to the Russian population [17]. The ACE1 gene is in chromosome 17 (17q23.3). The nature of the ACE1 rs1799752 gene polymorphism is in the insertion (insertion, I) or loss (deletion, D) of the Alu repeat in 289 nucleotide pairs in the 16th intron. Deletion of the Alu repeat is accompanied by a significant increase in the expression of the ACE1 gene and a rise of ACE1 levels [22]. The increase in ACE1 levels occurs even in case of heterozygous status (I/D). The highest level is observed in patients with homozygous genotype D/D rs1799752, which is twice higher than in patients with genotype I/I. The relation between the D/D genotype and a wide range of CVDs, including coronary heart disease (CHD), heart attack, left ventricular hypertrophy, hypertension, kidney disease, and neurodegenerative diseases has been detected [23].

The second gene involved in the formation of RAS activity and demonstrated significant differences in the distribution of its polymorphic variants was the AGTR1 A1166C A>C gene (rs5186). The frequency of the C allele in our cohort was significantly higher in patients with severe COVID-19 - 29.6% vs. 17% in the group of moderate disease. The AGTR1 gene is in chromosome 3 (3q24) and encodes type 1 receptors for AT-II, located in the vascular endothelium and mediating the majority of angiotensin II cardiovascular effects. More than 50 polymorphic variants of the AGTR1 gene are known. The A1166C A>C (rs5186) polymorphism, which was studied in our work, has the greatest clinical significance. It is characterized by the replacement of the nucleotide adenine with cytosine at position 1166 of DNA. The presence of the mutant allele C in this polymorphism leads to increased sensitivity of AGTR1 to normal levels of angiotensin II and, consequently, to higher BP levels. Studies have shown that hypertensives are significantly more common to have the A/C or C/C genotype of the AGTR1 gene compared to normotensives [24].

We have studied two more SNPs that are important for the functioning of the RAS: the AGT gene and AGTR2. The AGT gene is located on chromosome 1 (1q42). The replacement from cytosine (C) to thymine (T) in 521 positions leads to a change in the amino acid sequence of the protein structure of AGT with the replacement from tryptophan to methionine in 174 positions, which is designated as T207M C>T (rs4762). It has been shown that the presence of the T-allele is associated with a higher level of AGT expression and the development of hypertension [25]. In groups of older people with hypertension, the C/T genotype occurs about five times more often than in the control group without CVDs. Also, the presence of the T allele in the genotype increases the risk of developing cardiometabolic disorders and CHD [8, 9]. In our study, the frequencies of SNP AGT rs4762 have corresponded to the HWE and have not differed between groups of hospitalized patients with severe and moderate COVID-19.

SNP AGTR2 rs1403543 is characterized by a replacement from guanine (G) to adenine (A) at nucleotide position 1675 of the genome (genetic marker G1675A rs1403543) and is associated with a change in gene expression regulation. The G allele is associated with the activation of transcription and the increase in the number of AGTR2 on the cell membrane. This leads to effects opposite to those caused by angiotensin II, such as vasodilation, natriuresis, and slowing of smooth muscle hypertrophy. Carriers of the A allele have an increased risk of hypertension, pregnancy complications, and CHD, which is caused by a decrease in AGTR2 expression and a shift in the functional activity of the RAS towards AGTR1 [26]. The AGTR2 gene is in the X chromosome, that's why the distribution of its polymorphic variants has gender specificity. In our study, the frequencies of SNP AGTR2 rs1403543 alleles have deviated from the HWE in males with severe and moderate COVID-19. In females with different COVID-19 severity, a significant difference in the distribution of rs1403543 genotypes was revealed ($\chi^2 = 10.570$, $P = 0.006$).

The influence of polymorphism of the RAS genes on coronavirus infection has been studied in several research. The study by Kouhpayeh et al 2021 revealed differences in the frequencies of SNP genes in patients with COVID-19 and in the control group, which the authors explained by the different prevalence of CVDs, that might be caused by certain AGT, ACE1, AGTR1 genes polymorphisms of the [13]. However, in our study, in the subgroups with severe and moderate COVID-19, the frequency of comorbidities such as hypertension, CHD, diabetes, CKD, and chronic heart failure (CHF) has not differed.

The hypothesis of the role of the ACE 1 rs1799752 polymorphism in the pathogenesis of COVID-19 was formulated in 2020 by Gemmati et al [27]. The authors showed that more severe course of the disease and higher mortality rates among patients of the Caucasian race were correlated with D/D polymorphism in the ACE1 gene. This phenomenon was associated with hyperactivation of the RAS. However, there was no association of ACE1 rs1799752 polymorphism with the severity of COVID-19 infection in a systematic review and meta-analysis published in 2022 by Gupta et al [28]. However, this meta-analysis has significant limitations, as it compares only severe vs. non-severe COVID-19, without asymptomatic and control groups.

We also did not reveal differences in the frequency of ACE1 I/D polymorphism between the groups of severe and moderate COVID-19. However, an important result of our study was the deviation of the frequency distribution of ACE1 rs1799752 genotypes from the HWE and of population data in the whole group and each of the comparison groups. This fact may be related to the higher prevalence of the D-allele of the ACE1 gene among patients with COVID-19. The results of a study by Yamamoto et al about the negative correlation of the ACE1 I/I genotype with susceptibility to SARS-CoV-2 infection confirm this [29]. Cafiero et al [12] obtained similar data on a significantly higher frequency of I/D and D/D genotypes among symptomatic COVID-19 patients vs. asymptomatic.

The association of AGTR1 rs5186 polymorphism with COVID-19 has been studied by few scientific groups. Gupta and co-authors showed a reliable increase in the risk of severe COVID-19 in C-allele vs. A-allele (OR: 1.49, 95% CI: 1.13 - 1.98, P = 0.005) [28]. Our results are similar. The value of the AGTR2 rs1403543 polymorphism in COVID-19 has not been widely studied. The borderline relation between the AA genotype of the SNP AGTR2 rs1403543 and the presence of COVID-associated retinopathy in males (P = 0.05) was found in the only study by Jevnikar et al 2022 [14].

We analyzed the combination of SNP alleles of the RAS genes in our research and found that the DCG haplotype is more common in patients with severe COVID-19. It means that this haplotype increases the risk of severe COVID-19 with OR 3.996. Based on these data, this allelic combination can be used as a predictor of more severe forms of COVID-19.

The relation between RAS activity and COVID-19 severity seems to be mutual. On the one hand, decrease of ACE2 level due to blocking by viral particles, reduction in expression, and splitting by transmembrane metalloprotease 17 can contribute to reduced transformation of angiotensin I and II into angiotensin 1-9 and 1-7, respectively. Thus, it might lead to a shift of the RAS activity to activation of angiotensin II synthesis [30]. On the other hand, angiotensin II by acting on AGTR1 can significantly increase ACE2 level by mRNA and therefore potentiate SARS-CoV-2 activity, as evidenced by the data of Caputo et al [31]. Thus, high AGTR1 expression with the C-allele of rs5186 polymorphism, especially in high ACE1 concentrations in patients with D-allele predominance of the ACE1 rs1799752 gene, can significantly increase RAS activity during the active phase of COVID-19.

Our study showed significant shifts in the allelic distribution of the SNP genes ACE1 rs1799752, AGTR1 rs5186 and AGTR2 rs1403543 in the cohort of hospitalized patients with COVID-19. We have identified the DCG haplotype which carries a higher risk of severe COVID-19. A relatively small sample, the absence of outpatients with mild COVID-19 and a control group of patients without COVID-19 can be considered as limitations of our work, that is why additional research in this area remains feasible.

Conclusion

The modern paradigm of medicine, based on a personalized approach and predictive strategy, requires the search for genetic markers of socially significant diseases. Our data suggest that the SNP genes of the RAS components, namely ACE1 rs1799752, AGTR1 rs5186, and AGTR2 rs1403543, may allow us to identify groups of patients predisposed to a more severe course of COVID-19. Certainly, testing this hypothesis requires additional studies with larger samples and comparison groups from non-hospitalized patients with mild and asymptomatic forms of the disease.

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Conflict of Interest

The authors confirm that there is no potential conflict of interest to disclose in relation to this article.

Informed Consent

Completed written informed consent was obtained.

Author Contributions

Conceptualization: AB, AT, EO and VP; methodology: AB, AT, YR and EO; software: AS, ND; validation: TI, LV and IM; formal analyses: LV, AS and ND; investigation: EO, MB, AK, DG and AK; data curation: YR, EO, AS, ND, LV, TI, IM, MB, AK, DG and AK; writing - original draft preparation: AB, YN and EO; writing - review and editing: AB, AT and VP; writing - literacy search: AK, DG and AK; supervision: VP; project administration: VP. All authors have read and agreed to the published version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

ACE1: angiotensin-converting enzyme type 1; ACE2: angiotensin-converting enzyme type 2; AGT: angiotensinogen; AGTR1: angiotensin II receptor type 1; AGTR2: angiotensin II receptor type 2; CI: confidence interval; CRP: C-reactive protein; CVD: cardiovascular disease; DBP: diastolic blood pressure; DNA: deoxyribonucleic acid; OR: odds ratio; HWE: Hardy-Weinberg equilibrium; RAS: renin-angiotensin system; RR: respiratory rate; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SBP: systolic blood pressure; SNP: single nucleotide polymorphism; SpO_2: average value of oxygen saturation measured with a pulse oximeter

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