https://doi.org/10.25557/2073-7998.2024.02.27-33

Роль гена ACE в развитии тяжелой формы COVID-19 у беременных женщин

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Использование генетических полиморфизмов при определении патогенеза заболевания повышает эффективность ранней диагностики и профилактики тяжелой формы коронавирусной инфекции. COVID-19 и его осложнения пневмонией являются потенциальным фактором риска для беременных и могут иметь негативные последствия как для матери, так и для плода. В настоящее время особое внимание уделяется изучению роли генетических факторов в возникновении вспышки коронавируса. Цель исследования: определить роль полиморфизма I/D Alu-элемента гена *ACE* в патогенезе COVID-19. По результатам молекулярно-генетического обследования и статистического анализа частоты аллелей и генотипов полиморфизма I/D гена *ACE* у беременных, инфицированных коронавирусом, не имели достоверных отличий от таковых в контрольной группе (p=0,05) и, таким образом, этот полиморфизм не ассоциирован с развитием COVID-19 и его осложнений.

Ключевые слова: генотип, ген *ACE*, аллели, биомаркеры, синдром высвобождения цитокинов, хемокин, ОРДС, отношение шансов.

Для цитирования: Комилова М.О., Бобоев К.Т., Зуфарова Ш.А., Юлдашева А.С. Роль гена ACE в развитии тяжелой формы COVID-19 у беременных женщин. *Медицинская генетика* 2024; 23(2): 27-33.

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Финансирование. Исследование проведено без спонсорской поддержки.
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Поступила: 20.01.2024

The role of the ACE gene in the development of severe form of COVID-19 in pregnant women

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The use of genetic polymorphisms in determining the pathogenesis of the disease increases the effectiveness of early diagnosis and preventive measures of severe form of coronavirus. COVID-19 and its complications with pneumonia are a potential risk factor for pregnant women and can have negative consequences for both the mother and the fetus. Currently, special attention is paid to the study of the role of genetic factors in the outbreak of the coronavirus. The aim of the study: to determine the role of the *ACE* gene Alu-element I/D polymorphism in the pathogenesis of COVID-19. According to the results of molecular-genetic examination and statistical analysis, alleles and genotypes of *ACE* gene I/D polymorphism in pregnant women infected with coronavirus did not have significant differences compared to the control group (p=0.05). Conclusion: It is impossible to use this locus of the *ACE* gene to predict COVID-19 and its complications.

Keywords: Genotype, ACE gene, alleles, biomarkers, cytokine release syndrome, chemokine, ARDS, odds ratio.

For citation: Komilova M.O., Boboev K.T., Zufarova Sh.A., Yuldasheva A.S. The role of the *ACE* gene in the development of severe form of COVID-19 in pregnant women. *Medical genetics [Medicinskaya genetika]* 2024; 23(2): 27-33.

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Funding. The study was performed without external funding.
Conflict of interest. The authors declare no conflict of interest.
Accepted: 20.01.2024

Introduction

The *ACE* gene is located on chromosome 17q 23.3 and has 26 exons and 25 introns [1]. The I/D polymorphism is distinguished by the presence (Insertion) or absence (Deletion) of an Alu element in intron 16 of the *ACE* locus, resulting in three different genotypes: I/I, I/D, and D/D. Furthermore, serum *ACE* concentrations are associated with I/D polymorphism (D/D > I/D > I/I), suggesting that circulating enzyme levels should be determined by genotype at the *ACE* locus [2, 3].

The insertion/deletion (I/D) polymorphism of the angiotensin-converting enzyme (*ACE*) locus is an important genetic biomarker that has served in many genotype-phenotype association studies [4]. *ACE* plays a key role in the regulation of systemic blood pressure and renal electrolyte homeostasis by converting inactive angiotensin I to the potent vasoconstrictor and aldosterone-stimulating angiotensin II and by inactivating the anti-inflammatory vasodilator bradykinin [5].

Currently, it is recognized that there is a role of immune status and genetic factors in the pathogenesis of COVID-19 and its manifestation at different levels of severity in humans, including the *ACE* gene, which plays a crucial role in maintaining the homeostasis of the renin-angiotensin-aldosterone system. And that may be a suitable reason to explain the common mechanisms of multi-organ damage and multi-system dysfunction observed in COVID-19, because COVID-19 is not just lung disease affects many organs and systems throughout the body in different ways [6]. *ACE* is an important mediator in the entry of viral infection into the cell and binding to a special protein. Moreover, at the molecular level, the presence of the Alu element in intron 16 has been found to have affected the promoter activity of *ACE*, possibly serving as a transacting repressor of RNA polymerase II activity [7, 8].

The aim: to study the role of *ACE* gene I/D polymorphism in the pathogenesis of COVID-19 in pregnant women.

Methods

Blood samples were taken from 110 women infected with COVID-19 during pregnancy (all women were positive for PSR analysis) and formed the main group. The average age among women in the main group is 29.35+0.56. We divided the pregnant women taken for the study into 2 subgroups:

Group 1 is a group of women who are mildly infected with COVID-19 (there are no pathological foci on X-ray examination of the lungs)

Group 2 – women with severe cases of COVID-19 (changes characteristic of pneumonia were observed in the X-ray examination).

After the end of the pandemic, samples were taken from conditionally healthy donors who had a negative PSR test for COVID-19 and had no infection of coronavirus symptoms for the control group.

Biomaterial sampling was performed using standard vacuum tubes containing EDTA-K3 anticoagulant (Vacutainer Becton Dickinson International, USA). For PCR studies, genomic DNA was isolated using the AmpliPrime RIBO-prep reagent kit (NextBio, Russia). Genomic DNA concentration was measured in a NanoDrop 2000 spectrophotometer (NanoDrop Technologies, USA) at A260/280 nm wavelength. The purity of all DNA samples was 1.7/1.8. Identification of genetic loci was carried out by PCR analysis of alleles of *ACE* gene.

PCR analysis was performed using Rotor Gene Q (Guagen, Germany) and Applied Biosystems (model 2720, USA) instruments and according to the following amplification programs:

Initial denaturation for *ACE* gene – 94C^0 (3 min.1 cycle), 40 amplification cycles: 94C^0 (10 sec) – denaturation, 80C0 (2 min) – softening (heat treatment), 60C^0 (40 sec) – cho and final synthesis at 72 C^0 (1 min. 1 cycle), maintained for 10 min.

Fragments of the analyzed PCR products (DNA) were imaged in a UV transilluminator (wavelength 310 nm) with a built-in digital camera. The results of the fluorescence signal analysis for each of the samples allow to answer whether each allele is present in a heterozygous or homozygous form.

Deviation of the *ACE* gene genotype distribution from the canonical Hardy-Weinberg distribution (HWD) was performed using the computer program for genetic data analysis "GenePop" (Population Genetics).

The degree of association of allelic and genotypic variants was estimated by OR and RR values with 95% confidence intervals (95% CI).

The software package "OpenEpi 2009, Version 2.3" was used as a tool for calculating the obtained data.

The statistical significance of the data collected as a result of the research was studied using R Microsoft Office 2021 software, Epi info software package.

Results

In groups of pregnant women infected with COVID-19, the ratio of alleles and genotypes of the Alu element (I/D) polymorphism of the *ACE* gene was checked for Hardy-Weinberg equilibrium.

Theoretical and actual frequencies of alleles and genotypes (Hexp and Hobs, respectively) and gene diversity indicators in samples of pregnant women and healthy donors in the control group are presented in **Table 1**.

For the *ACE* gene Alu element (I/D) polymorphism, the empirically-observed (Hobs) distribution of genotypes in pregnant women infected with COVID-19 and the control group corresponds to the theoretically expected (Hexp) in Hardy-Weinberg equilibrium ($p>0.05$).

As can be seen from Table, the observed distribution of the homozygous I/I genotype in the group of infected pregnant women was the same as the theoretical one (0.54 vs. 0.54). The observed frequency of the heterozygous I/D genotype was insignificantly higher than expected ($\chi^2<3.84$; $p>0.05$). A similar result was observed in the mutant D/D genotype ($\chi^2<3.84$; $p>0.05$). The relative deviation of Hobs and Hexp turned out to be positive: D=+0.3.

When the frequency of the homozygous I/I genotype was studied in the control sample, the expected results were obtained: Hobs=0.51 and Hexp=0.51 ($\chi^2<3.84$ and $p>0.05$), heterozygous genotype I/D- Hobs=0, 4 and Hexp=0.41 ($\chi^2=0.02$ and $p=0.8$). Minor D/D genotype level is Hobs=0.09 and Hexp=0.08: $p>0.05$, relative deviation of fixed index between observed Hobs and Hexp is negative: D=-0, 02 (Tables1).

Thus, according to the genetic information obtained by the *ACE* gene Alu element (I/D) polymorphism, there is no heterogeneity between the actual observed and theoretically expected values of genotypes in pregnant women infected with COVID-19 and control sample groups. In the studied samples, the prevalence of ancestral I/I and unfavorable I/D genotypes of this locus was came out as expected, i.e. Hardy-Weinberg equilibrium was fulfilled in both cases, which shows the homogeneity of the studied samples and the quality of the genotyping.

According to the results of the association analysis of the *ACE* gene (I/D) polymorphism in the groups of infected pregnant women and control patients, the percentage of allele I in the main group of women infected with coronavirus was 73.6% and in the control group, it was 71.4%, and no significant results were obtained in the statistical analysis ($p>0.05$) (**Table 2** and **Figure 1**).

In the main group of 110 pregnant women diagnosed with a viral infection, the percentage of the D allele was 26.4%, in the control group it was 28.6%, this result shows that the D allele of the *ACE* gene has no statistical correlation with the development of the disease, which showed ($\chi^2<3.84$; $p>0.05$) (Figure 1 and Table 2).

Prevalence ratios of I/I, I/D, D/D genotypes of *ACE* gene in the main group of pregnant women infected with coronavirus, as well as in samples of conditionally healthy people in the control group were studied. The proportions of genotypes of pregnant women in the main group and the control group are illustrated in **Figure 2** and Table 2.

Table 1. Difference between distribution and heterozygosity frequencies of *ACE* gene Alu element (I/D) locus alleles and genotypes in primary and control groups in Hardy-Weinberg equilibrium.

Таблица 1. Разница между распределением и частотами гетерозиготности аллелей и генотипов локуса элемента Alu (I/D) гена *ACE* в первичной и контрольной группах в равновесии Харди-Вайнберга.

Distribution of alleles	Alleles											
			I				D					
	Main group		0.74				0.26					
	Control group		0.71				0.29					
	Genotypes											
Distribution of genotypes	Main group		I/I	I/D	D/D	Total	p	df	heterozygosity	Ho	He	D*
		Observed	0.54	0.4	0.06	1	0.719	1		0.4	0.39	0.03
		Expected	0.54	0.39	0.07	1						
		χ^2	0.01	0.04	0.05	0.1						
	Control group	Observed	0.51	0.4	0.09	1	0.804	1		0.4	0.41	-0.02
		Expected	0.51	0.41	0.08	1						
		χ^2	0	0.02	0.02	0.04						

Note: D*= (Ho – He)/He. For the main group D= (0.4-0.39)/0.39 =+0.03. For the control group D= (0.4-0.41)/0.41 =-0.02

Statistical results showed that this genotype does not have disease outbreak or protective properties: $\chi^2<3.84$; $p>0.05$; OR=1.1.

The concentration of the heterozygous I/D genotype in the main group of women infected with COVID-19 was 40.0%, which was the same as the result in healthy people, and as a result of statistical processing, it was found that there was no association of this genotype with the development of the disease ($\chi^2<3.84$; $p>0.05$). Among infected pregnant women, the percentage of mutant D/D homozygous genotype was 6.4%, and in the conditionally healthy control group, it was 8.6%, and the mutant genotype did not have statistically significant data on disease progression ($\chi^2<3.84$; $p>0.05$) (Figure 2 and Table 2).

During the investigation, the prevalence of *ACE* gene alleles and genotypes in 70 pregnant women with severe (complicated by pneumonia) COVID-19 and conditionally healthy subjects was studied and the results were compared. (**Figures 3, 4** and **Table 3**).

In the group of 70 pregnant women who developed pneumonia, the percentage of the I-allele of the *ACE* gene was 75.7%, in the control sample it was 71.4%, and this gene was found to be insignificant in the development of pneumonia in coronavirus disease ($\chi^2<3.84$; $p>0.05$). The share of D allele in women of this group was 24.3%, in the control sample it was 28.6% ($\chi^2<3.84$; $p>0.05$).

In the control group, the frequency of meeting the attenuated D/D genotype was 8.6%, which was slightly higher than in the subgroup of pregnant women infected with COVID-19, and no statistically significant results were obtained: $\chi^2<3.84$; $p>0.05$. Among the patients, the homozygous I/I genotype was determined in 58.6% of cases,

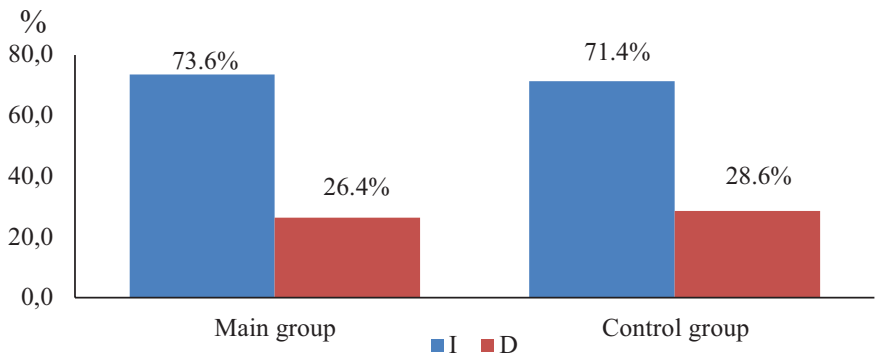

Figure 1. Frequency of *ACE* gene (I/D) polymorphism in the main group and the control group

Рисунок 1. Частота полиморфизма гена *ACE* (I/D) в основной и контрольной группах

Table 2. Association between *ACE* gene Alu-element (I/D) polymorphism alleles and genotypes in the main group of women with COVID-19 and the control group

Таблица 2. Ассоциация аллелей и генотипов полиморфизма Alu-элемента (I/D) гена *ACE* в основной группе женщин с COVID-19 и контрольной группе

Alleles and genotypes	The number of alleles and genotypes				χ^2	P	OR	95%CI
	Main group		Control group					
	n	%	N	%				
I	162	73.6	150	71.4	0.3	p = 0.70	1.1	0.73 – 1.71
D	58	26.4	60	28.6	0.3	p = 0.70	0.9	0.59 – 1.37
I/I	59	53.6	54	51.4	0.1	p = 0.80	1.1	0.64 – 1.87
I/D	44	40.0	42	40.0	0.0	p = 0.99	1.0	0 – 0
D/D	7	6.4	9	8.6	0.4	p = 0.60	0.7	0.26 – 2.02

and the following statistical data were obtained: $\chi^2<3.84$; $p>0.05$; OR=1.3; 95% CI: 0.73–2.46.

In the group of women infected with COVID-19 complicated by pneumonia during pregnancy, the percentage of genotype I/D was 34.3% ($\chi^2<3.84$; $p>0.05$), the result in the control group was 40.0%. The I/D genotype did not significantly differ from women who developed pneumonia in COVID-19 and conditionally healthy people in the control group ($\chi^2<3.84$; $p>0.05$).

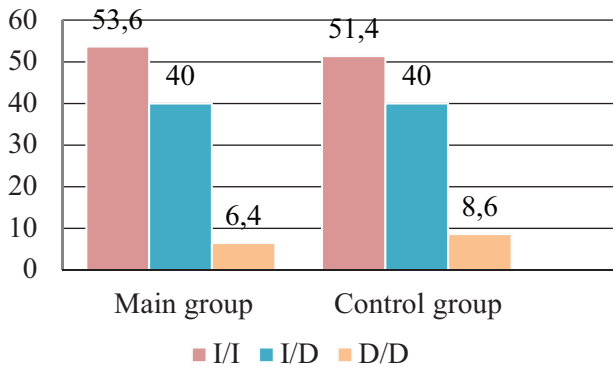

Figure 2. Distribution of *ACE* gene Alu-element (I/D) polymorphism genotypes in the main group of patients and the control group

Рисунок 2. Распределение генотипов полиморфизма Alu-элемента (I/D) гена *ACE* в основной группе пациентов и контрольной группе

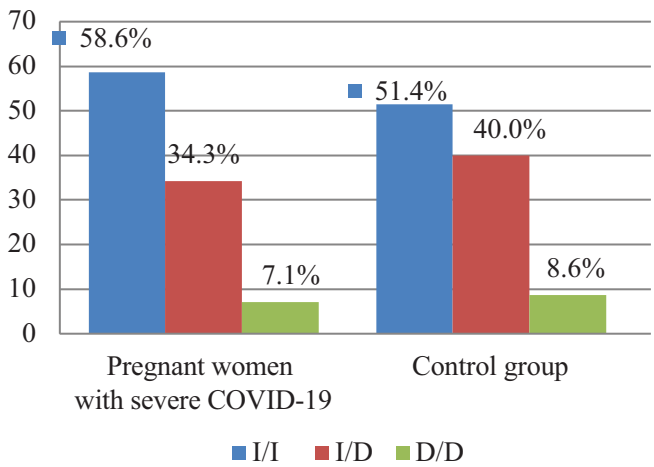

Figure 4. Prevalence of *ACE* gene Alu-element (I/D) polymorphism genotypes in a group of pregnant women with severe COVID-19 and in a control group

Рисунок 4. Частоты распространенности генотипов полиморфизма Alu-элемента(I/D) гена *ACE* в группе беременных с тяжелым течением COVID-19 и в контрольной группе

In addition, the distribution of *ACE* Alu element locus alleles and genotypes in pregnant women with mild infection with COVID-19 and control groups was studied and the results were analyzed (**Table 4** and **Figure 5**).

In the group of pregnant women with a relatively mild infection with COVID-19 (no pneumonia), the concentration

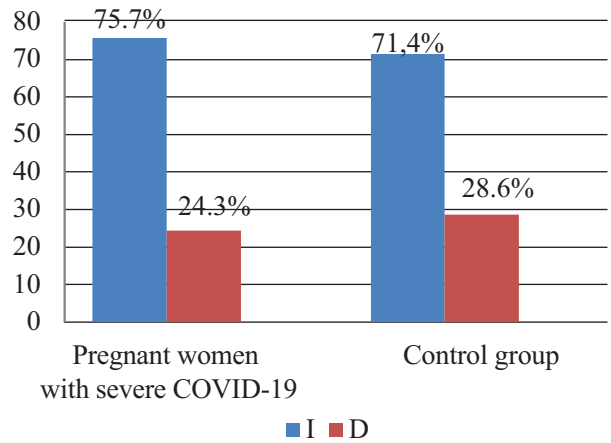

Figure 3. Prevalence of *ACE* gene Alu-element (I/D) polymorphism alleles in a group of pregnant women with severe COVID-19 and a control group

Рисунок 3. Распространенность аллелей полиморфизма Alu-элемента (I/D) гена *ACE* в группе беременных с тяжелым течением COVID-19 и контрольной группе

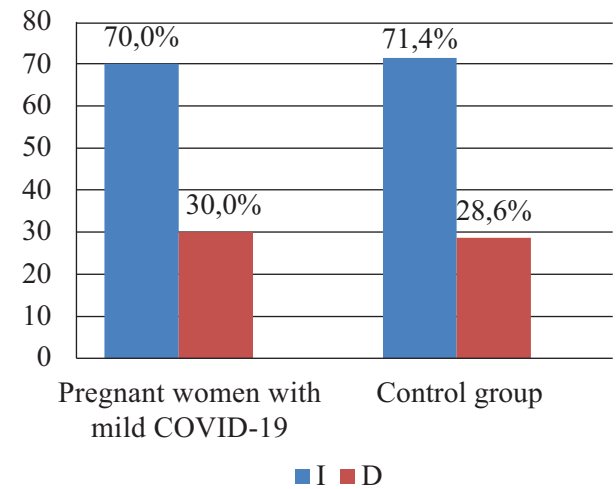

Figure 5. Ratio of *ACE* gene alleles in pregnant women with relatively mild infection with COVID-19 and in the control group

Рисунок 5. Соотношение аллелей гена *ACE* у беременных с относительно легкой инфекцией COVID-19 и в контрольной группе

of the I-allele was 70.0%, which was not much different from that of healthy people in the control group, where the percentage of the I-allele was 71.4% and no statistically significant results were obtained (χ^2<3.84; p>0.05). The frequency of the D-allele was 30.0% in women with mild COVID-19, its frequency was 28.6% in the conditionally healthy control group. Therefore, this allele has no significance in the development of the disease (χ^2<3.84; p>0.05).

The distribution of *ACE* gene Alu-element (I/D) polymorphism I/I, I/D and D/D genotypes in the group of women with mild COVID-19 and in the control group is presented in Table 4 and **Figure 6**. In the group of pregnant women who did not develop pneumonia, the percentage of the I/I genotype was 45.0%, which was statistically lower than that of the conditionally healthy group (the control group), its prevalence was 51.4%, and statistically significant proportions were not obtained (χ^2<3.84; p>0.05).

The detection rate of heterozygous I/D genotype was 50.0% and 40.0% in this group of pregnant women and control groups, respectively, and it was found that I/D genotype had a tendency to increase the incidence of mild disease by 1.5 times (χ^2<3.84; p>0.05; OR=1.5, 95%CI: 0.72–3.11). The minor D/D genotype was 5.0% (2) in 40 women who did not develop pneumonia, showing that it does not play a role in the origin of mild forms of infection: χ^2<3.84; p>0.05.

Therefore, it is known from the above that the results of the distribution of *ACE* gene genotypes in the groups of pregnant women infected with COVID-19 and in the control sample are statistically insignificant in the development of the disease and complications with pneumonia (p>0.05).

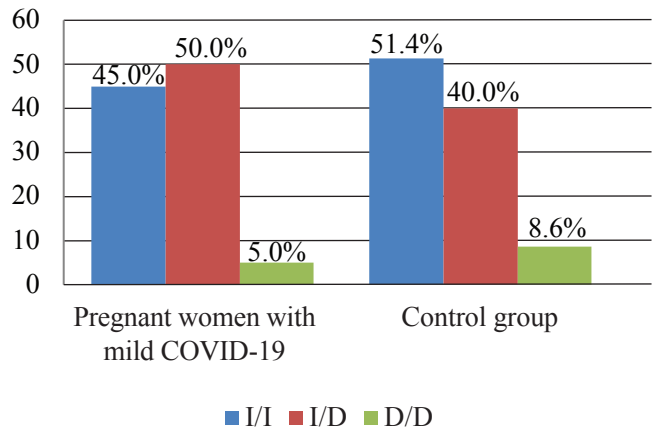

Figure 6. Distribution of *ACE* gene Alu-element (I/D) polymorphism genotypes in women infected with COVID-19 without pneumonia and in control group

Рисунок 6. Распределение генотипов полиморфизма Alu-элемента (I/D) гена *ACE* у женщин, инфицированных COVID-19 без пневмонии, и в контрольных группах

Discussion

The (I/D) polymorphism in *ACE* is thought to influence the development, clinical presentation, and complications of COVID-19 infection. Firstly, *ACE* can reduce *ACE*2; people with the D/D genotype have lower *ACE*2 expression and are therefore less susceptible to infection. This theory is epidemiologically supported by the negative correlation between the prevalence of COVID-19 and the frequency of *ACE* D-allele [9]. In addition, several studies have shown that individuals belonging to the *ACE* Alu-element D/D genotype have a high susceptibility to the development of ARDS in respiratory infections such as influenza A [10, 11]. Considering the results of the study of *ACE* I/D polymorphism in human population genetics, the role of

Table 3. Association between alleles and genotypes of the *ACE* gene (I/D) polymorphism in pregnant women with severe COVID-19 and in a control group

Таблица 3. Ассоциация между аллелями и генотипами полиморфизма гена *ACE* (I/D) у беременных с тяжелым течением COVID-19 и в контрольной группе

Alleles and genotypes	The number of alleles and genotypes				χ^2	p	OR	95%CI
	Pregnant women with severe Covid-19		Control group					
	n	%	n	%				
I	106	75.7	150	71.4	0.8	p = 0.40	1.2	0.77 – 2.03
D	34	24.3	60	28.6	0.8	p = 0.40	0.8	0.49 – 1.31
I/I	41	58.6	54	51.4	0.9	p = 0.40	1.3	0.73 – 2.46
I/D	24	34,3	42	40.0	0.6	p = 0.50	0.8	0.42 – 1.47
D/D	5	7.1	9	8.6	0.1	p = 0.80	0.8	0.26 – 2.56

race/ethnicity in clinical manifestations and complications of COVID-19 was observed [12].

Our results showed that the *ACE* I/D polymorphism did not play a significant role in the outbreak of COVID-19 and the development of pneumonia in the Uzbek population. But in a 2015 global meta-analysis study, it was observed that the D/D genotype of the I/D polymorphism may be a high risk factor for the development of ARDS [13].

The results of our study correspond to the conclusions of several studies [14-16]

There is an evidence that an ethnic difference in the insertion (I)/deletion (D) polymorphism of the *ACE* gene may explain the apparent difference in mortality between West and East Asians [17]. Furthermore, several studies contradict our findings, concluding that *ACE* (I/D) polymorphism genotypes play an important role in the development of and protection against disease severity and lung injury in COVID-19 [18-22].

Conclusions

Although several studies around the world have shown that *ACE* gene Alu-element genotypes and alleles are associated with the outbreak of COVID-19, our study did not show statistically significant results.

While analyzing the role of the *ACE* gene in the development of mild or severe forms of the coronavirus, it was found that I/I, I/D, D/D genotypes do not play any role in the aggravation of the disease in the development of pneumonia ($p>0.05$).

It was proved that the ratio of D/D genotype of *ACE* gene does not show statistical significance even in the origin of a mild form of viral infection ($p>0.05$).

Based on the overall results, the use of *ACE* gene I/D polymorphism in early prediction of the onset of COVID-19 and pneumonia in pregnant women is ineffective.

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