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ORIGINAL ARTICLE / ÖZGÜN MAKALE

The Impact of Genetic Variants of Angiotensin-converting enzymes (ACE1, ACE2) On the Severity of COVID-19 Disease

Anjiyotensin Dönüştürücü Enzimlerin (ACE1, ACE2) Genetik Varyantlarının COVID-19 Hastalığının Şiddeti Üzerine Etkisi

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Abstract

Objective: This study aimed to explore whether there is a potential link between ACE1 I/D and ACE2 rs2285666 polymorphisms and COVID-19 severity.
Materials and Methods: A prospective observational study was conducted involving 200 patients who were diagnosed with COVID-19 through polymerase chain reaction testing. Demographic and clinical data were collected, and genetic analyses of ACE1 I/D and ACE2 rs2285666 genes were carried out using next-generation sequencing. Patients were classified into three groups based on disease severity: mild, moderate, and severe.
Results: The average age of participants was 52 (±27) years, with 116 (58%) being male. Among them, 120 (60%) had at least one chronic illness, and one-fourth were smokers. Fifty-two (26%) patients with severe symptoms required intensive care, and 19 (9.5%) of these individuals unfortunately passed away. Meanwhile, the remaining 74% with mild or moderate symptoms were discharged after recovering. No statistically significant association was found between ACE1 I/D and ACE2 rs2285666 polymorphisms and COVID-19 severity or mortality.
Conclusion: The results indicate that ACE1 I/D and ACE2 rs2285666 polymorphisms do not significantly impact the severity of COVID-19. Further studies including diverse ethnic groups and examining other polymorphisms are needed to provide a more comprehensive understanding of these genetic influences.
Keywords: ACE, clinical severity, COVID-19, genetic polymorphism

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Öz

Amaç: Bu çalışmada, ACE1 I/D ve ACE2 rs2285666 polimorfizmleri ile COVID-19 şiddeti arasındaki ilişkinin araştırılması amaçlandı.
Yöntem: Bu çalışma, Polimeraz zincir reaksiyonu yöntemi ile COVID-19 tanısı konulan 200 hasta üzerinde prospektif, gözlemsel olarak gerçekleştirildi. Çalışmaya alınan olguların demografik ve klinik verileri kaydedilerek, ACE1 I/D ve ACE2 rs2285666 genlerinin genetik analizleri, yeni nesil dizi yöntemi kullanılarak gerçekleştirildi. Vakalar, hastalığın şiddetine göre hafif, orta ve ağır olarak üç gruba ayrıldı.
Bulgular: Çalışmaya alınan olguların ortalama yaşı 52 (±27) yıl olup, 116'sı (%58) erkekti. Olguların 120'sinde (%60) en az bir kronik hastalık mevcutken, dörtte birinde düzenli sigara kullanımı vardı. Ağır klinik bulguları olan 52 hasta (%26) yoğun bakım servisinde tedavi edilirken ve bunların 19'u (%9,5) hayatını kaybetti. Kalan %74'lük hafif veya orta şiddette klinik semptomları olan olguların tümü iyileşerek taburcu edildi. Çalışmada ACE1 I/D ve ACE2 rs2285666 gen polimorfizmleri ile COVID-19 şiddeti veya ölüm oranı arasında istatistiksel olarak anlamlı bir ilişki bulunamadı.
Sonuç: Bulgular, ACE1 I/D ve ACE2 rs2285666 polimorfizmlerinin COVID-19 şiddetini etkilemediğini göstermektedir. Bu ilişkinin daha kapsamlı bir şekilde anlaşılabilmesi için, farklı etnik grupları içeren ve farklı polimorfizmleri araştıran daha fazla çalışmaya ihtiyaç vardır.
Anahtar Kelimeler: ACE, klinik ağırlık, COVID-19, genetik polimorfizm

INTRODUCTION

The COVID-19 pandemic, which began in Wuhan, China, has led to a global outbreak, causing millions of infections and deaths worldwide, including in our country (1). While some individuals experience COVID-19 without symptoms, others may develop severe pneumonia, multiple organ failure, or even succumb to the disease (2). The notable variation in disease progression among infected individuals has sparked extensive research to better understand the pathogenesis, identify high-risk populations, and develop effective treatments (3). While the World Health Organization's guidelines and other sources highlight that individuals with chronic conditions and the elderly are at increased risk for COVID-19, severe cases in previously healthy individuals without apparent risk factors suggest that genetic differences may also play a role (4).

The renin-angiotensin system (RAS) significantly influences cardiovascular, respiratory, and renal systems, and it plays a key role in COVID-19 pathogenesis. SARS-CoV-2, the virus responsible for COVID-19, binds to angiotensin-converting enzyme 2 (ACE2) on cell membranes of nasopharyngeal mucosa and alveolar pneumocytes using its spike (S) protein (5). Therefore, ACE2 gene expression may influence susceptibility to SARS-CoV-2 infection (6). Moreover, the balance between angiotensin-converting enzyme 1 (ACE1) and ACE2 activity is known to impact the pathogenesis of respiratory diseases and may similarly affect COVID-19 severity (7). Limited prior studies have reported associations between ACE1 and ACE2 gene variants and disease severity, though some were based on small

sample sizes, low statistical significance, or hypothetical data (8-11). Further well-controlled clinical studies with larger patient groups are needed to deepen our understanding of COVID-19 pathogenesis and identify high-risk groups.

This study aims to investigate the role of ACE1 insertion/deletion (I/D), ACE1 deletion/deletion (D/D) gene variants, and ACE2 polymorphisms in the progression of COVID-19.

MATERIALS AND METHODS

Study Design and Population

This prospective observational study was conducted at Ege University School of Medicine, one of the largest tertiary care hospitals in Türkiye. Our study included 200 patients diagnosed with COVID-19 via polymerase chain reaction (PCR) testing. Patient demographic and clinical characteristics, chronic illness status, smoking habits, treatment settings (outpatient/inpatient/intensive care unit), and outcomes were recorded in case report forms.

Ethics approval was obtained from the Scientific Research Ethics Committee of Ege University School of Medicine. To ensure confidentiality, no patient-identifiable data was collected. The study procedures complied with the ethical standards outlined in the 1964 Helsinki Declaration, as revised in 2008, and followed national regulations.

Patients were categorized into three groups based on disease severity: "mild," "moderate," and "severe." Patients without signs of viral pneumonia or hypoxia, but with other symptoms or who were asymptomatic, were classified as "mild." Those with clinical symptoms of pneumonia not requiring hospitalization were managed at home or outpatient settings and categorized as "moderate." Patients with severe pneumonia, ARDS, sepsis, septic shock, or requiring intensive care were classified as "severe."

Chronic conditions considered included hypertension, diabetes, coronary artery disease, heart failure, COPD, malignancy, chronic kidney failure, liver failure, immunodeficiency, and conditions requiring immunosuppressive drugs.

Genetic analysis

Peripheral blood samples were collected in EDTA tubes, and genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Kit (Qiagen, Germany). Extracted DNA was quantified and stored at -80°C until further use. Sequencing of targeted regions was conducted to assess the specified polymorphisms.

Genotyping for the ACE1 I/D polymorphism was performed using PCR with custom-designed primers. The amplicons generated were 192 base pairs for the ACE I allele and 490 base pairs for the ACE D allele, and gel electrophoresis was used to verify amplified PCR products. Bands of 192 base pairs indicated ACE1 I/I, 490 base pairs indicated ACE1 D/D, and both bands indicated ACE1 I/D.

Genotyping for the ACE2 rs2285666 polymorphism was also performed by PCR, and the amplified products were analyzed using gel electrophoresis. After successful amplification, samples were sequenced on the Illumina Miniseq platform.

Sequencing data were analyzed using a bioinformatics pipeline, and allelic status was visualized on the Integrative Genomics Viewer (IGV) software. Allele frequencies and genotypes (homozygous or heterozygous) were recorded.

Data Analysis

Statistical analyses were conducted to assess differences in allele frequencies, homozygous/heterozygous status, and under both recessive and dominant genetic models. Categorical variables were

compared using the chi-square test, while continuous variables were analyzed using one-way ANOVA. A significance threshold of $p < 0.05$ was set. All analyses were performed using SPSS software (version 26.0).

RESULTS

Among the study participants, 116 (58%) were male, and 84 (42%) were female, with an average age of 52 (±27) years. Sixty-four participants (32%) were children under 18. One hundred and twenty patients (60%) had at least one chronic illness, while 48 (24%) were regular smokers. About 75% of those with mild/moderate symptoms recovered without complications. However, 52 patients (26%) with severe symptoms required intensive care, and 19 (9.5%) did not survive.

Severely affected patients were generally older, had more chronic conditions, and were more likely to smoke compared to those with milder symptoms ($p < 0.001$, $p = 0.004$, and $p < 0.001$, respectively) (Table 1).

Table 1. Associations between disease severity and demographic and clinical characteristics of the patients

Cases' Characteristics	Mild/Moderate Cases	Severe Cases		
N (%)	N=148 (74)	N=52 (26)	OR (95% CI)	P-value
Age, years (mean, ± SD)	38 ± 27	64 ± 20	-	**<0.001**
Gender, (n, %)				
Female	68(81)	16(19)		
Male	80(69)	36(31)	1.93 (0.98-3.74)	0.056
Comorbidities (+) – no.(%)	80 (54)	40 (76)	2.22 (1.24-3.96)	**0.004**
Smoking (+) – no.(%)	17 (11)	31 (60)	4.67 (2.98-7.32)	**<0.001**

CI = Confidence interval; OR = Odds ratio

Deceased patients were more often male, older, had chronic illnesses, and smoked more frequently than survivors ($p = 0.001$, $p < 0.001$, $p = 0.004$, and $p < 0.001$, respectively) (Table 2).

Table 2. Associations between mortality and demographic and clinical characteristics of the patients

Cases' Characteristics	Survivors	Died		
N (%)	N=181 (90.5)	N=19 (9.5)	OR (95% CI)	P-value
Age, years (mean, ± SD)	43 ± 27	69 ± 12	-	**<0.001**
Gender, (n, %)				
Female	83 (99)	1 (1)		
Male	98 (84)	18 (16)	15.24 (1.99-116.63)	**0.001**
Comorbidities (+) – no.(%)	104 (57)	16 (84)	3.55 (1.07-11.80)	**0.024**
Smoking (+) – no.(%)	17 (19)	14 (74)	8.86 (3.36-23.34)	**<0.001**

CI = Confidence interval; OR = Odds ratio

No statistically significant associations were observed between the ACE1 I/D or ACE2 rs2285666 polymorphisms and disease severity or mortality (Tables 3-6).

Table 3. The relationship between ACE1 I/D gene polymorphism and disease severity

Genetic model N (%)	Mild/Moderate Cases N=148 (74)	Severe Cases N=52 (26)	OR (95% CI)	P-value
DI & II	55 (72.4) / 40 (83.3)	21 (27.6) / 8 (16.7)	1.90 (0.76-4.74)	0.160
DD & II	53 (69.7) / 40 (83.3)	23 (30.3) / 8 (16.7)	0.46 (0.18-1.13)	0.089
DD & DI	53 (69.7) / 55 (72.4)	23 (30.3) / 21 (27.6)	0.88 (0.43-1.77)	0.721
DD + DI & II (Dominant model)	108 (71.1) / 40 (83.3)	44 (28.9) / 8 (16.7)	0.49 (0.21-1.13)	0.091
II + DI & DD (Recessive model)	95 (76.6) / 53 (69.7)	29 (23.4) / 23 (30.3)	0.70 (0.37-1.33)	0.282

ACE= Angiotensin-converting enzymes; CI = Confidence interval; OR = Odds ratio

Table 4. The relationship between ACE1 I/D gene polymorphism and mortality

Genetic model N (%)	Survivors N=181 (90.5)	Died N=19(9.5)	OR (95% CI)	P-value
DI & II	71 (93.4) / 44 (91.7)	5 (6.6) / 4 (8.3)	0.77 (0.19-3.04)	0.714
DD & II	66 (86.8) / 44 (91.7)	10 (13.2) / 4 (8.3)	0.60 (0.17-2.03)	0.563
DD & DI	66 (86.8) / 71 (93.4)	10 (13.2) / 5 (6.6)	0.46 (0.15-1.43)	0.174
DD + DI & II (Dominant model)	137 (90.1) / 44 (91.7)	15 (9.9) / 4 (8.3)	0.83 (0.26-2.63)	0.503
II + DI & DD (Recessive model)	115 (92.7) / 66 (86.8)	9 (8.3) / 10 (13.2)	0.51 (0.20-1.33)	0.167

ACE= Angiotensin-converting enzymes; CI = Confidence interval; OR = Odds ratio

Table 5. The relationship between ACE2 rs2285666 gene polymorphism and disease severity

Genetic model N (%)	Mild/Moderate Cases N=148 (74)	Severe Cases N=52 (26)	OR (95% CI)	P-value
CT & TT	27 (81.8) / 19 (67.9)	6 (18.2) / 9 (32.1)	0.46 (0.14-1.53)	0.207
CC & TT	102 (73.4) / 19 (67.9)	37 (26.6) / 9 (32.1)	1.30 (0.54-3.14)	0.551
CC & CT	102 (73.4) / 27 (81.8)	37 (26.6) / 6 (18.2)	0.61 (0.23-1.60)	0.314
CC + CT & TT (Dominant model)	129 (75) / 19 (67.9)	43 (25) / 9 (32.1)	1.42 (0.59-3.37)	0.424
TT + CT & CC (Recessive model)	46 (75.4) / 102 (73.4)	15 (24.6) / 37 (26.6)	0.89 (0.44-1.79)	0.763

ACE= Angiotensin-converting enzymes; CI = Confidence interval; OR = Odds ratio

Table 6. The relationship between ACE2 rs2285666 gene polymorphism and mortality

Genetic model N (%)	Survivors N=181 (90.5)	Died N=19(9.5)	OR (95% CI)	P-value
CT & TT	32 (97) / 26 (92.9)	1 (3) / 2 (7.1)	0.40 (0.03-4.73)	0.438
CC & TT	123 (88.5) / 26 (92.9)	16 (11.5) / 2 (7.1)	0.59 (0.12-2.73)	0.386
CC & CT	123 (88.5) / 32 (97)	16 (11.5) / 1 (3)	0.24 (0.03-1.88)	0.121
CC + CT & TT (Dominant model)	155 (71.1) / 26 (92.9)	17 (90.1) / 2 (7.1)	0.70 (0.5-3.21)	0.484
TT + CT & CC (Recessive model)	58 (76.6) / 123 (88.5)	3 (23.4) / 16 (11.5)	0.39 (0.11-1.41)	0.193

ACE= Angiotensin-converting enzymes; CI = Confidence interval; OR = Odds ratio

DISCUSSION

This study analyzed the association between ACE1 I/D and ACE2 rs2285666 polymorphisms and COVID-19 severity in a cohort of 200 patients diagnosed across all age groups. Our findings indicated that neither the ACE1 I/D nor the ACE2 rs2285666 polymorphisms significantly influenced the clinical course of COVID-19. However, disease severity was more pronounced in male, elderly, chronically ill, and smoking patients.

Previous studies, such as those by Hubacek et al. in the Czech Republic, Aladağ et al. in Turkey, and Verma et al. in India, reported various associations between ACE1 gene polymorphisms and symptomatic or severe COVID-19, although results were not always consistent and did not conclusively link these variants to hospitalization or mortality outcomes (12-14).

Delanghe et al. conducted a study to compare the prevalence and mortality rates of COVID-19 across several European countries with the geographical distribution of the I/D polymorphism in the ACE gene (4). Unlike other studies, the authors found a negative correlation between the frequency of the D allele of the ACE I/D polymorphism and COVID-19 prevalence and mortality in 33 countries. Its results conflicted with data from East Asian populations[15,16]. The study suggested an inverse relationship between the frequency of the ACE D allele and COVID-19 prevalence. Given that the D allele frequency is lower in Asian populations compared to European populations, a higher prevalence and mortality rate of COVID-19 would be expected in Asia (14-16).

In Poland Sienko et al. have determined that patients with ACE2 rs2285666 AA, ACE2 rs2074192 TT, and ACE2 rs4646174 GG gene variants had a more severe course of COVID-19 (16). However, other studies conducted in Turkey and Germany did not find associations between ACE2 rs2285666 polymorphisms and disease progression (17,18). The observed discrepancies could be attributed to the different distribution of alleles across populations.

Since the onset of the COVID-19 outbreak, numerous researchers have examined the epidemiological characteristics of individuals who were more frequently affected or experienced a more severe form of the disease (18-22). Consistent with our findings, most of them have indicated that those infected were more likely to have chronic illnesses, be male, older in age, and/or be smokers.

There are some limitations to this study, including being conducted at a single center, which limits generalizability. Furthermore, variation in clinical assessment may have influenced severity classification. The results may also be influenced by the fact that many COVID-19 cases recover without hospitalization.

CONCLUSION

This study, the largest of its kind in Turkey, explored the impact of ACE1 I/D and ACE2 rs2285666 polymorphisms on COVID-19 severity across all age groups. Our study does not provide evidence supporting the hypothesis that ACE1 I/D and ACE2 rs2285666 polymorphisms are associated with the severity of COVID-19. Additionally, our findings indicate that age, gender, chronic illnesses, and smoking play significant roles in determining the clinical severity of COVID-19. Genetic factors may still contribute to COVID-19 severity, but underlying health conditions seem to play a more decisive role. Further research with larger, ethnically diverse cohorts is required to clarify the role of genetic variations in COVID-19 outcomes.

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Ethical Decleration: This study was approved by the Scientific Research Ethics Committee of Ege University Faculty of Medicine (IRB-20-12.1T/59). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants or from relatives included in the study.

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