Research Article

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The D allele of angiotensin-converting enzyme gene insertion/deletion polymorphism is associated with the lung involvement in COVID-19

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Abstract

Objectives: In COVID-19, severe lung involvement develops in some patients. The reason for the predisposition to lung involvement in some patients is not yet fully understood. Genetic variabilities in angiotensin-converting enzyme (ACE) may explain why some patients are more susceptible to lung injury. Thus, the ACE gene insertion/deletion (I/D) polymorphism was investigated in COVID-19 patients with and without lung involvement.

Methods: The study involved 216 patients who were divided into two groups as with and without pulmonary involvement according to their thoracic computed tomography (CT) scan findings. The ACE I/D gene polymorphism was determined.

Results: Carriers of the DD genotype had a 4.05-fold (OR=4.05, 95% CI: 1.66–9.86, p=0.001) greater incidence of pulmonary involvement. The probability of lung involvement was 2.41-fold higher in D allele carriers (OR=2.41, 95% CI: 1.62–3.60, p=0.000). The I allele was found to be protective and diminished the occurrence of lung involvement (OR=0.41, 95% CI: 0.28–0.62, p=0.000).

Conclusions: In COVID-19 patients, the I allele may lower the risk of lung injury and provide a protective effect. Conversely, the D allele may raise the risk of lung injury and lead to poor outcomes.

Keywords: ACE I/D gene; pneumonia; polymorphism; SARS-CoV-2; viral.

Introduction

The coronavirus disease 2019 (COVID-19) is generated by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. COVID-19 has several clinical signs, including asymptomatic, moderate symptoms, serious pulmonary injury, and acute respiratory distress syndrome (ARDS) [2]. Dyspnea and hypoxia are frequent symptoms of lung disease that can progress to ARDS, shock, multi-organ loss, or even death [3]. In a recent study, the percentage of COVID-19 patients requiring invasive mechanical ventilation due to significant hypoxia was found to be 14% and 12%, respectively [4]. The reason why some people are more likely to have lung problems is not yet clear.

The angiotensin-converting enzyme (ACE) gene is found on the 17q23 chromosome and has a polymorphism in intron 16 that results in either an insertion (I) or deletion (D) of a 287-base pair segment. Polymorphism consists of three types within intron 16 (DD, ID, II) and is affected by
heredity, ethnicity, and regional factors [5, 6]. The ACE I/D gene polymorphism is known to have a considerable impact on plasma ACE levels. The D allele is related to higher ACE activity. A study found that ACE activity levels in DD genotype carriers were higher than in II and ID genotype carriers [2, 7].

There was a lot of discussion when the pandemic first started on how ACE I/D alleles affect the epidemiology and prognosis of COVID-19. To date, different investigations have been performed that look into the connection between the ACE I/D gene polymorphism and the severity of COVID-19, but the results are inconsistent rather than consistent. The majority of these studies are based on data from medical databases on the frequency of ACE alleles as well as COVID-19 prevalence and intensity in diverse populations [2]. The aim of this study is to see if there is a link between the ACE I/D gene polymorphism and the severity of the disease and lung involvement in the Turkish COVID-19 patient population.

Materials and methods

Study design

This prospective cross-sectional study was conducted using the Declaration of Helsinki principles at the Department of Medical Biochemistry, Evilya Celebi Research and Education Hospital of Kutahya Health Sciences University, Kutahya City, Turkey, between January 2021 and June 2021 (after the second wave of the pandemic). The local Human Research Ethics Committee gave their clearance (No: 2020-07/06-11.12.2020-11,466), and the Turkish Ministry of Health gave their consent (2020-09-26T13_58_16). Each patient signed a written informed consent form.

The study included 216 adult patients (113 males and 103 females; mean age, 46 years) who applied to a pandemic outpatient clinic with suspicion of COVID-19. Each patient had a positive real-time quantitative polymerase chain reaction (RT-qPCR) test. All the patients were Caucasian from the same geographic area of Turkey. All patients were showing COVID-19 symptoms, whether mild, moderate, or severe. There were no exclusion criteria based on hospitalization requirements, disease severity, or disease outcomes. Only, the study did not include patients who were taking ACE inhibitors or angiotensin (AT) receptor blockers. According to their thoracic computed tomography (CT) findings, the patients were separated into two groups. According to the thoracic CT findings, group 1 consisted of 108 COVID-19 patients with lung involvement and group 2 consisted of 108 COVID-19 patients without lung involvement. Clinical data of patients were obtained from the hospital information system records.

SARS-CoV-2 in vitro diagnostic test

A positive result on RT-qPCR (Rotor-Gene Q, QIAGEN, Hilden, Germany) of nasopharyngeal swab specimens was used to assess COVID-19 laboratory confirmation. The presence of SARS-CoV-2 RNA was determined using in vitro diagnostic kits (Bio-speedy SARS-Cov-2 RT-qPCR detection kit, Bioeksen, Istanbul, Turkey). COVID-19 positivity was determined in patients who had positive RT-qPCR test results.

Thoracic computed tomography

A diagnostic thoracic CT scan was performed in patients with atypical pneumonia findings on chest X-ray and/or in patients with clinical symptoms suggestive of pneumonia such as dyspnea, tachypnea, cough, and decreased oxygen saturation (PO2<92%). A 16-slice multidetector CT scanner was used to obtain thoracic CT images (Aquilion, Toshiba Medical Systems, Otawara, Japan). A Thoracic CT examination was performed in the supine position without the use of intravenous contrast material during the inspiration phase. All CT scans were evaluated by a radiologist blinded to the RT-qPCR test results. The study included patients with classic COVID-19 pneumonia symptoms (peripheral, bilateral ground glass-consolidation densities, multifocal round ground glass densities, inverted halo sign) [8]. Patients with any of these CT results that could be linked to COVID-19 pneumonia but a negative RT-PCR test were ruled out of the study.

Study of the laboratory tests

The laboratory tests performed routinely in patients admitted to the pandemic outpatient clinic were as follows; complete blood count, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), c-reactive protein (CRP), fibrinogen, d-dimer, ferritin, and cardiac troponin I (cTnI). The automated hematology analyzer (Mindray Bio-Medical Electronics Co., Ltd, Shenzhen, China) with original reagents was used to analyze whole blood counts. Serum AST, ALT activities, and urea, creatinine, and CRP levels were measured on the Beckman Coulter AU5800 analyzer (Beckman Coulter, Miami, FL, USA) with the original reagents. Serum ferritin and cTnI levels were measured on the Beckman Coulter UniCel® Dxl 800 immunoassay system (Beckman Coulter, Miami, FL, USA) with the original reagents. On the Sysmex® CS-5100 SystemTM coagulation analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany), plasma fibrinogen and d-dimer levels were measured using original reagents. The blood samples taken into 4.0 mL heparinized tubes to study ACE I/D gene polymorphism analysis were stored at −80 °C until the study day.

ACE I/D gene polymorphism

The normal phenol-chloroform technique was used to isolate DNA from blood samples from both groups. Genotyping was performed by the PCR method using a thermal master cycler gradient (Thermo Scientific, EU, Lithuania). The primers’ sequences were as follows: 5′-CTG GAG ACC ACT CCC ATC CTG CT-3′ (forward primer) and 5′-GAT GTG GCC ATC ACA TTC GGA T-3′ (reverse primer). The PCR products were separated on 2% agarose gels and visualized using ethidium bromide staining under ultraviolet light. The polymorphism was detected as DD (190 bp), ID (190–490 bp), and II (490 bp) genotypes (Figure 1).
differences were found between the groups for eosinophil, urea, AST, CRP, d-dimer, fibrinogen, ferritin, and cTnl values (p=0.0004, p=0.047, p=0.005, p<0.0001, p=0.001, p<0.0001, p=0.002, respectively). Urea, AST, CRP, d-dimer, fibrinogen, ferritin, and cTnl values were higher in group 1 than in group 2. On the other hand, eosinophil levels were lower in group 1 than in group 2 (Table 1).

The comparison of demographic and laboratory data according to II, ID, and DD genotypes in COVID-19 patients with pulmonary involvement is shown in Table 2. There was a statistically significant difference among the mean ages of the patients with the II, ID, and DD genotypes in the

**Table 1:** Comparisons of demographic and laboratory data between thoracic CT (+) and thoracic CT (−) groups.

| Variables          | Thoracic CT (+) (n=108) | Thoracic CT (−) (n=108) | p-Value |
|--------------------|-------------------------|-------------------------|---------|
| Gender (n, %)       |                         |                         |         |
| Male               | 57 (53)                 | 52 (48)                 | 0.892   |
| Female             | 51 (47)                 | 52 (48)                 |         |
| Age, years         | 49 ± 17                 | 42 ± 16                 | 0.002a  |
| WBC (10³/ul)       | 6.3 (4.75–8.41)         | 6.05 (4.90–7.67)        | 0.390   |
| Neutrophil (10³/ul)| 4.15 (2.96–6.23)        | 3.81 (2.84–5.25)        | 0.118   |
| Lymphocyte         | 1.52 (1.1–1.96)         | 1.53 (1.02–2.1)         | 0.619   |
| Eosinophil (10³/ul)| 0.02 (0.0–0.08)         | 0.06 (0.01–0.11)        | 0.0004a |
| Hemoglobin, g/dl   | 14.3 (13.0–15.3)        | 14.8 (13.3–16.0)        | 0.061   |
| Platelet (10³/ul)  | 217.5 ± 57.4            | 225.0 ± 61.7            | 0.358   |
| Urea, mg/dL        | 30 (23–37)              | 26 (23–34)              | 0.047a  |
| Creatinine, mg/dL  | 0.98 (0.83–1.11)        | 0.93 (0.82–1.10)        | 0.542   |
| AST, U/L           | 27.5 (21.0–39.0)        | 24.0 (19.0–31.0)        | 0.005a  |
| ALT, U/L           | 26.0 (17.3–38.8)        | 23.0 (16.0–37.0)        | 0.358   |
| CRP, mg/L          | 20.7 (6.7–77.3)         | 6.5 (3.5–14.0)          | <0.0001a|
| D-dimer, ng/mL     | 585.0                   | 363.0                   | 0.001a  |
| Fibrinogen, mg/dL  | 427.0                   | 303.0                   | <0.0001a|
| Ferritin, ug/L     | (347.0–536.0)           | (256.5–376.0)           | <0.0001a|
| cTnl, ng/L         | 108.0                   | 53.5 (24.8–109.0)       | <0.0001a|

Data were presented as mean standard deviation (SD) for normally distributed data and median and interquartile ranges (IQRs) for non-normally distributed data. Numbers and percentages were used to express categorical variables. The comparisons of numerical variables between groups were analyzed with the independent-sample t-test and the Mann–Whitney U test according to the distribution of data. The comparisons of categorical variables between groups were analyzed with the chi-square (χ²) test.

*Statistical significance was defined as a p-value of less than 0.05.

**Results**

The demographic and laboratory data of patients are shown in Table 1. Patients in group 1 were 51 (47% female) and 57 (53% male), with a mean age of 49 ± 17 years. Patients in group 2 were 52 (48%) female and 56 (52%) male, with a mean age of 42 ± 16 years. The age difference between groups was statistically significant (p=0.002). Group 1 had a higher mean age than group 2. Significant
thoracic CT (+) group (p=0.07). CRP, fibrinogen, and ferritin levels were observed to differ significantly amongst
the groups (p=0.039, p=0.007, p=0.004, respectively). Patients with the DD genotype had higher fibrinogen and
ferritin levels than those with the II and ID genotypes. Patients with the DD genotype had greater CRP levels than those with the II genotype (Table 2).

The comparison of demographic and laboratory data according to the II, ID, and DD genotypes in COVID-19
patients without pulmonary involvement is demonstrated in Table 3. There was a statistically significant difference
among the eosinophil levels of the patients with II, ID, and DD genotypes in the thoracic CT (−) group (p=0.012). Eosinophil levels were lower in the patients with the DD
genotype than in the patients with the II genotype (Table 2).

Table 4 shows the frequency of ACE genotypes in thoracic CT (−) and thoracic CT (+) groups. There was a statistically significant difference between groups for ACE
genotype frequencies ($\chi^2=30.5, df=2, p=0.000$). The distributions of ACE genotypes were found to be 15.7% (17) for II, 64.8% (70) for ID, and 19.4% (21) for DD in the thoracic CT
(−) group, and 11.1% (12), 33.3% (36), and 55.6% (60) for II, ID, and DD, respectively, in the thoracic CT (+) group. With
a statistically significant difference, the DD genotype was
more frequent in the thoracic CT (−) group than in the thoracic CT (−) group. In the thoracic CT (+) group, the risk
of lung involvement in DD genotype carriers was 4.05-fold
higher than in II genotype carriers (OR=4.05, 95% CI: 1.66–
9.86, p=0.001) and 5.56-fold higher than in ID genotype
carriers (OR=5.56, 95% CI: 2.93–10.53, p=0.000) (Table 4). The allele frequencies for the ACE gene in the patients
with thoracic CT (−) and thoracic CT (+) are shown in Table 4. The distribution of ACE I alleles was found to be
48.1% (104) in the thoracic CT (−) group and 27.8% (60) in the thoracic CT (+) group; D alleles were found at 51.9%
(112) and 72.2% (156) in the thoracic CT (−) and thoracic CT
(+) groups, respectively. There was a statistically signifi-
cant difference between groups for allele frequency ($\chi^2=19.03, df=1, p=0.000$). The frequencies of the D allele
were higher in the thoracic CT (+) group than in the thoracic
CT (−) group, with a statistically significant difference. Indi-
viduals with the D allele had a 2.41-fold higher risk of
lung involvement (OR=2.41, 95% CI: 1.62–3.60, p=0.000).
The frequencies of the I allele were higher in the thoracic CT
(−) group. In the COVID-19 patients with the thoracic CT (−)
group, the I allele may reduce the risk of lung involvement

| Table 2: Comparisons of demographic and laboratory data in the thoracic CT (+) group according to genotypes. |
|-----------------------------------------------|
| **Thoracic CT (+)**                      | **II (n=12)** | **ID (n=36)** | **DD (n=60)** | **p-Value** |
| Age, years                              | 50 ± 14       | 54 ± 15       | 46 ± 18       | 0.07<sup>d</sup> |
| Gender (n, %)                            |               |               |               |               |
| Female                                   | 5 (42)        | 15 (42)       | 31 (52)       | 0.586        |
| Male                                     | 7 (58)        | 21 (58)       | 29 (48)       |              |
| WBC (10<sup>3</sup>/µL)                  | 6.10 (4.51–8.09) | 6.25 (4.86–8.29) | 6.43 (4.91–9.37) | 0.775        |
| Neutrophil (10<sup>3</sup>/µL)            | 4.03 (2.89–5.07) | 4.08 (3.0–6.07) | 4.53 (3.33–6.40) | 0.928        |
| Lymphocyte (10<sup>3</sup>/µL)            | 1.67 (1.12–2.31) | 1.56 (1.09–2.17) | 1.31 (0.92–1.85) | 0.136        |
| Eosinophil (10<sup>3</sup>/µL)            | 0.02 (0.01–0.09) | 0.01 (0.003–0.03) | 0.005 (0.00–0.03) | 0.054        |
| Hemoglobin, g/dL                        | 14.0 (12.2–14.8) | 14.1(13.2–15.6) | 14.5 (13.0–15.6) | 0.369        |
| Platelet (10<sup>5</sup>/µL)             | 233 (170–308) | 221 (174–254) | 206 (173–233) | 0.565        |
| Urea, mg/dL                             | 28 (21–32) | 29 (22–37) | 34 (25–45) | 0.209        |
| Creatinine, mg/dL                       | 0.92 (0.77–1.09) | 0.98 (0.93–1.12) | 0.99 (0.82–1.11) | 0.606        |
| AST, U/L                                | 34 (21–37) | 31 (23–49) | 26 (20–36) | 0.100        |
| ALT, U/L                                | 31 (17–44) | 28 (21–41) | 24 (15–33) | 0.113        |
| CRP, mg/L                               | 13.6 (3.8–70.1)<sup>a</sup> | 14.9 (9.6–56.4) | 28.6 (13.6–141.4)<sup>c</sup> | 0.039<sup>d</sup> |
| D-dimer, ng/mL                           | 335 (262–554) | 444 (254–908) | 633 (402–1,053) | 0.243        |
| Fibrinogen, mg/dL                       | 389 ± 82.5<sup>a</sup> | 411 ± 128.6<sup>a</sup> | 488 ± 125.6<sup>b</sup> | 0.007<sup>d</sup> |
| Ferritin, µg/L                           | 61.5 (12.3–187.5)<sup>a</sup> | 86.0 (32.0–169.0)<sup>b</sup> | 187.5 (100.0–530.8)<sup>abc</sup> | 0.004<sup>d</sup> |
| cTnI, ng/mL                              | 3.6 (2.0–6.3) | 3.8 (2.0–10.7) | 4.2 (1.7–16.8) | 0.566        |

Data were presented as mean standard deviation (SD) for normally distributed data and median and interquartile ranges (IQRs) for non-normally distributed data. Numbers and percentages were used to express categorical variables. The comparisons of numerical variables between groups were analyzed with the independent-sample t-test and the Mann–Whitney U test according to the distribution of the data. The comparisons of categorical variables between groups were analyzed with the chi-square ($\chi^2$) test. For d-dimer and ferritin levels, the multiple comparisons between II vs. ID, II vs. DD, and ID vs. DD were analyzed with the Dunnet T3 post-hoc test. For the other laboratory parameters, the multiple comparisons between II vs. ID, II vs. DD, ID vs. DD were analyzed with the Tukey’s post-hoc test. <sup>a</sup>In each line, the differences between the means with same letters are significant, p<0.05, <sup>b</sup>II vs. DD; <sup>c</sup>II vs. DD and ID vs. DD. <sup>d</sup>Statistical significance was defined as a p-value of less than 0.05.
and create a protective effect (OR=0.41, 95% CI: 0.28–0.62, p=0.000) (Table 4).

**Discussion**

While some people with COVID-19 have moderate symptoms, others develop severe lung involvement and even ARDS. The cause of some patients’ increased susceptibility to lung involvement is not entirely known. One of the main causes of morbidity and mortality in COVID-19 infection is pulmonary injury with accompanying respiratory distress [9]. As a result, we conducted a prospective case-control research to see whether the ACE I/D gene polymorphism plays a role in COVID-19 patients’ vulnerability to pulmonary involvement.

According to our data, the DD genotype frequencies were higher in COVID-19 patients with pneumonia than in patients without pneumonia. Individuals with the DD genotype had a 4.05-fold higher risk of lung involvement than those with the II genotype. Individuals with the DD genotype had a 4.05-fold higher risk of lung involvement...
than those with the II genotype. The D allele was found more frequently in COVID-19 patients with pneumonia than in patients without pneumonia. Patients with the D allele had a 2.41-fold increased risk of lung involvement. Furthermore, we found substantial correlations between laboratory tests, which serve as prognostic markers in COVID-19, and genotype frequencies. According to these findings, the I allele in COVID-19 patients may reduce the risk of lung injury, provide a protective effect, and improve disease progression. Conversely, the D allele may increase the risk of lung injury and result in poor results.

To date, several studies have been published investigating the relationship between the ACE I/D gene polymorphism and the severity of COVID-19. A positive link was discovered between the D allele and COVID-19, as well as mortality, in a study of the Asian population that encompassed 28 countries [1]. In a study conducted on 26 COVID-19 patients who were treated with mechanical ventilation due to respiratory failure, it has been found that 73% of the patients had the DD genotype [10]. A recent study revealed that patients with the DD genotype and D allele carriers had a 2.0-fold increased risk of serious disease compared to individuals with ID, II genotypes, and I carriers [11]. Similarly, a meta-analysis published by Yamamoto et al. reported that the number of COVID-19 cases and deaths were negatively linked with the ACE II genotype frequency [12]. In another meta-analysis, DD genotype carriers had a 47% higher risk of severe COVID-19 than carriers of II or ID [13]. According to a recently published study, patients with the DD genotype had a 3.69 times higher risk of COVID-19 severity [14]. Gómez et al. showed that the ACE DD genotype frequencies were higher (46%) in the severe COVID-19 patients [15]. A study by Gunal et al. reported that the DD frequency was higher (63.3%) in severe patients while the II genotype frequency was higher (50%) in asymptomatic patients [16]. In a study conducted by Livshits et al. in Ukraine and some European countries, a negative correlation was found between the carrier of ACE genotype II and susceptibility to COVID-19 infection, morbidity, mortality from COVID-19, per one million population [17]. Bellone and colleagues showed a direct relationship between the DD genotype and deaths from COVID-19 and an inverse relationship between the II genotype and deaths from COVID-19 in 25 European countries [18]. In another study including 112 COVID-19 patients, the frequencies of the DD genotype and D allele were higher than the II genotype and the I allele. Patients with COVID-19 pneumonia were classified as severe or nonsevere in the same study based on their symptoms and vital signs. Despite the fact that all patients with the II genotype developed pneumonia, none of them had severe pneumonia or needed oxygen therapy. 8% of patients with the DD genotype developed serious pneumonia [19]. The ACE DD polymorphism has been demonstrated to decrease the expression of ACE2. Reduced ACE2 enhances the severity of COVID-19 infection by amplifying the harmful effects of ATII on lung tissue [20–22].

On the other hand, there are also studies in the literature that have results contrary to the findings of our study. Karakas et al. observed that ACE I/D gene polymorphism has no effect on COVID-19 severity [23]. In another study, ACE gene D allele frequencies of the Bosnian–Herzegovinian population and 17 other European populations were compared with the prevalence, mortality, and severity of COVID-19. The findings demonstrated that there was no link between the frequency of the ACE D allele and the total number of reported infections, fatal cases, and serious cases [24]. Aung et al. found that the II genotype frequency was substantially connected with a reduction in COVID-19 mortality rates, whereas the DD genotype frequency did not [25]. Ristic et al. reported that there was no significant relationship between ACE I/D gene polymorphism and COVID-19 incidence and mortality rates in 34 European countries [26]. A study by Hubacek et al. suggested that individuals with the ACE II genotype could be at increased risk for symptomatic COVID-19 [27]. These inconsistent results are most likely due to differences in ethnicity, population heterogeneity, sampling bias, biological factors, study design, data analysis, timing of analysis (first or second wave of the pandemic), and the prevalence of the ACE I/D gene polymorphism in the analyses. Moreover, various environmental and social factors, such as nutrition and physical exercise, have been linked to changes in epigenetic state [28].

According to Staessen et al., ethnicity was a major factor in the D and I allele frequencies. The D allele was found in 39.1% of Asians and 56.2% of Caucasians, according to the authors. The prevalence of the I allele was 60.9% in Asians, 43.8% in Caucasians. The prevalence of the I allele was 60.9% in Asians, 43.8% in Caucasians. The genotype distributions of Asians and Caucasians were as follows: in Asians, DD was 17.9%, II was 39.7%, and ID was 42.4%; in Caucasians, DD was 32.5%, II was 20.1%, and ID was 47.4% [29]. The genotype and allele distribution ratios of randomly selected patients in our study are consistent with the ratios reported by Staessen et al. for the Caucasian race.

One of the findings of our study was the association between ACE I/D genotypes and various laboratory tests that have prognostic importance in the assessment and follow-up of COVID-19. CRP, fibrinogen, and ferritin levels were higher in the patients with the DD genotype than in the patients with the II and ID genotypes. Eosinophil levels were lower in the patients with the DD genotype than in the patients with the II genotype. A recent meta-analysis
reported that severe disease might be associated with higher levels of white blood cells, a higher concentration of tissue injury biomarkers such as aminotransferases, urea, creatinine, and cardiac troponin I, higher values of hemostasis tests such as fibrinogen, d-dimer, higher values of inflammatory biomarkers such as CRP, ferritin, and procalcitonin [30]. According to Ghahramani and colleagues’ meta-analysis, there is a link between the intensity of the COVID-19 and lymphopenia, eosinopenia, thrombocytopenia, and anemia [31]. It has been reported that reduced platelet, lymphocyte, hemoglobin, eosinophil, and basophil counts, as well as an increase in neutrophil counts, have been linked to COVID-19 infection and worse clinical results [32]. The findings of our study were also consistent with those of the published studies, and there was a significant relationship between ACE genotypes and some laboratory tests indicating serious disease.

Our study has several limitations, as follows: relatively small sample size and single center. Due to the high expense of genotypic analysis, the number of participants in this study is small. Second, we only looked at the ACE I/D gene polymorphism, not serum ACE levels. More research is needed to confirm these findings at the serum ACE level.

Conclusions

The results of this preliminary study demonstrated that there was a significant relationship between COVID-19 pneumonia and the ACE I/D gene polymorphism. Based on these results, we conclude that the ACE II genotype may be protective against the pulmonary involvement in COVID-19. Conversely, individuals with the ACE DD genotype and D allele carrier patients may be susceptible to lung involvement due to COVID-19. As a result, the ACE I/D gene polymorphism may be a useful marker for predicting disease progression, and DD genotype and D allele carrier patients may be suitable for ACE inhibitors and AT receptor blocker therapy. In addition, advanced age, eosinopenia, high urea, AST, CRP, d-dimer, fibrinogen, ferritin, and cTnl values were risk factors for lung involvement in COVID-19 infection. However, further studies should be performed in different and larger populations and different ethnicities to better understand the relationship between COVID-19 pneumonia and ACE I/D gene polymorphism.

Informed consent: Informed and written consent was obtained from all individuals included in this study.

Ethical approval: Ethical committee approval was received from the Kutahya Health Sciences University, Human Research Ethics Committee (No: 2020-07/06-11.12.2020-11466). Additionally, the Turkish Ministry of Health (2020-09-26T13_58_16) approved the study.

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