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Original Article

The Relationship between Serum ACE Level and Disease Severity in Patients Hospitalized Due To COVID-19 pneumonia

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ABSTRACT

Objective: The renin-angiotensin-aldosterone system (RAS) plays an important role in the pathophysiology of COVID-19. The role of the angiotensin-converting enzyme (ACE), which is part of RAS, in COVID-19 is unclear. The study aimed to investigate whether there was a relationship between serum ACE level at admission and disease severity in COVID-19.

Methods: A total of 158 patients hospitalized in our clinic between January 2021 and April 2021 due to COVID-19 pneumonia were included in this study. Patients were divided into two groups: mild-moderate and severe pneumonia, according to the severity of the disease. The two groups were compared in terms of age, gender, symptoms and signs, comorbidities, laboratory parameters, serum ACE level, and mortality. Serum ACE level was measured by a spectrophotometric method.

Results: The mean age of the patients was 61 years (min: 18, max: 89), and 85 (53.5%) were male. The most common symptoms were dyspnea (61%), cough (57.2%), and malaise (49.7%). The number of leukocytes, C-reactive protein, ferritin, D-Dimer, and days of hospitalization were higher in the severe pneumonia group compared to the mild-moderate pneumonia group, and the difference was statistically significant ($p=0.004$, $p<0.001$, $p=0.005$, $p=0.01$, $p<0.001$, respectively). The rates of intensive care unit admission, intubation, and mortality were higher in the severe pneumonia group ($p=0.035$, $p=0.035$, $p=0.035$, respectively). The mean serum ACE level of the patients was 25.14 (min: 3.39, max: 75.28) U/L; no significant difference was found between the groups ($p=0.61$).

Conclusion: No correlation was found between serum ACE levels at the time of hospitalization and COVID-19 severity. Serum ACE levels at admission did not reflect disease severity.

INTRODUCTION

In 2019, a new virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), from the coronavirus (CoV) family, emerged in China and caused a pandemic that affected the entire world, especially with viral pneumonia.[1,2] Coronavirus disease 2019 (COVID-19) is highly contagious and has the capacity to cause more severe clinical forms such as upper airway disease to acute respiratory distress syndrome (ARDS).[3] This virus poses a greater risk, especially in the elderly and comorbid population.[4,5] The virus binds to angiotensin-converting enzyme (ACE) 2 receptors to enter cells, similar to SARS-CoV.[6,7] The lung, most affected by SARS-CoV-2 infections, is related to its large surface area and the fact that 83% of the cells expressing ACE2 are type II alveolar epithelial cells.[8-11] In addition to type II alveolar cells, ACE2 is expressed in myocardial, bladder, esophageal, ileum and colon epithelial cells and oral mucosa cells[9,10]

ACE2 and ACE, which play a role in the renin-angiotensin-aldosterone system (RAS), have a similar structure, and the imbalance between them is considered to play a role in ARDS.[12,13] ACE stimulates vasoconstriction by converting Angiotensin I (Ang ı) to Angiotensin II (Ang II) and activates thrombotic, proinflammatory, and fibrotic processes by binding to Ang II angiotensin type 1 (AT1) receptors. Ang II, converted by ACE, is an important peptide of RAS that induces vasoconstriction and exerts multiple biologic functions. Another effect of Ang II is to increase interleukin-6 (IL-6), which is one of the poor prognostic factors for COVID-19.[14] It also increases Ang II, plasminogen activator inhibitor-1, and tissue factor levels, causing thrombus in great arteries and arterioles.[15] In the non-classic RAS pathway, ACE2 has the ability to metabolize Ang II to Ang1-7.[9] Thus, it causes a decrease in inflammation, fibrosis, and thrombosis.[16,17] It has been reported that Ang(1-7) formation, which is transformed by ACE2, plays an important role in the clinic in studies conducted on ARDS models.[18]

The classic RAS route worsens impaired respiratory conditions, and the non-classic route has a protective role in ARDS. Therefore, the role of RAS in the pathogenesis of COVID-19 is useful for managing and treating. There are studies on ACE2, the cell entry receptor of SARS-CoV-2,[19] but few studies have been performed on serum ACE activity. ACE/Ang II and ACE2/Ang (1-7) routes may be associated with COVID-19 pneumonia. ACE activity may be associated with disease severity. There are conflicting results in the literature regarding ACE activity. The decrease in serum ACE activity was associated with COVID-19 severity, and serum ACE levels increased with the disease regression.[20] In another study, it was found that there was no relationship with disease severity [21]. We aimed to investigate baseline serum ACE activity and disease severity in COVID-19.

MATERIALS AND METHODS

Between January 2021 and April 2021, 159 patients aged 18 years and over who had confirmed COVID-19 pneumonia and required inpatient follow-up and treatment were admitted to City Hospital. All patients were of Caucasian origin. This research was designed as a prospective and single-center study. The Ethics Committee (Decision no: 514/192/53) approved the study, and written informed consent was obtained. Nasopharyngeal or oropharyngeal swab samples defined as positive for SARS-CoV-2 using real-time reverse transcription polymerase chain reaction (RT-PCR) were determined as confirmed cases. The disease severity was defined as mild-moderate and severe pneumonia according to the COVID-19 guide.[22]

Tachypnea (respiratory rate ≥30/minute) or oxygen levels with a pulse oximeter ≤90% in room air and bilateral diffuse pneumonia findings on radiology were classified as having severe pneumonia, and others as having mild or moderate disease. Patients under the age of 18 years, those with negative PCR tests, and pregnant women were excluded from the study. Demographic data, symptoms, comorbidities, biochemistry results, and radiologic examinations were obtained from hospital records. All data were reviewed by pulmonary physicians. Thoracic imaging, electrocardiogram, complete blood count, biochemistry, C-reactive protein, D-dimer, ferritin, and serum ACE activity were evaluated on the 1st day of hospitalization. Cases were followed up until discharge or end of life in the hospital. Blood was taken from the patients immediately after they were admitted to the clinic. Samples were drawn into 5 mL Vacutainer® SST™ II tubes (BD, Franklin Lakes, NJ, USA) for CRP and ferritin and were centrifuged at 3000g for 10 minutes. For D-dimer test analyses, 2.7-mL BD Vacutainer Plus Plastic Citrate Tubes with 3.2% (109 mmol/L) sodium citrate with a ratio of 9:1 blood/citrate were used. Blood samples were drawn into 3-mL BD Vacutainer K2EDTA Plus plastic tubes. For CBCs, measurements were performed on the day of admittance. Ferritin was measured using a UniCel DxI 800 analyzer (Beckman Coulter, Brea, CA, USA), with a 2-site immunoenzymatic ("sandwich") assay. CRP was measured on a BN II analyzer (Siemens, Germany), using an immunoturbidimetric assay. D-dimer was analyzed using a turbidimetric method on a fully automated Sysmex CS-2500 device (Sysmex Corporation, Norderstedt, Germany). Only ACE test samples were studied within 6 days.

Serum ACE Activity Assay: Peripheral blood samples were collected in BD Vacutainer® Serum Separating Tubes II

Table 1. The characteristics of the patients

COVID-19 n =158	
Sex/male n %	85 (53,5)
Age/years*	61 (18-89)
Severe pneumonia n%	68 (42.8)
BMI*	28.89 (17.78-38.95)
Cough n%	91 (57.23)
Dyspnea n %	97 (%61)
Gastrointestinal symptoms n %	35 (22)
Fatigue n %	79 (49,7)
Miyalgia n %	48 (30,2)
Headache n %	11 (7)
Comorbidity n %	106 (66.7)
Hypertension n %	50 (31.4)
Diabetes mellitus	45 (28.3)
Cardiovascular disease n %	34 (31.5)
Asthma n%	12 (7.6)
Renal disease n %	12 (7.6)
Neurological disease n %	16 (10.1)
Serum ace U/L*	25,14 (3,39-75,28)
Intensive care support n %	23 (14.5)
Intubation n %	22 (13.8)
Number of days of hospitalisation	9 (3-39)
Mortality n %	22 (13.8)

Table 2. The characteristics of the mild-moderate pneumonia and severe group

	Severe pneumonia n=68	Mild to moderate pneumonia n=90	p
Age (years)	62 (30-88)	57 (18-89)	0.194
Sex Male n (%)	40 (58.8)	45 (49.4)	0.215*
Body mass index	28,24 (20,44-38,95)	29,4 (17,78-37,87)	0.187
Cough, n (%)	41 (60.29)	50 (55.56)	0,551
Shortness of breath, n (%)	48 (70,59)	48 (53.3)	0,028
GIS symptoms, n (%)	13 (19,12)	22 (24,44)	0,425
Fatigue, n (%)	40 (58,82)	39 (43,33)	0,054
Myalgia, n (%)	27 (39,71)	21 (23,33)	0,027
Headache n (%)*	4 (5,88)	7 (7.78)	0.64
Comorbidy n (%)	45 (66.18)	60 (66,67)	0,948
Hypertension, n (%)	17 (25.00)	33 (36.67)	0,118
Diabetes mellitus, n (%)	20 (29.41)	24 (26,67)	0,703
Renal disease, n (%)	4 (5.97)	8 (8,89)	0,496
Cardiovascular diseases, n (%)	15 (22.39)	18 (20)	0,716
Asthma, n (%)	5 (7.35)	7 (7.78)	0,920
Fever	36,65 (36-39,1)	36,6 (36-39,3)	0,820
Sp02 (%)	86.68±3.79	93.80±2.16	<0.001
Systolic (mmHg)	120 (90-180)	120 (90-164)	0.195
Diastolic (mmHg)	70 (50-100)	81 (57-110)	0.757
Heart rate (min)	81,5 (60-140)	81 (57-110	0.353
Leukocytes	7300 (1110-23080)	5740 (1110-16030)	0.004
Lymphocytes	1040 (200-7800)	1065 (180-3390)	0.472
Platelets	195500 (7000-493000)	186000 (83000-756000)	0.272
CRP (mg/dL)	96,6 (2-283)	55 (1,4-230)	<0.001
Ferritin (ng/mL)	552 (31,7-2000)	326 (22,3-2000)	0.005
D-dimer (ng/mL)	770 (190-4400)	575 (190-4400)	0.010
Serum ACE (U/L)	25.6 (4.14-65.12)	24.58 (3.39-75.28)	0.612
Serum ACE (U/L)**	27.85 (4,52-65.12)	25,06 (3,39-75,28)	0.455
ACEI, n (%)	5 (7.46)	6 (6.67)	0.847
ARB blockers, n (%)	7 (10.45)	9 (10.11)	0.94
The hospitalization days	11 (4-39)	7 (3-20)	<0.001
ICU admission, n (%)	14 (20.59)	8 (8.89)	0.035
Intubation, n (%)	14 (20,59)	8 (8,89)	0,035
Mortality n (%)	14 (20,59)	8 (8,89)	0,035

Mann Whitney-U Test. * chi-square test. ** Evaluated in patients not using ACE inh or ARB blockers.

Advance Tube (SST) (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Thirty minutes after blood collection, the tubes were centrifuged at 2000 g for 10 minutes, serum was separated, and stored at 2-8°C until studied. According to the manufacturer's recommendations, samples for ACE were studied within 6 days of being taken. Serum ACE activity was measured according to the instructions (Ben S.r.l. Biochemical Enterprise, Via Pietro Toselli, 4, 20127 Milano, Italy) and analyzed using the Saturno-300 plus biochemistry analyzer (CRNOY S.R.I, Italy). Measurements were made using a kinetic spectrophotometric method.

Statistical Analysis

Analyses were performed using SPSS version 25.0 software. Histogram plots and the Kolmogorov-Smirnov test were used to analyze the conformity of the variables to the normal distribution. For descriptive analyses, mean,

Table 3. Correlation between serum ACE and inflammation parameters

	Serum ACE
CRP	
r	0.029
p	0.714
Ferritin	
r	-0.059
p	0.461
D-dimer	
r	-0.007
p	0.928

Spearman correlation test

standard deviation, and median were used. Categorical variables were compared using the Chi-square test. P values below 0.05 were considered statistically significant.

RESULTS

A total of 158 patients who were hospitalized due to definite COVID-19 were included, 85 (53.8%) of whom were male. The median age in the patient group was 61 (min: 18, max: 89) years. Dyspnea (61%), cough (57.2%), and fatigue (49.7%) were, respectively, the most common initial symptoms. Hypertension (HT) (31.4%), diabetes mellitus (DM) (28.3%), and cardiovascular disease (CVD) (21.5%) were the most common comorbidities. The mean serum ACE level was 25.14 (3.39-75.28) U/L. The mean length of stay in the hospital was 9 (3-39) days. A total of 22 (13.8%) patients died.

The characteristics of the patients are presented below (Table 1).

The characteristics of the mild-moderate pneumonia and severe group are shown in Table 2. There was no statistically significant variation observed in the sex distribution, age, and body mass index averages when comparing the groups (respectively p=0.215, p=0.194, p=0.187). The rates of shortness of breath, myalgia, need for intensive care, intubation, and mortality were significantly higher in the severe pneumonia group (respectively p=0.028, p=0.027, p=0.035, p=0.035, p=0.035). The leukocyte values of the group with mild-moderate pneumonia were lower than those of the severe group (p=0.004). Ferritin, D-dimer, and CRP values were higher in severe pneumonia than in mild-moderate pneumonia (p=0.005, p=0.010, and p<0.001, respectively). Serum ACE levels were insignificant between the groups (p=0.61). Serum ACE levels were also insignificant after patients on RAS blockers were excluded (p=0.45). No correlation was found between serum ACE activity and inflammatory parameters (CRP, ferritin, D-dimer) (Table 3).

DISCUSSION

This study aimed to evaluate the relationship between ACE activity in COVID-19 and disease severity. No correlation was observed between serum ACE levels and the severity of COVID-19 disease. The outcomes remained consistent even after excluding individuals who used RAS blockers. Similar findings are reported in the literature.[21-24]

The RAS regulates blood pressure and electrolyte balance. It is regulated by the balance between ACE and ACE2. ACE plays a role in vasoconstriction, hypoxic, oxidative, and inflammatory changes. ACE2 is responsible for counteracting the negative effects of Ang II. Therefore, the amounts of the two enzymes are the main regulators of the RAS.[23]

In the study of Güler et al.,[21] serum ACE activity was unrelated to disease severity. It was also not correlated with inflammatory markers. In their study, it was found that there was no significant difference in serum ACE levels between patients with COVID-19 and controls. In another study of 79 patients by Henry et al.,[24] similar results were obtained. In a study of 103 patients conducted by Bayyiğit et al.,[25] no difference was determined between COVID-19 patient groups in terms of serum ACE levels. These findings suggest that the role of ACE2 may be more constructive than ACE in the pathophysiology and SARS-CoV-2 infection progression. ACE activity is mainly determined by its polymorphism. Studies have shown that the D allele of the ACE I/D polymorphism is associated with increased levels of serum and tissue ACE and Ang II.[26,27] ACE gene polymorphism could not be examined in our study.

Our study showed serum ACE activity was not correlated with inflammatory markers. Similar results were also observed in the literature.[21] There are studies in the literature with different results. In a study by Chen et al.,[28] lower levels of serum ACE on admission were reported as a risk factor for COVID-19 disease progression. In addition, patients with ACE ≤33.5 U/L had higher levels of IL-2R, IL-6, IL-10, CRP, and ferritin than those with ACE >33.5 U/L.

As shown in previous studies, disease severity and mortality are associated with advanced age.[29] In a meta-analysis by Levin et al.,[29] it was demonstrated that mortality increases with age in COVID-19. In our study, the severe group was older. HT, CVD, and DM are critical risk factors in COVID-19. Approximately 66% of COVID-19 cases had comorbidities. HT, DM, and CVD were associated with RAS in our study. Consistent with current results, previous studies revealed that the most common comorbidities in patients with COVID-19 were HT and DM.[30]

In our study, leukocyte, CRP, D-dimer, and ferritin values, which are inflammation parameters, were found to be higher in the group with severe pneumonia. These findings are consistent with the literature.[31]

This study has several limitations. First, it was a single-center study with a relatively small sample size. Second, serum ACE activity was measured only at admission; serial

measurements may better define the relationship between ACE and COVID-19 severity. Third, Ang II, ACE2 levels, and ACE gene polymorphism could not be evaluated.

Conclusion

This study demonstrated that serum ACE activity decreased in COVID-19 pneumonia and there was no correlation between serum ACE level and disease severity. Serum ACE activity could not be used as a marker to determine the severity of COVID-19. Evaluation of the relationship between ACE2 activity and Ang II may help to determine the role of serum ACE in the pathogenesis, and new studies are needed.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 30.12.2020, Decision No: 514/192/53).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.Z.E., Z.Y., S.Ş.C., N.K., E.D., E.T.P., A.B.; Design: B.Z.E., Z.Y., S.Ş.C., N.K., E.D., E.T.P., A.B.; Supervision: B.Z.E., Z.Y., S.Ş.C., N.K., E.D., E.T.P., A.B.; Fundings: Z.Y., B.Z.E.; Materials: B.Z.E., A.B., S.Ş.C.; Data: B.Z.E., Z.Y.; Analysis: B.Z.E., N.K.; Literature search: B.Z.E., E.D.; Writing: B.Z.E., E.D.; Critical revision: S.Ş.C., N.K.

Conflict of Interest

None declared.

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COVID-19 Nedeniyle Yatan Hastalarda Serum ACE Düzeyi ile Hastalık Şiddeti Arasındaki İlişki

Amaç: Renin-anjiyotensin-aldosteron sistemi (RAS) COVID-19 patofizyolojisinde önemli bir rol oynamaktadır. RAS'ın bir parçası olan anjiyotensin dönüştürücü enzimin (ACE) COVID-19'daki rolü belirsizdir. Bu çalışma, COVID-19'da başvuru sırasındaki serum ACE düzeyleri ile hastalık şiddeti arasında bir ilişki olup olmadığını araştırmayı amaçlamıştır.

Gereç ve Yöntem: COVID-19 pnömonisi nedeniyle Ocak 2021-Nisan 2021 tarihleri arasında kliniğimize yatırılan toplam 158 hasta çalışmaya dahil edilmiştir. Hastalar hastalığın şiddetine göre hafif-orta ve ağır pnömoni olarak iki gruba ayrılmıştır. İki grup yaş, cinsiyet, semptom ve bulgular, komorbiditeler, laboratuvar parametreleri, serum ACE düzeyi ve mortalite açısından karşılaştırılmıştır. Serum ACE düzeyi spektrofotometrik yöntemle ölçülmüştür.

Bulgular: Hastaların ortalama yaşı 61 (min: 18 maks: 89) olup 85 (%53.5)'i erkekti. 106 (%66.7) hastada ek hastalık mevcuttu. En sık semptom sırayla dispne (%61), öksürük (%57.2) ve halsizlikti (%49.7). Ağır pnömoni olan grupta lökosit, C-reaktif protein, Ferritin, D-Dimer ve yattığı gün sayısı hafif-orta pnömoni grubuna göre daha yüksek olup fark istatistiksel olarak anlamlı bulundu (sırayla p=0.004, p<0.001, p=0.005, p=0.01, p<0.001). Ağır pnömoni grubunda yoğun bakım ünitesine gidiş, entübasyon ve mortalite oranları daha yüksekti(sırayla p=0.035, p=0.035, p=0.035). Hastaların ortalama serum ACE düzeyi 25.14 (min: 3.39- max: 75.28) U/L olup her iki grup arasında anlamlı fark saptanmadı (p=0.61).

Sonuç: Hastaneye yatış sırasındaki serum ACE düzeyleri ile COVID-19 şiddeti arasında herhangi bir ilişki bulunmadı. Başvuru anındaki serum ACE düzeyinin hastalık şiddetini yansıtmadığı saptanmıştır.

Anahtar Sözcükler: Anjiyotensin dönüştürücü enzim; COVID-19; hastalık şiddeti; serum ACE.