Original Article

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Evaluation of the Association between Multilobar Involvement and ACE Inhibitor Use in SARS-CoV-2 Patients

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Abstract

Aim: Angiotensin-converting enzyme 2 (ACE2) acts not only as an enzyme but also as a thought to be central receptor by which severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) enters host cells. Angiotensin-converting enzyme inhibitors (ACEIs) are thought to $1 are central to SARS-CoV-2 progression. However, its effect on clinical outcomes is still not fully explained. In this study, we investigated the effects of ACEIs use on pulmonary computed tomography findings.

Methods: The data of the patients who were hospitalized for SARS-CoV-2 pneumonia and were using medications for the diagnosis of hypertension from 20th March to 20th June 2020 were evaluated retrospectively. Patients were divided into 2 groups patients using ACEIs and not using ACEIs.

Results: The study was conducted with 107 patients. Mild cases without signs of pneumonia were excluded from this study. Moderate cases were accepted as patients with symptoms related to the respiratory system and pneumonia detected on imaging. SpO2≤93%, ≥30 breaths/min respiratory rate, and patients who developed respiratory failure, mechanical ventilator need, shock, or multiorgan failure were included in the severe and critically ill cases group. Severe and critical cases were evaluated as a single group. When the radiological images of the patients were examined, it was remarkable that multilobar findings were less common in the ACEIs using group ($p<0.001$). At the clinical end point, mortality rates in patients using ACEIs (12.7%) were significantly lower than patients without using ACEIs (32.7%).

Conclusion: In our study, we showed that SARS-CoV-2 progresses with less multilobar involvement in pulmonary computed tomography in patients using ACEI.

Keywords: Angiotensin-converting enzyme 2, angiotensin-converting enzyme 2 receptor, angiotensin-converting enzyme inhibitors, SARS-CoV-2, lung injury

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to be a significant public health problem, affecting more than 50 million people worldwide. Although the mortality rate is below 5% (1), its mortality is significantly higher in individuals with a history of diabetes, hypertension, cardiovascular disease, or cerebrovascular disease, which has aroused considerable interest in the pathophysiological mechanisms triggered by this infection (2). Studies have shown that the novel-type coronavirus is from the betacoronavirus family, such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), and is similar to the bat coronavirus with >95% homology (3). It has also been shown in genomic analyses that the SARS-CoV-2 genome sequence is more than 75% similar to the SARS-CoV genome (4). Concerning its clinical course, the novel type of coronavirus may lead to severe pneumonic involvement similar to SARS-CoV and MERS-CoV (5).

Severe acute respiratory syndrome coronavirus-2 acts through the angiotensin-converting enzyme 2 (ACE2) receptor (6,7). Angiotensin-converting enzyme 2 receptor, which is highly expressed in lung alveolar epithelial cells in the heart, kidney, and vascular endothelium tissues, is

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also considered to act as the receptor that initiates cellular infection of the new type of coronavirus (6). The efficacy of ACE inhibitors (ACEIs), which have been used safely for treating hypertension for many years, is supported by hard evidence in the treatment of heart failure, post-myocardial infarction, and diabetes-related kidney failure (8). Whether ACEIs use is effective against SARS-CoV infection remains a matter of debate yet. Although it is considered that the number of ACE2 receptors will be up-regulated because of the use of ACEIs it will be easier for the virus to infect the cell (1), this opinion has not been confirmed with clarity. In this study, we evaluated the epidemiological and clinical features of patients with coronavirus disease-2019 (COVID-19) who had taken ACEIs as well as, patients who had not taken ACEIs, before the diagnosis.

Materials and Methods

Compliance with Ethical Standards

Approval was obtained from the Ethics Committee of the University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital (date: 29.06.2020, approval no: HNEAH-KAEK 2020/120). This was conducted in compliance with the principles of the Declaration of Helsinki. The hospital ethics committee waived written informed consent because the study was retrospective and evaluated only the clinical data of the patients and did not involve any potential risk.

Study Population and Data Collection

This study was approved by the University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital's Ethical Committee. Written informed consent was waived by the local ethics committee due to the retrospective non-invasive nature of this study. In our study, electronic medical records and emergency department archives of COVID-19 patients hospitalized in University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital from 20th March to 20th June 2020 were evaluated retrospectively. University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital is a tertiary care center, and approximately 200000-250000 patients apply to the emergency clinic a year. By the literature, the COVID-19 clinical classification was classified as mild, moderate, severe, and critically ill cases (9). Mild cases without signs of pneumonia were excluded from this study. Moderated cases were accepted as patients with symptoms related to the respiratory system and pneumonia detected on imaging. SpO_2 ≤93%, ≥30 breaths/min. respiratory rate, and patients who developed respiratory failure, mechanical ventilator need, shock, or multiorgan failure were included in the severe and critically ill cases group. Severe and critical cases were evaluated as a single group.

Epicrisis information was obtained from 623 patients diagnosed with COVID-19 in 3-months period starting from March 2020, 453 of these patients were evaluated in the mild case group and were excluded from the study. Six patients using angiotensin-receptor blockers (ARBs) were excluded from the study. Patients (n=9) who were not diagnosed with hypertension but who used ACEIs due to congestive heart failure or diabetic nephropathy were excluded from this study. Two researchers reviewed the case report forms independently to double-check the collected data. Patients (n=48) whose epidemiological, laboratory, or symptomatic information could not be found in electronic medical records, emergency department archives, or nurse records were excluded from this study. Because of this study, 107 patients whose moderate or severe/critically ill COVID-19 pneumonia diagnoses were confirmed from their medical records and who were using antihypertensive drugs due to hypertension were included in this study.

The diagnosis of COVID-19 pneumonia was confirmed in patients presenting with respiratory symptoms in accordance with the literature by the presence of pulmonary computed tomography (CT) findings showing viral pneumonia and by the positive viral nucleic acid test (reverse transcription-polymerase chain reaction) performed on oropharyngeal and nasopharyngeal swab samples. Radiological findings suggesting COVID-19 pneumonia were accepted as parenchymal multilobar lung lesions, ground-glass opacities, crazy paving signs, and peripheral distribution detected in pulmonary CT (10-12).

By examining the medical and nursing records of the patients, their age, sex, comorbid diseases, complaints during admission, duration of symptoms, and vital signs at the time of admission to the emergency clinic (systolic blood pressure, body temperature, oxygen saturation, heart rate), D-dimer, ferritin, CRP, leukocyte, lymphocyte, and procalcitonin levels, medications used by the patient, ward or intensive care follow-up notes and clinical outcomes (mortality or discharge) were noted.

Pulmonary Computed Tomography Protocols

High-resolution transverse pulmonary CT images were obtained using a Canon CT Scanner (Model TSX-035A). The tube voltage was 120 or 135 kV, and the automatic tube current modulation was 10-300 mA. All images were reconstructed with a slice thickness of 1.0 mm. Images were acquired while holding a breath during full inspiration. Pulmonary CT data at hospital admission were collected retrospectively from the hospital archive system. Radiological evaluation was performed a retrospective review of radiological records. Radiological findings were classified as unilateral ground glass opacity/consolidation, bilateral ground glass opacity/consolidation, and multilobar lesions (13).

After the collected data were organized, the patients included in this study were divided into two groups: patients who used ACEIs and patients who did not use ACEIs. The epidemiological characteristics, vital signs, comorbid diseases, and mortality rates of the two groups were compared with each other.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). The normality assumptions were controlled by the Shapiro-Wilk test. Categorical data were analyzed by Fisher's Exact or Pearson chi-square test. Descriptive analyses were presented using mean±SD (range), median (range), or n (%), where appropriate. Mann-Whitney U test and Student's t-test were used for the analysis of normally and non-normally distributed numerical data, respectively. The 95 percent confidence interval was used to evaluate all analyses, and significance was determined at the $p<0.05$ level.

Results

In this study, the records of 107 patients who were diagnosed with COVID-19 pneumonia and who had been using antihypertensive drugs before this diagnosis was examined. Fifty-five patients included in this study were using ACEIs due to hypertension. Fifty-two patients were using calcium channel blockers (34.6%, n=37), β-blockers (31.8%, n=34), alpha-2 blockers (3.7%, n=4), or diuretics (28.9%, n=31) alone or in combination. The mean age of 107 patients included in this study was 68.49±11.95 years. 50.5% (n=54) of them were male. The mortality rate was 22.4% (n=24). When all patients were evaluated together, their comorbid diseases included diabetes (47.7%), coronary artery disease (CAD) (31.8%), chronic obstructive pulmonary disease (COPD) (10.3%), and chronic renal failure (CRF) (14%). The comparative demographic and clinical characteristics of the patient groups using ACEIs and not using ACEIs are given in Table 1. The comorbidity rates of diabetes, CAD, COPD, and CRF were similar in both patient groups (p=0.103, p=0.540, p=0.135, p=0.341, respectively). There was no difference between the two groups concerning symptom duration or complaint characteristics (Table 1). When the two groups were compared, no difference was found between the characteristics of the patients' ward or intensive care follow-up processes (p=0.161). When the CT findings of the patients were classified as the presence of unilateral or bilateral ground-glass appearance, or the dispersal of multilobar lung lesions, less multilobar involvement was found in the ACEIs using group ($p<0.001$).

There was a statistically significant difference in death rates between the ACEIs using and non-ACEIs using groups (12.7% vs. 32.7%, respectively, p=0.013). When vital signs (systolic blood pressure, body temperature, oxygen saturation, heart rate) and D-dimer, ferritin, CRP, creatinine, hemoglobin, leukocyte, lymphocyte, and procalcitonin levels were compared between the patient groups using ACEIs and not using ACEIs, no statistically significant difference was found ($p>0.05$) (Table 2).

For predicting mortality in univariate regression analysis; age [odds ratio (OR)=1,075; 95% confidence interval (CI): 1,026-1,126, p=0.002], CRF (OR=3.86; 95% CI: 1,231-12,105, p=0.021), ACEIs (OR=0.3; 95% CI: 0.112-0.802, p=0.016), multilobar lung lesions, (OR=3,385; 95% CI: 1,221-9,382, p=0.019), fever (OR=2,182; 95% CI: 1,339-3,556, p=0.002), D-Dimer (OR=17,942; 95% CI: 4.39-73,321, $p<0.001$), leukocytes (OR=1,113; 95% CI: 1,025-1,208, p=0.011), creatinine (OR=2,283; 95% CI: 1.49-3,498, $p<0.001$), hemoglobin (OR=1,113; 95% CI: 1,025-1,208, p=0.011) values' significant efficacy was observed (Table 3).

Discussion

In this study, we have shown that patients with COVID-19 who use ACEIs as antihypertensive have less multilobar involvement compared to patients who use drugs other than ACEIs as antihypertensive treatment and have a diagnosis of COVID-19. That multilobar involvement was less common in patients using ACEIs in our study suggests that viral replication is limited and viral load decreases in these patients. The significance of multilobar involvement and ACEIs in predicting mortality in the univariate regression analysis supports these results.

Angiotensin-converting enzyme inhibitors treatment reduces viral load and inhibit viral replication in previous studies (14,15). The renin-angiotensin system (RAAS) is critical in maintaining electrolyte balance and regulating blood pressure (8). Therefore, blockade of the RAAS pathway with ACEIs is considered among the leading treatment options for treating hypertension (8). When the literature is examined, there are different views about the results of ACEIs use in SARS-CoV cases. It has been reported that ACE2 receptors act as binding sites for virions of beta coronaviruses (1), and the RAAS pathway is considered to play a critical role in acute lung injury caused by viruses in blood pressure regulation (1,15,16). Therefore, a view has been proposed that patients using ACEIs may be at higher risk for SARS-CoV-2 infections, given that the number of ACE2 receptors will increase (1). However, sufficient evidence was not obtained to support or reject this view. The reason for this uncertainty is that there are not enough studies showing the ACE2 receptor levels in patients using ACEIs (17). When the previous studies were examined, it was seen that no significant

difference was found concerning ACE2 activity between the patient groups who were using ACEIs and were not using ACEIs for treating heart failure, atrial fibrillation, and CAD (17-20).

Angiotensin 2 has pro-inflammatory properties, cause endothelial and microvascular dysfunction, and play a role in maintaining vascular tone (15,21,22). Therefore, the RAAS blockade will also likely to decrease inflammatory cytokine release (15). Through this mechanism, the RAAS blockade can contribute to hemodynamic stabilization in the case of inflammation and will play a critical role in preventing sepsis-related adverse clinical outcomes (15,23). However, it is still unclear whether angiotensin II blockade that arises from ACEIs is associated with an improved clinical outcome in patients with COVID-19. In previous studies, it was reported that mostly bilateral or multilobar lung involvement was detected during the admission of COVID-19 patients (24). In a study conducted with 102 patients with a confirmed diagnosis of COVID-19, the findings showed that the number of lung lobes affected by COVID-19 was associated with mortality (25). Lung injury correlates with the viral load in patients infected with COVID-19 (14,15).

In the prospective study of Bauer et al. (26) with 204 patients using ACEIs or ARBs and diagnosed with COVID-19, the patients were randomly divided into two groups according to RAS inhibition therapy: discontinuation or continuation status. Although there

Table 1. Demographic and clinical characteristics of the patients

	Total (n=107)	Not using ACEIs (n=52)	Using ACEIs (n=55)	p-value
Age (years)	68.49±11.95 (38-97)	70.13±10.16 (43-91)	66.93±13.33 (38-97)	0.163
Gender				
Male (n, %)	54 (50.5)	27 (51.9)	27 (49.1)	0.770
Female (n, %)	53 (49.5)	25 (48.1)	28 (50.9)	
Past medical history (n, %)				
Diabetes mellitus	51 (47.7)	29 (55.8)	22 (40)	0.103
CAD	34 (31.8)	18 (34.6)	16 (29.1)	0.540
COPD	11 (10.3)	3 (5.8)	8 (14.5)	0.135
CRF	15 (14)	9 (17.3)	6 (10.9)	0.341
Prognosis (n, %)				
Discharged	83 (77.6)	35 (67.3)	48 (87.3)	**0.013**
Death	24 (22.4)	17 (32.7)	7 (12.7)	
No ICU care (n, %)	84 (78.5)	40 (76.9)	44 (80)	0.161
ICU care (n, %)	19 (17.8)	12 (23.1)	7 (12.7)	
Radiologic findings (n, %)				
Unilateral ground-glass opacity	13 (12.1)	7 (13.5)	6 (10.9)	0.686
Bilateral ground-glass opacity	90 (84.1)	45 (86.5)	45 (81.8)	0.504
Multiple lobe lesions	57 (53.3)	37 (71.2)	20 (36.4)	**<0.001**
Symptom duration (days)	4 (1-30)	4 (1-30)	5 (1-30)	0.406
Clinical symptoms (n, %)				
Fever	51 (47.7)	26 (50)	25 (45.5)	0.638
Cough and sputum	57 (53.8)	23 (44.2)	34 (63)	0.053
Dyspnea	49 (45.8)	23 (44.2)	26 (47.3)	0.752
Sore throat	4 (3.7)	1 (1.9)	3 (5.5)	0.618
Fatigue	30 (28)	14 (26.9)	16 (29.1)	0.803
Diarrhea	15 (14)	9 (17.3)	6 (10.9)	0.341
Chest pain	4 (3.7)	1 (1.9)	3 (5.5)	0.618
Myalgia or arthralgia	6 (5.6)	3 (5.8)	3 (5.5)	0.999
Anosmia	2 (1.9)	0 (0)	2 (3.6)	0.496

Mann-Whitney U test, Student's t-test, Fisher's Exact test, Pearson chi-square test used for analysis. Data are presented as mean±SD (range), median (range), or n (%). ACEI: Angiotensin-converting enzyme inhibitor, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, ICU: Intensive care unit, SD: Standard deviation

Table 2. Clinical features and selected laboratory findings of the patients

	Total (n=107)	Not using ACEIs (n=52)	Using ACEIs (n=55)	p-value
Temperature °C	36.6 (36-40)	36.7 (36-40)	36.6 (36-39.5)	0.334
Heart rate, beats/min	85 (10-153)	85.5 (10-153)	84 (15-120)	0.638
SBP, mmHg	125.95±22.72 (60-176)	127.94±20.61 (80-170)	124.07±24.59 (60-176)	0.381
Oxygen saturation, %	96 (77-100)	95.5 (77-99)	96 (80-100)	0.508
D-dimer (ng/mL)	958 (198-9989)	1115 (250-9989)	920 (198-9440)	0.250
Ferritin (ng/L)	260 (9-5842)	253 (9-3952)	260 (18-5842)	0.311
Procalcitonin (ng/mL)	0.05 (0.05-50.64)	0.05 (0.05-50.64)	0.05 (0.05-23.63)	0.396
CRP (mg/L)	5.55 (0.2-38.8)	5.9 (0.2-38.8)	3.9 (0.2-31.2)	0.358
Leukocytes (10^3/μL)	6.89 (1.56-36.54)	6.84 (3.13-36.54)	6.89 (1.56-29.03)	0.594
Lymphocytes (10^3/μL)	1.33 (0.16-6.3)	1.28 (0.17-5.8)	1.48 (0.16-6.3)	0.566
Hemoglobin (g/dL)	12.3 (1.05-17.1)	12.25 (6.3-17.1)	12.3 (1.05-15.3)	0.874
Creatinine (mg/dL)	1.01 (0.39-7.54)	1.03 (0.59-7.54)	0.92 (0.39-3.76)	0.299

Mann-Whitney U test, Student's t-test used for analysis. Data are presented as mean±SD (range) or median (range).
CRP: C-reactive protein, SBP: Systolic blood pressure

Table 3. Univariate logistic regression analysis of factors affecting mortality

	Univariate regression analysis	
Variables	**OR (95% CI)**	**p-value**
Age	1.075 (1.026-1.126)	0.002
Male gender	2.368 (0.914-6.138)	0.076
Diabetes mellitus	1.4 (0.562-3.483)	0.470
CAD	1.096 (0.417-2.883)	0.852
COPD	1.833 (0.423-7.954)	0.418
CRF	3.86 (1.231-12.105)	**0.021**
ACEIs	0.3 (0.112-0.802)	**0.016**
CCBs	0.559 (0.201-1.559)	0.266
β-blockers	0.655 (0.234-1.834)	0.420
Alpha-2 blockers	1.159 (0.115-11.683)	0.900
Diuretics	2.164 (0.649-7.211)	0.209
Multilobar lung lesions	3.385 (1.221-9.382)	**0.019**
D-dimer (ng/mL)	17.942 (4.39-73.321)	**<0.001**
Leukocytes (10^3/μL)	1.113 (1.025-1.208)	0.011
Lymphocytes (10^3/μL)	0.986 (0.605-1.607)	0.955
Hemoglobin (g/dL)	0.788 (0.639-0.971)	**0.025**
Creatinine (mg/dL)	2.283 (1.49-3.498)	**<0.001**

ACEIs: Angiotensin-converting enzyme inhibitors, CAD: Coronary artery disease, CCBs: Calcium channel blockers, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, OR: Odds ratio

was no significant difference between the groups in terms of 30-day mortality, it was emphasized that the discontinuation of the drug could accelerate the healing process. Azad and Kumar (27) meta-analysis with 1,566 subjects did not show a significant relationship between the use of ACEIs/ARB and death due to COVID-19. In another study conducted with 849 patients, a lower risk of death was observed in COVID-19 patients using ACEIs/ARBs for hypertension (28). In a meta-analysis examining 1321 COVID-19 patients, no association was found between the use of ACEIs/ARB and mortality and disease severity (29). In our study, baseline laboratory values and comorbidities of patients using and not using ACEIs were found to be similar. In the study by Aparisi et al. (28), the comorbidities and clinical features of COVID-19 patients using and not using ACEIs were found to be similar, and it was emphasized that the use of drugs in this group during COVID-19 would not adversely affect the prognosis of the patient.

In a cohort study in which 52,727 patients with a diagnosis of sepsis were included, it was shown that mortality rates were lower in patients using ACEIs or ARBs compared to the patients who did not use them regardless of the infectious agent and underlying comorbid diseases (23). Consistent with this study, other studies have also found an association between ACEI use and reduced mortality rates in patients hospitalized with a diagnosis of community-acquired pneumonia (23,30,31). In our study, the mortality rate was statistically different between the two groups. This difference may arise from the decreased viral load and multilobar involvement in patients using ACEIs.

Study Limitations

The most important limitations of our study are that it was single-centered and the sample size was small. Second, it was retrospective. However, in an ED with a high volume of pandemic patients, all consecutive patients meeting the criteria were included, thereby limiting patient selection bias. Prospective studies that would be conducted with a higher number of patients may reflect the effects of ACEIs use on mortality more accurately.

Conclusion

The findings obtained in this study suggest that COVID-19 progresses with less multilobar lung involvement in patients who have been using ACEIs before their diagnosis with infection. The positive effects of RAAS blockade on the radiological findings in patients with COVID-19 who also have hypertension suggest that the use of ACEIs as an antihypertensive treatment has clinical benefits during infection if there is no contraindication.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of the University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital (date: 29.06.2020, approval no: HNEAH-KAEK 2020/120).

Informed Consent: The hospital ethics committee waived written informed consent because the study was retrospective and evaluated only the clinical data of the patients and did not involve any potential risk.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.S., S.C., Design: D.S., B.G.Y., Data Collection or Processing: B.G.Y., S.C., Analysis or Interpretation: B.G.Y., S.C., Literature Search: D.S., B.G.Y., Writing: D.S., B.G.Y., S.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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