

Clinical effects of angiotensin-converting-enzyme inhibitors on lung computed tomography findings in patients with COVID-19 pneumonia: Is it useful?

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Abstract

Aim: Angiotensin-converting enzyme 2 (ACE2) has a significant physiological role in the renin – angiotensin – aldosterone system (RAAS) pathway. The ACE2 receptor acts as a virus receptor in the pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease. In this study, we aimed to investigate the effects of ACEIs use on radiological imaging and clinical course in COVID-19. **Methods:** In this study, patients who had been using medications for the diagnosis of hypertension and who were hospitalized in Haydarpaşa Numune Training and Research Hospital due to COVID-19 pneumonia were retrospectively evaluated. **Results:** The mean age of 107 patients included in this study was $68,49 \pm 11,95$, and 50.5% (n = 54) of them were male. The patients were divided into two separate study groups as ACEIs users and non-users. In the first of these groups, 55 patients were using ACEIs due to hypertension. In the second group, 52 patients were using calcium channel blockers (CCBs), β -blockers, alpha-2 blockers, or diuretics, alone or in combination. When the lung computed tomography images were examined, multilobar findings were less common in the ACEIs group, which was remarkable ($p < 0.001$). When the clinical endpoint was evaluated, the findings showed that the mortality rates were different in the groups ACEIs users and non-users (12.7% vs. 32.7%, respectively, $p=0.013$). **Conclusion:** Although the role of RAAS blockade in COVID-19 is still not fully elucidated, we have shown that COVID-19 progresses with less damage in the lungs with patients who have been using ACEIs.

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Methods: In this study, patients who had been using medications for the diagnosis of hypertension and who were hospitalized in Haydarpaşa Numune Training and Research Hospital due to COVID-19 pneumonia were retrospectively evaluated.

Results: The mean age of 107 patients included in this study was $68,49 \pm 11,95$, and 50.5% ($n = 54$) of them were male. The patients were divided into two separate study groups as ACEIs users and non-users. In the first of these groups, 55 patients were using ACEIs due to hypertension. In the second group, 52 patients were using calcium channel blockers (CCBs), β -blockers, alpha-2 blockers, or diuretics, alone or in combination. When the lung computed tomography images were examined, multilobar findings were less common in the ACEIs group, which was remarkable ($p < 0.001$). When the clinical endpoint was evaluated, the findings showed that the mortality rates were different in the groups ACEIs users and non-users (12.7% vs. 32.7%, respectively, $p = 0.013$).

Conclusion: Although the role of RAAS blockade in COVID-19 is still not fully elucidated, we have shown that COVID-19 progresses with less damage in the lungs with patients who have been using ACEIs.

Keywords: ACEIs, COVID-19, Multilobar lesions, Radiographic findings

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 infection². Studies have shown that the novel-type coronavirus is from the betacoronavirus family, such as SARS-CoV and MERS-CoV, and is similar to the bat coronavirus with >95% homology³. It has also been shown in genomic analyses that the SARS-CoV-2 genome sequence is more than 75% similar to the SARS-CoV genome⁴. Concerning its clinical course, the novel type of coronavirus may lead to severe pneumonic involvement similar to SARS-CoV and MERS-CoV⁵.

SARS-CoV acts through angiotensin-converting enzyme 2 (ACE2) receptor^{6, 7}. ACE 2 receptor, which is highly expressed in lung alveolar epithelial cells besides heart, kidney, and vascular endothelium tissues, is also considered to act as the receptor that initiates cellular infection of the new type of coronavirus⁶. The efficacy of angiotensin-converting enzyme inhibitors (ACEIs), which have been used safely in the treatment of hypertension for many years, is supported by hard evidence in the treatment of heart failure, post-myocardial infarction, and diabetes-related kidney failure⁸. Whether ACEIs use is effective against COVID 19 infection remains a matter of debate yet. Although it is considered that the number of ACE2 receptors will be up-regulated as a result of the ACEIs use, it will be easier for the virus to infect the cell¹, this opinion has not been confirmed with clarity.

In this study, we aimed to evaluate the epidemiological features, clinical features, and findings in lung computed tomography of patients who were diagnosed with COVID-19 and who were using ACEIs for hypertension since before this diagnosis.

Materials and methods

Study population and data collection

This study was approved by the University of Health Sciences Haydarpasa Numune Training and Research Hospital's Ethical Committee. Written informed consent was waived by the local ethical committee due to the retrospective non-interventional nature of this study. In our study, electronic medical records and emergency department archives of patients with COVID-19 who were hospitalized in Haydarpasa Numune Hospital analyzed during three months from March 2020, retrospectively. Haydarpasa Numune Hospital is a tertiary care center, and approximately 200000-250000 patients apply to the emergency clinic in a year. In accordance with the literature, the COVID-19 clinical classification was made as mild, moderate, severe and critically ill cases⁹. Mild cases without signs of pneumonia were not included in this study. Moderated cases were accepted as patients with symptoms related to the respiratory system and pneumonia detected on imaging. Respiratory rate [?] 30 breaths/min; SpO2 [?] 93% at rest; and PaO2 / FIO2 [?] 300, patients who developed respiratory failure, mechanical ventilator need, shock or multiorgan failure were included in the severe and critically ill cases group. In this study, 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. Patients who were not diagnosed with hypertension but who used ACEIs due to congestive heart failure or diabetic nephropathy were excluded from 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 findings showing viral pneumonia and by the positive viral nucleic acid test (RT-PCR) 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 sign, and peripheral distribution detected in pulmonary computed tomography¹⁰⁻¹².

By examining the medical and nursing records of the patients, their age, sex, comorbid diseases, complaints during admission, duration of symptoms, 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. Findings seen on pulmonary computed tomography were evaluated by two independent physicians who were blinded to the clinical outcomes of the patients.

Radiological findings were classified as bilateral or unilateral parenchymal opacities, bilateral or unilateral ground glass appearance, and multilobar involvement.

Two researchers reviewed the case report forms independently to double-check the collected data. Patients 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.

After the collected data were organized, the patients included in this study were divided into two groups as 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.

Chest CT protocols

High-resolution transverse 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.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). The normality assumptions were controlled by the Shapiro-Wilk test. Descriptive analyses were presented using mean \pm SD (range), median (range), or n (%), where appropriate. Categorical data were analyzed by Pearson chi-square or Fisher's Exact test. Mann-Whitney U test and Student's t-test were used for the analysis of non-normally and normally distributed numerical data, respectively. A p-value of less than 0.05 was considered statistically significant.

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 were examined. 55 patients included in this study were using ACEIs due to hypertension. 52 patients were using calcium channel blockers (CCBs) (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. Six patients using angiotensin-receptor blockers (ARBs) were excluded from the study. The mean age of 107 patients included in this study was 68.49 \pm 11.95 years. 50.5% (n = 54) of them were male. 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 computed tomography 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 (OR = 1.075; 95% 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.

ACEIs treatment has been shown to reduce viral load and inhibit viral replication in previous studies^{13, 14}. The renin-angiotensin system (RAAS) is critical in maintaining electrolyte balance and regulating blood pressure⁸. Therefore, blockade of the RAAS pathway with ACEIs is considered among the leading treatment options in the treatment of hypertension⁸. When the literature is examined, there are different views about the results of ACEIs use in COVID 19 cases. It has been reported that ACE2 receptors act as binding sites for virions of betacoronaviruses¹, and the RAAS pathway is considered to play a critical role in acute lung injury caused by viruses besides blood pressure regulation^{1, 14, 15}. 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 increase¹. 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 ACEIs¹⁶. When the previous studies were examined, it is seen that no significant difference was found concerning ACE2 activity between the patient groups who were using ACEIs and were not using ACEIs for the treatment of heart failure, atrial fibrillation, and coronary artery disease¹⁶⁻¹⁹.

Angiotensin 2 has been shown to have pro-inflammatory properties, cause endothelial and microvascular dysfunctions, and play a role in maintaining vascular tone^{14, 20, 21}. Therefore, the RAAS blockade will also likely to decrease inflammatory cytokine release¹⁴. 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^{14, 22}. 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 cases²³. 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 mortality²⁴. Lung injury has been shown to correlate with viral load in patients infected with COVID-19^{13, 14}.

In previous studies, it was reported that mortality rates in patients using ACEIs were lower than the patients who did not. 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 diseases²². Consistent with this study, other studies have also found an association between ACEIs use and reduced mortality rates in patients hospitalized with a diagnosis of community-acquired pneumonia^{22, 25, 26}.

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. The small sample size and being single-centred are the major limitations of our study. Prospective studies that would be conducted with a higher number of patients may reflect the effects of ACEIs use on the 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 antihypertensive treatment has clinical benefits in the course of infection if there is no contraindication.

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Competing Interests

The authors declare no conflict of interest.

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