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Effect of Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers on Prognosis in COVID-19 Patients

Anjiyotensin Dönüştürücü Enzim İnhibitörleri veya Anjiyotensin II Reseptör Blokerleri Kullanımının COVID-19 Hastalarında Prognoza Etkisi

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ABSTRACT

Objectives: Studies suggest that Coronavirus Disease 2019 (COVID-19) may enter the human body via the angiotensin-converting enzyme 2 (ACE2) receptor, and that the use of renin-angiotensin system (RAS) blockers could increase ACE2 receptor expression. We aimed to investigate the effects of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on the prognosis of COVID-19 patients with hypertension.

Methods: This retrospective, single-center study included 1,130 hospitalized patients aged 18 and over who were diagnosed with COVID-19 via a positive PCR test or based on chest CT radiological findings between March 15, 2020, and July 1, 2021. Patients were divided into two groups: those with and without hypertension. Additionally, hypertensive patients were further categorized based on ACEI/ARB usage to evaluate the impact of these medications on disease prognosis. Statistical analyses were performed using SPSS Statistics 22.

Results: The study included 511 (45%) female and 619 (55%) male patients. The prevalence of hypertension was significantly higher in patients admitted to the intensive care unit compared to those in the ward (63% vs. 41%; p<0.001; OR: 2.51; CI: 1.73–3.65). Similarly, hypertension was more prevalent among deceased patients than among those discharged (68% vs. 40%; p<0.001; OR: 2.9; CI: 1.99–4.21). Regression analysis revealed that ACEI/ARB use did not significantly affect mortality. Among biochemical parameters, a significant difference was observed only in CRP levels between ACEI/ARB users and non-users (7.19±9.75 vs. 8.74±10.18; p=0.032).

Conclusion: No adverse effects of ACEI/ARB use on COVID-19 outcomes were observed. ACEIs and ARBs, which are primary agents in the treatment of coronary artery disease, heart failure, diabetes, and hypertension, can be safely used in patients with COVID-19.

Keywords: Angiotensin converting enzyme inhibitors; angiotensin converting enzyme-2; angiotensin receptor blockers; COVID-19; hypertension.

ÖZET

Amaç: Coronavirus Hastalığı-19'un (COVID-19) patogenezinde, anjiyotensin dönüştürücü enzim-2 (ACE2) reseptörü aracılığıyla insan vücuduna girebileceği ve renin-anjiyotensin sistemi (RAS) blokerlerinin kullanımının ACE2 reseptör ekspresyonunu artırarak 'Severe Acute Respiratory Syndrome-Coronavirus 2' (SARS-CoV-2) ile enfekte olma olasılığını artırabileceğini gösteren çalışmalar mevcuttur. Bu çalışmada, hipertansif hastalarda anjiyotensin dönüştürücü enzim inhibitörleri (ACEİ) ve anjiyotensin reseptör blokerlerinin (ARB) COVID-19 prognozu üzerindeki etkilerini araştırmayı amaçladık.

Yöntem: Bu retrospektif, tek merkezli çalışmaya, 15 Mart 2020 ile 1 Temmuz 2021 tarihleri arasında pozitif polimeraz zincir reaksiyonu (PCR) testleri veya göğüs bilgisayarlı tomografi (BT) radyolojik bulgularına dayanarak COVID-19 tanısı konulan, 18 yaş ve üzeri 1130 hastaneye yatırılmış hasta dahil edilmiştir. Veriler hastane bilgi sistemi üzerinden elde edilmiştir. Hastalar, hipertansiyonu olan ve olmayanlar olarak iki gruba ayrıldı. Hipertansif hastalar ise ACEİ/ARB kullananlar ve kullanmayanlar olarak sınıflandırılarak bu ilaçların hastalık prognozu üzerine etkileri incelendi. İstatistiksel analizler SPSS Statistics 22 programı ile yapıldı.

Bulgular: Çalışmaya 511 (%45) kadın ve 619 (%55) erkek hasta dahil edildi. Yoğun bakımda yatan hastalarda hipertansiyon görülme oranı belirgin olarak daha fazlaydı (%63'e karşı %41; p<0,001; OR: 2,51; GA: 1,73–3,65). Ölen hastalarda hipertansiyon görülme oranı da taburcu olanlara göre anlamlı olarak daha yüksekti (%68'e karşı %40; p<0,001; OR: 2,9; GA: 1,99–4,21). Hipertansif hastalarda ACEİ/ARB kullanımı ile hastanede kalış süresi ve yoğun bakım yatışı arasında anlamlı fark bulunmadı. ACEİ/ARB kullanan hastaların taburcu oranı, ölenlere kıyasla daha yüksekti (sırasıyla %71 ve %60; OR: 0,62; p=0,043). Hastalığın şiddet belirteçlerinden yalnızca CRP düzeylerinde anlamlı fark saptandı (ACEİ/ARB kullananlar: 7,19±9,75; kullanmayanlar: 8,74±10,18; p=0,032).

Sonuç: ACEİ/ARB kullanımının COVID-19 hastalarında olumsuz bir etkisine rastlanmamıştır. RAS inhibitörlerinin hastalık şiddeti ve mortalitesi üzerinde olumlu etkileri olabileceği düşünülmektedir. Bu bulgular doğrultusunda, koroner arter hastalığı, kalp yetmezliği, diyabet ve hipertansiyon tedavisinde birincil ilaçlar olan ACEİ/ARB'lerin COVID-19 hastalarında güvenle kullanılabileceği sonucuna varılmıştır.

Anahtar sözcükler: Anjiyotensin dönüştürücü enzim inhibitörleri; Anjiyotensin dönüştürücü enzim-2; Anjiyotensin reseptör blokerleri; COVID-19; Hipertansiyon.

Coronavirus disease-19 (COVID-19), first identified in December 2019 in Wuhan, rapidly spread worldwide as a pandemic due to its high mortality and morbidity associated with both pulmonary and cardiac complications. On May 5, 2023, the World Health Organization (WHO) announced that COVID-19 was no longer classified as a Public Health Emergency of International Concern. However, during the more than three years that COVID-19 was declared a pandemic, over 765 million people were affected globally, and as of May 7, 2023, it had officially claimed the lives of more than 6.8 million people worldwide.[1] Although COVID-19 is no longer considered a public health emergency, it continues to pose a significant global health threat and presents serious challenges for humanity.

Studies have suggested that COVID-19 may enter the human body through the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of type II alveolar cells.[2] Additionally, there are studies indicating that the Renin-Angiotensin-Aldosterone System (RAAS), which is responsible for regulating sodium, potassium levels, and blood pressure, may play a critical role in modulating acute lung injury caused by viruses such as severe acute respiratory syndrome (SARS) and H7N9.[3,4]

The ACE2 receptor, a homolog of the angiotensin-converting enzyme (ACE) receptor, is highly expressed in heart and lung tissues.[5] ACE inhibitors initially inhibit ACE, leading to decreased angiotensin II levels, which may result in a possible negative feedback loop that upregulates more ACE2 receptors.[6] The upregulation of ACE2 receptors results in increased binding sites for SARS-CoV-2, potentially leading to COVID-19 infection.[7] Regarding this subject, some of the studies have shown a 5-fold increase in ACE2 levels with Lisinopril and a 3-fold increase with Losartan.[8] Despite this, a meta-analysis revealed that ACEI/ARB use does not increase the risk of a positive COVID-19 test, severe infection, or mortality in COVID-19 patients. This has been attributed to the vasoprotective effects of angiotensin 1-7, which are enhanced through its interaction with Mas receptors following RAS blockade. Furthermore, various studies have associated the use of ACEI/ARB in hypertensive patients with a lower risk of death.[9] Although studies have been conducted on the expected positive and negative aspects of RAS inhibition, definitive conclusions regarding its impact on prognosis have not yet been established, and more detailed studies with larger patient populations are needed.

In this study, we aimed to determine whether the use of ACEI or ARBs has any positive or negative effects on the prognosis of COVID-19 patients.

Methods

This retrospective, single-center observational study included 1130 patients aged 18 and over who were diagnosed with COVID-19 either through a positive PCR test or based on radiological findings from chest computed tomography and were hospitalized for COVID-19 treatment at Fatih Sultan Mehmet Training and Research Hospital between March 15, 2020, and July 1, 2021. The data used in the study were collected through the hospital's information management system. Patients were classified based on the presence of hypertension and the antihypertensive medications they

were using. In accordance with the data obtained, the effects of antihypertensive drugs on the morbidity and mortality of the disease were investigated. Ethical approval for this study was obtained from our hospital's ethics committee with the decision numbered FSM EAH-KAEK 2021/71 dated 24.06.2021. Our study complies with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Statistical Analysis

SPSS Statistics 22 software was used for statistical analyses. Descriptive statistics for continuous variables were presented as mean±standard deviation. The Kolmogorov–Smirnov test was employed to assess whether the numerical data were normally distributed. For comparisons between two groups, the Student's t-test was applied to parameters with a normal distribution, while the Mann-Whitney U test was used for those that did not. Logistic regression analysis was performed to control for potential confounding factors. The Chi-square test and Fisher's Exact Chi-square test were used for the comparison of qualitative data. Significance was evaluated at a level of $p<0.05$ for all tests.

Results

The study included 1130 patients with a mean age of 61.11±16.50. Among the patients included in the study, 488 (43%) had hypertension, while 642 (57%) did not have hypertension. Table 1 shows the effects of the presence of hypertension on demographic data and mortality. As shown in Table 1, the ages of hypertensive patients were significantly higher compared to non-hypertensive patients (Hypertensive vs. Non-Hypertensive: 69.82±12.59 vs. 54.49±16.05; $p<0.001$). Among hospitalized patients, the presence of hypertension was significantly more common in females (Hypertension Female/Male (%): 50.3/37.3; $p<0.001$).

The time between the onset of symptoms and hospital admission was not found to be associated with the presence of hypertension. However, the length of hospital stay was significantly longer in patients with hypertension compared to those without (Hypertensive vs. Non-Hypertensive: 8.80±5.71 vs. 5.77±3.83 days; $p<0.001$).

When hospitalized patients were examined, the presence of hypertension was significantly higher in those admitted to the intensive care unit compared to those in the regular ward (Hypertension (%) in Ward–ICU: 41% vs. 63%; OR: 2.51, $p<0.001$). The incidence of hypertension was found to be significantly lower in patients who were discharged in good health compared to those who died (Hypertension (%) in Discharged–Deceased patients: 40% vs. 68%; OR: 2.9, $p<0.001$).

Table 1. Demographic data and the effects of the presence of hypertension on patients' morbidity, and mortality

	Non-Hypertensive	Hypertensive	p
Age			
Mean±SD	54.49±16.05	69.82±12.59	<0.001
Median(IQR)	52 (17)	70 (17)	
Gender, n (%)			
Female	254 (49.7)	257 (50.3)	<0.001
Male	388 (62.7)	231 (37.3)	
Time from Symptom Onset to Hospitalization			
Mean±SD	5.77±3.83	5.66±4.28	0.267
Median (IQR)	5 (4)	5 (4)	
Length of Hospital Stay			
Mean±SD	7.97±7.64	8.80±5.71	<0.001
Median (IQR)	6 (4)	7 (6)	
Hospital Ward, n (%)			
Ward	593 (59)	404 (41)	<0.001
Intensive Care Unit	49 (37)	84 (63)	
Mortality, n (%)			
Discharged	595 (60)	397 (40)	<0.001
Deceased	47 (32)	91 (68)	

Regression analyses were performed considering that gender and chronic diseases (diabetes, dementia, tumor presence, chronic lung disease, chronic renal failure) may affect ICU admission and mortality rates.

The relationship between ICU admission and hypertension was also found to be significant in the regression analysis, with hypertension, dementia, chronic kidney failure, gender, and the presence of malignancy as important factors for ICU admission (Table 2). As shown in the table, the risk of ICU admission was significantly increased in hypertensive patients, with an odds ratio of 1.936 (95% CI: 1.272–2.947; $p=0.002$). This finding highlights the significant impact of hypertension on the need for intensive care.

Based on the regression analysis presented in Table 3, gender, dementia, chronic renal failure, and hypertension were all identified as independent predictors of increased mortality risk. Specifically, the presence of hypertension was associated with a significantly higher risk of mortality, with an odds ratio of 2.445 (95% CI: 1.611–3.712; $p<0.001$). This un-

Table 2. Regression Analysis of Factors that may influence ICU Admission

	B	S.E.	Sig.	Exp(B)	Confidence interval 95% CI. EXP(B)	
					Lower	Upper
Gender	0.516	0.202	0.011	1.675	1.126	2.490
Hypertension	0.661	0.214	0.002	1.936	1.272	2.947
Malignancy	0.747	0.342	0.029	2.110	1.080	4.124
Dementia	1.268	0.341	0.000	3.554	1.822	6.931
Chronic lung disease	0.323	0.262	0.217	1.382	0.827	2.309
Diabetes	0.097	0.213	0.650	1.102	0.725	1.673
Chronic renal failure	1.121	0.248	0.000	3.069	1.886	4.993
Constant	-3.064	0.220	0.000	0.047		

Table 3. Regression Analysis of Factors that may influence the mortality

	B	S.E.	Sig.	Exp(B)	Confidence interval 95% CI. EXP(B)	
					Lower	Upper
Gender	0.601	0.201	0.003	1.824	1.230	2.704
Hypertension	0.894	0.213	0.000	2.445	1.611	3.712
Malignancy	0.470	0.359	0.191	1.600	0.791	3.235
Dementia	1.399	0.332	0.000	4.053	2.114	7.769
Chronic lung disease	0.208	0.265	0.432	1.232	0.733	2.071
Diabetes	-0.050	0.213	0.815	0.951	0.627	1.445
Chronic renal failure	1.035	0.247	0.000	2.815	1.734	4.570
Constant	-3.115	0.222	0.000	0.044		

derscores the critical role that hypertension plays in influencing patient outcomes.

Among the biochemical parameters thought to be associated with the severity of the disease, C-Reactive Protein (CRP), D-dimer, and LDH levels were found to be significantly higher in hypertensive patients. Additionally, lymphocyte levels were significantly lower in hypertensive patients, which can be considered an important indicator related to the severity of the disease ($p<0.05$) (Table 4).

Of the 488 patients with hypertension, 338 (69%) were using either ACE inhibitors or ARBs (RAS inhibitors), while 150 (31%) were using other types of antihypertensive medications. Table 5 shows the effects of RAS inhibitors on the morbidity and mortality of the patients.

As seen in Table 5, there was no statistically significant difference between patients using RAS blockers and those using other antihypertensive medications in terms of age, gender, time from symptom onset to hospitalization, length

Table 4. The effects of the presence of hypertension on laboratory parameters

	Non-hypertensive	Hypertensive	p
C-Reactive Protein			
Mean±SD	6.17±13.43	7.66±9.90	<0.001
Median(IQR)	3 (8)	6 (10)	
Lymphocyte			
Mean±SD	1520.67±752.76	1401±762.33	0.001
Median(IQR)	1400 (800)	1300 (800)	
Ferritin			
Mean±SD	476.63±927.30	493.23±663.18	0.203
Median(IQR)	247 (413)	270 (493)	
Fibrinogen			
Mean±SD	536.29±151.10	555.52±165.35	0.159
Median(IQR)	519 (221)	544 (220)	
D-dimer			
Mean±SD	1.30±2.04	2.96±16.85	<0.001
Median(IQR)	0.7 (0.9)	0.95 (1.2)	
LDH			
Mean±SD	345.51±262.86	351.14±171.96	0.006
Median(IQR)	276 (181)	296 (201s)	

LDH: lactate dehydrogenase.

Table 5. Demographic data and the effects of ACE inhibitor/ ARB use on morbidity and mortality in hypertensive patients

	Non- ACE-i/ARB	ACE-i/ARB	p
Age			
Mean±SD	71.08±12.72	69.26±12.51	0.191
Median(IQR)	72 (8)	69 (17)	
Gender, n (%)			
Female	70 (27)	187 (73)	0.095
Male	80 (35)	151 (65)	
Time from Symptom Onset to Hospitalization			
Mean±SD	5.45±3.80	5.76±4.48	0.880
Median(IQR)	5 (3-7)	5 (2.25-7)	
Length of Hospital Stay			
Mean±SD	8.72±5.27	8.65±5.08	0.965
Median(IQR)	7 (5-11)	7 (5-11)	
Hospital Ward, n (%)			
Ward	118 (29)	286 (71)	0.108
Intensive Care Unit	32 (38)	52 (62)	
Mortality, n (%)			
Discharged	114 (29)	283 (71)	0.043
Deceased	36 (40)	55 (60)	

ACE-i/ARB: Angiotensin converting enzyme inhibitors/ angiotensin receptor blocker.

of hospital stay, and need for intensive care (p>0.05). On the other hand, it is observed that the use of RAS inhibitors was significantly higher in discharged patients compared to deceased patients (ACEI/ARB usage: Discharged–Deceased: 71% vs. 60%; p=0.043).

Although mortality rates were lower in patients using ACE inhibitors/ARBs when considered alone, regression analyses were performed to account for the potential effects of gender and existing chronic conditions (such as diabetes, dementia, presence of tumors, chronic lung disease, and chronic kidney failure) on mortality rates (Table 6).

As seen in Table 6, the use of ACE inhibitors/ARBs alone does not significantly impact mortality and may be influenced by other factors affecting mortality. The regression analysis indicates that the most significant factors affecting mortality in hypertensive COVID-19 patients are chronic kidney failure and dementia.

When comparing the effects of ACE inhibitor/ARB use on biochemical parameters related to the severity of the disease, such as CRP, lymphocytes, ferritin, fibrinogen, D-dimer, and LDH, it was observed that only CRP levels were significantly affected. CRP levels were found to be significantly lower in patients using RAS inhibitors compared to other patients (ACEI/ARB vs. Non-ACEI/ARB: 7.19±9.75 vs. 8.74±10.18; p=0.032) (Table 7).

Discussion

COVID-19, which was first seen in China in 2019 and spread worldwide as a pandemic, although its effect has decreased recently, is still considered an important public health problem.[1] In our study, we investigated the effect of RAS inhibitors, key medications for treating hypertension, on the severity and mortality of COVID-19. Following the analyses, hypertension was found to be an independent risk factor for the severity and mortality of this disease. Although RAS blockers did not show significant differences in biochemical parameters indicative of disease severity, except for CRP levels, they appeared to have a slight but significant effect

Table 6. Regression analysis of factors influencing mortality of hypertensive Covid 19 patients

	B	S.E.	Sig.	Exp(B)	Confidence interval 95% CI. EXP(B)	
					Lower	Upper
ACE-i/ARB usage	-0.367	0.250	0.142	0.693	0.425	1.131
Gender	0.426	0.244	0.081	1.531	0.949	2.473
Malignancy	0.142	0.461	0.758	1.153	0.467	2.845
Dementia	1.094	0.414	0.008	2.986	1.327	6.718
Chronic lung disease	0.405	0.301	0.179	1.499	0.831	2.703
Diabetes	-0.092	0.246	0.708	0.912	0.563	1.477
Chronic renal failure	0.823	0.268	0.002	2.277	1.348	3.848
Constant	-1.785	0.291	0.000	0.168		

ACE-i/ARB: Angiotensin converting enzyme inhibitors/ angiotensin receptor blocker.

Table 7. Comparison of Biochemical Parameters Related to Disease Severity with ACEI/ARB Usage

	Non-ACE-i/ ARB	ACE-i/ ARB	p	Hct (%)	p
C-Reactive Protein					
Mean±SD	8.74±10.18	7.19±9.75			0.032
Median (IQR)	7 (11)	5 (10)			
Lymphocyte					
Mean±SD	1348.99±652.91	1424.40±727.45			0.588
Median (IQR)	1200 (800)	1300 (800)			
Ferritin					
Mean±SD	466.26±504.49	505.96±727.45			0.869
Median (IQR)	264 (627)	274 (458)			
Fibrinogen					
Mean±SD	571.35±163.04	547.89±166.34			0.346
Median (IQR)	560 (228)	541 (221)			
D-dimer					
Mean±SD	3.94±26.55	2.50±8.99			0.707
Median (IQR)	0.98 (1.12)	0.95 (1.2)			
LDH					
Mean±SD	357.23±167.11	348.41±174.29			0.468
Median (IQR)	312 (204)	285 (199)			

LDH: lactate dehydrogenase; ACE-i/ARB: Angiotensin converting enzyme inhibitors/ angiotensin receptor blocker.

on mortality rates when considered alone. However, after performing regression analyses, this effect was no longer significant, likely due to the influence of other factors.

Due to its high morbidity and mortality, the factors that lead to the development and progression of this severe acute respiratory infection have gained importance. Studies have shown that the most common comorbid diseases and factors in patients with COVID-19 are hypertension, diabetes, smoking, COPD, malignancies, and chronic kidney failure.[10]

Hypertension is the most prominent chronic disease, with a global prevalence of 31.1% among adults.[11] In recent studies conducted in Türkiye, the prevalence of hypertension in adults has also been reported to be around 30%.[12] In our study, 43% of the patients had hypertension. Just as in the general population, hypertension is a common comorbidity among patients with COVID-19.

Recent meta-analyses on COVID-19 have shown that hypertension and cardiovascular diseases are associated with the severity and mortality of COVID-19.[10] In addition to the negative effects of hypertension, it has been suggested that the use of ACE inhibitors and ARBs, which are widely used in its treatment, may increase ACE2 receptor expression, potentially increasing the likelihood and severity of the disease.

In many studies on COVID-19, the severity of the disease has been demonstrated through ICU admission and mortality rates. In a study conducted in Italy with 1,591 patients, hypertension was found to be the most common comorbidity among those requiring intensive care, with a prevalence of 49%.[13] In our study, consistent with other studies, the proportion of hypertensive patients in the ICU was significantly higher than that of other patients. Mortality rates among hypertensive patients have been reported as high in nearly all clinical studies. In a study involving 1,833 patients diagnosed with COVID-19, 40.5% had hypertension, and both severe disease and mortality rates were found to be twice as high in those with hypertension compared to those without.[14] Similarly, in our study, the mortality rate among hypertensive patients was 2.9 times higher than that of non-hypertensive patients, in line with previous studies.

Although high levels are generally expected in COVID-19 patients, it has been shown that laboratory parameters such as D-dimer and fibrinogen are higher in hypertensive patients compared to non-hypertensive patients, independent of the presence of infection, and that these elevated levels are associated with mortality.[15] In our study, consistent with other research, CRP, D-dimer, and LDH levels were elevated, while lymphocyte counts were significantly lower among the laboratory parameters related to disease severity.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are part of the renin-angiotensin-aldosterone system (RAS) inhibiting agents and are considered first-line drugs for the treatment of a large proportion of patients with hypertension.[16] However, with the emergence of COVID-19, a pandemic characterized by high mortality and morbidity, the use of ACEI/ARB has become a topic of debate. The RAS plays a crucial role in regulating electrolyte balance and blood pressure and consists of two pathways: the ACE/Ang II/AT1R pathway and the ACE2/Ang(1-7)/Mas receptor pathway (Fig. 1). Under normal physiological conditions, the activity of the ACE/Ang II/AT1R axis and the ACE2/Ang(1-7)/Mas receptor axis maintains a dynamic balance that sustains the normal function of the corresponding system.[17] Similar to SARS, SARS-CoV-2 invades the host via the ACE2 cell entry receptor.[18]

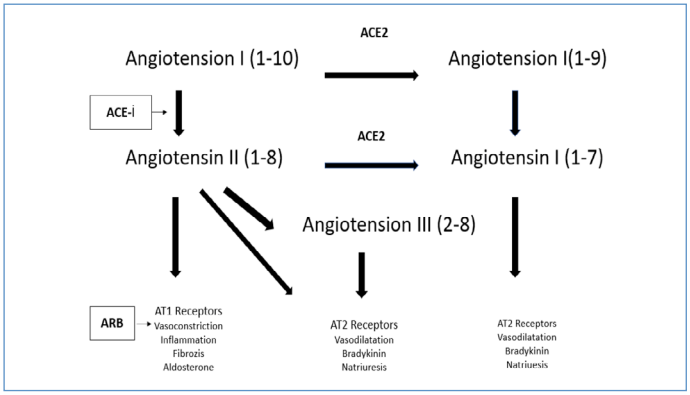

Figure 1. The Renin-Angiotensin System Pathway and the Role of ACE Inhibitors and ARBs.

SARS-CoV infections reduce ACE2 expression, leading to an imbalance between the ACE/Ang II/AT1R axis and the ACE2/Ang(1–7)/Mas receptor axis.[2] Targeting the ACE/Ang II/AT1R axis is a novel therapeutic strategy for hypertension. ACEIs and ARBs not only inhibit the ACE/Ang II/AT1R pathway but also modulate the ACE2/Ang(1-7)/Mas receptor pathway.[19] Considering these mechanisms, the use of RAS blockers may increase SARS-CoV-2 binding capacity due to elevated ACE2 levels on one hand, but on the other hand, by disrupting the Ang II/AT1 receptor relationship and increasing ACE2 levels, it may enhance MasR through Ang(1-9) and Ang(1-7), leading to increased vasodilation and reduced inflammation and fibrosis. While these mechanisms suggest both negative and positive effects, and these have been demonstrated in clinical studies, some studies have not observed significant effects of RAS blocker use on the disease outcomes.

Fang and colleagues hypothesized that the use of drugs that increase ACE2 expression could increase the risk of developing severe and fatal COVID-19. In this context, they suggested that patients with cardiac diseases, hypertension, or diabetes who are treated with drugs that increase ACE2 expression should be closely monitored.[7] One of the rare studies on this topic was conducted in the Wuhan region of China, including a total of 274 patients, 75 of whom were hypertensive and 199 were not. In this study, which included older patients with more comorbidities, it was noted that the rate of developing severe pneumonia was higher in those using ACEI/ARB compared to those not using these medications. In contrast to other findings, although not statistically significant, mortality rates (7% vs. 11%) and hospital stay durations (21 days [IQR: 15–25 days] vs. 22 days [IQR: 16–28 days]) were observed to be lower in those using ACEI.[20]

While there are clinical studies showing negative outcomes with the use of ACEI/ARB, there are also many studies demonstrating the benefits of ACEI/ARB use. In a meta-analysis of 12 studies conducted by Zhang and colleagues, it was indicated that ACEI/ARB use did not increase the development of COVID-19 (OR=0.99; 95% CI: 0–1.04; p=0.672) or the severity of the disease (OR=0.98; 95% CI: 0.87–1.09; p=0.69) and even had positive (lower risk) effects on mortality (OR=0.48; 95% CI: 0.29–0.81; p=0.006).[9] In another multicenter study involving 3430 patients hospitalized with a diagnosis of COVID-19, 1128 of whom were hypertensive, it was shown that the unadjusted mortality rates of 188 patients using ACEI/ARB were significantly lower compared to those not using ACEI/ARB (3.7% vs. 9.8%; p=0.01). The same study also found a significant difference in all-cause mortality risk in Cox regression analyses (adjusted HR=0.42; 95% CI: 0.19–0.92; p=0.03).[21]

In addition to studies with good or poor prognostic data, there are also numerous studies showing that ACEI/ARB use does not affect the mortality and morbidity of COVID-19 patients. In a study with 18,472 participants who had undergone PCR testing, 1735 patients were found to be COVID-19 positive. Among these patients, 116 were using ACEI, while 98 were using ARB. A total of 421 patients (24.3%) were hospitalized, 111 (6.4%) required mechanical ventilation, and 161 (9.3%) required intensive care. No significant differences were found between those using ACEI/ARB and those not using them in terms of hospital admission, ICU need, and ventilator need.[22] In our study, similar to this study, no significant difference was found between ICU admission and the use of RAS inhibitors. Although a significant difference was observed between ACEI/ARB use and mortality when other additional factors were not considered (p=0.043), similar to Mehta and colleagues' study, this difference disappeared after regression analysis, and no statistical difference was found between those using ACEI/ARB and those not.[22]

In another study by Li and colleagues, no significant difference was found between those using RAS inhibitors and those not using them in terms of disease severity and mortality, similar to our study, and no significant differences were found in lymphocyte, ferritin, fibrinogen, D-dimer, and LDH levels. However, although CRP levels were not found to be different in that study, a significant difference was found in our study.[23] In another study by Yang and colleagues involving 126 hypertensive patients, hs-CRP levels were signif-

icantly lower in those using ACE inhibitors/ARBs, similar to our study. The results were again similar to ours, with no significant difference found between ACEI/ARB use and mortality or disease severity.[24] In this study, as in our study, no significant differences were found between RAS inhibitor usage and other biochemical parameters.

Our study has several limitations. First, since this was designed as a retrospective study, a causal relationship between ACEI/ARB use and COVID-19 outcomes cannot be established in this study. Another issue is that the study provides a single-center experience, and these analyses should be examined in different cohorts.

Conclusion

In conclusion, no negative effects of ACEI/ARB use on COVID-19 were observed. Although not significantly, RAS inhibitors may positively influence the severity and mortality of the disease. Based on this data, we believe that ACEIs/ARBs, which are primary drugs in the treatment of coronary artery disease, heart failure, diabetes, and hypertension, can be safely used in patients with COVID-19.

Disclosures

Ethics Committee Approval: The study was approved by Health Sciences University Istanbul Fatih Sultan Mehmet Training and Research Hospital ethics committee (Ethics Approval Number: FSM EAH-KAEK 2021/71, Date: 24/06/2021).

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