original article

Patients with hypertension hospitalized with COVID-19 pneumonia using angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers or other antihypertensives: retrospective analysis of 435 patients

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Citation: Baslilar S, Saylan B. Patients with hypertension hospitalized with COVID-19 pneumonia using angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers or other antihypertensives: retrospective analysis of 435 patients. Ann Saudi Med 2021; 41(5): 268-273. DOI: 10.5144/0256-4947.2021.268

Received: May 17, 2021

Accepted: June 21, 2021

Published: October 7, 2021

Funding: None.

BACKGROUND: The angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) are widely used for the treatment of hypertension (HT). Whether the use of these drugs increases the infectivity of novel coronavirus and results in an additional risk for morbidity and mortality of COVID-19 is a matter of interest.
OBJECTIVES: Assess the effect of ACEI/ARBs compared with other hypertensives on the clinical course and outcome in COVID-19 pneumonia.
DESIGN: Retrospective.
SETTINGS: Tertiary care hospital.
PATIENTS AND METHODS: We collected data on adult inpatients with COVID-19 pneumonia using ACEI/ARBs versus other antihypertensives between 15 March 2020, and 15 February 2021.
MAIN OUTCOME MEASURES: Severity, clinical course, mortality, and time to PCR negativity between patients using ACEI/ARBs and other antihypertensives.
SAMPLE SIZE: 435.
RESULTS: ACEI/ARBs were used by 203 patients (46.6%) (median age: 71 [41-94] years), while 232 patients (53.4%) were using other antihypertensives (median age: 69 [22-93] years, *P*=.645 vs age of ACEI/ARB users). There were no statistically significant differences between the ACEI/ARBs users and non-users in the number of patients admitted to intensive care (65 cases [32%] vs. 74 cases [31.9%], *P*=.978), the median duration of stay in hospital (8 [1-54] days vs. 7 [1-55] days, *P*=.806) the median duration of ICU stay (8 [1-40] days vs. 6 [1-25] days), and the mortality rate (48 cases [23.6%] vs. 61 [26.3%], *P*=.525). While the median days before transfer to the ICU was shorter in ACE/ARBI non-users (2 [1-15] days vs. 3 [1-21] days, *P*=.02), the difference was not important clinically. The median time to PCR negativity was similar in ACEI/ARBs users and non-users (13 [7-34] days for users and 13 [5-45] days for non-users), (*P*=.083).
CONCLUSIONS: ACEI/ARB use is probably unrelated to poor prognosis in COVID-19 pneumonia inpatients. ACEI/ARBs did not prolong the time to PCR negativity. We conclude that using ACEI/ARBs probably does not increase the infectivity of SARS-CoV-2.
LIMITATIONS: Pharmacological therapies were not discussed in detail. The use of corticosteroids may affect the time to PCR negativity. We could not analyze the effect of obesity because of a lack of data.
CONFLICT OF INTEREST: None.

Hypertension is reportedly a risk factor for increased morbidity and mortality in COVID-19.[1,2] The number of angiotensin converting enzyme 2 (ACE2) receptors (the target receptors for entry of the SARS-CoV-2 virus)[3] increased with the use of ACE inhibitors (ACEI) in animal studies;[4] therefore, it was suggested that these drugs may facilitate and increase the infectivity of the virus. However, these drugs have cardioprotective effects and decrease the pulmonary inflammatory response.[5-7] This was a retrospective observational study to assess the effect of the use of ACEI and angiotensin receptor blockers (ARBs) on COVID-19 clinical outcomes and disease severity, along with time to PCR negativity.

PATIENTS AND METHODS

Adult hypertensive inpatients aged over 18 years, treated for COVID-19 pneumonia in the Sultan 2 Abdulhamid Han Training and Research Hospital Chest Diseases Clinic in Istanbul between 15 March 2020, and 15 February 2021, were included in the study. COVID-19 pneumonia was diagnosed based on PCR positivity in nasopharyngeal swab or lower respiratory tract samples and radiological findings consistent with COVID-19 pneumonia on chest computed tomography (CT). This study was approved by the local ethics committee (Approval number 58, date 11 March 2021). The following data were obtained from the hospital medical records: demographic information, medical history, smoking status, comorbidities (coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, arrhythmia, and asthma), clinical features, prognostic laboratory parameters (leukocyte count, lymphocyte count, thrombocyte count, and serum levels of C-reactive protein, lactate dehydrogenase, D-dimer on the day of admission, and number of lymphocytes on hospitalization days 3, 5, and 10) radiological severity of the disease, clinical course, and outcome (lowest percentage of oxygen saturation [SpO_2] value on the day of admission, need for oxygen treatment, intubation and intensive care unit (ICU) follow-up and mortality, the days from hospitalization to transfer to the ICU if necessary, duration of hospitalization and/or ICU follow-up, and the number of days to PCR test negativity by nasopharyngeal swab. Radiological manifestations on chest CT were graded on a scale of 1-4 by modifying the radiological scoring system offered by Bernheim et al:[8,9] mild for a total score of 1-5, moderate for a total score of 6-10, severe for a total score of 11-15, and very severe for a total score >15. Chest CT scans were evaluated for the presence of ground-glass opacities, consolidation, nodules, linear opacities, prominent interlobular septations, bronchial thickening/dilatation, crazy-paving, halo, reversed halo, reactive mediastinal lymphadenopathy, and pleural effusion. Each of the five lung lobes was assessed for degree of involvement and classified as none (0%), minimal (1%-25%), mild (26%-50%), moderate (51%-75%), or severe (76%-100%). Each lobe was assigned a score as follows: 0=no involvement, 1=minimal involvement, 2=mild involvement, 3=moderate involvement, and 4=severe involvement. Finally, the scores for the five lobes were summed.

The patients were divided into two groups: those using ACEI/ARBs, defined as users, and those using other antihypertensive drugs, defined as non-users. The groups were compared in terms of age, smoking status, comorbidities other than hypertension, laboratory parameters, radiological severity, clinical outcome, and the day PCR became negative in the nasopharyngeal swab sample. The relationship of risk factors such as older age (≥65 years), sex, comorbidities, ACEI/ARB use, long hospital stay, and PCR negativity time with transfer to ICU and mortality as the dependent variables. The relationship between PCR negativity time and demographic features, comorbidities, and antihypertensive drug use was also evaluated.

Patient data collected in the study were analyzed with the IBM SPSS for Windows (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Discrete data was given as frequency and percentage. The variables were not normally distributed so the median (range) is given for continuous data. The Mann Whitney U test was used to compare the two groups. The Pearson Chi-Square Test was used to compare categorical groups. Logistic regression analysis was used to examine the risk factors for mortality and intensive care unit admission. The results were considered statistically significant when the *P* value was <.05.

RESULTS

A total of 435 patients (203 ACEI/ARB users [46.6%] and 232 non-users [53.4%]) were hospitalized with SARS-CoV-2 pneumonia during the study period. The median age of the patients and the number of patients under 65 and over 65 was similar between the two groups (**Table 1**). There was no statistically significant difference between the two groups in smoking status. Diabetes and other comorbidities were similar, except for hypertension. Laboratory data on admission and clinical parameters were not statistically different between the groups except for the median days from hos-

pitalization to transfer to ICU was significantly shorter in ACE/ARBI non-users (*P*=.02)]. The difference was not related to the more frequent occurrence of diabetes in the nonusers group (**Table 2**). Based on radiological findings, the median number of patients with mild, moderate, severe, and very severe pneumonia was similar between the two groups (*P*=.398). The median time to PCR negativity following admission was similar in ACEI/ARB users (13 [7-34] days) and non-users (13 [5-45] days), (*P*=.083). The number of patients transferred to the ICU who died was 48 (23.6%) for ACEI/ARB users vs. 61 (26.3%) for users of other antihypertensives (*P*=.525). In the multiple logistic regression analyses, older age (≥65 years), male sex, diabetes, chronic obstructive pulmonary disease, congestive heart failure, long hospital stay, and longer PCR negativity time increased the risk for transfer to ICU (**Table 2**). The risk for mortality was increased with older age, male sex, diabetes, chronic obstructive pulmonary disease, and longer hospital stay (**Table 3**).

DISCUSSION

In this retrospective observational study, the use of ACEI/ARBs was not related to poor prognosis in hospitalized patients with COVID-19 pneumonia. The radiological severity, percentage of patients followed up in the ICU, median duration of stay in the hospital and ICU, and the mortality rate were similar between the ACEI/ARB users and non-users. On the other hand, the median days of hospitalization before the transfer to ICU was significantly shorter in ACEI/ARB non-users, although the difference was not clinically important. These findings are consistent with the results of previous studies.[10-16] Yang et al[10] reported a lower mortality rate in ACEI/ARB users than in non-users (4.7% vs. 13.3%), while the difference was insignificant. They explained the difference between the two groups as due to the presence of a lower proportion of critical and severe patients in the ACEI/ARB users group. In our study, the distribution of patients according to radiological and clinical severity was similar; therefore, we could better assess the effect of ACEI/ARBs. In a prospective study, Hakeam et al[16] showed that the use of ACEI and ARBs was not associated with ICU admission, mechanical ventilation, and mortality in patients with COVID-19. They also reported that the continuation of ACEI/ARB therapy decreased the risk of mortality. Senkal et al[13] also reported that ACEI use was related to mild disease on admission and shorter duration of hospitalization. In our study, the clinical course and outcome were similar in ACEI/ARB users and non-users, and we concluded that the use of these drugs does not worsen the prognosis of COVID-19 pneumonia in hospitalized patients.

Many studies have addressed the effect of ACEI/ARBs on COVID-19, inflammation, and clinical outcome in hospitalized hypertensive patients.[11-25] It is hypothesized that by increasing the expression of ACE2 receptors, these drugs may facilitate and increase the infectivity of SARS-CoV-2.[18] It was reported that the affinity of SARS-CoV-2 to the ACE2 receptor was much stronger than that of SARS-CoV-1.[24,25] ARBs and ACEI increased the number of ACE receptors in animal studies.[4] Therefore, it was suggested that these drugs might increase the infectivity of SARS-CoV-2 and result in worse clinical course and outcomes. However, these drugs may have protective effects on the lungs by decreasing lung inflammation.[5] We hypothesized that since these drugs increase the infectivity of SARS-CoV-2, the time to PCR negativity in nasopharyngeal swabs may be longer in ACEI/ARB users, and patients using ARBs and ACEI may worsen clinical course and outcome. To our knowledge, this is the first study to determine the time for PCR negativity in ACEI/ARB users and non-users with COVID-19 pneumonia. In this study, the median time to PCR negativity was similar between the two groups. It was reported that older age, comorbidities, male sex, delayed admission to hospital after illness onset, and invasive mechanical ventilation were associated with prolonged SARS-CoV-2 RNA conversion.[26,27] In our study, these factors were similar between groups except for diabetes, and further analysis showed that older age, sex, comorbidities, time between onset of symptoms and hospital admission, and ACEI/ARB use did not affect the duration of PCR conversion. These data support the results of previous studies,[10-16] which reported that the use of ACEI/ARBs does not pose an added risk for COVID-19. Therefore, the use of these drugs should not be stopped in patients with COVID-19, as suggested in previous studies.[21,22]

This study had a few limitations. First, the pharmacological therapies administered to the patients were not discussed in detail. The use of systemic corticosteroids may prolong the time to PCR negativity;[28] therefore, the use of systemic corticosteroids should also be compared between groups. However, as the distribution of severity of patients was similar between the two groups and we used the same treatment protocol for patients according to clinical and radiological severity, we suggest that the use of steroids was similar in the two groups. Second, because of lack of information on body mass index in most patients, we could not determine the effect of obesity on the clinical course and time for PCR negativity. Future multicenter stud-

Table 1. Demographic, clinical, radiological, and laboratory data of users and nonusers of the antihypertensive drugs (n=435).

	ACEI/ARBs users (n=203)	Nonusers (n=232)	*P* value
Age, years	71 (41-94)	69 (22-93)	.645
<65 years ≥65 years	76 (37.4) 127 (62.6)	101 (43.5) 131 (56.5)	.197
Male Female	105 (51.7) 98 (48.3)	135 (58.2) 97 (41.8)	.176
Smoker Non-smoker	45 (22.2) 158 (77.8)	54 (23.3) 178 (76.7)	.873
Comorbidities other than hypertension Coronary arterial disease Diabetes mellitus Chronic obstructive pulmonary disease Congestive heart failure Arrhythmia Asthma	163 (80.3) 47 (23.2) 72 (35.5) 27 (13.3) 16 (7.9) 17 (8.4) 14 (6.9)	177 (76.3) 65 (28) 106 (45.7) 33 (14.2) 20 (8.6) 15 (6.5) 12 (5.2)	.373 .247 .031 .78 .917 .564 .58
Serum CRP on admission (mg/dL)	58.7 (1.5-350)	61.6 (2-350)	.729
Serum LDH on admission (U/dL)	491 (122-1712)	521.5 (124-4790)	.601
Serum D-dimer on admission (ng/mL)	1290 (354-14300)	1500 (359-27000)	.116
Lowest value of SpO_2 on admission	89 (57-98)	90 (53-99)	.450
Need for nasal oxygen treatment on admission	145 (71.4)	151 (65.1)	.157
Need for high flow oxygen treatment on admission	37 (18.2)	36 (15.5)	.451
Need for intubation on admission	45 (22.2)	56 (24.1)	.710
Number of lymphocytes on admission ($\times 10^3$/mL)	1.13 (0.11-3.46)	1.06 (0.13-3.17)	.656
Lymphocytes on day 5 ($\times 10^3$/mL)	1.07 (0.19-3.35)	1.12 (0.1-3.47)	.642
Lymphocytes on day 10 ($\times 10^3$/mL)	1.23 (0.15-3.48)	1.37 (0.14-3.72)	.145
Duration of hospitalization (days)	8 (1-54)	7 (1-55)	.806
Time from hospitalization to transfer to ICU (days)	3.0 (1-15)	1.5 (1-21)	.020
Duration of ICU stay (days)	8 (1-40)	6 (1-25)	.591
Radiological severity Mild Moderate Severe Very severe	 4 (2.0) 111 (54.7) 75 (36.9) 13 (6.4)	 1 (0.4) 137 (59.1) 82 (35.3) 12 (5.2)	 .398
The time to PCR negativity (days)	13 (7-34)	13 (5-45)	.083
Number transfered to ICU	65 (32)	74 (31.9)	.978
Deaths	48 (23.6)	61 (26.3)	.525

Data are median (range) or n (%). 298 values were missing on the duration of ICU stay and 293 values were missing on the days between hospitalization and transfer to ICU.

Table 2. Multiple logistic regression analysis of risk factors affecting transfer to the intensive care unit (dependent variable: Transfer to ICU) (n=319).

Risk factors (Independent variables)	Coefficient B	Standard error	Wald X	Odds ratio (95%CI)	*P* value
≥65 years	1.060	.229	21.417	2.9 (1.8-4.5)	**<.0001**
Male sex	.447	.210	4.516	1.6 (1.04-2.36)	**.034**
ACEI/ARBs use	.006	.206	.001	1.01 (0.7-1.5)	.978
Coronary artery disease	.388	.229	2.859	1.5 (0.9-2.3)	.091
Diabetes mellitus	.656	.209	9.877	1.9 (1.3-2.9)	**.002**
Chronic obstructive pulmonary disease	.573	.284	4.072	1.8 (1.0-3.1)	**.044**
Congestive heart failure	.709	.351	4.076	2.0 (1.0-4.0)	**.044**
Arrhythmia	.408	.376	1.181	1.5 (0.7-3.1)	.277
Asthma	.128	.426	.090	1.1 (0.5-2.6)	.764
Hospital stay duration	.123	.019	42.081	1.13 (1.09-1.17)	**<.0001**
PCR negativity time	.082	.025	11.050	1.09 (1.03-1.14)	**.001**

Model summary measures: -2 likelihood = 196.566; Cox and Snell R square=0.150, Nagelkerke R square=0.275

Table 3. Multiple logistic regression analysis of risk factors affecting mortality (dependent variable: mortality) (n=435).

Risk factors (Independent variables)	Coefficient B	Standard error	Wald X	Odds ratio (95% CI)	*P* value
≥65 years	1.277	.263	23.535	3.6 (2.1-6.0)	**<.0001**
Male sex	.767	.235	10.681	2.2 (1.4-3.4)	**.001**
ACEI/ARBs use	-.141	.223	.404	0.87 (0.56-1.34)	.525
Coronary artery disease	.245	.247	.989	1.3 (0.8-2.1)	.320
Diabetes mellitus	.921	.226	16.632	2.5 (1.6-3.9)	**<.0001**
Chronic obstructive pulmonary disease	.906	.290	9.783	2.5 (1.4-4.4)	**.002**
Congestive heart failure	.579	.366	2.498	1.8 (0.9-3.7)	.114
Arrhythmia	.638	.383	2.771	1.9 (0.9-4.0)	.096
Asthma	.103	.457	.051	1.1 (0.4-2.7)	.821
Hospital stay duration	.053	.015	11.613	1.05 (1.02-1.09)	**.001**
PCR negativity time	-.063	.093	.460	0.94 (0.78-1.13)	.498

Model summary measures: -2 likelihood = 35.595; Cox and Snell R square=0.72, Nagelkerke R square=0.425

ies including more patients are necessary to gain more information on these issues.

In conclusion, our data shows that ACEI/ARBs are not related to poor prognoses in COVID-19 pneumonia inpatients. In addition, these agents did not prolong the time to PCR negativity in patients using these drugs. We conclude that using ACEI/ARBs does not increase the infectivity of SARS-CoV-2.

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