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ORIGINAL ARTICLE

The effect of ACE inhibitors and ARBs on outcomes in hospitalized patients with COVID-19

Narges Najafi[1] · Alireza Davoudi[1] · Hamideh Izadyar[1] · Abbas Alishahi[1,2,3] · Armaghan Mokhtariani[1,2,3] · Bahareh Soleimanpourian[1,2,3] · Mina Tabarrayi[1,2,3] · Mahmood Moosazadeh[4] · Zahra Daftarian[5] · Fatemeh Ahangarkani[1]

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Abstract

Background Contradictory opinions exist regarding the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in patients with hypertension, which is the most common comorbidity associated with COVID-19. Herein, the effects of ACEIs and ARBs on outcomes of COVID-19 patients were evaluated.

Methods In this cross-sectional study, the outcomes of COVID-19 patients were compared between patients who received pretreatment ACEIs or ARBs and those who did not.

Results The incidence of moderate and severe forms of COVID-19 was significantly higher in patients taking ACEI/ARB drugs (P-value = 0.012). Also, patients taking ACEI/ARB drugs (P-value = 0.034), patients with hypertension (P-value = 0.011), and patients with dyslipidemia (P-value = 0.011) experienced more severe forms of COVID-19. There was an association between increased length of hospital stay and dyslipidemia (P-value = 0.033) and the use of ACEI/ARB drugs (P-value = 0.041), while no correlation was found between other parameters in univariate linear regression analysis as well as multivariate linear regression. There was an association between increased mortality of patients with increasing age (P-value < 0.001), BMI greater than 30 kg/m^2 (P-value = 0.02), asthma (P-value = 0.003), and dyslipidemia (P-value = 0.045).

Conclusions ACEI/ARB drugs put COVID-19 patients at high risk for moderate to severe forms of COVID-19 and higher length of hospital stay. Although, it is notable that these drugs did not significantly affect specific adverse outcomes of COVID-19, such as the need for admission to the intensive care unit (ICU), length of ICU stay, ventilation, and mortality.

Keywords Angiotensin receptor blockers (ARBs) · Angiotensin-converting enzyme inhibitors (ACEIs) · COVID-19 · Outcome

✉ Fatemeh Ahangarkani
fkani63@gmail.com

1 Antimicrobial Resistance Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

2 Universal Scientific Education and Research Network (USERN), Tehran, Iran

3 Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran

4 Gastrointestinal Cancer Research Center, Non-Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

5 Northbay Medical Center, Vacaville Center for Primary Care, Vacaville, CA, USA

Background

December 2019 marked the beginning of the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2([1, 2]. According to research, the life expectancy index, a sign of community health, has decreased following the COVID-19 pandemic. For example, in the USA, the life expectancy index has decreased by 0.87 years at age 65. The high prevalence of morbidity and mortality of COVID-19, and, subsequently, the destructive economic effects have made access to a safe and highly effective vaccine an urgent need to control the pandemic [3, 4]. Due to the lack of complete vaccination of many people worldwide (47%), the implication of this disease remains remarkable

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[3–9]. Patients with COVID-19 develop symptoms from mild to severe (fatal) based on genetics, underlying diseases, and immune profiles. Many individuals infected with COVID-19 remain asymptomatic and show no clinical findings but can infect others [7, 10, 11]. Although some new drugs such as paxlovid and molnupiravir have been approved by the Food and Drug Administration (FDA) for the treatment of mild-moderate COVID19 infection [12], it is important for clinicians to identify the predisposing factors for COVID-19 infection and the risk factors that increase mortality in order to take appropriate preventive measures. Old age, male gender, and comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease, interstitial lung disease, cardiovascular disease, cancer, chronic liver disease, chronic kidney disease, chemo/radiotherapy, pregnancy, and immune system deficiency are risk factors for exacerbation of COVID-19 infection [13]. Hypertension and cardiovascular disease are the most critical and common comorbidities in patients with COVID-19, who are more prone to exacerbation of disease and death [14]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are involved in decreasing the production or action of angiotensin II in the renin-angiotensin system (RAS), respectively. These drugs are widely used in the medical management of patients with these comorbidities. The renin-angiotensin (RAS) system plays an important role in regulating blood pressure, water and electrolytes, and vascular resistance. In this system, ACE1 converts angiotensin I to angiotensin II, which results in vasoconstriction and elevated blood pressure. Angiotensin II is converted and inactivated by angiotensin 1–7 under the influence of ACE2 [15, 16]. ACEI and ARBs are paradoxically involved in both the pathogenicity of COVID-19 and protection against COVID-19. Li et al. showed that one of the SARS-Cov receptors for cell entry and ACE2 is on the surface of tissue cells. On the other hand, Zhou et al. demonstrated that SARS-Cov2 also enters the cell by binding to ACE2. However, other coronavirus receptors such as aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP4) are not pathways for SARS-Cov2 to enter the cell [17–19]. ACE2 is an analog of ACE1, and usually, the performance of ACE1 and ACE2 is in equilibrium [20]. SARS-CoV-2 binds to ACE2 on its viral coat using the receptor-binding domain (RBD) of the spike glycoprotein and enters the cells together. Downregulation of ACE2 reduces the amount of ACE2 available, and the balance between ACE2 and ACE1 is lost. Thus, the severe form of COVID-19 occurs. Since ACE2 receptor is present in organs such as the lungs, heart and arteries, and kidneys, there is a possibility of infection in all of these organs. ACEI and ARBs can help restore the balance between ACE1 and ACE2 and have beneficial effects in controlling COVID-19 [14, 21]. Several animal studies have also confirmed the protective effect of ARBs against COVID-19 by increasing ACE2 levels [22–24]. The effect of the use of ACEI and ARBs and the increase in ACE2 expression in the pathogenicity of the COVID-19 is not known. The virus may enter the cell due to increased ACE2 expression following the use of ACEI and ARBs. In addition, ACE2 converts vasoconstriction (by angiotensin 2) to vasodilation (by angiotensin 1–7) by converting angiotensin 2 to angiotensin 1–7. Some animal studies show that this vasodilation has an unspecified mechanism involved in the pathogenesis of COVID-19 [18]. Despite the contradictory effects of ACEI and ARBs, there is no evidence to discontinue the routine use of these drugs in COVID-19 patients, and it is recommended to continue their routine usage [24–26]. Evaluation of various factors affecting the improvement or worsening of COVID-19 (including drugs) and complete vaccination of people worldwide can play a vital role in controlling the pandemic and reducing the number of deaths. Considering the contradictory opinions about the use of ACEI and ARBs in patients with hypertension and the high prevalence of hypertension among individuals in Iran [27], in this study, the influence of ACE inhibitors and ARBs in the outcome of COVID-19 patients was evaluated.

Methods

In a cross-sectional study, we evaluated the medical records of all patients over 18 years old who were hospitalized with COVID-19 in Razi Hospital (an infectious disease referral center in Mazandaran province in north of Iran). Data documented in the patient's health record were collected from hospitalized COVID-19 patients from February 20 to May 21, 2020. The census method was used for sampling. This study was approved by the ethics committee of Mazandaran University of medical sciences (code number: 1400.7978). The definitive diagnosis was based on a positive RT-PCR test of the nasopharyngeal swab sample. Demographics data included age, sex, and body mass index (BMI); clinical features such as underlying diseases and severity of diseases and both ACE (including losartan and valsartan) and ARB (including captopril and enalapril) medications were recorded. Age was categorized into three classifications (50 >, 50–65, and > 65 years old). Definitions of COVID-19 severity (mild, moderate, severe, critical) were based on the World Health Organization COVID-19 clinical management guideline. Severe and critical categories were grouped together as "severe" in our study [27]. The outcomes of COVID-19 were compared between patients receiving pretreatment ACE inhibitors or ARBs and those who did not receive these drugs. The outcomes were inpatient mortality, length of hospital stay, admission in intensive care unit (ICU), length of admission in the ICU, invasive mechanical ventilator use, and non-invasive ventilation. Statistical

analysis was performed using the SPSS software version 16.0 (SPSS Inc. Chicago, IL, USA). Differences between groups, i.e., ACEI/ARB users and non-ACEI/ARB using patients were determined by the chi-square test or Fisher's exact test. Ordinal logistic regression was used to determine the association between variables and severity of diseases. Univariate linear regression was performed to evaluate the association between ACEI/ARB using status, demographic characteristics and existing comorbidities with adverse outcomes of COVID-19. Variables with a *P*-value of less than 0.2 according to a univariate analysis, were included in the multivariable analysis. The descriptive values below 5% (P-value < 0.05) were considered statistically significant.

Results

Patient features

Data of 896 patients with confirmed COVID-19 were analyzed in this study. In total, 18.86% ($n = 169$) of patients used ACEI or ARB drugs as follows; losartan: 82.84%, enalapril: 12.42%, captopril: 4.14%, and 0.59% of patients used both captopril and losartan. The majority of patients were under 50 years old (37.6%), while 30.8% were between 50 and 65 years old, and 31.6% were over 65. The prevalence of COVID-19 in male patients was 56.1%, and 91.7% of patients had a BMI less than 30 kg/m^2. Most patients had at least one underlying disease including diabetes (29.5%), hypertension (28.8%), dyslipidemia (23.8%), cardiovascular disease (20.3%), chronic kidney disease (5.7%), hypothyroidism (5%), asthma (3.3%), cancer (2.9%), and chronic liver disease (1.9%). Overall, 29.7% of patients had no underlying disease and 40.2% of them had more than one underlying disease. There were no significant differences in the socio-demographic, baseline characteristics, and comorbidities (except dyslipidemia) between ACEI/ARB users and other patients. Socio-demographic characteristics and preexisting comorbidities of patients based on ACEI/ARB taking status are presented in Table 1.

Clinical outcomes

The clinical outcomes of COVID-19 patients based on ACEI/ARB taking is shown in Fig. 1. The proportion of patients with the mild form of COVID-19 was lower in patients taking ACEI/ARB drugs (54.4% vs. 68.8%),

Table 1 Characteristics of COVID-19 patients based on ACEI/ARB use

	Total *N* (%)	**ACEI/ARB *n* = 169 N (%)**	**Non-ACEI/ARB *n* = 727 N (%)**	***P*-value**
Socio-demographic characteristics				
Gender				0.621
Female	393 (43.9)	77 (45.6)	316 (43.5)	
Male	503 (56.1)	92 (54.4)	411 (56.5)	
Age group (years old)				0.433
50>	336 (37.6)	70 (41.4)	266 (36.7)	
50–65	276 (30.8)	46 (27.2)	230 (31.6)	
>65	283 (31.6)	53 (31.4)	230 (31.6)	
Body mass index (BMI)				0.746
<30	822 (91.7)	154 (91.1)	668 (91.9)	
>30	74 (8.3)	15 (8.9)	59 (8.1)	
Preexisting comorbidities				
Diabetes	264 (29.5)	54 (32.0)	210 (28.9)	0.431
Hypertension	257 (28.7)	49 (29.0)	208 (28.6)	0.921
Dyslipidemia	213 (23.8)	77 (45.6)	136 (18.7)	**< 0.001**
Cardiovascular disease	182 (20.3)	34 (20.1)	148 (20.4)	0.944
Chronic kidney disease	51 (5.7)	11 (6.5)	40 (5.5)	0.611
Hypothyroidism	45 (5.0)	10 (5.9)	35 (4.8)	0.554
Asthma	30 (3.3)	2 (1.2)	28 (3.9)	0.082
Cancer	26 (2.9)	7 (4.1)	19 (2.6)	0.286
Chronic liver disease	17 (1.9)	4 (2.4)	13 (1.8)	0.619

Significance is shown in boldface

COVID-19 coronavirus disease 2019, *ACEI* angiotensin-converting-enzyme inhibitors, *ARB* angiotensin II receptor blockers

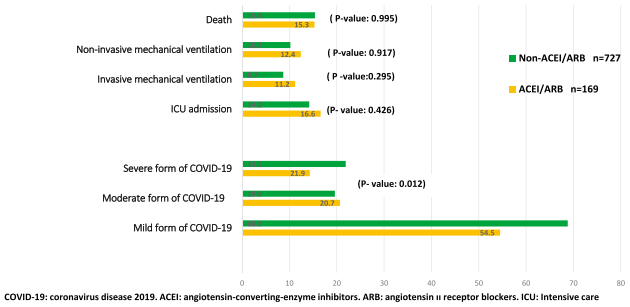

Fig. 1 Clinical outcomes of COVID-19 patients based on ACEI/ARB use

while the incidence of moderate and severe forms was significantly higher in patients taking ACEI/ARB drugs (*P*-value = 0.012). The mean length of hospital stay was 6.64 ± 4.62 days (minimum 1 day and maximum 37 days). There was no statistically significant relationship between length of hospital stay and demographic features including age, sex, and BMI as well as the underlying diseases. In general, the mean length of hospital stay of patients taking ACEI/ARBs was longer, but there was no statistically significant relationship (*P*-value = 0.108).

In total, 132 patients were admitted to the ICU, of which 73 (55.3%) were initially admitted to the general ward and then transferred to the ICU. The average length of hospital stay in the ICU was 5.69 ± 4.97 days (minimum 1 day and maximum 32 days). Among these patients, 29 (22%) were taking ACEI/ARB drugs with a mean length of stay in the ICU (5.37 ± 4.09 days vs. 5.78 ± 5.2 days) (*P*-value = 0.311). A total of 138 patients (15.4%) expired; there was no significant difference in mortality rates between the patients taking ACEI/ARBs and those not taking these drugs (*P*-value = 0.995). The highest mortality rate was in patients over 65 years of age (*P*-value = < 0.001). Among the underlying diseases, only a statistical relationship was observed between the mortality rate of patients with hypertension (*P*-value = 0.011) and asthma (*P*-value < 0.001). A total of 15.51% of patients underwent ventilation; 10.6% used non-invasive ventilators, with a lower rate in patients who did not take ACEI/ARB drugs than patients who were taking ACEI/ARB drugs (10.2% vs. 12.4%, respectively) (*P*-value = 0.917). Also, 9.2% of patients were under invasive ventilation which was more common in patients taking ACEI/ARBs (11.2% vs. 8.7%) (*P*-value = 0.295).

Ordinal logistic regression analyses for severity of COVID-19

Ordinal logistic regression analysis on parameters including age, sex, BMI, ACEI/ARB usage status, and underlying diseases showed that patients taking ACEI/ARB drugs (adjusted odds ratios [adjOR] 1.253, 95% CI (1.017–1.543), *P*-value = 0.034), patients with hypertension (adjOR 0.786, 95% CI (0.653-0.947), *P*-value = 0.011), and patients with dyslipidemia (adjOR 1.289, 95% CI (1.061-1.565), *P*-value = 0.011) experienced the severe form of COVID-19 more than other patients. However, no correlation was found between the other parameters and the severity of COVID-19.

Univariate and multivariable regression analysis for adverse outcomes of COVID-19

There were few patients with some adverse outcomes of COVID-19 such as ICU admission (32/896) and invasive ventilation (82/896). Therefore, the univariate and multivariable linear regression was performed for hospitalization duration, and multinomial logistic regression was performed on the mortality (Tables 2 and 3). Univariate linear regression analysis showed an association between increased length of hospital stay and dyslipidemia (Beta = 0.071, 95% CI (0.062–1.484), *P*-value = 0.033) as well as the use of ACEI/ARB drugs (Beta = 0.068, 95% CI (0.034–1.581), *P*-value = 0.041); while no correlation was found between other parameters in univariate linear regression analysis as well as multivariate linear regression. Multinomial logistic regression analysis showed an association between increased mortality of patients with increasing age (OR 0.447, 95% CI (0.347–0.577), *P*-value < 0.001), BMI greater than 30 kg/m^2 (OR 2.047, 95% CI (1.119–3.745), *P*-value = 0.02),

Table 2 The univariate and multivariate linear regression analysis of COVID-19 patients for hospitalization days

Outcome variable	Univariate regression		Multivariate regression	
	Duration of hospitalization (days)			
	Beta[a]	***P*-value**	**Beta[a]**	***P*-value**
ACEI/ARB use	0.068	**0.041**	0.052	0.131
Age	0.023	0.5	NA	NA
Gender	0.026	0.443	NA	NA
Body mass index (BMI)	−0.016	0.629	NA	NA
Diabetes	0.057	0.09	0.047	0.158
Hypertension	0.04	0.235	NA	NA
Dyslipidemia	0.071	**0.033**	0.05	0.147
Cardiovascular disease	0.043	0.2	NA	NA
Chronic kidney disease	0.055	0.103	0.048	0.152
Hypothyroidism	0.021	0.526	NA	NA
Asthma	−0.026	0.441	NA	NA
Solid tumor	0.054	0.105	0.048	0.15
Chronic liver disease	0.023	0.488	NA	NA

Significance is shown in boldface

NA not applicable

[a]Coefficient regression

Table 3 The multinomial logistic regression analysis of COVID-19 patients for mortality rate

Outcome variable	Univariate regression		Multivariate regression	
	Mortality rate			
	OR[a]	*P*-value	OR[a]	*P*-value
ACEI/ARB use	0.998	0.995	1.188	0.498
Age	0.447	**< 0.001**	0.447	**< 0.001**
Gender	1.019	0.921	NA	NA
Body mass index (BMI)	1.88	**0.029**	2.047	**0.02**
Diabetes	1.388	0.137	0.967	0.88
Hypertension	1.631	**0.012**	1.138	0.562
Dyslipidemia	0.709	0.14	0.605	**0.045**
Cardiovascular disease	0.998	0.994	NA	NA
Chronic kidney disease	0.867	0.733	NA	NA
Hypothyroidism	1.614	0.197	1.555	0.261
Asthma	3.915	**< 0.001**	3.314	**0.003**
Solid tumor	1.768	0.223	NA	NA
Chronic liver disease	1.711	0.354	NA	NA

Significance is shown in boldface

OR odds ratio, *NA* not applicable

[a]Coefficient regression

asthma (OR 3.314, 95% CI (1.492–7.363), *P*-value = 0.003), and dyslipidemia (OR 0.605, 95% CI (0.371–0.988), *P*-value = 0.045), while no correlation was observed between other parameters and the rate of mortality.

Discussions

Numerous studies on the effect of ACEI/ARBs on the outcomes of COVID-19 patients have shown conflicting results. An important finding of our study was that the use of ACEI/ARBs could increase the severity of COVID-19 infection, but no significant relationship was found between the length of hospital stay in the ICU, the need for ICU hospitalization, and the need for mechanical ventilation. It should be noted that the effect of ACEI/ARB usage on univariate analysis did show an increased length of hospital stay, but in a multivariate analysis no significant relationship was found between the use of ACEI/ARBs and the length of hospital stay [28].

According to Xue et al.'s meta-analysis, the use of ACEI/ARB drugs in patients with underlying kidney disease increases the risk of disease progression to severe forms by increasing creatinine, and the direct invasion of COVID-19 into the renal tubules via ACE2, increasing the likelihood of acute kidney injury (28). ACE2 overexpression due to ACE/ARB use can thereby increase invasion of COVID-19 within the renal tubules [29]. According to the mechanism of action of ACEI/ARBs and their effects on organs such as the kidneys, this increased risk of severe COVID-19 infection can be explained.

In the present study, the use of ACEI/ARB drugs in univariate analysis increased the duration of hospitalization. On the other hand, in the study of Zhou et al., a relationship between hospital stay and ACEI/ARB use was not seen [30]. However, in the study of Braude et al., patients with hypertension taking ACEI/ARB medications regardless of age, other comorbidities, and COVID-19 severity had decreased hospital stay lengths compared to other patients [28]. In the present study, 14.73% of patients were admitted to the ICU, but no correlation was found between the use of ACEI/ARB usage and the need for ICU care as well as the duration of ICU admission. Similar to our results, in Mehta et al.'s study on the relationship between ACEI/ARB use and ICU hospitalization in COVID-19 patients, ICU hospitalization rates were higher in patients receiving ACEI, but no association was found between ARB use and ICU hospitalization [31]. Also in the study of Reynolds et al., no significant relationship was found between the use of ACEI/ARB drugs and hospitalization in the ICU [32].

Several studies have found the use of ACEI/ARBs in patients with COVID-19 to have no influence on mortality [14, 32, 33]. We also did not find a significant relationship between ACEI/ARB use and mortality. Ip et al., in a similar retrospective study, found that taking RAASI in hypertension patients with COVID-19 reduced the mortality rate. The proinflammatory activity of ANG2 in COVID-19 patients is offset by taking RAASI medication, as these drugs cause a decrease in ANG2 production thereby reducing the level of inflammation in COVID-19 patients [34]. Our study has several limitations that should be noted. A retrospective design of the study with a small sample size and probable bias can influence the findings. The data were gathered from patient medical records; nevertheless, some records were misclassified, or some data were missing.

Furthermore, in a study conducted by Reus et al., the effects of ACEI (lisinopril, captopril) and ARB (telmisartan, olmesartan) on ACE2 mRNA and protein expression, as well as their effects on COVID-19 infection, were investigated using the Caco-2 cell model. These studies showed that a 25 µg/mL concentration of telmisartan significantly reduced virus replication, while olmesartan, lisinopril, and captopril did not affect virus infectivity [12]. Thus, the effect of different drugs from the ACE family can be further evaluated. Alternatively, ARBs can influence the COVID-19 patient outcomes, but in our study, only captopril, enalapril, and losartan were studied. This suggests the need to study patients taking other drugs in the ACE or ARB family.

Conclusion

We concluded that ACE and ARB drugs put COVID-19 patients at high risk for moderate to severe forms of infection. ACE and ARB users' mean length of hospital stay was higher than those of non-ACE/ARB users. However, these drugs did not significantly affect specific outcomes of COVID-19, such as the need for admission to ICU, length of ICU stay, ventilation, and mortality.

Abbreviations ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; BMI: Body mass index; ICU: Intensive care unit; FDA: Food and Drug Administration; APN: Aminopeptidase N; DPP4: Dipeptidyl peptidase 4; OR: Odds ratio; NA: Not applicable

Author contribution NN, AD, and FA conceived and designed the research, collected the data, and wrote the manuscript. NN, AD, HI, AA, AM, BS, MT, MM, ZD, and FA collected the data. All the authors read and approved the final manuscript.

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Availability of data and materials All the data analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences with code: IR.MAZUMS.RIB.REC.1400. 7978. In addition, written informed consent was obtained from all subjects or, for subjects under the age of 18, from a parent and/or legal guardian. In this study, all the applied methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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