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Original Article

COVID-19 Prognosis in Patients With/Without a History of ACEI/ARB Consumption

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ABSTRACT

Background: Hypertension is a critical risk factor in increasing the mortality rate of COVID-19 inpatients. This association can be confounded by a history of consuming some angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs). **Objective:** This study aimed to assess the COVID-19 prognosis in patients with/without a history of taking ACEIs and ARBs.

Methods: This single-center, prospective, observational study was performed on 345 patients with COVID-19 hospitalized in Baqiyatallah Hospital. The patients were categorized into 2 groups: with a history of ACEI/ARB consumption (the case group, n=115) and without such a history (the control group, n=230).

Results: After the exclusion of some patients, the COVID-19 prognosis of 294 patients ($n_{control}$ =184, n_{case}=110, 53% female) at a mean age of 64±9.7 years was evaluated. Unequal variables were adjusted between the case and control groups, and the results showed no significant differences in oxygen saturation, the computed tomography scan score, the erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, D-dimer, the white blood cell count, lymphocytes, hemoglobin, platelets, and mortality between the 2 groups. However, a significant difference in the average length of hospital stay was found between the control (6.55±0.56 d) and case (8.53±0.55 d) groups (P=0.013).

Conclusions: The dosage adjustments and changes of ACEIs and ARBs are not recommended due to increased referrals to health centers involved with the COVID-19 risk. The prognosis, safety, and efficacy of ACEI/ARB consumption should be assessed further in larger studies on middle-aged to old patients with COVID-19. ***(Iranian Heart Journal 2022; 23(1): 129-139)***

KEYWORDS: ACE inhibitors, Angiotensin II receptor blockers, Antihypertensive drugs, COVID-19, Hypertension

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The novel coronavirus diseases-2019 (COVID-19) was first reported in Wuhan, China. This viral pneumonia led to a high death rate due to acute respiratory distress syndrome (ARDS). The clinical manifestations of COVID-19 were similar to those of the severe acute respiratory syndrome-coronavirus 1 (SARS-CoV-1), with a higher mortality risk. [1] Studies have shown that most patients with COVID-19 were male with underlying diseases such as diabetes mellitus, hypertension, and cardiovascular diseases. [2,3] The common symptoms of this viral disease include fever, dry cough, myalgia, fatigue, and shortness of breath. [4] Huang et al [4] reported that 29% of patients with COVID-19 suffered ARDS, 32% were admitted to the intensive care unit (ICU), 12% developed pulmonary and heart complications, and 15% died. Moreover, all the patients exhibited pulmonary involvement in computed tomography (CT) scans and 63% had lymphopenia. Until now, there has been no effective drug for this newly emerged pandemic. The current use of antiviral drugs is based on SARS-CoV-1 and the Middle East respiratory syndrome (MERS) experiences. [1]

The major comorbidities and risk factors for this viral disease are age and noncommunicable diseases, especially cardiovascular diseases. [5] Hypertension is one of the most prevalent diseases in the elderly. Most of these patients consume blood-pressure-lowering drugs to modulate the renin-angiotensin system (RAS). [6] On the other hand, the angiotensin-converting enzyme II (ACE2) acts as a high-affinity receptor for binding the spike antigens of the COVID-19 virus for entrance into host cells. [7] As ACE2 expresses in vital organs such as the kidney, the heart, and the lung, it plays a key role in cardiovascular and immune systems, hence the link with the development of diabetes mellitus and hypertension. [8] Accordingly, ACE2 has a protective role in the pathogenesis of COVID-19 in the lung and vascular endothelium. [9]

A recent study showed that hypertension had a hazard ratio of 3.05 for COVID-19 inpatients' mortality. [7] Nonetheless, there has been a growing concern regarding this remarkable correlation with a history of consuming some antihypertensive drugs. [10] It has also been proposed that the drugs administered to activate the RAS, especially on angiotensin II type I receptors (AT1R), may be beneficial in patients with COVID-19. [11] Other studies have suggested that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) be replaced with other antihypertensive drugs for the therapy of COVID-19 patients. [12] This suggestion is based on the confirmed high-potential inhibitory functions of other antihypertensive drugs against ACEIs on ACE2 [13] and the upregulating effects of ACEIs and ARBs on ACE2, increasing the chance of viral attachment. [10] Finally, some reference cardiovascular societies have currently mentioned the necessity of continuing ACEIs and ARBs in the context of COVID-19 because of insufficient clinical evidence about the risk of these drugs in patients infected with COVID-19. [14,15]

According to the bridging role of ACE2 in dynamic vascular pressure and COVID-19 pathogenesis, the existence of controversial proposals to take ACEIs and ARBs led us to evaluate the prognosis of COVID-19 in Iranian hypertensive patients taking these drugs in terms of a prospective, observational investigation.

METHODS

Study Design, Participants, and Sample Size

A single-center, prospective, observational study was carried out on 345 COVID-19 patients hospitalized in Baqiyatallah Hospital, Tehran, Iran, from February 21, through April 19, 2020. Patients (n=115) who took

ARBs or ACEIs before hospitalization were considered the case group, while patients (n=230) who did not consume ARBs or ACEIs were categorized as the control group. The required sample size was estimated based on the unequal *t*-test formula (n1=2×n2) with an effect size of 0.4 and a dropout rate of 15% (α=5%, β=10%).

Inclusion and Exclusion Criteria

The inclusion criteria for entering the study were as follows: (i) the approved diagnosis of COVID-19 using the real-time polymerase chain reaction (RT-PCR) of throat-swab specimens or the chest CT scans according to the WHO interim guidance, including ground-glass opacity in addition to ill-defined margins, smooth or irregular interlobular septal thickening, air bronchograms, crazy-paving patterns, and thickening the adjacent pleura, [5,16,17] (ii) an oxygen saturation level less than 93%, (iii) an age range between 50 and 100 years, (iv) not having uncontrolled diabetes mellitus, a history of gastrointestinal bleeding, pregnancy, or lactation, and (v) not taking immunosuppressive drugs and chemotherapy treatment in the past month. On the other hand, patients with high missing information in medical records were excluded.

Outcomes and Variables

Demographic data (ie, age, sex, weight, and height), the disease history, symptoms (eg, fever, dry cough, dyspnea, weakness and lethargy, headache, diarrhea, palpitation, orthopnea, chest pain, and myalgia), and the average length of stay in the hospital (ALOS) were recorded. CT scans were reviewed to observe the usual characteristic signs of COVID-19; then, CT scan scores were determined based on the procedure described by Pan et al. [18] Serum biochemical and blood hematological factors, including white blood cells, lymphocytes, the erythrocyte sedimentation rate, hemoglobin, platelets, C-reactive protein, D-dimer, potassium, sodium, lactate dehydrogenase, troponin, and creatinine, were also analyzed. Additionally, vital signs in the hospitalization time such as temperature, the respiratory rate, the pulse rate, blood pressure, and oxygen saturation were evaluated for all the inpatients. Systolic and diastolic blood pressures, as well as the pulse rate, were electronically assessed with a bedside monitor (BSM-5132; Nihon- Kohden, Tokyo, Japan). A digital thermometer (Omega Engineering Ltd, Manchester, UK) with a precision of ±0.1 °C was used to determine the body temperature. The respiratory rate was also counted at the bedside for 1 minute.

Statistical Analysis

Statistical analysis was performed with R software for Windows, version 3.1.2 (R Project for Statistical Computing, Vienna, Austria) at a significance level of a *P* value less than 0.05. Qualitative and quantitative variables were reported as frequencies (percentages) and the mean (the ±standard division), respectively. The distribution normality of the quantitative variables was checked by using the Kolmogorov–Smirnov test. The Mann–Whitney *U* test or the *t* test and the χ^2 test were used to compare the quantitative and qualitative variables between the case and control groups, respectively. For continuous and binary responses, linear and logistic regression methods were respectively employed to adjust unbalanced variables between the 2 groups.

RESULTS

Demographics Characteristics

The present study was conducted on 294 patients: 110 patients in the case group and 184 patients in the control group. The median body mass index and age values (±SD) in the control group were 28.60±5.37 kg/m^2 and 63±9.01 years, respectively. Eighty-nine patients (48.4%) in the control group were male. The most commonly self-reported symptoms at the onset of illness were cough

(n=119 [64.7%]), dyspnea (n=108 [58.7%]), fever (n=92 [50%]), fatigue or myalgia (n=87 [47.3%]), headache (n=46 [25%]), diarrhea (n=27 [14.7%]), chest pain (n=12 [6.5%]), and palpitation (n=1 [0.5%]), with a CT scan score of 10.77. Comorbid diseases included risk factors such as diabetes mellitus (n=52 [28.3%]), hyperlipidemia (n=31 [16.8%]), hypertension (n=29 [15.8%]), percutaneous coronary intervention (n=11 [6%]), congestive heart failure (n=7 [3.8%]), and coronary artery bypass grafting (n=6 [3.3%]). The mean age and the mean body mass index (±SD) in the case group were 66±10.39 years and 30.18±5.28 kg/m^2, respectively. There was a similar number (n=49, 44.5%) of male patients in the case group compared with the control group. The most frequent self-reported clinical symptoms in the case group were cough (n=62 [56.4%]), dyspnea (n=69 [62.7%]), fever (n=56 [50.9%]), fatigue or myalgia (n=50 [45.5%]), headache (n=24 [21.8%]), diarrhea (n=15 [13.6%]), chest pain (n=4 [3.6%]), and palpitation (n=2 [1.8%]), with a CT scan score of 10.99. Comorbid diseases in this group were diabetes mellitus (n=52 [47.3%]), hyperlipidemia (n=23 [20.9%]), hypertension (n = 98 [89.1%]), percutaneous coronary intervention (n=28 [25.5%]), congestive heart failure (n=12 [10.9%]), and coronary artery bypass grafting (n=8 [7.3%]). From the above variables, diabetes mellitus (P=0.002), hypertension (P<0.001), percutaneous coronary intervention (P<0.001), and age (P=0.001) significantly differed between the case and control groups.

Utilized Treatments

The majority of the 184 patients in the control group received 2 treatments: empirical antibiotics and antiviral therapy. The drugs consumed were ribavirin (n=5 [2.7%]), intravenous immunoglobulin (n=6 [3.3%]), vancomycin (n=7 [3.8%]), levofloxacin (n=14 [7.6%]), oseltamivir (n=15 [8.2%]), methylprednisolone (n=22 [12.0%]), meropenem (n=33 [17.9%]), prednisolone (n=56 [30.4%]), cefriaxone (n=78 [42.4%]), KALETRA (n=91 [49.5%]), naproxen (n=142 [77.2%]), hydroxychloroquine (n=120 [65.2%]), and azithromycin (n=145 [78.8%]. In addition, 110 patients in the case group mostly received vancomycin (n=5 [4.5%], intravenous immunoglobulin (n=5 [4.5%]), oseltamivir (n=6 [5.5%]), ribavirin (n=8 [7.3%]), levofloxacin (n=8 [7.3%]), methylprednisolone (n=17 [15.5%]), meropenem (n=19 [17.3%]), prednisolone (n=31 [28.2%]), cefriaxone (n=43 [39.1%]), hydroxychloroquine (n=59 [53.6%]), KALETRA (n=67 [60.9%]), azithromycin (n=81 [73.6%]), and naproxen (n=86 [78.2%]). Thus, the most frequent drugs administered for both control and case groups were azithromycin and naproxen, respectively. Moreover, intravenous immunoglobulin in both groups was less frequently used to treat this viral disease. The frequencies of the received drugs were not significantly different between the case and control groups.

Laboratory Indices

In the control group, the mean number (×1000±SD) of white blood cells (P=0.798), the mean number of lymphocytes (P=0.148), the mean oxygen saturation level (P=0.429), and the mean number of platelets (P=0.052) were 7.27±3.36, 0.21±0.12, 87.03±9.25%, and 218.2±91.09, respectively. On the other hand, the mean number (×1000±SD) of white blood cells, lymphocytes, and platelets, as well as the mean oxygen saturation level, in the case group were 7.50±4.46, 0.20±0.11, 198.75±85.29, and 86.25±9.75%, respectively. Therefore, there were no significant differences in these biomarkers between the 2 groups. The levels of C-reactive protein and D-dimer in the control and case groups were 15.62±12.18 and 17.24±16.46 and 1.32±1.60 and 1.15±1.28 mg/L, respectively (P>0.05). There were no significant differences in the levels of creatinine (1.06±0.36 mg/dL vs

1.26±0.84 mg/dL; *P*<0.001), sodium (138.37±3.99 mg/dL vs 137.87±4.21 mg/dL; *P*=0.521), and potassium (4.27±0.53 mg/dL vs 4.28±0.56 mg/dL; *P*=0.821) between the control and case groups. The hemoglobin level (*P*=0.145), the erythrocyte sedimentation rate (*P*=0.340), the troponin level (*P*=0.004), and the lactate dehydrogenase level (*P*=0.539) were 14.05±1.76 g/dL, 48.69±27.64 mm/h, 0.01±0.05 ng/mL, and 700.89±419.92 U/L, respectively. The corresponding values in the case group were 13.75±1.77 g/dL, 52.32±29.50 mm/h, 0.02±0.05 ng/mL, and 642.56±236.03 U/L, respectively. Similarly, no remarkable discrepancies were found concerning these biomarkers between the 2 groups (Table 2).

Vital Signs

In the control group, the average (±SD) values of systolic blood pressure (*P*=0.004), diastolic blood pressure (*P*=0.557), the pulse rate (*P*=0.459), the respiratory rate (*P*=0.658), and the body temperature (*P*=0.195) were 123.66±16.61 mm Hg, 74.53±9.70 mm Hg, 93.32±17.78 bpm, 21.25±4.73 bpm, and 36.78±2.81 °C, respectively. On the other hand, the mean (±SD) values of systolic blood pressure, diastolic blood pressure, the pulse rate, the respiratory rate, and the body temperature were 127.82±15.66 mm Hg, 75.45±11.08 mm Hg, 95.55±16.75 bpm, 21.42±4.56 bpm, and 37.13±0.87 °C, respectively. Therefore, there were no significant differences in these vital signs between the 2 groups.

Risk Factors for CCU/ICU Hospitalization

The patients hospitalized in the CCU/ICU with high COVID-19 severity compared with their non-hospitalized counterparts significantly exhibited a higher coronary artery bypass grafting percentage (*P*=0.022), a higher pulse rate (*P*<0.001), more headache symptoms (*P*=0.02), a higher white blood cell count (*P*=0.001), a higher C-reactive protein level (*P*=0.005), a higher creatinine level (*P*=0.01), a higher lactate dehydrogenase level (*P*=0.003), and a higher high-sensitivity cardiac troponin (*P*=0.018) (Table 1). In contrast, the hospitalized patients in these care units showed a lower level of dyspnea, a lower lymphocyte count, a lower oxygen saturation level, and a lower sodium level than the patients not hospitalized in the CCU/ICU (*P*=0.001 and *P*=0.03).

Table 1. Patients' demographic, clinical, laboratory, and radiographic findings on admission

Elements [a]	CCU/ICU Hospitalization		*P* value
	Yes (n=52)	No (n=242)	
Demographic Variables			
Age (y)	66.69±10.73	64.03±9.45	0.007
Sex	..	..	> 0.999
Female (n (%))	28(18)	128(82)	
Male (n (%))	24(17)	114(83)	
Comorbidities			
HTN (%)	48.1	42.1	0.445
DM (%)	36.5	35.1	0.874
CHF (%)	13.5	5.0	0.054
CABG (%)	11.5	3.3	0.022
PCI (%)	15.4	12.8	0.653
HLP (%)	9.6	20.2	0.078
CP (%)	5.8	5.4	>0.999
RR (bpm)	24.02±6.55	20.73±3.93	0.207
PR (bpm)	96.31±20.92	93.69±16.57	<0.001
SBP (mm Hg)	122.65±15.67	125.77±16.48	0.173
DBP (mm H)	73.46±9.62	75.18±10.35	0.381
Fever (%)	51.2	46.2	0.534
Cough (%)	63.6	51.9	0.119

Myalgia (%)	48.8	36.5	0.126
Diarrhea (%)	16.1	5.8	0.078
Chest pain (%)	5.4	5.8	>0.999
Headache (%)	26.4	11.5	0.020
Dyspnea (%)	55.8	80.8	0.001
Orthopnea (%)	35.1	36.5	>0.999
Palpitation (%)	1.2	0.0	>0.999
Laboratory Findings			
WBC (×10^9 per L)	10073.08±6507.5	6768.05±2578.68	0.001
Lymphocyte (×10^9 per L)	0.15±0.11	0.22±0.11	0.001
Hemoglobin (g/L)	13.67±1.92	14±1.74	0.366
Platelet count (× 10^9per L)	228442.31±107852.19	206971.66±84552.22	0.377
CRP (mg/L)	21.39±16.67	15.13±13.22	0.005
ESR(mm/h)	55.08±30.79	48.97±27.76	0.155
Oxygen saturation (%)	75.81±15.27	89.09±5.25	0.001
Cr (µmol/L)	1.22±0.4	1.11±0.63	0.010
LDH(U/L)	876.48±679.66	637.94±233.3	0.003
Sodium (mg/dL)	137.1±4.06	138.41±4.05	0.030
Potassium (mg/dL)	4.35±0.71	4.25±0.5	0.502
High-sensitivity cardiac troponin I (pg/mL)	0.03±0.08	0.01±0.04	0.018
D-dimer (µg/mL)	1.39±1.54	1.25±1.5	0.827
Imaging Features (Lesion Type)			0.115
Ground-glass (%)	9.1	27.4	
Ground-glass crazy paving (%)	22.7	9.7	
Consolidation (%)	0.0	2.7	
Ground-glass + consolidation (%)	68.2	60.2	
CT Scan Distribution			0.589
Unilateral pulmonary (%)	0	5.3	
Bilateral pulmonary (%)	100	94.7	
Focality (%)			> 0.999
Unifocal (%)	0	2.7	
Multifocal (%)	100	97.3	

HTN, Hypertension; DM, Diabetes mellitus; CHF, Congestive heart failure; CABG, Coronary artery bypass grafting; PCI, Percutaneous coronary intervention; HLP, Hyperlipidemia; CP, Chest pain; RR, Respiratory rate; PR, Pulse rate; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; WBC, White blood cell; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; Cr, Creatinine; LDH, Lactate dehydrogenase

Table 2. Clinical and paraclinical outcomes of COVID-19 patients with or without a history of ACEIs and ARBs

Variable Type	**Group**				***P* value**
	Control (without)		Case (with)		
Continues Variables [a]	Mean	Std. Error	Mean	Std. Error	
Hospital stay (d)	6.55	0.56	8.53	0.55	0.013
Oxygen saturation (%)	87.19	1.18	86.28	1.17	0.588
CT score	10.77	0.95	10.99	0.86	0.862
ESR (mm/h)	49.35	3.42	47.16	3.38	0.653
CRP (mg/L)	16.11	1.77	16.46	1.74	0.890
LDH (U/L)	613.20	48.84	658.92	45.72	0.497
D-dimer (µg/mL)	1.22	0.29	1.04	0.33	0.691
WBC (×10^9/L)	7.70	0.47	7.01	0.47	0.311
Lymphocyte (×10^9/L)	0.22	0.01	0.20	0.01	0.299
Hemoglobin (g/L)	13.90	0.22	13.95	0.22	0.859
Platelet (×10^9/L)	216.91	11.00	185.27	10.83	0.050
Categorical Variables [b]	n	%	n	%	p-value
Death	17	9.2	17	15.6	0.865
CCU/ICU	30	16.3	22	20.0	0.922

[a]: Adjusted *P* values with multiple regression adjustments for age, diabetes mellitus (DM), hypertension (HTN), percutaneous coronary intervention (PCI), systolic blood pressure (SBP), and troponin (TROP)
[b]: Adjusted *P* values with logistic regression adjustments for age, DM, HTN, PCI, SBP, and TROP

Adjusted Clinical Outcomes

The linear regression analysis was used to adjust confounding factors (ie, age, diabetes mellitus, hypertension, percutaneous coronary intervention, systolic blood pressure, and troponin) in this study. After these parameters were controlled, there was a significant difference in the mean ALOS between the 2 groups (6.55±0.56 d vs 8.53±0.55 d; *P*=0.013), while such a difference was not shown in other variables such as the oxygen saturation level (87.19±1.18 vs 86.28±1.17%; *P*=0.588), the CT scan score (10.77±0.95 vs 10.99±0.86; *P*=0.862), the erythrocyte sedimentation rate (49.35±3.42 mm/h vs 47.16±3.38 mm/h; *P*=0.653), the C-reactive protein level (16.11±1.77 mg/L vs 16.46±1.74 mg/L; *P*=0.890), the lactate dehydrogenase level (613.20±48.84 U/L vs 658.92±45.72 U/L; *P*=0.497), the D-dimer level (1.22±0.29 vs 1.04±0.33; *P*=0.691), the white blood cell count (7.70±0.47 vs 7.01±0.47; *P*=0.311), the lymphocyte count (0.22±0.01 vs 0.20±0.01; *P*=0.299), the hemoglobin level (13.90±0.22 vs 13.95±0.22; *P*=0.859), and the platelet count (216.91±11.00 vs 185.27±10.83; *P*=0.05). No remarkable difference in the development of ARDS (9.1% vs 9.2%) and acute kidney injury (1.1% vs 1.8%) was found between the case and control groups. A few patients with disseminated intravascular coagulation and septic shock (0 vs 0.9%) in both groups were observed. In the control and case groups, 30 (16.3%) and 22 (20.0%) patients were, respectively, admitted to the ICU/CCU. The results revealed that the mortality rate of the patients in the control and case groups, respectively, was 9.2% and 15.6%. Consequently, there was no statistically significant difference in the mortality rate (17 patients in each group) between the 2 groups (Table 2). ARDS was the most common disease causing death, although there was no difference in this complication between the 2 groups. Other death-causing diseases were acute kidney injury, disseminated intravascular coagulation, septic shock, myocardial infarction, and sudden death, respectively. However, the cause of sudden death in this study was unknown.

Nonetheless, there were no significant differences in the development of ARDS (9.2% vs 14.5%), sudden death (0.5% vs 1.8%), myocardial infarction (0% vs 0.9%), and acute kidney injury (1.1% vs 1.8%). There were a few patients with disseminated intravascular coagulation and septic shock (0% vs 0.9%) in both groups. Thirty (16.3%) and 22 (20.0%) patients in the control and case groups, respectively, were admitted to the ICU/CCU. The same mortality rate was recorded in each group (17 patients).

Radiological Findings

The distribution of CT scan results in the control group was composed of 95.5% bilateral pulmonary and 4.5% unilateral pulmonary (*P*>0.999). The periapical lucent lesions in 98.9% and 1.1% of the patients in the control group were multifocal and unifocal, respectively (*P*=0.294). The frequency of lesion type (*P*=0.221) in the control group was ground-glass opacity plus consolidation (68%), ground-glass opacity (22%), ground-glass crazy paving (9%), and consolidation (1%), respectively. In the case group, the distribution of CT scan results was bilateral pulmonary (95.9%) and unilateral pulmonary (4.1%). The majority of the patients in the case group (95.9%) showed a multifocal pulmonary lesion, whereas 4.1% of these patients had a unifocal lucent lesion. The lung lesions in the control group were composed of ground-glass opacity plus consolidation (51%), ground-glass opacity (22%), ground-glass crazy paving (16%), and consolidation (4%), respectively. Therefore, there were no

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significant differences in radiological data between the 2 groups.

DISCUSSION

In recent months, the COVID-19 pandemic has exerted a notable impact on the mortality rate and socioeconomic costs of the health system in different countries. Not only is the available information about this viral disease in various age groups scarce and contradictory, but also racial and geographical differences among countries add to the complexities of achieving effective strategies in the prevention, control, and treatment of COVID-19. Accordingly, we designed the present investigation as a prospective, observational study.

We found no significant differences in clinical and paraclinical outcomes of COVID-19 patients with or without a history of ACEI/ARB consumption except for the ALOS. Indeed, the only effect of a history of the consumption of these antihypertensive drugs in our study was the prolongation of the ALOS by about 2 days. Although we adjusted our multiple regression analysis for potential confounding variables, a major limitation of the current study is the absence of hypertensive samples (in both case and control groups). A recent study on hypertensive case and control samples reported that the use of ACEIs/ARBs in COVID-19 inpatients was associated with a low risk of all-cause mortality compared with non-users. [19] Reynolds et al [20] observed no substantial effects for 5 common classes of antihypertensive medications on the infection chance and the severity of COVID-19. Similarly, Zhou et al [21] pointed out that the prognosis of COVID-19 patients with hypertension was not affected by taking ACEIs/ARBs. In a systematic review, Singh et al [22] assessed the theoretical paradoxical (harm and benefit) effect of RAS blockers on patients with COVID-19 and concluded that there was not enough evidence to stop these blockers. However, a meta-analysis demonstrated that a history of ACEI/ARB consumption was associated with a decrease in the mortality rate of inpatients infected with COVID-19 (OR=0.32, 95% CI, 0.22 to 0.46). [20] Another research group reported a strong association between inpatient use of ACEIs/ARBs and lower risks of all-cause mortality among patients with COVID-19. [23] Meng et al [24] concluded that the administration of ACEIs/ARBs had an effective role in promoting clinical outcomes of COVID-19 patients with hypertension by improving the immune system. These antihypertensive agents indirectly reduce the peak viral population by escalating the number/density of CD3 and CD8 T-cells in peripheral blood, lowering the ratio of Th1/Th2 cytokines, and diminishing the generation of inflammatory cytokines. [24,25] The non-consumption of ACEIs/ARBs can rapidly damage some vital organs, particularly the lungs, by increasing hypertension and exerting adverse impacts on the blood pressure-regulation system of renin-angiotensin. [26] Thus, an increase in the ALOS among patients with a history of ACEI/ARB consumption in the present study may also be due to our methodological limitation. Accordingly, pulmonary involvement in our CT scan analysis was not significantly different between the 2 groups. However, Feng et al [27] demonstrated that a lower consumption rate of ACEIs/ARBs in patients with severe COVID-19 was associated with multiple lung lobe involvement and pleural effusion. Overall, the conclusion of this study is in favor of not stopping or changing the current antihypertensive drugs of patients in COVID-19 settings. Changing or adjusting a new medication requires multiple referrals to clinics and hospitals, associated with an increased risk of COVID-19 infection.

CONCLUSIONS

This single-center, prospective, observational study was performed to evaluate the prognosis potential of COVID-19 in patients with/without a history of ACEI/ARB consumption. Among the clinical and paraclinical outcomes, only the ALOS was significantly different between the control and case groups. Although a 30.2% increase in COVID-19 patients with a history of taking antihypertensive drugs was observed, the limitation of the applied methodology during the study implementation might have affected the final results. Another limitation of this study was the low number of hypertensive patients in the control group. Since no definitive treatment has been found for COVID-19, the drug treatments utilized in this study were varied. As a result, if there was a definitive cure to treat COVID-19, it would be possible to better understand the effects of ACEIs/ARBs in the prognosis assessment of this viral infection. In general, the present study does not recommend the dosage adjustment and changes of ACEIs/ ARBs due to the increase in the referrals to health centers involved with the COVID-19 risk. Further large-scale studies are required to assess the prognosis, safety, and efficacy of taking antihypertensive medications in middle-aged to old patients with COVID-19.

Declarations

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Authors' Contributions

MSG performed the research. YD and LKH designed the study and wrote the first draft. SVM, MAZA, RJ, HM, MGF, and AA collected clinical data and clinical interpretation, participated in literature search, drafted the manuscript, analyzed the data, and read and revised the paper. LKH and YD were involved in drafting and reviewing the manuscript and gave the final approval for publication. All the authors read and approved the final manuscript.

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Availability of Data and Materials

All the data of this research are available on reasonable request from the corresponding authors. The data are not publicly available due to privacy or ethical restrictions.

Ethical Approval and Consent to Participate

All the participants in this research program were aware of the used methodology after a comprehensive explanation. Written informed consent was obtained from the participants after they had received comprehensive explanations about the study's objectives. The research procedure was in accordance with the guidelines of the Human Ethics Committee of Baqiyatallah University of Medical Sciences and (ethics code: IR.BMSU.REC.1399.050).

Consent for Publication

Written informed consent was obtained from the patients for the publication of this research.

Conflict of Interest

The authors have no conflicts of interest to disclose.

REFERENCES

1. Rajan R, Al Jarallah M, Dashti R. Cardiovascular complications of novel Wuhan Coronavirus COVID ndash: A 2020

update. J Cardiol Curr Res. 2020;13(13), 28. doi: 10.15406/jccr.2020.13.00468

2. Mirzadeh M, Khedmat L. Pregnant women in the exposure to COVID-19 infection outbreak: the unseen risk factors and preventive healthcare patterns. J Matern-Fetal Neonatal Med. 2020; doi: 10.1080/14767058.2020.1749257.

3. Khedmat L. New coronavirus (2019-nCoV): An insight toward preventive actions and natural medicine. Int J Travel Med Glob Health. 2020;8(1):44-5. doi: 10.34172/ijtmgh.2020.07.

4. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5):475-481. doi: 10.1016/S2213-2600(20)30079-5.

5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.

6. Amiri P, Vahedi-Notash G, Naseri P, Khalili D, Nazari SS, Mehrabi Y, et al. National trends of pre-hypertension and hypertension among Iranian adolescents across urban and rural areas (2007–2011). Biol Sex Differ. 2019;10(1):15. doi: 10.1186/s13293-019-0230-1.

7. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; doi:10.1016/S0140-6736(20)30566-3.

8. Kloor D, Osswald H. S-Adenosylhomocysteine hydrolase as a target for intracellular adenosine action. Trends Pharmacol Sci. 2004;25(6):294-7. doi: 10.1016/j.tips.2004.04.004.

9. Ciaglia E, Vecchione C, Puca AA. COVID-19 infection and circulating ACE2 levels: protective role in women and children. Front Pediatr. 2020;8:206. doi: 10.3389/fped.2020.00206.

10. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence?. JAMA. 2020; 323(18):1769-70. doi:10.1001/jama.2020.4812

11. Sun ML, Yang JM, Sun YP, Su GH. Inhibitors of RAS might be a good choice for the therapy of COVID-19 pneumonia. Chin J Tuberc Respir Dis. 2020;43:E014. doi:10.3760/cma.j.issn.1001-0939.2020.0014

12. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nature Rev Cardiol. 2020;17(5):259-60. doi: 10.1038/s41569-020-0360-5

13. Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. Biochem J. 2004;383(1):45-51. doi: 10.1042/BJ20040634

14. American Heart Association. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. Accessed March 20, 2020.https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp

15. European Society of Cardiology. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers. Accessed March 20,2020.https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang

16. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. Mil Med Res. 2020;7(1):article no.11. doi: 10.1186/s40779-020-00240-0.

17. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet

Infect Dis. 2020; 20(4):425-434. doi: 10.1016/S1473-3099(20)30086-4.

18. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology. 2020:200370. doi: 10.1148/radiol.2020200370.

19. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circulation Res. 2020; 126:1671–81. doi: 10.1161/CIRCRESAHA.120.317134

20. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, et al. Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. N Engl J Med. 2020; 382:2441-8. doi: 10.1056/NEJMoa2008975.

21. Zhou X, Zhu J, Xu T. Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on renin–angiotensin system inhibitors. Clin Exp Hypertens. 2020; 42(7):656-660.doi:10.1080/10641963.2020.1764018

22. Singh AK, Gupta R, Misra A. Comorbidities in COVID-19: Outcomes in hypertensive cohort and controversies with renin angiotensin system blockers. Diabetes Metab Syndr: Clin Res Rev. 2020; 14(4):283-7. doi: 10.1016/j.dsx.2020.03.016

23. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ.Res. 2020; 126:1671-81. doi: 10.1161/CIRCRESAHA.120.317134

24. Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microb Infect. 2020;9(1):757-60. doi: 10.1080/22221751.2020.1746200

25. Gage JR, Fonarow G, Hamilton M, Widawski M, Martínez-Maza O, Vredevoe DL, et al. Beta Blocker and angiotensin-converting enzyme Inhibitor therapy is associated with decreased Th1/Th2 cytokine ratios and inflammatory cytokine production in patients with chronic heart failure. Neuroimmunomodulation.2004;11(3):173-180. doi: 10.1159/000076766

26. Andersen LB, Przybyl L, Haase N, von Versen-Höynck F, Qadri F, Jørgensen JS, et al. Vitamin D depletion aggravates hypertension and target-organ damage. J Am Heart Assoc. 2015; 4(2):e001417. doi: 10.1161/JAHA.114.001417.

27. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with different severities: a multicenter study of clinical features. Am JRespir CritCare Med. 2020;201(11):1380-8.doi:10.1164/rccm.202002-0445