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Effect of clinical progress in antihypertensive medications among COVID-19 patients

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ABSTRACT

Objective: Many chronic diseases, such as hypertension, diabetes, and coronary heart disease, paving the way for the disease to progress unfavorably in Covid-19. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-2 receptor blockers (ARBs) can upregulate ACE2 receptors (which SARS-COV-2 uses to enter the host cell) or protect against infection by limiting the effects of Angiotensin 2. This study aimed to reveal the impact of antihypertensive drugs on the hospital staying, and mortality in Covid-19 patients followed in the hospital.

Methods and Results: One hundred patients were randomly selected with hypertension, diabetes mellitus and coronary artery disease hospitalized in Kayseri City Training and Research Hospital due to Covid-19 infection. Patients were grouped as taking ACEIs and ARBs group and not taking ACEIs and ARBs group. There were no differences among the groups in terms of the frequency of chronic disease and treatment modalities. The length of the hospital stays, bedding into the Intensive Care Unit (ICU), and mortality rates were higher in the group without ACEIs or ARBs. Mortality was significantly lower among patients who used ACEIs and ARBs (P=0.00, P=0.02, respectively) and incredibly high among beta-blocker users (P=0.00). It was found that the advanced age, male gender and use of beta-blockers were associated with mortality.

Conclusion: Although antihypertensive medications are allegedly associated with increased mortality rates, the risk of mortality has not been detected in people taking ACEIs and ARBs. Further studies involving a greater number of patients are needed.

Keywords: Angiotensin receptor blockers (ARBs); Angiotensin-converting enzyme inhibitors (ACEIs); Antihypertensive regimen; Beta-adrenergic blockers, mortality; prolonged hospitalization; Covid-19.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for Covid-19, a global pandemic that had devastating effects on the health system.and populations worldwide. In March 2020 declared a pandemic by the World Health Organization.

Many studies has been shown that the mortality increases in patients with hypertension due to Covid-19 infection (1). Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) inhibit the renin-angiotensin-aldosterone system (RAAS) and play an important role in the treatment of hypertension.

Researchers believe that the Angiotensin-converting enzyme 2 (ACE2) receptor on alveolar epithelial cell serves as a high-affinity receptor and co-transporter for SARS-CoV-2 to enter the lungs (2). It has been reported that ACE2 expression is down-regulated in Covid-19 infection and causes pneumonia progression due to RAAS over-activation (3). Therefore, ACEIs and ARBs can prevent lung injury via preventing RAAS activation by preventing down-regulation of ACE2. However, due to insufficient clinical evidence, it is unclear how the treatment approach will be in the presence of Covid-19 infection in hypertensive patients.

In this study, the effect of ACEIs/ARBs treatment on mortality rate in Covid-19 infected patients with hypertension has been searched.

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MATERIAL and METHODs

Study Design and Participants

This retrospective study was carried out in a tertiary hospital with a total of 1607 beds and also includes 253 intensive care beds. Between March 2020 and October 2020, patients with positive RT-PCR (Reverse Transcription Polymerase Chain Reaction) tests obtained from nasopharyngeal swab samples and taking antihypertensive were selected randomly. Patients who suspected SARS-COV2 but negative RT-PCR test were excluded from the study. Patient information was recorded electronically.

Statistical Analysis

The collected information was processed using Statistical Package for Social Sciences (SPSS) for Windows (version by 22.0). Categorical variables are expressed as numbers and percentages, and Chi-square or Fisher's Exact Test analysis was used for comparisons. Histogram analyzes were performed to determine whether continuous variables show normal distribution. Non-parametric data: median (min-max), while the significance between groups was determined using Mann Whitney U test. In all analyzes, $p<0.05$ was considered statistically significant.

RESULTS

A total of 102 patients were included in the study. The characteristics of the patients are shown in **Table 1**. The mean hospital stay of all patients was 13.5±6.7 SD (min-max: 2-44) days.

Patients' classifications according to the ongoing treatment: ACEIs (38 patients, 37.6%), ARBs (25 patients, 24%), beta-blockers (45 patients, 44%), calcium channel blockers (32 patients, 31%), diuretics (38 patients, 37%).

The mean age of the patients was 67.6 ±12.2 years. Fifty-four patients (52.9%) were male. Diabetes mellitus (40 patients, 39%) was the most common underlying disease. The most common symptom was cough (50 patients, 49%). According to the status of receiving oxygen support, 79% (81) of the patients received high-flow cannula O2 support, 5% (6) of the patients received CPAP (Continuous positive airway pressure), 20% (21) of the patients received invasive mechanical ventilation. The 37% (38) of the patients needed ICU (Intensive care unit) admissions, and 24% (25) of them died.

Table 1. Demographic characteristics of the Patient groups.

	ACEIs/ARBs group n=60 (%)	Non-ACEIs/ARBs group n=42 (%)	P-value
Age -Median (min-max)	66.3 (63.3-69.3)	69 (65.3-72.1)	0.46
Male	26 (43%)	28 (67%)	0.02*
Symptoms			
Fever	20 (33%)	21 (50%)	0.91
Cough	26 (43%)	24 (57%)	0.17
Dyspnea	22 (37%)	16 (38%)	0.88
Fatigue	19 (32%)	13 (31%)	0.93
Headache	10 (16%)	1 (2%)	0.02*
Diarrhea	2 (3%)	6 (14%)	0.04*
Vomiting	2 (3%)	1 (2%)	0.77
Comorbidities			
Diabetes Mellitus	25 (42%)	15 (35%)	0.54
Coronary artery disease	7 (11%)	10 (23%)	0.10
Chronic Obstructive Pulmonary Disease	9 (15%)	4 (10%)	0.41
Treatment			
Hydroxychloroquine	11 (18%)	3 (7%)	0.10
Corticosteroid	14 (23%)	13 (31%)	0.39
Favipiravir	44 (73%)	36 (86%)	0.13
Enoxaparin sodium	37 (61%)	33 (79%)	0.07
Coumadin	3 (5%)	1 (2%)	0.50
Antibiotics	53 (88%)	40 (95%)	0.22
Respiratory support			
High flow O2	47 (78%)	34 (81%)	0.74
Non-invasive Mechanical Ventilation	1 (2%)	5 (12%)	0.31
Invasive Mechanical Ventilation	3 (5%)	18 (43%)	0.00*
Prognosis			
Median day of hospitalization (min-max)	13 (11-14)	17 (13-20)	0.03*
Hospitalization in intensive care	12 (20%)	26 (62%)	0.00*
Mortality	4 (7%)	21 (50%)	0.00*

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Mortality risk factors

The death rate is 3.9 times higher among patients aged 65 and over than those under 65. Mortality rates for men are higher than those for women (p=0.02).

Mortality was significantly lower among patients using ACEIs and ARBs (P=0.00, P=0.02, respectively) and incredibly high among beta-blocker users (P=0.00). Beta-blocker use rate in patients with coronary artery diseaswas significantly higher than other antihypertensives (p=0.004). There was no effect of comorbidity on mortality.

While the white blood cell and neutrophil counts, BUN (blood urea nitrogen), creatinine and SGOT (for the first two weeks), lactate dehydrogenase, procalcitonin, c-reactive protein, D-dimer values were found to be higher in patients who died, but the lymphocyte levels were found to be considerably lower than in surviving patients.

Platelet levels were found significantly lower in patients who died 14th day after hospitalization, and there was no significant difference in creatinine and AST levels.

Monocyte, fibrinogen, ferritin, and ALT levels were similar to patients who died and survived.

The patients were divided into two groups, those who received ACEIs and ARBs and those who did not use (Non-ACEIs and ARBs). D-dimer, BUN, and LDH levels were significantly lower in patients who use at least one ACEIs and/or ARBs. Lymphocyte levels were found significantly higher in this group. CRP levels were substantially lower except for the seventh day in ACEIs and ARBs groups. No significant differences were observed between the two groups regarding monocytes count, fibrinogen, glucose creation, and ALT values. Like the dead patient, platelet count was significantly lower in patients' Non-ACEIs and ARBs on the fourteenth day (**Table 3**).

Table 2. Comparison of Overall Mortality Rates

	Cases of Death (n=25)	Cases of Surviving (n=77)	Multivariate Analysis OR (95% CI) P	*P-Value*
Age -Median (min-max) (65 years and older)	74 (70-79)	65 (62-67)	3.93 (1.23-12.56)	0.01**
Male gender	18 (72%)	36 (46%)	0.34 (1.09-7.81)	0.17**
Antihypertensives				
ACEIs	2 (4%)	36 (46%)	10.09 (2.25-45.83)	0.00**
ARBs	2 (4%)	24 (31%)	5.20 (1.13-23.88)	0.02**
Beta Blocker	20 (80%)	25 (32%)	0.12 (0.04-0.35)	0.00**
Calcium Channel Blocker	7 (28%)	25 (32%)	1.23 (0.45-3.34)	0.67
Diuretic	9 (36%)	29 (37%)	1.07 (0.42-2.74	0.88
Comorbidities				
Diabetes Mellitus	9 (36%)	31 (40%)	1.19 (0.47-3.05)	0.70
Coronary artery disease	3 (12%)	14 (18%)	1.91 (0.39-9.30)	0.41
Chronic Obstructive Pulmonary Disease	5 (20%)	8 (10 %)	0.46 (0.13-1.57)	0.21
Treatment				
Hydroxychloroquine	3 (12%)	11 (14%)	1.22 (0.31- 4.78)	0.77
Corticosteroid	10 (40 %)	17 (22%)	0.42 (0.16-1.11)	0.07
Favipiravir	23 (92%)	57 (74%)	0.24 (0.05-1.14)	0.05
Enoxaparin	20 (80 %)	50 (64 %)	0.46 (0.15- 1.37)	0.15
Coumadin	0	4 (5 %)	0.74 (0.66-0.83)	0.24
Antibiotic	24 (96%)	69 (89 %)	0.35 (0.04-3.02)	0.32
Respiratory support				
High flow O2	21	60	0.31 (0.01-5.24)	0.39
Non-invasive Mechanical Ventilation	4 (16%)	2 (2.6%)	0.19 (0.03-1.24)	0.05**
Invasive Mechanical Ventilation	21 (84%)	0 (0%)	0.23 (0.16-0.32)	0.01**

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Table 3: Laboratory findings of first, 7th, and 14th day of hospitalization in ACEIs/ARBs group and Non-ACEIs/ARB's group

	First day of hospitalization			7th day of hospitalization			14th day of hospitalization		
Laboratory measures-median (min-max)	**ACE/ARB Group n=60 (%)**	**Non-ACE/ARB Group n=42 (%)**	**P**	**ACE/ARB Group n=60 (%)**	**Non-ACE/ARB Group n=42 (%)**	**P**	**ACE/ARB group n=60 (%)**	**Non-ACE/ARB Group n=42 (%)**	**P**
White blood cell count, $\times 10^9$/	6735 (2700-18950)	7550 (3140-16360)	0.097	6670 (2560-19720)	7850 (3040-18950)	0.195	8430 (3430-18490)	8200 (1780-39090)	0.804
Lymphocyte count, $\times 10^9$/L	1565 (350-7390)	1270 (340-2890)	0.039*	1380 (430-5860)	960 (350-2180)	0.007*	1320 (440-7380)	725 (170-1890)	0.000*
Neutrophil	4055 (300-16500)	5450 (2210-14890)	0.010*	4650 (810-18770)	6340 (2410-17290)	0.053*	5820 (1890-16860)	6750 (840-37390)	0.131
Monocytes	600 (40-1780)	520 (50-1430)	0.629	500 (180-1140)	525 (100-8430)	0.942	625 (240-1420)	500 (80-1360)	0.082
Platelets	205 (116-399)	197 (119-1160)	0.994	236 (125-463)	244 (113- 520)	0.934	308 (145-495)	234 (105-468)	0.029*
Blood urea nitrogen (BUN)	18 (7-176)	26 (10-111)	0.003*	18 (2-97)	24 (8-95)	0.026*	18 (5-48)	27 (9-111)	0.026*
Creatinine	1 (0.54-2.89)	1.15(0.3-2.99)	0.192	0.83 (0.16-5.70)	1.01 (0.46-5.4)	0.183	0.81 (0.65-3.28)	0.95 (0.49-4.59)	0.423
Aspartate aminotransferase, U/L	23 (10-169	30 (12-333)	0.041*	28 (14-146)	32 (11-146)	0.167	22.5 (11-122)	26 (12-90)	0.300
Alanine aminotransferase, U/L	20 (6-200)	21(4-353)	0.422	23 (9-292)	25 (8-281)	0.978	29 (11-297)	27 (13-105)	0.933
Lactate dehydrogenase IU/L	274 (158-4022)	330 (137-880)	0.038*	294 (187-4462)	417 (125-747)	0.009*	306 (82-4443)	409 (174-645)	0.027*
Glucose mg/dL	144 (70-465)	125 (74-354)	0.375	124 (65-377)	133 (70-427)	0.996	134 (59-314)	127 (61-374)	0.293
Procalcitonin, ng/ml	0.08 (0.02-0.90)	0.22 (0.02-7.34)	0.000*	0.09 (0.02-4.61)	0.16 (0.02-6.63)	0.395	0.06 (0.03-0.33)	0.13 (0.02-1.48)	0.076
C-reactive protein, mg/dl	21.5 (0.50-278)	83 (1.8-330)	0.006*	38 (0.70-304)	53 (3.7-242)	0.250	16.9 (1.6-20)	37.8 (1.2-144)	0.014*
Ferritin, ng/ml	239 (6-1526)	440 (44-5560)	0.019*	487 (158-1687)	575 (43-8898)	0.666	433 (76-2204)	718 (246-5971)	0.261
D- dimer, ng/ml	550 (40-7670)	1070 (100-16260)	0.021*	675 (90-2750)	1245 (140-20000)	0.009*	630 (90-22660)	2035 (250-18020)	0.001*
Fibrinogen	4750 (209-8890)	5190 (208-10700)	0.217	5310 (2100-10880)	5665 (250-97602)	0.936	5050 (1910-8000)	4770 (250 -6820)	0.929

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DISCUSSION

In this study, we tried to evaluate the effects of antihypertensive drugs on survival and length of hospitalization for Covid-19 patients, retrospectively. A meta-analysis of 52 studies indicated no higher risks of multivariable-adjusted mortality associated with the receipt of ACEIs/ARBs, which is consistent with recommendations for the continuation of these medications among patients for whom they are prescribed for the treatment [4]. We observed that ACEIs and ARBs users reduced the length of hospital stay and mortality compared to non-users. These findings support some published studies to continue ACEIs/ARBs in patients with Covid-19 [5] [6] But there is limited information about reducing mortality rates and length of stay [7].

It has been argued that over-activation of the RAAS system may contribute to the progression of Covid-19-related lung injury by causing an inflammatory response and cytokine storm, stimulating the NADH/NADPH oxidase system and triggering cell contraction and vasoconstriction [5]. Angiotensin II (AT2) has proinflammatory, profibrotic, vasoconstrictor, and prothrombotic effects via the Angiotensin type 1 (AT1) receptor, which have mechanical complications associated with severe Covid-19 infection. Therefore, decreased AT2 levels or inhibition of the AT1 receptor may reduce these harmful effects [8]. However, evidence for the efficacy of ARBs or ACEIs is lacking outside of animal models and observational studies of SARS-CoV.

Beta-blockers have been used to treat cardiovascular conditions such as hypertension, arrhythmias, and myocardial infarction. Observational retrospective studies have established a link between beta-blocker therapy and increased survival in critically ill patients caused by different conditions, such as sepsis acute respiratory failure. The beneficial effects of β-blockers in Covid-19 in including improved oxygenation, reducing bronchial secretion, inhibiting the entry of SARS-CoV-2 through ACE2 and CD147, inhibiting the release of pro-inflammatory cytokines, reduce the development of pulmonary edema and ARDS, inhibiting the growth of endothelial dysfunction and coagulopathy, blocking proliferation of SARS-CoV-2, suppression of NLRP3 inflammasome and NF-κB signaling and prevention development of neural-cytokine loop in SARS-CoV-2 infection [9] [10]. Most of our patients were using metoprolol (39/45 patients). Clemente-Moragón et al. demonstrated that metoprolol was safe. It has effects on reduced exacerbated intravenous lung inflammation, and improved oxygenation in Covid-19–associated ARDS [11]. In this study, metoprolol was used during infection, unlike our study. Our patients were already taking metoprolol because of hypertension or coronary artery disease. Although using beta-blockers was associated with mortality in our study, this was attributed to the fact that beta-blockers are more frequently used in coronary artery disease.

Our study showed that advanced age and male gender were independent variables associated with mortality in Covid-19, consistent with the literature [12]. Pre-existing conditions such as cardiovascular disease, chronic kidney disease, chronic lung diseases (especially chronic obstructive airways disease), diabetes mellitus, hypertension, immunosuppression, and obesity may predispose patients to an adverse clinical course and an increased risk of intubation and death [13]. However, our study detected no significant relationship between comorbidity, mortality, and prolonged hospitalization.

In our study, the most important prognostic factors affecting mortality in the patients included advanced age, male gender and beta-blocker use, non-invasive and invasive mechanical ventilation. These data need to be confirmed by prospective cohort studies.

Although white blood cell levels were found to be useful in estimating mortality, no significant correlation was detected with the levels of white blood cells in ACEIs and ARBs groups. However, increased neutrophil levels and decreased lymphocyte levels were demonstrated in ACEIs and ARBs groups. Neutrophilic inflammation contributes to the higher mortality of Covid-19 in patients with underlying co-morbidities such as diabetes and cardiovascular diseases [14].

High D-dimer levels suggest extensive thrombin production and fibrinolysis. In our study, D-dimer levels were significantly lower in ACEIs and ARBs groups, while considerably higher during the first fourteen days in patients who died. Some researchers have suggested using D-dimer levels for patient triage [15].

Our limitations are patients' vital signs could not be accessed and small number of patients since it was a retrospective study. The disease could not be classified as mild-moderate or severe-critical concerning mortality, and evaluations were made outside of this information. Another limitation is the single-center nature of the study.

CONCLUSION

In our study, similar to the studies in the literature, it was thought that the use of ACEIs/ARBs in hypertensive patients would not worsen the disease. ICU admission, mechanical ventilation, and mortality are not associated with ACEIs/ARBs therapy. Evidence from this study triggers an idea for future prospective studies to confirm the potential role of β-blockers in the management of Covid-19.

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