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# The effect of RAAS inhibitors on acute hypoxemic respiratory failure and in-hospital mortality in the hypertensive Covid-19 patients

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## ABSTRACT

**Introduction:** We have aimed to investigate the relationship between use of angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin-receptor-blocker (ARB) drugs and acute hypoxemic respiratory failure (AHRF) and in-hospital mortality in hypertensive Covid-19 patients.

**Material and method:** Consecutive 1345 patients diagnosed with Covid-19 between April and October 2020 who met inclusion criteria were divided into two groups based on presence and absence of AHRF and mortality. The groups were compared regarding epidemiological, clinical, radiological, laboratory findings and treatments methods. The patient groups ACEI, ARB and other antihypertensive drugs (non-ACEI/ARB) were compared regarding same parameters.

**Results:** Median age was 68 (60–76) years in the patient group including 805 (59.9.1%) females. Of the patients, 475 (35.3%), 644 (47.9%) and 226 (16.8%) were using ACEIs, ARBs and non-ACEI/ARB, respectively. AHRF and in-hospital mortality developed in 1053 (78.3%) and 290 (21.6%) patients, respectively. Age, gender, coronary artery disease, diabetes mellitus (DM), neutrophil, lymphocyte, creatinine, D-dimer, C-reactive protein (CRP), ACEI, beta blocker and aspartate transaminase (AST) found statistically significant in the univariable logistic regression performed to identify independent predictors of mortality were included multivariable logistic regression model. Age (OR: 1.066, 95%CI: 1.049–1.083; $p < .001$), DM (OR: 1.682, 95%CI: 1.238–2.286; $p = .001$), neutrophil (OR: 1.041, 95%CI: 1.007–1.077; $p = .019$), creatinine (OR: 1.178, 95%CI: 1.048–1.325; $p = .006$), CRP (OR: 1.008, 95%CI: 1.006–1.010; $p < .001$), ACEI (OR: 0.718, 95%CI: 0.521–0.988; $p = .042$), AST (OR: 1.005, 95% CI: 1.001–1.010; $p = .010$) were found associated with in-hospital mortality.

**Conclusion:** In our study, it was not detected clinically significant difference between three groups with regard to their relation with in-hospital mortality.

## Introduction

Coronavirus 2019 (Covid-19) disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus has been defined as a pandemic threatening public health worldwide (1). The development of acute hypoxemic respiratory failure (AHRF) after respiratory system exposure is considered as one of the most common reasons for worsening the clinical course of Covid-19 disease and this is the most important cause of mortality (2,3). It has been demonstrated that SARS-CoV-2 which is the agent of the disease enters the cell by using angiotensin-converting enzyme 2 (ACE2) located on the cell surface as a receptor (4). ACE2 is predominantly expressed in heart, intestines, kidneys and Type 2 alveolar lung cells in humans (5,6).

It has been reported that hypertension was the most common comorbidity in both patients who admitted to the hospital and died due to Covid-19 (7). Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) acting through renin–angiotensin–aldosterone (RAAS) system are the primarily preferred antihypertensive drugs and these drugs increase the expression of ACE2 (8,9). Hence, it has been suggested that severity of Covid-19 disease may increase in the patients using RAAS inhibitors (ACEI, ARB) after exposure to SARS-CoV-2 (10–12). Besides, since ACEIs and ARBs show different effects on angiotensin II which is the primary substrate of ACE2, the effects of these drugs on the levels and activities of ACE2 may differ (13). However, there is no sufficient powerful study that has compared the effects of these drugs.

The aim of our study was to investigate whether there is a significant difference between ACEIs and ARBs regarding relationship with AHRF and in-hospital mortality in Covid-19 patients.

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## Material and methods

### Data collection

This double-center retrospective study has received conformity certificate from of Turkish Ministry of Health and was accepted also by the collaborator hospital. Also, our study protocol was approved by the ethics committee of our hospital. This research included all the patients with hypertension and Covid-19 who consecutively admitted to the hospitals between the dates 1st April 2020 and 30th October 2020. The last follow-up visit date was 30th November 2020. The presence of Covid-19 disease was confirmed in the patients with at least one of diagnostic criteria such as finding by chest computed tomography (CT) and real-time reverse transcriptase polymerase chain reaction (RT-PCR) analysis (14,15).

The inclusion criteria of the study were being hypertensive Covid-19 patient over 18 years of age and admitted in the hospitals. The exclusion criteria of the study were incomplete medical records, hospitalization longer than 28 days, decompensated or end-stage chronic organ failure (e.g., decompensated heart failure, decompensated cirrhosis or decompensated chronic kidney failure), development of acute fatal organ injury (e.g., acute coronary syndrome, acute myocarditis, acute pulmonary embolism or acute stroke), pregnancy, acquired immunodeficiency syndrome (AIDS) and active malignancy.

Demographic characteristics (age and gender), clinical characteristics (fever, coughing, fatigue, dyspnea, respiration rate and blood pressure), radiological imaging features and laboratory findings of the patients were obtained from the patient files and hospital database. Data related with accompanying diseases and medications prescribed for these diseases were obtained from their medical history. Intrahospital medication administrations and interventions were performed in accordance with Covid Guidelines published by the Turkish Ministry of Health (16).

Each patient was given a system code before data collection to protect patient confidentiality. The accuracy of patient data was meticulously controlled twice by the experienced physicians for confirmation. The increased levels of laboratory parameters such as ferritin ve D-dimer were defined as exceeding upper limit of normal (ULN) according to the laboratory standards since reference values of the two hospitals were different (see Supplementary Table 1).

### Definitions

The subjects with systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg and ongoing antihypertensive medication in their medical history were defined to be hypertensive. The patients who were using ACE inhibitors, ARBs and other antihypertensive drugs (beta blockers, calcium channel blockers, alpha blockers and diuretics) except these medications were classified as ACEI, ARB and nonACE/ARB groups, respectively. ARDS and septic shock were defined according to the intermediary guideline of World Health Organization (WHO) (17).

AHRF was defined as partial oxygen pressure ($PaO_2$) <60 mmhg or oxygen saturation ($SaO_2$) less than 93% measured by pulse oximeter accompanied with respiratory distress symptoms and need for oxygen greater than 6 L/min. The patients with a partial arterial carbon dioxide (PaCO2) pressure higher than 50 mm Hg were excluded (18,19).

The required medical interventions such as nasal cannulation, simple face mask, high flow nasal cannula (HFNC) oxygen therapy, noninvasive mechanical ventilation (NIMV) and mechanical ventilation (MV) were implemented depending on the need in the patients who developed AHRF (20).

### Statistical analysis

All statistical analyses were performed using IBM SPSS software package (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). The continuous variables were presented given as mean±SD and median interquartile range 25–75% (IQR) in case of non-normally distribution. The categorical variables were expressed as percentages. Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. The continuous variables were compared with Student's t-test or Mann-Whitney U test according to data distribution. The categorical variables were compared using Chi-square or Fisher's exact tests if appropriate. The nonnormally distributed numerical and categorical variables were analyzed with Kruskal-Wallis test in the three groups. Univariate and multivariate logistic regression analyses were performed to evaluate the relationship of ACEI or ARB use with development of AHRF and mortality. In stepwise multivariable regression analysis (Backward, Wald); effect size was adjusted with an univariate significance level of <0.05 for all variables. Adjusted odds ratios (OR) along with the confidence interval (CI) 95% were presented. A 2-tailed $p$-value<0.05 was considered to be statistically significant.

## Results

Totally 1345 hypertensive patients who were admitted in two hospitals with diagnosis of Covid-19 between the dates 1st April 2020 and 30th October 2020 were included based on inclusion criteria of the study. RT-PCR test result was positive in 1014 (75.4%) patients included in our study. Median age of the patients was 68 (60–76) years, 789 (58.7%) patients were over 65 years of age, 805 (59.9.1%) patients were female while 475 (35.3%), 644 (47.9%) and 226 (16.8%) of the patients were using ACEIs, ARBs and nonACEI/ARB, respectively. AHRF and in-hospital mortality developed in 1053 (78.3%) and 290 (21.6%) patients, respectively. The characteristic, laboratory and clinical features of the patients with current use of ACEI, ARB and non-ACEI/ARB drugs are summarized in Table 1. In-hospital mortality was detected 86 (18.1%), 147 (22.8%), 57 (25.2) in ACEI, ARB and non-ACEI/ARB group, respectively (Figure 1.)

The study patients were divided into two groups that developed and did not develop mortality, and the clinical characteristics of the patients are presented in Table 2. Age, respiratory rate and systolic blood pressure ($p < .001$, $p < .001$ and $p = .01$, respectively) values were higher in the group that developed mortality. The rate of female gender and unilateral lesion ($p = .008$ and $p < .001$, respectively) in thoracic CT was higher in the group that did not develop mortality, respectively. The

**Table 1.** Demographic, clinical, laboratory characteristics and treatment of ACEI, ARB and non-ACEI/ARB groups.

| Parameters | ACEI (n = 475) | ARB (n = 644) | Non-ACEI/ARB (n = 226) | P value |
|---|---|---|---|---|
| Age, years | 68(60–76) | 69(60–76) | 68(58–76) | 0,071 |
| Gender (female), n (%) | 256(53.9) | 416(64.6) | 133(58.8) | 0.001 |
| Respiratory rate | 21 (17–23) | 22 (17–24) | 22 (17–24) | 0.112 |
| SBP, mmHg | 120(110–130) | 120(110–130) | 120(110–130) | 0.274 |
| DBP, mmHg | 70(70–80) | 70(70–80) | 70(70–80) | 0.455 |
| Fever, n (%) | 297(62.5) | 428(66.5) | 143(63.3) | 0.361 |
| Cough, n (%) | 299(62.9) | 391(60.7) | 139(61.5) | 0.749 |
| Dyspnea, n (%) | 257(54.1) | 384(59.6) | 134(59.3) | 0.155 |
| Fatigue, n (%) | 189(39.8) | 244(37.9) | 76(33.6) | 0.290 |
| Coronary heart disease, n (%) | 154(32.4) | 152(23.6) | 48(21.2) | 0.001 |
| Chronic heart failure, n (%) | 53(11.2) | 29(4.5) | 12(5.3) | <0.001 |
| Diabetes mellitus, n (%) | 210(44.2) | 269(41.8) | 78(34.5) | 0.050 |
| Chronic pulmonary disease (COPD, asthma), n (%) | 88(18.5) | 134(20.8) | 40(17.7) | 0.483 |
| Cerebrovascular diseases, n (%) | 45(9.5) | 42(6.5) | 17(7.5) | 0.187 |
| Chronic renal diseases, n (%) | 15(3.2) | 22(3.4) | 42(18.6) | <0.001 |
| Renal transplantation n (%) | 7(1.5) | 7(1.1) | 12(5.3) | 0.001 |
| Chronic AF, n (%) | 52(10.9) | 30(4.7) | 8(3.5) | <0.001 |
| Unilateral lesion, n (%) | 31(6.5) | 29(4.5) | 14(6.2) | 0.301 |
| Bilateral lesions, n (%) | 436(91.8) | 607(94.3) | 208(92.0) | 0.228 |
| Leukocyte, $10^3/\mu L$ | 7.43(5.60–10.25) | 7.27(5.52–9.70) | 7.52(5.48–10.51) | 0.682 |
| Neutrophil, $10^3/\mu L$ | 5.50(3.89–8.17) | 5.50(3.83–7.67) | 5.53(3.91–8.37) | 0.921 |
| Lymphocyte, $10^3/\mu L$ | 1.20(0.85–1.61) | 1.11(0.80–1.51) | 1.01(0.73–1.49) | 0.016 |
| Platelets, $10^3/\mu L$ | 210.0(169.0–275.0) | 210.0(171.0–269.0) | 210.0(168.7–282.5) | 0.981 |
| Hemoglobin, g/dl | 13.4(12.3–14.5) | 12.8(11.7–14.0) | 12.8(11.1–14.1) | 0.001 |
| Creatinine, mg/dl | 1.0(0.80–1.34) | 1.04(0.84–1.43) | 1.00(0.80–1.75) | 0.071 |
| Potassium, mmol/l | 4.20(3.83–4.63) | 4.25(3.81–4.67) | 4.19(3.76–4.68) | 0.624 |
| AST, U/L | 28.0(22.0–40.0) | 30.0(23.0–42.0) | 29.0(20.0–42.0) | 0.317 |
| ALT, U/L | 23.0(16.0–34.0) | 22.0(16.0–35.8) | 20.0(14.0–33.0) | 0.128 |
| LDH, U/L | 301.5(249.8–393.0) | 316(248.0–417.0) | 324.0(249.0–405.5) | 0.325 |
| Ferritin increase >ULN*, n (%) | 371(78.0) | 503(78.1) | 176(78.0) | 0.376 |
| D-dimer increase >ULN*, n (%) | 282(59.4) | 389(60.4) | 149(65.9) | 0.193 |
| Procalcitonin, ng/ml | 0.10(0.06–0.28) | 0.13(0.07–0.27) | 0.13(0.07–0.52) | 0.061 |
| C-reactive protein, mg/l | 66.0(24.3–117.2) | 68.6(28.2–118.8) | 68.0(24.8–124.9) | 0.494 |
| Beta-blocker, n (%) | 227(47.8) | 215(33.4) | 116(51.3) | <0.001 |
| Calcium channel blocker, n (%) | 190(40.0) | 286(44.4) | 174(77.0) | <0.001 |
| Thiazide diuretic, n (%) | 209(44.0) | 463(71.9) | 18(8.0) | <0.001 |
| Loop diuretic, n (%) | 54(11.4) | 22(3.4) | 11(4.9) | <0.001 |
| Spironolactone, n (%) | 18(3.8) | 17(2.6) | 4(1.8) | 0.284 |
| Alpha-blocker, n (%) | 10(2.1) | 19(3.0) | 24(10.6) | <0.001 |
| Digoxin, n (%) | 8(1.7) | 8(1.2) | 2(0.9) | 0.661 |
| Statin, n (%) | 106(22.3) | 94(14.6) | 26(11.5) | <0.001 |
| Antiaggregant, n (%) | 255(53.7) | 302(46.9) | 104(46.0) | 0.047 |
| OAC, n (%) | 46(9.7) | 24(3.7) | 6(2.7) | <0.001 |
| Oral antidiabetic, n (%) | 183(38.5) | 210(32.6) | 53(23.5) | <0.001 |
| Insulin, n (%) | 65(13.7) | 84(13.0) | 28(12.4) | 0.887 |
| $SaO_2$, % | 90.0(85.0–93.0) | 88.0(83.0–92.0) | 88.0(82.0–93.0) | 0.054 |
| Nasal/mask O2, n (%) | 343(72.2) | 461(71.6) | 169(74.8) | 0.651 |
| HFNC, n (%) | 42(8.8) | 65(10.1) | 20(8.8) | 0.736 |
| NIMV, n (%) | 72(15.7) | 118(18.3) | 40(17.7) | 0.368 |
| MV, n (%) | 85(17.9) | 150(23.3) | 57(25.2) | 0.036 |
| AHRF, n (%) | 367(77.3) | 507(78.7) | 179(79.2) | 0.787 |
| ARDS, n (%) | 75(15.8) | 135(21.0) | 49(21.7) | 0.057 |
| Septic shock, n (%) | 49(10.3) | 75(11.6) | 30(13.3) | 0.504 |
| Hospital stay, days | 9 (6–12) | 8(6–12) | 8(6–13) | 0.550 |
| ICU stay, n (%) | 140(29.5) | 202(31.4) | 79(35.0) | 0.343 |
| Mortality, n (%) | 86(18.1) | 147(22.8) | 57(25.2) | 0.056 |

Data were Show as % for categorical and as median (interquartile range) for continuous variables. Categorical data were compared using chi-square test and continuous data using Kruskal-Wallis test. **Abbreviations**: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; AHRF, Acute hypoxemic respiratory failure; ALT, alanine transaminase; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HFNC, high flow nasal cannula; ICU, intensive care unit; LDH, lactate dehydrogenase; MV, mechanical ventilation; NIMV, noninvasive mechanical ventilation; OAC, oral anticoagulant; $SaO_2$, oxygen saturation; SBP, systolic blood pressure. * Upper limit of normal (ULN) was defined according to criteria in each hospital and normal ranges of tests in each hospital were provided in Supplementary Table 1.

rate of dyspnea, coronary artery disease, DM and bilateral lesions in thoracic CT ($p < .001$, $p = .008$, $p = .045$ and $p < .001$, respectively) was higher in the group that developed mortality. From the laboratory parameters; leukocyte count, neutrophil count, creatinine level, potassium level, AST level, LDH level, ferritin level, D-dimer level, procalcitonin level and CRP level ($p < .001$, $p < .001$, $p < .001$, $p = .020$, $p < .001$, $p < .001$, $p < .001$, $p < .001$, $p < .001$ and $p < .001$, respectively) were significantly higher whereas lymphocyte and hemoglobin ($p < .001$ and $p = .025$, respectively) levels were significantly lower in the group that developed mortality. With respect to ongoing medications; the rate of ACEI use ($p = .023$) was higher in the patients who did not develop mortality whereas the rate of beta blocker and insulin use ($p = .025$ and $p < .001$, respectively) was higher in those who developed mortality. $SaO_2$ ($p < .001$) was lower whereas the rate of HFNC oxygen

**Table 2.** Demographic, clinical, laboratory characteristics and treatment of study patients according to absence and presence of in-hospital mortality.

| Parameters | Mortality absent (n = 1055) | Mortality present (n = 290) | P value |
|---|---|---|---|
| Age, years | 66(59–74) | 74(68–81) | <0.001 |
| Gender (female), n (%) | 651(61.7) | 154(53.1) | 0.008 |
| Respiratory rate | 20 (17-23) (17–22,25) | 28 (26–32) | <0.001 |
| SBP, mmHg | 120.0(110.0–130.0) | 120.0(110.0–134.0) | 0.011 |
| DBP, mmHg | 70.0(70.0–80.0) | 64.0(70.0–80.0) | 0.234 |
| Fever, n (%) | 678(64.3) | 190(65.5) | 0.693 |
| Cough, n (%) | 663(62.8) | 166(57.2) | 0.082 |
| Dyspnea, n (%) | 538(51.0) | 237(81.7) | <0.001 |
| Fatigue, n (%) | 403(38.2) | 106(36.6) | 0.608 |
| Coronary heart disease, n (%) | 260(24.6) | 94(32.4) | 0.008 |
| Chronic heart failure, n (%) | 74(7.0) | 20(6.9) | 0.945 |
| Diabetes mellitus, n (%) | 422(40.0) | 135(46.6) | 0.045 |
| Chronic pulmonary disease (COPD, asthma), n (%) | 201(19.1) | 61(21.0) | 0.450 |
| Cerebrovascular diseases, n (%) | 77(7.3) | 27(9.3) | 0.256 |
| Chronic renal diseases, n (%) | 58(5.5) | 21(7.2) | 0.263 |
| Renal transplantation n (%) | 18(1.7) | 8(2.8) | 0.249 |
| Chronic AF, n (%) | 64(6.1) | 26(9.0) | 0.080 |
| Unilateral lesion, n (%) | 73(6.9) | 1(0.3) | <0.001 |
| Bilateral lesions, n (%) | 963(91.3) | 288(99.3) | <0.001 |
| Leukocyte, $10^3/\mu L$ | 7.18(5.44–9.41) | 8.48(6.06–12.23) | <0.001 |
| Neutrophil, $10^3/\mu L$ | 5.20(3.69–7.39) | 6.91(4.69–10.40) | <0.001 |
| Lymphocyte, $10^3/\mu L$ | 1.20(0.87–1.63) | 0.86(0.62–1.25) | <0.001 |
| Platelets, $10^3/\mu L$ | 213(172–275) | 205(164–259) | 0.072 |
| Hemoglobin, g/dl | 13.1(11.9–14.2) | 12.8(11.5–14.0) | 0.025 |
| Creatinine, mg/dl | 1.00(0.80–1.30) | 1.27(0.90–1.79) | <0.001 |
| Potassium, mmol/l | 4.20(3.80–4.60) | 4.30(3.85–4.84) | 0.020 |
| AST, U/L | 28 (21–24,26-39) | 34 (23–49) | <0.001 |
| ALT, U/L | 22 (16–35) | 22 (15–34) | 0.689 |
| LDH, U/L | 296(243–379) | 373(281–521) | <0.001 |
| Ferritin increase >ULN*, n (%) | 800 (75.8) | 249(86.0) | <0.001 |
| D-dimer increase >ULN*, n (%) | 607(57.5) | 212(73.0) | <0.001 |
| Procalcitonin, ng/ml | 0.10(0.06–0.20) | 0.33(0.12–1.01) | <0.001 |
| C-reactive protein, mg/l | 54 (20–103) | 115(65–164) | <0.001 |
| ACE, n (%) | 389(36.9) | 86(29.7) | 0.023 |
| ARB, n (%) | 497(47.1) | 147(50.7) | 0.280 |
| Non-ACEI/ARB, n (%) | 169(16.0) | 57(19.7) | 0.142 |
| Beta-blocker, n (%) | 421(39.9) | 137(47.2) | 0.025 |
| Calcium channel blocker, n (%) | 504(47.8) | 146(50.3) | 0.438 |
| Thiazide diuretic, n (%) | 552(52.3) | 138(47.6) | 0.153 |
| Loop diuretic, n (%) | 71(6.7) | 16(5.5) | 0.457 |
| Spironolactone, n (%) | 29(2.7) | 10(3.4) | 0.530 |
| Alpha-blocker, n (%) | 37(3.5) | 16(5.5) | 0.119 |
| Digoxin, n (%) | 11(1.0) | 7(2.4) | 0.084 |
| Statin, n (%) | 174(16.5) | 52(17.9) | 0.562 |
| Antiaggregant, n (%) | 508(48.2) | 153(52.8) | 0.165 |
| OAC, n (%) | 57(5.4) | 19(6.6) | 0.453 |
| Oral antidiabetic, n (%) | 349(33.1) | 97(33.4) | 0.906 |
| Insulin, n (%) | 121(11.5) | 56(19.3) | <0.001 |
| $SaO_2$, % | 90(87–94) | 80(70–84) | <0.001 |
| Nasal/mask $O_2$, n (%) | 762(72.2) | 211(72.8) | 0.858 |
| HFNC, n (%) | 48(4.5) | 79(27.2) | <0.001 |
| NIMV, n( %) | 46(4.4) | 184(63.4) | <0.001 |
| MV, n (%) | 4(0.4) | 288(99.3) | <0.001 |
| Septic shock, n (%) | 0(0) | 154(53.1) | <0.001 |
| ARDS, n (%) | 34(3.2) | 225(77.6) | <0.001 |
| Hospital stays, days | 8 (6–11) | 10 (7–15) | <0.001 |
| ICU stays, n (%) | 137(13.0) | 284(97.9) | <0.001 |
| AHRF, n (%) | 763(72.3) | 290(100) | <0.001 |

Data are shown as % for categorical and as median (interquartile range) for continuous variables. Categorical data were compared using chi-square test and continuous data using Mann-Whitney U test. **Abbreviations**: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; AHRF, Acute hypoxemic respiratory failure; ALT, alanine transaminase; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HFNC, high flow nasal cannula; ICU, intensive care unit; LDH, lactate dehydrogenase; MV, mechanical ventilation; NIMV, noninvasive mechanical ventilation; OAC, oral anticoagulant; $SaO_2$, oxygen saturation; SBP, systolic blood pressure. * Upper limit of normal (ULN) was defined according to criteria in each hospital and normal ranges of tests in each hospital were provided in Supplementary Table 1.

therapy, NIMV, MV, septic shock, ARDS, length of hospital stay, number of the patients that were admitted in the ICU and that developed AHRF ($p < .001$, $p < .001$, $p < .001$, $p < .001$, $p < .001$, $p < .001$, $p < .001$ and $p < .001$, respectively) were higher in the group that developed mortality. Multivariate logistic regression model was carried out using the parameters that were found statistically significant in the univariate analysis and that may affect mortality (age, gender, coronary artery disease, diabetes mellitus, neutrophil count, lymphocyte count, creatinine level, D-dimer level, CRP level, ACEI, beta blocker, AST) as presented in Table 3. According to this model; age (OR: 1.066, 95%CI: 1.049–1.083; $p < .001$), DM (OR: 1.682,
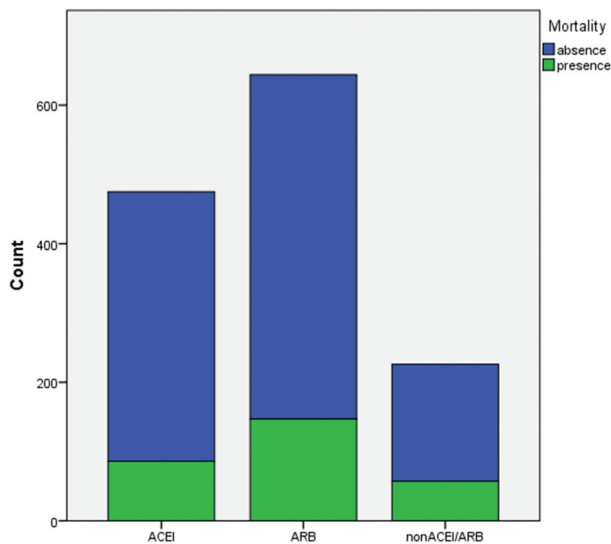
**Figure 1.** Comparison of in-hospital mortality between ACEI, ARB and nonACEI/ARB groups.

95%CI: 1.238–2.286; $p$ = .001), neutrophil count (OR: 1.041, 95%CI: 1.007–1.077; $p$ = .019), creatinine level (OR: 1.178,95% CI: 1.048–1.325; $p$ = .006), CRP level (OR: 1.008, 95%CI: 1.006–1.010; $p$ < .001), ACEI (OR: 0.718, 95%CI: 0.521–0.988; $p$ = .042) and AST level (OR: 1.005, 95%CI: 1.001–1.010; $p$ = .010) were found correlated with mortality. The patients were divided into two groups as patients that developed and did not develop AHRF, and the characteristic features of the patients are presented in Table 4. No statistically significant difference was found regarding use of ACEI, ARB or nonACEI/ARB ($p$ = .500, $p$ = .710 and $p$ = .715, respectively) between the groups that developed and did not develop AHRF. Univariate and multivariate analyses were carried out using predictors found statistically significant between the groups that developed and did not develop AHRF revealed that age, neutrophil count, lymphocyte count, D-dimer and CRP levels ($p$ < .001, $p$ = .044, $p$ = .015, $p$ = .011, $p$ < .001, respectively) and found correlated with AHRF (Table 5).

## Discussion

In the present double-center retrospective study, we have determined that age, DM, neuthrophil count, creatinine, CRP and AST levels were associated with increased mortality. There was not detected clinically significant difference between ACEI, ARB and nonACE/ARB with regard to their relation with in-hospital mortality in our study. Although the ACEI $p$ value was found to be statistically significant in the regression analysis, it would be more accurate to evaluate that there is no clinically significant difference in hospital mortality between the three groups in our study. Besides, increased age, D-dimer, CRP and reduced lymphocyte count were found correlated with development of AHRF. It has been detected that the rate of connection to MV was lower in ACEI group, even though, ACEI, ARB or nonACEI/ARB use was not significantly correlated with AHRF.

**Table 3.** Univariable and multivariable logistic regression analysis for in-hospital mortality.

| Variable | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | Unadjusted OR | 95% CI | P-value | Adjusted OR | 95% CI | P-value |
| Age, years | 1.060 | 1.046–1.074 | <0.001 | 1.066 | 1.049–1.083 | <0.001 |
| Gender (female), n(%) | 0.703 | 0.541–0.913 | 0.008 | 0.782 | 0.573–1.066 | 0.120 |
| SBP, mmHg | 1.012 | 1.004–1.020 | 0.003 | 1.005 | 0.997–1.014 | 0.236 |
| Coronary heart disease, n (%) | 1.466 | 1.105–1.946 | 0.008 | 1.156 | 0.798–1.674 | 0.443 |
| Chronic heart failure, n (%) | 0.982 | 0.589–1.639 | 0.945 | | | |
| Diabetes mellitus, n (%) | 1.306 | 1.006–1.697 | 0.045 | 1.682 | 1.238–2.286 | 0.001 |
| Chronic pulmonary disease (COPD, asthma), n (%) | 1.132 | 0.821–1.561 | 0.450 | | | |
| Cerebrovascular diseases, n (%) | 1.304 | 0.824–2.064 | 0.257 | | | |
| Chronic renal diseases, n (%) | 1.342 | 0.800–2.250 | 0.265 | | | |
| Renal transplantation n (%) | 1.634 | 0.703–3.798 | 0.253 | | | |
| Chronic AF, n (%) | 1.525 | 0.948–2.454 | 0.082 | | | |
| Leukocyte, $10^3/\mu L$ | 1.073 | 1.044–1.104 | <0.001 | | | |
| Neutrophil, $10^3/\mu L$ | 1.101 | 1.068–1.134 | <0.001 | 1.041 | 1.007–1.077 | 0.019 |
| Lymphocyte, $10^3/\mu L$ | 0.564 | 0.445–0.716 | <0.001 | 0.845 | 0.665–1.072 | 0.166 |
| Platelets, $10^3/\mu L$ | 0.999 | 0.997–1.000 | 0.173 | | | |
| Hemoglobin, g/dl | 0.936 | 0.874–1.002 | 0.059 | | | |
| Creatinine, mg/dl | 1.253 | 1.139–1.377 | <0.001 | 1.178 | 1.048–1.325 | 0.006 |
| Ferritin>ULN*, n (%) | 1.967 | 1.354–2.858 | <0.001 | | | |
| D-dimer>ULN*, n (%) | 2.002 | 1.495–2.680 | <0.001 | 1.118 | 0.797–1.570 | 0.518 |
| Procalcitonin, ng/ml | 1.070 | 1.023–1.120 | 0.003 | | | |
| C-reactive protein, mg/l | 1.010 | 1.008–1.011 | <0.001 | 1.008 | 1.006–1.010 | <0.001 |
| ACEI, n (%) | 0.655 | 0.448–0.959 | 0.030 | 0.718 | 0.521–0.988 | 0.042 |
| ARB, n (%) | 0.877 | 0.617–1.247 | 0.465 | | | |
| Non-ACEI/ARB, n (%) | 1.283 | 0.919–1.789 | 0.143 | | | |
| Beta-blocker, n (%) | 1.348 | 1.038–1.751 | 0.025 | 1.258 | 0.894–1.769 | 0.187 |
| Antiaggregant, n (%) | 1.203 | 0.927–1.560 | 0.165 | | | |
| OAC, n (%) | 1.228 | 0.718–2.099 | 0.454 | | | |
| AST, U/L | 1.006 | 1.002–1.010 | 0.002 | 1.005 | 1.001–1.010 | 0.010 |

Multivariable logistic regressions was performed with a pre-defined covariate set, which included age, gender, SBP, coronary heart disease, diabetes mellitus, neutrophil, lymphocyte, creatinine, D-dimer, C-reactive protein, ACEI, beta-blocker and AST. **Abbreviations**: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; AST, aspartate transaminase; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OAC, oral anticoagulant; SBP, systolic blood pressure; OR, odds ratio. * Upper limit of normal (ULN) was defined according to criteria in each hospital and normal ranges of tests in each hospital were provided in Supplementary Table 1.

**Table 4.** Demographic, clinical, laboratory characteristics and treatment of study patients according to absence and presence of acute hypoxemic respiratory failure.

| Parameters | Acute hypoxemic respiratory failure absent (n = 292) | Acute hypoxemic respiratory failure present (n = 1053) | P value |
|---|---|---|---|
| Age, years | 63(55–72) | 70(61–77) | <0.001 |
| Gender (female), n (%) | 188(64.4) | 617(58.6) | 0.086 |
| Respiratory rate | 16 (15,16,25) | 23 (19–24,26) | <0.001 |
| SBP, mmHg | 120.0(110.0–130.0) | 120.0(110.0–130.0) | 0.093 |
| DBP, mmHg | 70.0(70.0–80.0) | 70.0(70.0–80.0) | 0.149 |
| Fever, n (%) | 170(58.2) | 698(66.3) | 0.011 |
| Cough, n (%) | 207(70.9) | 622(59.1) | <0.001 |
| Dyspnea, n (%) | 39(13.4) | 736(69.9) | <0.001 |
| Fatigue, n (%) | 68(23.3) | 441(41.9) | <0.001 |
| Coronary heart disease, n (%) | 61(20.9) | 293(27.8) | 0.017 |
| Chronic heart failure, n (%) | 18(6.2) | 76(7.2) | 0.532 |
| Diabetes mellitus mellitus, n (%) | 106(36.3) | 451(42.8) | 0.045 |
| Chronic pulmonary disease (COPD, asthma), n (%) | 54(18.5) | 208(19.8) | 0.631 |
| Cerebrovascular diseases, n (%) | 11(3.8) | 93(8.8) | 0.004 |
| Chronic renal diseases, n (%) | 6(2.1) | 73(6.9) | 0.002 |
| Renal transplantation n (%) | 2(0.7) | 24(2.3) | 0.080 |
| Chronic AF, n (%) | 14(4.8) | 76(7.2) | 0.143 |
| Unilateral lesion, n (%) | 53(18.2) | 21 (2) | <0.001 |
| Bilateral lesions, n (%) | 224(76.7) | 1027(97.5) | <0.001 |
| Leukocyte, $10^3/\mu L$ | 6.66(4.99–8.98) | 7.63(5.66–10.40) | <0.001 |
| Neutrophil, $10^3/\mu L$ | 4.56(3.23–6.54) | 5.73(4.07–8.47) | <0.001 |
| Lymphocyte, $10^3/\mu L$ | 1.34(0.96–1.85) | 1.07(0.75–1.48) | <0.001 |
| Platelets, $10^3/\mu L$ | 220(170–272) | 208(170–272) | 0.432 |
| Hemoglobin, g/dl | 13.5(12.1–14.4) | 12.9(11.7–14.1) | <0.001 |
| Creatinine, mg/dl | 0.94(0.77–1.20) | 1.05(0.83–1.51) | <0.001 |
| Potassium, mmol/l | 4.24(3.84–4.67) | 4.20(3.80–4.63) | 0.576 |
| AST, U/L | 27 (20–24,26–36) | 30 (22–42) | 0.001 |
| ALT, U/L | 24 (17–36) | 21 (15–34) | 0.052 |
| LDH, U/L | 262(217–341) | 324(256–421) | <0.001 |
| Ferritin increase >ULN*, n (%) | 186(63.6) | 859(81.6) | <0.001 |
| D-dimer increase >ULN*, n (%) | 156 (53.3) | 662(62.9) | 0.005 |
| Procalcitonin, ng/ml | 0.08(0.04–0.15) | 0.14(0.07–0.34) | <0.001 |
| C-reactive protein, mg/l | 28 (11–73) | 78 (37–131) | <0.001 |
| ACE, n (%) | 108(37.0) | 367(34.9) | 0.500 |
| ARB, n (%) | 137(46.9) | 507(48.1) | 0.710 |
| Non-ACEI/ARB, n (%) | 47(16.1) | 179(17.0) | 0.715 |
| Beta-blocker, n (%) | 11(38.0) | 447(42.5) | 0.173 |
| Calcium channel blocker, n (%) | 125(42.8) | 525(49.9) | 0.033 |
| Thiazide diuretic, n (%) | 141(48.3) | 549(52.1) | 0.244 |
| Loop diuretic, n (%) | 19(6.5) | 68(6.5) | 0.976 |
| Spironolactone, n (%) | 8(2.7) | 31(2.9) | 0.854 |
| Alpha-blocker, n (%) | 9(3.1) | 44(4.2) | 0.394 |
| Digoxin, n (%) | 6(2.1) | 12(1.1) | 0.249fis |
| Statin, n (%) | 46(15.8) | 180(17.1) | 0.588 |
| Antiaggregant, n (%) | 116(39.7) | 545(51.8) | <0.001 |
| OAC, n (%) | 12(4.1) | 64(6.1) | 0.197 |
| Oral antidiabetic, n (%) | 90(30.8) | 356(33.8) | 0.338 |
| Insulin, n (%) | 31(10.6) | 146(13.9) | 0.146 |
| $SaO_2$, % | 95(94–96) | 87(81–90) | <0.001 |
| Nasal/mask $O_2$, n (%) | 0(0) | 973(92.4) | <0.001 |
| HFNC, n (%) | 0(0) | 127(12.1) | <0.001 |
| NIMV, n (%) | 0(0) | 230(21.8) | <0.001 |
| MV, n (%) | 0(0) | 292(27.7) | <0.001 |
| Septic shock, n (%) | 0(0) | 154(14.6) | <0.001 |
| ARDS, n (%) | 0(0) | 259(24.6) | <0.001 |
| Hospital stays, days | 6 (5–7) | 10 (7–13) | <0.001 |
| ICU stays, n (%) | 4(1.4) | 417(39.6) | <0.001 |
| Mortality, n (%) | 0(0) | 290(27.5) | <0.001 |

Data are shown as % for categorical and as median (interquartile range) for continuous variables. Categorical data were compared using chi-square test and continuous data using Mann-Whitney U test. **Abbreviations**: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ALT, alanine transaminase; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HFNC, high flow nasal cannula; ICU, intensive care unit; LDH, lactate dehydrogenase; MV, mechanical ventilation; NIMV, noninvasive mechanical ventilation; OAC, oral anticoagulant; SaO2, oxygen saturation; SBP, systolic blood pressure. * Upper limit of normal (ULN) was defined according to criteria in each hospital and normal ranges of tests in each hospital were provided in Supplementary Table 1.

The mortality rate in our study (21.6%) was similar with the mortality rate in the hypertensive Covid-19 patients in the study of Li J et al. (21.6%) (21). Similarly with the previous studies (7,22,23), we have identified a correlation with increased mortality and age, neutrophil count, increased levels of creatinine, CRP and AST in the presence of DM. The development of AHRF was identified in 78.3% of the patients in our study. There is no study that has investigated the relationship

**Table 5.** Univariable and multivariable logistic regression analysis for acute hypoxemic respiratory failure.

| Variable | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | Unadjusted OR | 95% CI | P-value | Adjusted OR | 95% CI | P-value |
| Age, years | 1.046 | 1.034–1.059 | <0.001 | 1.043 | 1.029–1.058 | <0.001 |
| Gender (female), n (%) | 0.783 | 0.598–1.025 | 0.075 | 0.929 | 0.653–1.322 | 0.682 |
| SBP, mmHg | 1.009 | 1.000–1.018 | 0.040 | 1.001 | 0.991–1.011 | 0.861 |
| Coronary heart disease, n (%) | 1.460 | 1.068–1.996 | 0.018 | 1.077 | 0.721–1.609 | 0.717 |
| Chronic heart failure, n (%) | 1.184 | 0.696–2.014 | 0.533 | | | |
| Diabetes mellitus, n (%) | 1.315 | 1.006–1.719 | 0.045 | 1.306 | 0.955–1.786 | 0.095 |
| Chronic pulmonary disease (COPD, asthma), n (%) | 1.085 | 0.778–1.512 | 0.631 | | | |
| Cerebrovascular diseases, n (%) | 2.475 | 1.306–4.688 | 0.005 | 1.611 | 0.818–3.172 | 0.168 |
| Chronic renal diseases, n (%) | 3.551 | 1.529–8.247 | 0.003 | 2.059 | 0.688–6.159 | 0.196 |
| Renal transplantation n (%) | 3.382 | 0.795–14.394 | 0.099 | | | |
| Chronic AF, n (%) | 1.545 | 0.860–2.774 | 0.145 | | | |
| Leukocyte, $10^3/\mu L$ | 1.084 | 1.044–1.125 | <0.001 | | | |
| Neutrophil, $10^3/\mu L$ | 1.139 | 1.089–1.191 | <0.001 | 1.051 | 1.001–1.104 | 0.044 |
| Lymphocyte, $10^3/\mu L$ | 0.681 | 0.569–0.816 | <0.001 | 0.845 | 0.737–0.967 | 0.015 |
| Platelets, $10^3/\mu L$ | 1.000 | 0.999–1.001 | 0.985 | | | |
| Hemoglobin, g/dl | 0.878 | 0.817–0.944 | <0.001 | 0.915 | 0.829–1.010 | 0.079 |
| Creatinine, mg/dl | 1.480 | 1.210–1.810 | <0.001 | 1.127 | 0.916–1.387 | 0.257 |
| Ferritin>ULN*, n (%) | 2.536 | 1.862–3.454 | <0.001 | | | |
| D-dimer>ULN*, n (%) | 1.484 | 1.125–1.958 | 0.005 | 1.524 | 1.103–2.105 | 0.011 |
| Procalcitonin, ng/ml | 1.017 | 0.980–1.057 | 0.370 | | | |
| C-reactive protein, mg/l | 1.013 | 1.011–1.016 | <0.001 | 1.011 | 1.008–1.014 | <0.001 |
| ACEI, n (%) | 0.892 | 0.606–1.313 | 0.563 | | | |
| ARB, n (%) | 0.972 | 0.669–1.410 | 0.880 | | | |
| Non-ACEI/ARB, n (%) | 1.068 | 0.752–1.517 | 0.715 | | | |
| Beta-blocker, n (%) | 1.203 | 0.922–1569 | 0.174 | | | |
| Antiaggregant, n (%) | 1.628 | 1.250–2.119 | <0.001 | 1.208 | 0.863–1.691 | 0.272 |
| OAC, n (%) | 1.510 | 0.804–2.837 | 0.200 | | | |
| Loop diuretic, n (%) | 0.992 | 0.586–1.678 | 0.976 | | | |

Multivariable logistic regressions was performed with a pre-defined covariate set, which included age, gender, SBP, coronary heart disease, diabetes mellitus, cerebrovascular diseases, chronic renal diseases, neutrophil, lymphocyte, hemoglobin, creatinine, D-dimer, C-reactive protein, and antiaggregant. **Abbreviations**: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OAC, oral anticoagulant; SBP, systolic blood pressure; OR, odds ratio * Upper limit of normal (ULN) was defined according to criteria in each hospital and normal ranges of tests in each hospital were provided in Supplementary Table 1.

between antihypertensive medication groups and AHRF and that compared the efficacy of these medication groups in the hypertensive Covid-19 patients. Out study is the first study that has been carried out on this subject although no relationship was identified between these medication groups and AHRF.

ACE2 which plays an important role in RAAS metabolizes angiotensin II and converts to angiotensin (1–7,24). Angiotensin II binds to the angiotensin type 1 receptor (AT1R) and cause lung injury by leading to vasoconstriction of lung vessels, increased pulmonary vascular permeability, inflammation and interstitial fibrosis (25,26). Angiotensin (1–7) against lung injury by showing an exactly opposite effect (vasodilatation, antiinflammatory, antifibrotic) to angiotensin II/AT1R pathway (27). This system is on an equilibrium in the healthy individuals. It has been reported that SARS-CoV which is classified in the same family with SARS-CoV-2 and similarly uses membrane-bound ACE2 as the receptor for entrance into the cell, leads to a reduced expression of ACE2 and causes a shift in equilibrium to the side of angiotensin II/AT1R (25). That condition increases the level of angiotensin II in the body. It has been reported that serum angiotensin II level significantly increases and that it is positively correlated with viral load and lung injury in the Covid-19 patients (28). In the animal experiments, loss in ACE2 expression resulted in increased vascular permeability, pulmonary edema, neutrophil accumulation and worsening pulmonary function (25)(24). All these outcomes have manifested to what extent angiotensin II and ACE2 have a critical importance with respect to acute lung injury and

consequently developing AHRF and mortality. ACE2 is a membrane-bound enzyme and its soluble level in the blood serum is very low (29,30). Even if ACE2 in body fluid levels increase to 2-fold, it does not significantly change the amount of ACE2 bound to the membrane. This fact indicates that this increase does not affect the entrance of SARS-CoV-2 that uses membrane-bound ACE2 as receptor into the cell seriously. Even though, increased ACE2 expression in the body fluids has been shown in the patients who used ACEI and ARB, however, it could not be shown that this increase caused an elevation in the level of membrane-bound ACE2 expression on the tissue. Furthermore, increased level of soluble ACE2 may indicate a reduction in the level of membrane-bound ACE2 (31). Additionally, it is also possible that soluble form of ACE2 in the circulation may function as a trapper receptor which binds to SARS-CoV-2 and competitively inhibits virus entry into the host target cells mediated by membrane-bound ACE2 (32). Indeed, it has been reported in a study that hypertensive Covid-19 patients who use RAAS inhibitor have significantly lower SARS-CoV-2 peak viral load than Covid-19 patients who do not use RAAS inhibitor (33). All these outcomes have induced the idea that use of ACEIs and ARBs is not harmful but useful for Covid-19 patients who had pneumonia (34).

Zhang et al. have evaluated ACEI and ARB in the same antihypertensive medication group in a multi-center retrospective study on 1128 hypertensive Covid-19 patients and have figured out that mortality rate was significantly lower in ACEI or ARB group compared with nonACEI/ARB group (35). It has

not been stated by which drug group recovery was obtained since ACEI and ARB were evaluated in the same antihypertensive drug group. Even though, there is no larger study that has evaluated ACEI and ARB as the different drug groups yet, meta-analyses have been published on this subjects. Two considerable meta-analyses have been published and demonstrated that use of RAAS inhibitors may be clinically useful in hypertensive Covid-19 patients. Wang et al. have carried out a meta-analysis of 26 studies involving 16,307 patients and determined lower mortality and MV support rates in the hypertensive Covid-19 patients who use RAAS inhibitors (36). However, in a meta-analysis consistent with our study, it was stated that there was no statistically significant difference between ACEI and ARB use. Pirola and Sookoian have manifested in their meta-analysis based on 16 studies involving 24,676 hypertensive Covid-19 patients that use of ACEI or ARB was not associated with risk for higher in-hospital mortality and/or severe disease in the hypertensive Covid-19 patients. Contrarily, this analysis carried out focusing on predicting individual efficacy scale of each drug group including ACEI, ARB and non ACEI/ARB drugs have manifested that RAAS inhibitors have an overall protective effect with reduced risk for mortality and/or critical disease by approximately 23%. It has been highlighted that this protective effect of RAAS has resulted from the patients who used ACEI (37).

It was detected according to our results in the present article similarly with the outcomes of the previous studies that use of ACEI or ARB caused no increase in the mortality rate compared with those who used non-ACEI/ARB drugs. Beside that, it was determined that RAAS inhibitors have no different impact than other antihypertensive medications in protection from AHRF. However, need to MV was lower in the group that used ACEIs although those patients showed a similary rate of need to nasal/mask oxygen therapy, HFNC oxygen therapy and NIMV with other groups. This outcome suggest that AHRF may progress more mildly in the patients who use ACEIs. Both ACEIs and ARBs were found useful against lung injury in the experimental animal studies (38,39), however, both drugs might have been useful since lung injury is a not specific damage directly affecting on RAAS. Whereas, these two drugs may present different results in a pathology which has a direct impact on RAAS system such as SARS-CoV-2. Taking RAAS into consideration, the level of ACE2 decreases, angiotensin II cannot be catabolized and angiotensin II/AT1R pathway gains predominancy in the patients infected with Covid-19. It is known that increased angiotensin II is associated with poor prognosis in the Covid-19 patients (28). The use of ACEI inhibits angiotensin II production and may be advantageous by reducing the potential deleterious effect of angiotensin II especially on the lung as well as on other organs. ARBs may show their effect on angiotensin II by inhibiting AT1R. However, they may remain inadequate in blockading huge amount of angiotensin II in the environment and that may suggest that contribution of ARBs may be limited. Besides, efficacies of ACEIs and ARBs may differ on the levels and activities of ACE2 since these drugs have different effects on angiotensin II which is the primary susbtrate of ACE2. In-vitro and/or in-vivo studies are needed to compare the effect of ACEIs or ARBs on membrane-bound ACE2 expression or activity in the lung. In addition, it should be keep in mind that different action mechanisms may also occur taking into consideration that complicated mechanism of RAAS is not yet exactly clarified.

## Limitations of the study

The present study has several limitations. The first limitation our outcomes do not reflect general population due to absence of ethnically or geographically different populations. The second limitation is the sampling size was small. The detection strength to determine whether there is a different efficacy between ACEI, ARB and nonACEI/ARB was limited. A third limitation was that confusing parameters such as body mass index and history of cigarette smoking were not reported in the patient files.

## Conclusions

Our study showed that use of ACEI or ARB were not found to be associated in-hospital mortality when compared by nonACEI/ARB drugs in hypertensive Covid-19 patients. No significant difference was detected between the groups regarding development of AHRF. Our study revealed a similar result with recent studies investigating the relationship between ACEI, ARB and other antihypertensive drugs with mortality. However, it is obvious that large size studies with different designs are needed on this contraversial issue. On the other hand, our outcomes have suggested that the hypertensive Covid-19 patients who have been using RAAS inhibitors should be seriously supported to continue this treatment regimen.

## Disclosure statement

## Funding

## Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. The ethics committee approved the design of the present study. Informed consent was waived due to the retrospective design of the study.

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