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BRIEF COMMUNICATION

Could Anti-Hypertensive Drug Therapy Affect the Clinical Prognosis of Hypertensive Patients With COVID-19 Infection? Data From Centers of Southern Italy

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BACKGROUND: Coronavirus disease 2019 (COVID-19) is the cause of a pandemic disease, with severe acute respiratory syndrome by binding target epithelial lung cells through angiotensin-converting enzyme 2 in humans. Thus, patients with hypertension with COVID-19 could have worse prognosis. Indeed, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers may interfere with angiotensin-converting enzyme 2 expression/activity. Thus, patients with hypertension undergoing angiotensin-converting enzyme inhibitor and/or angiotensin receptor blockers drug therapy may be at a higher risk of contracting a serious COVID-19 infection and should be monitored. Moreover, in the present study we investigated the effects of angiotensin-converting enzyme inhibitor versus angiotensin receptor blockers versus calcium channel blockers on clinical outcomes as mechanical ventilation, intensive care unit admissions, heart injury, and death in 62 patients with hypertension hospitalized for COVID-19 infection.

METHODS AND RESULTS: The multicenter study was prospectively conducted at Department of Infectious Diseases of Sant'Anna Hospital of Caserta, and of University of Campania "Luigi Vanvitelli" of Naples, at Department of Advanced Surgical and Medical Sciences of University of Campania "Luigi Vanvitelli," Naples, and at General Medical Assistance Unit "FIMG," Naples, Italy. Lowest values of left ventricle ejection fraction predicted deaths (1.142, 1.008–1.294, $P<0.05$), while highest values of interleukin-6 predicted the admission to intensive care unit (1.617, 1.094–2.389), mechanical ventilation (1.149, 1.082–1.219), heart injuries (1.367, 1.054–1.772), and deaths (4.742, 1.788–8.524).

CONCLUSIONS: Anti-hypertensive drugs didn't affect the prognosis in patients with COVID-19. Consequently, tailored anti-inflammatory and immune therapies in addition to chronic antihypertensive therapy, could prevent a worse prognosis, as well as improve the clinical outcomes in patients with hypertension with COVID-19 infection.

Key Words: Angiotensin-converting enzyme 2 ■ anti-hypertensive drugs ■ COVID-19 ■ hypertension

Coronavirus disease 2019 (COVID-19) is the cause of a pandemic disease, with 80 572 cases diagnosed in Italy and 13 155 deaths.[1] COVID-19 causes a severe acute respiratory syndrome by binding target epithelial lung cells through angiotensin-converting enzyme 2 (ACE2) in humans.[2] ACE2 is a ubiquitously distributed carboxypeptidase, implicated in clinical effects of hypertension.[2–4] Higher binding affinity between COVID-19 and ACE2 could explain the higher rate of affected patients with hypertension and their worse prognosis.[2,3] Therefore, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) may interfere with ACE2 expression/activity.[2–4] Hence, patients with hypertension undergoing ACE inhibitor and/or ARB therapy may have greater risk of contracting serious COVID-19 infection

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and should be monitored.[2,3,5] On the other hand, increased ACE2 activity could mediate COVID-19 protection, by anti-inflammatory effects with upregulation of ACE2/Angiotensin 1-7/Mas axis, and improvement of lung function.[3] Thereafter, the benefits of ACE inhibitors/ARBs in COVID-19 could outweigh the risks and should not be withheld.[3] Thus, the effects of anti-hypertensive therapy in patients with COVID-19 have not been deeply evaluated in recent studies.[2,3,5] Moreover, here we analyzed the effects of ACE inhibitors versus ARBs versus calcium channel blockers (CCBs) drugs on clinical outcomes as mechanical ventilation, intensive care unit admissions, heart injuries and deaths in patients with hypertension hospitalized for COVID-19.

METHODS

For purposes of reproducing the results or replicating the procedure, the data, methods used in the analysis, and materials used to conduct the research are available from the corresponding author upon reasonable request. The study was prospectively conducted at Department of Infectious Diseases of Sant'Anna Hospital, Caserta, at Department of Advanced Surgical and Medical Sciences of University of Campania "Luigi Vanvitelli," Naples, at Department of Infectious Diseases of University of Campania "Luigi Vanvitelli" of Naples, and at General Medical Assistance Unit "FIMG," Naples, Italy. The institutional review boards ethics committee approved the study. Patients and patient families signed informed consent to participate in the study. The study population respected following inclusion and exclusion criteria.

Inclusion Criteria

Inclusion criteria included hypertension with clinic systolic blood pressure <150 mm Hg; stable dose of current anti-hypertensive medications for at least 4 weeks before study entry; patients aged >18 and <80 years with COVID-19, and able to give informed consent for study participation.

Exclusion Criteria

Exclusion criteria were secondary hypertension, previous accelerated or malignant hypertension, unstable dose of current anti-hypertensive medications for at least 4 weeks before study entry; patients under ACE inhibitors plus ARBs and/or ACE inhibitors plus CCBs and/or ARBs plus CCBs before study entry; patients aged <18 and >80 years, and unable to provide consent for study participation.

Data were collected prospectively from electronic medical records, used in clinical setting at participants' institutions. Thus, we used electronic systems for data capture, collection, and monitoring, with on-site and real timing data entry. However, the patients' files were collected in each participating institution and then analyzed.

Laboratory and Imaging Evaluations

Real-Time Reverse Transcription Polymerase Chain Reaction Assay for COVID-19

We collected respiratory specimens from each patient, then shipped to specialized laboratories designated by the Italian government for confirming COVID-19 infection. The presence of COVID-19 in respiratory specimens was detected by established reverse transcription-polymerase chain reaction methods. Laboratory analyses were obtained on admission before starting COVID-19 medical therapy and during hospitalization.

Clinical and Laboratory Parameters

We tested respiratory specimens, including nasal and pharyngeal swabs or sputum, to exclude evidence of other viral infections, including influenza, respiratory syncytial virus, avian influenza, parainfluenza, and adenovirus. The laboratory tests were performed in participants' institutions and hospitals on the day of hospital admission. These tests were performed ensuring the use of adequate standard operating procedures by a staff well trained for management and analysis of blood infected with COVID-19 (blood collection, storage, and analysis). Indeed, serum samples for laboratory investigations were all infectious. However, all physicians involved in serum managing and analysis adhered rigorously to infection prevention. Therefore, laboratory tests were performed in appropriately equipped laboratories by staff trained in the relevant technical and safety procedures. Laboratory assessments consisted of a complete blood count, blood chemical analysis, coagulation testing, evaluation of liver and renal function, and measures of electrolytes, C-reactive protein, procalcitonin, lactate dehydrogenase, and creatine kinase. Venous blood for interleukin-6 (IL-6) (Human ELISA Kit, RD System) and D-dimer (Human ELISA Kit, Invitrogen) levels was collected in EDTA-coated tubes immediately after patients arrived at the department and weekly during hospitalization. In the present study, cardiac injury was diagnosed in patients with COVID-19 by the evidence of blood levels of cardiac biomarkers as high-sensitivity Troponin I >99th-percentile upper reference limit, regardless of new abnormalities in electrocardiography and echocardiography.[6]

Statistical Analysis

Categorical variables are shown as frequency rates and percentages and continuous variables as mean

(SD) and median (interquartile range). We applied the 2-tailed Student *t*-test to test normally distributed variables for paired or unpaired data. We used 1-way ANOVA for >2 independent groups of data. Chi-square or Fisher exact test were used to compare categorical variables. $P<0.05$ was defined as statistically significant. Wilcoxon rank sum matched-pair tests were used to assess differences among the intensive care unit admission, mechanical ventilation, cardiac injury, and deaths. We performed a multivariable logistic regression analysis for mechanical ventilation, intensive care unit admissions, heart injuries and deaths risk, and corrected for demographic variables that were significantly different amongst the groups. Thus, only variables presenting $P\leq0.25$ at the univariate analysis were included in the model. We used a stepwise method with backward elimination. And we calculated odds ratios with 95% CIs. The model was evaluated with the Hosmer and Lemeshow test. A 2-sided $P<0.05$ was considered statistically significant. All statistical analyses were performed with SPSS, version 19.0 (IBM Corp), for Windows.

RESULTS

From a study population of 297 consecutive patients with COVID-19 we screened 152 (51.2%) patients with hypertension; 140 (92.1%) patients were under anti-hypertensive therapy, and 69 (45.7%) patients reached blood pressure target. Finally, according to inclusion and exclusion study criteria, we enrolled 62 consecutive patients with hypertension hospitalized for COVID-19. However, the study population consisted of 62 consecutive patients with hypertension with COVID-19, divided in patients under ACE inhibitors (n=24), patients under ARBs (n=21) and patients under CCBs (n=17).

Patients in the ACE inhibitors group were from Department of Infectious Diseases of the Sant'Anna Hospital, Caserta (n=8), from Department of Infectious Diseases of the University of Campania "Luigi Vanvitelli" of Naples (n=7), from the Department of Advanced Surgical Medical Sciences of the University of Campania "Luigi Vanvitelli" (n=5), and from General Medical Assistance Unit "FIMG," Naples, Italy (n=4). Patients in the ARB group were from Department of Infectious Diseases of the Sant'Anna Hospital, Caserta (n=5), from Department of Infectious Diseases of the University of Campania "Luigi Vanvitelli" of Naples (n=5), from Department of Advanced Surgical Medical Sciences of the University of Campania "Luigi Vanvitelli" (n=6), and from General Medical Assistance Unit "FIMG," Naples, Italy (n=5). Patients in the CCB group were from Department of Infectious Diseases of the Sant'Anna Hospital, Caserta (n=4), from Department of Infectious Diseases of the University of Campania "Luigi Vanvitelli" of Naples (n=4), from Department of Advanced Surgical Medical Sciences of the University of Campania "Luigi Vanvitelli" (n=5), and from General Medical Assistance Unit "FIMG," Naples, Italy (n=4).

Thus, we reported the daily dose for each group of patients under ACE inhibitors, ARBs, or CCB therapy. However for ACE inhibitors group (n=24) we had: 3 patients under ramipril 10 mg/daily, 6 patients under ramipril 5 mg/daily, and 2 patients under ramipril 2.5 mg/daily; 4 patients under enalapril 20 mg/daily, 7 patients under enalapril 10 mg/daily, and 2 patients under enalapril 5 mg/daily. For the ARBs group (n=21) we had: 2 patients under telmisartan 80 mg/daily, and 7 patients under telmisartan 40 mg/daily, and 2 patients under telmisartan 20 mg/daily; 2 patients under losartan 100 mg/daily, 6 patients under losartan 50 mg/daily, and 2 patients under losartan 25 mg/daily. For the CCBs group (n=17) we had: 6 patients under amlodipine 10 mg/daily, 8 patients under amlodipine 5 mg/daily, and 3 patients under amlodipine 2.5 mg/daily.

For study population, we reviewed chest radiography and computed tomography (CT) findings in relationship to the time between symptom onset and the initial CT scan: early (0–2 days for 23 patients), intermediate (3–5 days for 22 patients), late (6–12 days for 17 patients). However, in the study population we performed chest CT, that was obtained at ≈4 days intervals. Thus, these patients underwent a total of 241 pulmonary CT scans with a mean interval of 4±1 days (range: 1–8 days). Data about unilateral, bilateral, and multiple chest CT findings were reported in Table 1.

In this cohort we did not observe a significant difference in the study end points when comparing ACE inhibitors with ARBs and CCBs, ($P>0.05$) (Table 1). From multivariate Cox regression analysis corrected for study variables (95% CI, $P<0.05$), lowest values of left ventricle ejection fraction (LVEF) predicted deaths (1.142, 1.008–1.294, $P<0.05$), while highest values of IL-6 predicted intensive care unit admission (1.617, 1.094–2.389), mechanical ventilation (1.149, 1.082–1.219), cardiac injury (1.367, 1.054–1.772), and deaths (4.742, 1.788–8.524).

DISCUSSION

In the present study, anti-hypertensive drugs did not affect the prognosis in patients with COVID-19; patients with higher LVEF values had lowest risk of deaths, and IL-6 predicted admissions to intensive care unit, mechanical ventilation, heart injury, and deaths. LVEF is an index of systolic function in

Table 1. Clinical Characteristics of Study Population

Clinical Study Variables	Overall (n=62)	ACE inhibitor (n=24)	ARBs (n=21)	CCBs (n=17)	*P* Value
Age, y	58±18	56±19	58±16	59±17	0.522*; 0.293†;0.520‡
Sex (men, %)	41 (66.1)	15 (62.5)	14 (66.7)	12 (70.5)	0.509*; 0.318†; 0.539‡
Smoking (%)	7 (11.2)	3 (12.5)	2 (9.5)	2 (11.7)	0.565*; 0.692†; 0.613‡
Body mass index, kg/m^2	25.7±7.2	25.4±6.9	26.1±7.3	25.8±7.1	0.686*; 0.917†; 0.582‡
Systolic blood pressure values, mm Hg	130±5	131±4	129±5	131±5	0.337*; 0.826†; 0.608‡
Diastolic blood pressure values, mm Hg	81±6	82±6	80±7	82±7	0.456*; 0.501†; 0.447‡
Signs and symptoms at admission					
Fever	50 (80.6)	19 (79.2)	17 (80.9)	14 (82.3)	0.590*; 0.408†;0.440‡
Cough	22 (35.4)	8 (33.3)	8 (38)	6 (35.2)	0.491*; 0.585†; 0.565‡
Shortness of breath	18 (29)	7 (29.2)	6 (28.6)	5 (29.4)	0.613*; 0.533†; 0.617‡
Fatigue	12 (19.3)	4 (16.7)	5 (23.8)	3 (17.6)	0.410*; 0.592†; 0.478‡
Sputum production	3 (4.8)	1 (4.2)	1 (4.7)	1 (5.8)	0.721*; 0.646†; 0.701‡
Muscle ache	4 (6.4)	2 (8.3)	1 (4.7)	1 (5.8)	0.551*; 0.652†; 0.701‡
Diarrhea	3 (4.8)	1 (4.2)	1 (4.7)	1 (5.8)	0.721*; 0.646†; 0.701‡
Chest pain	4 (6.4)	2 (8.3)	1 (4.7)	1 (5.8)	0.551*; 0.652†; 0.701‡
Sore throat	3 (4.8)	1 (4.2)	1 (4.7)	1 (5.8)	0.721*; 0.646†; 0.701‡
Rhinorrea	3 (4.8)	1 (4.2)	1 (4.7)	1 (5.8)	0.721*; 0.646†; 0.701‡
Headache	3 (4.8)	1 (4.2)	1 (4.7)	1 (5.8)	0.721*; 0.646†; 0.701‡
Chronic medical illness					
Diabetes mellitus (%)	16 (25.8)	6 (25)	5 (23.8)	5 (29.4)	0.602*; 0.649†; 0.643‡
Coronary heart disease (%)	21 (33.9)	8 (33.3)	7 (33.3)	6 (35.2)	0.625*; 0.524†; 0.584‡
Previous AMI	11 (17.8)	4 (16.7)	4 (19)	3 (17.6)	0.422*; 0.456†; 0.624‡
CABG	3 (9)	1 (4.2)	1 (4.7)	1 (5.8)	0.721*; 0.646†; 0.701‡
PTCA	18 (5.6)	7 (29.2)	6 (28.6)	5 (29.4)	0.613*; 0.580†; 0.617‡
Chronic obstructive pulmonary disease (%)	10 (16.1)	4 (16.7)	3 (14.3)	3 (17.6)	0.578*; 0.592†; 0.560‡
Cerebrovascular disease (%)	7 (11.3)	3 (12.5)	2 (9.5)	2 (11.7)	0.565*; 0.692†; 0.613‡
Chronic renal failure (%)	6 (9.7)	2 (8.3)	2 (9.5)	2 (11.7)	0.643*; 0.529†; 0.613‡
Cancer	5 (8)	2 (8.3)	2 (9.5)	1 (5.8)	0.643*; 0.652†; 0.613‡
Laboratory findings at admission					
Red blood cells, n ×10^6 (µ/L)	3.8 (3.6–4.4)	3.8 (3.7–4.0)	3.9 (3.6–4.1)	3.8 [3.6–4.5]	0.212*; 0.254†; 0.115‡
Hemoglobin, g/dL	12.1 (10.8–13.9)	12 (11.5–13.4)	12.2 (11.7–13.3)	12.2 (10.7–14.1)	0.132*; 0.322†; 0.205‡
White blood cells, n (µ/L)	7948 (3810–11 040)	7973 (3496–10 389)	8263 (3727–10 593)	8021 (3682–11 102)	0.171*; 0.216†; 0.156‡
Lymphocytes, n (µ/L)	974 (560–1128)	983 (672–1347)	978 (589–1132)	964 (546–1212)	0.426*;0.182†; 0.345‡
Neutrophils, n (µ/L)	6936 (2410–10 118)	6875 (1852–7899)	6943 (1972–8101)	6836 (1824–10 201)	0.150*; 0.181†; 0.342‡
Pro-thrombin time, s	12.7 (12.1–15.3)	12.8 (12.1–13.3)	12.7 (12.3–13.2)	12.7 (12.2–15.5)	0.181*; 0.085†; 0.214‡
APTT, s	29.9 (27.5–35.6)	28.5 (27.8–32.2)	31.1 (20.1–32.1)	29.2 (20.3–36.8)	0.476*; 0.406†; 0.159‡
D-dimer, mg/mL	3.72 (0.12–22.38)	3.21 (0.49–19.1)	3.70 (0.52–20.7)	4.01 (0.26–22.38)	0.094*; 0.076†; 0.101‡
Cholesterol, mg/dL	148±14.7	146±14.4	150±14.2	146±14.9	0.076*; 0.173†; 0.082‡
AST, mg/dL	42.3±3.1	40.4±4.5	42.1±3.7	42.3±3.3	0.105*; 0.092†; 0.643‡
ALT, md/dL	39±2.8	38±2.5	38±3.2	39±2.5	0.109*; 0.074†; 0.086‡
CK-MB, mg/dL	166±17.1	167±14.5	165±16.8	164±18.2	0.238*; 0.146†; 0.139‡
LDH, mg/dL	620±139	622±136	620±142	623±140	0.093*; 0.082†; 0.105‡
High-sensitivity Troponin I, µg/L	0.39 (0.12–1.47)	0.38 (0.12–1.49)	0.40 (0.13–1.57)	0.43 (0.21–1.62)	0.577*; 0.195†; 0.081‡
Myohemoglobin, µg/L	49.67±28.2	49.81±28.1	49.37±30.3	50.05±28.1	0.469*; 0.337†; 0.878‡
Creatinine, mg/dL	0.81±0.22	0.92±0.18	0.88±0.25	0.89±0.23	0.128*; 0.243†; 0.341‡

(*Continued*)

Table 1. Continued

Clinical Study Variables	Overall (n=62)	ACE inhibitor (n=24)	ARBs (n=21)	CCBs (n=17)	*P* Value
BNP, pg/mL	36.4±3.1	36.1±2.9	36.9±2.8	35.9±3.3	0.062*; 0.498†; 0.148‡
Glucose, mg/dL	121±29	123±27	118±33	120±30	0.055*; 0.325†; 0.701‡
Hb1Ac, %	5.8±0.4	5.8±0.6	5.7±0.9	5.6±0.8	0.201*; 0.084†; 0.110‡
Sodium, mEq/L	135.3±2.6	136.8±2.8	134.4±2.4	135.4±2.4	0.070*; 0.312†; 0.568‡
Potassium, mEq/L	3.7±0.3	3.7±0.2	3.8±0.3	3.6±0.4	0.104*; 0.120†; 0.064‡
PaO_2/FiO_2, mm Hg	81 (64–109)	78 (66–108)	82 (72–110)	79 (67–112)	0.085*; 0.148†; 0.092‡
Inflammatory markers					
Interleukin-1, pg/dL	387.5 (321.8–422.1)	383.4 (332.6–404.5)	389.9 (339.8–408.9)	392.4 (329.8–431.9)	0.093*; 0.074†; 0.203‡
Interleukin-6, pg/dL	243.2 (202.7–251.2)	242.1 (216.8–248.9)	245.3 (222.1–250.1)	248.3 (222.1–253.2)	0.083*; 0.064†; 0.126‡
Tumor necrosis alpha, mg/dL	3.1 (1.94–4.89)	2.9 (2.6–4.32)	3.3 (3.0–4.64)	3.2 (3.0–4.92)	0.093*0.184†; 0.233‡
High-sensitivity C-reactive protein, mg/dL	6.2 (1.2–17.12)	5.7 (4.3–16.7)	5.6 (1.2–18.7)	6.4 (3.6–19.7)	0.341*; 0.072†; 0.063‡
Pro-calcitonin, ng/mL	0.21 (0.04–0.44)	0.22 (0.06–0.39)	0.24 (0.05–0.46)	0.20 (0.04–0.47)	0.075*; 0.091†; 0.062‡
Echocardiographic parameters					
LVTDd, mm	49.4±4.5	49.3±4.7	48.6±4.6	49.8±4.2	0.121*; 0.122†; 0.317‡
LVTSd, mm	34.1±2.8	34.1±2.8	36.1±2.7	35.6±3.1	0.469*; 0.383†; 0.151‡
LVEF, %	53.8±8.2	54.5±6.7	52.2±6.4	55.1±8.4	0.446*; 0.317†; 0.121‡
Mitral insufficiency					
Low (%)	41 (66.1)	16 (66.7)	14 (66.7)	11 (64.7)	0.623*; 0.524†; 0.584‡
Moderate (%)	21 (33.9)	8 (33.3)	7 (33.3)	6 (35.3)	0.625*; 0.524†; 0.584‡
Severe (%)	…				
Chest radiography and computed tomography findings					
Pneumonia					
Unilateral	15 (24.1)	6 (25)	5 (23.8)	4 (23.5)	0.602*; 0.649†; 0.643‡
Bilateral	47 (75.8)	18 (77.5)	16 (76.2)	13 (76.5)	0.454*; 0.475†; 0.624‡
Multiple motting and ground-glass opacity	33 (53.2)	13 (54.2)	11 (52.4)	9 (52.9)	0.555*; 0.475†; 0.615‡
Chronic drug therapy					
Anti-platelets (%)					
Cardioaspirin (%)	24 (38.7)	9 (37.5)	8 (38.1)	7 (41.2)	0.604*; 0.472†; 0.555‡
Clopidrogel, %	14 (22.6)	5 (225)	5 (23.8)	4 (23.5)	0.546*; 0.525†; 0.643‡
Prasugrel (%)	…				
Beta blockers (%)	21 (33.9)	8 (33.3)	8 (38.1)	5 (29.4)	0.491*; 0.585†; 0.416‡
Loop diuretics (%)	8 (12.9)	3 (12.5)	3 (14.2)	2 (11.8)	0.846*; 0.565†; 0.565‡
Thiazides (%)	12 (19.3)	4 (16.7)	5 (23.8)	3 (17.6)	0.410*; 0.592†; 0.478‡
Statins (%)	27 (43.5)	10 (41.6)	10 (47.6)	7 (41.2)	0.587*; 0.576†; 0.527‡
Hypoglycemic drugs (%)	13 (21)	5 (20.8)	5 (23.8)	3 (17.6)	0.546*; 0.601†; 0.478‡
Insulin therapy (%)	4 (6.5)	2 (0.8)	1 (0.5)	1 (0.6)	0.551*; 0.652†; 0.701‡
COVID-19 therapy					
Antiviral (%)	62 (100)	24 (100)	21 (100)	17 (100)	…
Antibiotics (%)	53 (85.5)	21 (87.5)	17 (80.9)	15 (88.2)	0.601*; 0.471†; 0.387‡
Hydroxyl-chloroquine (%)	51 (82.2)	20 (83.3)	17 (80.9)	14 (82.3)	0.578*; 0.592†; 0.560‡
Glucocorticoids (%)	48 (77.4)	19 (79.2)	16 (76.2)	13 (76.5)	0.590*; 0.408†; 0.624‡
Oxygen inhalation (%)	50 (80.6)	19 (79.2)	17 (80.9)	14 (82.3)	0.431*; 0.212†; 0.604‡
Non-invasive ventilation (%)	13 (21)	5 (20.8)	5 (23.8)	3 (17.6)	0.546*; 0.601†; 0.478‡
Anticoagulant (%)	12 (19.3)	4 (16.7)	5 (23.8)	3 (17.6)	0.410*; 0.592†; 0.478‡
Complications					
VT/VF (%)	10 (16.1)	4 (16.7)	3 (14.2)	3 (17.6)	0.578*; 0.592†; 0.560‡
ARDS (%)	32 (51.6)	12 (50)	11 (52.3)	9 (52.9)	0.571*; 0.578†; 0.615‡

(*Continued*)

Table 1. Continued

Clinical Study Variables	Overall (n=62)	ACE inhibitor (n=24)	ARBs (n=21)	CCBs (n=17)	*P* Value
Coagulopathy (%)	36 (58)	14 (58.3)	12 (57.1)	10 (58.8)	0.491*; 0.524†; 0.555‡
Liver injury (%)	11 (17.7)	4 (16.7)	4 (19)	3 (17.6)	0.168*; 0.592†; 0.592‡
Kidney injury (%)	21 (33.9)	8 (33.3)	7 (33.3)	6 (35.2)	0.625*; 0.524†; 0.584‡
Study end points					
Hospital admissions at intensive care unit (%)	12 (19.3)	4 (16.7)	5 (23.8)	3 (17.6)	0.410*; 0.592†; 0.478‡
Mechanical ventilation (%)	26 (41.9)	10 (41.7)	9 (42.9)	7 (41.2)	0.578*; 0.576†; 0.590‡
Cardiac injury (%)	14 (22.5)	5 (20.8)	5 (23.8)	4 (23.5)	0.546*; 0.525†; 0.643‡
Deaths (%)	9 (14.5)	4 (16.6)	3 (14.3)	2 (11.8)	0.592*; 0.061†; 0.565‡

Characteristics of study population of 62 consecutive patients with hypertension with COVID-19. ACE indicates angiotensin-converting enzyme; ALT, alanine aminotransferase; AMI, acute myocardial infarction; APTT, activated pro-thrombin time; ARBs, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CCBs, calcium channel blockers; CK-MB, creatinine kinase-myocardial band; Hb1Ac, glycated hemoglobin; LDH, lactate dehydrogenase; LVEF, left ventricle ejection fraction; LVTDd, left ventricle end-diastolic diameter; LVTSd, left ventricle end-systolic diameter; PaO_2/FiO_2, Pressure of Arterial Oxygen to Fractional Inspired Oxygen Concentration; PT, Pro-thrombin time; PTCA, percutaneous coronary angioplasty; and VT/VF, ventricular tachycardia/ventricular fibrillation.

First *P* value is for angiotensin-converting enzyme inhibitors vs angiotensin receptor blockers and marked with "*"; second *P* value is for angiotensin-converting enzyme inhibitors vs calcium channel blockers and marked with "†"; third *P* value is for angiotensin receptor blockers vs calcium channel blockers and marked with "‡". Analysis began February 29, 2020.

hypertensive heart disease.[3,4] The blood pressure overload by excessive inflammation alters heart structure, through hypertrophy, interstitial fibrosis, apoptosis, and myocardial ischemia, with consequent LVEF decrease.[3–5] Patients with hypertension have excessive inflammation, that could be mediated by ACE2.[4] However, COVID-19 by cardiac ACE2 receptors binding could accelerate these negative events.[2,3,5] In this setting, IL-6 is a cytokine and a serum marker of excessive inflammation and activation of immune T cells during blood pressure increase.[5–9] Indeed, T cell activation causes heightened expression of IL-6, as immune response/memory to hypertension.[3] This could be excessively reactivated by COVID-19.[3,5] On the other hand, ACE inhibitors/ARBs have cardioprotective functions, and could improve LVEF by reduction of inflammation.[3–5] Moreover, we might suggest not to stop taking ACE inhibitors/ARBs, to control hypertension and to prevent more serious and dangerous complications, such as to monitor inflammatory markers and IL-6 in patients with hypertension with COVID-19. Consequently, tailored anti-inflammatory and immune therapies in addition to chronic anti-hypertensive therapy could improve clinical outcomes, and prevent worse prognosis in patients with hypertension with COVID-19.

In this study we didn't assay ACE2 expression in patients with hypertension, and we didn't use magnetic resonance to evaluate cardiac injury; we didn't test heart expression of ACE2 in animal models of COVID-19 infection during ACE inhibitors versus ARBs versus CCBs therapy. In addition, we did not report data about chest echocardiography imaging, because we did not perform this exam for the total study population. Again, limited follow-up time and reduced sample size dimension cannot drive us towards definitive conclusions about anti-hypertensive drugs' effects in patients with hypertension with COVID-19. Finally, we included only patients with anti-hypertensive medications and well controlled hypertension, and this could reduce the generalizability of study results. Moreover, these points need to be investigated in larger clinical trials.

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