

The Effect of Renin-Angiotensin Blockers on COVID-19 Related Mortality: A Tertiary Center's Experience

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Kontext: První zprávy o onemocnění koronavirem v roce 2019 (coronavirus disease 2019, COVID-19) ukázaly na zvýšenou mortalitu jedinců s hypertenzí, což vyvolalo obavy ohledně užívání inhibitorů angiotenzin konvertujícího enzymu (ACEI) a blokátorů receptoru AT₁ pro angiotenzin II (ARB). Cílem naší studie bylo posoudit možnost nepříznivého vlivu onemocnění covid-19 na závažnost hypertenze a účinnost antihypertenzní léčby.

Metody: Do studie bylo zařazeno 183 pacientů s onemocněním covid-19 prokázaným PCR testem, kteří byli v období od 15. března do 15. dubna 2020 přijati do naší nemocnice a následně odesláni na kardiologickou kliniku. Údaje byly získány z nemocničních záznamů.

Výsledky: Celkem 32 ze 183 pacientů s onemocněním covid-19 zemřelo v nemocnici. Incidence hypertenze se mezi pacienty, kteří přežili a zemřeli, statisticky významně nelišila (76 [50,3 %] vs. 19 [59,4 %]; $p = 0,352$). I když podíly pacientů užívajících inhibitory ACE byly v obou skupinách podobné, léčiva ze skupiny ARB užívalo statisticky významně více pacientů, kteří zemřeli, než těch, kteří přežili (11 [34,4 %] vs. 23 [15,2 %]; $p = 0,011$). Binární regresní analýza prokázala souvislost mezi užíváním ARB a mortalitou (OR: 0,032; 95% CI 1,045–2,623; $p = 0,032$).

Závěr: Naše studie potvrdila původní obavy týkající se možných škodlivých účinků lékové skupiny ARB na mortalitu v souvislosti s onemocněním covid-19.

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ABSTRACT

Background: The first reports on coronavirus disease 2019 (COVID-19) revealed an exaggerated mortality rate in hypertensive patients. In this regard, concerns about angiotensin-converting enzyme (ACE) inhibitors' and angiotensin-receptor blockers' (ARBs) have been aroused. Our aim in this study was to evaluate the potential bad outcome effect of hypertension and anti-hypertensive therapy on COVID-19.

Methods: 183 patients with polymerase-chain-reaction (PCR)-proven COVID-19, who were admitted to our hospital and consulted to cardiology department between 15th of March and 15th of April 2020 were included. Data were recruited from hospital records.

Results: Thirty-two out of 183 patients with COVID-19 died in hospital. Hypertension incidence was not statistically different between patients who survived and died (76 [50.3%] vs 19 [59.4%, $p = 0.352$]). Although the usage rate of ACEI were similar among groups, ARB usage rate was significantly higher in patients who died than survived (11 [34.4%] vs 23 [15.2%], $p = 0.011$). Binary regression analysis showed an association between ARBs and mortality (OR: 0.032, 95% CI 1.045–2.623, $p = 0.032$).

Conclusion: Our study confirmed previous concerns regarding a potential harmful effects of ARBs on COVID-19 related mortality.

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Introduction

The preliminary reports regarding coronavirus disease 2019 (COVID-19) demonstrated a higher complication and death rate in patients with cardiovascular disease (CVD), especially hypertension.¹ Vice versa, there was a significant increase in the number of cardiac complications, from asymptomatic QT prolongation to cardiac death reported in several studies and case series about COVID-19.² The association between acute respiratory infections and CVD has been recognized previously during seasonal influenza outbreaks.³ Some viruses are now known to attack cardiac system by activating coagulation pathways, releasing proinflammatory mediators, and disturbing endothelial cell function.³

Nevertheless, there had been a distinct interest in angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) in patients with COVID-19 after unrevealing which cellular factors are used by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for cell entry.⁴ Hoffman et al. identified angiotensin converting enzyme II (ACE2) as cell entry receptors for SARS-CoV-2.⁴ ACE2 is expressed in human airway epithelia as well as lung parenchyma, heart, kidneys and intestine. An interaction between a receptor-binding domain of SARS-CoV-2's spike with the ACE2 receptor enables viral entry into human cells.⁵

ACE2 is a zinc metalloendopeptidase that functions as a C-terminal peptidyl dipeptidase, and acts to convert Angiotensin II to Angiotensin 1-7.⁵ Some animal models have demonstrated increased ACE2 expression with ACEi and ARBs.^{6,7} However, this is controversial, because, first of all, not all the trials could reveal augmented ACE2 expression with ACEi and ARBs. Secondly, this uncertain effect seems to be a drug-specific effect, not a class effect.⁶ Even so, the American Heart Association, and the Council on Hypertension of the European Society of Cardiology have stated that therapy with ACEi and ARBs should be continued unless proven to be harmful.^{8,9}

Hence, our aim in this study was to evaluate whether hypertension or ACEi-ARBs are potential risk factors for mortality in COVID-19 or not.

Methods

Data collection

Hospital electronic medical recordings was used as a resource to analyze data from all patients with COVID-19 who were admitted to the hospital and consulted to cardiology clinic between March 15, 2020 and April 15, 2020 and who were recorded as having either died in the hospital or survived to hospital discharge as of May 1, 2020. COVID-19 was diagnosed on the basis of the World Health Organization guidance.¹⁰ A positive laboratory finding for SARS-CoV-2 was defined as a positive result on high-throughput sequencing or real-time reverse-transcriptase-PCR (RT-PCR) assay of nasal or pharyngeal swab specimens. Patients who did not undergo testing, had no record of testing in the collaborative database, or had a negative test were not included in the present study. For this study, only one positive test was necessary for the

patient to be included in the analysis. Data on patients' demographic characteristics, coexisting conditions, and cardiovascular drug therapy were included in this analysis. Clinical information included age, sex, and underlying coexisting conditions as saved in the inpatient electronic health record. Laboratory findings recorded at the day of hospital admission were recorded. Estimated glomerular filtration rate was measured from MDRD equation.

The study was approved by the local ethics committee review board. The study complied with the Declaration of Helsinki and voluntary informed written consent was obtained from all patients included in this study.

Statistical analysis

The data are presented as the mean, median, standard deviation (SD) and percentages. All analysis was performed using IBM SPSS Statistics, V.20.0 (Armonk, NY: IBM Corp.). A Kolmogorov-Smirnov test used for normality of all quantitative variables. The comparison between groups of quantitative variables was performed with Mann-Whitney U test for two independent subgroups. Distribution for categorical variables were compared by chi-square or Fisher's exact test. Multiple binary logistic regressions with a backward stepwise method were used to assess risk factors on mortality and intensive care as dependent variables. All tests were two-tailed and $p < 0.05$ was considered as statistically significant.

Results

Among 183 patients hospitalized with COVID-19, 151 were successfully treated and discharged, and 32 patients died. Demographic features of the patients are described in Table 1. Accordingly, while age, hypertension, diabetes, hyperlipidemia, coronary artery disease, heart failure, chronic obstructive pulmonary disease, and cerebrovascular event incidence was similar among groups, chronic renal failure incidence was higher in patients who

Table 1 – Demographic features of the patients

	COVID-19 survivors N = 151 n (%)	COVID-19 deaths N = 32 n (%)	p-value
Age	60.73±13.24	65.09±10.85	0.091
Hypertension	76 (50.3)	19 (59.4)	0.352
Diabetes	41 (27.2)	13 (40.6)	0.129
Hyperlipidemia	13 (8.6)	4 (12.5)	0.505
Coronary artery disease	28 (18.5)	9 (28.1)	0.235
Chronic renal failure	10 (6.6)	10 (31.2)	<0.001
Heart failure	10 (6.6)	6 (18.8)	0.040
Chronic obstructive pulmonary disease	8 (5.2)	4 (12.5)	0.231
Cerebrovascular event	9 (6.0)	0	0.364
Sex (male)	64 (42.4%)	12 (37.5%)	0.611

Table 2 – Laboratory findings of the patient groups

	COVID-19 survivors N = 151 n (%)	COVID-19 deaths N = 32 n (%)	p-value
Troponin (ng/L)	570.18±2640.15	3535.81±15424.04	<0.001
eGFR (mL/min)	83.56±27.93	56.31±35.27	<0.001
CRP (mg/dL)	76.30±73.94	175.19±107.65	<0.001
Ferritin	383.33±725.85	2594.26±7821.23	<0.001
Procalcitonin (ng/mL)	0.46±3.14	8.68±12.31	<0.001
D dimer (µg/ml)	1.03±3.01	3.28±3.68	<0.001
WBC count (/µL)	6.77±2.84	12.64±6.72	<0.001
Hb (g/dL)	12.05±1.79	14.90±28.01	<0.001
Lymphocyte count (/µL)	1.69±3.31	1.40±2.55	<0.001

CRP – C reactive protein; eGFR – estimated glomerular filtration rate; Hb – hemoglobin; WBC – white blood cell count.

Table 3 – Antihypertensive treatment analysis of the patients

	COVID-19 survivors N = 151 n (%)	COVID-19 deaths N = 32 n (%)	p-value
ACEi	29 (19.2)	6 (18.8)	0.953
ARB	23 (15.2)	11 (34.4)	0.011
Other	26 (17.2)	2 (6.2)	0.175
Valsartan	8 (5.2)	4 (12.5)	0.228
Candesartan	4 (2.6)	3 (9.3)	0.105
Losartan	4 (2.6)	1 (3.1)	1.000
Olmесartan	2 (1.3)	1 (3.1)	0.440
Irbesartan	3 (1.9)	1 (3.19)	0.540
Telmisartan	3 (1.9)	0	1.000

died than survived (10 (31.2%) vs 10 (6.6%), $p < 0.001$). All the associated laboratory findings were elevated in patients who died than survived ($p < 0.001$) (Table 2). Antihypertensive treatment analysis of the patients are given in Table 3. Accordingly, while ACEi usage rate was

similar among survivors and non-survivors (29 [19.2%] vs 6 [18.8%], $p = 0.953$), ARB usage rate was significantly higher in patients who died compared to patients who survived (11 [34.3%] vs 23 [15.2%], $p = 0.011$). The usage rates of ARB subtypes were not different among groups, yet the sample size was too small for a more powerful analysis. Table 4 demonstrates binary logistic regression analysis for mortality predictors. ARB treatment, CRP, and ferritin serum levels were correlated with mortality (OR: 0.032, 95% CI 1.045–2.623, $p = 0.032$; OR: 1.007, 95% CI: 1.002–1.013, $p = 0.008$, OR: 1.001, 95% CI: 1.000–1.002, $p = 0.023$; respectively).

Discussion

Our study demonstrated that ARB usage was higher in patients with COVID-19 who died compared to those who survived, while neither ACEi nor different type of ARB treatment was different among groups. It is also important to note that we were not able to confirm previous concerns regarding a potential harmful association of hypertension with in-hospital mortality in this clinical context.

Most people who are infected with SARS-CoV-2 have mild symptoms and recover quickly, while others suffer from acute respiratory distress syndrome which is associated with hyperinflammatory syndrome, multi-organ dysfunction, and death. SARS-CoV-2 enters the pulmonary cells via the cellular surface receptor ACE2. After the entrance, ADAM metalloproteinase domain 17 (ADAM17) is activated to cleave ACE2, which results in the release of pro-inflammatory cytokines into the circulation. It has been postulated that patients with cardiovascular diseases, especially hypertension, are more prone to worse COVID-19 related outcomes than the general population. Moreover, a concern about potential harmful effect of ACEi and ARBs emerged as several studies had shown altered ACE2 expression with these medications.⁴ Besides, ACEi and ARB types appear to affect ACE2 expression differently.^{4,6} For instance, Ferrario et al demonstrated surged cardiac ACE2 mRNA and cardiac ACE2 activity with losartan, but not with lisinopril in a rat model.⁶ Ishiyama et al. showed upregulation of ACE2 after myocardial infarction by losartan and olmesartan in rats.¹⁰ Similarly,

Table 4 – Binary logistic regression analysis for mortality

Dependent: Mortality	B	SE	p	OR	95% CI for OR	
					Lower	Upper
ACEi	0.074	0.269	0.782	1.077	0.636	1.825
ARB	0.504	0.235	0.032	1.656	1.045	2.623
Other antihypertensives	-0.448	0.393	0.255	0.639	0.296	1.381
Age	0.018	0.022	0.414	1.018	0.975	1.064
Sex	-0.222	0.291	0.446	0.801	0.453	1.417
Troponin	0.000	0.000	0.073	1.000	0.999	1.000
CRP	0.007	0.003	0.008	1.007	1.002	1.013
Ferritin	0.001	0.001	0.023	1.001	1.000	1.002
D-dimer	0.129	0.085	0.128	1.138	0.963	1.345

Sukumaran et al. revealed augmented ACE2 activity by telmisartan in an experimental myocarditis model.¹²

On the other hand, nor ramipril neither valsartan increased ACE2 activity in an experimental myocardial infarction model.¹³ As against several cardiac ACE2 studies and few renal ACE2 studies, there are not any concerning ACEi and ARBs effect on pulmonary ACE2.¹⁴ In cross-sectional studies, plasma ACE2 activity was not elevated among patients who received long-term treatment with ACEi or ARBs due to various types of CVD, such as atrial fibrillation, heart failure, aortic stenosis, and coronary artery disease.^{14–17} In a Japanese longitudinal cohort study conducted on patients with hypertension, compared to untreated control patients urinary ACE2 levels were higher among patients who were administered olmesartan, but not enalapril or other ARBs (losartan, candesartan, valsartan, and telmisartan).¹⁸ In this manner, mortality rates were similar among ARB types in our study, however, the number of individuals using different types of ARBs were too small to make a powerful analysis. These conflicting data suggests that the potential ACEi and ARB effect on ACE2 expression and plasma levels is complicated, not uniform among subtypes, and lacks human studies to clarify their impact on pulmonary ACE2 expression.¹⁴ More importantly, it is not proven yet that any ACEi or ARB related ACE2 expression assists entry of SARS-CoV-2.¹⁴

On the other hand, it is argued that SARS-CoV-2 may be attacking residuary ACE2 receptors in hypertensive patients because the drugs have been bounded the receptors.¹⁹ Yet, angiotensin II levels increase and augments severe pulmonary disease development.¹⁹ This phenomenon has been also observed in patients with pneumonia and ARDS.²¹ Hence, hypertension and SARS-CoV-2 may have an interdependent effect, rather than a causality effect on disease prognosis.¹⁹ In early studies and case series hypertension was mostly reported to be related with fatality in COVID-19.¹⁹ A meta-analysis of 13 studies with 2893 patients with COVID-19, hypertension was found to increase disease severity by 2.5-fold.¹⁹ Our study found that hypertension was the most prevalent comorbidity in both group of COVID-19 patients (50.3% in survivors and 59.4% in non-survivors). However, the incidence of hypertension was not statistically different among groups ($p = 0.352$). Similar to our findings, Zhou et al. reported hypertension as the most common comorbidity in patients with COVID-19 (30%); however, they did not find hypertension as an independent risk factor for severe respiratory disease or death.²¹

Lymphopenia, decreased glomerular filtration rate (GFR), and elevated liver enzymes, lactate dehydrogenase (LDH), inflammatory markers like procalcitonin, C-reactive protein (CRP) and ferritin, D-dimer, prothrombin time (PT), troponin, and creatine phosphokinase (CPK) have been associated with worse outcome in COVID-19 patients.^{21–23} Similarly, all the particular laboratory features were significantly different among survivors and non-survivors in our study. Moreover, CRP and ferritin was found out to be associated with mortality in regression analysis (OR: 1.007, 95% CI: 1.002–1.013, $p = 0.008$, OR: 1.001, 95% CI: 1.000–1.002, $p = 0.023$; respectively). In a series of 1099 adult patients hospitalized with CO-

VID-19 in China, 83.2% had lymphopenia on admission.²⁴ Another meta-analysis of 7 studies with 1905 patients revealed that increased CRP, LDH and lymphopenia were significantly associated with COVID-19 severity.²⁵ Sharma et al. defined high D-dimer ($>1 \mu\text{g/L}$) levels as poor prognostic factor for COVID-19 infection.²⁶ In another series of 603 survivors and 249 non-survivors, an increased risk of in-hospital death was associated with elevated white blood cells, neutrophils, urea, creatinine, CPK, troponin, LDH and D-dimer.²⁷ Despite all the facts regarding increased mortality and morbidity as well as deteriorated laboratory features, Ugurlucan et al. indicated safe cardiac procedures in pediatric population with meticulous care and precautions.²⁸

Study limitations

This study was a retrospective, single-center, observational study with a small number of patients. Further study recruiting a larger number of hypertensive patients naive to treatment will be needed. Besides, we only included hospitalized patients with COVID-19. A group of patients who were not hospitalized and a control group would increase the power of the study.

Conclusion

In conclusion, this retrospective one-centered observational study involving patients hospitalized with COVID-19, we found an association between ARBs and mortality in this clinical context. We were not able to confirm previous concerns regarding a potential harmful association of hypertension with COVID-19 related mortality.

Funding

None.

Conflict of interest

None.

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