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Associations between Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blocker Use, Gastrointestinal Symptoms, and Mortality among Patients with COVID-19

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R Mao and MH Chen conceived and supervised the overall study. Y Qiu and ND Tan wrote the manuscript. ND Tan, XB Xing and S Ghosh critically revised the manuscript.

Short title: ACEI/ARB on digestive system in COVID-19 patients

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Keywords: COVID-19; ACEI/ARB; digestive system; liver injury

Introduction

The gastrointestinal (GI) tract and liver represent common target organs of Coronavirus disease 2019 (COVID-19) [1]. Recent meta-analysis showed 17.6% of patients with COVID-19 had gastrointestinal symptoms [2]. Digestive system involvement is associated with a poor disease course [3].

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are commonly used in patients with hypertension. A recent landmark study including 1,128 COVID-19 patients with hypertension demonstrated that inpatient use of ACEI/ARB was associated with lower risk of mortality compared with ACEI/ARB non-users [4]. We aimed to determine the impact of ACEI/ARB use on the digestive system in COVID-19 patients with hypertension.

Method

A retrospective study investigating the clinical and virologic characteristics of COVID-19 between 28th January 2020 and 8th April 2020 was performed. All COVID-19 patients cared for by the rescue medical team of the First Affiliated Hospital of Sun Yat-sen University were recruited consecutively from West Campus of Wuhan Union Hospital.

The primary outcome was the comparison of rate of GI symptom and abnormal liver function between COVID-19 patients with hypertension with or without using ACEI/ARB during the disease course. The secondary outcome was prognosis of these patients including complications, mortality and time of discharge from hospital.

The definition of GI symptoms included abdominal pain, diarrhea, nausea and vomiting [3]. The definition of abnormal liver function was alanine aminotransferase (ALT) >40 U/L, aspartate aminotransferase (AST) >40 U/L or total bilirubin (TBIL) >20 umol/L.

The cumulative probabilities of GI involvement and abnormal liver function were estimated using the Kaplan–Meier method. Statistical significance was set at $p < 0.05$.

Result

Participants

This study cohort included 204 consecutive patients with COVID-19. Among the 100 participants with hypertension, 31 were classified as ACEI/ARB group and the remaining 69 were classified as non-ACEI/ARB group. The characteristics of the ACEI/ARB group versus the non-ACEI/ARB group on admission are provided in **Supple Table 1**. The comorbidity including GI disease, chronic obstructive pulmonary disease, coronary heart disease, diabetes and chronic renal disease were comparable between the two groups (all $p>0.05$). The rate of the critical/severe type was comparable between ACEI/ARB group and non-ACEI/ARB group (87.1% vs 87.0%, $p>0.05$).

Compared to the ACEI/ARB group, the non-ACEI/ARB group had higher prevalence of dyspnea and bilateral lung lesion at presentation. In terms of in-hospital treatment, the ACEI/ARB group had a higher percentage of using beta-blocker (32.3% vs. 4.3%; P <0.001) and lower percentage of systemic corticosteroids use (9.7% vs. 37.7%; P<0.01) than patients in the non- ACEI/ARB group (**Supple Table 1**).

Primary outcome

As shown in **Figure 1A**, patients on ACEI/ARB had a significantly lower risk of GI symptoms (38.7% vs. 58%, p=0.031) and abnormal liver function (22.6% vs. 42%, p=0.043) throughout the disease course. On admission, there was a trend towards, though not significantly, lower rate of GI symptom in ACEI/ARB group compared to non-ACEI/ARB group (12.9% [4/31] vs. 29% [20/69], p=0.082). The spectrum of GI

symptoms includes diarrhea (6.5% vs. 14.5%), nausea and vomiting (9.7% vs. 11.6%) , and abdominal pain (2.9% vs. 6.5%) in ACEI/ARB group versus non-ACEI/ARB group.

As demonstrated in **Figure 1B and 1C**, the cumulative rate of GI involvement is significantly lower in ACEI/ARB group versus non-ACEI/ARB group (p=0.032, HR 1.95, 95%CI 1.11-3.42). Furthermore, the risk of abnormal liver function is also significantly lower in ACEI/ARB group versus non-ACEI/ARB group (p=0.033, HR 2.15, 95%CI 1.07-4.27).

Secondary outcome

As shown in **Figure 1A**, during the follow-up period, 11 of the included 100 hypertensive patients died. The risk of all-cause mortality was significantly lower in ACEI/ARB group versus non-ACEI/ARB group (0 [0/31] vs. 15.9% [11/69]; $P < 0.01$).

Among patients using ACEI/ARB, only 2(6.4%) patients used invasive ventilation, 2(6.4%) patients had GI bleeding, and no patient had sepsis, multiple organ dysfunction syndrome（MODS）or needed intensive care. All but two patients were discharged within a median of 33(25.5-39.5) days of hospital stay. On the contrary, in the non-ACEI/ARB group, 11(16.4%) patients were on mechanical ventilation (2 on noninvasive and 9 were on invasive ventilation), 1(1.5%) patient had sepsis, 1(1.5%) patient had MODS, 4 (9%) patients had GI bleeding, and 3 (4.5%) patients needed

intensive care. Forty-six (66.7%) patients were discharged with a median of 36.5(22.8-43.8) days of hospital stay.

Discussion

The present study explored GI system involvement with the use of ACEI/ARB among COVID-19 patients with hypertension. Our result showed that inpatient treatment with ACEI/ARB was associated with lower risk of GI system involvement compared with ACEI/ARB non-users. Recently, it has been reported that serum level of angiotensin II is significantly elevated in COVID-19 patients and exhibits a linear positive correlation to viral load and abnormal liver function [5] Activation of the RAS can cause widespread endothelial dysfunction and varying degrees of multiple organ (heart, kidney, lung and digestive system) injuries. Thus, intake of ACEIs/ARBs might relieve organ damage including GI and liver injury resulting from RAS activation.

Consistent with a previous study from Zhang et al [4], our study also showed that use of ACEI/ARB was associated with lower risk of all-cause mortality. Theoretically, ACEI/ARB could upregulate ACE-2 expression, which might increase SARS-CoV-2 entry into cells [4]. Alternatively, increased ACE-2 activity could increase conversion of angiotensin II to angiotensin, a peptide with potentially protective anti-inflammatory properties. Several hypotheses have been proposed to date regarding the net effect of ACEI/ARB on COVID-19 infections without a firm conclusion [6]. The recent statement from cardiovascular societies recommended continuation of ACEI or ARB among patients with co-existing hypertension and COVID-19 [7].

This study has certain limitations. Firstly, due to the small sample-size, we could not detect if there was a differential effect between ACEI and ARB. Secondly, the

differences in proportions of patients using beta-blocker and systematic corticosteroids between ACEI/ARB and non-ACEI/ARB groups might have an unappreciated confounding effect.

Our study showed that inpatient treatment with ACEI/ARB was associated with lower risk of digestive system involvement and lower mortality compared with ACEI/ARB non-users in COVID-19 patients with hypertension. Large-scale prospective cohort studies and randomized controlled trials are needed to validate the preliminary findings of our study.

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Figure Legend

Figure 1. (A) Prognosis of patients with hypertension in ACEI/ARB and non-ACEI/ARB groups. Kaplan-Meier curves for cumulative probability of (B) gastrointestinal involvement and (C) abnormal liver function during 30-day follow-up in ACEI/ARB or non-ACEI/ARB group among 100 COVID-19 patients with hypertension (abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; IQR, interquartile range; CCB, calcium channel blockers)

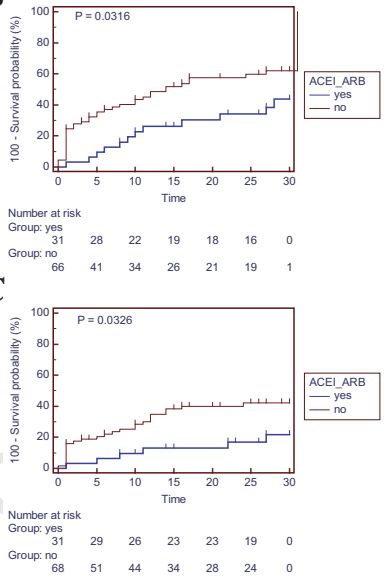
Figure 1

A **Table 1.** Prognosis of COVID-19 patients in ACEI/ARB group versus non-ACEI/ARB group

	ACEI/ARB group (n=31)	non-ACEI/ARB group (n=69)	*P*
Gastrointestinal involvement, n(%)	**12(38.7)**	**40(58)**	**0.031**
Abnormal liver function	**7(22.6)**	**29(42)**	**0.043**
Events, n(%)	**4(12.9)**	**25(30.4)**	**0.014**
ARDS	0	9(13)	0.176
Acute kidney injury	0	6(8.7)	0.085
Sepsis	0	1(1.4)	0.382
MODS	0	1(1.4)	0.382
GIB	2(6.5)*	4(8.7)#	0.674
Outcomes			
Discharged	**29(93.5)**	**46(66.7)**	**<0.01**
Death	**0**	**11(15.9)**	**<0.01**
Hospital stay, median(IQR)	33(25.5-39.5)	36.5(22.8-43.8)	0.314

*One patient was diagnosed with ischemic colitis.
#Two were caused by peptic ulcer confirmed by endoscopic examination.
ARDS, acute respiratory distress syndrome; MODS; multiorgan dysfunction syndrome; GIB, gastrointestinal bleeding.

B



C

Supple Table 1. Characteristics of COVID-19 patients with hypertension in ACEI/ARB and non-ACEI/ARB groups

	ACEI/ARB group (n=31)	**non-ACEI/ARB group (n=69)**	***P***
Gender	14:17	37:32	0.285
Age, median(IQR)	67(62-70)	67.5(57-71)	0.479
Duration, median(IQR)	**10(7-16.5)**	**12(8.8-16)**	**0.041**
Respiratory symptoms, n(%)	20(64.5)	48(69.6)	0.359
Fever	24(77.4)	53(76.8)	0.850
Cough/expectoration	15(48.4)	37(53.6)	0.528
Shortness of breath	5(16.1)	24(34.8)	0.047
Chest distress	3(9.7)	5(7.2)	0.710
GI symptoms, n(%)	**4(12.9)**	**20(29)**	**0.082**
Diarrhea	2(6.5)	10(14.5)	0.211
Vomiting	3(9.7)	8(11.6)	0.738
Abdominal pain	2(2.9)	2(6.5)	0.436
Comorbidities on admission, n(%)			
Diabetes	8(25.8)	20(29)	0.616
GI Comorbidities	6(19.4)	17(24.6)	0.513
Chronic renal diseases	4(12.9)	5(7.2)	0.398
Coronary heart disease	5(16.1)	13(18.8)	0.697
COPD	2(6.5)	7(10.1)	0.524
Tumor	1(3.2)	4(5.8)	0.566
Laboratory examination on admission, median(IQR)			
AST	27.5(24-30.75)	31.5(22-49)	0.103
ALT	34(20-48)	32(18-59.7)	0.409
TBIL	11.6(7.8-13.9)	11.4(7.4-17.1)	0.153
CRP	23.97(4-43)	24(6.7-62.5)	0.406
Lymphocyte	1.16(0.8-1.6)	1.01(0.73-1.3)	0.109
D-dimer	0.76(0.26-2.39)	0.96(0.58-2.1)	0.609

Severity, n(%)			0.613
Mild	0(0)	2(2.9)	
Moderate	4(12.9)	7(10.1)	
Severe	24(77.4)	38(55.1)	
Critical	3(9.7)	22(31.9)	
In-hospital management			
Antiviral drug, n (%)	19(61.3)	52(75.4)	0.093
Antibiotics drug, n (%)	17(54.8)	40(58)	0.650
Antifungal medications, n (%)	0	4(5.8)	0.077
Systemic corticosteroids, n (%)	**3(9.7)**	**26(37.7)**	**0.003**
Lipid lowering drug, n (%)	8(25.8)	10(14.5)	0.196
CCB, n (%)	15(48.4)	24(34.8)	0.237
beta-blocker, n (%)	**10(32.3)**	**3(4.3)**	**<0.001**
alpha-blocker, n (%)	1(3.2)	1(1.4)	0.573
ACEI, n (%)	4(12.9)	0	
ARB, n (%)	27(87.1)	0	
Renal replacement therapy, n(%)	1(3.2)	5(7.2)	0.416
Noninvasive ventilation, n (%)	**0**	**5(7.2)**	**0.048**
Invasive ventilation, n (%)	2(6.5)	9(13)	0.287

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, Chronic obstructive pulmonary disease; ALT, alanine transaminase; AST, Aspartate transaminase; TBIL, total bilirubin; CRP, C-reactive protein; IQR, Interquartile range; CCB, Calcium channel blockers.