COVID-19 clinical outcomes in patients with and without ongoing therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers

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Abstract

Background: The are conflicting reports on the effects of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) continued treatment on clinical outcomes in COVID-19 patients.

Material and methods: Patients presented with symptoms suggestive of COVID-19 infection were enrolled between 5 April 2021,and 5 June 2021. Patients who survived acute stage of the disease were asked to attend out-patient clinic after six months following COVID-19 infection diagnosis.

Results: A total of 162 patients were enrolled in this study. ARB users showed significant independent association with lower fatality rate as compared to ACEI/ARB-naïve patients [OR (CI) = 0.1(0.0–0.5), p = 0.01]. The prevalence of respiratory support use and intensive care unit (ICU) admission was numerically, but not statically significant, lower among ARB users than non-ARB users. The distribution of in-hospital adverse outcome was numerically lower among ACEI users than in non ACEI users, though the association did not reach statistical significance. ARB users showed significant independent association with persistent cough [OR (CI) = 2 (1.1–10), p = 0.02]. No significant differences in other long term symptoms were found between ARB users and nonusers. On the other hand, chest pain showed higher prevalence among ACEI users than in non-ACEI users. After adjusting for baseline comorbidities, chest pain association with ACEI user was not persisted. No significant differences in other long term symptoms were found between ACEI users and nonusers.

Conclusion: ARB and ACEI users showed low prevalence of in-hospital adverse outcome compared to ARB/ACEI nonusers. ARB showed significant and independent association with persistent cough.

Key words: COVID-19; ARB; ACEI; outcome; long term

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a worldwide pandemic that is associated with adverse clinical outcome and increased mortality [1–3]. Thus, proper detection of patients with COVID-19 infection at high risk for adverse outcome is of paramount importance.

Hypertension is a common baseline comorbidity among patients with COVID-19 infection and is associated with adverse prognosis and increased mortality [1, 2]. It has been suggested that SARS-CoV-2 may adhere to angiotensin-converting enzyme 2 (ACE2),which is a component of renin-angiotensin system, to enter human cell for replication. Initial studies reported that Angiotensin II receptor blockers (ARB) and Angiotensin converting enzyme inhibitors (ACEI) were associated with severe form of COVID-19 infection due to increased expression of ACE2 caused by ARB or ACEI use. However, later studies showed no significant association between these drugs and COVID-19 related morbidity and mortality [1–4]. Besides the conflicting results of anti-hypertensive medication with COVID-19 prognosis in the literature, the possible effects of these drugs in long term post-acute COVID-19 symptoms remains unclear.

We aimed to assess the possible association of ARB and ACEI users with in-hospital adverse outcome and long term symptoms following acute COVID infection.

Materials and methods

Adult patients presented with symptoms suggestive of COVID-19 infection who were admitted to hospital or attended outpatient clinic at Al-Amal hospital for communicable disease between 5 April 2021, and 5 June 2021, were enrolled in the present study. Baseline comorbidities, including age, sex, hypertension, anti-hypertensions drugs, diabetes mellitus, smoking, and body mass index (BMI) of patients were collected from chart review of hospital medical records by trained physicians. Hypertension was defined as any established diagnosis before acute COVID-19 infection. All the patients had similar ethnic characteristics and diagnosis of COVID-19 infection was confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) test on nasopharyngeal swabs. according to the severity of COVID-19 infection, the patients were classified into two groups: symptomatic patients without pneumonia or not requiring hospital admission were classified as mild-moderate disease, while those with pneumonia requiring intensive care unit (ICU) admission or respiratory support were classified as severe-critical disease. Primary in-hospital adverse outcomes included the need for ICU admission, use of respiratory support [continuous positive airway pressure (CPAP) or mechanical ventilation], and death.

With regard to assessment of long term post-acute COVID-19 symptoms, patients who survived acute illness were asked to attend out-patient clinic after six months following COVID-19 infection diagnosis. Pre-defined list of questionnaire was used to collect the data. Each patient was asked to complete a questionnaires, including questions on shortness of breath while routine daily activities, easy fatigue, persistent cough, chest pain, palpitation, joint pain, dizziness, headache, smell loss, and taste loss. If there was a new symptom not mentioned in the questionnaire, the patient was asked to report this symptom. All patients continued receiving ACEI or ARB after hospital discharge. Verbal consent was obtained from the patients or their relatives. This study was approved by our institution (University of Kufa).

Statistical analysis

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) Version 23.0 (SPSS Inc., Chicago, IL, USA). Baseline comorbidities and long term symptoms were described as mean ± standard deviation for continuous variables or as numbers with percentages for categorical data. The distribution of in-hospital outcomes and long term post-COVID-19 symptoms among ARB and ACEI users was calculated using Chi-square test .in-hospital adverse outcomes or long term symptoms that showed significant associations with ARB or ACEI use were further assessed by logistic regression to compute the odds ratio (OR) and confidence interval (CI) after adjusting for baseline comorbidities. p-value < 0.05 were considered statistically significant.

Results

From April 5, 2021 to June 5, 2021, a total of 162 patients were enrolled in this study. Of these, 43% (n = 70, 63% were males) had hypertension prior to COVID-19 infection while 57% (n = 92, 68% were males) did not have hypertension. The clinical characteristics of patients are shown in Tables 1.

Patients with hypertension were older (62 ± 9 year versus 49 ± 15, p < 0.01) and showed a high prevalence of diabetes [29 (41%) *vs.* 13 (14%), p < 0.01) compared to patients without hypertension. Other comorbidities, including sex, smoking, and BMI were evenly distributed hypertension and without hypertension groups (Tab. 1)

The prevalence of in-hospital adverse outcomes was numerically higher in hypertension group than in non-hypertension group, but the statistical difference was not significant.

Regarding long term symptoms at 6 months following acute COVID-19 phase, we were able to collect and analysis the data of long term symptom from 112 patients after excluding 40 patients who died at hospital and 10 patients who did not attend follow up visits. Only those long term symptoms with a prevalence ≥ 10 were mentioned and included in the statistical analysis. Patients with hypertension showed higher prevalence of at least one symptom and chest pain than patients without hypertension (Tab. 1)

ARB and ACEI and in-hospital adverse outcome

ARB users showed a significant lower fatality compared to non-ARB users. This phenomenon persisted after adjusting for baseline comorbidities [OR (CI) = 0.1 (0.0–0.5), p = 0.01] (Tab. 2 and 3).

The need for respiratory support use and ICU admissions was numerically lower among ARB users than non-ARB users, but the statistical difference was not significant (Tab. 2).

The distribution of in-hospital adverse outcome was numerically lower among ACEI users than in non ACEI users, though the association did not reach statistical significance (Tab. 2 and 3)

Table 1. Patients' characteristics

	Hypertension (n = 70) n(%) or mean ± SD	Non-hypertension (n = 92) n(%) or mean ± SD	p value
Age, year	62 ± 9	49 ± 15	< 0.01
Male sex	44/70 (63)	63/92 (68)	0.36
BMI	30 ± 5	29 ± 5	0.51
Diabetes	29/70 (41)	13/92 (14)	< 0.01
Smoking	5/70 (7)	11/92 (12)	0.42
Mild-moderate illness	40/70 (57)	64/92 (69)	0.13
Severe-critical illness	30/70 (43)	28/92 (30)	0.13
Anti-hypertension drugs			
ARB use	46/70 (66)	–	–
ACEI	18/70 (26)	–	–
Others	14/70 (20)	–	–
In-hospital adverse outcome			
Death	19/70 (27)	21/92 (23)	0.49
Respiratory support	30/70 (43)	28/92 (30)	0.13
ICU admission	30/70 (43)	28/92 (30)	0.13
Long term symptoms			
At least one symptom	43/47 (91)	50/65 (77)	< 0.01
Shortness of breath	19/47 (40)	15/65 (23)	0.06
Fatigue	34/47 (72)	35/65 (54)	0.05
Cough	12/47 (25)	8/65 (12)	0.08
Chest pain	14/47 (30)	8/65 (12)	0.03
Palpitation	11/47 (23)	7/65 (11)	0.11
Dizziness	8/47 (17)	9/65 (14)	0.79
Smell and taste loss	3/47 (6)	7/65 (11)	0.48

BMI — body mass index; ARB — angiotensin II receptor blockers; ACEI — angiotensin-converting enzyme inhibitors; ICU — intensive care unit; SD — standard deviation

Table 2. Distribution of in-hospital adverse outcome and long-term persistent symptoms related to COVID-19 among angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI) users

	ARB users	Non-ARB users	p value
In-hospital adverse outcome			
Death	9/46(19)	10/24(42)	0.01
Respiratory support use	16/46(35)	14/24(58)	0.07
ICU admission	16/46(35)	14/24(58)	0.07
Long term symptoms			
At least one symptom	25/27(93)	18/20(90)	0.65
Shortness of breath	11/27(41)	8/20(40)	0.24
Fatigue	19/27(70)	15/20(75)	0.18
Palpation	7/27(26)	4/18(22)	0.14
Dizziness	4/27(15)	4/18(22)	0.68
Cough	10/27(37)	2/18(11)	0.01
Chest pain	7/27(26)	7/18(39)	0.51
Taste and smell loss	2/27(7)	1/18(5)	0.56
	ACEI users	**Non-ACEI users**	**p value**
In-hospital adverse outcome			
Death	5/18 (28)	14/32 (44)	0.06
Respiratory support use	10/18 (56)	20/32 (62)	0.12
ICU admission	10/18 (56)	20/32 (62)	0.12
Long term symptoms			
At least one symptom	7/7 (100)	36/40 (90)	0.35
Shortness of breath	4/7 (57)	15/40 (37)	0.19
Fatigue	5/7 (71)	29/40 (72)	0.24
Palpation	2/7 (29)	9/40 (23)	0.15
Dizziness	1/7 (14)	7/40 (18)	0.75
Cough	2/7 (29)	10/40 (25)	0.15
Chest pain	4/7 (57)	10/40 (25)	0.02
Taste and smell loss	1/7 (14)	2/40 (5)	0.55

Table 3. Regression analysis

	OR (CI)	p value
ARB		
Death	0.1 (0.0–0.5)	0.01
Cough	2 (1.1–10)	0.02
ACEI		
Chest pain	2 (0.5–12)	0.18

ARB — angiotensin II receptor blockers; ACEI — angiotensin-converting enzyme inhibitors; OR — odds ratio; CI — confidence interval

ARB and ACEI and long term post-COVID-19 symptoms

ARB users showed a high prevalence of cough compared to non-ARB-users. The association of ARB with cough persisted after adjustment for baseline comorbidities [OR (CI) = 2 (1.1–10), p = 0.02]. No significant differences in other long term symptoms were found between ARB users and nonusers (Tab. 2 and 3).

Chest pain showed higher prevalence among ACEI users than in non-ACEI users. After adjusting for baseline comorbidities, chest pain association with ACEI user was not persisted [OR (CI) = 2 (0.5–12), p = 0.18]. No significant differences in other long term symptoms were found between ACEI users and nonusers (Tab. 2 and 3).

Discussion

In the literature, hypertension has been recognized as a major comorbidity associated with increased COVID-19 severity, activation of several inflammatory responses, multi-organ damage and mortality com-

pared to patients without hypertension [5]. During the early months of COVID-19 epidemic, it has been suggested that have the use of ACEI/ARBs increases the levels of ACE2 in different tissues, including lung and cardiovascular system, which may linked to infectivity rate or disease burden of SARS-COV-2 infection [6].

Our findings are consistent previous clinical and meta-analyses studies that reported a negative association between ARB and ACEI use with COVID-19 related morbidity and mortality [1, 3, 7, 8] besides, a significant bulk of the previous published studies have reported that there is no benefit to stop ACEI/ARB use in patients with hypertension and COVID-19 regarding clinical outcomes [9]. Several clinical reports have suggested that chronic use of ARB/ACEI may be associated with deactivation of renin–angiotensin–aldosterone system, which may limit the inflammatory process linked with lung injury during acute phase of COVID-19 infection [10].

In the present study, ARB use showed significant and independent association with persistent cough at 6 months following acute infection. To the best of our knowledge, this is the first study to assess the possible association between ARB and ACEI and long term symptoms of COVID-19 at 6 months following acute infection.

A recent multicenter study showed that ACEI/ARB use reduced the risk of septic shock without reducing the risk of other serious complications, suggesting that ACEI/ARB therapy led to a different type of severity of COVID-19 [11]. Furthermore, it has been suggested that long term use of ACEIs/ARBs may suppress the inflammatory response in COVID-19 patients, driven by changes in ACE2 expression, and could be associated with persistently decreased lymphocytes, leading to slow viral clearance from the body. Also, bradykinin and substance P produced by ACE inhibitors can be associated with sensitization of the sensory nerves of the airways and may stimulate the cough reflex, which may be linked to persistence of cough following acute infection [12, 13].

The present study has several limitations that need consideration. This is single center with small sample size which might limit the statistical power for the detection of small differences in outcome measures. Thus, our findings need to be interpreted with caution. there was a possibility of recall and information bias regarding assessment of long term symptoms. Also, there could be a possibility of selection bias as asymptomatic patients were not enrolled in this study and therefore the results may not representative of COVID-19 patients. Some unmeasured confounders, such as treatment guideline or COVID-19 related cardiac or vascular involvement, which could not be ruled out in our study, or lack of information regarding the control status or duration of hypertension, which may lead to inconsistencies in study findings. Additional studies are needed to address these limitations and confirm our results.

Conclusion

ARB and ACEI users showed low prevalence of in-hospital adverse outcome compared to ARB/ACEI nonusers. ARB showed significant and independent association with persistent cough. Larger studies are required to confirm these results.

Conflict of interest

The authors declare that they have no conflict of interest.

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