Relationship between angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) use with outcome and cardiovascular involvement in patients with COVID-19

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Received: *24 September 2023* / ***Revised:*** *20 October 2023* ***Accepted:*** *25 October 2023*

Background: COVID-19 used the Angiotensin-converting enzyme 2 (ACE2) receptors for cell entry. ACE inhibitors (ACEI) and angiotensin II receptor type 2 blockers (ARBs) are one of the medications used in COVID-19 patients. Some studies suggested that both of them may increase the virulence of COVID-19.

Objectives: The study aimed to determine whether the clinical condition of ACEI/ARB users is significantly different from non-ACEI/ARB users or not.

Methods: In this cross-sectional study, 671 patients who were recognized by RT-PCR participated in the study. ACEIs/ARB users in these positive participants were 175 (26%). All of them had been using ACEs/ARBs before got COVID-19. Demographic, clinical, and paraclinical data were collected through medical records and laboratory results.

Results: Our analysis demonstrated that both groups did not differ significantly interms of death (p value=0.12). The prevalence of severe clinical course was significantly higher than non-ACEIs/ARBs users. However, we matched both groups in terms of gender and age. Surprisingly, it represented ACEIs/ARB users had no more chance to experience a severe clinical course [p=0.35, OR=1.22, CI (0.79, 1.87)]. Moreover, the mean ejection fraction (EF) was higher in them (51.6 ± 8.3, p<0.001). Also, the frequency of CRP-positive patients was higher in them (73.1%, p=0.09). Other laboratory results (leukocytes and lymphocyte counts, LDH) were not significant.

Conclusions: We could not find evidence that ACEI/ARBs treatment could be a risk factor for the severity of COVID-19. Thus, their treatment regime should not be altered for COVID-19.

Keyword: ACE inhibitors; Angiotensin Receptor blockers; COVID-19; Mortality; Risk factor

1. Introduction

Since the outbreak of COVID-19 spread in Wuhan Habie province almost 20 million people have been infected resulting in 732499 deaths until 11 August [1, 2]. The lack of confident anti-viral therapy causes a significant burden on physicians to manage COVID-19 patients. [1] Hypertension is the most common comorbidity seen in COVID-19 patients, especially in severe patients [3, 4]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor type 2 blockers (ARBs) are the first treatment line for hypertension, heart failure, post-myocardial infarction, and chronic kidney disease [5]. COVID-19 uses ACE2 to enter the body cells like SARS-COV in 2002 [6, 7]. However, its affinity is so higher than SARS-COV that could explain why it is more harmful than it [8]. ACE2 is effective in controlling vasoconstriction and blood pressure [9]. Some studies showed that the ACE2 is expressed in some organs like the heart, lungs, and kidneys [10]. A review study indicated ACE inhibitors and ARBs can increase ACE2 expression. Therefore, this hypothesis was formed that ACE inhibitors and ARBs can increase the virulence of COVID-19 [11]. On the other hand, COVID-19 had some effects such as cardiac injuries, cytokine storm, and increasing activation of the renin-angiotensin-aldosterone system (RAAS) that ACE inhibitors can improve them [12, 13]. Besides, ACE inhibitors activate the kallikrein-bradykinin system. The increase in bradykinin level causes pulmonary edema. Consequently, the condition of patients becomes more severe [14, 15]. However,

DOI: 10.33892/aph.2023.93.63-69

Table I *Demographic and clinical characteristic of patients*

Characteristic	Patients (n=673)
Gender (male/female)	366/307
Age	58.9±17.1
Clinical course n (%) Non-ICU ICU ICU-intubation	 541 (80.4%) 92 (13.6%) 40 (6.0%)
ACE inhibitor user	175 (26.1%)
Death (%) Survived (%)	82 (12.3%) 580 (87.6)

some studies claimed ACEs/ARBs should not intensify the severity of COVID-19. [16, 17] Also, there is limited information about the type of antihypertensive drugs during infection. [18] The relation between ACE inhibitors and COVID-19 patients needs more investigation. In this study, we investigate whether ACE inhibitors are a risk factor for COVID-19 patients or not.

2. Methods

2. 1 patients and study design

This cross-sectional study was done on 671 COVID-19 hospitalized patients. Then we collected the essential information by the checklist that included age, gender, body mass index (BMI), drugs, intensive care unit (ICU) admission, intubation, death, systolic blood pressure (SBP), diastolic blood pressure (DBP), ejection fraction (EF), arrhythmias, leukocytes count, lymphocytes count, LDH level, and CRP positive (>10). In this study, COVID-19 patients were recognized by RT-PCR test. The test was done by Snsure kit which is produced by the Chinese Sansure company. The test results would be positive if we could trace both N and RD-RP genes. If the test results were suspicious, we would repeat the test again. All the hospitalized COVID-19 patients were included without any gender and age limitations. Exclusion criteria included: 1) underlying chemotherapy or dialysis 2) using a high dose of corticosteroids, and immunosuppressive drugs 3) history of chronic kidney disease, acute cancer, and chronic inflammation disease 4) very high or low body mass index (BMI). In the end, we divided patients into two groups including ACEIs/ARBs and non- ACEIs/ARBs users.

2. 2 Definitions

High systolic and diastolic blood pressure were defined as SBP> 120 and DBP>80 respectively [19]. Based on references low systolic blood pressure was SBP<90mmHg [20]. Abnormal EF and arrhythmia were recognized based on the AHA guideline [21, 22]. The normal range for laboratory findings: leukocytes count (4-10×10^9 leukocytes per liter), lymphocytes count (1-3×10^9 lymphocytes per liter), LDH level (140-280 U/L), CRP (0-10 mg/l) [23-25]. The clinical course divided into three groups: 1) mild: hospitalized patients that were not in ICU 2) moderate: patients hospitalized in ICU but did not need intubation 3) severe: patients hospitalized in ICU and needed intubation

2. 3 Statistical analysis

Statistical analysis was done using descriptive statistical tests including estimating the frequency and mean and examining the relationship between variables using Chi-square, independent T-test, and regression model. The level of 0.05 was considered significant and all statistical analyses were done by SPSS version 22.

3. Result

In this cross-sectional study, we assessed 673 COVID-19 patients. Three hundred sixty-six male and Three hundred seven women took part in the study. Of 673 patients, 82(12.2%) patients died, and 175 patients (26.1%) were ACEIs/ARBs users (Table I).

The prevalence of death in males (59.8%) was more than in females (40.2%) but it was not significant. Also, we could not find a difference in the clinical course between males and females (p=0.19) (Table II).

The mean age of the non-ACEIs/ARBs and ACEIs/ARBs users was 56.1 ± 17.5 and 66.8 ± 13.0 respectively (p<0.001). Also, there was a difference in terms of gender between both groups (p=0.07). The mean BMI was almost equal in two groups (p=0.32) (Table III).

Our analysis showed the prevalence of severe

Table II *Analysis of some clinical characteristic base on gender*

Variables	Male=366	Female= 307	P value
Age (mean ±SD)	57.8±17.9	60±16.1	0.95
Death (%) Survived (%)	49 (13.4%) 313 (86.6%)	33 (10.7%) 267 (89.3%)	0.32
Clinical course n (%) Mild Moderate Severe	 285 (77.9%) 57 (15.6%) 24 (6.5%)	 256 (83.4%) 35 (11.0%) 16 (5.6%)	0.19

Table III *Clinical condition analysis of ACE users and non-user groups*

Characteristic	ACEIs/ARBs-users (n=175)	Non-ACEIs/ARBs users (n=498)	P value
Age (mean ±SD)	66.8 ± 13.0	56.1 ± 17.5	<0.001
Gender (male/female)	85/90	281/217	0.07
Clinical course (%) Mild Moderate Severe	 129 (73.7%) 34 (19.4%) 12 (6.9%)	 412 (82.7%) 58 (11.6%) 28 (5.7%)	0.02
Death (%) Survived (%)	27 (15.7%) 145 (84.3%)	55 (11.0%) 435 (89.0%)	0.12
SBP* mean ±SD High>119 (%) 90<Normal<119 (%) Low<90 (%)	129.3±17.3 107 (80.4%) 25 (18.8%) 1 (0.8%)	119.0±16.0 220 (57.3%) 147 (38.3%) 17 (4.4%)	<0.001
DBP* mean ±SD High (>80) (%) 60<Normal<80 (%) Low<60 n (%)	78.8±10.5 35 (26.3%) 95 (71.4%) 3 (2.3%)	75.2±10.9 56 (14.5%) 321 (83.6%) 7 (1.9%)	0.008
EF* mean(%) ±SD	51.6±8.3	54.4±5.4	0.001
Arrhythmia n (%)	9 (5.1%)	19 (3.8%)	0.86
BMI	27.76±5.76	27.31±4.80	0.32
leukocytes	6.7±3.4	6.9±4.8	0.63
lymphocytes	1.7 ±0.8	1.8±0.9	0.38
LDH	513.0±20.7	498.6±15.8	0.7
CRP positive	128 (73.1%)	354 (71.0)	0.09

EF: ejection fraction; SBP: systolic blood pressure; DBP; diastolic blood pressure

and moderate patients was significantly higher in the ACEIs/ARBs group (severe= 19.4%, moderate=6.9%, p=0.02). Besides, we used the regression model and adjusted the result in terms of age, gender, and BMI. However, the odds ratio of severe clinical course for ACEIs/ARBs users was not significant [p=0.35, OR=1.22, confidence interval (0.79, 1.87)]. Similarly, the frequency of death (15.7%) was higher in the ACEIs/ARBs group (p=0.12). Moreover, the high SBP and DBP were more prevalent in this group ($p_{\text{high DBP}}$ value<0.001, $p_{\text{high DBP}}$ value=0.008). The mean blood pressure (SBP/DBP) in the ACEIs/ARBs and non- ACEIs/ARBs groups were 129.3/78.8 and 119.0/75.3 respectively. Assesses of trans-thoracic echocardiography (TTE) results showed that the mean of EF was significantly lower in ACEIs/ARBs users (p= 0.001). Though we observed arrhythmia was more seen in the non- ACEIs/ARBs group, it was not significant.

The mean of leukocyte (6.9 ± 4.8×10^9, p=0.63) and lymphocyte count (1.8 ± 0.9×10^9, p=0.38) were higher in the non- ACEIs/ARBs group. The mean of LDH was higher in the ACEIs/ARBs group (513, p=0.7). In addition, the prevalence of CRP positive was higher in this group (73.1%, p=0.09).

4. Discussion

In this study, the mean age of the ACEIs/ARBs group was significantly higher than the non-ACEIs/ARBs group. Our findings showed that the

ACEIs/ARBs group was not at high risk of severe clinical course (OR=1.22, confidence interval (0.79, 1.87)). The prevalence of high SBP and DBP was higher in them which could affect their clinical condition. The frequency of positive CRP was significantly higher in this group. In addition, the mean of EF was lower in the ACEIs/ARBs group. The mean of leukocyte count and LDH was more in the ACEIs/ARBs group, but this difference was not statistically significant.

The epidemiologic data demonstrated patients with heart failure, chronic kidney disease, hypertension (HTN) and diabetes comorbidities were more at risk for poor outcome [26, 27]. However, it was not clear whether patients with those comorbidities used the ACEIs/ARBs before getting infected by COVID-19 or not, these drugs would mostly remedy hypertension and diabetes patients [28, 29]. Tian C et al showed discontinuing ACEIs/ARBs in COVID-19 patients with HTN resulted in a prolonged hospitalization. Thus, they advised ACEI/ARBs should be continued in COVID-19 patients with HTN [30]. Some editorial studies offered that this high mortality and morbidity rate in the patients can be a result of ACE inhibitors due to long-term use that lead to overexpression of ACE receptor on cell membranes [31-33]. In addition, some studies done on diabetes and hypertension proved that claim [34, 35]. However, overexpression of ACE2 has not been reported by all the human and animal models [36]. The RAAS system is one of the most important systems that regulate some systems such as cardiovascular, renal, neural, and pulmonary systems [37]. ACE-2, which down-regulates angiotensin II, can suppress the RAS system. SARS-COV-2 uses ACE2 receptors to enter the cells. This is thought to lead to the degradation of ACE2 and ultimately to the overstimulation of RAS systems [38].

A study from Belgium demonstrated that there was not any significant risk for ACE inhibitors users to experience severe conditions [OR=0.79, CI(0.26, 1.95), p=0.62]. Also, after adjusting their results based on sex and age it was not significant [39]. Fosbøl, *et al*., showed that patients who use ACE inhibitor medications were more at risk for the severe condition [hazard ratio =2.34, CI(1.97, 2.77), p<0.001], even if it was significant after adjusting for age and gender [40]. However, a randomized control trial represented patients with mild to moderate COVID-19 who were taking ACEI/ARBs before hospital admission, there was not any significant difference in terms of average survival day between ACEI/ARBs group and not ACEI/ARBs group. Thus, they advised that patients should continue ACEI/ARBs if there is any indication for treatment [41]. Also, a study from the USA assessed patients of 5 hospitals in New York city they realized there was not any significant association between ACEI or ARBs and the severity of the disease. Moreover, there was two points about the study: 1) the study's patients were from diverse ethics 2) its sample size was large (n=2736) [42]. In addition, Abbas.S et al demonstrated taking ARBs was not related to poor in-hospital outcome results [43]. In this study, the prevalence of patients who experienced severe clinical course in ACE inhibitor users was higher than non-ACE inhibitor users (p=0.02). However, when we used the regression model and adjusted the result in terms of age, gender, and BMI it was not significant (OR=1.22, confidence interval (0.79, 1.87)). Some studies supported this hypothesis that ACEI drugs could not be a risk factor for COVID-19 patients and their results demonstrated that ACEI can't increase the mortality rate [5, 39]. On the other hand, Murat *et al*., showed an increase in mortality rate in ACEI users [OR=6.30, CI(2.03, 19.58), p=0.001]. Also, other studies supported this result but some of them did not get the same result after adjusting [40, 44, 45]. Besides, in our findings, we did not reach a significant result in terms of death. Results of a study represented the mean of lymphocyte count, LDH level, and CRP level was higher in ACEIs/ARBs users but was not significant. However, the mean of leukocyte count was significantly higher in ACEI users. There was a point about their result and that was their sample size was so small [44]. Guang *et al*., could not find a significant difference between ACEI and non-ACEI users in laboratory results such as lymphocyte count, and LDH [46]. In our findings, there was not any significant difference in laboratory results except for the CRP level. The prevalence of CRP positive was higher in ACEIs/ARBs users than non- ACEIs/ARBs users (p= 0.09).

Myocardial dysfunction was more prevalent in COVID-19 patients and can be a result of dysregulation of ACE2 as knockout the ACE2 in the animal model represented injury caused by angiotensin II [47, 48]. The report by Rohan *et al*., represented the prevalence of heart failure in patients using ACEI that was higher than ARBs users (p=0.03) [49]. But, the results of the Turkish study that excluded patients who had heart failure his-

tory, demonstrated there was no a difference between the case (ACEI/ARBs user) and control group (p=0.41) [44]. Another study from Korea demonstrated there was a difference between ACEI and non-ACEI users in terms of congestive heart failure (frequency $_{ACEI}$ vs. frequency $_{non\text{-}ACEI}$ =14% vs. 3%, p<0.001) [45]. The mean of EF in this study for ACEIs/ARBs users (51.6 ± 8.3) was significantly lower than the non- ACEIs/ARBs group (54.4 ± 5.4; p=0.001). One thing to note about our result was that there were some missing data. So, it can have an impact on the outcome. Our research showed in this essay that ACE/ARB inhibitor medications may not be a risk factor for COVID-19 patients. Nevertheless, because the study was cross-sectional, we were unable to evaluate the casualty. As a result, we propose to conduct a cohort research to further understand this association.

5. Conclusion

In this study, all of the laboratory results except for CRP were positive. Moreover, the prevalence of death and arrhythmia was not significant. Also, the regression model represented ACEIs/ARBs users were not more at risk than the non- ACEIs/ARBs users. Therefor according to the results of this study, ACEIs/ARBs may not be as a risk factor to increase severity of COVID-19 patients. Also, if patients have been using, they should have not altered their treatment regimen.

Acknowledgments

The authors are grateful to all staff of the Deputy of Health at Imam Hossein Hospital of Shahroud for their great cooperation. Also, The study is the result of a research project approved by the University of Medical Sciences with grant number 98126. The fund was used in order to collect data.

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