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Angiotensin Converting Enzyme Inhibitors, A Risk Factor of Poor Outcome in Diabetic Patients with COVID-19 Infection

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Original Paper

Introduction. Diabetes mellitus and hypertension are described as the most common comorbidities among COVID-19 patients. We investigated the adverse effect of ACEIs in diabetic and nondiabetic patients with COVID-19.

Methods. This prospective study consisted of 617 RT-PCR-confirmed COVID-19 inpatients. Demographic and baseline characteristics, underlying comorbid diseases, and antihypertensive drugs were evaluated. Study outcome (in-hospital death) was evaluated with the Kaplan-Meyer method and Cox regression model. Statistical analyses were performed with SPSS software for Windows. *P* values < .05 were considered significant.

Results. Mean ± SD age was 58.49 ± 15.80 (range: 18 to 94) years old. Cox regression analysis revealed that age (adjusted hazard ratio [HR] = 1.04, 95% CI: 1.03 to 1.06), diabetes mellitus (adjusted HR = 2.07, 95% CI: 1.32 to 3.26), immunocompromised patients (adjusted HR = 2.33, 95% CI: 1.29 to 4.21), acute kidney injury (AKI) (adjusted HR = 3.23, 95% CI: 2.01 to 5.19), ICU admission (adjusted HR = 2.48, 95% CI: 1.46 to 4.21), Asthma and COPD (adjusted HR = 2.13, CI:1.6 to 4.28) and ACEI (adjusted HR = 3.08, 95% CI: 1.56 to 6.06), respectively were associated with in-hospital death. Among diabetic patients, ACEI (adjusted HR = 3.51, 95% CI: 1.59 to 7.75), AKI (adjusted HR = 3.32, 95% CI: 1.76 to 6.45) and ICU admission (adjusted HR = 3.64, 95% CI: 1.530 to 8.65) were associated with increased mortality. The Kaplan-Meier survival curve showed a lower survival rate in diabetic patients with ACE inhibitor (adjusted HR = 3.36, 95% CI: 2.25 to 7.71).

Conclusion. ACEIs may harm the diabetic patient's outcome with COVID-19. Further studies can confirm if ACE inhibitors have an adverse effect on COVID-19 diabetic patient's mortality.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), the cause of pandemic severe acute respiratory syndrome was first described in Wuhan, China in December 2019 and dramatically spread worldwide.[1,2] Epidemiologic studies reported that hypertension and diabetes mellitus were the most common comorbidities among COVID-19 patients.[3] In adult patients, COVID-19 seems to manifest in the most severe forms in those with diabetes and

other comorbidities, such as high blood pressure, cardiovascular disease, and obesity.[4] Angiotensin-converting enzyme 2 (ACE2) is an enzyme within the renin-angiotensin system, and the receptor of SARS- CoV-2 with a 10-20-fold higher affinity than that of SARS- CoV.[5,6] It is expressed on the cell surface of type 2 alveolar epithelial cells in the lungs, as well as on cells in many other tissues.[7] There is a suggestion that ACE2 expression is increased in diabetic patients. This may facilitate infection with COVID-19 and leads to a severe and fatal outcome.[8]

Treatment with Angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs) may play a role in ACE2 expression and cause severe infection however, there is no consensus to stop these drugs in diabetic COVID-19 patients. Accordingly, we designed a prospective study in 617 of COVID-19 inpatients to evaluate whether ACEIs and ARBs may have any adverse effect on diabetic patient outcomes.

MATERIALS AND METHODS

Between March 1st and June 30th, 2020 a consecutive of 617 RT-PCR-confirmed COVID-19 (362 males and 255 females) who were admitted in Firoozgar hospital were enrolled in this prospective study. This study was approved by the Ethical Committee of Iran University of Medical Sciences (IR.IUMS.REC 1395.8723215111). Informed written consent was obtained from each patient. Demographic and baseline characteristics were obtained from all participants. Underlying comorbid diseases such as diabetes mellitus, hypertension, cardiovascular disease, asthma/ COPD were investigated.

Antihypertensive drugs (ACI inhibitors, ARBs, calcium channel blockers, diuretics) and immunosuppressive agents were also evaluated. The patients were admitted to the intensive care unit (ICU) if there were hemodynamic instability, sepsis, decrease the level of consciousness, multiple organ failure and, $SPO_2 < 90\%$ despite $FIO_2 > 50\%$. Baseline serum creatinine was defined as the serum creatinine value on admission. Acute kidney injury (AKI) was defined as an increase in serum creatinine by 0.3 mg/dL within 48 hours or a 50% increase in serum creatinine from baseline within 7 days according to the KDIGO criteria.[9] Patients who received chemotherapy or immunosuppressive drugs categorized as the immunocompromised group (Table 1). The antiviral protocol designed by the Ministry of health and was the same for all of the patients. We did not prescribe Remdesivir in the study period due to a lack of this drug on the study period. ICU admitted patients received two-three pulses of 250 mg methylprednisolone after rule out of active bacterial infection. Steroid therapy continued with Dexamethasone 8 mg/d during hospitalization. Few patients received plasma exchange and hemoperfusion.

Table1. Patients Baseline Characteristics and Demographics

Variables	Total (617)	Diabetic (153)	Non Diabetic (464)	*P*
Age, means	58.5 ± 15.8	64.4 ± 11.7	56.5 ± 16.5	< .05
Male (%)	58.7	59.5	58.4	> .05
Hypertension	182 (29.5%)	89 (58.2%)	93 (20%)	< .001
Cardiac Disease	99 (16%)	53 (34.6 %)	46 (9.9%)	< .001
COPD	26 (4.2%)	7 (4.6%)	19 (4.1%)	> .05
Immunosuppression	40 (6.5%)	8 (5.2%)	82 (6.9%)	> .05
Acute Kidney Injury	55 (8.9%)	19 (12.4%)	36 (7.8%)	> .05
Chronic Kidney Disease	20 (3.2%)	13 (8.5%)	7 (1.5%)	< .001
Hospital Stay, days	8.03 ± 5.1	8.6 ± 5.5	7.85 ± 4.9	> .05
ICU / Ward	326 / 291	86 / 67	240 / 224	> .05
ACE	38 (6.2%)	17 (11.1%)	21 (4.5%)	< .05
ARB	114 (18.5%)	56 (36.6%)	58 (12.5%)	< .001
Calcium Channel Blocker	58 (9.4%)	28 (18.3%)	30 (6.5%)	< .001
Diuretic	32 (5.2%)	17 (11.1)	15 (3.2%)	< .001
Beta Blocker	71 (11.5 %)	43 (28.1%)	1 (0.2)	< .001
Death	84 (13.6%)	40 (26.1%)	44 (9.5%)	< .05

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019.

Statistical Analysis

Data were presented as means ± SD and qualitative variables as frequency (percentage). Statistical analyses were performed with SPSS software for Windows (Statistical Product and Service Solutions, version 20.0, SSPS Inc., Chicago, IL, USA). The student t-test for quantitative variables and the chi-squared test for quantitative variables were used.

Study outcome (in-hospital death) was evaluated with the Kaplan-Meyer method and Cox proportional hazard models were fitted to both unadjusted and adjusted measures. *P* values < .05 were considered statistically significant.

RESULTS

Mean ± SD age was 58.49 ± 15.80 (range: 18 to 94) years old. Among 617 participants 291 patients were admitted to the ward and 326 patients were admitted to the intensive care unit (ICU) due to admission criteria. Patients' demographics are shown in Table 1. Underlying medical diseases such as hypertension (HTN), Diabetes mellitus (DM), coronary artery disease (CAD), and obstructive airway disease (asthma or COPD) were the most commonly diagnosed comorbidities in 182 (29.5%), 153(24.8%), 99 (16%), and 26 (4.2%); respectively.

The mean hospital length of stay was 8 ± 5.1 days. Evaluation of hospitalization outcome revealed that the overall mortality rate was 84 (13.6%). This rate was 6.5% and 19.9% of patients admitted to the ward and ICU, respectively. Patients admitted in ICU were not significantly older compared with the non-ICU group (59.4 ± 16.1 vs. 57.3 ± 15.3 years old, *P* > .05). The use of ACEI / ARBs was detected in 152 (24.6%) patients (38 ACEIs and 114 ARBs users). Table 2 shows the adjusted HRs from the Cox regression analysis.

Cox regression analysis revealed that age (fully adjusted HR = 1.04, 95% CI: 1.03 to 1.06; *P* < .05), diabetes mellitus (fully adjusted HR = 2.07, 95% CI: 1.32 to 3.26; *P* < .05), immunocompromised patients (fully adjusted HR = 2.33, 95% CI: 1.29 to 4.2; *P* < 0.05), Acute kidney injury (AKI) during hospitalization (fully adjusted HR = 3.23, 95% CI: 2.01 to 5.19; *P* < .05), ICU admission due to severe illness (fully adjusted HR, 2.48; 95% CI, 1.46–4.23; *P* < .05), COPD and asthma(fully adjusted = 2.13, 95 %CI: 1.06 -4.3; *P* < .05) and ACEI (fully adjusted HR = 3.08, 95% CI: 1.56 to 6.06; *P* < .05); respectively were associated with in-hospital death. According to our results, hypertension and, coronary artery disease were determined as underlying conditions with increased COVID-19 patients' mortality in unadjusted analysis (HR = 1.55, 95% CI: 1.00 to 2.08; *P* < .05) and (HR = 2.03, 95% CI: 1.02 to 4.04; P < .05); respectively. This association was not significant after adjusting for other comorbidities.

In our study, 26.4% and 23% of patients in ICU (86 / 326) and ward (67 / 291) were diabetics respectively, which was not statistically different (*P* > .05).

ACEI/ARBs and Diabetes Mortality

We investigated risk factors for mortality in diabetic and non-diabetic patients separately. As shown in Table 3, AKI (fully adjusted HR = 3.32, 95% CI: 1.70 to 6.45; *P* < .05), ACEI use (fully adjusted HR = 3.51, 95% CI: 1.59 to 7.75; *P* < .05), and ICU admission due to severe illness (fully adjusted HR = 3.64, 95% CI: 1.53 to 8.66; *P* < .05) were associated with increased mortality in diabetic patients with COVID-19.

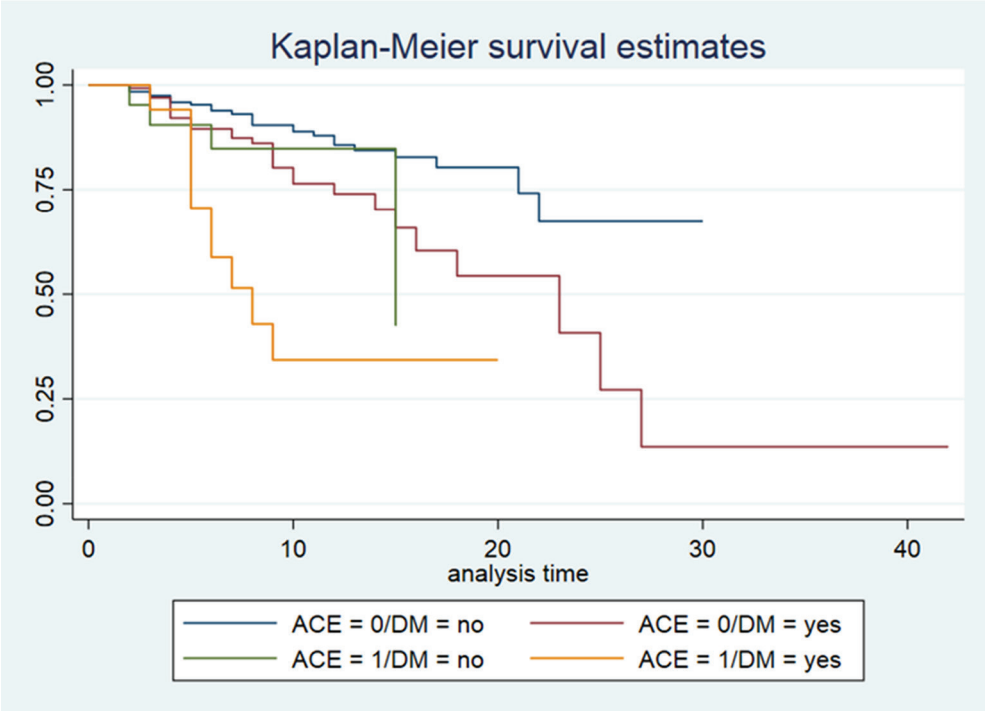
The Kaplan-Meier survival curve showed a lower survival rate in diabetic patients with ACE inhibitor (fully adjusted HR = 3.51, 95% CI: 1.59 to 7.75; *P* < .05) (Figure 1).

Table 2. Adjusted Hazard Ratios for Mortality in COVID-19 Patients

	B	SE	Sig.	Hazard Ratio	95% CI for Hazard Ratio	
					Lower	Upper
Age	0.042	0.009	< .05	1.043	1.025	1.061
AKI	1.17	0.24	< .05	3.23	2.01	5.19
ACE Inhibitor	1.124	0.346	< .05	3.078	1.563	6.061
DM	0.728	0.231	< .05	2.071	1.316	3.257
Immunocompromised	0.846	0.301	< .05	2.330	1.291	4.206
ICU Admission	0.910	0.272	< .05	2.484	1.458	4.231
Asthma/COPD	0.755	0.356	< .05	2.127	1.059	4.271

Table 3. Hazard Ratios for Mortality in Diabetic and Non-diabetic Patients

	Sig.	Hazard Ratio	95% CI for Hazard Ratio	
			Lower	Upper
Non-diabetic (n = 464)				
Age	< .001	1.06	1.03	1.08
AKI	< .001	7.13	3.88	13.08
Immunocompromised	< .001	5.32	2.45	11.55
ACE Inhibitor	> .05	1.20	0.42	3.42
Coronary Artery Disease	> .05	0.48	0.21	1.12
ICU Admission	> .05	1.41	0.71	2.79
Diabetic (n = 153)				
Age	> .05	1.01	0.97	1.04
AKI	< .05	3.32	1.70	6.45
Immunocompromised	> .05	0.78	0.27	2.29
ACE Inhibitor	< .05	3.51	1.59	7.75
Coronary Artery Disease	> .05	1.96	0.98	3.93
ICU Admission	< .05	3.64	1.53	8.65



The Kaplan-Meier survival curve in diabetic patients with ACEIs

DISCUSSION

This cohort study showed that age, AKI, underlying lung disease (asthma/COPD), diabetes, immunosuppression, and ACE inhibitors were considered as independent risk factors for mortality in COVID-19 patients. Risk factors attributed to mortality in diabetic patients were investigated and after adjusting for age, sex, and other covariates, we observed that consumption of ACE inhibitors, increased creatinine during hospitalization were associated with increased in-hospital mortality in diabetic patients with COVID-19 compared with nondiabetics. According to adjusted Cox regression analysis hypertension and the use of ARBs did not increase the risk of death in COVID-19 patients. Despite the adverse effect of ACEs on diabetic patients' outcomes, it was noteworthy that the use of ACEI/ARBs was not associated with mortality in non-diabetic patients in the adjusted Cox regression analysis. This effect was independent

of cardiovascular disease in this group.

Our data demonstrated that diabetes and hypertension were the most common comorbidities among COVID-19 patients. Recent studies revealed diabetes has a crucial role in patients with severe COVID-19. Diabetes and hyperglycemia induce inflammatory cytokines and immune system imbalance.[3,10]

Recent studies indicate that diabetes was associated with increased lung ACE2 expression and clearance of SARS-CoV-2 was delayed in patients with DM.[11] Kuba *et al.* first showed that ACE2 is essential for SARS-CoV infection, acting as its effective host receptor in vivo,[12] which could lead to ARDS (acute respiratory distress syndrome) via pulmonary vasoconstriction, decreased flow, and increased vascular permeability.[12] Gravin *et al.* described that the bradykinin storm is a better explanation for COVID-19 manifestations due to the high presentations of bradykinin receptors and substrates in the analysis of bronchoalveolar lavage of COVID-19 patients.[13] ACE inhibitors can increase bradykinin levels which induce the side effects of these groups of antihypertensive drugs in comparison to ARBs.[14]

ACEI / ARBs were used in 24.8% (152 / 617) of our patients. We had the same rate of ACIs and ARBs consumption as other reports.[15] The use of ACEI / ARBs in patients with COVID-19 is challenging due to several drug indications and has been controversial. An experimental study on rodents showed previous treatment with ACE inhibitors was associated with increased intestinal messenger RNA levels of ACE2, but no association with ARBs, hence besides the higher bradykinin level and receptor's upregulation this can explain different effects of ACE inhibitors vs. ARBs on angiotensin II, the primary substrate of ACE2, and the effects of these agents on ACE2 levels.[5,6] As a consequence, they might increase the risk and severity of SARS-CoV-2 infection by increased cell entry via the ACE2 receptor.[6] Polymorphism of the receptor is another risk factor of infection that we did not check in this study.[8]

Our data could not support the adverse effect of ARBs on the patient's outcome. ACEIs had a hazard ratio of 1.59 to 7.75 in the diabetic patient which was independent of the history of cardiovascular disease. These results were not extensible to non-diabetic patients with COVID-19. Our study was a single-center study with a retrospective method. We did not check Remdesivir antiviral effects since those were not unavailable in that era.

CONCLUSION

In conclusion, our study showed ACEIs may harm diabetic patient's outcome with COVID- 19. Further studies can confirm the adverse effect of ACE inhibitors on COVID-19 diabetic patient's mortality.

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