Original Article

Renin-Angiotensin-Aldosterone Axis Inhibition Improves Outcome of Diabetic Patients with Chronic Hypertension and COVID-19: An Iranian Perspective

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Abstract

Background: Safe use of drugs such as angiotensin-converting enzyme 2 (ACE2) inhibitors and angiotensin receptor blockers (ARBs) in COVID diabetic patients needs comprehensive studies. This study addressed this issue from the Iranian perspective.

Materials and Methods: Admitted COVID-19 patients were divided into four groups in this historical cohort study. Group 1 included 740 non-diabetic, non-hypertensive patients. Group 2 included 132 non-hypertensive diabetic patients. Group 3 included 154 non-diabetic hypertensive patients. Group 4 included 183 diabetic patients who were under ACE inhibitors or ARBs. Death, intensive care unit (ICU) admission, and length of hospitalization were compared between the groups.

Results: After considering associated factors such as age, gender, dyslipidemia, cardiovascular diseases, rheumatoid arthritis (RA), chronic kidney disease (CKD), history of surgery, and corticosteroid use, diabetic patients (group 2) were associated with increased mortality (CI 95%, OR 1.93 [1.11–3.33]). Presence of diabetes (group 2) and hypertension were associated with an increased need for ICU admission (CI 95%, OR 1.69 [1.04–2.76]; CI 95%, OR 1.71 [1.08–2.71], respectively). Group 4 patients although having a similar rate of ICU admission with group 2 and 3 patients, had significantly better ICU survival.

Conclusions: The current study suggests that ACE inhibitors and ARBs are associated with decreased mortality, ICU admission, and better ICU survival in the diabetic subgroup of hypertensive patients.

Keywords: ACE inhibitor, ARB, COVID-19, diabetes, hypertension, outcome

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Submitted: 19-Jun-2021; **Revised:** 31-Jan-2022; **Accepted:** 17-Feb-2022; **Published:** 26-Dec-2022

Introduction

The exponential outbreak of COVID-19 severely affected countries since December 2019 and was associated with notable mortality and exhaustion of health care systems.[1] The majority of mortality was observed in patients with concomitant comorbidities such as diabetes and hypertension.[2,3] Besides, these comorbidities were more common among hospitalized

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_177_21

How to cite this article: Kheyri Z, Alizadeh M, Akbarpour S, Hosamirudsari H, Niya MH, Aliasgharpour F, *et al*. Renin-Angiotensin-Aldosterone axis inhibition improves outcome of diabetic patients with chronic hypertension and COVID-19: An Iranian perspective. Adv Biomed Res 2022;11:109.

patients.[4] SARS-CoV-2 uses its peculiar spikes to attach angiotensin-converting enzyme 2 (ACE2) and enter host cells.[5] ACE inhibitors that target ACE2 and angiotensin receptor blockers (ARBs) are widely prescribed to manage blood pressure and might affect ACE2 expression.[6] Since the initiation of the COVID-19 pandemic an increasing concern raised for their safety during COVID-19 pandemic. Mechanistically, several articles proposed renin–angiotensin–aldosterone system (RAAS) inhibitors as a protective agent but others suggested that their administration might be associated with an increased risk of COVID-19 infection.[7-9] The RAAS is a hormone system that is mainly comprised of renin, angiotensin II and aldosterone. This pathway includes renin, angiotensinogen (AGT) and its receptor regulate glucose metabolism, blood pressure, and fluid and electrolyte homeostasis.[10] Soon, retrospective studies revealed that administration of ACE inhibitors and ARBs is not associated with increased risk of COVID-19 and its associated mortality rate.[11-14] Diabetic patients prevalently consume ACE inhibitors and ARBs to control their blood pressure and nephropathy.[15,16] Most previous studies have focused on the general effect of ACE inhibitors and ARBs on all subgroups of hypertensive patients who were afflicted with COVID-19. Francisco *et al*. showed that ACE inhibitors and ARBs may decrease the need for hospital admission in diabetic patients with COVID-19(17).[17] Furthermore, diabetic patients are at increased risk of COVID-19 mortality(18). Uncovering the effects of these drugs in the diabetic subgroup can improve the quality of their treatment and contribute to their survival from COVID-19. In this study, we aimed to determine the effect of ACE inhibitors and ARBs on clinical outcomes of diabetic patients who were hospitalized because of COVID-19 and used these drugs to control hypertension.

Materials and Methods

Target population and source of data

This single-center, historical cohort study was performed in Tehran, Baharloo hospital. Admitted patients with the diagnosis of COVID-19 from February 20, 2020, to August 26, 2020, entered this retrospective study. Data were extracted from patients' files. All patients were hospitalized because of severe symptoms and a documented Real-time polymerase chain reaction (PCR) or computed tomography (CT)-scan result in favor of COVID-19.

Chest CT-scan findings in favor of COVID-19

Bilateral and peripheral ground-glass opacity (GGO) and consolidation on chest CT-scan, in the presence of clinical signs and symptoms, were presumed to be COVID-19.[18,19] Additionally, other findings such as reticular pattern, crazy paving pattern, and air Broncho gram were observed on imaging. These findings contributed to diagnose COVID-19 in real-time PCR negative patients who had the typical clinical manifestation of COVID-19 and their signs or symptoms were not justified by other diseases. Some of the patients had normal imaging but it was replaced by signs of COVID-19 in the following imaging.

Criteria of hospitalization

Patients with the following criteria were hospitalized; Decreased O_2 saturation (<93%), >50% pulmonary involvement in chest radiography (chest x-ray or CT scan), clinical signs of dyspnea such as labored and shallow breathing, and particularly tachypnea (>30 breathes/min), inability to eat due to gastrointestinal symptoms, cardiovascular instability, and acute respiratory distress syndrome (ARDS) were the reasons for hospitalization.

Treatment protocol

Patients with dyspnea or decreased O_2 saturation received respiratory supports according to their general condition which ranges from nasal O_2 and non-invasive ventilation (NIV) to intensive care unit (ICU) admission and invasive ventilation. Hydration and fever management was considered for patients. Fever and pain were controlled by acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). Symptomatic treatment was performed to relieve gastrointestinal symptoms such as diarrhea and vomiting.

Exclusion criteria

Patients who received remdesivir, intravenous immunoglobulin (IVIG), tocilizumab, interferon-β (IFN-β), hemoperfusion, and extracorporeal membrane oxygenation (ECMO) counting for about 10% of patients and also patients who were <20 years of age, were excluded from this study.

Groups of patients

Patients were divided into four groups to find out how diabetes, hypertension, ACE inhibitors, and ARBs can interact with COVID-19 as shown in Table 1. The first group included non-diabetic, non-hypertensive patients with COVID-19. The second group included diabetic patients with COVID-19. This group of patients had normal blood pressure and did not consume ACE inhibitors or ARBs. The third group included COVID-19 patients with concomitant hypertension. This group was non-diabetic patients. About half of the patients in this group consumed ACE inhibitors and ARBs. The fourth group included diabetic patients with COVID-19 who consumed ACE inhibitors or ARBs to control their hypertension.

During hospitalization, patients' informed consent was obtained to use their file as a source of the data. The study was conducted by the ethical standards stated in the 2013 Declaration of Helsinki. As well, the ethical committee of Tehran University of Medical Sciences (TUMS) approved the protocol of this study. After precise ethical evaluations, the study received the ethical code, IR.TUMS.VCR.REC.1399.171.

Data analysis

Quantitative variables are presented as mean (SD) and qualitative variables as percentages and frequencies. Differences in means were measured using one-way analysis of variance formula (ANOVA) followed by post-hoc Tukey test

and student's *t*-test. Differences in percentages were measured using Chi-square test. Stata software version 14 was used for the analysis of data.

We described the demographic features of each group such as age, sex, and body mass index (BMI). We assessed their pre-existing conditions such as cardiovascular diseases (including ischemic heart disease, congestive heart failure, and valvular heart diseases), malignancy, chemotherapy, radiotherapy, chronic obstructive pulmonary disease (COPD), organ transplantation, HIV infection, chronic kidney disease (CKD), cirrhosis, systemic lupus erythematous (SLE), rheumatoid arthritis (RA), dyslipidemia, thyroid disorders (hypo- and hyperthyroidism), tuberculosis (TB), and inflammatory bowel disease (IBD). Moreover, the off-label use of drugs such as hydroxychloroquine and corticosteroids has been measured and shown in a separate table [Table 2].

Outcomes such as death, ICU admission, and median length of hospital stay were compared between the groups as shown in Table 3. To remove the effect of confounders, logistic regression was used to adjusted odds ratio. Each one of pre-existing conditions and drugs was compared between the groups. If there was a significantly different distribution among the groups, the condition or drug were involved in the assessment of the adjusted odds ratio.

We also divided group 3 (non-diabetic hypertensive group) into two subgroups of patients who received ARBs/ACE inhibitors and those who did not receive ARBs/ACE inhibitors. Death, ICU admission, and length of hospital stay were compared between these two subgroups. Also, we assessed adjusted odds ratios for different outcomes of these subgroups.

Results

According to our inclusion criteria, 1209 patients including 676 (55.9%) male were participated in this study, and a few patients who were <20 years or received remdesivir, IVIG, tocilizumab, IFN-β, hemoperfusion and ECMO were excluded from this study. Groups 1–4 included 740, 132, 154, and 183 patients, respectively. Except for their clinical signs and symptoms, 53.6% of patients had positive real-time PCR test with concomitant CT-scan findings. Others (46.4%) were not real-time PCR positive but they had clinical manifestations and CT-scan findings, in favor of COVID-19. Interestingly, a

Table 1: Association between diabetes, hypertension, and positive findings in CT-scan and real-time PCR, in favor of COVID-19

	All patients (*n*=1209)	Group 1 (*n*=740)	Group 2 (*n*=132)	Group 3 (*n*=154)	Group 4 (*n*=183)	*P*
Diagnosis based on real-time PCR positive + relevant CT-scan findings and clinical manifestations	648 (53.6)	413 (55.8)	77 (58.3)	67 (43.5)	91 (49.7)	<0.0001
Diagnosis only based on CT-scan and clinical manifestations (%)	561 (46.4)	327 (44.2)	55 (41.7)	87 (56.5)	92 (50.3)	<0.0001

Data are presented as number (%). Group 1 (non-hypertensive, non-diabetic patients), group 2 (non-hypertensive, diabetic patients), group 3 (non-diabetic, hypertensive patients), group 4 (patients with both diabetes and hypertension who are consuming ACE inhibitors or ARBs)

Table 2: Distribution of pre-existing conditions of patients and types of medication prescribed for them

	All patients (*n*=1209)‡	Group 1 (*n*=740)	Group 2 (*n*=132)	Group 3 (*n*=154)	Group 4 (*n*=183)	*P*
Age	55.28±17.34	49.35±16.74	57.98±14.80	67.03±13.65	67.46±11.38	<0.001
BMI	27.74±6.13	27.37±5.53	28.08±8.79	28.19±6.20	28.09±5.42	0.493
Male	676 (55.9)	444 (60)	79 (59.8)	67 (43.5)	86 (47)	<0.001
Age >60 years	486 (40.2)	189 (25.5)	57 (43.2)	108 (70.1)	132 (72.1)	<0.001
Dyslipidemia	59 (4.9)	14 (1.9)	5 (3.8)	10 (6.5)	30 (16.4)	<0.001
Cardiovascular diseases*	160 (13.2)	54 (7.3)	16 (12.1)	37 (24)	53 (29)	<0.001
Thyroid disorders†	43 (3.6)	20 (2.7)	7 (5.3)	7 (4.5)	9 (4.9)	0.24
COPD/TB	54 (4.5)	32 (4.3)	2 (1.5)	11 (7.1)	0 (4.9)	0.15
RA	13 (1.1)	2 (0.3)	1 (0.8)	7 (4.5)	3 (1.6)	<0.001
CKD	29 (2.4)	4 (0.5)	4 (3)	11 (7.1)	10 (5.5)	<0.001
History of surgery	206 (17)	87 (11.8)	34 (25.8)	36 (23.4)	49 (26.8)	<0.001
Hydroxychloroquine	973 (80.5)	604 (81.6)	98 (74.2)	125 (81.2)	146 (79.8)	0.26
Kaletra	447 (37)	253 (34.2)	57 (43.2)	60 (39)	77 (42.1)	0.07
Ribavirin	167 (13.8)	91 (12.3)	26 (19.7)	23 (14.9)	27 (14.8)	0.14
Corticosteroids	182 (15.1)	88 (11.9)	26 (19.7)	26 (16.9)	42 (23)	0.001
Favipiravir	60 (5)	40 (5.4)	6 (4.5)	8 (5.2)	6 (3.3)	0.69

Data are presented as number (%). Age and BMI are presented as mean±SD. *Cardiovascular diseases were defined as ischemic heart disease, congestive heart failure and valvular heart disease. †Thyroid disorders were defined as hyperthyroidism and hypothyroidism. ‡The number of patients has been inserted in parenthesis. Group 1 (non-hypertensive, non-diabetic patients), group 2 (non-hypertensive, diabetic patients), group 3 (non-diabetic, hypertensive patients), and group 4 (patients with both diabetes and hypertension who are consuming ACE inhibitors or ARBs)

Table 3: Outcomes of this study and their incidence in each groups

	All patients (*n*=1209)	Group 1 (*n*=740)	Group 2 (*n*=132)	Group 3 (*n*=154)	Group 4 (*n*=183)	*P*
Death	162 (13.4)	64 (8.6)	27 (20.5)	34 (22.1)	37 (20.2)	<0.001
ICU admission	238 (19.6)	101 (13.6)	34 (25.8)	47 (30.5)	56 (30.6)	<0.001
Median length of hospital stay (days)	5 (6)	4 (6)	6 (4)	6 (4)	6 (4)	<0.001

Death and ICU admission are presented as number (percentage) and median length of hospital stay is presented as median (interquartile range (IQR)). Group 1 (non-hypertensive, non-diabetic patients), group 2 (non-hypertensive, diabetic patients), group 3 (non-diabetic, hypertensive patients), group 4 (patients with both diabetes and hypertension who are consuming ACE inhibitors or ARBs).

higher percentage of diabetic patients were positive in real-time PCR test than hypertensive patients and a higher percentage of hypertensive patients were diagnosed only based on CT-scan findings and clinical manifestations. It might be due to earlier admission of diabetic patients (subsequently earlier sampling) than hypertensive groups.

The pre-existing conditions of patients were measured and compared between the groups. A larger group of the patients were male (55.9%) and groups 3 and 4 included older patients (70.1 and 72.1%, respectively). BMI showed no significant difference between the groups. Likewise, a greater proportion of group 4 was affected by dyslipidemia and CKD. Hypertension (27.9%), diabetes (26.1%), ischemic heart disease (IHD) (11.0%), COPD (4.9%), and congestive heart failure (CHF) (4.9%) were the most prevalent pre-existing conditions in our study population. In addition to hypertension and diabetes, most of these conditions such as cardiovascular diseases, dyslipidemia, and age >60, were more common in group 4. Other less prevalent co-existing conditions were hypothyroidism (3.2% patients), RA (1.0% patients), inflammatory bowel disease (six patients) (0.49%), hyperthyroidism (four patients) (0.33%), organ transplantation (two patients) (0.16%), and cirrhosis (one patient) (0.08%). None of the patients were complicated with HIV infection/AIDS and SLE. Nine patients had a recent course of chemotherapy and one patient had a recent course of radiotherapy.

Medications that were prescribed to decrease viral load or alleviate inflammation have been listed in Table 2. Among them, hydroxychloroquine was prescribed more than others, followed by Kaletra, ribavirin, corticosteroids, and favipiravir, respectively. Corticosteroids had significantly unequal distribution and were used for adjustment of odds ratio.

Among patients, as shown in Figure 1, 13.4% deceased during hospitalization. The absence of both diabetes and hypertension (group 1) was associated with 8.6% mortality. The presence of each one of diabetes (group 2) and hypertension (group 3) separately was associated with 20.5% and 22.1% mortality, respectively. The mortality rate among patients who were simultaneously affected by diabetes and hypertension and those who consumed ACE inhibitors or ARBs (group 4) was 20.2%. ICU admission rate was 30.6% in group 4, 30.5% in group 3, 25.8% in group 2, and 19.6% in the group 1. The median length of hospitalization was 5 days in the group 1. The hospitalization period of group 2, group 3, and group 4 was significantly more than group 1. Additionally, death, ICU admission, and length of hospitalization have been compared between the subgroups of group 3, that is, patients of this group have been divided into two subgroups. One group included patients who received ACE inhibitors or ARBs and the other group included patients who did not receive these groups of drugs and just consumed other medications for hypertension. Of all patients in group 3, 44 (28.5%) patients received ARBs/ACE inhibitors and 110 (71.4%) patients did not receive ARBs/ACE inhibitors. There were no significant differences between these two subgroups in their mortality, ICU admission, and length of hospital stay.

When comparing drugs and pre-existing conditions between the groups, we observed that age, gender, dyslipidemia, cardiovascular diseases, RA, CKD, history of surgery, and prescription of corticosteroids have significantly different distribution between the groups. Hence, all of these variables have been used to assess multiple adjusted odds ratio. Groups 2, 3, and –4 were associated with increased mortality before adjustment of odds ratio. After age and sex adjustment, and multiple adjustments of odds ratio, it was shown that only group 2 was associated with a significantly increased mortality rate. Crude odds ratio, and sex and age-adjusted odds ratio revealed that group 2, 3, and –4 needed ICU admission more than group 1 as shown in Table 4. However, after multiple adjustments just groups 2 and 3 were associated with an increased need for ICU admission. The odds ratio for group 4 was borderline and was not completely significant. Furthermore, groups 2, 3, and –4 had an increased length of hospital stay which remained significant even after adjustment of odds ratio.

After adjustment of confounders, mortality was higher in both subgroups of group 3, compared with group 1 ([95%CI, aOR 1.36 (0.75–2.46), $P = 0.315$] for those who did not use ARBs/ACE inhibitors, and [95%CI, aOR 1.81 (0.79–4.14), $P = 0.16$] for ARBs/ACE inhibitors consumers). Furthermore, their outcome was not better than group 4. Moreover, it was shown that among non-diabetic hypertensive patients ARBs/ACE inhibitors were not protective, compared with other anti-hypertensive medications. Compared with group 1, ICU admission ([95%CI, aOR 1.81 (1.07–3.04), $P = 0.025$] for who did not use ARBs/ACE inhibitors, and [95%CI, aOR 1.50 (0.70–3.21), $P = 0.29$] for ARBs/ACE inhibitors consumers) and length of hospital stay ([95%CI, aOR

1.88 (1.17–3.03), $P = 0.01$] for who did not use ARBs/ACE inhibitors, and [95%CI, aOR 2.09 (1.02–4.29), $P = 0.044$] for ARBs/ACE inhibitors consumers) were also increased in both the subgroups of group 3.

Altogether, as shown in Figure 2, patients who were not complicated with neither diabetes nor hypertension had a lower mortality rate (48.51%) in ICU, while diabetes was associated with 64.7% mortality rate and hypertension was associated with 61.7% mortality.

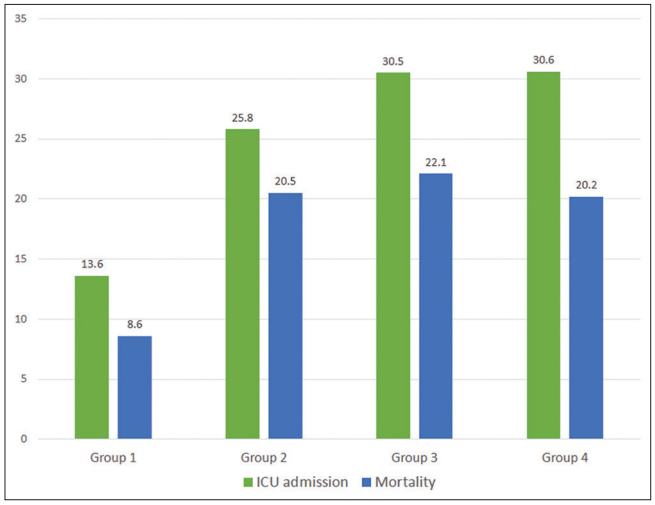

Figure 1: ICU admission rate (green) and mortality rate (blue) in each group. Group 1 (non-hypertensive, non-diabetic patients), group 2 (non-hypertensive, diabetic patients), group 3 (non-diabetic, hypertensive patients), and group 4 (patients with both diabetes and hypertension who are consuming ACE inhibitors or ARBs)

Discussion

In this study, group 2 (diabetes) was significantly associated with increased mortality and ICU admission. Similarly, group 3 (hypertension) was associated with an increased risk of ICU admission. Their presence together is theoretically expected to be more dangerous than alone, but multiple adjusted odds ratio showed that group 4 was not associated with increased mortality. Additionally, group 4 had a slightly but not significantly increased risk of ICU admission. Age and comorbidities peculiarly cardiovascular comorbidities profoundly affected mortality and the need for ICU admission. Patients in group 4 were older and more complicated with

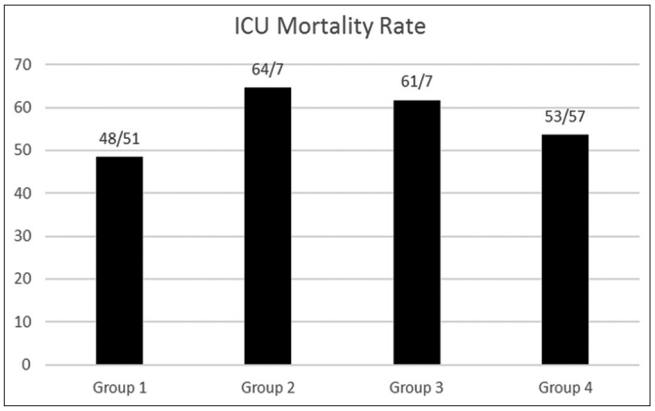

Figure 2: Mortality rate among ICU admitted patients of each group. Group 1 (non-hypertensive, non-diabetic patients), group 2 (non-hypertensive, diabetic patients), group 3 (non-diabetic, hypertensive patients), and group 4 (patients with both diabetes and hypertension who are consuming ACE inhibitors or ARBs)

Table 4: Crude, age, and sex adjusted and multiple adjusted odds ratio for death, ICU admission, and prolonged hospitalization

	Crude odds ratio (CI 95%)	*P*	Age and sex adjusted odds ratio (CI 95%)	*P*	Multiple adjusted odds ratio (CI 95%)	*P*
Logistic regression analysis for death						
Group 1	1		1		1	
Group 2	2.71 (1.65-4.45)	<0.001	2.02 (1.20-3.41)	0.008	1.93 (1.11-3.33)	0.02
Group 3	2.99 (1.89-4.73)	<0.001	1.44 (0.87-2.38)	0.15	1.47 (0.87-2.49)	0.17
Group 4	2.67 (1.72-4.16)	<0.001	1.29 (0.80-2.08)	0.29	1.16 (0.71-1.92)	0.54
Logistic regression analysis for ICU admission						
Group 1	1		1		1	
Group 2	2.19 (1.40-3.41)	0.001	1.74 (1.10-2.75)	0.02	1.69 (1.04-2.76)	0.03
Group 3	2.77 (1.85-4.15)	<0.001	1.73 (1.12-2.68)	0.01	1.71 (1.08-2.71)	0.02
Group 4	2.79 (1.91-4.07)	<0.001	1.71 (1.13-2.58)	0.01	1.53 (0.99-2.37)	0.06
Logistic regression analysis for prolonged hospitalization (more than median of total population)						
Group 1	1		1		1	
Group 2	2.14 (1.45-3.15)	<0.001	1.97 (1.33-2.92)	0.001	1.73 (1.14-2.62)	0.009
Group 3	2.44 (1.69-3.54)	<0.001	2.04 (1.37-3.02)	<0.001	1.93 (1.27-2.95)	0.002
Group 4	3.30 (2.29-4.74)	<0.001	2.74 (1.85-4.04)	<0.001	2.33 (1.53-3.52)	<0.001

Age, gender, dyslipidemia, cardiovascular diseases, RA, CKD, history of surgery, and corticosteroids were used for multiple adjustment of odds ratio. 95% CI was considered in odds ratio assessment. Group 1 (n=740, non-hypertensive, non-diabetic patients), group 2 (n=132, non-hypertensive, diabetic patients), group 3 (n=154, non-diabetic, hypertensive patients), group 4 (n=183, patients with both diabetes and hypertension who are consuming ACE inhibitors or ARBs)

several comorbidities. Hence, crude odds ratio and adjusted odds ratio were very different in group 4. Also, the worsening of pre-existing comorbidities effectively increased the need for ICU admission in group 4 and exacerbated their health condition. Additionally, we compared the proportion of patients who survived in ICU from each group. Even in the presence of these comorbidities and older age, a lower percentage of patients from group 4 died in ICU. A similar condition for the prevalence of pre-existing comorbidities, ICU admission, and discharge from ICU was observed in group 3. After adjustment of odds ratio, group 4 had better outcomes than group 2 and 3 in accordance with mortality and ICU admission. Also, group 3 had better outcomes than group 2 according to mortality rate. However, even after adjustment the length of hospital stay was increased in group 2, 3, and 4. Despite the protective effects of ARBs/ACE inhibitors among diabetic hypertensive patients, these drugs were not protective among non-diabetic hypertensive patients.

SARS-CoV-2 virus uses its special spikes to interact with ACE2, a transmembrane protein, on the cell's surface in organs such as the lung, heart, kidney, and intestine. This kind of interaction leads to the internalization of the newly formed complex.[20] ACE inhibitors and ARBs counteract RAAS system. ACE1 converts angiotensin I into angiotensin II to stimulate angiotensin receptor type II and increase blood pressure. Conversely, ACE 2 degrades angiotensin II into angiotensin 1-7 which is a vasodilator.[21] Previously, it was observed that administration of ACE inhibitors and ARBs is associated with overexpression of ACE2.[22-24] Although, ACE2 lets SARS-CoV-2 enter host cells, at the same time it accelerates the resolution of inflammatory response in the lungs.[25-27] Patients who received ACE inhibitors or ARBs during their COVID-19 infection had lower levels of highly sensitive C-reactive protein (hs-CRP) and procalcitonin.[28]

It was uncovered that the ACE2/angiotensin 1-7/Mas axis protects against lung fibrosis and pulmonary hypertension.[29] On the other hand, ACE inhibitors and ARBs do not increase the expression of ciliary ACE2.[30] Hence, these drugs cannot mechanistically increase the risk of COVID-19 infection. Consistently, a recent study has shown that ACE2 inhibitors and ARBs do not increase the risk of COVID-19 infection and interestingly they decrease the risk of COVID-19 requiring hospitalization in the diabetic subgroup.[17] Another study also suggested inhibitors of renin-angiotensin system RAS as a good choice for treatment of COVID-19 pneumonia.[31] In multiple studies, lower risk of hospitalization or mortality was observed in COVID-19 patients with the use of ACEi/ARB.[17,32]

Studies have shown that older age, diabetes, hypertension, cardiovascular diseases, COPD, and CKD are predictive of death in COVID-19 patients.[33-35] Consistently, these variables have been adjusted for outcomes, except diabetes and hypertension which were parts of groups' definition. Several studies have shown that general administration of RAAS inhibitors during the COVID-19 pandemic is not linked with increased mortality and even some of them claimed that RAAS inhibitors are protective.[11,12,36] Surprisingly, our study revealed that these drugs can bring further benefits to diabetic subgroup of hypertensive patients.

Our study faced several limitations. First, as a retrospective study our source of data relied on patients' files. Our second major problem was the diversity of treatment among patients. We chose to exclude the patients who received a non-prevalent type of treatment to improve the homogeneity of our study population. Moreover, we included drugs in an adjustment of the odds ratio. The third major issue was that we did not know the quality of glycemic control or blood pressure control before hospitalization. These variables are necessary to interpret the results of studies like this. However, after hospitalization control of hyperglycemia and blood pressure was properly performed for all patients. Studies have shown that glycemic control vigorously affects the death rate.[37,38] Unfortunately, this tip has been neglected in the majority of previous studies or there was not enough information in this regard. Maybe, future prospective studies can overcome these critical issues and deliver more precise results.

To sum up, the present study suggests that ACE inhibitors and ARBs are protective in diabetic patients hospitalized with moderate to severe COVID-19 infection, or at least they are safe. Results of this study indicate that the continuation of these drugs in the diabetic subgroup of hypertensive patients brings several benefits during COVID-19 pandemic. Larger and prospective studies are required to evaluate these results.

Ethics approval

This study was conducted in accordance with 2013 Declaration of Helsinki and was approved by Tehran University of Medical Sciences (TUMS), IR.TUMS.VCR.REC.1399.171.

Acknowledgements

We thank Tehran University of Medical Sciences (TUMS) to support this study (grant no. 99-1-101-47509). The authors would like to thank the Clinical Research Development Unit (CRDU) of Baharloo Hospital and Occupational Sleep Research Center, Tehran University of Medical Sciences, Tehran, Iran for their support, cooperation, and assistance throughout the period of study.

Financial support and sponsorship

This study was funded by Tehran University of Medical Sciences (TUMS).

Conflicts of interest

There are no conflicts of interest.

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