ORIGINAL ARTICLE

Association of RASis and HMG-CoA reductase inhibitors with clinical manifestations in coronavirus disease 2019 patients: Results from the Khorshid Coronavirus Disease Cohort Study

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Background: Angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEinhs) may deteriorate or improve the clinical manifestations in severe acute respiratory syndrome coronavirus 2 infection. A comparative, cross-sectional study was conducted to evaluate the association of ARBs/ACEinhs and hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (HMGRis) with clinical outcomes in coronavirus disease 2019 (COVID-19). **Materials and Methods:** From April 4 to June 2, 2020, 659 patients were categorized according to whether they were taking ARB, ACEinh, or HMGRi drugs or none of them. Demographic variables, clinical and laboratory tests, chest computed tomography findings, and intensive care unit-related data were analyzed and compared between the groups. **Results:** The ARB, ACEinh, and HMGRi groups significantly had lower heart rate ($P < 0.05$). Furthermore, a lower percent of O_2 saturation (89.34 ± 7.17% vs. 84.25 ± 7.00%; $P = 0.04$) was observed in the ACEis group than non-ACEinhs. Mortality rate and the number of intubated patients were lower in patients taking ARBs, ACEinhs, and HMGRis, although these differences failed to reach statistical significance. **Conclusion:** Our findings present clinical data on the association between ARBs, ACEinhs, and HMGRis and outcomes in hospitalized, hypertensive COVID-19 patients, implying that ARBs/ACEinhs are not associated with the severity or mortality of COVID-19 in such patients.

Key words: Coronavirus disease 2019, critical care, hydroxymethylglutaryl-CoA reductase inhibitors, renin–angiotensin system, severe acute respiratory syndrome coronavirus 2, X-ray computed tomography

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic viral disease – originated from Wuhan, China – in December 2019.[1] According to recent findings, 10.5% of fatal cases occurred in patients with cardiovascular disease and 6% in patients with arterial hypertension.[2] In another report, hypertension was estimated as the most frequent coexisting condition in 1099 patients.[3]

Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and SARS-CoV-2 bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung,

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intestine, kidney, and blood vessels.[4] This receptor is substantially increased in patients with hypertension, who are treated with ACE inhibitors (ACEinhs) and angiotensin II type I receptor blockers (ARBs).[5] The interaction between SARS-CoV-2 and ACE2 has been proposed as a potential factor in its infectivity.[6,7] Some researchers believed that these drugs are responsible for disease virulence in the ongoing COVID-19 pandemic.[8,9] Indeed, ACE2 reduces inflammation and has been suggested as a new therapeutic goal for inflammatory lung diseases, diabetes, and hypertension, claiming a protective impact of ACEinhs/ARBs on COVID-19-related pneumonia.[10]

Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (HMGRis), also known as statins, are a class of lipid-lowering drugs that reduce mortality in people at higher risk of cardiovascular diseases.[11] Recently, some evidence supported the efficacy of HMGRis for treating COVID-19[12] due to the anti-inflammatory effects.[13] It is known that HMGRis have the ability to block Toll-like receptors and NF-B signaling, which stimulates the compensatory immune response and lowers disease complications.[14] Some researchers found that HMGRis can limit the "cytokine storm" in severe COVID-19 patients,[15] however, controversies exist.

The use of ACEinh/ARB/HMGRi drugs is common as age increases; therefore, we tried to evaluate the association of taking these drugs with COVID-19-related outcomes.

MATERIALS AND METHODS

Study population

This single-center cross-sectional study was derived from Khorshid COVID Cohort. It was carried out under the principles of the Declaration of Helsinki and was issued by the Ethical Board at University of Medical Sciences (Clinical Ethical Approval No. IR.MUI.MED.REC.1399.064). Between April 4 and June 2, 2020, 659 positive SARS-CoV2 cases were recruited from Center Hospital of COVID-19. Participants were divided into three groups (based on taking ACEinhs/ARBs/HMGRis).

Hospitalized patients with preexisting hypertension who received ACEinhs (captopril, enalapril, and lisinopril), ARBs (valsartan and losartan), and HMGRis (lovastatin, rosuvastatin, atorvastatin, and simvastatin) – lonely or together – and aged between 50 and 70 years were included in this study. Indeed, subjects who had other viral infections, major pulmonary illnesses (preexisting asthma, pneumonia, bronchitis, emphysema, and any history of lobectomy), consume special food supplements (beta-carotene, caffeine), and bronchodilator drugs were excluded. In the final analysis, the statistician also removed the cases that did not fill out more than 60% of the questionnaire items. Each participant provided written informed consent that expressed the study objectives.

Data collection

General characteristics

Three trained medical doctors evaluated all cases in terms of sociodemographics (age, gender, marital, smoking status), common signs and symptoms (fatigue, body pain, fever, cough, sneeze, headache), vital signs (temperature, respiration rate, heart rate, O2 arterial blood saturation), and hospitalization-related variables (the number of intubation, ICU admission, mortality rate, hospitalization, ICU duration).

Laboratory data

Blood samples (5 cc) taken from patients were centrifuged for 15 min at 3000 rpms, and separated serums were stored at −70°C with batch testing until final analysis. Serum C-reactive protein (CRP) concentration and erythrocyte sedimentation rate (ESR) were measured to evaluate the level of inflammation. Cell blood count checking was performed for measuring the number of white blood cells (WBCs), lymphocytes (Lymph), and neutrophils (Neut). The level of serum ferritin was also assessed.

Chest computed tomography analysis

Multislice computed tomography (CT) was performed on a scanner (Brilliance CT 64-channel scanner, Philips, Cleveland, USA) with a standard protocol (low-dose noncontrast chest CT). Chest CT results were interpreted by a trained chest radiologist blinded to the final diagnosis. All CT images were assessed according to the Radiological Society of North America guidelines for COVID-19.[16] A semi-quantitative scoring system for estimating the pulmonary involvement of all these abnormalities on the basis of the percentage of the total lung involved per lobe-reported by Pan *et al*.[17] and Bernheim *et al*.[18] was applied. First, the number and severity of lobes involved were determined. Second, the extension of the lung opacification was visually estimated from 1 to 5 as follows: score 1, 1%–5% involvement; score 2, 6%–25% involvement; score 3, 26%–50% involvement; score 4, 51%–75% involvement; and score 5, 76%–100% involvement. Total lung scores were calculated as the sum of individual lobe scores; it ranged from 5 to 25 points.

Statistical analysis

Continuous and categorical variables were presented as means ± standard deviation and number (percent), respectively. The Kolmogorov–Smirnov test was used to assess the normality of numeric variables. Chi-square test or Fisher's exact test is used to determine whether there was a significant association between two categorical variables. An independent Student's *t* and paired *t*-tests or nonparametric

Mann–Whitney *U* and Wilcoxon tests were used to compare the means of continuous variables in two groups.

To assess the relationship between ICU and hospitalization duration and ACEinhs/ARBs/HMGRis (adjusted by age, sex, and comorbidities), multiple linear regression model was designed. The Cox regression was used to evaluate the association between ICU-related variables (ICU admission, intubation status, and mortality rate) and taking the selected drugs.

Hazard ratio (HR, followed by 95% confidence interval [CI]) and regression coefficient (standard error) were also reported. Because some patients used two groups of inhibitors at the same time (ARBs/HMGRis, and ACEinhs/HMGRis), we performed descriptive statistics for sociodemographic characteristics/signs and symptoms/laboratory and CT variables based on taking two groups of inhibitors for all participants to examine the differences between these variables. All the analyses were done using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA version 24.0). In all analyses, $P < 0.05$ was considered statistically significant.

RESULTS

General outcomes

After the initial screening, 659 patients with positive SARS-CoV2 infection were assessed across the three groups (ACEinhs, ARBs, and HMGRis) and two groups (ARBs/HMGRis, and ACEinhs/HMGRis); each group was further distributed into two subgroups based on the usage of the selected drugs (yes/no: yes for ARBs, $n = 114$; yes for ACEinhs, $n = 8$; yes for HMGRis, $n = 86$) [Table 1].

The sociodemographic characteristics of the participants are summarized in Table 1. The majority were male. The mean age was 57.29 ± 15.36 years. The majority (~90%) did not report any history of taking ACEinh/ARB/HMGRi drugs. Almost 10% were current smokers, and 80% of the participants had been married.

Signs and symptoms

In general, the frequency of signs and symptoms (fatigue, body pain, fever, cough, sneeze, and headache) was higher in patients who did not previously use ACEinh/ARB/HMGRi drugs. Non-ARB patients with fever had significantly more frequent than ARB users (62.52% vs. 10.93%; $P = 0.001$). There were no major differences in vital signs between the two subgroups in each drug group except for the higher number of HR in the non-ARB (91.31 ± 16.58 vs. 84.88 ± 13.69; $P < 0.01$), non-ACEinh (90.25 ± 16.13 vs. 62.50 ± 10.60; $P = 0.01$), and non-HMGRi (91.11 ± 16.30 vs. 82.38 ± 13.69; $P < 0.01$) patients, in comparison with the selected drug users. The saturation of arterial O_2 was higher in non-ACEinh patients than ACEinh users [89.34 ± 7.17 vs. 84.25 ± 7.00; $P = 0.04$, Table 1]. When we distributed the patients across the ARB + HMGRi and ACEinh + HMGRi groups, the differences for HR persisted [$P < 0.05$, Table 2].

Laboratory and computed tomography data

There were no major differences in selected biomarkers (WBC, Neut, Lymph, ferritin, ESR, and CRP) between the two subgroups in each drug group, except for the lower serum levels of ferritin in the HMGRi users in comparison with non-HMGRis [365.73 ± 255.50 vs. 595.72 ± 253.71 ɥg/L; $P < 0.01$, Table 1]. The significant differences were also observed across the ARB + HMGRi group [nonusers vs. users: 572.7 ± 268.04 vs. 358.8 ± 173.75 ɥg/L; $P = 0.01$ for ferritin; 73.51 ± 11.24 vs. 69.23 ± 13.41; $P = 0.01$ for Neut, Table 2]. There were no major differences in CT scoring across the subgroups.

Hospitalization-related variables

According to findings, non-ACEinh/ARB/HMGRi users had more possibility of being intubated and admitted to ICU. The rate of ICU admission in non-ACEinhs was 13.8% more than ACEinh users (HR: 1.70; 95% CI: 0.99–2.94; $P = 0.05$). Mortality rate was also lower for ACEinh/ARB/HMGRi users in a nonsignificant manner. Furthermore, patients on ARB drugs had a significantly lower number of days in ICU [−3 days; $P = 0.02$, Table 3].

DISCUSSION

To the best of our knowledge, this is the first cohort study aimed to evaluate and compare the association of ACEinh/ARB/HMGRi drugs with clinical outcomes (CT findings, signs and symptoms, laboratory data, hospitalization) in patients with COVID-19 and preexisting hypertension. The current findings showed that ACEinh/ARB/HMGRi treatment is related to a lower frequency of signs and symptoms, mortality rate, and ICU staying time, although these differences failed to reach statistical significance.

Hypertension is a critical risk factor for poor clinical outcomes in patients with COVID-19. ACEinhs and ARBs, which are capable of reducing the production of inflammatory markers, are potential candidate drugs for treatment of patients with COVID-19 and preexisting hypertension. In previous studies, ACEinhs/ARBs have been shown to upregulate ACE2 activity; therefore, they may be efficient in COVID-19 patients.[19]

Yang *et al.*[20] in a retrospective study observed that COVID-19 cases on either ACEinhs or ARBs had significantly lower concentrations of hs-CRP. Furthermore, a lower proportion of critical patients (9.3% vs. 22.9%; $P = 0.061$)

Table 1: Descriptive statistics for variables based on selected drug groups

Variables	ARBs		*P*	ACEis		*P*	HMGRis		*P*
	No	Yes		No	Yes		No	Yes	
Number of cases	545 (82.7)	114 (17.3)		651 (98.8)	8 (1.2)		573 (86.9)	86 (13.1)	
Age (years)	55.72±15.53	64.88±11.97	**0.00**	57.15±15.36	68.88±11.01	**0.03**	55.98±15.47	66.16±11.16	**0.00**
Sex (male)	342 (51.9)	63 (9.6)	0.13	401 (60.8)	4 (0.6)	0.50	362 (54.9)	43 (6.5)	**0.01**
Marital status									
Single	23 (3.50)	2 (0.30)	0.08	23 (3.49)	0	**0.00**	34 (5.16)	0	0.16
Married	501 (76.03)	111 (16.84)		606 (91.96)	6 (0.91)		529 (80.27)	83 (12.59)	
Divorced-widowed	21 (3.18)	1 (0.15)		22 (3.34)	2 (0.30)		10 (1.52)	3 (0.46)	
Smoking status									
Current smoker	63 (9.55)	11 (1.66)	0.68	74 (11.23)	0	0.76	91 (13.81)	8 (1.21)	0.80
Passive smoker	48 (7.28)	8 (1.21)		10 (1.52)	0		21 (3.19)	7 (1.06)	
X-smoker	45 (6.82)	8 (1.21)		7 (1.06)	0		15 (2.28)	3 (0.46)	
Signs and symptoms (yes)									
Fatigue	319 (48.41)	73 (11.08)	0.38	441 (66.92)	4 (0.61)	0.25	386 (58.57)	54 (8.19)	0.97
Body pain	314 (47.65)	72 (10.93)	0.50	421 (63.88)	4 (0.61)	0.39	370 (56.15)	51 (7.74)	0.96
Fever	412 (62.52)	72 (10.93)	**0.001**	478 (75.53)	6 (0.91)	0.93	424 (64.34)	60 (9.10)	0.36
Cough	424 (64.34)	93 (14.11)	0.42	512 (77.69)	6 (0.92)	0.55	454 (68.89)	63 (9.56)	0.28
Sneeze	152 (23.07)	33 (5.01)	0.61	122 (18.1)	0	0.37	101 (15.33)	16 (2.43)	0.49
Headache	258 (39.15)	49 (7.44)	0.38	306 (46.43)	2 (0.30)	0.14	274 (41.58)	33 (5.01)	0.10
Laboratory parameters									
WBC (count/μL)	6361.68±3898.76	6312.61±2975.45	0.97	6331.60±3729.57	6534.54±3442.58	0.74	6425.43±3979.14	6217.83±3172.70	0.90
Neutrophils (%)	73.15±11.63	73.06±11.47	0.10	73.02±11.57	74.21±11.75	0.94	73.14±11.83	73.11±11.17	0.04
Lymphocytes (%)	20.54±9.65	22.36±10.84	0.07	20.86±10.06	20.60±10.12	0.90	20.87±10.49	20.76±9.27	0.23
Ferritin (μg/L)	514.57±114.19	521.92±116.84	0.14	515.81±115.53	521±107.69	0.26	595.72±253.71	365.73±255.50	**0.00**
ESR (mm/h)	47.41±29.11	43.88±28.85	0.10	47.16±28.99	40.89±29.43	0.77	46.79±27.50	52.26±27.36	0.09
CRP (mg/L)	30.63±17.21	28.82±16.24	0.21	30.37±17.01	28.65±16.88	0.42	30.04±16.15	30.51±18.41	0.71
Vital signs									
Temperature (°C)	37.35±1.06	37.48±1.07	0.62	37.36±1.08	37.52±0.882	0.50	37.38±1.06	37.38±1.08	0.16
RR	22.11±5.33	21.58±5.16	0.94	21.93±5.18	22.55±6.32	0.31	22.07±5.38	21.84±5.13	0.61
HR	91.31±16.58	84.88±13.69	**0.00**	90.25±16.13	62.50±10.60	**0.01**	91.11±16.30	82.38±13.69	**0.00**
O_2 sat (%)	89.25±7.50	89.66±6.65	0.29	89.34±7.17	84.25±7.00	**0.04**	89.20±7.77	89.60±6.43	0.31
CT scoring for severity	9.87±4.12	9.43±4.28	0.32	9.84±4.21	9.04±4.34	0.46	9.73±4.26	9.84±4.17	0.12

Data were presented as *n* (%) or mean±SD. Values<0.5 were bolded. *P* values were obtained from χ^2 test, Fisher's exact tests, *t*-tests, or Mann-Whitney *U*-tests when appropriate. ARBs=Angiotensin II type I receptor blockers; ACEis=Angiotensin-converting Enzyme inhibitors; HMGRis=Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors; WBC=White blood cell; ESR=Erythrocyte sedimentation rate; CRP=C-reactive protein; RR=Respiration rate; HR=Heart rate; O_2 sat=O_2 arterial blood saturation; SD=Standard deviation; CT=Computed tomography

Table 2: Descriptive statistics for variables based on taking two simultaneous groups of inhibitors

Variables	ARBs + HMGRis		*P*	ACEis + HMGRis		*P*
	No	Yes		No	Yes	
Number of cases	615 (93.3)	44 (6.7)		655 (99.4)	4 (0.6)	
Age (years)	56.81±15.48	64.16±11.65	**0.00**	57.15±15.32	77.0±10.13	**0.01**
Sex (male)	381 (57.8)	24 (3.6)		403 (61.2)	2 (0.3)	0.63
Marital status						
Single	35 (5.31)	0	0.33	29 (4.40)	0	**0.00**
Married	569 (86.34)	44 (6.68)		614 (93.17)	3 (0.46)	
Divorced-widowed	11 (1.67)	0		11 (1.67)	1 (0.15)	
Smoking Status						
Current smoker	115 (17.45)	4 (0.61)	0.73	110 (16.69)	0	0.90
Passive smoker	9 (1.37)	1 (0.15)		20 (3.03)	0	
X-smoker	5 (0.76)	1 (0.15)		6 (0.91)	0	
Signs and symptoms (yes)						
Fatigue	414 (62.82)	34 (5.16)	0.69	443 (67.22)	3 (0.46)	0.87
Body pain	394 (59.79)	30 (4.55)	0.47	423 (64.19)	2 (0.30)	0.62
Fever	456 (69.20)	28 (4.25)	0.07	480 (72.84)	4 (0.61)	0.26
Cough	480 (72.84)	37 (5.61)	0.32	514 (78)	3 (0.46)	0.79
Sneeze	115 (17.45)	10 (1.52)	0.45	123 (18.66)	0	0.47
Headache	289 (43.85)	17 (2.58)	0.74	306 (46.43)	1 (0.15)	0.65
Laboratory parameters						
WBC (count/μL)	6391.34±3830.44	6032±2494.26	0.92	6354.39±3719.87	6229.96±3217.80	0.94
Neutrophils (%)	73.51±11.24	69.23±13.41	**0.01**	73.07±11.66	74.93±9.41	0.43
Lymphocytes (%)	20.67±9.91	23.51±9.12	0.06	20.85±10.12	20.42±8.04	0.82
Ferritin (μg/L)	572.7±268.04	358.8±173.75	**0.01**	516.87±114.50	499.16±123.72	0.33
ESR (mm/h)	47.13±29.43	42.41±25.85	0.28	46.76±29.22	41.60±24.38	0.47
CRP (mg/L)	30.31±16.93	29.41±17.54	0.64	30.54±16.92	29.24±19.42	0.77
Vital signs						
Temperature (°C)	37.38±1.07	37.35±1.06	0.96	37.38±1.07	37.39±0.97	0.87
RR	22.10±5.32	21.11±4.97	0.73	21.96±5.24	22.88±6.64	0.39
HR	90.68±16.20	80.22±13.88	**0.008**	90.25±16.13	62.50±10.60	**0.01**
O_2 sat (%)	89.28±7.53	89.81±5.34	0.68	89.38±7.31	88.44±7.36	0.39
CT scoring for severity	9.87±4.12	9.43±4.28	0.12	9.84±4.21	9.04±4.34	0.27

Data were presented as *n* (%) or mean±SD. Values<0.5 were bolded. *P* values were obtained from χ^2 test, Fisher's exact tests, *t*-tests, or Mann-Whitney *U*-tests when appropriate. ARBs=Angiotensin II type I receptor blockers; ACEis=Angiotensin-converting enzyme inhibitors; HMGRis=Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors; WBC=White blood cell; ESR=Erythrocyte sedimentation rate; CRP=C-reactive protein; RR=Respiration rate; HR=Heart rate; O_2 sat=O_2 arterial blood saturation; SD=Standard deviation; CT=Computed tomography

Table 3: Intensive care unit-related outcomes based on the selected drug groups

Outcomes (yes)	ARBs		*P*	ACEis		*P*	HMGRis		*P*
	No	Yes		No	Yes		No	Yes	
Intubation status	29 (4.4)	6 (0.9)	0.98	35 (5.3)	0	0.50	31 (4.7)	4 (0.6)	0.77
HR (95% CI)	0.90 (0.26-3.06)		0.86	1.19 (0.927-1.535)		0.17	0.85 (0.22-3.27)		0.81
ICU admission	79 (12.0)	14 (2.1)	0.53	92 (14.0)	1 (0.2)	0.89	84 (12.7)	9 (1.4)	0.29
HR (95% CI)	1.01 (0.53-1.89)		0.97	1.70 (0.99-2.94)		0.05	0.92 (0.42-2.01)		0.83
Mortality rate	40 (6.1)	9 (1.4)	0.83	48 (7.3)	1 (0.2)	0.58	43 (6.5)	6 (0.9)	0.86
HR (95% CI)	1.88 (0.74-4.76)		0.18	1.76 (0.73-4.20)		0.20	1.08 (0.39-2.99)		0.87
Hospitalization duration (days)	6.59±6.04	6.46±4.26	0.82	6.57±5.79	6.50±4.30	0.97	6.63±5.94	6.21±4.48	0.53
Regression coefficient (SE)	−0.054 (0.60)		0.17	−0.016 (2.02)		0.68	−0.068 (0.68)		0.08
ICU duration (days)	9.67±8.54	6.47±3.70	0.02	9.23±8.09	7.33±2.93	0.60	9.22±8.24	8.78±6.36	0.87
Regression coefficient (SE)	−0.15 (2.39)		0.15	−0.054 (8.35)		0.60	−0.006 (3.17)		0.95

Data were presented as *n* (%) or mean±SD. ARBs=Angiotensin II type I receptor blockers; ACEis=Angiotensin-converting enzyme inhibitors; HMGRis=Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors; ICU=Intensive care unit; HR=Hazard ratio; SE=Standard error; SD=Standard deviation; CI=Confidence interval

and a lower mortality rate (4.7% vs. 13.3%; $P = 0.216$) were detected in ACEinh/ARB group than non-ACEinh/ARB group. Moreover, Meng *et al.*[21] found that patients receiving ACEinh or ARB therapy have a lower rate of severe diseases and a trend toward a lower level of interleukin-6 (IL-6). Aside from previous studies, we did not see any significant difference for CRP/ESR between drug subgroups, but a lower mortality rate and ICU admission were observed. We

also evaluated the chest CT scans; there were no definable differences across the selected drug subgroups.

Like ACEinhs/ARBs,[22] HMGRis might reduce lung injury in people with COVID-19. By interrupting lipid rafts, HMGRis have the potential to reduce viral entry into cells.[23] A retrospective analysis of the findings of a multicenter clinical trial on the efficacy of rosuvastatin against infection-induced acute respiratory distress syndrome showed higher IL-18 level and mortality rate in statin-treated patients.[24] The potential effects of HMGRis on ventilator-associated pneumonia are also conflicting.[25]

Similar to our findings, Spigeleer *et al*.[26] reported that HMGRi intake among 153 elderly people with COVID-19 was significantly associated with the absence of symptoms. In more details, the effects on long-stay hospitalization or mortality rate were positive in a nonsignificant manner (odds ratio: 0.75; CI: 0.25–1.85). Administration of atorvastatin as adjunctive therapy in COVID-19 is an ongoing trial, looking at the effects of atorvastatin on disease progression and mortality in people hospitalized with COVID-19, compared to standard care.[27]

On the basis of the current evidence, and despite the theoretical concerns and uncertainty regarding the effect of ACEinhs/ARBs/HMGRis on ACE2, we believe that these drugs should be continued in patients except for special conditions in which there are certain health risks.

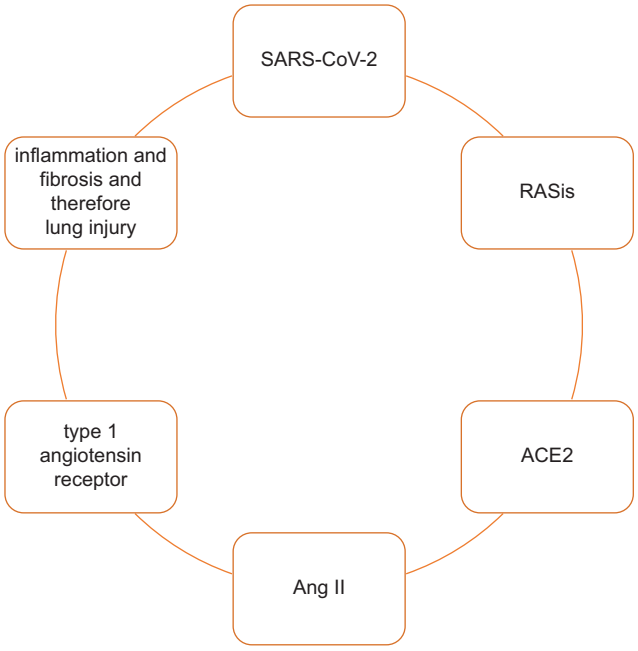
Limitations

Selection bias was a relevant danger. We classified drugs in each drug group during data collection process, however, due to irregular administration patterns, the comparative analysis was done for headings only (i.e. ACEinhs, ARBs, and HMGRis). Some confounders such as the frequency, dose and intake duration of selected drugs, and dietary patterns of participants were not adjusted. CRP-lowering effect of HMGRis[28] was likely to affect the laboratory data. Our results may not be generalizable to all hypertensive patients, and it is possible that ACEinhs/ARBs/HMGRis affect the chance of hospitalization and ICU admission. Although protease inhibitors such as lopinavir/ritonavir inhibit the metabolism of most HMGRis,[29] these drugs were not administered during routine treatment; so we did not receive any HMGRi toxicity. There was no comprehensive information regarding the history of vaccination, the type of vaccine, and the number of doses received in the current research. Finally, it must be noted that this study was cross-sectional; therefore, we could not evaluate causality.

CONCLUSION

The current findings support continuing ACEinh/ARB/HMGRi drugs in patients with positive SARS-CoV2 infection and preexisting hypertension. Although the majority of clinical variables have a positive trend across the patients who received ACEinh/ARB/HMGRi drugs, the associations were not statistically significant. These findings need to be confirmed by larger cohort studies and clinical trials to uncover the mechanisms by which ACEinhs/ARBs/HMGRis influence COVID-19 clinical manifestations.

Two conflicting identified ideas for RASis and COVID-19:



1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) simply enters into the cell by binding to angiotensin-converting enzyme 2 (ACE2). This may enhance viral entry
2. Angiotensin II (Ang II) activates the type 1 angiotensin receptor. Renin–Angiotensin System inhibitors (RASis) diminishes the production of Ang II, which attenuates inflammation and fibrosis and therefore attenuates lung injury.

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Conflicts of interest

There are no conflicts of interest.

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