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Is prior use of renin-angiotensin system (RAS) inhibitors associated with more favourable outcome in COVID-19 hospitalized patients?

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Abstract: **Objective:** We aimed to investigate the extent of pulmonary involvement and adverse outcomes in patients receiving angiotensin-converting enzyme inhibitor (ACEI)/ angiotensin II receptor blocker (ARB) versus who did not, in hospitalized coronavirus infectious disease 2019 (COVID-19) patients.

Method: All COVID-19 patients with a positive polymerase chain reaction (PCR) test, who were admitted to our tertiary referral hospitals in Tehran, Iran between January 2021 and May 2021, and had an on-admission chest computed tomography (CT) scan, were included. The patients were divided into two groups (receiving ACEI/ARB and who did not) for further analysis. The outcomes of interest in our study were the extent of pulmonary involvement, intensive care unit (ICU) admission, and death.

Results: A total of 893 participants (mean age of 58.6±15.4 years; female, 522 (58.4%)) were enrolled. Among them, 368 (41.2%) participants had hypertension, and use of ACEI/ARB was reported in 183 (20.5%) participants. Of all, 409 (45.8%) participants required ICU admission, and 259 (29%) participants succumbed to death. We found that participants who received ACEI/ARB were less likely to progress critical disease and experienced significantly lower ICU admission (P=0.022) and death (P<0.001). On multivariable analysis adjusting for age, sex, and comorbidities, this relationship remained statistically significant for death (odds ratio (OR): 0.23 [0.14-0.38], P<0.001) and ICU admission (OR: 0.49 [0.32-0.73], P=0.001).

Conclusion: Our findings showed that COVID-19 patients who receiving ACEI/ARB prior to hospitalization vs. those who did not, had more favorable outcomes.

Keywords: Angiotensin-Converting Enzyme Inhibitors; Angiotensin Receptor Antagonists; COVID-19; Hypertension; Patient Outcome Assessment; X-Ray Computed Tomography

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1. Introduction

SARS-CoV-2, the etiologic pathogen of coronavirus infectious disease 2019 (COVID-19), requires the angiotensin-converting enzyme 2 (ACE2) receptor to internalize into host cells and undergo replication (1). Chronic treatment with renin-angiotensin system (RAS) inhibitors, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptor blockers (ARB), which are generally utilized to manage hypertension (HTN), diabetes mellitus (DM), or cardiovascular disorders (CAD), has been shown to boost the ACE2 receptor expression in host tissues (2, 3). Furthermore, previous studies also showed that HTN was linked to negative outcomes in the COVID-19 patients (4-6). Hence, scientists hypothesized that the patients receiving chronic RAS inhibitor agents may be more susceptible to SARS-CoV-2 infection or develop a severe disease (1).

In contrast, it was claimed that upregulation of ACE2 receptors has been associated with better outcomes and lower pulmonary involvement (PI) in COVID-19 infected patients (7). Besides, the withdrawal of RAS inhibitor agents in high-risk patients could accompany worse outcomes in the current outbreak (8).

There is a discrepancy in the literature regarding the advantages and disadvantages of continuing the RAS inhibitors in the COVID-19 pandemic. To elaborate on, several studies found significantly lower risk of all-cause mortality, mechanical ventilation, and intensive care unit (ICU) admission in patients on RAS inhibitors (9-11). On the other hand, other distinct studies reported the opposite findings (12, 13). Using

systematic review and meta-analysis, scientists tried to solve this controversy and showed no significant association (14, 15). Therefore, it seems that the RAS inhibitors have paradoxical effects in being infected or progression of COVID-19 disease, raising concerns regarding the beneficial or harmful effect of RAS inhibitors in COVID-19 patients. The optimal management of HTN in the COVID-19 pandemic is uncertain and requires more clarification. Besides, no previous study has compared the extent of PI between two groups. Hence, we aimed to investigate the extent of PI and adverse outcomes in patients receiving RAS inhibitors vs. no-RAS inhibitors in hospitalized COVID-19 patients as well as in hypertensive COVID-19 patients.

2. Methods

2.1. Study design and participants

This cross-sectional retrospective study was reviewed and approved by the Institutional Review Board (IRB) of our institute and local ethics committee (IR.AJAUMS.REC.1399.22), and due to the study's retrospective design, the written informed consent was waived. All COVID-19-infected patients with a positive rRT-PCR who were admitted to our tertiary referral hospitals (Imam Khomeini Hospital Complex (IKHC) and AJA 501 hospital) in Tehran, Iran between January 2021 and May 2021 and had an on-admission chest CT scan were included. Exclusion criteria were: (a) patients with an uncertain outcome; and (b) incomplete required medical data: including past medical and drug history and on-admission vital signs. All hospital or ICU admission criteria, treatment regimens, and discharge criteria were based on the most recent edition of the relevant national guidelines. The adverse outcomes of interest in our study were: (a) the extent of PI; (b) ICU admission; and (c) in-hospital mortality.

2.2. Data collection

All the following data were recorded: (a) demographic data: age (year) and sex; (b) on-admission vital signs: oxygen saturation (SpO2, %), respiratory rate (RR, per minute), systolic and diastolic blood pressure (BP, mmHg), pulse rate (PR, per minute), and temperature (°C); (c) comorbidities: HTN, DM, and immunocompromised conditions (patients with cancer treated with chemoradiation therapy, hereditary or acquired immunodeficiency diseases, transplant, or long-term corticosteroid usage); (d) use of ACEI and/or ARB medications; and (e) adverse events: ICU admission or death.

2.3. Image acquisition and interpretation

All CT images were acquired on-admission with full inspiration in the supine position with no contrast injection. All CT scans were obtained on a 16-slice (Siemens SOMATOM Emotion, Erlangen, Germany) multi-detector CT scanner. CT parameters were set at tube current 70 mAs, tube voltage 130 kVp, slice width 5 mm, beam collimation 1.2 mm, and tube rotation time 0.6 seconds; slices were reconstructed with a lung B70f sharp kernel and a mediastinum B20f smooth kernel (Siemens Healthineers, Erlangen, Germany), along with coronal and sagittal multiplanar reconstructions, with a 1.2 mm reconstructed slice thickness.

Chest CT images were independently assessed by two board-certified diagnostic radiologists who were blinded to the clinical data of the patients. To measure inter-rater reliability, the intraclass correlation coefficient (ICC) was determined. If the ICC was less than 0.8, any discrepancy in image interpretation was resolved by consensus. If the ICC was higher than 0.8, the values provided by the radiologist with more experience were considered. To determine the severity of PI, a semi-quantitative scoring method was used. GGO and consolidation were evaluated in all five lobes of the lung. Each lobe was given a score from 0 to 5 based on its percentage of involvement (0: no involvement, 1: ≤5%, 2: 6–25%, 3: 26–50%, 4: 51–75%, and 5: >76%). Each lobe has a maximum score of 5 points; hence, the overall score varies from 0 to 25 (16, 17).

2.4. Statistical analysis

All the statistical analyses were performed in the SPSS for Windows (Version 16, Chicago, IL, USA). Frequency (percentage) and mean (standard deviation (SD)) were reported as qualitative and quantitative variables, respectively. The Kolmogorov–Smirnov two-sample test was used to determine the data's normality. Association analyses were performed using either t-test, Man–Whitney U test, or Chi-square test. ICC—two-way mixed, single measures, absolute agreement—was used to evaluate the inter-rater reliability of two radiologists' measurements. Multivariable binary logistic regression with enter method was performed to adjust for possible confounders.

3. Results

A total of 893 participants were enrolled in the current study. The mean age was 58.6 ± 15.4 years, and women (522 (58.4%)) comprised the most participants. Among them, 368 (41.2%) participants had HTN, and treatment with ACEI/ARB was reported in 183 (20.5%) participants. Among all participants, 409 (45.8%) participants required ICU admission, and 259 (29%) participants succumbed to death (Table 1). Of note, there was an excellent agreement between two radiologists (ICC= 0.91, P < 0.001).

Our analysis indicated that patients on ACEI/ARB were older (63.4 ± 14.6 vs. 57.4 ± 15.4 years; P < 0.001) and had higher rates of HTN (89.1% vs. 28.9%; P < 0.001), DM (47.0% vs. 33.0%; P < 0.001). Systolic (131.9 ± 22.9 vs. 122.9 ±19.9; P < 0.001) and diastolic (79.7 ±15.1 vs. 75.7 ±12.5; P = 0.005) BP were significantly higher in the participants who received ACEI-ARB; however, PR (93.0 ± 18.3 vs. 96.6 ± 17.9; P = 0.047), RR (23.3 ± 4.9 vs. 24.5 ± 6.5; P = 0.028), and temperature (37.3 ± 0.9 vs. 37.6 0.9; P < 0.001) were significantly lower in those patients. We found that patients who received ACEI/ARB were less likely to progress critical disease and experienced

Table 1 demographic and clinical variables between two groups of ACEI/ARB users

Variable	All n=893	ACEI/ARB		P-value
		Yes (n=183)	No (n=710)	
	N (%) / mean±SD			
Age	58.6 ± 15.4	63.4 ± 14.6	57.4 ± 15.4	< 0.001
Sex (M)	371 (41.5)	71 (38.8)	300 (42.3)	0.398
Comorbidities				
HTN	368 (41.2)	163 (89.1)	205 (28.9)	< 0.001
DM	320 (35.8)	86 (47.0)	234 (33.0)	< 0.001
Immunocompromised	105 (11.8)	24 (13.1)	81 (11.4)	0.523
Vital signs				
SpO2	85.5 ± 9.9	86.3 ±10.7	85.3 ± 9.6	0.252
Systolic BP	124.4 ± 20.7	131.9 ± 22.9	122.9 ±19.9	< 0.001
Diastolic BP	76.3 ± 13.0	79.7 ±15.1	75.7 ±12.5	0.005
PR	95.9 ± 18.0	93.0 ± 18.3	96.6 ± 17.9	0.047
RR	24.3 ± 6.2	23.3 ± 4.9	24.5 ± 6.5	0.028
Temperature	37.5 ± 0.9	37.3 ± 0.9	37.6 0.9	0.001
Outcome				
Pulmonary involvement score	9.5 ± 5.3	9.4 ± 5.6	9.5 ± 5.2	0.921
ICU admission	409 (45.8)	70 (38.3)	339 (47.7)	0.022
Death	259 (29.0)	29 (15.8)	230 (32.4)	< 0.001

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; HTN: hypertension; DM: diabetes mellitus; BP: blood pressure; ICU: intensive care unit.

Table 2 results of multivariable regression analysis for death and ICU endpoints.

Variable	Death model		P-value	ICU model		P-value
	Exp(B)	95%CI		Exp(B)	95%CI	
All patients						
ACE/ARB (reference: no)	0.23	0.14 – 0.38	<0.001	0.49	0.32 – 0.73	0.001
Age	1.03	1.02 – 1.04	<0.001	1.02	1.01 – 1.03	<0.001
Sex (reference: male)	1.08	0.79 – 1.48	0.627	1.22	0.92 – 1.62	0.172
HTN (reference: no)	1.85	1.29 – 2.65	0.001	1.18	0.84 – 1.66	0.337
DM (reference: no)	0.67	0.48 – 0.94	0.020	1.05	0.78 – 1.41	0.760
Immunocompromised (reference: no)	1.40	0.88 – 2.23	0.149	2.17	1.40 – 3.34	<0.001
Patients with HTN						
ACE/ARB (reference: no)	0.28	0.17 – 0.46	<0.001	0.51	0.33 – 0.79	0.003
Age	1.02	1.007 – 1.04	0.006	1.04	1.02 – 1.05	<0.001
Sex (reference: male)	1.05	0.65 – 1.70	0.841	1.18	0.76 – 1.83	0.464
DM (reference: no)	0.59	0.36 – 0.95	0.031	1.05	0.68 – 1.63	0.820
Immunocompromised (reference: no)	0.44	0.17 – 1.18	0.102	0.75	0.35 – 1.62	0.464

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; HTN: hypertension; DM: diabetes mellitus; ICU: intensive care unit.

significantly lower ICU admission (P = 0.022) and death (P < 0.001) (Table 1). On multivariate analysis controlling for age, sex, and comorbidities, this relationship remained statistically significant for death (odds ratio (OR): 0.23, 95% CI: [0.14-0.38], P < 0.001) and ICU admission (OR: 0.49, 95% CI: [0.32-0.73], P = 0.001) (Table 2).

Further analysis on hypertensive COVID-19 patients revealed that those using ACE/ARB drugs experienced fewer adverse events (Table 3). On multivariable analysis adjusting for age, sex, and comorbidities, this relationship remained statistically significant for death (OR: 0.28, 95% CI: [0.17-0.46], P < 0.001) and ICU admission (OR: 0.51, 95% CI: [0.33-0.79], P = 0.003) (Table 2).

The severity of PI showed no difference between ACEI/ARB users and nonusers in all patients (9.4 ± 5.6 vs. 9.5 ± 5.2; P = 0.921) and hypertensive patients (9.6 ± 5.8 vs. 9.4 ± 4.9; P = 0.750) diagnosed with COVID-19.

4. Discussion

The possibility of a link between chronic RAS inhibitor therapy and severity of COVID-19 disease has been widely discussed. Although there is a common consensus that the upregulation of ACE2 receptors results in a higher probability of infection by SARS-CoV-2 (1), its effect on disease progression and development of adverse events remains uncertain.

Table 3 demographic and clinical variables between two groups of ACEI/ARB users in patients with hypertension

Variable	All n=368	ACEI/ARB		P-value
		Yes (n=163)	No (n=205)	
		N (%) / mean±SD		
Age	63.9 ± 14.0	63.7 ± 15.0	64.2 ± 13.3	0.702
Sex (M)	164 (44.6)	65 (39.9)	99 (48.3)	0.107
Comorbidities				
DM	178 (48.4)	82 (50.3)	96 (46.8)	0.507
Immunocompromised	33 (9.0)	20 (12.3)	13 (6.3)	0.048
Vital signs				
SpO2	85.6 ± 10.0	86.5 ±10.9	84.9 ± 9.1	0.148
Systolic BP	128.2 ± 21.4	131.6 ± 22.4	126.3 ±20.6	0.063
Diastolic BP	77.9 ± 13.6	80.0 ±15.0	76.7 ±12.6	0.070
PR	93.5 ± 16.5	93.9 ± 18.0	93.2 ± 15.5	0.740
RR	23.8 ± 4.9	23.2 ± 5.0	24.2 ± 4.9	0.065
Temperature	37.4 ± 0.9	37.2 ± 1.0	37.5 ± 0.8	0.042
Outcome				
Pulmonary involvement score	9.5 ± 5.3	9.6 ± 5.8	9.4 ± 4.9	0.750
ICU admission	174 (47.3)	62 (38.0)	112 (54.6)	0.002
Death	119 (32.3)	29 (17.8)	90 (43.9)	< 0.001

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; DM: diabetes mellitus; BP: blood pressure; ICU: intensive care unit.

Efforts have been taken to clear this relationship to establish a common protocol for treating hypertensive patients during the current outbreak. Previously published studies found that patients on ACEI/ARB are more vulnerable to being infected by SARS-CoV-2 in the general population. A recent meta-analysis demonstrated that ACEI/ARB usage has been linked to an increased risk of SARS-COV2 infection (OR: 1.20 [1.07-1.33]) among the general population. In hypertensive population or after correcting for HTN in the general population, however, no significant correlation was seen (18). Despite this, there is no agreement on the impact of ACEI/ARB medications on the progression of COVID-19 disease. We realized that participants who received ACEI/ARB experienced significantly fewer adverse outcomes. In line with our findings, a large study on 1128 adult COVID-19 patients with hypertension revealed that patients on ACEI/ARB had a lower risk of COVID-19 mortality than those who were not on ACEI/ARB (OR: 0.37 [0.15–0.89]) (10). Another case-control study found that the ACEI/ARB group had a lower proportion of ICU-admitted patients (9.3 percent vs. 22.9 percent) and a lower mortality rate (4.7 percent vs. 13.3 percent) than the non-ACEI/ARB inhibitors group (19). Similarly, a previous study on 1200 COVID-19 patients detected a significantly lower risk of severe COVID-19 infection in patients who received ACEI/ARB (OR: 0.63 [0.47-0.84]) after adjustment for age, sex, and comorbidities (20). Consistently, adverse events, including invasive mechanical ventilation and death, were significantly higher in ACEI/ARB users compared to ACEI/ARB nonusers (21). However, a recent systematic review and meta-analysis revealed no significant link between ACEI/ARB usage and adverse outcomes (18).

Taken together, it seems difficult to draw a firm conclusion regarding the net effect of ACEI/ARB medications as they have a dual effect on COVID-19 infection. Although ACEI/ARB users are more likely to become infected with COVID-19, they are less susceptible to develop critical diseases requiring intensive care. This is the first study to look into the link between ACEI/ARB usage and the extent of PI. Although ACEI/ARB users experienced fewer adverse outcomes, the severity of PI was not significantly different between two groups in both all included patients and hypertensive patients. Therefore, despite the confirmed prognostic value of the extent of PI in predicting the outcome (22), it appears that ACEI/ARB usage leads to better outcomes through a different mechanism. There is a notion that elevated ACE2 activity may boost the transformation of ACE2 to angiotensin, a peptide with putative anti-inflammatory properties. Consistently, the patients on ACEI/ARB had significantly lower levels of inflammatory indicators, including C-reactive protein (CRP), procalcitonin, and IL-6 (23). Besides, downregulation of ACE2 after SARS-CoV-2 contamination is claimed to cause acute pulmonary injury, indicating a protective feature of ACE2 upregulation and ACEI/ARB medications in COVID-19 (24).

Our findings support the continued use of ACEI/ARB in SARS-CoV-2-infected hypertensive individuals. As stated by the American Heart Association (AHA), the Heart Failure Society of America (HFSA), and the American College of Car-

diology (ACC), and another announcement from the International Society of Hypertension (10, 25). However, our study has several limitations. Drawing a conclusion might be limited by the retrospective nature of the study design, the sample size, or selection bias. We just included hospitalized patients, so the results of ACEI/ARB usage in the general population might be different. Laboratory testing, notably inflammatory indicators, were left out. To better understand the link between ACEI/ARB medicines and outcome in COVID-19 and possibly relevant underlying processes, large-scale multi-centric prospective studies using randomized controlled trial design are necessary in ethnically and geographically varied cohorts. These efforts might ultimately result in developing novel treatment medications against ACE2 receptor in the management of COVID-19 patients without influencing blood pressure.

5. Limitations

Our findings should be interpreted in light of several limitations. This was a retrospective study and causal relationship cannot be concluded. Besides, we enrolled hospitalized COVID-19 patients and our findings cannot be extrapolated to the general population. Lastly, we did not include the laboratory tests as co-variables and this study was conducted before national vaccination program (26) and future prospective studies are required to confirm our findings.

6. Conclusion

In conclusion, we found significantly lower critical disease and death in patients on ACEI/ARB, which remained statistically significant after adjusting for age, sex, and comorbidities. However, the severity of PI was not significantly different between the two groups.

7. Declarations

7.1. Acknowledgment

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7.2. Authors' contribution

Conception and design: MM, NA, SM, BS; Acquisition of data, analysis, and interpretation: MM, HB, FS, BS; Drafting or revising the manuscript critically and final approval of the manuscript: all authors.

7.3. Conflict of Interest

The authors of this manuscript declare conflicts of interest.

7.4. Funding

None to declare.

References

1. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271–80.e8.
2. Igase M, Kohara K, Nagai T, Miki T, Ferrario CM. Increased expression of angiotensin converting enzyme 2 in conjunction with reduction of neointima by angiotensin II type 1 receptor blockade. Hypertens Res. 2008;31(3):553-9.
3. Babaniamansour S, Atarodi A, Babaniamansour P, Firouzabadi MD, Majidi M, Karkon-Shayan S. Clinical Findings and Prognosis of COVID-19 Patients with Benign Prostatic Hyperplasia: A Case Series. J Biomed Res Environ Sci. 2021;2(5):328-32.
4. Jalali A, Karimialavijeh E, Babaniamansour P, Aliniagerdroudbari E, Babaniamansour S. Predicting the 30-day Adverse Outcomes of Non-Critical New-Onset COVID-19 Patients in Emergency Departments based on their Lung CT Scan Findings; A Pilot Study for Derivation an Emergency Scoring Tool. Front Emerg Med. 2021;5(4):e40.
5. Abkhoo A, Shaker E, Mehrabinejad M-M, Azadbakht J, Sadighi N, Salahshour F. Factors Predicting Outcome in Intensive Care Unit-Admitted COVID-19 Patients: Using Clinical, Laboratory, and Radiologic Characteristics. Crit Care Res Pract. 2021;2021:9941570.
6. Yazdi NA, Seyedalinaghi S, Jafari F, Jafari S, Hasannezad M, Koochak HE, et al. Predictors of The Chest CT Score in COVID-19 Patients: A Cross-Sectional Study. Virol J. 2021;18(1):225.
7. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nat Med. 2005;11(8):875-9.
8. Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol. 2020;17(6):613–20.
9. Dalan R, Ang LW, Tan WY, Fong SW, Tay WC, Chan YH, et al. The association of hypertension and diabetes pharmacotherapy with COVID-19 severity and immune signatures: an observational study. Eur Heart J Cardiovasc Pharmacother. 2021;7(3):e48-51.
10. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. 2020;126(12):1671-81.
11. Zhou F, Liu YM, Xie J, Li H, Lei F, Yang H, et al. Comparative impacts of ACE (angiotensin-converting enzyme) inhibitors versus angiotensin II receptor blockers on the risk of COVID-19 mortality. Hypertension. 2020;76(2):e15-e7.

12. Liabeuf S, Moragny J, Bennis Y, Batteux B, Brochot E, Schmit JL, et al. Association between renin–angiotensin system inhibitors and COVID-19 complications. Eur Heart J Cardiovasc Pharmacother. 2021;7(5):426-34.
13. Selçuk M, Çınar T, Keskin M, Çiçek V, Kılıç Ş, Kenan B, et al. Is the use of ACE inb/ARBs associated with higher in-hospital mortality in Covid-19 pneumonia patients? Clin Exp Hypertens. 2020;42(8):738-42.
14. Lee HW, Yoon CH, Jang EJ, Lee CH. Renin-angiotensin system blocker and outcomes of COVID-19: a systematic review and meta-analysis. Thorax. 2021;76(5):479-86.
15. Bavishi C, Whelton PK, Mancia G, Corrao G, Messerli FH. Renin–angiotensin-system inhibitors and all-cause mortality in patients with COVID-19: a systematic review and meta-analysis of observational studies. J Hypertens. 2021;39(4):784-94.
16. Feng Z, Yu Q, Yao S, Luo L, Zhou W, Mao X, et al. Early prediction of disease progression in COVID-19 pneumonia patients with chest CT and clinical characteristics. Nat Commun. 2020;11:4968.
17. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID-19). Radiology. 2020;295(3):715-21.
18. Ma Z, Wang MP, Liu L, Yu S, Wu TR, Zhao L, et al. Does taking an angiotensin inhibitor increase the risk for COVID-19?–a systematic review and meta-analysis. Aging (Albany NY). 2021;13(8):10853.
19. Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, et al. Effects of angiotensin II receptor blockers and ACE (angiotensin-converting enzyme) inhibitors on virus infection, inflammatory status, and clinical outcomes in patients with COVID-19 and hypertension: a single-center retrospective study. Hypertension. 2020;76(1):51-8.
20. Bean DM, Kraljevic Z, Searle T, Bendayan R, Pickles A, Folarin A, et al. Treatment with ACE-inhibitors is associated with less severe disease with SARS-Covid-19 infection in a multi-site UK acute Hospital Trust. MedRxiv. 2020.
21. Tan ND, Qiu Y, Xing XB, Ghosh S, Chen MH, Mao R. Associations between angiotensin-converting enzyme inhibitors and Angiotensin II Receptor blocker use, gastrointestinal symptoms, and mortality among patients with COVID-19. Gastroenterology. 2020;159(3):1170-2. e1.
22. Salahshour F, Mehrabinejad M-M, Toosi MN, Gity M, Ghanaati H, Shakiba M, et al. Clinical and chest CT features as a predictive tool for COVID-19 clinical progress: introducing a novel semi-quantitative scoring system. Eur Radiol. 2021;31(7):5178-88.
23. Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, et al. Effects of ARBs and ACEIs on virus infection, inflammatory status and clinical outcomes in COVID-19 patients with hypertension: a single center retrospective study. Hypertension. 2020;76(1):51-8.
24. Diaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. J Travel Med. 2020:taaa041.
25. Bozkurt B, Kovacs R, Harrington B. Joint HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. J Card Fail. 2020;26(5):370.
26. Mehrabi Nejad MM, Moosaie F, Dehghanbanadaki H, Haji Ghadery A, Shabani M, Tabary M, et al. Immunogenicity of COVID-19 mRNA vaccines in immunocompromised patients: a systematic review and meta-analysis. Eur J Med Res. 2022;27:23.