Renin-Angiotensin-Aldosterone System Inhibitors and COVID-19: A Meta-Analysis and Systematic Review

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Abstract

Introduction

Increased virulence, the severity of illness, and mortality have all been hypothesized with respect to angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) use in coronavirus disease 2019 (COVID-19) infection. Our study aims to assess whether ACEi/ARB use in patients with COVID-19 conferred worsened severity of illness or increased mortality. Additionally, we explore the possibility of an unearthed protective benefit due to their interruption of the RAS signaling pathway as observed in cardiovascular diseases.

Methods

The Cochrane Library, MEDLINE, and EMBASE were searched for studies relevant to COVID-19 severity, mortality, and inflammation in the context of ACEi/ARB use. Eight studies were included with a total of 17,943 patients, 4,292 (23.9%) of which were taking an ACEi or an ARB. The study population was 47.9% female and the average age across all studies was 65. The studies chosen had a sample size of at least 100 patients.

Results

Mortality outcomes were assessed in six studies and showed no significant difference in mortality among the ACEi/ARB and control groups (odds ratio [OR]: 0.99, 95%CI: 0.48-2.04). Seven studies assessed the severity of COVID-19 and showed no statistically significant difference in disease severity when comparing the ACEi/ARB group to the control group (odds ratio [OR]: 1.30, 95% CI 0.87-1.94). Four studies reported the length of stay with no significant difference between the ACEi/ARB groups as compared to non-users. Four studies included inflammatory markers C-reactive protein (CRP) and D-Dimer, which were noted to be consistently lower in the ACEi/ARB groups when compared to control groups, however, this was not statistically significant.

Conclusion

Our study found no significant difference in mortality, severity of illness, or length of stay between ACEi/ARB users and non-users with COVID-19 infection. These results support the continuation of ACEi and ARBs in the setting of COVID-19 as advised by the American College of Cardiology (ACC)/American Heart Association (AHA). The decrease in CRP and D-dimer suggests a possible protective effect related to ACEi/ARB use in COVID-19, however, more studies with larger sample sizes are needed to establish this effect.

Introduction

In December of 2019, the world was awakened to the news that a new virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had been isolated and was spreading within mainland China. By March of 2020, this virus was present worldwide and the coronavirus disease 2019 (COVID-19) pandemic had started. It was a perfect storm of globalization with a new, highly infectious coronavirus that sparked a cascade of scientific thoughts, opinions, and hypotheses. The topics ranged from prevention and treatment to potential cures of this novel disease. One of the most intriguing subjects revolved around angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) due to both SARS-COV-2 and ACEi/ARB’s relation to the renin-angiotensin-aldosterone signaling pathway (RAAS). The potential for increased virulence, the severity of illness, and mortality were postulated in a person who contracted SARS-CoV-2 and was being treated with an ACEi/ARB due to an upregulation of angiotensin-converting enzyme 2 (ACE2). SARS-CoV-2 uses ACE2 to gain entry to lung epithelial cells, thus promoting viral replication and...
in intracellular transmission [1]. Furthermore, an imbalance of the RAAS to Mas signaling pathway is currently thought to promote inflammation and fibrosis due to an eventual down-regulation of ACE2 after a SARS-CoV-2 infection. The combination of these mechanisms in the real world may be contributing to the acute lung injury we are observing with the current SARS-CoV-2 pandemic [2]. As ACEis and ARBs are among the most common anti-hypertensive medications prescribed, up to 48% of monotherapy prescriptions [3], these concerns led to an unclear scientific message on how to manage patients currently on these medications. Many of these patients were on these medications due to their demonstrated benefits in comorbid conditions, such as heart disease, heart failure, and chronic kidney disease, for which alternative medications are not yet available. However, data from various cohorts have demonstrated conflicting results about whether ACEi/ARB use is associated with increased severity or worsened outcomes in the setting of COVID-19 infection. Our meta-analysis aims to assess whether ACEi/ARB use in patients with COVID-19 conferred worsened severity or increased mortality, and the possibility that an unearthen protective benefit exists, as hypothesized by Li et al. [4], due to a negative feedback mechanism leading to increased angiotensin I levels.

Materials And Methods

MEDLINE, the Cochrane Library, and EMBASE were searched up to June 9, 2020. Only articles published in English were considered for inclusion. Furthermore, abstract data were excluded and only complete observational studies that underwent the peer-review process were included. The following Medical Subject Headings (MeSH) terms and keywords (including suffix variations of the root words) were used alone or in combination: Angiotensin-converting enzyme inhibitor(s)/ACEi, angiotensin II receptor blocker(s)/ARBs, COVID-19, SARS-CoV-2, coronavirus 2019, and 2019 novel coronavirus disease. Two investigators (Mohab Hassib and Steven Hamilton) independently assessed the identified titles for relevance. Absents were screened for all potentially relevant titles, and full papers were obtained for all relevant abstracts. The reference lists of the selected papers were also screened for articles that may have been missed in the initial search.

This meta-analysis was conducted and reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and followed a detailed, prespecified protocol that set out using the participants, intervention, control, outcome, study design (PICOS) structure.

Studies were considered for inclusion if they met the following criteria: The study subjects were patients with both laboratory-confirmed (polymerase chain reaction) COVID-19 [1]; the intervention group included patients who were taking an ACEi or ARB prior to hospitalization, which was continued or stopped during hospitalization [2]; the control group included patients who had not taken ACEi/ARB prior to or during hospitalization [3]; the studies reported the outcomes of COVID-19 infection, including mortality, intensive care unit (ICU) admission, invasive ventilation, and length of stay [4]; the minimum number of participants was 100 in the included studies to minimize bias [5].

We collected the following information by using a standardized data extraction form: last name of the first author, publication year, study design, number of patients, patient characteristics, inflammatory markers related to COVID-19, and outcomes. The primary outcome was defined as mortality. Secondary outcomes were ICU admission, invasive ventilation, and length of stay. Data were analyzed using Review Manager Software (RevMan version 5.3; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The results were expressed in terms of odds ratio (OR) and 95% confidence intervals (95% CI).

The I2 test and associated P values were used to assess the heterogeneity of the studies. Results ranged between 0% (i.e. no observed heterogeneity) and 100%, and I2 values >50% were used to define a significant degree of heterogeneity. P values < 0.10 according to the Cochrane Q test were considered statistically significant. All analyses were based on the random-effects model. The robustness of the meta-analysis for publication bias was assessed by various bias indicators, including the Egger’s test and the Begg’s test; P values less than 0.05 indicated publication bias.

Results

The total search included 191 studies, 169 of which were excluded after removing duplicates and reviewing the title and abstract. Subsequently, the full texts of 22 articles were reviewed. Of these, 14 articles were excluded due to non-English publication, ongoing trials, study retraction, inadequate sample size, and studies outside of the context of our analysis. A total of eight studies were included in the final meta-analysis, with a total of 17,943 patients in the study population (Figure 1). Of this study population, 4,292 (23.9%) patients were receiving an ACEi or ARB. The study population was 52.1% male and 47.9% female with an average age of 65.
FIGURE 1: Flow chart outlining study selection

All of the studies compared the mortality and clinical severity-related outcomes in COVID-19 patients on an ACEi or ARB with non-users. Unfortunately, there was no clear and uniform definition of the outcome of severity among these studies. Five studies (Tan et al. [5], Yang et al. [6], Gao et al. [7], Feng et al. [8], and Li et al. [4]) were conducted in China and defined the clinical severity of COVID-19 based on guidelines established by the National Health Commission of the People’s Republic of China (7th edition). In the majority of the studies, age and sex were matched in both the control and ACEi/ARB groups. Comorbidities, including coronary artery disease, hypertension, diabetes mellitus, and chronic kidney disease, were fairly distributed among both ACEi/ARB and control groups; such an observation helped minimize any confounding that may affect severity or mortality (Table 1).
| Study | Design | Country | Age | Sex | Sample Size | Hypertension | Diabetes mellitus | Cardiovascular disease | Respiratory disease | Cerebrovascular disease | Renal disease |
|-------|--------|---------|-----|-----|-------------|--------------|------------------|---------------------|-------------------|----------------------|--------------|
| Yang et al. 2020 | Retro | CHN | 52.3 | 65 | 67 | 135 | 43 | 83 | Diabetes mellitus 30.2, Chronic renal disease 0, Cardiovascular disease 18.8, Respiratory disease 7, Hepatic disease 7, Neurological disease 0.3 | Diabetes mellitus 30.1, Chronic renal disease 3.6, Cardiovascular disease 10.1, Respiratory disease 6.1, Neurological disease 7.2 |
| Mehta et al. 2020 | CS | USA | 45 | 64* | 53* | 1735 | 212 | 1533 | Diabetes mellitus 52, Coronary artery disease 22, Heart failure 16, Hypertension 94, Obsecity 50 | Diabetes Mellitus 36, Coronary artery disease 18, Heart failure 17, Hypertension 76, Respiratory disease 13, Obsecity 53 |
| Mancia et al. 2020 | CS | ITA | 36.7 | 68** | 6272 | 286 | 3376 | N/A | N/A |
| Feng et al. 2020 | Retro | CHN | 45.1 | 53*** | 476 | 35 | 443 | Diabetes mellitus 10.3, Cardiovascular disease 6, Malignancy 3.5, Hypertension 20.3, Respiratory disease 4.6, Cerebrovascular disease 3.6, Co-morbidities for all COVID-positive patients | Hypertension 90.1 |
| Gao et al. 2020 | Retro | CHN | 46.9 | 62* | 64* | 2877 | 260 | 2677 | Hypertension 100, Diabetes Mellitus 30.1, Angina 17.5, Myocardial Infarction 0.5, Heart failure 3.5, COPD 3.6, Stroke 3.3, Renal failure 1.1 | Hypertension 100, Diabetes Mellitus 26.6, Angina 15.2, Myocardial Infarction 0.6, Heart failure 1.5, COPD 1.5, Stroke 3.6, Renal failure 1.0 |
| Jung et al. 2020 | CS | KOR | 50 | 62.3* | 41.3* | 5179 | 782 | 4117 | Hypertension 94, Diabetes mellitus 48, Myocardial Infarction 4, Heart failure 14, Chronic lung disease 40, Cerebrovascular disease 19, CKD 19 | Hypertension 100, Diabetes mellitus 11, Myocardial Infarction 1, Heart failure 3, Chronic lung disease 27, Cerebrovascular disease 4, CKD 3 |
| Li et al. 2020 | Retro | CHN | 53.7 | 65 | 67 | 1178 | 115 | 1083 | Hypertension 100, Diabetes mellitus 36.5, Coronary artery disease 20.5, Heart failure 4.3, Long disease 7, Cerebrovascular disease 20.5 | Hypertension 100, Diabetes mellitus 34.4, Coronary artery disease 14.2, Heart failure 2, Long disease 6, Cerebrovascular disease 16.6 |

**Note:** The tables and data are based on the extracted text from the provided image.
Mortality outcomes were assessed in six studies: Gao et al. [7], Jung et al. [9], Li et al. [4], Mehta et al. [10], Tan et al. [5], and Yang et al. [6]. In Gao et al. [7], Tan et al. [5], and Yang et al. [6], a lower mortality event rate was observed in the ACEi/ARB group as compared to the control group, with an odds ratio of 0.62 [95% CI 0.21-1.85], 0.17 [95% CI 0.02-1.38], and 0.32 [95% CI 0.07-1.51], respectively. In contrast, Jung et al. [9] and Mehta et al. [10] showed a higher mortality event rate in the ACEi/ARB group as compared to the control group with an odds ratio of 2.87 [95% CI 1.82-4.52] and 1.69 [0.77-3.71], respectively. In a pooled analysis of six peer-reviewed studies, there was no statistical significance of mortality between the ACEi/ARB group as compared to the control group with an OR of 0.99 (95% CI = 0.48-2.04, I² = 77, P-value = 0.97) (Figure 2). There is possible minimal publication bias seen in Figure 3.
Association of the severity of COVID-19 between ACEi/ARB and the control group was assessed in seven studies: Feng et al. [8], Gao et al. [7], Jung et al. [9], Mancia et al. [11], Mehta et al. [10], Tan et al. [5], and Yang et al. [6]. There was no clear and uniform definition for severity outcome in these studies. In our study, we defined severe COVID-19 infection as ICU admission, use of mechanical ventilation, or septic shock. In a pooled analysis of seven peer-reviewed studies, the use of an ACEi/ARB showed no statistically significant association in disease severity versus non-users (OR = 1.30, 95% CI 0.87-1.94 I2 = 69 and P-value = 0.20), which is portrayed in Figure 4. There is a possible minimal publication bias seen in Figure 5.
FIGURE 5: Funnel plot depicting publication bias for studies evaluating clinical severity based on Chinese guidelines in COVID-19 patients on an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)

COVID-19=coronavirus disease 2019

Four studies reported the length of stay. Tan et al. [5] and Li et al. [4] reported the length of stay as a median while Yang et al. [6] and Feng et al. [8] reported it as a mean. There was no difference in overall length of stay between the ACEi/ARB groups as compared to non-users, which can be seen in Table 2. The exception to this was the study by Feng et al. [8], which showed a lower overall length of stay in comparison to Tan et al. [5] and Yang et al. [6].

| Study            | ACEi/ARB group | Non-ACEI/ARB group | Overall length of stay |
|------------------|----------------|--------------------|------------------------|
| Tan et. al 2020* (5) | 33             | 36.5               | N/A                    |
| Yang et. al 2020 (6) | 35.2±12.8      | 37.5±12.3          | 36.7 +/-12.4           |
| Feng et. al 2020 (8) | N/A            | N/A                | 16 (12-24)             |
| Li et. al 2020* (4)  | 19             | N/A                | N/A                    |

TABLE 2: Comparison of overall length stay in COVID-19 patients on an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) vs. non-users

*Median

COVID-19=coronavirus disease 2019

There was no significant difference in the levels of C-reactive protein (CRP) and D-dimer in the ACEi/ARB groups as compared to control groups, as seen in Table 3. Although Yang et al. [6] did show a lower CRP level in ACEi/ARB as compared to control with a P-value of < 0.49, other studies failed to show similar findings.
TABLE 3: Comparison of inflammatory markers COVID-19 patients on an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) vs. non-users.

*Median
CRP=C-Reactive Protein; COVID-19=coronavirus disease 2019

| Study          | CRP            | D-dimer         |
|----------------|----------------|-----------------|
|                | ACEI/ARB Group | Control Group   | ACEI/ARB Group | Control Group |
| Tan et. al 2020* (5) | 23.97 (4-43) (n=31) | 24 (6.7-62.5) (n=69) | 0.76 (0.26-2.39) (n=31) | 0.96 (0.58-0.21) (n=31) |
| Yang et. al 2020* (6) | 11.5 (4.0–58.2) (n=43) | 33.9 (5.1–119.2) (n=83) | 0.40 (0.30–0.61) (n=43) | 0.47 (0.29–1.82) (n=31) |
| Gao et. al 2020 (7) | 2.72 (1.18-11.67) | 3.18 (1.07-12.29) | 0.45 (0.27-0.94) | 0.53. (0.27- 1.06) |
| Li et. al 2020 (4) | 2.1 (0.3 - 5.2) | 2.6 (0.4 - 6.0) | 0.7 (0.4 - 1.6) | 1.7 (0.3 - 2.5) |

Discussion

Despite the physiological basis that underlies concerns for the use of ACEi/ARBs in the context of COVID-19 infection, our study found no significant difference in mortality, severity, or length of stay between patients with ACEi/ARB exposure and those without.

We included eight studies with a minimum sample size of 100 participants, which allowed us to analyze 17943 patients. Our findings, while having moderate to high heterogeneity, have been in line with other recently published data, which also did not reveal a signal for harm associated with exposure to ACEi/ARBs in COVID-19 infection [12-13]. These results further support the AHA, ACC, Centers for Disease Control and Prevention (CDC), and World Health Organization position statements that ACEi/ARBs should be continued in COVID-19 infection in patients already taking them at the time of diagnosis unless another indication for discontinuation is present, other than SARS-COV-2 positivity.

Much of the concern involving SARS-COV-2 and ACEi/ARBs revolves around RAAS signaling imbalance causing inflammation due to ATR1 activation. Studies performed by Hayiroglu et al. [14], Gormez et al. [15], and Al-Samkari et al. [16] have revealed a linear relationship with inflammatory markers and severity of illness. Therefore, potential treatment targets for this virus may revolve around limiting RAAS activation. This led researchers, including us, to look into the available data to see if there is an association with ACEi/ARB use and a possibility of lower levels of inflammation due to their interactions within the RAAS signaling pathway. Our results, which consisted of data from four of the eight studies, showed a consistent decrease in both D-dimer and CRP levels in ACEi/ARB-exposed patients as compared to controls. These differences were not statistically significant but if the linear relationship between inflammation and severity of illness is true then our study would support the notion that ACEi/ARB use for RAAS blockade may be beneficial in patients with COVID-19 infection. Zhang et al.’s study [17], which studied patients taking ACEi/ARBs for hypertension, a significant decrease in severity and mortality was observed, which supports our conclusion.

There was no difference in overall length of stay between the ACEi/ARB groups compared to the control groups, with the exception of the study by Feng et al. [8], which showed a lower overall length of stay in comparison to Tan et al. [5] and Yang et al. [6]. This may be due to smaller sample size or a younger patient population with a mean age of 55 in Feng et al.’s study [8]. Further studies are therefore required to demonstrate any possibility of a difference in length of stay with ACEi/ARB users with COVID-19 infection.

There are a number of potential limitations of our study. One, there was no differentiation between ACEi and ARBs with regards to the outcomes measured; the studies we analyzed grouped the use of ACEi and ARBs as a single entity. Though these medications are usually grouped together and used synonymously in practice, they have different modes of action and if studied individually in the context of COVID-19 could yield different outcomes, which is potentially an area for further research. Currently, there is conflicting data on this topic, as Flacco et al.’s study [18] suggested that results did not differ when ACEis and ARBs were analyzed separately versus together in this context, whereas Pranata et al.’s study [19] specifically found that the ARB group showed decreased mortality but not the ACEi group. A second limitation is the heterogeneity of the definition of severe COVID-19 infection among the studies analyzed. For example, Mehta et al. [10] described severe infection as ICU admission or use of mechanical ventilation, whereas Mancia et al. described severe disease as ICU admission or death [11]. This discordance is expected among studies, which led us to construct our own definition of severe COVID-19 infection to be used as an outcome. The aim was to accurately represent severe COVID-19 infection across all studies chosen for our analysis, however, some
patients from our chosen studies will have not met our study’s criteria for severe infection. Lastly, while we showed a decrease in inflammatory markers in our ACEi/ARB-exposed group, this finding likely relied on an included study by Yang et al. [6], and, therefore, the true correlation of our findings to clinical practice should be taken more as a means to guide further research rather than change current practice.

Conclusions

Our study found no significant difference in mortality, severity, or length of stay between ACEI/ARB users and non-users with COVID-19 infection and therefore supports the continuation of ACEIs and ARBs in the setting of COVID-19. The decrease in CRP and D-dimer may suggest a protective effect related to ACEi/ARB use in COVID-19; however, more studies with larger sample sizes are needed to establish this effect.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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References

1. Hoffmann M, Kleine-Weber H, Schroeder S, et al.: SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020, 16:271-280. 10.1016/j.cell.2020.02.052
2. D’ardes B, Boccatonda A, Rossi I, Guagnano MT, Santilli F, Cipollone F, Bucci M: COVID-19 and RAS: unravelling an unclear relationship. Int J Mol Sci. 2020, 17:5005. 10.3390/ijms21085005
3. Suchard MA, Schuemie MJ, Krumholz HM, et al.: Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. Lancet. 2019, 16:1816-1826. 10.1016/S0140-6736(19)32317-7
4. Li J, Wang X, Chen J, Zhang H, Deng A: Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. JAMA Cardiol. 2020, 18:825-830. 10.1001/jamacardio.2020.1624
5. Tan N-D, Qiu Y, Xing X-hun, Ghoosh 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, 18:1170-1172. 10.1053/j.gastro.2020.05.054
6. Yang G, Tan Z, Zhou L, 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, 18:51-58. 10.1161/HYPERTENSIONAHA.120.15143
7. Gao C, Gao C, Cai Y, et al.: Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. Eur Heart J. 2020, 22:2058-2066. 10.1093/eurheartj/ehaa433
8. Feng Y, Ling Y, Bai T, et al.: COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med. 2020, 18:1380-1388. 10.1164/rccm.202002-0445OC
9. Jung S-Y, Choi JC, You S-H, Kim W-Y: Association of renin-angiotensin-aldosterone system inhibitors with coronavirus disease 2019 (COVID-19)-related outcomes in Korea: a nationwide population-based cohort study. Clin Infect Dis. 2020, 18:2121-2128. 10.1093/cid/cigaa24
10. Mehta N, Kalra A, Nowacki AS, et al.: Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020, 18:1020-1026. 10.1001/jamacardio.2020.1855
11. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G: Renin-angiotensin-aldosterone system blockers and the risk of COVID-19. N Engl J Med. 2020, 25:2451-2440. 10.1056/NEJMoa2006925
12. Fosbøl EL, Butt JH, Østergaard L, et al.: Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. JAMA. 2020, 14:1668-177. 10.1001/jama.2020.11301
13. Usman MS, Siddiqui TJ, Khan MS, et al.: A meta-analysis of the relationship between renin-angiotensin-aldosterone system inhibitors and COVID-19. Am J Cardiol. 2020, 130:159-161. 10.1016/j.amjcard.2020.05.038
14. Hayrinen MI, Cinat T, Tekkens AI: Fibrinogen and D-dimer variances and anticoagulation recommendations in COVID-19: current literature review. Rev Assoc Med Bras. 2020, 66:842-848. 10.1590/1806-982x.66.842
15. Gormez S, Ekiciibasi E, Degirmencigou A, et al.: Association between renin-angiotensin-aldosterone system inhibitor treatment, neutrophil-lymphocyte ratio, D-dimer and clinical severity of COVID-19 in hospitalized patients: a multicenter, observational study. J Hum Hypertens. 2020, [Epub]: 10.1038/s41371-020-00405-3
16. Al-Samkari H, Karp Leaf RS, Dzik WH, et al.: COVID-19 and coagulation: bleeding and thrombotic
manifestations of SARS-CoV-2 infection. Blood. 2020, 18:489-500. 10.1182/blood.2020006520
17. Zhang P, Zhu L, Cai 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, 12:1671-1681. 10.1161/CIRCRESAHA.120.317154
18. Flacco ME, Acuti Martellucci C, Bravi F, et al.: Treatment with ACE inhibitors or ARBs and risk of severe/lethal COVID-19: a meta-analysis. Heart. 2020, 19:1519-1524. 10.1136/heartjnl-2020-317336
19. Pranata R, Permana H, Huang I, et al.: The use of renin angiotensin system inhibitor on mortality in patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Diabetes Metab Syndr. 2020, 18:983-990. 10.1016/j.dsx.2020.06.047