Subject category: Hypertension

Mortality and Pre-Hospitalization use of Renin-Angiotensin System Inhibitors in Hypertensive COVID-19 Patients

Running title: Chen et al.; Mortality and RAS inhibitors in COVID-19

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Abstract

Background: There has been significant controversy regarding the effects of pre-hospitalization use of renin-angiotensin system (RAS) inhibitors on the prognosis of hypertensive COVID-19 patients.

Methods and Results: We retrospectively assessed 2,297 hospitalized COVID-19 patients at Tongji Hospital in Wuhan, China, from January 10th to March 30th, 2020; and identified 1,182 patients with known hypertension on pre-hospitalization therapy. We compared the baseline characteristics and in-hospital mortality between hypertensive patients taking RAS inhibitors (N=355) versus non-RAS inhibitors (N=827). Of the 1,182 hypertensive patients (median age 68 years, 49.1% male), 12/355 (3.4%) patients died in the RAS inhibitors group vs. 95/827 (11.5%) patients in the non-RAS inhibitors group (p<0.0001). Adjusted hazard ratio for mortality was 0.28 (95% CI 0.15-0.52, p<0.0001) at 45 days in the RAS inhibitors group compared with non-RAS inhibitors group. Similar findings were observed when patients taking angiotensin receptor blockers (N=289) or angiotensin converting enzyme inhibitors (N=66) were separately compared with non-RAS inhibitors group. The RAS inhibitors group compared with non-RAS inhibitors group had lower levels of C-reactive protein (median 13.5 vs. 24.4 pg/mL; p=0.007) and interleukin-6 (median 6.0 vs. 8.5 pg/mL; p=0.026) on admission. The protective effect of RAS inhibitors on mortality was confirmed in a meta-analysis of published data when our data were added to previous studies (odd ratio 0.44, 95% CI 0.29–0.65, p<0.0001).

Conclusions: In a large single center retrospective analysis we observed a protective effect of pre-hospitalization use of RAS inhibitors on mortality in hypertensive COVID-19 patients; which might be associated with reduced inflammatory response.

Key words: COVID-19; angiotensin converting enzyme-2, angiotensin converting enzyme inhibitors; angiotensin receptor blockers; severe acute respiratory syndrome coronavirus-2

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Clinical Perspective

What is new?

- Reduced mortality has been observed in hypertensive COVID-19 patients taking renin-angiotensin system (RAS) inhibitors before hospitalization compared with those not treated with these medications.
- A similar effect on mortality was found in a subanalysis comparing patients taking angiotensin receptor blockers or angiotensin converting enzyme inhibitors versus non-RAS inhibitors group.
- RAS inhibitors were associated with reduced inflammatory markers, suggesting an explanation to mortality reduction.

What are the clinical implications?

- This retrospective single-center study can further reassure hypertensive patients on RAS inhibitors that they are not at increased risk of mortality if infected by severe acute respiratory syndrome coronavirus 2 compared with patients taking other classes of antihypertensive drugs.
- These results can open the debate if RAS inhibitors can be the drugs of choice for hypertensive patients during the COVID-19 pandemic, even if RAS inhibitors cannot be interpreted as COVID-19 treatment based on these retrospective analyses.

Non-standard Abbreviations and Acronyms

ACE, aminopeptidase angiotensin-converting enzyme; ACEi, angiotensin converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; BMI, body mass index; CHD, chronic heart disease; CI, confidence interval; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; DIC, disseminated intravascular coagulation; HR, hazard ratios; hs-cTnI, high sensitivity cardiac troponin I; ICU, intensive care unit; IL, interleukin; IMV,
invasive mechanical ventilation; KM, Kaplan-Meier; OR, odds ratio; RAS, MODS, multiorgan dysfunction syndrome; NT-proBNP; N-terminal pro-B type natriuretic peptide; Renin-angiotensin system; RR, respiratory rate; SARS-CoV, severe acute respiratory syndrome coronavirus; SD, standard deviation; TNF, tumor-necrosis factor.
The ongoing outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV)-2 has spread worldwide. Hypertension is a common co-morbidity in COVID-19 patients, reported from 15 to 56.6% of cases,1-6 and correlates increased severity of infection and mortality.2,5,7 Renin-angiotensin system (RAS) inhibitors, including angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), are first-line medications for hypertension management.8,9 However, there is a significant debate about the safety of using RAS inhibitors for the COVID-19 patients with hypertension.10-12 These concerns have stemmed from SARS-CoV-2 entering human cells by binding of its viral spike protein to the membrane-bound form of the aminopeptidase angiotensin-converting enzyme (ACE)-2.13 ACE2 plays a critical role in RAS, with pre-clinical data,14 suggesting that ACEi and ARB may up-regulate ACE2 expression, thus increasing the availability of target molecules for SARS-CoV-2 and potentially increasing SARS-CoV-2 infectivity and virulence.10 Alternatively, RAS inhibitors might benefit COVID-19 patients by reducing pulmonary inflammation through the ACE2 action.10, 15 While recent data from North American and Italy suggest no association between ACEi or ARB use and COVID-19 test positivity,16-19 uncertainty remains on the association between RAS inhibitors use and in-hospital mortality.20 Initial clinical data from 4 series of hypertensive COVID-19 patients in Wuhan and Shenzhen, China, including 1,658 individuals reported inconclusive results.1, 3, 21 The largest of these studies reported lower mortality in patients taking ACEi/ARB compared with patients without ACEi/ARB use.1 However, the other three studies observed no significant difference in mortality between patients treated with RAS inhibitors and those who did not.3, 21 This inconsistence might be because of the different severity of the enrolled COVID-19 patients or the numbers of patients under ACEi/ARB, ranging from 17 to 188.1,3,21,22 More recent studies assessed the association among five classes of anti-hypertensive drugs (ACEi, ARB, beta-blockers, calcium-channel blockers and thiazide diuretic) and the risk of intensive care unit (ICU) admission, invasive mechanical ventilation (IMV) or death among 2,573 hypertensive COVID-19 patients in New York. No substantial increase (predefined as an absolute 10% difference) in the likelihood in the risk of ICU admission or IMV or death in association with these classes of antihypertensive medications were found.17 On the other hand, an international study including 8,910 COVID-19 patients from 169 hospitals worldwide found a reduced risk of in-hospital death associated with ACEi, but not with ARB on multivariate logistic-regression analysis.6
Definitive data on the safety or potential benefit of RAS inhibitors are of paramount importance due to the severity of COVID-19 especially in hypertensive patients. Thus, we further investigated the association between RAS inhibitors and mortality in a large single-center retrospective study including hospitalized COVID-19 patients at Tongji Hospital in Wuhan, China. We also reported the association with mortality analyzing separately patients taking ACEi and ARB.
Methods
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study design and participants
The study was approved by the Ethics Review Board of Tongji Hospital and Tongji Medical College (IRB ID: TJ-IRB20200229) and conformed to the principles of the Declaration of Helsinki. The requirement for written informed consent was waived by the Ethics committee because of the retrospective and anonymous nature of the data, collected during an emerging infectious disease as reported in other hospitals in Wuhan.23
A total of 2,297 patients with COVID-19 admitted from January 10th to March 30th, 2020, were enrolled in the current study. The clinical follow-up was terminated on April 24th, 2020, when the last COVID-19 patient was discharged. Thus, all patients were followed up to in-hospital death or discharge. The diagnosis of COVID-19 was based on symptoms, positive real-time polymerase chain reaction for SARS-CoV-2 on nasopharyngeal swab and radiological findings of interstitial pneumonia on computed tomography (CT) scan. Accordingly to the Guidance for Corona Virus Disease 2019 (5th edition) released by the National Health Commission of China1,24, hospitalized patients included in the analysis had moderate (symptoms plus radiological confirmed pneumonia), severe (presenting with shortness of breath, respiratory rate [RR] ≥30 counts/min, oxygen saturation <93% at rest or the ratio between arterial partial pressure of oxygen and fraction of inspired oxygen ≤300 mmHg), or critical disease (requiring IMV, in shock or multiorgan failure).

Data Collection
All clinical data were extracted from patients’ electronic medical records and were carefully checked by two experienced physicians (C.C and F.W.). Personal information, medical history, and coexisting comorbidities included chronic heart disease (CHD) including coronary artery disease and chronic heart failure, diabetes, and chronic kidney disease (CKD) were self-reported or evaluated by the attending physician on admission. CKD was diagnosed on admission if estimated glomerular filtration rate was <60 mL/min/1.73 m². Vital signs, symptoms, laboratory test, and radiological findings were recorded on admission.
Statistical analysis

The Kolmogorov-Smirnov test was performed to determine the distribution of continuous data. Continuous values were shown as mean ± standard deviation (SD) if normally distributed, or medians and first to third quartile (Q1-Q3) if not normally distributed. Student’s t test was used to compare the differences in normally distributed continuous values, Mann Whitney test was used to evaluate the differences in non-normal distributed continuous values. Categorical variables were described as counts and percentages, $\chi^2$ test and Fisher test were used to evaluate the differences in categorical variables, as appropriate. These tests were used to compare baseline characteristics between hypertensive patients (N=1,267) vs. non-hypertensive patients (N=1,019), RAS inhibitors group (N=355) vs. non-RAS inhibitors group (N=827), and finally patients on ARB (N=289) vs. non-RAS inhibitors group, and patients on ACEi (N=66) vs. non-RAS inhibitors group.

The association between RAS inhibitors group vs. non-RAS inhibitors group, and between ARBs and ACEi vs. non-RAS inhibitors group and in-hospital mortality was evaluated by Kaplan-Meier (KM) survival curves and the log-rank test. Adjusted hazard ratios (HR) and 95% confidence interval (CI) were determined by multivariable Cox proportional hazards regression analyses. The proportional-hazards assumption was examined by including an interaction term between the group and log-transformed follow-up time, and extended Cox models where group was included as a time-varying covariate was used if a violation of the proportional-hazards assumption. The covariates of age, sex, history of CHD, diabetes mellitus, creatinine levels, use of calcium channel blockers, beta-blockers, diuretics, antidiabetic drugs and lipid lowering drugs were used at 30 and 45 days of follow up. All statistical analyses were performed using SPSS 21.0 software. Methods regarding systematic review and metanalysis (Table S1) are reported in Data S1.

Results

We identified 1,278 COVID-19 patients who carried a diagnosis of hypertension on admission, representing 55.6% of all admitted patients, and 1,019 normotensive COVID-19 patients. Among hypertensive COVID-19 patients, 1,182 (92.5%) patients were taking at least one antihypertensive drug on admission, which was continued during hospitalization, whereas in 11 (0.9%) patients, antihypertensive therapy was stopped, and another 85 (6.7%) patients were diagnosed with hypertension by the attending physician on admission. To assess the role that antihypertensives may play in the prognosis of COVID-19, we focused on 1,182 patients with hypertension diagnosis prior to admission on antihypertensive medications before admission. We assessed
whether ACE inhibitors or ARB preferentially accounted for the improved prognosis by comparing patients taking ARB and patients taking ACEi (RAS inhibitors group, N=355, 30.0%) to non-RAS inhibitors group (N=827, 70.0%) (Figure S1).

Clinical characteristics and outcomes of hypertensive vs. non-hypertensive COVID-19 patients

As shown in Table 1, the median age of patients with hypertension was significantly higher than patients without hypertension (median 67 vs. 54 years, p<0.0001), while the proportion of male were 49.5% vs. 45.4% (p=0.054). Overall, the hypertensive patients had an increased cardiovascular risk profile with a higher body mass index (BMI), and a greater prevalence of CHD, diabetes and CKD. On chest CT there were more severe radiological findings, such as lung consolidations in hypertensive patients. On laboratory tests there was an increase of markers of cardiac injury such as high sensitivity cardiac troponin I (hs-cTnI) and N-terminal pro-B type natriuretic peptide (NT-proBNP) and inflammatory markers, such as C-reactive protein (CRP) (median 21.5 vs. 6.8 pg/mL; p<0.0001) and interleukin (IL)-6 (median 8.0 vs. 3.2 pg/mL; p<0.0001) in hypertensive patients compared non-hypertensive patients. The outcomes of hypertensive patients were worse compared to non-hypertensive patients, both in term of in-hospital mortality (10.2% vs. 5.4% in hypertensive vs. non-hypertensive patients, p<0.0001, Table 1), and other complications such as need for IMV, multiorgan dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), septic shock, acute myocardial infarction (AMI), congestive heart failure, and cerebral hemorrhage.

Clinical characteristics and outcomes of hypertensive COVID-19 patients taking RAS inhibitors vs. patients non-taking RAS inhibitors

In Table 2 clinical characteristics of hypertensive COVID-19 patients taking anti-hypertensive drugs before hospitalization are reported. When comparing RAS inhibitors vs. non-RAS inhibitors group, the RAS inhibitors group had similar median age (68 vs. 68 years, p=0.73) and proportion of male (49.6% vs. 48.9%, p=0.82). The RAS inhibitors group had a higher prevalence of CHD (24.5% vs. 14.4% in non-RAS inhibitors group, p<0.0001), while the BMI, and prevalence of diabetes and CKD was similar compared to non-RAS inhibitors group. There were no significant differences in the proportion of radiological abnormal findings on chest CT and some laboratory findings in RAS inhibitors compared to non-RAS inhibitors group, including hs-cTnI levels (8.6
vs. 7.5 pg/mL in RAS vs. non-RAS inhibitors group; p=0.84), NT-proBNP levels (178 vs. 201 pg/mL in RAS vs. non-RAS inhibitors group; p=0.59). However, RAS inhibitors compared to non-RAS inhibitors group had a significantly reduced levels of inflammatory markers (CRP: 13.5 vs. 24.4 pg/mL; p=0.007; IL-6: 6.0 vs. 8.5 pg/mL; p=0.026, compared to non-RAS inhibitors group) and d-dimer (0.76 vs. 1.05 μg/mL, p=0.0003 compared to non-RAS inhibitors group).

Importantly, RAS inhibitors group had more favorable prognosis compared to non-RAS inhibitors group, both in terms of in-hospital mortality (3.4% vs. 11.5% in hypertensive vs. non-hypertensive patients, p<0.0001; Table 2), and other complications such as need for IMV (11.3% vs. 16.8%, p=0.015), disseminated intravascular coagulation (DIC, 0.0% vs. 1.6%, p=0.018) and cerebral hemorrhage (0.3% vs. 1.7%, p=0.047) in RAS inhibitors group vs. non-RAS inhibitors group. When the HR for mortality was adjusted, RAS inhibitors vs. non-RAS inhibitors group still showed a reduced mortality both at 30 days (HR 0.28; 95% CI 0.15-0.53, p<0.0001) and 45 days (HR 0.28; 95% CI 0.15-0.52, p<0.0001) of follow (Figure 1A-B).

Finally, we did not observe differences in the relative proportion of immediate causes of death between hypertensive COVID-19 patients taking RAS inhibitors vs. patients with non-RAS inhibitors. Specifically, most of deaths were related to COVID-19 pneumonia (Table 3).

Clinical characteristics and outcomes of hypertensive COVID-19 patients taking ARB or ACEi vs. non-RAS inhibitors group

As shown in Table 4, patients on ARB vs. non-RAS inhibitors group had similar median age (68 vs. 68 years, p=0.86), and proportion of male (47.1% vs. 48.9%, p=0.60). The ARB group had a higher prevalence of CHD (23.2% vs. 14.4% in non-RAS inhibitors group, p=0.0005), while the BMI, and prevalence of diabetes and CKD was similar compared to non-RAS inhibitors group. On chest CT there was no significant difference in the proportion of radiological findings in ARB vs. non-RAS inhibitors group. Likewise, laboratory tests showed no difference in the majority of results, including hs-cTnI levels or creatinine levels; however, ARB group showed reduced levels of inflammatory markers (CRP: 11.8 vs. 24.4 pg/mL; p=0.006; IL-6: 6.0 vs. 8.5 pg/mL; p=0.017, and tumor-necrosis factor [TNF]-α 8.4 vs. 8.8 pg/mL, p=0.038 compared to non-RAS inhibitors group) and d-dimer (0.73 vs. 1.05 μg/mL, p=0.0001 compared to non-RAS inhibitors group). The outcomes of ARB group were more favorable compared to non-RAS inhibitors group, in term of in-hospital mortality (3.1% vs. 11.5% compared to non-RAS inhibitors group, p<0.0001; Table 4), as well as the need for IMV (9.0% vs. 16.8%, p=0.001), and DIC (0.0% vs. 1.6%, p=0.027).
When the HR for mortality was adjusted, ARB group vs. non-RAS inhibitors group still showed a reduced mortality both at 30 days (HR 0.26; 95% CI 0.13-0.55, p=0.0004) and 45 days (HR 0.28; 95% CI 0.14-0.55, p=0.0003) of follow (Figure 1C-D).

Finally, patients on ACEi vs. non-RAS inhibitors group had similar median age (65 vs. 68 years, p=0.18) with a trend for a higher proportion of male (60.6% vs. 48.9%, p=0.066) respectively (Table 4). The ACEi group had a higher prevalence of CHD (30.3% vs. 14.4% in non-RAS inhibitors group, p=0.0006), while the prevalence of diabetes and CKD was similar compared to non-RAS inhibitors group. On chest CT there was a higher prevalence of patch shadow lesions (89.4% vs. 73.2%, p=0.004) vs. non-RAS inhibitors group. On laboratory tests there was a significant increase of creatinine levels (77 vs. 70 mmol/L, p=0.024), and markers of cardiac injury such as hs-cTnI (11.7 vs. 7.5 pg/mL, p=0.047) in ACEi group vs. non-RAS inhibitors group, while no significant differences were observed in the levels of inflammatory markers and d-dimer. There was a trend for reduced mortality in the ACEi group compared to non-RAS inhibitors group (4.6% vs. 11.5%, p=0.082; Table 4), while a higher proportion of AMI (6.1% vs. 1.5%, p=0.025) and congestive heart failure (10.6% vs. 4.1%, p=0.026) were observed in the ACEi group vs. non-RAS inhibitors group. When the HR for mortality was adjusted, ACEi group vs. non-RAS inhibitors showed a trend at 30 days (HR 0.32; 95% CI 0.10-1.01, p=0.053), and a significant reduction in mortality at 45 days (HR 0.30; 95% CI 0.09-0.95, p=0.041) of follow up (Figure 1E-F).

**Metanalysis**

Literature search identified 393 studies. Amongst these, 380 were excluded during screening based on title and abstract. Of the 13 remaining studies, 8 were excluded at a second verification phase (Figure S2) and 5 observational, retrospective studies including a total of 1,658 hypertensive COVID-19 patients were included in the analysis.\(^1,3,20-22\) Four-hundred thirty-one out of 1,754 subjects were treated with RAS inhibitors, which yielded a pooled rate of 38.3% (95% CI 21.4-55.3%). When data from the present work were included, the total number of patients rose to 2,936. Among these subjects, 786 were on RAS inhibitors, for a pooled rate of RAS inhibitors use of 36.5% (95% CI 25.41-47.7%). The use of RAS inhibitors was associated with a reduced risk of COVID-19 associated mortality when only previously published papers were analyzed (odds ratio [OR] 0.54, 95% CI 0.37-0.79; p=0.002; Figure 2A). Low heterogeneity was evident for this analysis (I\(^2\)=0%). The protective effect of RAS inhibitors with respect to mortality was reinforced.
when data from the present work were also included (OR 0.44, 95% CI 0.29-0.65; p<0.0001; Figure 2B). Moderate heterogeneity was present for this analysis ($I^2=27\%$).

**Discussion**

In this large single-center study, hypertensive patients on RAS inhibitors prior to hospitalization showed a significantly lower in-hospital mortality (3.4%) compared to patients non-taking RAS inhibitors (11.5%), despite the RAS inhibitors group having a higher prevalence of CHD. After adjustment for age, sex, pre-existing conditions and concurrent medications, pre-hospitalization use of RAS inhibitors still showed a significant decreased HR for mortality at 45 days. Of interest, patients on RAS inhibitors on admission presented with reduced markers of inflammation, and coagulation that have been previously associated with favorable prognosis.\textsuperscript{5} Pre-hospitalization use of RAS-inhibitors was also associated with reduced need for IMV, lower proportion of DIC and cerebral hemorrhage. Given the large number of patients taking RAS inhibitors in our study, we performed sub-analyses on patients taking ARB or ACEi and observed a similar beneficial effect on mortality at 45 days on patients taking either drug. This protective effect was less pronounced in the ACEi group although this could be due to lower number of patients being on ACEi compared to ARB. Finally, a meta-analysis, juxtaposing our results with previous studies, support the potential beneficial effects of pre-hospitalization use of RAS inhibitors on prognosis of hypertensive COVID-19 patients.\textsuperscript{1,3,21,22}

Most data on the association between the use of RAS inhibitors and mortality in hypertensive COVID-19 patients are derived from hospitals in Wuhan, China (Figure 2C). Specifically, a multicenter study coordinated by the Renmin hospital showed in-hospital mortality of 3.7% in the RAS inhibitors group vs. 9.8% in non-RAS inhibitors group, that was very closed to our findings.\textsuperscript{1} The results by Zhang et al. held true after propensity score-matched analysis.\textsuperscript{1} Here we utilize the larger number patients in our cohort (almost twice the number of patients on RAS inhibitors compared to the previous study) to further assess the individual benefit from ACEi and ARB. The previous study by Zhang et al.\textsuperscript{1} was based on 188 patients on ACEiARB, of which only 31 on ACEi, with data being derived from nine hospitals increasing the variability of the outcome related to the different recruiting sites. Still, other studies that have been done assessing the baseline risk of RAS inhibitors on hypertensive COVID-19 patients included even small number of patients (range of 17-115 patients on RAS inhibitors depending on the study).\textsuperscript{3,21,22} Partial confirmation of our findings is also derived by a multicenter international registry that reported an independent

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survival benefit among patients taking ACEi, but not with ARB, even if that study was not aimed
to compare specifically ACEi or ABR versus non-RAS inhibitors in hypertensive COVID-19
patients.6 Another interesting study from New York that investigated the association among five
classes of anti-hypertensive drugs (ACEi, ARB, beta-blockers, calcium-channel blockers and
thiazide diuretic) with the risk of IMV, admission in ICU or mortality found that calcium channel
blockers were significantly associated with this combined outcome (OR of 1.24, p=0.04) in a
multivariate logistic regression analysis after adjustment for demographic and comorbidities.17
ACEi and ARB were not associated with this combined outcome. Potential explanations for
different results can be the following: (1) in our study, the combination of antihypertensive drugs
and the use of calcium channel blockers (up to 81.3% vs. 36.2%, respectively) were more
frequently used compared to the study by Reynolds et al.,17 (2) there were also different
demographic characteristics (significantly increased BMI and higher racial diversity in the New
Yorker cohort), and proportion of comorbidities (greater proportion of patients with CHD, CKD,
and diabetes in the New Yorker cohort).
To further provide hypotheses for the protective effects of RAS inhibitors, we assessed biomarkers
of inflammation and coagulation in our patients. We observed that patients taking RAS inhibitors
have decreased levels of CRP, IL-6, and D-dimer, makers of inflammation and coagulation that
have been associated with prognosis in COVID-19 patients.5, 7 It must be noted that in our
hypertensive population these inflammatory markers as well as d-dimer were significantly
increased compared to non-hypertensive patients; in addition, mortality was significantly higher.
Even if we cannot completely rule out that the lower inflammatory response in patients with RAS
inhibitors in this retrospective analysis might be due to their relatively modest symptoms and
organ damage compared to non-RAS inhibitors group. Still, further research is needed, and other
possible hypotheses could account for the protection conferred by RAS inhibitors. It is possible
that chronic use of RAS inhibitors decreases the levels of angiotensin II, leading to lower the
expression of ACE2 on type II pneumocytes, decreasing viral entry and viral load.10 A decreased
viral load at the interface between alveoli and bloodstream could curtail the inflammatory and
coagulative responses often observed in COVID-19 patients leading to severe clinical
manifestations.5, 7 However, human data are lacking regarding the effects of RAS inhibitors on
lung-specific expression of ACE2,10 and our retrospective study cannot provide any evidence on
changes in ACE2 expression in the lungs. It is also possible that hypertensive patients have higher
levels of angiotensin II compared with non-hypertensive, leading to increased levels of ACE2,
potentially explaining a higher viral load in the lungs as trigger of a more florid inflammatory response and associated lung injury. Of note, patients in our cohort were taking RAS inhibitors, and they did not start these medications on admission. Thus, we cannot interfere that an acute administration of an ACEi or ARB can lead results observed in the present study. A trial of losartan among COVID-19 patients who have not previously received a RAS inhibitor and are hospitalized will try addressing this issue (NCT04312009).\textsuperscript{10}

A major limitation of our study is its observational and retrospective nature. In addition, the impact of combination of antihypertensive therapies cannot completely be controlled for even after multivariate adjustment. However, we were able to account potential changes in hypertensive treatment during hospitalization. Only in 11 patients were anti-hypertensive therapies stopped on admission. We excluded such patients in our analysis. Nevertheless, our study is the largest study to date to assess pre-hospitalization use of RAS inhibitors on prognosis in hypertensive COVID-19 patients.

In conclusion, in this large single center retrospective study, we reported a protective effect of pre-hospitalization use of RAS inhibitors on mortality compared with hypertensive COVID-19 patients non-taking RAS inhibitors. This observation holds true after multivariate adjustments and considering either the chronic use of ARB or ACEi compared with non-RAS inhibitors group. RAS inhibitors were associated with reduced inflammatory and coagulation markers, suggesting an explanation to mortality reduction. The clinical impact of the current finding is relevant. In fact, it can further reassure hypertensive patients on RAS inhibitors that they are not at increased risk of mortality if infected by SARS-CoV-2 compared with patients taking other classes of antihypertensive drugs.\textsuperscript{10} Finally, these results can open the debate if RAS inhibitors can be the drugs of choice for hypertensive patients during the COVID-19 pandemic, even if RAS inhibitors cannot be interpreted as COVID-19 treatment based on these retrospective analyses.

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Supplemental Material: Data S1, Table S1, Figures S1-S2.

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Table 1. Characteristics of COVID-19 patients with hypertension vs. without hypertension.

| Characteristics                         | All patients (n=2286) | Patients without hypertension (n=1019) | Patients with hypertension (n=1267) | P value |
|-----------------------------------------|-----------------------|---------------------------------------|-----------------------------------|---------|
| Demographics, median (Q1-Q3)            |                       |                                       |                                   |         |
| Age (y)                                 | 63 (51-71)            | 54 (40-64)                            | 67 (60-74)                        | <0.0001 |
| Male (%)                                | 1090/2286 (47.7%)     | 463/1019 (45.4%)                      | 627/1267 (49.5%)                  | 0.0540  |
| BMI (kg/m²)                             | 23.7 (21.5-25.5)      | 22.9 (21.1-24.9)                      | 24.0 (22.2-26.0)                  | <0.0001 |
| Personal history, no./total no. (%)     |                       |                                       |                                   |         |
| CHD (%)                                 | 240/2286 (10.5%)      | 22/1019 (2.2%)                        | 218/1267 (17.2%)                  | <0.0001 |
| Diabetes (%)                            | 355/2286 (15.5%)      | 73/1019 (7.2%)                        | 282/1267 (22.3%)                  | <0.0001 |
| CKD (%)                                 | 83/2286 (3.6%)        | 14/1019 (1.4%)                        | 69/1267 (5.5%)                    | <0.0001 |
| Vital signs on admission, median (Q1-Q3) |                       |                                       |                                   |         |
| RR (bpm)                                | 20 (20-22)            | 20 (20-21)                            | 20 (20-24)                        | <0.0001 |
| Heart rate (bpm)                        | 89 (80-100)           | 88 (80-99)                            | 90 (80-103)                       | 0.0096  |
| SBP (mmHg)                              | 138 (125-151)         | 120 (112-128)                         | 140 (125-152)                     | <0.0001 |
| DBP (mmHg)                              | 82 (74-92)            | 77 (70-81)                            | 83 (75-93)                        | <0.0001 |
| Signs and symptoms, no./total no. (%)   |                       |                                       |                                   |         |
| Fever                                   | 1596/2286 (69.81%)    | 742/1019 (72.82%)                     | 854/1267 (67.40%)                 | 0.0051  |
| Cough                                   | 1220/2286 (53.37%)    | 518/1019 (50.83%)                     | 702/1267 (55.41%)                 | 0.0294  |
| Dyspnea                                 | 740/2286 (32.37%)     | 293/1019 (28.75%)                     | 447/1267 (35.28%)                 | 0.0009  |
| Oxygen therapy                          | 1567/2286 (68.5%)     | 596/1019 (58.5%)                      | 971/1267 (76.6%)                  | <0.0001 |
| CT findings on admission, no./total no. (%) |                   |                                       |                                   |         |
| Ground-glass opacity                    | 1135/2286 (49.7%)     | 508/1019 (49.9%)                      | 627/1267 (49.5%)                  | 0.8620  |
| Patch shadow                            | 1648/2286 (72.1%)     | 717/1019 (70.4%)                      | 931/1267 (73.5%)                  | 0.0986  |
| Consolidation                           | 405/2286 (17.7%)      | 151/1019 (14.8%)                      | 254/1267 (20.1%)                  | 0.0011  |
| Pleural involved | 857/2286 (37.5%) | 335/1019 (32.9%) | 522/1267 (41.2%) | <0.0001 |
|------------------|------------------|------------------|------------------|---------|

**Laboratory data, median (Q1-Q3) or mean ± SD**

| WBC (*10^9/L) | 5.78 (4.56-7.47) | 5.47 (4.29-6.96) | 6.02 (4.78-7.91) | <0.0001 |
| Neut (*10^9/L) | 3.81 (2.70-5.42) | 3.41 (2.46-4.75) | 4.17 (2.98-6.00) | <0.0001 |
| Lymph (*10^9/L) | 1.18 (0.80-1.62) | 1.31 (0.89-1.76) | 1.08 (0.72-1.52) | <0.0001 |
| Hb (g/dL) | 12.7 (11.5-13.8) | 12.8 (11.7-14.0) | 12.6 (11.4-13.6) | <0.0001 |
| PLT (*10^9/L) | 219 (165-282) | 217 (168-273) | 220 (164-291) | 0.3548 |
| ALT (U/L) | 22 (14-37) | 21 (14-37) | 22 (15-37) | 0.2592 |
| AST (U/L) | 25 (18-36) | 23 (18-34) | 25 (19-37) | 0.0043 |
| Cr (mmol/L) | 68 (56-84) | 65 (54-78) | 71 (58-89) | <0.0001 |
| TC (mmol/L) | 3.77 (3.77-4.45) | 3.85 (3.27-4.54) | 3.69 (3.15-4.37) | <0.0001 |
| LDL (mmol/L) | 2.50 ± 0.85 | 2.57 ± 0.83 | 2.44 ± 0.86 | 0.0034 |
| K⁺ (mmol/L) | 4.17 (3.82-4.49) | 4.19 (3.90-4.47) | 4.14 (3.76-4.50) | 0.0291 |
| Glu (mmol/L) | 5.96 (5.17-7.58) | 5.58 (4.95-6.81) | 6.34 (5.36-8.18) | <0.0001 |
| D-Dimer (μg/mL) | 0.70 (0.34-1.71) | 0.50 (0.27-1.10) | 0.96 (0.44-2.16) | <0.0001 |

**Myocardial injury, median (Q1-Q3)**

| CK-MB (ng/mL) | 0.70 (0.40-1.30) | 0.50 (0.40-0.90) | 0.90 (0.50-1.60) | <0.0001 |
| hs-cTnI (pg/mL) | 4.90 (2.30-12.25) | 2.00 (1.90-4.20) | 7.70 (3.90-17.90) | <0.0001 |
| NT-proBNP (pg/mL) | 130 (47-429) | 53 (21-143) | 194 (74-616) | <0.0001 |

**Inflammatory factors, median (Q-Q3)**

| hs-CRP (pg/mL) | 13.1 (2.1-57.1) | 6.8 (1.2-39.8) | 21.5 (3.4-67.6) | <0.0001 |
| ESR (mm/H) | 28 (14-56) | 22 (10-43) | 37 (18-63) | <0.0001 |
| IL-6 (pg/mL) | 5.2 (2.1-20.9) | 3.2 (1.5-12.7) | 8.0 (3.1-26.4) | <0.0001 |
| TNF-α (pg/mL) | 8.0 (6.1-10.6) | 7.2 (5.5-9.3) | 8.8 (6.6-11.5) | <0.0001 |
| Outcomes, no./total no. (%) | 45-day | in-hospital | Mortality |
|-----------------------------|--------|-------------|-----------|
|                             | 184/2286 (8.1%) | 55/1019 (5.4%) | 129/1267 (10.2%) | <0.0001 |
| IMV                         | 259/2286 (11.3%) | 58/1019 (5.7%) | 201/1267 (15.9%) | <0.0001 |
| MODS                        | 50/2286 (2.2%) | 13/1019 (1.3%) | 37/1267 (2.9%) | 0.0075 |
| ARDS                        | 32/2286 (1.1%) | 4/1019 (0.4%) | 28/1267 (2.2%) | 0.0002 |
| Septic shock                | 48/2286 (2.1%) | 10/1019 (1.0%) | 38/1267 (3.0%) | 0.0008 |
| DIC                         | 23/2286 (1.0%) | 7/1019 (0.7%) | 16/1267 (1.3%) | 0.1703 |
| AMI                         | 19/2286 (0.8%) | 1/1019 (0.1%) | 18/1267 (1.4%) | 0.0005 |
| Congestive heart failure    | 66/2286 (2.9%) | 7/1019 (0.7%) | 59/1267 (4.7%) | <0.0001 |
| Cerebral hemorrhage         | 19/2286 (0.8%) | 3/1019 (0.3%) | 16/1267 (1.3%) | 0.0112 |
| Acute kidney injury         | 18/2286 (0.8%) | 4/1019 (0.4%) | 14/1267 (1.1%) | 0.0554 |

BMI indicates body mass index; CHD, chronic heart disease; CKD, chronic kidney disease; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; Neut, neutrophil; Lymph, lymphocyte; Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; TC, total cholesterol; LDL, low-density lipoprotein; K+, potassium; Glu, glucose; CK-MB, creatine kinase-MB; hs-cTnI, highly sensitive cardiac troponin I; NT-proBNP, N-terminal pro-natriuretic peptide; hs-CRP, highly sensitive C reaction protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α; IMV, invasive mechanical ventilation; MODS, multiple organ dysfunction syndrome; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; AMI, acute myocardial infarction. LDL are shown as mean ± SD, other data are shown as median (first to third quartile, Q1-Q3).
Table 2. The clinical characteristics and in-hospital outcome of hypertensive COVID-19 patients taking renin angiotensin system (RAS) inhibitors vs. patients non-taking RAS inhibitors drugs.

| Demographics, median (Q1-Q3) | Hypertension patients treated with antihypertensive drugs (n=1182) | RAS inhibitors group (n=355) | Non-RAS inhibitors group (n=827) | P value |
|------------------------------|---------------------------------------------------------------|-----------------------------|---------------------------------|---------|
| Age (y)                      | 68 (60-75)                                                   | 68 (59-75)                  | 68 (60-74)                      | 0.7269  |
| Male (%)                     | 580/1182 (49.1%)                                             | 176/355 (49.6%)             | 404/827 (48.9%)                 | 0.8189  |
| BMI (kg/m²)                  | 24.0 (22.1-26.0)                                            | 24.1 (21.6-26.0)            | 24.0 (22.3-26.0)                | 0.9231  |
| Personal history, no./total no. (%) |                                 |                             |                                 |         |
| CHD (%)                      | 206/1182 (17.4%)                                             | 87/355 (24.5%)              | 119/827 (14.4%)                 | < 0.0001|
| Diabetes (%)                 | 261/1182 (22.1%)                                             | 87/355 (24.5%)              | 174/827 (21.0%)                 | 0.1877  |
| CKD (%)                      | 62/1182 (5.3%)                                               | 19/355 (5.3%)               | 43/827 (5.2%)                   | 0.9141  |
| Vital signs on admission, median (Q1-Q3) or mean ± SD |                                 |                             |                                 |         |
| RR (bpm)                     | 20 (20-24)                                                   | 20 (20-23)                  | 20 (20-24)                      | 0.0850  |
| Heart rate (bpm)             | 89 (80-102)                                                  | 88 (78-101)                 | 90 (80-103)                     | 0.3134  |
| SBP (mmHg)                   | 139 ± 20                                                     | 139 ± 21                    | 139 ± 20                        | 0.8098  |
| DBP (mmHg)                   | 82 (74-92)                                                   | 83 (73-90)                  | 82 (74-93)                      | 0.4974  |
| Signs and symptoms, no./total no. (%) |                                 |                             |                                 |         |
| Fever                        | 798/1182 (67.51%)                                            | 123/355 (65.35%)            | 566/827 (68.44%)                | 0.2987  |
| Cough                        | 646/1182 (54.65%)                                            | 191/355 (53.80%)            | 455/827 (55.01%)                | 0.7004  |
| Dyspnea                      | 413/1182 (34.94%)                                            | 139/355 (39.15%)            | 274/827 (33.13%)                | 0.0465  |
| Oxygen therapy               | 903/1182 (76.4%)                                             | 253/355 (71.3%)             | 650/827 (78.6%)                 | 0.0065  |
| CT findings on admission, no./total no. (%) |                                 |                             |                                 |         |
| Ground-glass                 | 598/1182 (52.2%)                                             | 166/355 (46.8%)             | 432/827 (34.1%)                 | 0.0843  |
|opacity          | 879/1182 (74.4%) | 274/355 (77.2%) | 605/827 (73.2%) | 0.1460   
|------------|----------------|----------------|----------------|---------|
|Patch shadow | 254/1182 (20.7%) | 68/355 (19.2%) | 177/827 (21.4%) | 0.3822  
|Consolidation| 497/1182 (42.1%) | 158/355 (44.5%) | 339/827 (41.0%) | 0.2617  

|Laboratory data, median (Q1-Q3) or mean ± SD |
|---------------------------------------------|
|WBC (*10⁹/L)       | 6.00 (4.78-7.84) | 6.13 (4.82-7.80) | 5.97 (4.75-7.99) | 0.5389  
|Neut (*10⁹/L)      | 4.17 (2.98-5.95) | 4.12 (2.99-5.68) | 4.18 (2.96-5.99) | 0.8128  
|Lymph (*10⁹/L)     | 1.09 (0.73-1.52) | 1.18 (0.77-1.65) | 1.06 (0.72-1.48) | 0.0022  
|Hb (g/dL)          | 12.5 (11.4-13.6) | 12.7 (11.3-13.7) | 125 (11.4-13.6) | 0.3454  
|PLT (*10⁹/L)       | 220 (163-292)    | 219 (165-290)    | 222 (163-294)    | 0.9160  
|ALT (U/L)          | 22 (15-37)       | 23 (15.-43)      | 22 (15-35)       | 0.0752  
|AST (U/L)          | 25 (18-37)       | 25 (18-36)       | 25 (18-37)       | 0.4646  
|Cr (mmol/L)        | 71 (59-89)       | 72 (62-91)       | 70 (58-88)       | 0.0650  
|TC (mmol/L)        | 3.69 (3.16-4.36) | 3.71 (3.17-4.44) | 3.68 (3.15-4.31) | 0.7025  
|LDL (mmol/L)       | 2.38 (1.85-2.91) | 2.3 (1.73-2.90)  | 2.41 (1.89-2.91) | 0.1322  
|K⁺ (mmol/L)        | 4.17 ± 0.57      | 4.17 ± 0.49      | 4.15 ± 0.60      | 0.4399  
|Glu (mmol/L)       | 6.33 (5.36-8.09) | 6.36 (5.37-7.92) | 6.31 (5.36-8.19) | 0.7584  
|D-Dimer (μg/ml)    | 0.97 (40.4-2.12) | 0.76 (0.36-1.86) | 1.05 (0.48-2.25) | 0.0003  

|Myocardial injury, median (Q1-Q3) |
|----------------------------------|
|CK-MB (ng/mL)                    | 0.90 (0.50-1.60) | 1.00 (0.60-1.60) | 0.80 (0.50-1.50) | 0.0515  
|hsc-TnI (pg/mL)                  | 7.7 (4.0-17.5)   | 8.6 (3.9-16.8)   | 7.5 (4.1-17.8)   | 0.8378  
|NT-proBNP (pg/mL)                | 193 (74-598)     | 178 (70-617)     | 201 (75-596)     | 0.5929  

|Inflammatory factors, median (Q1-Q3) |
|-------------------------------------|
|hs-CRP (pg/mL)                      | 20.8 (3.3-66.9)  | 13.5 (2.8-52.1)  | 24.4 (3.6-71.5)  | 0.0071  
|ESR (mm/H)                          | 36 (18-63)       | 29 (17-54)       | 39 (19-66)       | 0.0093  

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|                     | IL-6 (pg/mL) | TNF-α (pg/mL) |  |  |
|---------------------|--------------|---------------|---|---|
|                     | 7.9 (3.1-26.2) | 6.0 (2.7-23.2) | 8.5 (3.3-27.8) | 0.0258 |
| Anti-inflammatory therapy, no./total no. (%) |  |  |  |  |
| ACEi                | 66/1182 (5.6%) | 66/355 (18.6%) | 0/827 (0.0%) | <0.0001 |
| ARB                 | 289/1182 (24.5%) | 289/355 (81.4%) | 0/827 (0.0%) | <0.0001 |
| CCB                 | 961/1182 (81.3%) | 256/355 (72.1%) | 705/827 (85.3%) | <0.0001 |
| Beta-blocker        | 388/1182 (32.8%) | 136/355 (38.3%) | 252/827 (30.5%) | 0.0085 |
| Alpha-blocker       | 21/1182 (1.8%) | 7/355 (2.0%) | 14/827 (1.7%) | 0.7393 |
| Diuretic            | 240/1182 (23.3%) | 107/355 (30.1%) | 133/827 (16.1%) | <0.0001 |
| Use of other chronic drugs, no./total no. (%) |  |  |  |  |
| Antidiabetic drugs  | 299/1182 (25.3%) | 112/355 (31.5%) | 187/827 (22.6%) | 0.0012 |
| Lipid lowering drug | 282/1182 (23.9%) | 124/355 (34.9%) | 158/827 (19.1%) | <0.0001 |
| Outcomes, no./total no. (%) |  |  |  |  |
| 45-day in-hospital  | 107/1182 (9.1%) | 12/355 (3.4%) | 95/827 (11.5%) | <0.0001 |
| Mortality           |  |  |  |  |
| IMV                 | 179/1182 (15.1%) | 40/355 (11.3%) | 139/827 (16.8%) | 0.0149 |
| MODS                | 31/1182 (2.6%) | 6/355 (1.7%) | 25/827 (3.0%) | 0.1887 |
| ARDS                | 26/1182 (2.2%) | 5/355 (1.4%) | 21/827 (2.5%) | 0.2243 |
| Septic shock        | 31/1182 (2.6%) | 8/355 (2.3%) | 23/827 (2.8%) | 0.6028 |
| DIC                 | 13/1182 (1.1%) | 0/355 (0.0%) | 13/827 (1.6%) | 0.0132 |
| AMI                 | 18/1182 (1.5%) | 6/355 (1.7%) | 12/827 (1.5%) | 0.7583 |
| Congestive heart failure | 55/1182 (4.7%) | 21/355 (5.9%) | 34/827 (4.1%) | 0.1770 |
| Cerebral hemorrhage | 15/1182 (1.3%) | 1/355 (0.3%) | 14/827 (1.7%) | 0.0490 |
| Acute kidney injury | 14/1182 (1.2%) | 2/355 (0.6%) | 12/827 (1.5%) | 0.2511 |

BMI indicates body mass index; CHD, chronic heart disease; CKD, chronic kidney disease; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; Neut, neutrophil; Lymph, lymphocyte; Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; TC, total cholesterol; LDL, low-density lipoprotein; K⁺, potassium; Glu, glucose; CK-MB, creatine kinase-MB; hs-cTnI, highly sensitive cardiac troponin I; NT-proBNP, N-terminal pro-natriuretic peptide; hs-CRP, highly sensitive C reaction protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; IMV, invasive mechanical ventilation; MODS, multiple organ dysfunction syndrome; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; AMI, acute myocardial infarction. SBP and K⁺ are shown as mean ± SD, other data are shown as median (first to third quartile, Q1-Q3).
Table 3. Immediate cause of death in hypertensive COVID-19 patients taking renin angiotensin system (RAS) inhibitors vs. patients non-taking RAS inhibitors drugs.

| Immediate cause of death in COVID-19 hypertensive patients no./total no. (%) | RAS inhibitors group (n=12) | Non-RAS inhibitors group (n=95) | P value |
|---|---|---|---|
| Pneumonia-related | 8/12 (66.7%) | 81/95 (85.3%) | 0.116 |
| Cardiovascular-related | 0/12 (0.0%) | 8/95 (8.4%) | 0.593 |
| Cerebrovascular-related | 2/12 (16.7%) | 3/95 (3.2%) | 0.096 |
| Other conditions | 2/12 (16.7%) | 3/95 (3.2%) | 0.096 |

Cardiovascular-related group includes acute myocardial infarction and acute heart failure; Other conditions group includes acute gastrointestinal bleeding, acute lymphocytic leukemia, acute renal failure, pulmonary embolism and severe aplastic anemia.
Table 4. The clinical characteristics of hypertensive COVID-19 patients treated with angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEi) comparing with patients non-taking renin angiotensin system inhibitors on admission.

| Demographics, median (Q1-Q3)          | Hypertensive patients | P value | Hypertensive patients | P value |
|---------------------------------------|-----------------------|---------|-----------------------|---------|
|                                       | treated with ARB      |         | treated with ACEi     |         |
|                                       | (n=289)               |         | (n=66)                |         |
| Age (y)                               | 68 (59-76)            | 0.8611  | 65 (60-71)            | 0.1798  |
| Male (%)                              | 136/289 (47.1%)       | 0.5997  | 40/66 (60.6%)         | 0.0661  |
| BMI (kg/m^2)                          | 24.3 (21.7-26.3)      | 0.5966  | 22.7 (21.6-24.2)      | 0.0714  |
| Personal history, no./total no. (%)   |                       |         |                       |         |
| CHD (%)                               | 67/289 (23.2%)        | 0.0005  | 20/66 (30.3%)         | 0.0006  |
| Diabetes (%)                          | 69/289 (23.9%)        | 0.3147  | 18/66 (27.3%)         | 0.2356  |
| CKD (%)                               | 13/289 (4.5%)         | 0.6383  | 6/66 (9.1%)           | 0.1664  |
| Vital signs on admission, median (Q1-Q3) or mean ± SD | |         | |         |
| RR (bpm)                              | 20 (20-23)            | 0.0756  | 20 (20-24)            | 0.6590  |
| Heart rate (bpm)                      | 88 (80-100)           | 0.4159  | 89 (76-102)           | 0.4319  |
| SBP (mmHg)                            | 140 ± 21*             | 0.3114  | 134 ± 19              | 0.0807  |
| DBP (mmHg)                            | 84 (75-92) *          | 0.8324  | 80 (68-88)            | 0.0209  |
| Signs and symptoms, no./total no. (%) |                       |         |                       |         |
| Fever                                 | 190/289 (65.7%)       | 0.3986  | 42/66 (63.6%)         | 0.4204  |
| Cough                                 | 153/289 (52.9%)       | 0.5416  | 38/66 (57.6%)         | 0.6876  |
| Dyspnea                               | 110/289 (38.1%)       | 0.1288  | 29/66 (43.9%)         | 0.0743  |
| Oxygen therapy                        | 207/289 (71.6%)       | 0.0157  | 46/66 (79.7%)         | 0.0933  |
| CT findings on admission, no./total no. (%) |                       |         |                       |         |
| Ground-glass                          | 132/289 (45.7%)       | 0.0548  | 34/66 (51.5%)         | 0.9100  |
| Feature                | Comparison | Value 1 (Median, Q1-Q3) | Value 2 (Median, Q1-Q3) | p-value |
|------------------------|------------|-------------------------|-------------------------|---------|
| Opacity                |            |                         |                         |         |
| Patch shadow           |            | 215/289 (74.4%) **      | 59/66 (89.4%)           | 0.0036  |
| Consolidation          |            | 53/289 (18.3%)          | 15/66 (22.7%)           | 0.8010  |
| Pleural lesions        |            | 131/289 (45.3%)         | 27/66 (40.9%)           | 0.9895  |
| Laboratory data, median (Q1-Q3) or mean ± SD | | | | |
| WBC (*10^9/L)          |            | 6.13 (4.79-7.77)        | 6.23 (5.11-9.32)        | 0.1534  |
| Neut (*10^9/L)         |            | 4.07 (2.96-5.66)        | 4.33 (3.17-6.49)        | 0.3479  |
| Lymph (*10^9/L)        |            | 1.19 (0.77-1.65)        | 1.15 (0.76-1.63)        | 0.2768  |
| Hb (g/dL)              |            | 12.7 (11.3-13.7)        | 12.9 (11.4-13.8)        | 0.3091  |
| PLT (*10^9/L)          |            | 222 (169-283)           | 215 (155-295)           | 0.7242  |
| ALT (U/L)              |            | 23 (14.00-41.00)        | 25 (16-44)              | 0.5334  |
| AST (U/L)              |            | 25 (18-36)              | 28 (19-39)              | 0.7242  |
| Cr (mmol/L)            |            | 71 (61-90)              | 77 (65-99)              | 0.0237  |
| TC (mmol/L)            |            | 3.71 (3.16-4.47)        | 3.73 (3.17-4.18)        | 0.7395  |
| LDL (mmol/L)           |            | 2.36 (1.74-2.97)        | 2.12 (1.71-2.79)        | 0.0447  |
| K⁺ (mmol/L)            |            | 4.17 ± 0.48             | 4.21 ± 0.53             | 0.3805  |
| Glu (mmol/L)           |            | 6.18 (5.32-7.83) **     | 7.18 (5.88-9.35)        | 0.0098  |
| D-Dimer (μg/ml)        |            | 0.73 (0.36-1.72)        | 0.86 (0.36-2.75)        | 0.6674  |
| Myocardial injury, median (Q1-Q3) | | | | |
| CK-MB (ng/ml)          |            | 1.0 (0.6-1.6)           | 1.1 (0.7-1.9)           | 0.0100  |
| hs-cTnI (pg/ml)        |            | 8.2 (3.8-16.1) *        | 11.7 (4.7-29.2)         | 0.0466  |
| NT-proBNP (pg/ml)      |            | 175 (69-542)            | 194 (75-1193)           | 0.2736  |
| Inflammatory factors, median (Q1-Q3) | | | | |
| hs-CRP (pg/ml)         |            | 11.8 (2.6-49.5)         | 17.5 (3.9-58.3)         | 0.4263  |
| ESR (mm/H)             |            | 30 (17-59)              | 26 (15-48)              | 0.0516  |
| IL-6 (pg/ml)           |            | 6.0 (2.7-20.9)          | 6.5 (2.6-26.3)          | 0.7041  |
|                          | 8.4 (6.3-10.9) | 9.0 (7.2-10.9) | 0.8086 |
|--------------------------|----------------|----------------|--------|
| **Anti-hypertensive therapy, no./total no. (%)** |                |                |        |
| ACEi                     | 0/289 (0.0%)   | 66/66 (100%)   |        |
| ARB                      | 289/289 (100%) | 0/66 (0.0%)    |        |
| CCB                      | 211/289 (73.0%)| <0.0001        | 45/66 (68.2%) | 0.0003 |
| Beta-blocker             | 102/289 (35.3%)| 0.1294         | 34/66 (51.5%) | 0.0004 |
| Alpha-blocker            | 4/289 (1.4%)   | 0.7198         | 3/66 (4.6%)   | 0.1245 |
| Diuretic                 | 79/289 (27.3%) | <0.0001        | 28/66 (42.4%) | <0.0001 |
| **Use of other chronic drugs, no./total no. (%)** |                |                |        |
| Antidiabetic drugs       | 89/289 (30.8%) | 23/66 (34.8%)  | 0.0241 |
| Lipid lowering drug      | 97/289 (33.6%) | <0.0001        | 27/66 (40.9%) | <0.0001 |
| **Outcomes, no./total no. (%)** |                |                |        |
| 45-day in-hospital       |                |                |        |
| Mortality                |                |                |        |
| IMV                      | 26/289 (9.0%) **| 0.0013         | 14/66 (21.2%) | 0.3608 |
| MODS                     | 4/289 (1.4%)   | 0.1317         | 2/66 (3.0%)   | 1.0000 |
| ARDS                     | 3/289 (1.0%)   | 0.1299         | 2/66 (3.0%)   | 0.6848 |
| Septic shock             | 6/289 (2.1%)   | 0.5167         | 2/66 (3.0%)   | 0.7067 |
| DIC                      | 0/289 (0.0%)   | 0.0266         | 0/66 (0.0%)   | 0.6147 |
| AMI                      | 2/289 (0.7%) **| 0.5388         | 4/66 (6.1%)   | 0.0252 |
| Congestive heart failure |                |                |        |
| Cerebral hemorrhage      |                |                |        |
| Acute kidney injury      |                |                |        |
BMI, body mass index; CHD, chronic heart disease; CKD, chronic kidney disease; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; Neut, neutrophil; Lymph, lymphocyte; Hb, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; TC, total cholesterol; LDL, low-density lipoprotein; K⁺, potassium; Glu, glucose; CK-MB, creatine kinase-MB; hs-cTnI, highly sensitive cardiac troponin I; NT-proBNP, N-terminal pro-natriuretic peptide; hs-CRP, highly sensitive C reaction protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α; IMV, invasive mechanical ventilation; MODS, multiple organ dysfunction syndrome; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; AMI, acute myocardial infarction.

SBP and K⁺ are shown as mean ± SD, other data are shown as median (first to third quartile, Q1-Q3).

Comparisons between hypertensive COVID-19 patients treated with ARB group and ACEi group were indicated as *P<0.05, **P<0.01, ***P<0.001, and ****P<0.0001.
Figure Legends:

Figure 1. Adjusted Kaplan Meier curves in renin angiotensin (RAS) inhibitors group versus non-RAS inhibitors groups and sub-analyses comparing patients taking angiotensin receptor blockers (ARB) or angiotensin receptor enzyme inhibitors (ACEi) compared with non-RAS inhibitors group. A) The 30 days in-hospital mortality in RAS inhibitors group vs. non-RAS inhibitors group adjusted for age, sex, chronic heart disease, diabetes mellitus, creatinine, use of antidiabetic, lipid lowering drugs, use of diuretics, and use of beta blockers and calcium channel blocker at 30 days B) and at 45 days. C) Similar analysis comparing patients taking ARB vs. non-RAS inhibitors group at 30 days D) and at 45 days. E) Similar analysis comparing patients taking ACEi vs. non-RAS inhibitors group at 30 days F) and at 45 days. Both of 30-day and 45-day survival curve didn’t violate Cox proportional hazards assumption. Adjusted hazard ratios (HR) and 95% confidence interval (CI) were determined by multivariable Cox proportional hazards regression analyses.

Figure 2. Forest plot displaying the Odds Ratio (OR) for mortality associated with Renin Angiotensin system (RAS) inhibition among hypertensive patients with coronavirus disease 2019 (COVID-19). A: previously published literature. Panel B: including data from the present work. C: Map of Wuhan city divided by the Yangtze river in China, showing the position of the hospitals where hypertensive COVID-19 patients have been enrolled. The study by Zhang et al. was a multicenter hospital where the Wuhan Renmin hospital was the coordinating center. The study by Meng et al. (N=42) included in the metanalysis was performed in Shenzhen city in China, and it is not represented in this map. The map is adapted from Google Maps.
### A

| Study or Subgroup | RAS inhibitors | Events | Total | No RAS inhibitors | Events | Total | Weight | M.H, Random, 95% CI | Odds Ratio M.H, Random, 95% CI |
|-------------------|----------------|--------|-------|-------------------|--------|-------|--------|-------------------|-----------------------------|
| Conversano 2020   | 21             | 68     | 13    | 20                | 17.8   | 0.52  | 0.21   | 1.27             |                             |
| Li, 2020          | 21             | 115    | 56    | 247               | 46.4   | 0.76  | 0.44   | 1.33             |                             |
| Meng, 2020        | 0              | 17     | 1     | 25                | 1.4    | 0.47  | 0.02   | 12.14            |                             |
| Yang, 2020        | 4              | 43     | 19    | 83                | 11.0   | 0.36  | 0.11   | 1.09             |                             |
| Zhang, 2020       | 7              | 168    | 92    | 940               | 23.5   | 0.36  | 0.16   | 0.79             |                             |
| **Total**         | **431**        |        | **1323** | **100.0%**     |         | 0.54  | 0.37   | 0.79             |                             |

**Total events:** 53

Heterogeneity: $\tau^2 = 0.00$, Chi$^2 = 3.17$, df = 4 ($P = 0.53$); $I^2 = 0$

Test for overall effect: $Z = 3.16$ ($P = 0.002$)

### B

| Study or Subgroup | RAS inhibitors | Events | Total | No RAS inhibitors | Events | Total | Weight | M.H, Random, 95% CI | Odds Ratio M.H, Random, 95% CI |
|-------------------|----------------|--------|-------|-------------------|--------|-------|--------|-------------------|-----------------------------|
| Chen, 2020        | 12             | 355    | 95    | 827               | 25.7   | 0.27  | 0.15   | 0.50             |                             |
| Conversano 2020   | 21             | 68     | 13    | 28                | 15.2   | 0.52  | 0.21   | 1.27             |                             |
| Li, 2020          | 21             | 115    | 56    | 247               | 20.6   | 0.76  | 0.44   | 1.33             |                             |
| Meng, 2020        | 0              | 17     | 1     | 25                | 1.5    | 0.47  | 0.02   | 12.14            |                             |
| Yang, 2020        | 4              | 43     | 19    | 83                | 10.3   | 0.35  | 0.11   | 1.09             |                             |
| Zhang, 2020       | 7              | 168    | 92    | 940               | 18.6   | 0.36  | 0.16   | 0.79             |                             |
| **Total**         | **786**        |        | **2150** | **100.0%**     |         | 0.44  | 0.29   | 0.65             |                             |

**Total events:** 65

Heterogeneity: $\tau^2 = 0.07$, Chi$^2 = 6.83$, df = 5 ($P = 0.23$); $I^2 = 27$

Test for overall effect: $Z = 4.04$ ($P < 0.0001$)

### C

**Chen et al. Wuhan Tongji Hospital**
Mortality in RAS inhibitors 3.4% vs. in non-RAS inhibitors 11.5%; $p < 0.0001$
**N=1182** hypertensive COVID19 patients

**Yang et al. Hubei Provincial Hospital of Traditional Chinese Medicine**
Mortality in RAS inhibitors 4.7% vs. in non-RAS inhibitors 13.3%; $p=0.22$
**N=126** hypertensive COVID19 patients

**Zhang et al. Wuhan Renmin Hospital**
Mortality in RAS inhibitors 3.7% vs. in non-RAS inhibitors 9.8%; $p=0.03$
(after adjustment)
**N= 1128** hypertensive COVID19 patients

**Li et al. Wuhan Central Hospital**
Mortality in RAS inhibitors 18.2% vs. in non-RAS inhibitors 24.3%; $p=0.41$
**N=362** hypertensive COVID19 patients
SUPPLEMENTAL MATERIAL
Data S1.

**Systematic Review and Meta-Analysis**

*Systematic search.* Two Authors (F.M. and E.A.) independently searched MEDLINE and Embase from their inception to June 3rd, 2020. Literature query search included the following combination of key words: “COVID-19”, “SARS-CoV-2”, “RAAS”, “ACEi” and “ARB”. Detailed queries can be found in Table S1. All published articles reporting mortality data among hypertensive COVID-19 patients on RAS inhibitors vs not treated with RAS inhibitors were included in the analysis. Two investigators (F.M., E.A.) independently extracted data on study design, patient characteristics and outcomes using pre-specified forms. In case of disagreement, consensus was sought by involving a third senior investigator (J.J.M.).

*Statistical analysis.* Cumulative event rates for the relevant endpoints were calculated. A random-effects model meta-analysis was performed with the Mantel-Haenszel method to calculate the pooled estimate rates and 95%CI of study outcomes. Statistical significance was set at p-value <0.05 (two-sided) and with a 95% CI not crossing 1.00. To assess heterogeneity across studies, we used Cochrane Q-statistic to compute I² values: <25%, 25-50%, or >50% indicated low, moderate, or high heterogeneity, respectively. Sensitivity analysis including original data from the present work was performed to thoroughly summarize available evidence. Statistical analyses were conducted with Review Manager (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).
Table S1. Literature query search for Systematic review in MEDLINE and Embase (June 3rd, 2020).

| Query for Embase |
|------------------|
| #1 ‘COVID-19’/exp |
| #2 ‘Coronavirus disease 2019’ |
| #3 ‘SARS-CoV-2’/exp |
| #4 ‘Severe Acute Respiratory Syndrome Coronavirus 2’ |
| #5 #1 OR #2 OR #3 OR #4 |
| #6 ‘RAAS’ |
| #7 ‘Renin angiotensin aldosterone system’ |
| #8 ‘ACEi’ |
| #9 ‘Angiotensin converting enzyme inhibitor’ |
| #10 ‘ARB’ |
| #11 ‘Angiotensin receptor blocker’ |
| #12 #6 OR #7 OR #8 OR #9 OR #10 OR #11 |
| #13 #5 AND #12 |

Query for MEDLINE

(((COVID-19) OR (Coronavirus disease 2019)) OR (SARS-CoV-2)) OR (Severe Acute Respiratory Syndrome Coronavirus 2) AND ((RAAS) OR (Renin Angiotensin Aldosterone System) OR (Angiotensin Converting Enzyme inhibitors) OR (ACEi) OR (Angiotensin receptor blocker) OR (ARB))
A total of 2,297 patients with COVID-19 admitted from January 10th to March 30th, 2020, were enrolled in the current study. Eleven patients that were hypotensive and stopped antihypertensive therapy on admission were excluded. These eleven patients were not on RAS inhibitors. We further identified 1,019 normotensive COVID-19 cases and 1,267 COVID-19 patients with hypertension, of whom 1,182 patients were taking at least one antihypertensive drug before admission, whereas 85 patients were diagnosed by the attending physician on admission and were without any hypertensive drug. The 1,182 hypertensive COVID-19 patients on antihypertensive medication before admission were divided into two groups: the renin angiotensin system (RAS) inhibitors group (patients taking...
ACEi or ARB before hospitalization; N=355, 30.0%) and the non-RAS inhibitors group (patients not taking ACEi or ARB, but on other anti-hypertensive medications before hospitalization, N=827, 70.0%). The comparison between the RAS inhibitors group and the non-RAS inhibitors group was the main analysis of the study. Among the RAS inhibitors group, 289 (81.4%) patients were treated with ARB and 66 (18.6%) individuals with ACEi. Comparisons between patients on angiotensin receptor blockers (ARB, N=289), and patients on angiotensin converting enzyme inhibitors (ACEi, N=66) vs. patients non-taking RAS inhibitors were sub-analyzed.
Figure S2. Study selection diagram for the meta-analysis.

MEDLINE: 274

Embase: 214

After duplicate removal: 393

Exclusion after Title or Abstract screening: 380
- Reviews: 191
- Position papers/Expert opinions: 111
- In vitro: 31
- Not reporting outcome of interest: 27
- Correspondence: 19

Full texts assessed for eligibility: 13

Exclusion after full text evaluation:
- Not on hypertensives: 5
- Not reporting on mortality: 3

Studies included: 5