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

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 China[1, 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 ≤300mmHg), 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 m^2. 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.[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.[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.[1] The results by Zhang et al. held true after propensity score-matched analysis.[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.[1] was based on 188 patients on ACEi/ARB, 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).[3, 21, 22] Partial confirmation of our findings is also derived by a multicenter international registry that reported an independent

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).[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.[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/m^2)	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.

	Hypertension patients treated with antihypertensive drugs (n=1182)	RAS inhibitors group (n=355)	Non-RAS inhibitors group (n=827)	P value
Demographics, median (Q1-Q3)				
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/m^2)	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				
Patch shadow	879/1182 (74.4%)	274/355 (77.2%)	605/827 (73.2%)	0.1460
Consolidation	254/1182 (20.7%)	68/355 (19.2%)	177/827 (21.4%)	0.3822
Pleural lesions	497/1182 (42.1%)	158/355 (44.5%)	339/827 (41.0%)	0.2617
Laboratory data, median (Q1-Q3) or mean ± SD				
WBC (*10^9/L)	6.00 (4.78-7.84)	6.13 (4.82-7.80)	5.97 (4.75-7.99)	0.5389
Neut (*10^9/L)	4.17 (2.98-5.95)	4.12 (2.99-5.68)	4.18 (2.96-5.99)	0.8128
Lymph (*10^9/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 (*10^9/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
hs-cTnI (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

IL-6 (pg/mL)	7.9 (3.1-26.2)	6.0 (2.7-23.2)	8.5 (3.3-27.8)	0.0258
TNF-α (pg/mL)	8.7 (6.6-11.5)	8.50 (6.5-10.9)	8.80 (6.7-11.7)	0.0844
Anti-hypertensive 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 Mortality	107/1182 (9.1%)	12/355 (3.4%)	95/827 (11.5%)	<0.0001
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.

	Hypertensive patients treated with ARB (n=289)	P value	Hypertensive patients treated with ACEi (n=66)	P value
Demographics, median (Q1-Q3)				
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

opacity				
Patch shadow	215/289 (74.4%) **	0.6814	59/66 (89.4%)	0.0036
Consolidation	53/289 (18.3%)	0.2677	15/66 (22.7%)	0.8010
Pleural lesions	131/289 (45.3%)	0.1986	27/66 (40.9%)	0.9895
Laboratory data, median (Q1-Q3) or mean ± SD				
WBC (*10^9/L)	6.13 (4.79-7.77)	0.9278	6.23 (5.11-9.32)	0.1534
Neut (*10^9/L)	4.07 (2.96-5.66)	0.5019	4.33 (3.17-6.49)	0.3479
Lymph (*10^9/L)	1.19 (0.77-1.65)	0.0024	1.15 (0.76-1.63)	0.2768
Hb (g/dL)	12.7 (11.3-13.7)	0.5213	12.9 (11.4-13.8)	0.3091
PLT (*10^9/L)	222 (169-283)	0.9756	215 (155-295)	0.7242
ALT (U/L)	23 (14.00-41.00)	0.1470	25 (16-44)	0.5334
AST (U/L)	25 (18-36)	0.2704	28 (19-39)	0.7242
Cr (mmol/L)	71 (61-90)	0.2565	77 (65-99)	0.0237
TC (mmol/L)	3.71 (3.16-4.47)	0.5625	3.73 (3.17-4.18)	0.7395
LDL (mmol/L)	2.36 (1.74-2.97)	0.4186	2.12 (1.71-2.79)	0.0447
K^+ (mmol/L)	4.17 ± 0.48	0.6271	4.21 ± 0.53	0.3805
Glu (mmol/L)	6.18 (5.32-7.83) **	0.4491	7.18 (5.88-9.35)	0.0098
D-Dimer (μg/ml)	0.73 (0.36-1.72)	0.0001	0.86 (0.36-2.75)	0.6674
Myocardial injury, median (Q1-Q3)				
CK-MB (ng/ml)	1.0 (0.6-1.6)	0.2568	1.1 (0.7-1.9)	0.0100
hs-cTnI (pg/ml)	8.2 (3.8-16.1) *	0.5309	11.7 (4.7-29.2)	0.0466
NT-proBNP (pg/ml)	175 (69-542)	0.2745	194 (75-1193)	0.2736
Inflammatory factors, median (Q1-Q3)				
hs-CRP (pg/ml)	11.8 (2.6-49.5)	0.0062	17.5 (3.9-58.3)	0.4263
ESR (mm/H)	30 (17-59)	0.0369	26 (15-48)	0.0516
IL-6 (pg/ml)	6.0 (2.7-20.9)	0.0171	6.5 (2.6-26.3)	0.7041

TNF-α (pg/ml)	8.4 (6.3-10.9)	0.0375	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%)	0.0055	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	9/289 (3.1%)	<0.0001	3/66 (4.6%)	0.0825
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	14/289 (4.8%)	0.5970	7/66 (10.6%)	0.0261
Cerebral hemorrhage	1/289 (0.4%)	0.1341	0/66 (0.0%)	0.6157
Acute kidney injury	1/289 (0.4%)	0.2028	1/66 (1.5%)	0.9666

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.

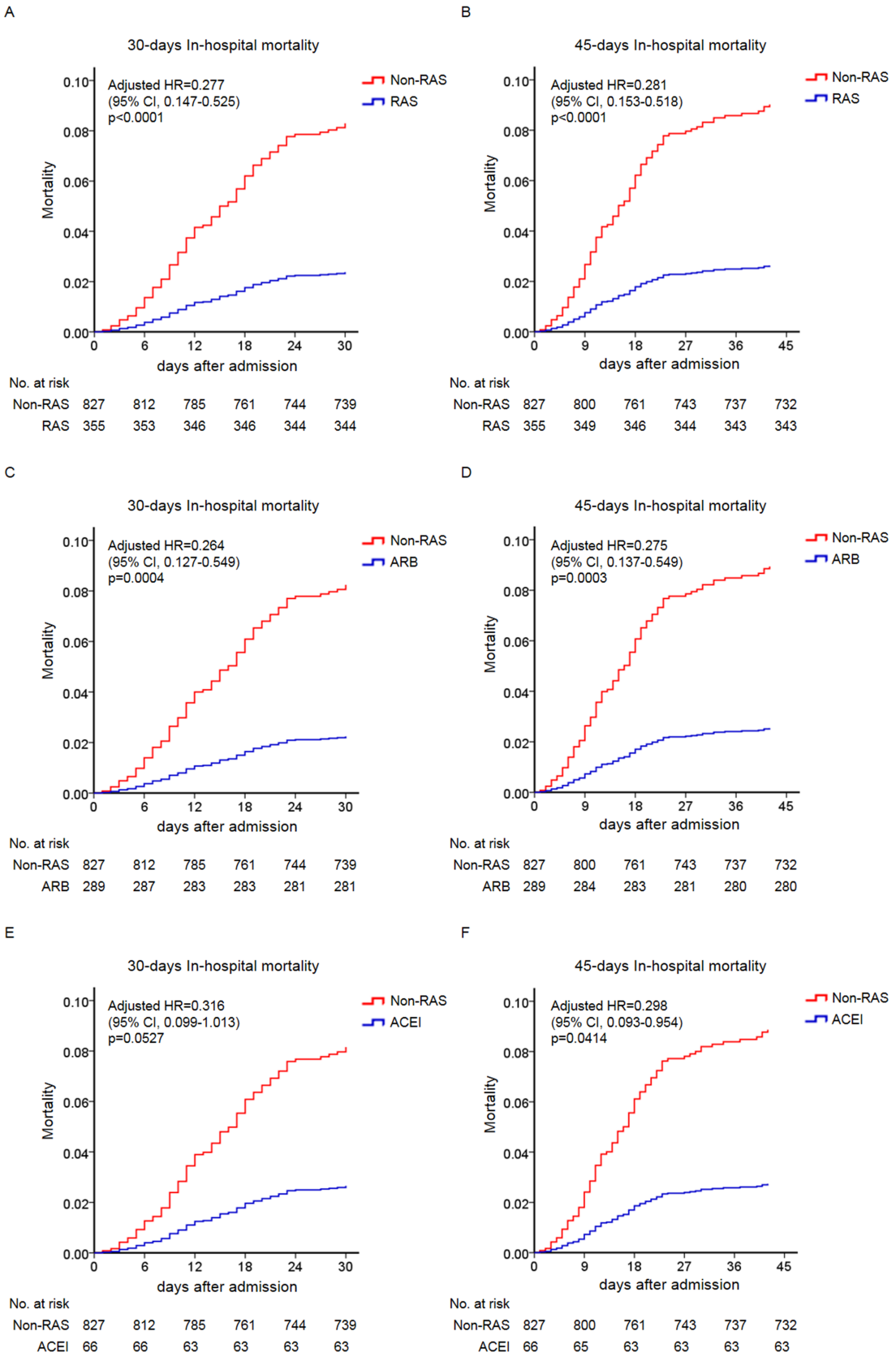
SBP and K^+ are shown as mean ± SD, other data are shown as median (first to third quartile, Q1-Q3).

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.



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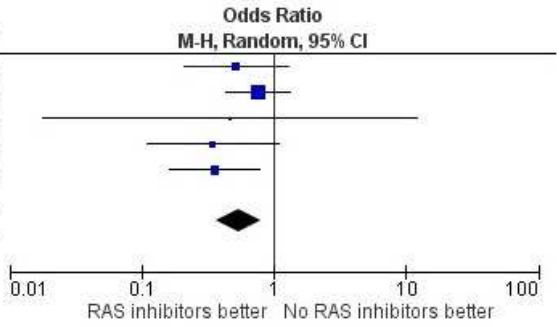
A

Study or Subgroup	RAS inhibitors Events	Total	No RAS inhibitors Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Conversano 2020 [19]	21	68	13	28	17.8%	0.52 [0.21, 1.27]
Li, 2020 [3]	21	115	56	247	46.4%	0.76 [0.44, 1.33]
Meng, 2020 [22]	0	17	1	25	1.4%	0.47 [0.02, 12.14]
Yang, 2020 [21]	4	43	19	83	11.0%	0.35 [0.11, 1.09]
Zhang, 2020 [1]	7	188	92	940	23.5%	0.36 [0.16, 0.78]
Total (95% CI)		**431**		**1323**	**100.0%**	**0.54 [0.37, 0.79]**
Total events	53		181			

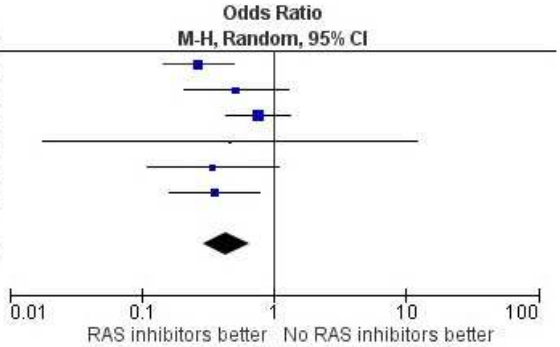
Heterogeneity: Tau² = 0.00; Chi² = 3.17, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 3.16 (P = 0.002)



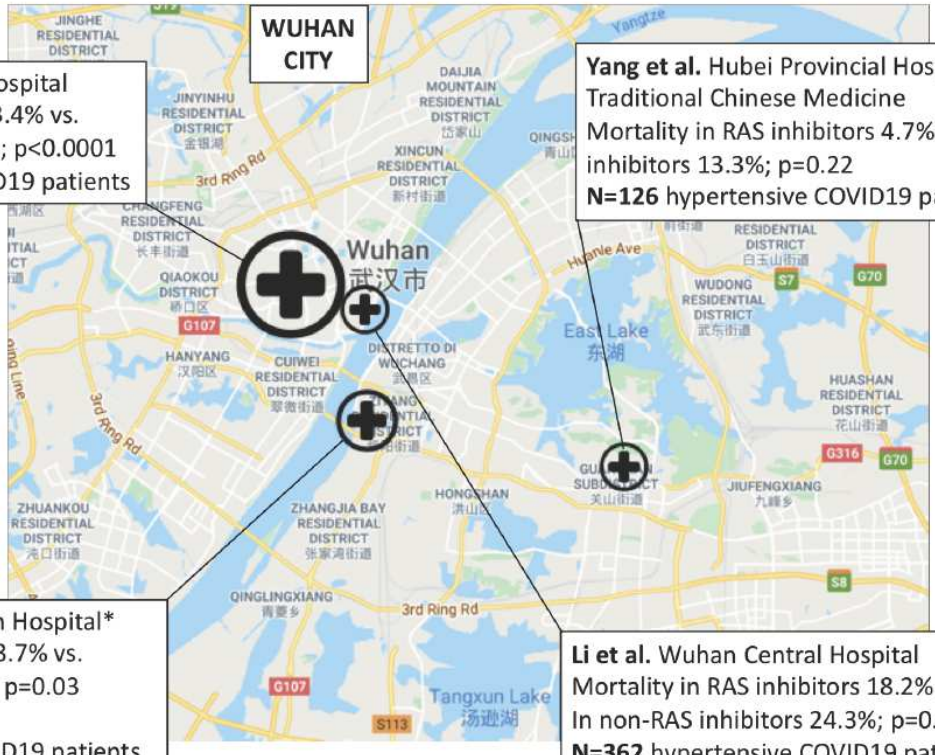
B

Study or Subgroup	RAS inhibitors Events	Total	No RAS inhibitors Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen, 2020	12	355	95	827	25.7%	0.27 [0.15, 0.50]
Conversano 2020 [19]	21	68	13	28	15.2%	0.52 [0.21, 1.27]
Li, 2020 [3]	21	115	56	247	28.7%	0.76 [0.44, 1.33]
Meng, 2020 [22]	0	17	1	25	1.5%	0.47 [0.02, 12.14]
Yang, 2020 [21]	4	43	19	83	10.3%	0.35 [0.11, 1.09]
Zhang, 2020 [1]	7	188	92	940	18.6%	0.36 [0.16, 0.78]
Total (95% CI)		**786**		**2150**	**100.0%**	**0.44 [0.29, 0.65]**
Total events	65		276			

Heterogeneity: Tau² = 0.07; Chi² = 6.83, df = 5 (P = 0.23); I² = 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

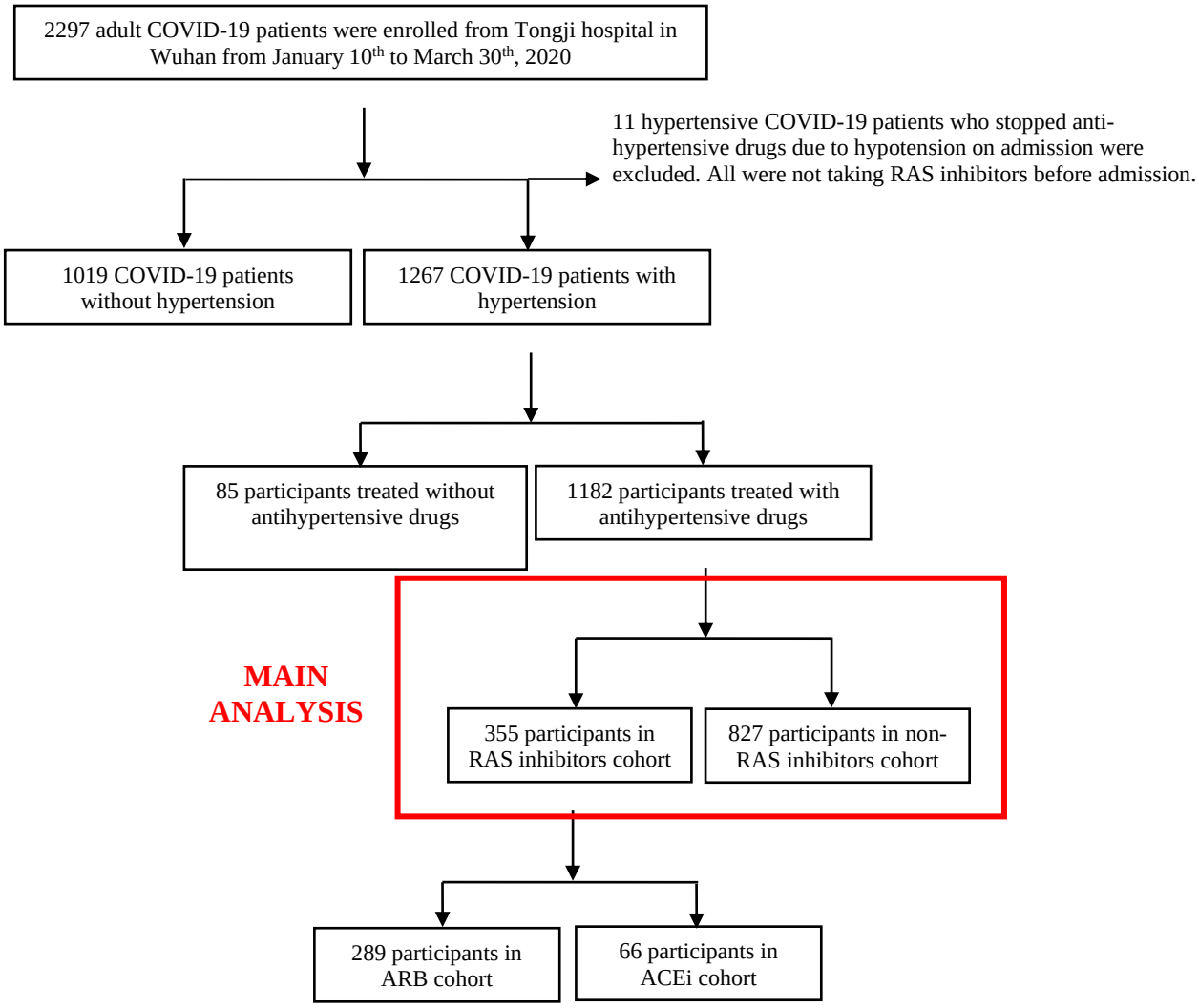
Systematic search. Two Authors (F.M. and E.A.) independently searched MEDLINE and Embase from their inception to June 3rd, 2020. Literature query search included the following combination of key words: “COVID-19”, “SARS-CoV-2”, “RAAS”, “ACEi” and “ARB”. Detailed queries can be found in **Table S1**. 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))

Figure S1. Study flowchart.



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.