Renin–angiotensin–aldosterone system blockers and region-specific variations in COVID-19 outcomes: findings from a systematic review and meta-analysis

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Abstract
Background and aims: Coronavirus disease 2019 (COVID-19) has been observed to cause a high mortality in people with cardiometabolic diseases. Renin–angiotensin–aldosterone system (RAAS) blockers enhance the expression of ACE2, the binding receptor of SARS-CoV-2, and can enhance viral infectivity. We aim to provide a pooled estimate of the effect of RAAS blockers on COVID-19 outcomes.

Methods: A literature search was performed using MEDLINE/PubMed, Google Scholar and preprint servers. All clinical studies analyzing the effect of RAAS blockers on clinical outcomes in COVID-19 patients were included in this study. Newcastle–Ottawa scale was used for quality assessment of studies. MOOSE checklist was followed. Mortality and severity outcomes were recorded as pooled odds ratio (OR) with 95% Confidence Intervals (CIs) and level of heterogeneity ($I^2$). Odds of mortality was the primary outcome. Odds of severity, hospitalization, intensive care unit (ICU) admission, mechanical ventilation (MV), steroid use and acute kidney injury were the secondary outcomes. Severity outcomes were chosen depending upon the definition used by respective authors. Country-specific variations and effects of individual class of RAAS blockers were also explored.

Results: In total 47 published studies were included in the final analysis, with a total of 26,432 patients from 31 studies in mortality analysis and 20,127 patients from 23 studies in severity analysis. No increased risk of mortality [Pooled OR 0.91 (0.65–1.26), $I^2 = 89\%$] or severity [Pooled OR 1.08 (0.79–1.46), $I^2 = 88\%$] was seen with RAAS blockers. The drug class was protective in hypertension [pooled OR 0.63 (0.46–0.86), $I^2 = 58\%$]. Severity of COVID-19 outcomes was high for Europeans [Pooled OR 2.08 (1.52–2.85), $I^2 = 77\%$] and US patients [Pooled OR 1.87 (1.62–2.17)]. Nearly 4 times higher risk of hospitalization and 2 times higher risk of ICU admission and MV were observed in US patients. Class-wise, angiotensin receptor blocker use was associated with 1.6 times higher odds of severity, mainly in Europeans.

Conclusion: RAAS blockers are not associated with increased mortality in COVID-19 patients and should be continued in hypertensives. US and European patients are at higher risk of severe outcomes. Pharmacogenetic differences may explain the ethnicity-related variations.

Plain language summary

Effect of RAAS-blocking medicines on COVID-19

Background and aims: Higher deaths have been observed in COVID-19 patients who have other long-term diseases such as heart disease, diabetes, and high blood pressure. Many of these patients are prescribed a class of medicines called RAAS blockers (ramipril, telmisartan, etc). We studied whether the use of these medicines worsens the course of COVID-19 disease in these patients or causes excess deaths.
Methods: We conducted a pooled analysis of 47 observational studies on the use of RAAS blocker drugs in COVID-19 patients.

Results: We found that RAAS blockers do not cause excess deaths in patients with COVID-19. On the contrary, they have benefits if prescribed to those with high blood pressure. We also found that whereas European and US patients of COVID-19 taking these medicines had higher disease severity, this was not the case for Chinese patients.

Conclusion: There may be some genetic and other factors responsible for differences by ethnicity.

Keywords: Cardiometabolic disorders, COVID-19, genetic polymorphisms, hypertension, mortality, RAAS, regional, SARS-CoV-2, severity

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Introduction
Corona Virus Disease-2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) has affected 141 million individuals worldwide and claimed 3 million lives as of 20th April 2021.1 ACE2 is the major binding receptor of SARS-CoV-2 and is located on pulmonary epithelial cells, endothelial cells and in cells of the kidney, among others. Acute respiratory distress syndrome, myocardial injury, multiorgan failure and disseminated intravascular coagulation including diffuse pulmonary intravascular coagulopathy are responsible for the majority of the deaths, and stem from a state of inflammatory cytokine storm and vascular thrombosis.2,3 Older individuals and those with co-morbidities such as hypertension, diabetes mellitus and ischemic heart disease are at increased risk of severe disease. The use of renin–angiotensin–aldosterone system (RAAS) blockers such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists in such patients is not uncommon. With experimental evidence of upregulation of ACE2 by RAAS blockers, concerns were raised regarding the increased risk of infection and severity of disease in users of these drugs.4,5

Following this, multiple observational studies were conducted to assess the relationship between use of RAAS blockers and COVID-19 severity. This systematic review and meta-analysis aim to compile the information obtained from these studies and elucidate the association between the use of RAAS blockers and clinical outcomes in patients of COVID-19. Few such meta-analyses have been published, but these have shortcomings such as inclusion of only a small number of studies, absence of subgroup analysis, and inclusion of retracted studies. The current meta-analysis of 47 studies provides a comprehensive view of the issue by involving larger number of patients, analyzing for multiple health outcomes, and performing region-specific analyses. We hypothesized that RAAS blockers may not be detrimental to COVID-19 outcomes.

Methods
Search criteria
A comprehensive search was conducted in PubMed, Google Scholar, and the preprint servers medRxiv.org and bioRxiv.org using keywords: ACEI OR ACE-I OR Angiotensin converting enzyme inhibitors AND COVID-19/SARS-CoV-2, Angiotensin receptor blocker OR AT-1 receptor blocker OR Ang II blocker OR ARB AND COVID-19/SARS-CoV-2, RAAS blocker AND COVID-19/SARS-CoV-2, Aldosterone antagonist AND COVID-19/SARS-CoV-2, Renin inhibitor AND COVID-19/SARS-CoV-2. The final search was conducted on 9 July 2020. Only articles published in English language were included. MOOSE checklist was followed for the present study.

Selection criteria
Inclusion criteria
• All clinical studies (observational studies/clinical trials) analyzing the effect of RAAS
blockers on clinical outcomes in laboratory confirmed COVID-19 patients were included in this study. Thus, the review involved inclusion of studies which compared the disease outcomes between users and non-users of RAAS blockers as well as those which assessed the use of RAAS blockers in COVID-19 patients of varying severity. RAAS blockers include ACEIs, ARBs, aldosterone antagonists and renin inhibitors. Studies were considered irrespective of the dose and duration of drug use.

- Studies should have provided comparative data of mortality and/or severity between users and non-users of RAAS blockers in COVID-19 patients.
- All types of study setting (outpatient, inpatient, nursing homes, home care) were included.
- All age groups of study population were included.

Exclusion criteria
- Studies focusing on individual RAAS blockers only.
- Studies focusing only on outcomes based on laboratory parameters (e.g. serum/urinary ACE2 expression).
- Non-comparative studies, review articles, in vitro studies, animal studies, viewpoints.

All relevant abstracts were scrutinized, and full text and bibliography was searched for those found useful. In case of lack of clarity in the abstracts, full text was analyzed. This was done by author UK assisted by author SSC and confirmed by author TKP assisted by author SSC.

Data extraction. From the included studies, data were extracted in a Microsoft Excel sheet. Data included author name, publication year, country, study design, total duration of study, mean/median follow-up, characteristics of patients or specific population of COVID-19 patients in whom the particular study was conducted, age, gender, sample size, use of RAAS blockers, mortality outcomes, severity outcomes, need of hospitalization, care in intensive care unit (ICU), need of mechanical ventilation, corticosteroid use and occurrence of acute kidney injury (AKI).

Risk of bias. Two investigators (TKP and SSC) assessed the risk of bias in the included studies as per the Newcastle–Ottawa quality assessment scale (NOS) adapted for cross-sectional design. Criteria considered were representativeness of the study sample, sample size, non-respondents, ascertainment of exposure, comparability of study groups for confounders (age and major co-morbidities), assessment of outcome and statistical tests. The maximum possible score was 10.6

Outcomes
Outcomes with the use of RAAS blockers. The primary outcome was odds of mortality in the users of RAAS blockers with respect to non-users among confirmed cases of COVID-19. The secondary outcomes were odds of severity, hospitalization, ICU admission, mechanical ventilation, steroid use, and AKI in users of RAAS blockers with respect to non-users. A subgroup analysis of all outcomes was performed based on the geographical locations (country or continent of origin) of the included studies. The mortality outcome was further analyzed as per study sub-populations (e.g. patients with hypertension) and severity outcome as per definitions used by the individual study authors.

Outcomes with the use of subclass of RAAS blockers (ACEIs and ARBs). Both the subclasses were explored for the mortality and severity outcomes as per the availability of studies. Both outcomes were analyzed according to the geographical locations (country or continent of origin) of the included studies. In the absence of universally accepted definitions, severity was considered as defined by the authors in the included studies. When outcomes were reported both under “critical” and “severe” headings, we considered the more serious outcome under severity analysis. In case of multiple time-points for the outcome estimation, we considered data at the end of study period.

A sensitivity analysis was performed for each outcome after excluding studies with high risk of bias. The studies with score \( \leq 7 \) on the modified NOS scale were considered to have high risk of bias.

Data synthesis
All outcomes being dichotomous variables were reported as odds ratio (OR) with 95% confidence intervals (CIs). The meta-analysis was weighted with inverse variance method. An \( I^2 \) test was used to assess the heterogeneity between studies.
Fixed-effect model was used if heterogeneity was <50% and random-effect was applied in case heterogeneity exceeded 50%. The funnel plot method was used for reporting publication bias. The meta-analysis was performed using Review Manager Software version 5.4.

Results

Characteristics of included studies
A total of 1348 articles were retrieved (Figure 1). Out of 70 full-text articles assessed, 47 studies satisfying the selection criteria were included for detailed qualitative and quantitative analysis in this review. Table 1 shows the demographic features of the patients in included studies. The sample size of individual studies varied from 36 to 9519. In the majority of the studies, the mean or median age of patients was >60 years.

Thirty-two (68.1%) studies assessed mortality, out of which 31 were included in mortality analysis as raw data was not available in one (Zhang et al.). Thirty-five studies (74.5%) assessed composite severity or individual health outcomes (hospitalization, ICU admission, mechanical ventilation, steroid use, and AKI). Twelve studies defined severity as per guidelines of the National Health Commission (NHC) of China. Six studies defined severity as composite of ICU admission and death. Two studies used the severity definition issued by the Infectious Diseases Society of America (IDSA). Composite of hospitalization for ≥7 days and death, composite of death/severe infection (definition described in the table

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**Figure 1.** Flow diagram of number of studies screened and selected.
Table 1. Studies included in meta-analysis of impact of renin angiotensin aldosterone system blockers on mortality and severity outcomes of COVID-19.

| Author          | Country   | Design     | Total duration | Follow-up per patient | Age (in years) | Sample size studied (M/F) | Indication for RAAS blocker | Outcome tested | Co-morbidities | Confounder adjustment (for included variables) | Quality (NOS score) |
|-----------------|-----------|------------|----------------|-----------------------|----------------|---------------------------|-----------------------------|----------------|----------------|-----------------------------------------------|--------------------|
| Andrea et al.    | Italy     | Retrospective | 43d           | 28d                   | Mean [SD] entire sample 63.4 (14.9) | 191 [131/60]; HTN=96 | HTN                         | Mortality            | In HTN gp-CKD: 41.6%, CAD: 28.1%, DM: 22.9%     | No                 | 8                 |
| Argenziano et al.| USA       | Retrospective | 61d           | NM                    | Median [IQR] entire sample 63 [50–75] | 1000 [596/404]   | NM                         | Severity assessed as hospitalization/ ICU admission/ IV | HTN: 60%, DM: 37%, CAD: 13% | No                 | 7                 |
| Baker et al.     | UK        | Retrospective | 119d          | 28d                   | Median [IQR] 75 [60–83] | 316 [173/143]   | NM                         | Mortality            | HTN: 42%, Respiratory diseases: 32%, DM: 26.6%       | Yes                | 10                |
| Bean et al.      | UK        | Retrospective | 22d           | 7d                    | Mean [SD] entire sample 63 [20] | 205 [106/99]     | NM                         | Severity            | HTN: 51%, DM: 30%, IHD/HF: 14.6%                 | Yes                | 10                |
| Bravi et al.     | Italy     | Retrospective | NM            | 24d                   | Mean [SD] entire sample 58 [20.9] | 1603 [758/845]; HTN=543 | HTN                        | Severity and as hospitalization | HTN: 34%, Major CVD: 16%, DM: 12%                  | Yes                | 10                |
| Caraballo et al. | USA       | Retrospective | NM            | NM                    | Median entire sample [IQR] 78 [65–87] | 206 [93/113]     | HF                         | Mortality            | HTN: 80%, Renal disease: 38.3%, CAD: 35.4%        | No                 | 8                 |
| Chen et al.      | China     | Retrospective | 77d           | NM                    | Median entire sample [IQR] 58 [42–62] | 71 [with known history of medication] | DM and HTN               | Mortality            | HTN: 36.6%, CVD: 14.7%, DM: 14.4%                 | No                 | 6                 |
| Choi et al.      | South Korea | Retrospective | 116d          | NM                    | Mean [SD] Users gp- 65 [13] Non-users group-68 [15] | 1585 [679/906] | HTN                        | Mortality and severity | Users gp: DM: 46.5%, Major neurologic diseases: 28% Non-users gp: DM: 43%, Major neurologic diseases: 42.7% | Yes                | 9                 |
| de Abajo et al.  | Spain     | Case Control | 24d           | NM                    | Mean [SD] entire sample 69.1 [15.4] | 1139 [695/444] | NM                         | Severity            | HTN: 54.2%, DLP: 39%, DM: 27.2%                  | Yes                | 10                |
| Du et al.        | China     | Retrospective | 40d           | NM                    | Median [IQR] Users gp- 71 [63.5–77] Non-users gp- 69 [62–77] | 154 [79/75] | Raised Troponin I          | Mortality and severity assessed as IV | Users gp- HTN: 100%, DM: 41.2%, CVD: 29.4% Non-users gp- HTN: 38.7%, DM: 19%, CVD: 18.3% | Yes                | 7                 |

(Continued)
| Author          | Country | Design         | Total duration | Follow-up per patient | Age (in years) | Sample size studied (M/F) | Sample size studied (M/F) | Indication for RAAS blocker | Outcome tested | Co-morbidities | Confounder adjustment (for included variables) | Quality (NOS score) |
|-----------------|---------|----------------|----------------|-----------------------|----------------|--------------------------|--------------------------|----------------------------|----------------|----------------|-----------------------------------------------|---------------------|
| Dublin et al.   | USA     | Retrospective  | 106 d          | NM                    | Mean [SD] entire tested sample 66 [12.2] | 56,105 [29,455/26,650]; Tested positive = 720 | NM                       | Severity assessed as hospitalization | Users gp-HTN: 71.5%, DM: 33.5%, Renal disease: 12.2% Non-users gp-HTN: 9.9%, DM: 3.8%, Renal disease: 2.3% | Yes                  | 10             |
| Felice et al.   | Italy   | Retrospective  | 23 d           | NM                    | Mean [SD] ACE users 73.1 [11.5] ARB users 69 [13.4] Non-users 76.2 [11.9] | 133 [86/47] | HTN                      | Mortality and Severity assessed as Hospitalization/ ICU/Non-IV | Users gp-HTN: 24%, Cancer: 17%, COPD: 9% Non-users gp-HTN: 28%, Cancer: 14%, COPD: 14% | Yes                  | 9              |
| Feng et al.     | China   | Retrospective  | 46 d           | NM                    | Median [IQR] entire sample53 [40–64] | 476 [271/205] | NM                       | Severity* | HTN: 24%, DM: 10.3%, CVD: 8%, COPD: 4.6% | No                    | 4              |
| Feng et al.     | China   | Retrospective  | 59 d           | NM                    | Median [IQR] entire sample47 [36–58] | 564 [284/280] | HTN                      | Severity* | HTN: 14.5%, DM: 8%, CVD: 3.9% | Yes                  | 10             |
| Fosbøl et al.   | Denmark | Retrospective  | 94 d           | NM                    | Median [IQR] entire sample 56.7 [40.9–72] Users gp- 72.8 [61.0–81.0] Non-users gp- 50.1 [37.2–64.5] | 4480 [2144/2336] | NM                       | Mortality and Severity* | Users gp-HTN: 70.8%, DM: 24.2%, MI: 21.6% Non-users gp-HTN: 5.8%, DM: 5.4%, MI 5.2% | Yes                  | 10             |
| Gao et al.      | China   | Retrospective  | 57 d           | Median [IQR] 21 d [12 d–32 d] | Mean [SD] 64.24 [11.2] | 850 [443/407] | HTN                      | Mortality and Severity* | Users gp-HTN: 30.1%, Angina: 17.5%, PCI/CABG: 4.9% Non-users gp-HTN: 26.6%, Angina: 15.2%, PCI/CABG: 5.3% | Yes                  | 10             |
| Guo et al.      | China   | Retrospective  | 32 d           | NM                    | Mean [SD] of entire sample 58.5 [14.66] | 187 [91/96] | NM                       | Mortality               | HTN: 32.6%, DM: 15%, CHD: 11.2% | No                   | 8              |
| Hu et al.       | China   | NM             | 23 d           | NM                    | Median [IQR] 57 [49.5–66] | 149 [88/61] | HTN                      | Mortality and Severity* | Users gp-HTN: 24.6%, CLD: 7.7%, Renal disease: 6.1% Non-users gp-HTN: 16.7%, CLD: 4.76%, Renal disease: 2.4% | No                   | 5              |

(Continued)
| Author            | Country | Design      | Total duration | Follow-up per patient | Age (in years) | Sample size studied (M/F) | Indication for RAAS blocker | Outcome tested | Co-morbidities | Confounder adjustment (for included variables) | Quality (NOS score) |
|-------------------|---------|-------------|----------------|-----------------------|---------------|--------------------------|-----------------------------|----------------|---------------|-----------------------------------------------|------------------|
| Huang et al.      | China   | Retrospective | 40d            | NM                    | Mean (SD) entire sample 58 [17] | 200 [115/85] | NM | Mortality and Severity assessed by OF/IV³ | Users gp- HTN: 75%, DM: 25%, CHD: 18% Non-users HTN: 22%, DM: 14%, CHD: 8% | No | 8 |
| Huang et al.      | China   | Retrospective | 26d            | NM                    | Mean (SD) Users gp- 52.65 [13.12] Non-users gp- 67.77 [12.84] | 50 [27/23] | HTN | Mortality and Severity⁴ | Users gp- COPD, Anemia: 5%, CAD, DM: 0% Non-users gp- DM: 13.3%, CAD: 3.3%, COPD, anemia: 0% | No | 6 |
| Inciardi et al.   | Italy   | NM          | 22d            | entire sample 67 [12] | Mean (SD) entire sample 59 [17] | 99 [80/19] | NM | Mortality | HTN: 64%, DM: 31%, DLP: 30% | No | 6 |
| Ip et al.         | USA     | Retrospective | NM             | NM                    | <50 to >80 years | 1584 with HTN, 1216 with known outcomes | HTN | Mortality | NM | No | 7 |
| Jung et al.       | South Korea | Cohort study | NM             | NM                    | Mean (SD) Users gp- 62.5 [14.7] Non-users gp- 41.5 [16.6] | 5179 [2295/2884] | NM | Mortality and Severity assessed as IV | Users gp- HTN: 94%, DM: 48%, COPD: 40% Non-users gp- DM: 11%, HTN: 10% | Yes | 10 |
| Li et al.         | China   | Retrospective | 61d            | NM                    | Median [IQR] entire sample 55.5 [38–67] HTN, cohort 66 [59–73] | 362 [189/173] | HTN | Mortality and Severity⁴ | Users gp- DM: 36.5%, CbVD, CHD: 23.5% Non-users gp- DM: 34.4%, CHD: 14.2%, CbVD: 16.6% | No | 7 |
| Li et al.         | China   | Retrospective | 38d            | 32d                   | Median [IQR] entire sample 60 [48–69] | 548 [279/269] | NM | Severity⁴ | HTN: 30.3%, DM: 15.1%, CHD: 6.2% | No | 8 |
| Liabeuf et al.    | France  | Retrospective | 47d            | NM                    | Median [IQR] 73 [61–84] | 268 [164 on at least one anti-HTN] | NM | Mortality and Severity assessed as ICU admission | HTN: 57%, type 2 DM: 18%, Stroke: 14% | Yes | 10 |

(Continued)
| Author          | Country | Design      | Total duration | Follow-up | Age (in years) | Sample size studied (M/F) | Indication for RAAS blocker | Outcome tested              | Co-morbidities                             | Confounder adjustment (for included variables) | Quality (NOS score) |
|-----------------|---------|-------------|----------------|-----------|---------------|---------------------------|-----------------------------|----------------------------|-------------------------------------------|-------------------------------------------------|-----------------|
| Mehta et al.    | USA     | Retrospective | 36 d          | NM        | Mean [SD]     | 1735                      | NM                         | Mortality and Severity asessed as hospitalization/ICU admission/IV | ACEI users gp versus non-users gp- HTN: 97% versus 37%, DM: 54% versus 17%, CAD: 21% versus 9% ARB users gp versus non-users gp- HTN: 93% versus 38%, DM: 50% versus 18%, CAD: 24% versus 9% | Yes                                               | 10              |
| Meng et al.     | China   | Retrospective | 44 d          | NM        | Median [IQR]  | 24 [18]                   | HTN                        | Mortality and Severity' Users gp - DM and CHD: 29.4% Non-users gp - DM and CHD: 32% | Non-users gp - DM and CHD: 32% HTN: 73.7%, DM: 48.8% | No                                               | 6               |
| Mohamed et al.  | Australia| NM         | NM            | NM        | Median 25[d, minimum 14 d] | 575 [312/263] | NM                        | Severity assessed as AKI Users gp - HTN: 98.6%, DLP: 60%, DM: 27.6% Non-users gp - DLP: 19.2%, HTN: 12.1%, DM: 8.7% | Non-users gp - DM and CHD: 32%, CVD: 19%, DM: 14% | No                                               | 7               |
| López-Otero et al. | Spain    | Retrospective | 28 d          | NM        | Mean [SD] 59.5 [20.3] Users gp- 72.1 [13.2] Non-users gp- 56 [20.5] | 965 [425/540] | NM                        | Mortality and Severity assessed as hospitalization/ICU admission and composite of HF/death Users gp - HTN: 98.6%, DLP: 60%, DM: 27.6% Non-users gp - DLP: 19.2%, HTN: 12.1%, DM: 8.7% | Non-users gp - DM and CHD: 32%, CVD: 19%, DM: 14% | Yes                                              | 10              |
| Oussalah et al. | France  | Retrospective | 31 d          | NM        | Median [IQR] 65 [54-77] | 149 [91/58] | NM                        | Mortality and Severity assessed as acute respiratory failure/IV Users gp - HTN: 86%, DM: 58%, CVD: 49% Non-users gp - HTN: 32%, CVD: 19%, DM: 14% | Non-users gp - DM and CHD: 32%, CVD: 19%, DM: 14% | Yes                                              | 10              |
| Regina et al.   | Switzerland   | Retrospective | 25 d          | 14 d minimum | Median [IQR] 70 [55-81] | 200 [120/80] | NM                        | Severity assessed as IV HTN: 43.5%, DM: 21.5%, CAD: 17.5% | Non-users gp - HTN: 32%, CVD: 19%, DM: 14% | No                                               | 8               |
| Reilev et al.   | Denmark  | NM         | 64 d          | 30 d       | Median [IQR] 9519 [4010/5509] | 9519 [4010/5509] | NM                        | Mortality and Severity assessed as ICU admission/hospitalization HTN: 25%, Chronic lung disease: 13%, IHD: 9.1% | Non-users gp - HTN: 32%, CVD: 19%, DM: 14% | No                                               | 8               |
| Rentsch et al.  | USA     | Retrospective | 52 d          | NM        | Median [IQR] 66.1 [60.4-71] | 585 [558/27] | NM                        | Severity assessed as hospitalization/ICU admission HTN: 72.3%, DM: 44.4%, Vascular disease: 27.9% | Non-users gp - DM and CHD: 32%, CVD: 19%, DM: 14% | Yes                                              | 10              |
| Author            | Country     | Design       | Total duration | Follow-up per patient | Age (in years) | Sample size studied (M/F) | Indication for RAAS blocker | Outcome tested | Co-morbidities                                      | Confounder adjustment (for included variables) | Quality (NOS score) |
|-------------------|-------------|--------------|----------------|-----------------------|---------------|---------------------------|------------------------------|----------------|-----------------------------------------------------|-------------------------------------------------|-------------------|
| Reynolds et al.   | USA         | NM           | 46 d           | NM                    | Median [IQR] full sample 49 [34–63] HTN sample 64 [54–75] | 5894; HTN = 2573 | HTN | Severity† | HTN: 34.6%, DM: 18%, OLC: 14.6% | Yes | 10 |
| Rhee et al.       | South Korea | NM           | NM             | NM                    | Mean [SD] Users gp- 64.85 [13.23] Non-users gp- 59.9 [16.7] | 832 [445/387] | DM | Severity‡ | Users gp-HTN: 99.7%, DLP: 92.6%, CVD: 31.2% Non-users gp-HTN: 47.9%, DLP: 84.5%, CVD: 24.7% | Yes | 9 |
| Richardson et al. | USA         | NM           | 35 d           | NM                    | Median entire sample [IQR] 63 [52–75] 5700 [3437/226]; HTN with known outcomes = 1366 | 154 [51/103] | HTN | Mortality and Severity assessed as ICU admission/IV/AKI | HTN: 56.6%, DM: 33.8% and, CAD 11.1% | No | 6 |
| De Spiegeleer et al. | Belgium     | Retrospective | 47 d           | NM                    | Mean [SD] 86 [7] | | NM | Severity** | Users gp-HTN: 93.3%, DM: 20% Non-users gp-HTN: 8.8%, DM: 17.8% | Yes | 9 |
| Tan et al.        | China       | Retrospective | 71 d           | 30 d                  | Median [IQR] 67 [62–70] in users gp, 67.5 [57–71] in non-users gp | 100 [51/49] | HTN | Mortality and Severity* | Users gp - DM: 25.8%, GI illness: 19.4%, CHD: 16.1% Non-users gp - DM: 29%, GI illness: 24.6%, CHD: 18.8% | No | 5 |
| Trecarichi et al. | Italy       | Retrospective | 41 d           | NM                    | Mean [SD] 80 [12] | 50 [24/26] | NM | Mortality | CVD: 82%, Neurologic disease: 52%, Psychiatric disease: 30% | No | 6 |
| Xie et al.        | China       | Retrospective | 32 d           | NM                    | <65 years: 36.3% ≥65 years: 63.7% | 102 [46/56] | ACRI | Mortality and Severity* | HTN: 54%, DM: 22.5%, CHD: 14.7% | No | 7 |
| Xu et al.         | China       | Retrospective | 59 d           | NM                    | Median [IQR] 65 [58–73] | 101 [53/48] | HTN | Mortality and Severity assessed as ICU and IV | Users gp-HTN: 100%, DM: 20%, CHD: 13% Non-users gp-HTN: 100%, DM: 18%, CHD: 11% | Yes | 10 |

(Continued)
| Author            | Country | Design   | Total duration | Follow-up per patient | Age (in years) | Sample size studied (M/F) | Indication for RAAS blocker | Outcome tested | Co-morbidities | Confounder adjustment (for included variables) | Quality (NOS score) |
|-------------------|---------|----------|----------------|-----------------------|---------------|---------------------------|-----------------------------|----------------|----------------|-----------------------------------------------|-------------------|
| Yang et al.       | China   | Retrospective | 59 d          | NM                    | Median [IQR] 66 [61–73], Users gp- 65 [57–72], Non-users gp- 67 [62–75] | 126 [62/64] | HTN | Mortality and Severity* | Users gp-DM: 30.2%, Cardiopathy: 16.3%, Neurologic disease: 9.3%, Non-users gp-DM: 30%, Cardiopathy: 19.3%, Neurologic disease: 7.2% | No | 8 |
| Zeng et al.       | China   | Retrospective | 64 d          | 14 d minimum          | Mean [SD], HTN gp- 67 [11], Users gp- 64 [12], Non-users gp- 69 [10] | 75 [41/34] | HTN | Mortality and Severity# | DM: 31%, CVD: 21%, CbVD: 15% | No | 6 |
| Zhang et al.      | China   | Retrospective | 68 d          | 28 d                  | Median [IQR], Users gp- 64 [55–68], Non-users gp- 64 [57–69] | 1128 [603/525] | HTN | Mortality as HR, raw data not available and Severity assessed as IV and steroid use | Users gp-DM: 23.6%, CHD: 15.4%, CRD: 3.7%, Non-users gp-DM: 20.9%, CHD: 10.9%, CRD: 3% | No | 7 |
| Zhou et al.       | China   | Retrospective | 145 d         | NM                    | Median [IQR] 35 [32–37], n = 976 with known medication history | 1043 [563/480], n = 976 with HTN | NM | Severity assessed as ICU admission | Respiratory diseases: 43%, GIT diseases: 32.5%, HTN: 20.2% | No | 10 |
| Zhou et al.       | China   | Retrospective | 27 d          | NM                    | Mean [SD], HTN gp- 64.8 [10.1] | 110 [60/50], n = 36 with HTN | HTN | Mortality | HTN: 32.7%, DM: 10%, CVD: 9.1% | Yes | 6 |

Table 1. (continued)

"Users" refers to patients on RAAS blockers, "non-users" refers to those not on RAAS blockers.

Severity in terms of composite of ICU or CCU admission/death;

Severity as per Severity Criteria of National Health Commission of China;

Severity as per SARS/ICU admission;

Severity as defined by American Thoracic Society and Infectious Diseases Society of America;

Valsartan Sacubitril was also taken as ARB;

Study did not mention male–female distribution clearly;

DOH ≥ 7d or death;

The criteria resembled "Critical" of Chinese criteria and the study data were therefore analyzed under the subgroup of "critical" outcomes as per Chinese definition.

ACRI, acute cardiac-related injury; AKI, acute kidney injury; CAD, coronary artery disease; CbVD, cerebrovascular disease; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; d, days; D, death; DLP, dyslipidemia; DM, diabetes mellitus; ECMO, extra corporeal membrane oxygenation; GIT, gastrointestinal tract; gp, group; HF, heart failure; HTN, hypertension; ICU, intensive care unit; IHD, ischemic heart disease; IV, invasive ventilation; Major CVD, major cardiovascular disease (congestive heart failure, myocardial infarction, or stroke); NM, not mentioned; NOS, Newcastle–Ottawa scale; OF, organ failure; OLD, obstructive lung disease; RAAS, renin-angiotensin–aldosterone system; RRT, renal replacement therapy.
Mortality analysis

A total of 26,432 patients from 31 studies (6030 users of RAAS blockers and 20,402 non-users) were included in the mortality analysis. The use of RAAS blockers was not associated with increased risk of mortality [pooled OR 0.91 (0.65–1.26), $I^2 = 89\%$] (Figure 2). A similar trend was observed in the sensitivity analysis [pooled OR 1.09 (0.71–1.67), $F = 91\%$]. Funnel plot was asymmetrical on visual inspection (Supplemental Figure 1).

Subgroup analysis of mortality outcome based on geographical locations showed that the use of RAAS blockers conferred protection in the Chinese population [OR 0.71 (0.52–0.97), $F = 0\%$] (Figure 2). However, in sensitivity analysis, no difference in mortality was observed [pooled OR 0.85 (0.48–1.50), $F = 25\%$]. Neither benefit nor risk was observed with the use of RAAS blockers in patients in the US [pooled OR 0.96 (0.59–1.56), $F = 81\%$], Europe [pooled OR 1.19 (0.74–1.91), $F = 89\%$], and South Korea [pooled OR 1.12 (0.18–7.01), $F = 97\%$] (Figure 2). The results were consistent in the sensitivity analysis (Table 2).

On indication or disease-wise comparison, use of RAAS blockers was found to reduce the overall risk of mortality when prescribed for hypertension [pooled OR 0.63 (0.46–0.86), $F = 58\%$]. A similar trend was observed in sensitivity analysis [pooled OR 0.48 (0.36–0.63), $F = 0\%$]. Ten out of fifteen studies reporting mortality in hypertensive patients were from China. (Figure 3).

Severity analysis

A total of 20,127 patients (5460 RAAS blocker users and 14,667 non-users) from 23 studies were included in the severity analysis. The overall pooled summary showed no effect on the severity of disease with the use of RAAS blockers [pooled OR 1.08 (0.79–1.46), $F = 88\%$] (Figure 4). A similar result was observed in sensitivity analysis [pooled OR 1.32 (0.93–1.87), $F = 91\%$] (Table 2). Funnel plot was asymmetrical on visual inspection (Supplemental Figure 2).

Region/country-specific analysis also showed an increased risk of poor health outcomes in European patients [pooled OR 2.08 (1.52–2.85), $F = 77\%$] and US patients [OR 1.87 (1.62–2.17)] (Figure 4). A similar trend was observed in sensitivity analysis (Table 2). In contrast, no effect on severity with the use of RAAS blockers was evident in the Chinese population in overall [pooled OR 0.69 (0.45–1.06), $F = 51\%$], and sensitivity analysis [pooled OR 0.68 (0.3–1.53), $F = 58\%$] (Figure 4 and Table 2).

Hospitalization

Risk of hospitalization was analyzed in seven studies with 15,295 patients (2894 RAAS blocker users and 12,401 non-users). The use of RAAS blockers was associated with increased risk of hospitalization in overall analysis [pooled OR 2.49 (1.40–4.41), $F = 96\%$] as well as in sensitivity analysis [pooled OR 2.88 (1.61–5.15), $F = 96\%$]. Among the seven studies, four involved US patients, three enrolled Europeans while none was from China. Country-specific subgroup and sensitivity analysis showed a nearly 4 times higher risk of hospitalization in US patients [pooled OR 3.87 (1.21–12.34), $F = 97\%$].
Figure 2. Overall and region-specific mortality effects of renin–angiotensin–aldosterone system (RAAS) blockers in COVID-19 patients (the size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI).

while no such risk was evident in Europeans [pooled OR 2.07 (0.87–4.92), \( I^2 = 97\%\)] (Supplemental Figure 4 and Table 2).

ICU admission

In total, 16,441 patients (4060 RAAS blocker users and 12,381 non-users) from 13 studies were
analyzed for the assessment of risk of ICU admission. No increased risk of ICU admission was observed with the use of RAAS blockers in the overall [pooled OR 1.37 (0.86–2.19), $I^2 = 91\%$] and sensitivity analyses [pooled OR 1.55 (0.79–3.02), $I^2 = 93\%$]. Country-specific analysis showed an increased risk of ICU admission in the US population in overall [pooled OR 1.44 (1.14–1.83), $I^2 = 35\%$] and sensitivity analyses [pooled OR 1.82 (1.29–2.58), $I^2 = 0\%$]. No effect on ICU admission was observed in Chinese patients [pooled OR 0.65 (0.25–1.68), $I^2 = 0\%$] or in Europeans [pooled OR 1.51 (0.57–4.03), $I^2 = 93\%$] (Supplemental Figure 5 and Table 2).
Invasive ventilation

Need for invasive ventilation was assessed in 15 studies with 10,678 patients. Use of RAAS blockers was not associated with increased requirement of invasive ventilation [pooled OR 1.06 (0.7–1.59), I²=80%] and the result did not vary in sensitivity analysis [pooled OR 1.28 (0.58–2.83), I²=88%]. Country-specific analysis showed an increased risk of invasive ventilation in the US population [pooled OR 2.33 (1.02–5.36), I²=92%]. After excluding the studies with a high risk of bias, sensitivity analysis could be performed on one study by Mehta et al., which showed a significantly high risk of invasive ventilation with RAAS blocker usage [OR 9.72 (4.35–21.71)]. No such risk was seen in the Chinese population [pooled OR 0.79 (0.55–1.14), I²=0%] or in Europeans [pooled OR 0.64 (0.17–2.46), I²=86%]. Similar trends were observed in
Table 2. Meta-analysis of all outcomes: summary of results.

| Parameter                      | Number of studies (number of patients) | OR (CI) | OR (CI) sensitivity analysis |
|-------------------------------|---------------------------------------|---------|-----------------------------|
| **Mortality**                 |                                       |         |                             |
|                               |                                       | 0.91 [0.65–1.26], I² = 89% | 1.09 [0.71–1.67], I² = 91% |
| Country/Region-specific mortality |                                       |         |                             |
| China                         | 15 (2465)                             | 0.71 [0.52–0.97], I² = 0% | 0.85 [0.48–1.50], I² = 25% |
| Europe                        | 10 (16,022)                            | 1.19 [0.74–1.91], I² = 89% | 1.37 [0.84–2.23], I² = 90% |
| USA                           | 4 (4406)                              | 0.96 [0.59–1.56], I² = 81% | 1.04 [0.39–2.81], I² = 64% |
| Other Asian (South Korean)    | 2 (3539)                              | 1.12 [0.18–7.01], I² = 97% | 1.12 [0.18–7.01], I² = 97% |
| **Severity**                  |                                       |         |                             |
|                              |                                       | 1.08 [0.79–1.46], I² = 88% | 1.32 [0.93–1.87], I² = 91% |
| Definition-wise severity      |                                       |         |                             |
| “Critical” (Chinese classification) | 8 (3396)                             | 0.50 [0.33–0.76], I² = 29% | 0.63 [0.28–1.45], I² = 70% |
| “Severe” (Chinese classification) | 4 (571)                              | 0.71 [0.30–1.69], I² = 54% | 0.14 [0.02–1.13]                |
| ICU/death composite           | 6 (9941)                              | **1.82** [1.31–2.53], I² = 82% | **1.82** [1.31–2.53], I² = 82% |
| Severity (IDSA/ATS)           | 2 (620)                               | 1.36 [0.49–3.80], I² = 69% | 0.86 [0.45–1.61] |
| Others                        | 3 (5599)                              | 2.14 [1.22–3.74], I² = 69% | 2.14 [1.22–3.74], I² = 69% |
| Country/Region-wise severity  |                                       |         |                             |
| China                         | 13 (3002)                             | 0.69 [0.45–1.06], I² = 51% | 0.68 [0.3–1.53], I² = 58% |
| Europe                        | 7 (8814)                              | **2.08** [1.52–2.85], I² = 77% | **2.08** [1.52–2.85], I² = 77% |
| USA                           | 1 (5894)                              | **1.87** [1.62–2.17] | **1.87** [1.62–2.17] |
| Other Asians                  | 2 (2417)                              | 0.62 [0.32–1.23], I² = 69% | 0.62 [0.32–1.23], I² = 69% |
| Disease-wise mortality        |                                       |         |                             |
| HTN                           | 15 (6060)                             | 0.63 [0.46–0.86], I² = 58% | 0.48 [0.36–0.63], I² = 0% |
| Not specified                 | 12 (19,839)                           | 1.58 [1.1–2.27], I² = 82% | 1.81 [1.28–2.58], I² = 81% |
| Others#                       | 4 (533)                               | 0.55 [0.31–0.96], I² = 0% | 0.62 [0.25–1.50] |
| **Hospitalization**           | 7 (15,295)                            | **2.49** [1.40–4.41], I² = 96% | **2.88** [1.61–5.15], I² = 96% |
| Country/Region-wise hospitalization |                                       |         |                             |
| USA                           | 4 (4040)                              | **2.86** [1.13–7.24], I² = 97% | **3.87** [1.21–12.34], I² = 97% |
| Europe                        | 3 (11,255)                            | 2.07 [0.87–4.92], I² = 97% | 2.07 [0.87–4.92], I² = 97% |
| ICU admission                 | 13 (16,441)                           | 1.37 [0.86–2.19], I² = 91% | 1.55 [0.79–3.02], I² = 93% |
| Country/Region-wise ICU admission |                                       |         |                             |
| USA                           | 4 (3376)                              | **1.44** [1.14–1.83], I² = 35% | **1.82** [1.29–2.58], I² = 0% |
| Europe                        | 4 (10,154)                            | 1.51 [0.57–4.03], I² = 93% | 1.51 [0.57–4.03], I² = 93% |

(Continued)
### Table 2. (continued)

| Parameter                          | Number of studies (number of patients) | OR (CI)                      | OR (CI) sensitivity analysis |
|------------------------------------|----------------------------------------|------------------------------|------------------------------|
| China                              | 3 (350)                                | 0.67 (0.35–1.27), $I^2=0\%$  | 0.65 (0.25–1.68), $I^2=0\%$  |
| Other Asians                       | 2 (2561)                               | 2.64 (0.08–85.87), $I^2=97\%$ | 2.64 (0.08–85.87), $I^2=97\%$ |
| Invasive ventilation               | 15 (10,678)                            | 1.06 (0.7–1.59), $I^2=80\%$  | 1.28 (0.58, 2.83), $I^2=88\%$ |
| Country/Region-wise invasive ventilation |                                        |                              |                              |
| USA                                | 3 (4101)                               | 2.33 (1.02–5.36), $I^2=92\%$ | 9.72 (4.35–21.71)            |
| Europe                             | 2 (446)                                | 0.64 (0.17–2.46), $I^2=86\%$ | 0.64 (0.17–2.46), $I^2=86\%$ |
| China                              | 8 (2592)                               | 0.79 (0.55–1.14), $I^2=0\%$  | 1.03 (0.45–2.37), $I^2=50\%$ |
| Other Asians                       | 2 (3539)                               | 1.24 (0.27–5.66), $I^2=92\%$ | 1.24 (0.27–5.66), $I^2=92\%$ |
| Corticosteroid use                 | 7 (1854) [All from China]              | 0.82 (0.65–1.04), $I^2=38\%$ | 1.01 (0.64–1.6), $I^2=35\%$  |
| AKI                                | 5 (2143)                               | 0.94 (0.76–1.16), $I^2=0\%$  | 1.23 (0.52–2.89), $I^2=0\%$  |

*One study each of patients with heart failure, acute cardiac-related injury, diabetes mellitus and hypertension, and elevated cardiac biomarkers. Numbers in bold font indicate odds ratios deemed to be clinically relevant.*

AKI, acute kidney injury; ATS, American Thoracic Society; CI, confidence interval; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; OR, odds ratio.

**Corticosteroid use**

Seven studies ($n=1854$), all from China, commented on corticosteroid use in relation to RAAS blocker use. Use of RAAS blockers did not affect the requirement for corticosteroid use in the overall analysis [pooled OR 0.82 (0.65–1.04), $I^2=38\%$] and also in sensitivity analysis [pooled OR 1.01 (0.64–1.6), $I^2=35\%$] (Supplemental Figure 7 and Table 2).

**Acute kidney injury**

Five studies ($n=2143$) reporting on AKI were analyzed. Use of RAAS blockers was not associated with increased or decreased risk of AKI in overall analysis [pooled OR 0.94 (0.76–1.16), $I^2=0\%$] and also in sensitivity analysis [pooled OR 1.23 (0.52–2.89), $I^2=0\%$]. The latter was based on two studies, both from China (Supplemental Figure 8 and Table 2).

**Mortality and severity analysis of subclasses of RAAS blockers**

**Mortality analysis of patients on ACEIs.** A total of eight studies involving $n=9328$ patients of COVID-19 analyzed specifically the impact of ACEIs on mortality outcome (Supplemental Figure 9 and Supplemental Table 1). No effect of ACEIs on mortality was observed in overall [pooled OR 1.04 (0.63–1.71), $I^2=84\%$] and sensitivity analysis [pooled OR 1.17 (0.6–2.3), $I^2=65\%$]. No difference due to ACEIs could be observed in country-wise analysis of mortality.

**Mortality analysis of patients on ARBs.** A total of eight studies involving $n=9328$ patients of COVID-19 analyzed specifically the impact of ARBs on mortality outcome. The use of ARBs was not found to contribute to increased or decreased mortality [pooled OR 0.99 (0.71–1.39), $I^2=71\%$; and pooled OR 0.92 (0.46–1.81), $I^2=76\%$ in sensitivity analysis]. As with ACEIs, no region-specific differences were observed in mortality with the use of ARBs (Supplemental Figure 10 and Supplemental Table 1).

**Mortality analysis of patients on ACEIs with respect to those on ARBs.** No difference in mortality.
outcomes was seen between users of ACEIs and ARBs in overall analysis [pooled OR 1.07 (0.88–1.32), I²=22%] as well as in sensitivity analysis [pooled OR 1.32 (0.98–1.79), I²=1%] (Supplemental Table 1).

Severity analysis of patients on ACEIs. A total of 13 studies involving n=15,272 patients of COVID-19 explored the severity outcomes with the use of ACEIs and ARBs. The use of ACEIs was not significantly associated with increased risk of severity [pooled OR 1.41 (0.92–2.18), I²=91%] in overall analysis as well as in sensitivity analysis [pooled OR 1.45 (0.89–2.35), I²=92%]. Similarly, definition and region-wise analysis did not show significant effect on COVID severity with ACEI use, in overall and sensitivity analysis (Supplemental Figure 11 and Supplemental Table 1).

Severity analysis of patients on ARBs. Increased risk of severity of COVID-19 was seen with the use of ARBs [pooled OR 1.51 (1.06–2.15), I²=88%]. Results were consistent in sensitivity analysis [pooled OR 1.6 (1.07–2.4), I²=89%]. Region-wise differences in severity outcomes were observed with European studies showing increased risk of worse clinical outcomes [pooled OR 1.41 (1.02–1.95), I²=67%]. Results were replicated in sensitivity analysis [pooled OR 1.41 (1.02–1.95), I²=67%] (Supplemental Figure 12 and Supplemental Table 1).

Severity analysis of patients on ACEIs with respect to those on ARBs. No significant difference in severity outcomes was seen between ACEIs and ARBs in overall [pooled OR 1.00 (0.87–1.14), I²=0%] as well as in sensitivity analysis [pooled OR 0.99 (0.86–1.15), I²=0%] (Supplemental Table 1).

Discussion
Hypertension, diabetes mellitus, cerebrovascular disease, and ischemic heart disease are co-morbidities which are commonly prevalent and found to be responsible for adverse prognosis in patients with COVID-19.56 RAAS blockers are used in majority of these diseases and are known for their disease-modifying roles in ischemic heart disease, congestive heart failure, and diabetic nephropathy. With the observation that SARS-CoV-2 binds preferentially to ACE2, which is prone to upregulation by RAAS blockers, speculations were made that the continuation of RAAS blockers would increase virus binding to host cells and SARS-CoV-2 infectivity. On the contrary, ACE2 is known to be protective against lung injury via the Ang (1–7)–Mas–Mrg D axis.57,58 Ang (1–7) exerts cardiopulmonary protection via vasodilatory, anti-inflammatory, anti-thrombotic and anti-hypertrophic roles.59 Downregulation of ACE2 has been shown to exaggerate lung injury and decrease overall survival of mice subjected to agents with potential pulmonary toxicity.57,58 Some clinical studies and pooled analyses have shown a protective role of ACEIs against pneumonia particularly in older people with hypertension and diabetes mellitus.60,61 Considering this, some groups have hypothesized that upregulation of ACE2 by RAAS blockers might be protective after viral entry, and therapies causing enhancement of ACE2 might be useful in COVID-19.62,63 The confusion surrounding RAAS blockers led to a spurt of observational studies focused on RAAS blockers and COVID-19 outcomes. We have tried to compile information from all such studies and provide insights on association between RAAS blocker use and COVID-19 morbidity and mortality outcomes.

In our meta-analysis, RAAS blocker use was not associated with an increased risk of mortality. A reduced risk of mortality was seen in the Chinese population, but the effect was nullified in sensitivity analysis. RAAS blockers were also found to reduce mortality in hypertensive patients. On the other hand, an increased risk of composite outcome of ICU admission/death was seen with the use of RAAS blockers and this effect persisted in sensitivity analysis.

With respect to severity of COVID-19 disease, although no overall effect of RAAS blockers was evident, a reduced risk of “critical” form of the disease (NHC, China) was observed. This was not validated, however, in sensitivity analysis. Further, while RAAS blockers did not produce any adverse effect on disease severity when analyzed in the entire population, the outcomes differed between countries. RAAS blockers were found not to affect disease severity in Chinese patients but they were associated with nearly a two times higher risk of severe disease in US patients and Europeans. Nearly a four times higher risk of hospitalization was seen with RAAS blocker use in US patients. Similarly, no increase in the risk of ICU admission and invasive
ventilation was seen with RAAS blockers in Chinese patients, whereas US patients on RAAS blockers had an approximately two times higher risk of getting admitted in the ICU or receiving mechanical ventilation.

Though class-wise subgroup analysis did not show any effect on mortality by ACEIs and ARBs, the use of ARBs was associated with 1.6 times higher odds of severe disease, particularly as ICU admission. As with the combined RAAS blocker class, ARBs were also linked with region-specific differences, with high risk particularly in Europeans. Further, with respect to requirement of corticosteroids and causation of renal injury, no risk could be attributed to RAAS blockers. This interpretation is primarily based on sensitivity analysis involving Chinese studies.

These country-specific variations could be due to interplay of genetic factors which may include, but are not limited to, polymorphisms involving \( \text{ACE} \) or \( \text{ACE2} \) genes. \( \text{ACE2} \) is prone to multiple polymorphisms. Traditionally, these have been associated with hypertension as well as reduced blood pressure-lowering response to ACEIs. Some polymorphisms seen predominantly in Europeans, such as K26R, can enhance interaction between SARS-CoV-2 S protein and ACE2, which might lead to increased severity of disease. A preprint analyzed the relationship between \( \text{ACE2} \) polymorphisms and COVID-19 severity in a small cohort of 62 patients. Notably, single nucleotide polymorphisms (SNPs) increasing tissue expression of ACE2 were associated with higher rates of hospitalization while a lower odds of severe disease was seen with SNPs decreasing tissue expression. \( \text{ACE I/D} \) genotype can also influence the severity of COVID-19 pneumonia. Polymorphisms involving \( \text{ACE} \) can influence circulating and tissue levels of ACE as well as of cytokines like IL-6 and kallikreins. Higher enzyme and cytokine levels are seen in those with ID and DD genotypes. \( \text{ACE DD} \) genotype has been shown to be associated with increased cardiovascular morbidity and increased risk of pneumonia in some studies. The pneumonia-protective potential of ACEIs is commonly observed in Asians and is linked with II and ID genotypes prevalent in this population.

A recently published study assessed the relationship between allele frequency ratio of \( \text{ACE I/D} \) genotype and COVID-19 recovery. A trend of lesser severity and early recovery was observed with increasing I/D allele ratio. The study showed that I/D ratio of >1 is seen in China, Japan and East Asia, which are some of the less severely affected countries. On the other hand, I/D ratio of less than 1 (0.4–0.6) has been observed for countries like Italy, the US, Spain, Brazil, and the UK, which are affected the most by COVID-19. The sole contribution of genotypic variations behind severity and mortality is, however, unlikely as some countries like India have an I/D ratio of around 0.11 but have considerably low mortality and severity rates of COVID-19 compared with the West. Environmental, biological and immunological factors can also have additive or decisive roles in modulating COVID-19 severity and mortality.

Individually, the association of higher rates of worse clinical outcomes of COVID-19 with ARB use in Europeans lacks a clear understanding and warrants further research. The higher levels of Ang-I and Ang-II generated under the influence of AT1 receptor blockers can be shunted to Ang (1–7) or Ang-III pathways depending on ACE and ACE-2 and aminopeptidase A (APA) activity. SNPs affecting any of these components can therefore decide the net effect of ARB use. Europeans harbor a higher frequency of D allele of \( \text{ACE} \) to the tune of 82–87\%, which in turn is associated with higher ACE activity, cytokine levels and severity of lung injury.

The neutral effect of RAAS blockers on mortality and a protective effect in hypertensives are consistent with the results of some of the already published meta-analyses. However, among these, the study by Pranata et al. specifically included COVID-19 patients with hypertension, while those by Grover and Oberoi and Zhang et al. included a major study by Mehra et al. which has now been retracted. The number of studies included in these reviews varied from 12 to 16; moreover, severity definition varied considerably across the studies and therefore was difficult to interpret. By incorporating a much larger number of studies in our meta-analysis, we could analyze the correlation between RAAS blocker use and severity as per various definitions. Finally, our review focuses on multiple outcomes such as need for hospitalization, ICU admission, invasive ventilation, steroid use and renal insult, which as per
our knowledge have not been addressed in any pooled analyses so far.

One meta-analysis published while the present study was in peer review included 49 observational studies for main analysis and has also found no effect of RAAS blocker use on severity or mortality outcomes. Similar findings were seen in geographical location-dependent subgroup analysis. The definition of severity used in the study, however, differed from ours. The authors considered the composite of severe COVID-19 as defined in individual studies, ICU admission and mechanical ventilation. Further, individual outcomes were not explored for geographical differences. In contrast, our study assessed severity under specific headings and explored all outcomes for geographical variations. This may explain the ethnicity-related differences in severity outcomes by RAAS blockers observed in our study.

While the present study was in peer review process, numerous other observational studies addressing the association between RAAS blocker use and COVID-19 outcomes were published; their inclusion is, however, beyond the scope of the present study. One such study based on a retrospective cohort of around 43,000 COVID-19 patients is probably the largest observational study to date. No effect of RAAS blockers on overall mortality was seen, in concordance with the highlights of our present study. Similar findings were observed in a phase IV open-label, but observer-blinded, randomized trial (BRACE CORONA) that investigated the effect of continuing versus suspending RAAS blockers in more than 650 hospitalized COVID-19 patients. No difference was seen in the number of days alive and in all-cause mortality at 30 days between the two groups.

Whether dose or duration of treatment of RAAS blockers can influence the COVID-19 outcomes is another potential area to be explored. So far, the few studies addressing this issue have ruled out the possibility of dose or duration effect relationship between RAAS blockers and COVID-19 mortality and severity outcomes. However, for some outcomes such as AKI, 25–31% increase in renal dysfunction has been observed with every 10mg increase of lisinopril or equivalent RAAS blocker. This systematic review has some limitations. The pooled analysis is mainly based on observational studies, which are more likely to have study populations with difference in baseline characteristics and co-interventions than randomized controlled trials. Being observational, the elements of confounding, residual confounding and observer bias also cannot be ruled out. The country-specific subgroup analysis was based on only a small number of studies. Further, the current meta-analysis aimed to generate data related to RAAS blockers and therefore excluded those studies which focused on ACEI and ARB class in isolation and did not provide information about the outcomes in combined RAAS blocker class. However, from the included studies, subgroup analysis was performed to explore the effect of ACEIs and ARBs on mortality and severity outcomes.

Conclusion
There is a need to investigate racial or region/country-specific differences in the clinical outcomes of COVID-19. Genetic polymorphisms may govern the pharmacodynamic response to RAAS blockers in different population groups, as seen in our meta-analysis, and should be explored actively in future. There is a need to explore excess risk of ICU admission and mechanical ventilation in the US and increased severity of COVID-19 disease in Europeans, both of which were found to be associated with RAAS blocker usage. Increased risk of severe disease was replicated especially with ARBs. Overall, the use of RAAS blockers does not seem to have any impact on COVID-19 mortality and severity. In the presence of a protective effect in patients with hypertension, it may be advisable to continue these drugs in those patients with pre-COVID indication for the same. Randomized controlled trials and pharmacogenetic studies are required to generate clear and concise evidence on ethnicity and outcomes in the presence of RAAS blocker use.

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