Ther Adv Drug Saf
2021, Vol. 12: 1–23
DOI: 10.1177/20420986211011345

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

Upinder Kaur, Sankha Shubhra Chakrabarti and Tejas K. Patel

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.

Correspondence to:
Tejas K. Patel
Department of Pharmacology, All India Institute of Medical Sciences, Gorakhpur, UP 273008, India
dr.tkp2006@yahoo.co.in

Upinder Kaur
Department of Pharmacology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India

Sankha Shubhra Chakrabarti
Department of Geriatric Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India

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: Theremay 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

Received: 12 November 2020; revised manuscript accepted: 27 March 2021.

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 subpopulations (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 timepoints 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 $\leqslant 7$ 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.

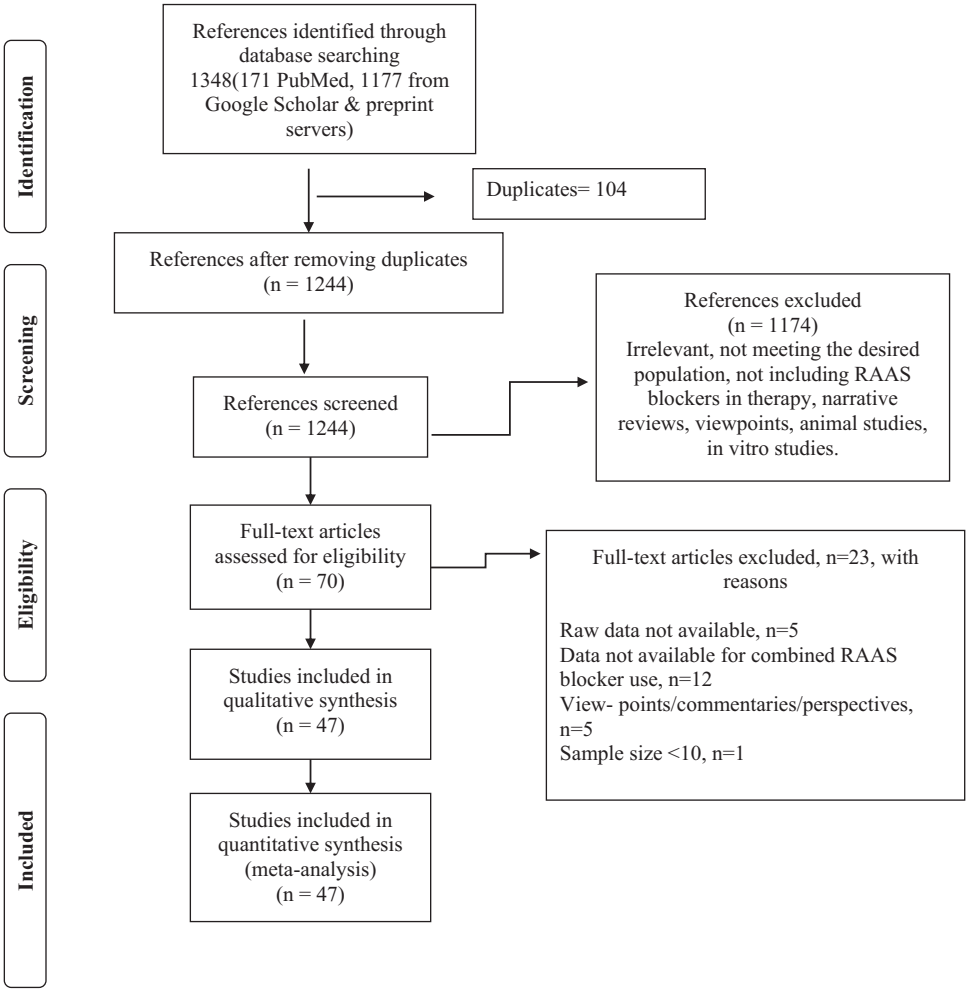

Figure 1. Flow diagram of number of studies screened and selected.

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.[3,7–54] The majority of the studies were from China ($N=20$, 42.5%) followed by Europe ($N=15$, 31.9%). 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.*).[50] 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

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.*[7]	Italy	Retrospective	43 d	28 d	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.*[8]	USA	Retrospective	61 d	NM	Median (IQR) entire sample63 (50–75)	1000 (596/404)	NM	Severity assessed as hospitalization/ ICU admission/ IV	HTN: 60%, DM: 37%, CAD: 13%	No	7
Baker *et al.*[9]	UK	Retrospective	119 d	28 d	Median (IQR) 75 (60–83)	316 (173/143)	NM	Mortality	HTN: 42%, Respiratory diseases: 32%, DM: 26.6%	Yes	10
Bean *et al.*[10]	UK	NM	22 d	7 d	Mean (SD) entire sample 63 (20)	205 (106/99)	NM	Severity¶	HTN: 51%, DM: 30%, IHD/HF: 14.6%	Yes	10
Bravi *et al.*[11]	Italy	Retrospective	NM	24 d	Mean (SD) entire sample58 (20.9)	1603 (758/845); HTN = 543	HTN	Severity¶ and as hospitalization	HTN: 34%, Major CVD: 16%, DM: 12%	Yes	10
Caraballo *et al.*[12]	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.*[13]	China	Retrospective	77 d	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.*[14]	South Korea	Retrospective	116 d	NM	Mean (SD) Users gp- 65 (13) Non-users group- 68 (15)	1585 (679/906)	HTN	Mortality and severityΦa	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.*[15]	Spain	Case Control	24 d	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.*[16]	China	Retrospective	40 d	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)

Table 1. (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)
Dublin *et al.*[17]	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.*[18]	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- DM: 24%, Cancer: 17%, COPD: 9% Non-users gp- DM: 28%, Cancer: 14%, COPD: 14%	Yes	9
Feng *et al.*[19]	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.*[20]	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.*[21]	Denmark	Retrospective	94 d (73 d of Nested CC)	NM	Median (IQR) entire sample 54.7 (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.*[22]	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- DM: 30.1%, Angina: 17.5%, PCI/CABG: 4.9% Non-users gp- DM: 26.6%, Angina: 15.2%, PCI/CABG: 5.3%	Yes	10
Guo *et al.*[3]	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.*[24]	China	NM	23 d	NM	Median (IQR) 57 (49.5–66)	149 (88/61)	HTN	Mortality and Severity*	Users gp- DM: 24.6%, CLD: 7.7%, Renal disease: 6.1% Non-users gp- DM: 16.7%, CLD: 4.76%, Renal disease: 2.4%	No	5

(Continued)

Table 1. (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.*[25]	China	Retrospective	40 d	NM	Mean (SD) entire sample 58 (17)	200 (115/85)	NM	Mortality and Severity assessed by OF/IV[a]	Users gp- HTN: 75%, DM: 25%, CHD: 18% Non-users HTN: 22%, DM: 14%, CHD: 8%	No	8
Huang *et al.*[26]	China	Retrospective	26 d	NM	Mean (SD) Users gp- 52.65 (13.12) Non -users gp- 67.77 (12.84)	50 (27/23)	HTN	Mortality and Severity*	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.*[27]	Italy	NM	22 d	14 d minimum	Mean (SD) entire sample 67 (12)	99 (80/19)	NM	Mortality	HTN: 64%, DM: 31%, DLP: 30%	No	6
Ip *et al.*[28]	USA	Retrospective	NM	NM	<50 to >80 years	1584 with HTN, 1216 with known outcomes	HTN	Mortality	NM	No	7
Jung *et al.*[29]	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- COPD: 27%, DM: 11%, HTN: 10%	Yes	10
Li *et al.*[30]	China	Retrospective	61 d	NM	Median (IQR) entire sample 55.5 (38–67) HTN cohort 66 (59–73)	362 (189/173)	HTN	Mortality and Severity*	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.*[31]	China	Retrospective	38 d	32 d	Median (IQR) entire sample 60 (48–69)	548 (279/269)	NM	Severity#	HTN: 30.3%, DM: 15.1%, CHD: 6.2%	No	8
Liabeuf *et al.*[32]	France	Retrospective	47 d	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)

Table 1. (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)
Mehta *et al.*[33]	USA	Retrospective	36 d	NM	Mean (SD) ACEI gp 63 (15) ARB gp 65 (13)	1735	NM	Mortality and Severity assessed 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.*[34]	China	Retrospective	44 d	NM	Median (IQR) 64.5 (55.8–69)	42 (24/18)	HTN	Mortality and Severity*	Users gp- DM and CHD: 29.4% Non-users gp- DM and CHD: 32%	No	6
Mohamed *et al.*[35]	Australia	NM	NM	Median25 d, minimum 14 d	Non-AKI gp- 66 (23–97) AKI gp- 65 (34–96)	575 (312/263)	NM	Severity assessed as AKI	HTN: 73.7%, DM: 48.8%	No	7
López-Otero *et al.*[36]	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/ HF/ICU admission and composite of HF/death	Users gp- HTN: 98.6%, DLP: 60%, DM: 27.6% Non-users gp- DLP: 19.3%, HTN: 12.1%, DM: 8.7%	Yes	10
Oussalah *et al.*[37]	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%	Yes	10
Regina *et al.*[38]	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%	No	8
Reilev *et al.*[39]	Denmark	NM	64 d	30 d	Median (IQR) entire sample 49 (34–63)	9519 (4010/5509)	NM	Mortality and Severity assessed as ICU admission/ hospitalization	HTN: 25%, Chronic lung disease: 13%, IHD: 9.1%	No	8
Rentsch *et al.*[40]	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%	Yes	10

(Continued)

Table 1. (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)
Reynolds *et al.*[41]	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%, OLD: 14.6%	Yes	10
Rhee *et al.*[42]	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.*[43]	USA	NM	35 d	NM	Median entire sample (IQR) 63 (52–75)	5700 (3437/226); HTN with known outcomes = 1366	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.*[44]	Belgium	Retrospective	47 d	NM	Mean (SD) 86 (7)	154 (51/103)	NM	Severity[ϕϕ]	Users gp- HTN: 93.3%, DM: 20% Non-users gp- HTN: 8.8%, DM: 17.8%	Yes	9
Tan *et al.*[45]	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.*[46]	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.*[47]	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.*[54]	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)

Table 1. (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.*[48]	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.*[49]	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.*[50]	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: 23.4%, CHD: 15.4%, CRD: 3.7% Non-users gp- DM: 20.9%, CHD: 10.9%, CRD: 3%	No	7
Zhou *et al.*[51]	China	Retrospective	145 d	NM	Median (IQR) 35 (32–37)	1043 (563/480), *n* = 976 with known medication history	NM	Severity assessed as ICU admission	Respiratory diseases: 43%, GIT diseases: 32.5%, HTN: 20.2%	No	10
Zhou *et al.*[52]	China	Retrospective	27 d	NM	Mean (SD) 57.7 (14.2) HTN gp- 64.8 (10.1)	110 (60/50), *n* = 36 with HTN (19/17)	HTN	Mortality	HTN: 32.7%, DM: 10%, CVD: 9.1%	Yes	6

"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;
ϕSeverity in terms of composite of death/severe infection, latter including respiratory failure or organ failure leading to mechanical ventilation, ICU admission, RRT and ECMO;
*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;
ϕϕDOH ⩾ 7 d or death;
aThe 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.

legend), and composite of SARS/ICU admission were taken as severe outcome in one study each. In 18 studies, individual health outcomes such as ICU admission, invasive ventilation, AKI, and hospitalization were assessed as mentioned in Table 1. RAAS blockers were used for hypertension in 20 studies (42.5%) while indication for their use was not mentioned in 25 studies (53.2%). Duration of follow-up was mentioned in 13 studies (range 7–32 days). Confounder adjustment had been performed in 22 (46.8%) studies for two major confounders. Twenty-nine studies were considered to have low risk of bias.

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, $I^2 = 91\%$]. 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), $I^2 = 0\%$] (Figure 2). However, in sensitivity analysis, no difference in mortality was observed [pooled OR 0.85 (0.48–1.50), $I^2 = 25\%$]. 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), $I^2 = 81\%$], Europe [pooled OR 1.19 (0.74–1.91), $I^2 = 89\%$], and South Korea [pooled OR 1.12 (0.18–7.01), $I^2 = 97\%$] (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), $I^2 = 58\%$]. A similar trend was observed in sensitivity analysis [pooled OR 0.48 (0.36–0.63), $I^2 = 0\%$]. 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), $I^2 = 88\%$] (Figure 4). A similar result was observed in sensitivity analysis [pooled OR 1.32 (0.93–1.87), $I^2 = 91\%$] (Table 2). Funnel plot was asymmetrical on visual inspection (Supplemental Figure 2).

Comparison of studies with respect to the definition of severity showed a protective effect of RAAS blockers against "critical" disease defined by NHC China [pooled OR 0.5 (0.33–0.76), $I^2 = 29\%$]. Seven out of eight studies assessing this parameter were from China. The effect, however, was nullified on sensitivity analysis [pooled OR 0.63 (0.28–1.45), $I^2 = 70\%$]. On the other hand, RAAS blockers were found to increase the risk of composite outcome of ICU admission and death [pooled OR 1.82 (1.31–2.53), $I^2 = 82\%$] with a similar trend in sensitivity analysis. Among the four studies showing negative impact of RAAS blockers, three involved the European population, one enrolled US patients while none was from China (Supplemental Figure 3 and Table 2).[11,15,32,41]

Region/country-specific analysis also showed an increased risk of poor health outcomes in European patients [pooled OR 2.08 (1.52–2.85), $I^2 = 77\%$] 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), $I^2 = 51\%$], and sensitivity analysis [pooled OR 0.68 (0.3–1.53), $I^2 = 58\%$] (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), $I^2 = 96\%$] as well as in sensitivity analysis [pooled OR 2.88 (1.61–5.15), $I^2 = 96\%$]. Among the seven studies, four involved US patients, three enrolled Europeans while none was from China.[8,17,18,33,39,40,55] 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), $I^2 = 97\%$]

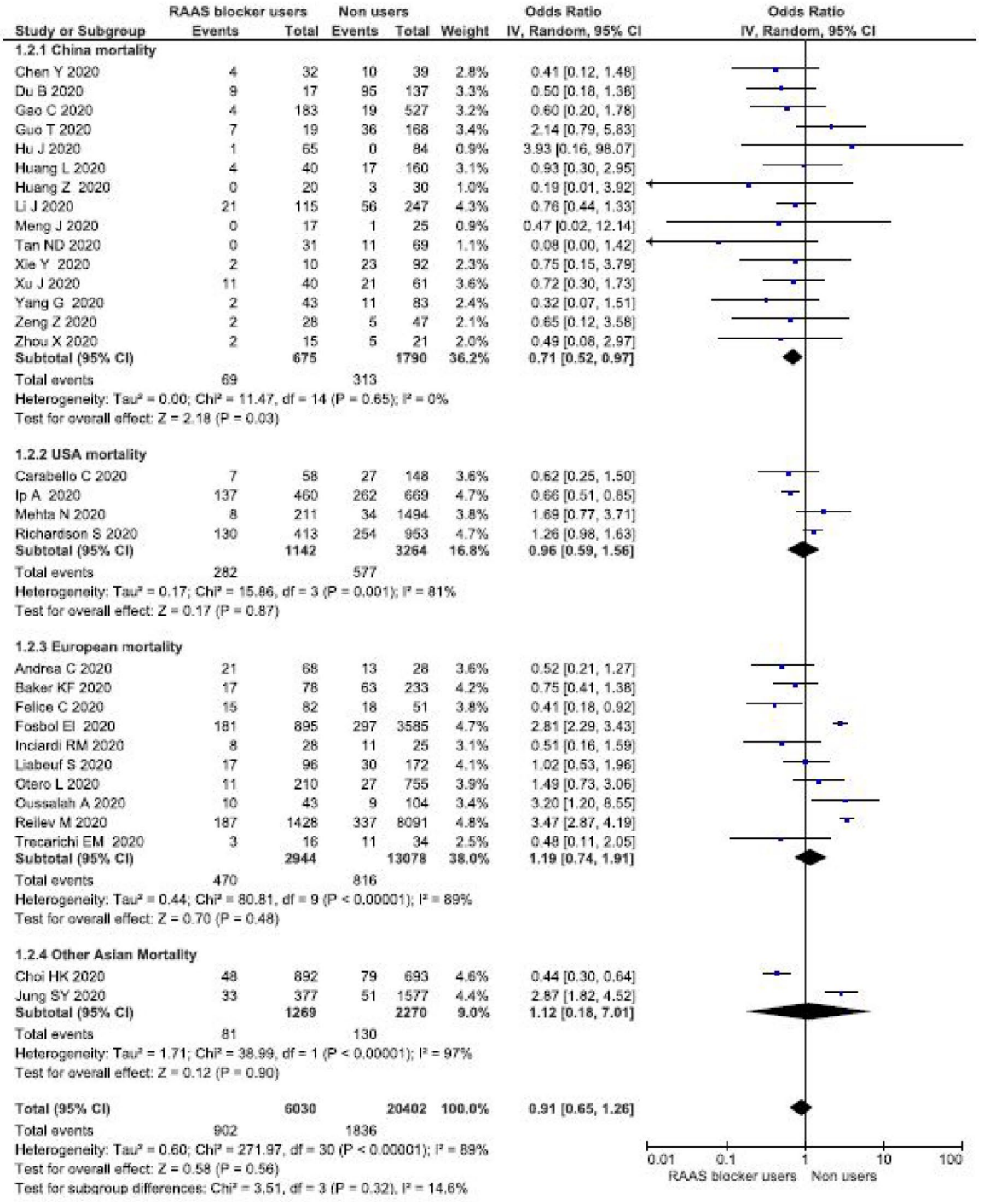

Figure 2. Overall and region-specific mortality effects of renin–angiotensin–aldosterone system (RAAS) blockers in COVID-19 patients (the size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI).

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

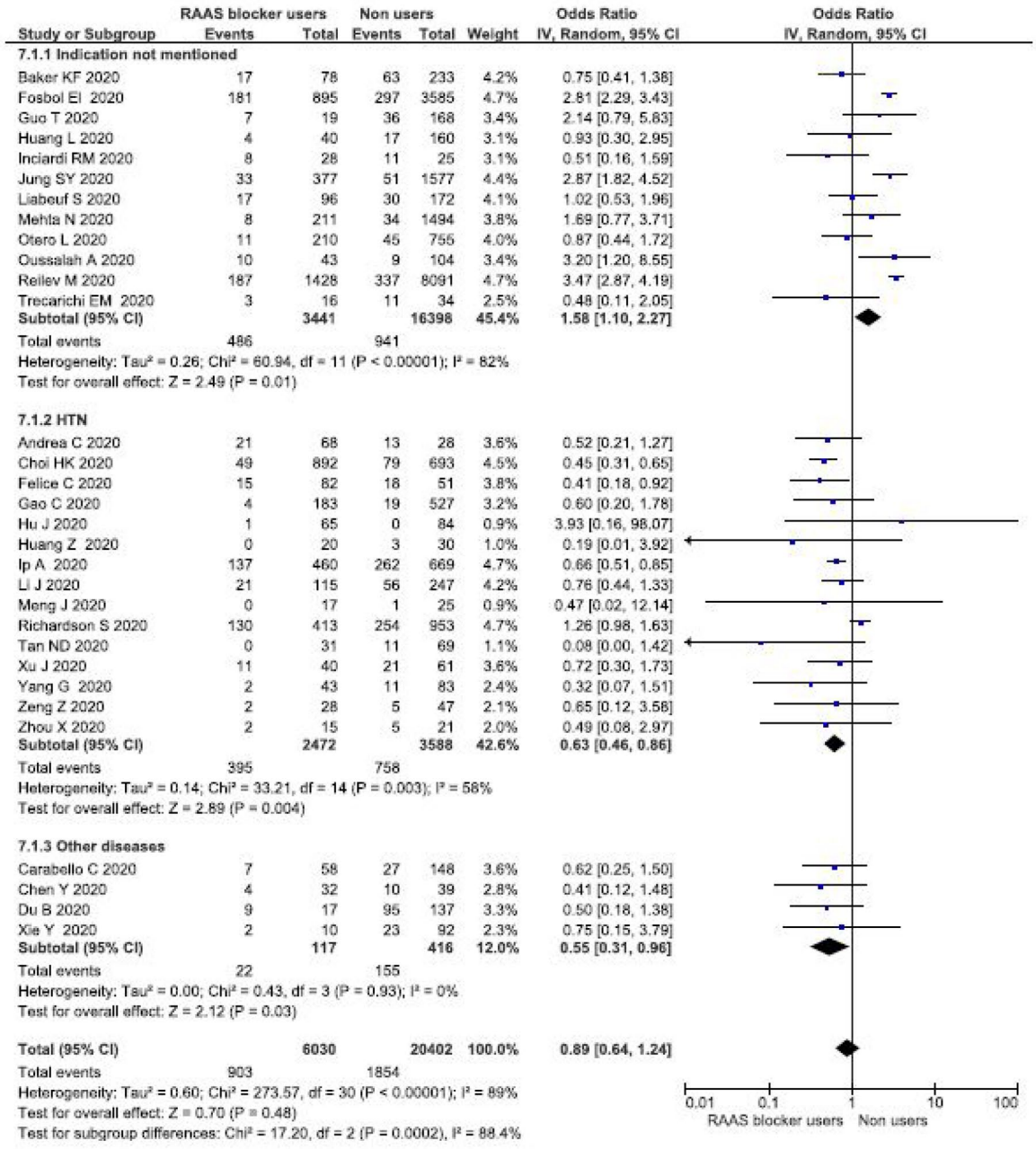

Figure 3. Disease/indication-specific mortality effects of renin–angiotensin–aldosterone system (RAAS) blockers in COVID-19 patients (the size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI).

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).

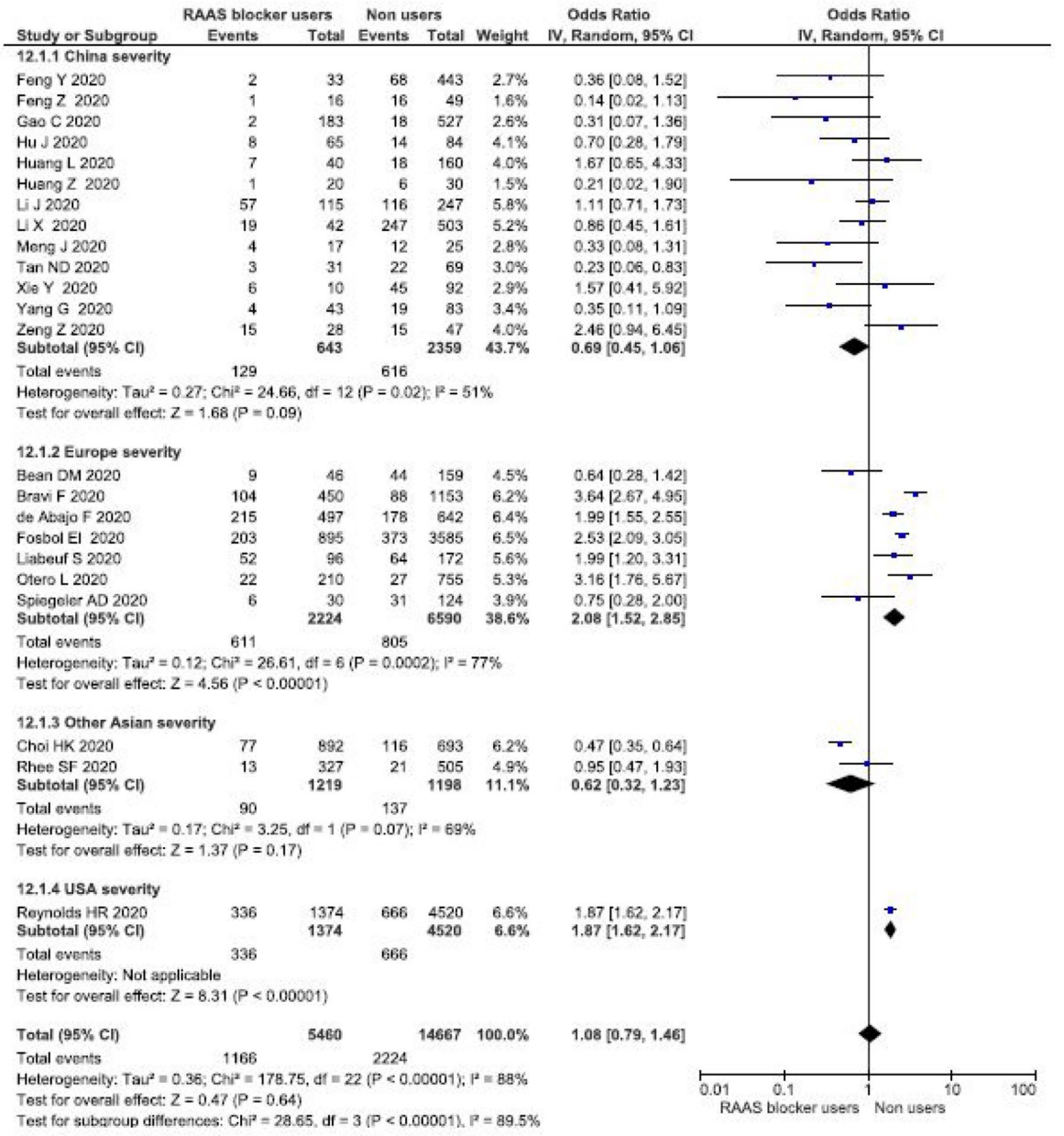

Figure 4. Region-specific severity effects of renin–angiotensin–aldosterone system (RAAS) blockers in COVID-19 patients (the size of squares is proportional to the weight of each study. Horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI).

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), $I^2 = 80\%$] and the result did not vary in sensitivity analysis [pooled OR 1.28 (0.58–2.83), $I^2 = 88\%$]. Country-specific analysis showed an increased risk of invasive ventilation in the US population [pooled OR 2.33 (1.02–5.36), $I^2 = 92\%$]. 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)].[33] No such risk was seen in the Chinese population [pooled OR 0.79 (0.55–1.14), $I^2 = 0\%$] or in Europeans [pooled OR 0.64 (0.17–2.46), $I^2 = 86\%$]. 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	31 (26,432)	0.91 (0.65–1.26), I^2 = 89%	1.09 (0.71–1.67), I^2 = 91%
Country/Region-specific mortality			
China	15 (2465)	0.71 (0.52–0.97), I^2 = 0%	0.85 (0.48–1.50), I^2 = 25%
Europe	10 (16,022)	1.19 (0.74–1.91), I^2 = 89%	1.37 (0.84–2.23), I^2 = 90%
USA	4 (4406)	0.96 (0.59–1.56), I^2 = 81%	1.04 (0.39–2.81), I^2 = 64%
Other Asian (South Korean)	2 (3539)	1.12 (0.18–7.01), I^2 = 97%	1.12 (0.18–7.01), I^2 = 97%
Severity	23 (20,127)	1.08 (0.79–1.46), I^2 = 88%	1.32 (0.93–1.87), I^2 = 91%
Definition-wise severity			
"Critical" (Chinese classification)	8 (3396)	0.50 (0.33–0.76), I^2 = 29%	0.63 (0.28–1.45), I^2 = 70%
"Severe" (Chinese classification)	4 (571)	0.71 (0.30–1.69), I^2 = 54%	0.14 (0.02–1.13)
ICU/death composite	6 (9941)	**1.82** (1.31–2.53), I^2 = 82%	**1.82** (1.31–2.53), I^2 = 82%
Severity (IDSA/ATS)	2 (620)	1.36 (0.49–3.80), I^2 = 69%	0.86 (0.45–1.61)
Others	3 (5599)	2.14 (1.22–3.74), I^2 = 69%	2.14 (1.22–3.74), I^2 = 69%
Country/Region-wise severity			
China	13 (3002)	0.69 (0.45–1.06), I^2 = 51%	0.68 (0.3–1.53), I^2 = 58%
Europe	7 (8814)	**2.08** (1.52–2.85), I^2 = 77%	**2.08** (1.52–2.85), I^2 = 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), I^2 = 69%	0.62 (0.32–1.23), I^2 = 69%
Disease-wise mortality			
HTN	15 (6060)	0.63 (0.46–0.86), I^2 = 58%	0.48 (0.36–0.63), I^2 = 0%
Not specified	12 (19,839)	1.58 (1.1–2.27), I^2 = 82%	1.81 (1.28–2.58), I^2 = 81%
Others[#]	4 (533)	0.55 (0.31–0.96), I^2 = 0%	0.62 (0.25–1.50)
Hospitalization	7 (15,295)	**2.49** (1.40–4.41), I^2 = 96%	**2.88** (1.61–5.15), I^2 = 96%
Country/Region-wise hospitalization			
USA	4 (4040)	**2.86** (1.13–7.24), I^2 = 97%	**3.87** (1.21–12.34), I^2 = 97%
Europe	3 (11,255)	2.07 (0.87–4.92), I^2 = 97%	2.07 (0.87–4.92), I^2 = 97%
ICU admission	13 (16,441)	1.37 (0.86–2.19), I^2 = 91%	1.55 (0.79–3.02), I^2 = 93%
Country/Region-wise ICU admission			
USA	4 (3376)	**1.44** (1.14–1.83) I^2 = 35%	**1.82** (1.29–2.58), I^2 = 0%
Europe	4 (10,154)	1.51 (0.57–4.03), I^2 = 93%	1.51 (0.57–4.03), I^2 = 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% (Based on two Chinese studies)

#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.

the Chinese and Europeans in sensitivity analysis [pooled OR for Chinese population 1.03 (0.45–2.37), I^2 = 50%; pooled OR for Europeans 0.64 (0.17–2.46), I^2 = 86%] (Supplemental Figure 6 and Table 2).

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).[25,54]

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), $I^2 = 22\%$] as well as in sensitivity analysis [pooled OR 1.32 (0.98–1.79), $I^2 = 1\%$] (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), $I^2 = 91\%$] in overall analysis as well as in sensitivity analysis [pooled OR 1.45 (0.89–2.35), $I^2 = 92\%$]. 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), $I^2 = 88\%$]. Results were consistent in sensitivity analysis [pooled OR 1.6 (1.07–2.4), $I^2 = 89\%$]. 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), $I^2 = 67\%$]. Results were replicated in sensitivity analysis [pooled OR 1.41 (1.02–1.95), $I^2 = 67\%$] (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), $I^2 = 0\%$] as well as in sensitivity analysis [pooled OR 0.99 (0.86–1.15), $I^2 = 0\%$] (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 *ACE* or *ACE2* genes. *ACE2* is prone to multiple polymorphisms. Traditionally, these have been associated with hypertension as well as reduced blood pressure-lowering response to ACEIs.[64] 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.[65] A preprint analyzed the relationship between *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.[66] *ACE* I/D genotype can also influence the severity of COVID-19 pneumonia. Polymorphisms involving *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.[67] *ACE* DD genotype has been shown to be associated with increased cardiovascular morbidity and increased risk of pneumonia in some studies.[68,69] The pneumonia-protective potential of ACEIs is commonly observed in Asians and is linked with II and ID genotypes prevalent in this population.[70,71]

A recently published study assessed the relationship between allele frequency ratio of *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.[72] 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.[73,74]

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 *ACE* to the tune of 82–87%, which in turn is associated with higher ACE activity, cytokine levels and severity of lung injury.[75]

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.*[76] specifically included COVID-19 patients with hypertension, while those by Grover and Oberoi[77] and Zhang *et al.*[78] 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.[79] 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.[80] 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.[81]

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.[17,21,80] However, for some outcomes such as AKI, 25–31% increase in renal dysfunction has been observed with every 10 mg increase of lisinopril or equivalent RAAS blocker.[37]

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 ($n = 11$) 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.

Acknowledgement

Dr Patel and Dr Kaur wish to thank the administration of the All India Institute of Medical Sciences, Gorakhpur for providing research support.

Conflict of interest statement

Dr Chakrabarti received consultancy honorarium from Lupin Limited, Intas Pharmaceuticals, Alkem, and lecture honorarium from Novartis. None of the other authors report any conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Upinder Kaur https://orcid.org/0000-0002-8147-4333

Supplemental material

Supplemental material for this article is available online.

References

1. worldometer. Coronavirus, https://www.worldometers.info/coronavirus (accessed 20 April 2021).
2. Xie M and Chen Q. Insight into 2019 novel coronavirus — an updated interim review and lessons from SARS-CoV and MERS-CoV. *Int J Infect Dis* 2020; 94: 119–124.
3. Guo T, Fan Y, Chen M, *et al*. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; 5: 811–818.
4. Ferrario CM, Jessup J, Chappell MC, *et al*. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005; 111: 2605–2610.
5. Ishiyama Y, Gallagher PE, Averill DB, *et al*. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension* 2004; 43: 970–976.
6. Modesti PA, Reboldi G, Cappuccio FP, *et al*. Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. *PLoS One* 2016; 11: e0147601.
7. Andrea C, Francesco M, Antonio N, *et al*. Renin-angiotensin-aldosterone system inhibitors and outcome in patients with SARS-CoV-2 pneumonia: a case series study. *Hypertension* 2020; 76: e10–e12.
8. Argenziano MG, Bruce SL, Slater CL, *et al*. Characterization and clinical course of 1000 patients with COVID-19 in New York: retrospective case series. *medRxiv 2020.04.20.20072116*. DOI: 10.1101/2020.04.20.20072116.
9. Baker KF, Hanrath AT, van der Loeff IS, *et al*. COVID-19 management in a UK NHS foundation trust with a high consequence infectious diseases centre a detailed descriptive analysis. *medRxiv 2020.05.14.20100834*. DOI: 10.1101/2020.05.14.20100834.
10. Bean DM, Kraljevic Z, Searle T, *et al*. ACE-inhibitors and Angiotensin-2 Receptor Blockers are not associated with severe SARS-COVID19 infection in a multi-site UK acute Hospital Trust. medRxiv 2020.04.07.20056788; doi: https://doi.org/10.1101/2020.04.07.20056788.
11. Bravi F, Flacco ME, Carradori T, *et al*. Predictors of severe or lethal COVID-19, including angiotensin converting enzyme inhibitors and angiotensin II receptor blockers, in a sample of infected Italian citizens. *PLoS One* 2020; 15: e0235248.
12. Caraballo C, McCullough M, Fuery M, *et al*. COVID-19 infections and outcomes in a live registry of heart failure patients across an integrated health care system. *medRxiv 2020.04.27.20082016*. DOI: 10.1101/2020.04.27.20082016.
13. Chen Y, Yang D, Cheng B, *et al*. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. *Diabetes Care* 2020; 43: 1399–1407.
14. Choi HK, Koo H-J, Seok H, *et al*. ARB/ACEI use and severe COVID-19: a nationwide case-control study. *medRxiv 2020.06.12.20129916*. DOI: 10.1101/2020.06.12.20129916.
15. de Abajo FJ, Rodríguez-Martín S, Lerma V, *et al*. Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet* 2020; 395: 1705–1714.
16. Du B, Si D, Yang B, *et al*. Modulation of cardiac injury by ACE inhibitor/ARB in patients with severe COVID-19. *Research Square* 2020; 1–11.
17. Dublin S, Walker RL, Floyd JS, *et al*. Renin-angiotensin-aldosterone system inhibitors and COVID-19 infection or hospitalization: a cohort study. *medRxiv 2020.07.06.20120386*. DOI: 10.1101/2020.07.06.20120386.
18. Felice C, Nardin C, Di Tanna GL, *et al*. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives. *Am J Hypertens*. Epub ahead of print 8 June 2020. DOI: 10.1093/ajh/hpaa096.

19. Feng Y, Ling Y, Bai T, *et al*. COVID-19 with different severities: a multicenter study of clinical features. *Am J Respir Crit Care Med* 2020; 201: 1380–1388.
20. Feng Z, Li J, Yao S, *et al*. The use of adjuvant therapy in preventing progression to severe pneumonia in patients with coronavirus disease 2019: a multicenter data analysis. *medRxiv 2020.04.08.20057539*. DOI: 10.1101/2020.04.08.20057539.
21. Fosbøl EL, Butt JH, Østergaard L, *et al*. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *JAMA* 2020; 324: 168–177.
22. Gao C, Cai Y, Zhang K, *et al*. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *Eur Heart J* 2020; 41: 2058–2066.
23. Ou X, Liu Y, Lei X, *et al*. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat Commun* 2020; 11: 1620.
24. Hu J, Zhang X, Zhang X, *et al*. COVID-19 patients with hypertension have more severity condition, and ACEI/ARB treatment have no infulence on the clinical severity and outcome. *J Infect*. Epub ahead of print 28 May 2020. DOI: 10.1016/j.jinf.2020.05.056.
25. Huang L, Chen Z, Ni L, *et al*. Impact of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on inflammatory responses and viral clearance in COVID-19 patients: a multicenter retrospective cohort study. *Research Square* 2020; 1–24.
26. Huang Z, Cao J, Yao Y, *et al*. The effect of RAS blockers on the clinical characteristics of COVID-19 patients with hypertension. *Ann Transl Med* 2020; 8: 430.
27. Inciardi RM, Adamo M, Lupi L, *et al*. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J* 2020; 41: 1821–1829.
28. Ip A, Parikh K, Parrillo JE, *et al*. Hypertension and renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *medRxiv 2020.04.24.20077388*. DOI: 10.1101/2020.04.24.20077388.
29. Jung S-Y, Choi JC, You S-H, *et al*. Association of renin-angiotensin-aldosterone system inhibitors with coronavirus disease 2019 (COVID-19)-related outcomes in Korea: a nationwide population-based cohort study. *Clin Infect Dis*. Epub ahead of print 22 May 2020. DOI: 10.1093/cid/ciaa624.
30. Li J, Wang X, Chen J, *et al*. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol* 2020; 5: 825–830.
31. Li X, Xu S, Yu M, *et al*. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol* 2020; 146: 110–118.
32. Liabeuf S, Moragny J, Bennis Y, *et al*. Association between renin–angiotensin system inhibitors and COVID-19 complications. *Eur Heart J Cardiovasc Pharmacother*. Epub ahead of print 12 June 2020. DOI: 10.1093/ehjcvp/pvaa062.
33. Mehta N, Kalra A, Nowacki AS, *et al*. Association of use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. Epub ahead of print 5 May 2020. DOI: 10.1001/jamacardio.2020.1855.
34. Meng J, Xiao G, Zhang J, *et al*. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect* 2020; 9: 757–760.
35. Mohamed MMB, Lukitsch I, Torres-Ortiz AE, *et al*. Acute kidney injury associated with coronavirus disease 2019 in Urban New Orleans. *Kidney360* 2020; 1: 614–622.
36. López-Otero D, López-Pais J, Cacho-Antonio CE, *et al*. Impact of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on COVID-19 in a western population. CARDIOVID registry. *Rev Esp Cardiol (English Ed)*. Epub ahead of print 5 June 2020. DOI: 10.1016/j.rec.2020.05.018.
37. Oussalah A, Gleye S, Clerc Urmes I, *et al*. Long-term ACE inhibitor/ARB use is associated with severe renal dysfunction and acute kidney injury in patients with severe COVID-19: results from a referral center cohort in the Northeast of France. *Clin Infect Dis*. Epub ahead of print 5 July 2020. DOI: 10.1093/cid/ciaa677.
38. Regina J, Papadimitriou-Olivgeris M, Burger R, *et al*. Epidemiology, risk factors and clinical course of SARS-CoV-2 infected patients in a Swiss university hospital: an observational retrospective study. *medRxiv 2020.05.11.20097741*. DOI: 10.1101/2020.05.11.20097741.

39. Reilev M, Kristensen KB, Pottegaard A, *et al*. Characteristics and predictors of hospitalization and death in the first 9519 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. *medRxiv 2020.05.24.20111823*. DOI: 10.1101/2020.05.24.20111823.

40. Rentsch CT, Kidwai-Khan F, Tate JP, *et al*. Covid-19 testing, hospital admission, and intensive care among 2,026,227 United States veterans aged 54-75 years. *medRxiv 2020.04.09.20059964*. DOI: 10.1101/2020.04.09.20059964.

41. Reynolds HR, Adhikari S, Pulgarin C, *et al*. Renin–angiotensin–aldosterone system inhibitors and risk of covid-19. *N Engl J Med* 2020; 382: 2441–2448.

42. Rhee SY, Lee J, Nam H, *et al*. Effects of a DPP-4 inhibitor and RAS blockade on clinical outcomes of patients with diabetes and COVID-19. *medRxiv 2020.05.20.20108555*. DOI: 10.1101/2020.05.20.20108555.

43. Richardson S, Hirsch JS, Narasimhan M, *et al*. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020; 323: 2052.

44. De Spiegeleer A, Bronselaer A, Teo JT, *et al*. The effects of ARBs, ACEis, and Statins on clinical outcomes of COVID-19 infection among nursing home residents. *J Am Med Dir Assoc* 2020; 21: 909–914.e2.

45. Tan N-D, Qiu Y, Xing X-B, *et al*. Associations between angiotensin-converting enzyme inhibitors and angiotensin II receptor blocker use, gastrointestinal symptoms, and mortality among patients with COVID-19. *Gastroenterology*. Epub ahead of print 16 May 2020. DOI: 10.1053/j.gastro.2020.05.034.

46. Trecarichi EM, Mazzitelli M, Serapide F, *et al*. Characteristics, outcome and predictors of in-hospital mortality in an elderly population from a SARS-CoV-2 outbreak in a long-term care facility. *medRxiv 2020.06.30.20143701*. DOI: 10.1101/2020.06.30.20143701.

47. Xie Y, You Q, Wu C, *et al*. Impact of cardiovascular disease on clinical characteristics and outcomes of coronavirus disease 2019 (COVID-19). *Circ J* 2020; 84: 1277–1283.

48. Yang G, Zhou L, Tan Z, *et al*. Effects of angiotensin II receptor blockers and ACE (Angiotensin-Converting Enzyme) inhibitors on virus infection, inflammatory status, and clinical outcomes in patients with COVID-19 and hypertension: a single-center retrospective study. *Hypertension* 2020; 76: 51–58.

49. Zeng Z, Sha T, Zhang Y, *et al*. Hypertension in patients hospitalized with COVID-19 in Wuhan, China: a single-center retrospective observational study. *medRxiv 2020.04.06.20054825*. DOI: 10.1101/2020.04.06.20054825.

50. Zhang P, Zhu L, Cai J, *et al*. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 2020; 126: 1671–1681.

51. Zhou J, Tse G, Lee S, *et al*. Identifying main and interaction effects of risk factors to predict intensive care admission in patients hospitalized with COVID-19: a retrospective cohort study in Hong Kong. *medRxiv 2020.06.30.20143651*. DOI: 10.1101/2020.06.30.20143651.

52. Zhou X, Zhu J and Xu T. Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on renin-angiotensin system inhibitors. *Clin Exp Hypertens* 2020; 42: 656–660.

53. Peng F, Tu L, Yang Y, *et al*. Management and treatment of COVID-19: the Chinese experience. *Can J Cardiol* 2020; 36: 915–930.

54. Xu J, Huang C, Fan G, *et al*. Use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in context of COVID-19 outbreak: a retrospective analysis. *Front Med*. Epub ahead of print 3 July 2020. DOI: 10.1007/s11684-020-0800-y.

55. Golpe R, Pérez-de-Llano LA, Dacal D, *et al*. Risk of severe COVID-19 in hypertensive patients treated with renin-angiotensin-aldosterone system inhibitors. *Med Clin (Barc)* 2020; 155: 488–490.

56. Yang J, Zheng Y, Gou X, *et al*. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis* 2020; 94: 91–95.

57. Imai Y, Kuba K and Penninger JM. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. *Exp Physiol* 2008; 93: 543–548.

58. Imai Y, Kuba K, Rao S, *et al*. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005; 436: 112–116.

59. Arendse LB, Danser AHJ, Poglitsch M, *et al*. Novel therapeutic approaches targeting the renin-angiotensin system and associated peptides in hypertension and heart failure. *Pharmacol Rev* 2019; 71: 539–570.

60. Caldeira D, Alarcão J, Vaz-Carneiro A, *et al*. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ* 2012; 345: e4260.
61. van de Garde EM, Souverein PC, Hak E, *et al*. Angiotensin-converting enzyme inhibitor use and protection against pneumonia in patients with diabetes. *J Hypertens* 2007; 25: 235–239.
62. Verdecchia P, Cavallini C, Spanevello A, *et al*. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med* 2020; 76: 14–20.
63. Kaur U, Acharya K, Mondal R, *et al*. Should ACE2 be given a chance in COVID-19 therapeutics: a semi-systematic review of strategies enhancing ACE2. *Eur J Pharmacol* 2020; 887: 173545.
64. Fan X, Wang Y, Sun K, *et al*. Polymorphisms of ACE2 gene are associated with essential hypertension and antihypertensive effects of captopril in women. *Clin Pharmacol Ther* 2007; 82: 187–196.
65. Calcagnile M, Forgez P, Iannelli A, *et al*. ACE2 polymorphisms and individual susceptibility to SARS-CoV-2 infection: insights from an *in silico* study. *bioRxiv 2020.04.23.057042*. DOI: 10.1101/2020.04.23.057042.
66. Wooster L, Nicholson CJ, Sigurslid HH, *et al*. Polymorphisms in the ACE2 locus associate with severity of COVID-19 infection. *medRxiv 2020.06.18.20135152*. DOI: 10.1101/2020.06.18.20135152.
67. Dai S, Ding M, Liang N, *et al*. Associations of ACE I/D polymorphism with the levels of ACE, kallikrein, angiotensin II and interleukin-6 in STEMI patients. *Sci Rep* 2019; 9: 19719.
68. Morimoto S, Okaishi K, Onishi M, *et al*. Deletion allele of the angiotensin-converting enzyme gene as a risk factor for pneumonia in elderly patients. *Am J Med* 2002; 112: 89–94.
69. Brown NJ, Blais C, Gandhi SK, *et al*. ACE insertion/deletion genotype affects bradykinin metabolism. *J Cardiovasc Pharmacol* 1998; 32: 373–377.
70. Takahashi T, Morimoto S, Okaishi K, *et al*. Reduction of pneumonia risk by an angiotensin I–converting enzyme inhibitor in elderly Japanese inpatients according to insertion/deletion polymorphism of the angiotensin I–converting enzyme gene. *Am J Hypertens* 2005; 18: 1353–1359.
71. Sagnella GA, Rothwell MJ, Onipinla AK, *et al*. A population study of ethnic variations in the angiotensin-converting enzyme I/D polymorphism. *J Hypertens* 1999; 17: 657–664.
72. Hatami N, Ahi S, Sadeghinikoo A, *et al*. Worldwide ACE (I/D) polymorphism may affect COVID-19 recovery rate: an ecological meta-regression. *Endocrine* 2020; 68: 479–484.
73. Chakrabarti SS, Kaur U, Banerjee A, *et al*. COVID-19 in India: are biological and environmental factors helping to stem the incidence and severity? *Aging Dis* 2020; 11: 480.
74. Mateus J, Grifoni A, Tarke A, *et al*. Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. *Science* 2020; 370: eabd3871.
75. Zheng H and Cao JJ. Angiotensin-converting enzyme gene polymorphism and severe lung injury in patients with coronavirus disease 2019. *Am J Pathol* 2020; 190: 2013–2017.
76. Pranata R, Permana H, Huang I, *et al*. The use of renin angiotensin system inhibitor on mortality in patients with coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Diabetes Metab Syndr* 2020; 14: 983–990.
77. Grover A and Oberoi M. A systematic review and meta-analysis to evaluate the clinical outcomes in COVID-19 patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. *Eur Heart J Cardiovasc Pharmacother*. Epub ahead of print 15 June 2020. DOI: 10.1093/ehjcvp/pvaa064.
78. Zhang X, Yu J, Pan L-Y, *et al*. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: a systematic review and meta-analysis. *Pharmacol Res* 2020; 158: 104927.
79. Xu J, Teng Y, Shang L, *et al*. The effect of prior angiotensin-converting enzyme inhibitor and angiotensin receptor blocker treatment on coronavirus disease 2019 (COVID-19) susceptibility and outcome: a systematic review and meta-analysis. *Clin Infect Dis*. Epub ahead of print 20 October 2020. DOI: 10.1093/cid/ciaa1592.
80. Trifirò G, Massari M, Da Cas R, *et al*. Renin–angiotensin–aldosterone system inhibitors and risk of death in patients hospitalised with COVID-19: a retrospective Italian cohort study of 43,000 patients. *Drug Saf* 2020; 43: 1297–1308.
81. Jia X, Al Rifai M, Hussain A, *et al*. Highlights from studies in cardiovascular disease prevention presented at the digital 2020 European Society of Cardiology Congress: prevention is alive and well. *Curr Atheroscler Rep* 2020; 22: 72.