Original Article

The divergent protective effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on clinical outcomes of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis

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Background: Some studies have speculated that patients on angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are more susceptible to adverse outcomes of coronavirus disease 2019 (COVID-19). Here, we performed a systematic review and meta-analysis to evaluate the safety and efficacy of administering ACEIs and ARBs to patients with COVID-19.

Methods: Studies of COVID-19 were collected from the PubMed, Embase, medRxiv and BioRxiv databases. The pooled relative risk odds ratio (OR) and 95% confidence interval (95% CI) were calculated. Subgroup analyses were conducted by medication (ACEIs and ARBs) and geographical location (China and outside China). Inter-study heterogeneity was assessed using meta-regression. Begg's test, Egger's test and funnel plots were adopted to evaluate possible publication bias.

Results: Thirty studies containing 10,434 adult patients were included in our meta-analysis. The pooled result indicated that the administration of ACEIs or ARBs reduced the risk of severe/death outcomes for COVID-19 patients. Meanwhile, a significant reduction in the risk of severe/death outcomes was observed to be associated with the administration of ACEIs or ARBs among COVID-19 patients in China, but this association was weaker for studies outside China. Furthermore, ACEI therapy was found to carry a significantly lower risk of an adverse clinical outcome.

Discussion: Our systematic review and meta-analysis found that neither ACEIs nor ARBs worsen the clinical outcomes of COVID-19 patients. On the contrary, we found that patients treated with ACEIs or ARBs have a reduced risk of severe/death outcomes, especially in Asia. Furthermore, ACEIs may reduce the risk of severe/death outcomes. Therefore, treatment interruption of ACEI or ARB therapy during COVID-19 infection is not recommended.

Keywords: Coronavirus disease 2019 (COVID-19); angiotensin-converting enzyme inhibitors (ACEIs); angiotensin receptor blockers (ARBs); clinical outcomes; meta-analysis

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first presented as an outbreak of atypical pneumonia in Wuhan, China, on December 12, 2019 (1). Since then, the virus has spread, and as of May 1, 2020, it had caused 3,175,207 infections and claimed 224,172 lives in over 200 countries.

SARS-CoV-2 infection disproportionately affects older people with hypertension, diabetes mellitus, and cardiovascular disease, and patients with these comorbidities are often treated with renin-angiotensin-aldosterone system (RAAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) (2,3).

Antihypertensive drugs, including RAAS inhibitors, have been reported to increase the levels of angiotensin-converting enzyme 2 (ACE2), which is a functional receptor for SARS-CoV-2 (4-6) (*Figure 1*). These observations have prompted concern that the administration of RAAS inhibitors may facilitate coronavirus disease 2019 (COVID-19) infection and worsen the prognosis. Recently, two large, well-conducted studies found that previous treatment with RAAS blockers does not raise the risk of onset or aggravation (including death) of COVID-19 (7,8). Controversially, other studies have reported that COVID-19 patients who received ACEI/ARB therapy were less susceptible to adverse outcomes (9-11).

Given the worldwide use of ACEIs and ARBs and the inconsistency of clinical research results, a comprehensive evaluation of the relationship between ACEIs and ARBs and the clinical outcomes of patients with COVID-19 is urgently needed. Here, we conducted a meta-analysis to comprehensively and quantitatively evaluate the safety and effectiveness of RAAS inhibitor administration in older patients with COVID-19. We present the following article in accordance with the PRISMA and MOOSE reporting checklists (available at https://apm.amegroups.com/article/

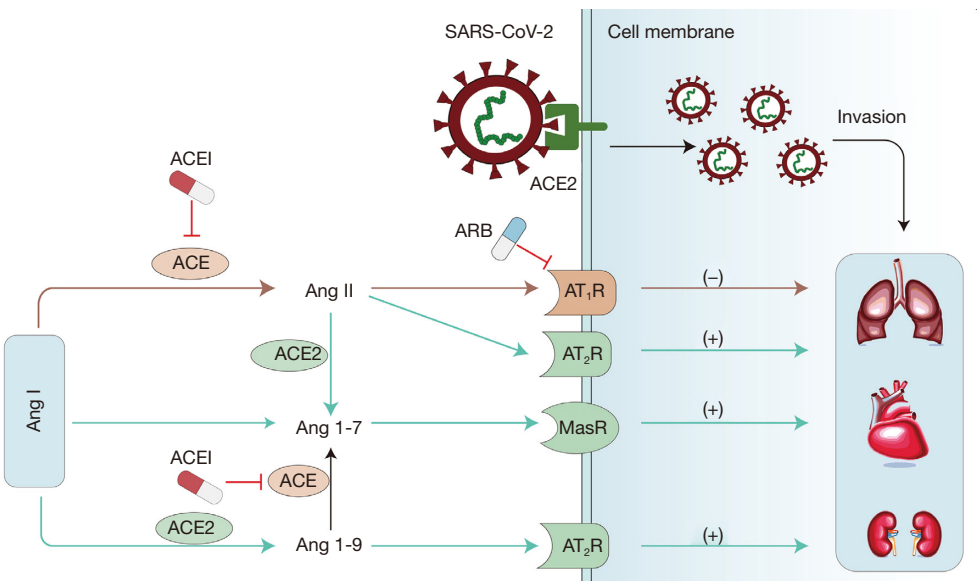

Figure 1 Schematic diagram of the RAS showing the role of ACE2 as a key element in the counter-regulatory axis of the RAS (elements in green). ACE2 opposes the harmful effects of the Ang II-AT_1R axis (elements in brown) on injury by activating MasR and AT_2R signaling. After infection, SARS-CoV-2 binds through its viral spike protein to host cell membrane-bound ACE2, thereby promoting viral cell entry and subsequent replication. Importantly, the binding of SARS-CoV-2 may lead to the downregulation of ACE2. Impairment of ACE2 activity results in the activation of the harmful Ang II-AT_1R axis, which aggravates the viral pathogenicity of SARS-CoV-2, tipping the scale in favor of lung, heart, and kidney damage. ARBs have been shown to increase ACE2 expression in various tissues. Treatment with ACEIs primarily protects against lung injury by reducing Ang II levels through the inhibition of Ang I to Ang II conversion. (+), protection; (–), injury. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; AT_1R, angiotensin II receptor type 1; AT_2R, angiotensin II receptor type 2; MasR, Mas receptor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RAS, renin-angiotensin system.

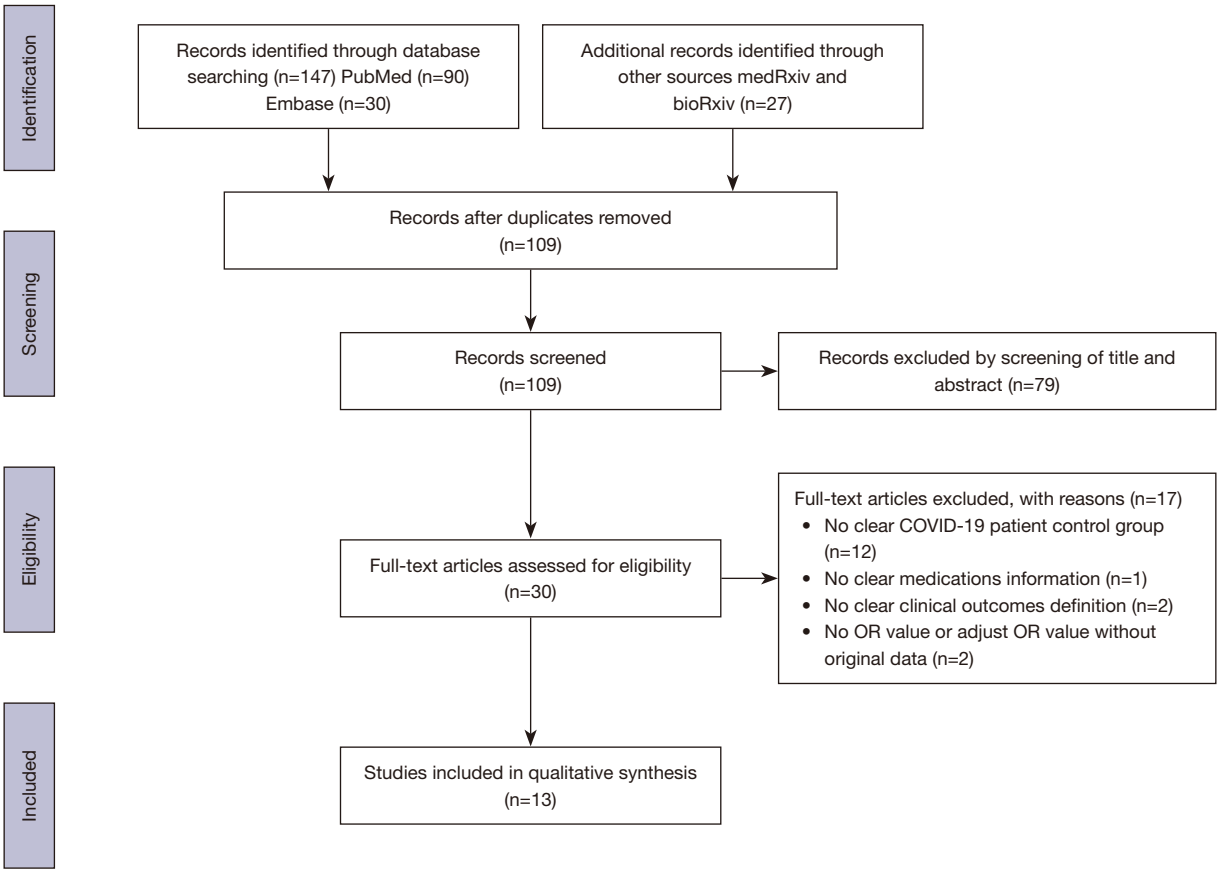

Figure 2 Flowchart depicting the literature search and selection strategy. After applying the inclusion and exclusion criteria, a total of 13 articles were included in the final meta-analysis. COVID-19, coronavirus disease 2019; OR, odds ratio.

view/10.21037/apm-21-972/rc).

Methods

Search strategy

Articles from online databases (PubMed and EMBASE) were searched using specific strategies introduced in Appendix. Preprint articles from medRxiv and BioRxiv were retrieved using the following keywords: COVID19, 2019 novel coronavirus disease, COVID-19 pandemic, SARS-CoV-2 infection, OR COVID-19 virus disease, 2019 novel coronavirus infection, 2019-nCoV infection, 2019-nCoV infection, COVID-19, 2019-nCoV disease, COVID-19 virus infection, and renin-angiotensin-aldosterone system, RAAS, angiotensin-converting enzyme inhibitors, ACEIs, angiotensin II receptor blockers, ARBs. The reference lists of the review articles and selected articles were manually searched to identify additional relevant studies. Studies published between January 01, 2020, and May 05, 2020, were included in our study. No patients were involved in this study.

Eligibility criteria

Studies evaluating the effects of RAAS inhibitor (ACEIs or ARBs) therapy on the clinical outcomes of patients with COVID-19 (severe disease or death during hospitalization) were enrolled (*Figure 2*). Clinical trials, such as those with a randomized or non-randomized, parallel-group, or cluster design, and clinical observational studies, including retrospective or prospective cohort studies and case-control studies, that reported on disease severity/death outcomes and the use of RAAS in patients with COVID-19 were also included in our analysis. Letters or comments with effective control groups were also included. Studies with peer-reviewed and preprint articles were included without language restrictions. Letters or comments, review articles,

case reports, and any articles without effective controls were excluded, as were articles with overlapping samples.

Data selection and extraction

The titles and abstracts of the retrieved articles were independently evaluated by two authors (QX and YL). Articles with titles and abstracts meeting the eligibility criteria were downloaded for further data selection and extraction. Two authors independently read and extracted data from the selected studies in duplicate. Any discordance in data was resolved by the third author (ST). Endnote (X9) was used to manage citations and data extraction. The following data were extracted for the meta-analysis: first authors, year of publication, country of recruitment, study design, type(s) of RAAS inhibitor, clinical outcomes (defined in each study), the number of events, and total cases in each group, crude odds ratio (cOR) value [95% confidence interval (CI)], adjusted OR (aOR) value (95% CI) (if available), and adjusted factors (*Table 1*).

Risk of bias assessment

The study quality was assessed using a qualitative classification method to evaluate the risk of bias (high, moderate or low) (Table S1). Reports were defined as having a low risk of bias if adjustment for both age and sex was reported. Studies reporting adjustment for age or sex were defined as having a moderate risk of bias, while those with no adjustment were classified as high risk. Publication bias was evaluated using Begg's and Egger's asymmetry tests (12,13) and was presented as a funnel plot.

Statistical analysis

In this study, the extracted aOR and cOR values were used to calculate pooled ORs with 95% CIs. I^2 statistics were used to appraise inter-study heterogeneity, with I^2 ≥50% defined as significant heterogeneity. In cases of I^2 <50%, a fixed effects model was used to calculate the pooled OR and 95% CI, and if I^2 ≥50%, a random effects model was used (13). Firstly, we analyzed the effects of primary RAAS inhibitors on severe/death outcomes in patients with COVID-19. Secondly, subgroup analyses were conducted by medication (ACEIs and ARBs) and geographical location (China and outside China). Sensitivity analyses were conducted by (I) deleting each eligible study, in turn, to assess whether one study dominated the results of the meta-analysis; (II) eliminating low-quality studies. Inter-study heterogeneity was calculated by meta-regression analysis. Stata software (Version 15.0) was used to perform all statistical analyses.

Results

Descriptions of the included studies

Our meta-analysis included 33 studies involving 10,434 patients, with 4,414 individuals in the RAAS inhibitor group [including 833 patients (18.87%) with severe/death outcomes] and 6,020 patients in the control group [including 1,134 patients (18.83%) with severe/death outcomes] (*Table 1*) (7-11,14). Besides, all 13 studies had a retrospective design, with 5 studies included from medRxiv (9,11,14-16) and 8 from peer-reviewed databases (7,10,17-20). There were 9 studies from Asia (China) (11,14-21), 2 studies from Europe [from Italy (8) and the UK (9)], and 1 from North America (USA) (7), while 1 study included COVID-19 patients from Asia, Europe and North America (10). Details of the study characteristics are presented in *Table 1*.

RAAS inhibitors were associated with a significantly reduced risk of severe/death outcomes in patients with COVID-19

In the 13 studies, 7 reported the aOR values comparing severe/death outcomes in COVID-19 patients on RAAS inhibitors, with inconsistent results (8-11,15,16,21). Of these studies, Bean *et al.* and Mehra *et al.* (9,10) reported that patients treated with ACEIs had a significantly reduced risk of severe/death outcomes than those who did not receive ACEIs. Feng *et al.* and Zhang *et al.* (11,16) reported that ACEI/ARB therapy had the significant effect of reducing the occurrence of severe/death outcomes. However, Mehra *et al.* did not report the same results for ARBs. The studies of Yan *et al.*, Mancia *et al.* and Feng *et al.* (8,11,15) revealed no significant effects of ACEI/ARB therapy on severe/death outcomes in patients with COVID-19.

In a pool of the 7 studies, we found that RAAS inhibitors reduced the risk of COVID-19 patients developing to severe/death outcomes (overall OR =0.79; 95% CI: 0.63–0.98; P<0.0001), with significant heterogeneity between the included studies (I^2 =54.6%) (*Figure 3*) (8-11,15,16,21). The risk of bias analysis showed that 5 of the 7 adjusted articles were low risk (8,9,15,16,21), while 2 were moderate risk (10,11) (Table S1). The sensitivity analyses revealed no significant differences from the primary analysis (Table S2),

Table 1 Characteristics of the 13 studies included in the meta-analysis

First author	Year, date	Study design	Study location	Medications	Events	Event n [total]	OR (95% CI)			Adjust factors	Adjust OR (95% CI)		
							OR	Low limit	Upper limit		OR	Low limit	Upper limit
Bean	2020.04.11	Retrospective study	UK	ACEI	Severity	5 [9]	0.42	0.14	1	Age, sex, hypertension	0.28	0.09	0.73
				ARBs	Severity	5 [37]	2.4	0.62	9.29	NA	NA	NA	NA
Yang	2020.04.04	Retrospective study	China	ACEI/ARBs	Severity	2 [43]	1.439	0.6	3.46	NA	NA	NA	NA
				ACEI/ARBs	Death	11 [43]	1.976	0.73	5.31	NA	NA	NA	NA
Guo	2020.03.27	Retrospective study	China	ACEI/ARBs	Death	7 [19]	1.976	0.73	5.31	NA	NA	NA	NA
Yan	2020.04.29	Retrospective study	China	ARBs	Severity	20 [53]	0.753	0.37	1.52	Age, sex and BMI	0.77	0.36	1.63
				ACEI	Severity	3 [5]	2.14	0.35	13.24	Age, sex and BMI	1.23	0.19	7.93
Zhang	2020.04.14	Retrospective study	China	ACEI/ARBs	ACEI/ARBs	7 [17]	2.45	0.39	15.5	–	0.73	0.08	6.79
Mancia	2020.03.02	Retrospective study	Italy	ACEI	Severity/death	139 [584]	0.943	0.71	1.17	Drugs and coexisting conditions	0.97	0.88	1.07
				ARBs	Severity/death	187 [739]	1.051	0.86	1.28	Drugs and coexisting conditions	0.96	0.87	1.07
Mehra	2020.03.01	Retrospective study	Asia, Europe and North America	ARBs	Death	16 [770]	1.188	0.84	1.67	Age, sex	1.23	0.87	1.74
				ACEI	Death	38 [556]	0.33	0.2	0.54	Age, sex	0.33	0.2	0.54
Feng	2020.04.10	Retrospective study	China	ACEI/ARBs	Severity	1 [16]	0.6	0.08	4.66	Age, sex	0.41	0.05	3.19
Peng	2020.03.02	Retrospective study	China	ACEI/ARBs	Severity	3 [22]	0.935	0.24	3.62	NA	NA	NA	NA
Reynolds	2020.05.01	Retrospective study	USA	ACEI	Severity	139 [584]	0.84	0.65	1.09	NA	NA	NA	NA
				ARBs	Severity	161 [629]	1	0.78	1.3	NA	NA	NA	NA
Li	2020.04.23	Retrospective study	China	ACEI/ARBs	Severity	57 [115]	1.11	0.71	1.73	NA	NA	NA	NA
				ACEI/ARBs	Death	21 [115]	0.762	0.44	1.33	NA	NA	NA	NA
Meng	2020.03.17	Retrospective study	China	ACEI/ARBs	Severity	4 [25]	0.238	0.06	0.88	NA	NA	NA	NA
Zhang	2020.04.17	Retrospective study	China	ACEI/ARBs	Death	7 [188]	0.353	0.16	0.78	Age, gender, comorbidities	0.42	0.19	0.92

OR, odds ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; NA, no value; BMI, body mass index.

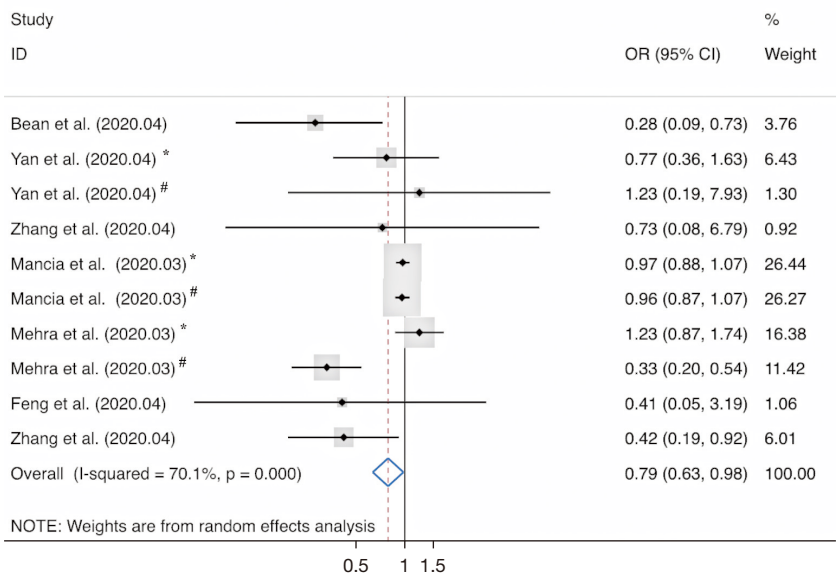

Figure 3 Forest plot showing the effect of RAAS therapy on the risk of adverse clinical outcomes in patients with COVID-19. In this and subsequent figures, the horizontal lines indicate the lower and upper limits of the 95% CI. *, COVID-19 patients with ACEI therapy; #, COVID-19 patients with ARB therapy. OR, odds ratio; CI, confidence interval; RAAS, renin-angiotensin-aldosterone system; COVID-19, coronavirus disease 2019; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

showing the results were reliable. However, no significant reducing effect was observed when the cOR values were pooled (overall OR =0.93; 95% CI: 0.84–1.02; P=0.001; I^2 =56.4%) (Figure S1).

Of the 7 studies included, 4 studies were conducted in China and reported the aOR values (11,15,16,21). Zhang *et al.*'s study reported that ACEI/ARB therapy reduces the effect on patients with COVID-19 (HR =0.42; 95% CI: 0.19–0.92), whereas the other 3 studies did not report the same result. However, in our subgroup analyses, we divided these 4 studies into a China group with aOR values by random effects model, and the results showed a significant reducing effect in this group (overall OR =0.60; 95% CI: 0.37–0.99; P=0.75) with no heterogeneity (I^2 =0.0%) (*Figure 4*). This result was coincident with those of fixed effects analyses (overall OR =0.60; 95% CI: 0.37–0.99; P=0.75) (Figure S2).

ACEIs may be effective in reducing the risk of severe/death outcomes among patients with COVID-19

In the preliminary analysis, no significant effect was observed in the subgroup analysis restricted to COVID-19 patients treated with ACEIs/ARBs (8 studies) (11,14,16-21), ACEIs (5 studies) and ARBs (5 studies) (7-10,15) (data not shown). We further combined data from the ACEI/ARB subgroup into subgroups exclusively, including ACEIs and ARBs, respectively, to obtain more robust results. No significant reducing effect was observed based on the random effects model using cOR values (overall OR =0.76; 95% CI: 0.58–0.99; P<0.002; I^2 =56.7%) (Figure S3). However, as shown in *Figure 5*, the benefits of ACEI and ACEI/ARB treatment on reducing the risk of severe/death outcomes were further observed depending on the aOR values (overall OR =0.52; 95% CI: 0.28–0.96; P<0.0001, I^2 =77.7%). In contrast, no significant effect was observed when the ACEI/ARB group was combined with the ARBs group (overall OR =0.96; 95% CI: 0.87–1.06; P=0.205; I^2 =30.7%) (Figure S4).

Meanwhile, subgroup analysis by China and outside China using aOR values were also performed. A reducing effect was observed in the China group (overall OR =0.50; 95% CI: 0.26–0.97; P<0.747; I^2 =0.0%) by fixed effects analysis (Figure S5).

Heterogeneity and publication bias

Significant heterogeneity was found in the pooled meta-analysis to estimate the association of medications and the occurrence of severe/death outcomes, with an I^2 of 70.1%

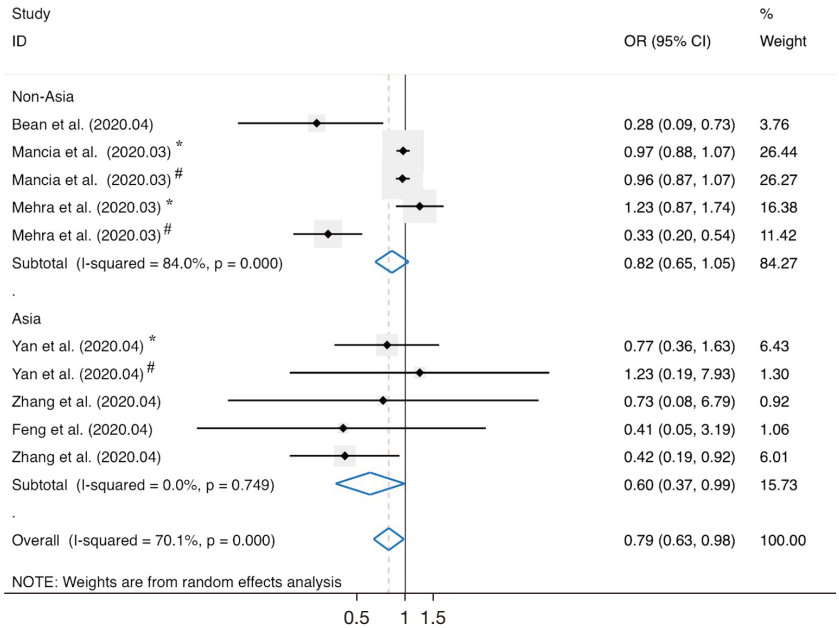

Figure 4 Forest plot showing the effect of different study locations on the risk of adverse clinical outcomes in patients with COVID-19. *, COVID-19 patients with ACEI therapy; #, COVID-19 patients with ARB therapy. OR, odds ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

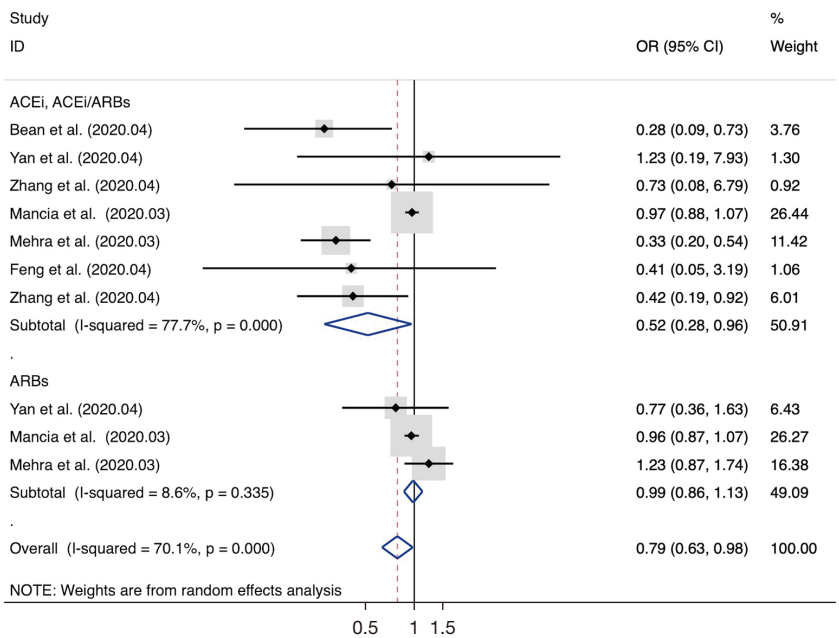

Figure 5 Forest plot showing the effect of different medications on the risk of adverse clinical outcomes in patients with COVID-19. OR, odds ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; COVID-19, coronavirus disease 2019.

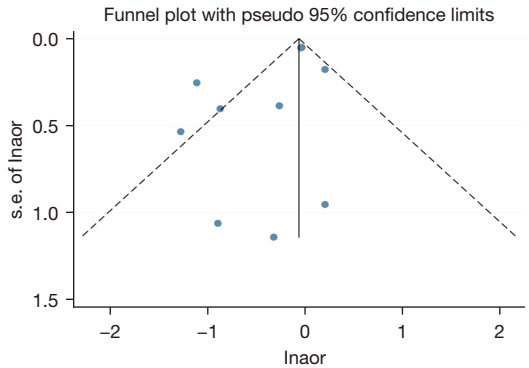

Figure 6 Funnel plot for the publication bias in the overall analysis.

(P<0.000). According to the meta-regression analyses based on factors including medications, clinical outcomes, journal, study location, and total case number, no variables were statistically significantly associated with the effects of medications and severe/death outcomes in patients with COVID-19 (Table S3).

In the overall analysis of the risk relationship between RAAS inhibitors and poor clinical outcomes in patients with COVID-19, the publication bias funnel plots were symmetrical, suggesting no evident publication bias (*Figure 6*). Both Begg's and Egger tests indicated no significant publication bias (P=0.833 and P=0.822 for cOR; P=0.324 and P=0.325 for aOR) (Tables S4,S5).

Discussion

Our meta-analysis of 13 eligible studies showed that neither ACEIs nor ARBs were harmful to COVID-19 outcomes. The odds of COVID-19 patients who are treated with ACEIs and/or ARBs having a severe/death clinical outcome were lower (21%) than those of patients without RAAS inhibitor treatment. These findings are in line with those of a previous systematic review study which identified a reduced risk of pneumonia in patients treated with ACEIs/ARBs along with an association between the use of ACEIs and a reduction in pneumonia-related mortality (22).

The mechanisms by which RAAS inhibitors reduce the risk of adverse outcomes of COVID-19 remain inconclusive. However, multiple animal studies have proved that activating the Ang II-AT_1R pathway triggered by the downregulation (or loss) of ACE2 in the RAAS system might be a contributing mechanism of SARS-CoV-mediated acute lung injury, especially acute respiratory distress syndrome (23-27). Therefore, we speculate that RAAS inhibitors might protect COVID-19 patients from severe acute lung injury in the same manner.

Meanwhile, extensive epidemiological evidence shows that COVID-19 infection can cause myocardial injury (28-32) and worsen and complicate pre-existing conditions, leading to death from cardiovascular events (2,28). Given that the role of RAAS inhibitors in the pathophysiology of cardiovascular disease is well-established (13,17), we hypothesized that the protective effect of RAAS inhibitors on COVID-19 outcomes might lie in their effects on both lung injury and the cardiovascular system.

Interestingly, a pooled OR calculated using the cOR values in our study failed to show any statistical correlation between the use of RAAS inhibitors and COVID-19 outcomes until we made an estimate using aOR values. Therefore, we assumed that some studies found no protective effect of RAAS inhibitors may contribute to concluding from the unadjusted results (16,29).In this respect, the findings from a landmark study involving 8,910 patients may more strongly justify the role of RAAS inhibitors in COVID-19 treatment by considering a wide range of confounders, including age and sex and comorbidities (10).

In our subgroup analysis, estimates using data exclusively regarding ACEIs and ARBs, respectively, failed to obtain a significant effect, mainly due to fewer studies including data for this exclusive group. However, the effect of ACEIs obtained from the pooled data of ACEIs, and ACEIs/ARBs might be underestimated since different medication stratification strategies obtained similar results, with COVID-19 patients on ACEIs being less susceptible to poor clinical outcomes compared with those not treated with RAAS inhibitors. Meanwhile, such a significant association was not observed in patients on ARBs. Although significant statistical heterogeneity for ACEIs existed, all estimates for study designs shared the same direction. Previous systematic meta-analyses have repeatedly demonstrated that ACEI treatment is more effective in reducing the risk of pneumonia, cardiovascular disease and death (22,30-33). In light of the above consistency, we interpreted that ACEIs might have a more favorable effect than ARBs for COVID-19 patients; however, further evidence is warranted to confirm this. Concerning the mechanism of action, bradykinin accumulation resulting from the use of ACEIs is regarded as an important and unique reason responsible for cardiovascular protection, especially in the prevention of ischemia-reperfusion injury and the improvement of endothelial function (34).

Our analyses showed that most of the potential protective benefits of RAAS inhibitors seemed to be observed in Chinese patients. This finding was inconsistent with Grover's meta-analysis (preprint publication) regarding the effect of ACEIs/ARBs on Chinese COVID-19 patients. However, we cast doubt on the rationality of the analytical method and the reliability of the results of Grover's study since all of its analyses were based on cORs, the ACEI and ARB data were pooled directly, and repetitive studies were included (studies from Meng *et al.* and Liu *et al.*) (20,29,35). In agreement with our findings, the previous meta-analysis also reported that Asian patients could benefit more from treatment with ACEIs in reducing the risk of pneumonia (22). Mechanistically, the high expression of ACE2 in Asians may account for the differences in the protective effect of ACEIs, since a higher level of ACE2 is related to a favorable prognosis of COVID-19 infection (36). However, in general, our conclusions are weak, as the studies from China were retrospective observational studies with small sample sizes. It is unclear whether the methodology of the studies or the clinical and genetic characteristics of the patients were responsible for this finding.

Our meta-analysis estimated the pooled effect using aOR values to obtain more robust results; however, this study still has limitations. Firstly, we analyzed factors using subgroup and meta-regression in our study, but we could not obtain individual data to address the within-study heterogeneity. Secondly, most studies were retrospective studies or included retrospective cohorts, which limited our ability to infer the real causal relationship. Thirdly, some studies included in this meta-analysis were collected from preprint manuscripts without peer review. Finally, the studies included from Asia were all conducted in native Chinese populations, and studies from broad geographic areas should be evolved over time. Strengths and limitations of this study are as follows: (I) our systematic review and meta-analysis found that neither ACEIs nor ARBs worsen the clinical outcomes of COVID-19 patients. (II) Patients who accepted ACEI or ARB therapy had a reduced risk of severe/death outcomes, especially in Asia. (III) ACEIs may play a more effective role in lowering the risk of severe/death outcomes in patients with COVID-19.

Conclusions

Our results suggest that neither ACEIs nor ARBs are harmful to COVID-19 outcomes, and ACEIs might have a more favorable effect than ARBs in treating COVID-19 patients with comorbidities. Therefore, interrupting ACEI/ARB therapy to prevent severe/death from COVID-19 infection is not recommended. Furthermore, for the first time, our study has identified that Asian COVID-19 patients with comorbidities might benefit more from treatment with ACEIs, although the robustness of the evidence is weak. Together, our findings provide new insights into clinical strategies to improve the treatment and prognosis of patients with COVID-19.

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Footnote

Reporting Checklist: The authors have completed the PRISMA and MOOSE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-972/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-972/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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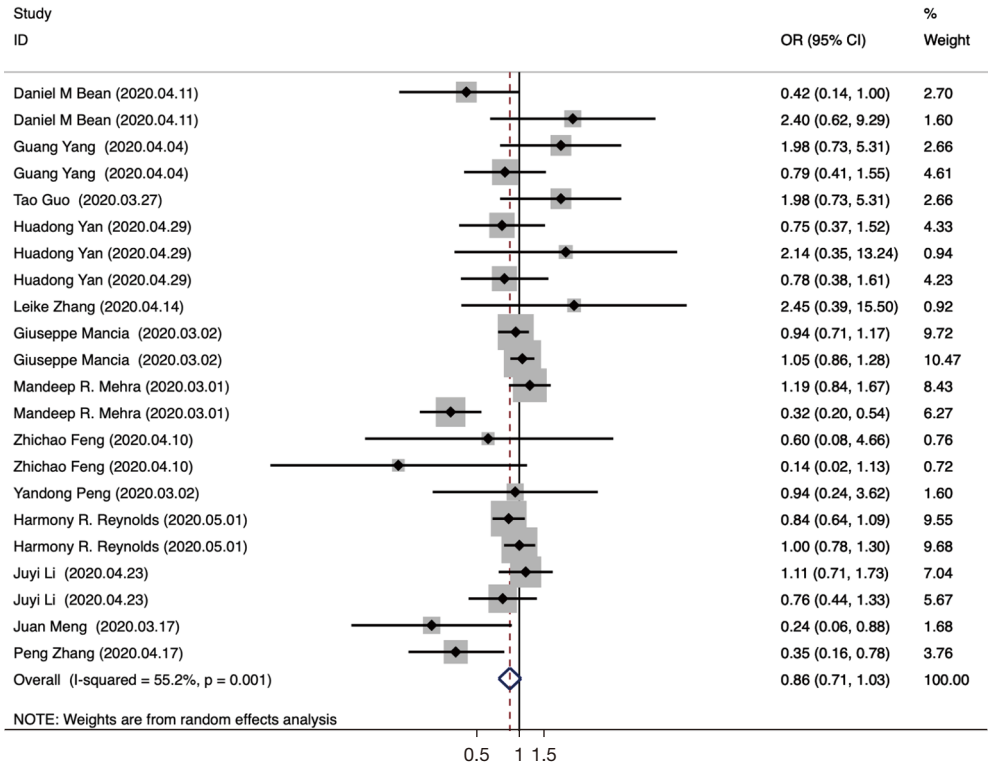

Figure S1 Forest plot showing the effect of medications on the risk of total and different clinical outcomes COVID-19-infected patients by random effects model analysis with crude OR values. In this and subsequent figures, the horizontal lines indicate the lower and upper limits of the 95% CI, the size of the gray squares reflects the relative weight of each study in the meta-analysis. COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval.

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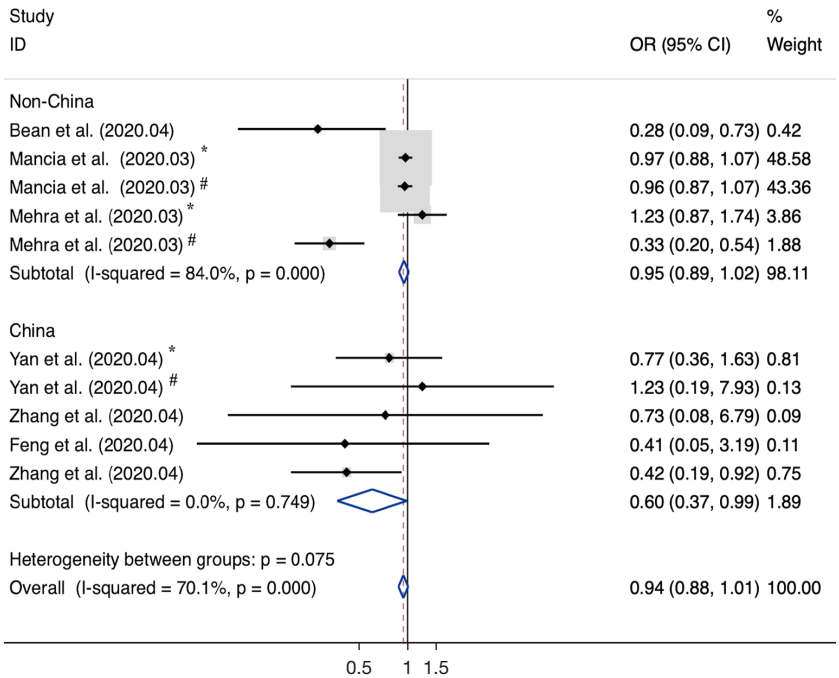

Figure S2 Forest plot showing the effect of study locations on the risk of clinical outcomes SARS-CoV-2-infected patients depending on adjust OR values using fixed effects model analysis. OR, odds ratio; CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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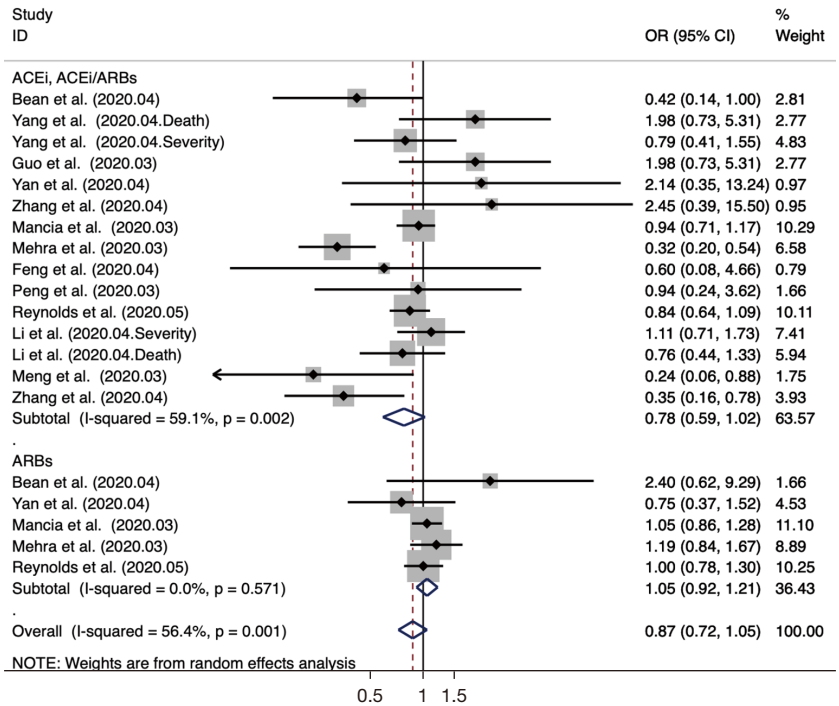

Figure S3 Forest plot showing the effect of different medications on the risk of COVID-19 patients' clinical outcomes by random effects model analysis with crude OR values. OR, odds ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; COVID-19, coronavirus disease 2019.

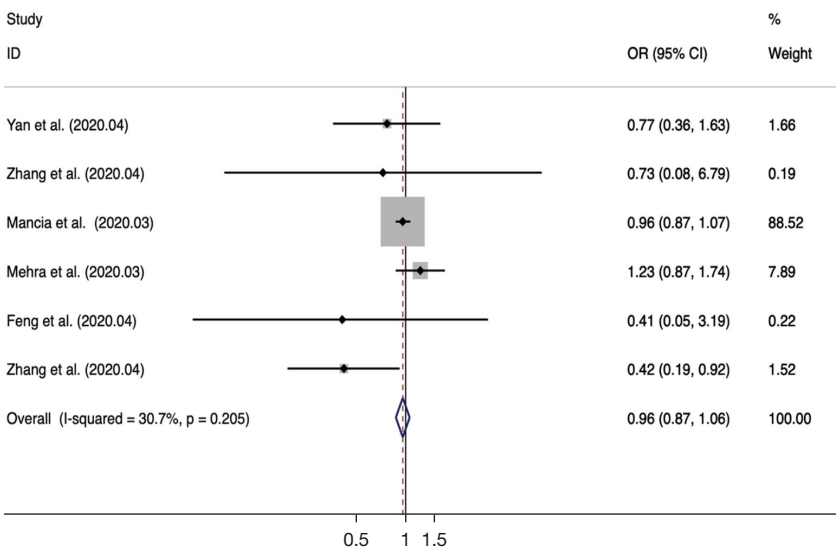

Figure S4 Forest plot showing the effect of ARBs, ACEI/ARBs medications on the risk of clinical outcomes SARS-CoV-2-infected patients depending on adjust OR values using random effects model analysis by fixed effects modle analysis. OR, odds ratio; CI, confidence interval; ARBs, angiotensin receptor blockers; ACEI, angiotensin-converting enzyme inhibitor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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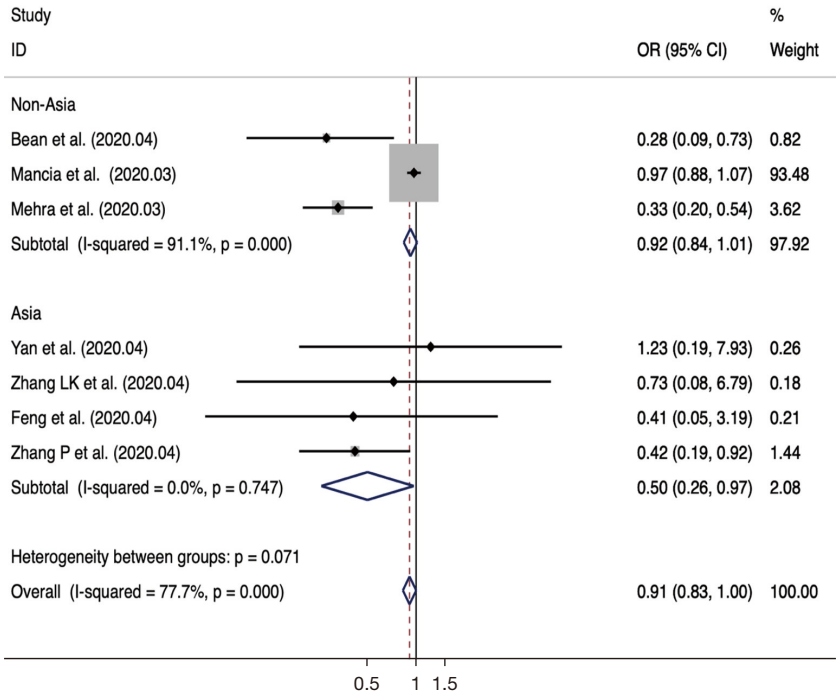

Figure S5 Forest plot showing the effect of ACEI, ACEI/ARBs medication on the risk of clinical outcomes SARS-CoV-2-infected patients depending on adjust OR values using random effects model analysis. OR, odds ratio; CI, confidence interval; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Table S1 Risk of bias in studies providing relative risk estimates

First author	Adjusted confounders				Risk of bias
	Year	Age	Sex	Other confounders	
Bean	2020	Yes	Yes	Hypertension, diabetes mellitus, ischaemic heart disease, heart failure	Low risk
Yang	2020	Yes	Yes	None	Moderate risk
Guo	2020	None	None	None	High risk
Yan	2020	Yes	Yes	BMI	Low risk
Zhang	2020	Yes	Yes	The delay from symptom onset to hospital admission, and therapies administration	Low risk
Mancia	2020	Yes	Yes	Drugs and coexisting conditions	Low risk
Mehra	2020	Yes	Yes	None	Moderate risk
Feng	2020	Yes	Yes	None	Moderate risk
Peng	2020	None	None	None	High risk
Reynolds	2020	Yes	Yes	Race; ethnic group; BMI; smoking history; history of hypertension, myocardial infarction, heart failure, diabetes, chronic kidney disease, and obstructive lung disease	Low risk
Li	2020	Yes	Yes	None	Moderate risk
Meng	2020	None	None	None	High risk
Zhang	2020	Yes	Yes	Conditions	Low risk

Risk of bias assessed by level of adjustment. Low risk, adjustment of age, sex, and at least one other covariate; Moderate risk, adjustment of at least age and sex; High risk, no adjustment. BMI, body mass index.

Table S2 Sensitivity analyses to evaluate the contribution of each study to the pooled estimation by excluding each of the studies one after the others

Study author	Atrial fibrillation OR with 95% CI after removing the study
Bean	0.83 (0.68–1.02)
Yang	0.79 (0.62–0.99)
Yan	0.78 (0.62–0.98)
Zhang	0.79 (0.63–0.98)
Mancia	0.65 (0.44–0.97)
	0.65 (0.44–0.97)
Mehra	0.72 (0.57–0.92)
	0.94 (0.82–1.08)
Feng	0.79 (0.64–0.99)
Zhang	0.83 (0.67–1.02)

OR, odds ratio; CI, confidence interval.

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Table S3 Meta regression estimate outcomes of between-study variance

Group	Covariates	Exp (B)	Std. Err	*t*	P value	95% CI	
By crude OR	Study location	–0.073	0.143	–0.51	0.620	–0.376	0.230
	Journal	–0.458	0.748	–0.61	0.549	–2.036	1.121
	Medications	0.177	0.216	0.82	0.424	–0.278	0.631
	Article risk	–0.150	0.298	–0.50	0.622	–0.779	0.479
	Total case number	–0.053	0.054	0.095	0.355	–0.064	0.016
By adjust OR	Study location	–0.057	0.289	–0.20	0.85	–0.763	0.845
	Journal	–0.353	0.953	–0.37	0.724	–2.685	1.980
	Medications	0.052	0.324	0.16	0.877	–0.740	0.845
	Article risk	–0.353	0.953	–0.37	0.724	–2.685	1.980
	Total case number	–0.646	0.860	–0.75	0.468	–2.586	1.564

Exp (B), exponential (B); Std. Err, standard error; CI, confidence interval; OR, odds ratio.

Table S4 Egger's test for small-study effects

Group	Std_Eff	Coef.	Std. Err.	*t*	P value	95% CI	
By crude OR	Slope	0.019	0.124	0.15	0.883	–0.240	0.277
	Bias	–0.539	0.532	–1.01	0.324	–1.649	0.572
By adjust OR	Slope	0.025	0.074	0.35	0.735	–0.145	0.197
	Bias	–1.222	0.673	–1.82	0.107	–2.775	0.330

Std_Eff, standard effects; Coef., coefficient; Std. Err, standard error; CI, confidence interval; OR, odds ratio.

Table S5 Begg's test for small-study effects

Group	Adj. Kendall's score	Std. Dev. of score	Number of studies	z	P value	z continuity corrected	P continuity corrected
By crude OR	–8	35.46	22	–0.23	0.822	0.20	0.844
By adjust OR	–11	11.18	10	–0.98	0.325	0.89	0.371

Adj., adjust; Std. Dev., standard deviation; OR, odds ratio.

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Appendix: search criteria

PubMed

#1. ((((((((((COVID19[Title/Abstract]) OR COVID-19[Title/Abstract]) OR 2019 novel coronavirus disease[Title/Abstract]) OR SARS-CoV-2[Title/Abstract]) OR COVID-19 virus disease[Title/Abstract]) OR 2019 novel coronavirus infection[Title/Abstract]) OR 2019-nCoV infection[Title/Abstract]) OR 2019-nCoV infection[Title/Abstract]) OR coronavirus disease 2019[Title/Abstract]) OR 2019-nCoV disease[Title/Abstract]) OR COVID-19 virus infection[Title/Abstract]

#2. (Renin–angiotensin–aldosterone System[Title/Abstract]) OR RAAS[Title/Abstract]

#3. (((angiotensin converting enzyme inhibitors[Title/Abstract]) OR ACEIs[Title/Abstract]) OR ACEis[Title/Abstract]) OR ACEi[Title/Abstract]

#4. ((angiotensin receptor blockers[Title/Abstract]) OR ARBs[Title/Abstract]) OR ARB[Title/Abstract]

#5. #3 OR #4

#6. #2 OR #5

#7. #1 AND #6

Embase

1. COVID19. ab. ti.
2. SARS-CoV-2. ab. ti.
3. 2019-nCoV disease. ab. ti.
4. 2019-nCoV. ab. ti.
5. coronavirus disease 2019. ab. ti.
6. 1or 2or 3or 4or 5or
7. Renin–angiotensin–aldosterone System. ab. ti.
8. RAAS. ab. ti.
9. angiotensin converting enzyme inhibitors. ab. ti.
10. ACEIs. ab. ti.
11. ACEis. ab. ti.
12. ACEi. ab. ti.
13. angiotensin receptor blockers. ab. ti.
14. ARBs. ab. ti.
15. ARB. ab. ti.
16. 7 or 8
17. 9 or 10 or 11 or 12
18. 13 or 14 or 15
19. 16 or 17 or 18
20. 6 and 19

https://dx.doi.org/10.21037/apm-21-972