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The use of renin angiotensin system inhibitor on mortality in patients with coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis

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ABSTRACT

Background: and Aims; To investigate the association between use of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin-receptor blocker (ARB) and outcomes of hypertensive COVID-19 patients, a systematic review and meta-analysis were performed.
Methods: We systematically searched PubMed, EuropePMC, ProQuest, and Cochrane Central Databases using the terms "(COVID-19 OR SARS-CoV-2) AND (angiotensin converting enzyme OR angiotensin receptor blocker)". The primary and second outcomes were mortality (non-survivor) and severe COVID-19, respectively.
Results: Totally, 7410 patients were included from 15 studies. Pooled analysis showed that the use of ACEI/ARB was not associated with mortality (OR 0.73 [0.38, 1.40], p = 0.34; I^2: 81%) and severity (OR 1.03 [0.73, 1.45], p = 0.87; I^2: 65%). Pooled adjusted OR showed no risk/benefit associated with ACEI/ARB use in terms of mortality (OR 0.83 [0.54, 1.27], p = 0.38; I^2: 0%). Subgroup analysis showed that the use of ARB was associated with reduced mortality (OR 0.51 [0.29, 0.90], p = 0.02; I^2: 22%) but not ACEI subgroup (OR 0.68 [0.39, 1.17], p = 0.16; I^2: 0%). Meta-regression showed that the association between ACEI/ARB use and mortality in patients with COVID-19 do not varies by gender (p = 0.104). GRADE showed a very low certainty of evidence for effect of ACEI/ARB on mortality and severity. The certainty of evidence was very low for both ACEI and ARB subgroups.
Conclusion: Administration of a renin angiotensin system (RAS) inhibitor, was not associated with increased mortality or severity of COVID-19 in patients with hypertension. Specifically, ARB and not ACEI use, was associated with lower mortality.

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1. Introduction

Coronavirus disease 2019, commonly known as COVID-19, is a raging global pandemic. To date, 7,553,182 cases and almost 423,349 deaths have resulted from this severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. While most patients with COVID-19 are asymptomatic or only develop mild influenza-like symptoms, a low but noteworthy number of patients experience more severe illness that could lead to acute respiratory distress syndrome (ARDS), multiple-organ failure (MOF), and death [2]. The susceptibility to deteriorate into critical conditions is higher in patients with advanced age and pre-existing comorbidities, such as cardiovascular diseases, chronic obstructive pulmonary disease, diabetes mellitus (DM), and hypertension [3–9]. Unfortunately, as of the time this paper is written, there is no single proven agent to cure COVID-19.

To gain entry into the host cells, the viral surface spike (S) protein of SARS-CoV-2 binds to the angiotensin converting enzyme 2 (ACE2) through the spike protein activation by transmembrane protease serine 2 (TMPRSS2) [10]. The hypothesis is that the complex interplay between ACE2 and renin angiotensin system (RAS) may provide insights into curing COVID-19. RAS inhibitors such as angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) are widely used for the treatment of hypertension, heart failure, and DM. Although the harmful or beneficial effects associated with these drugs are still controversial [11–13], a recent study showed that the use of ACEI or ARB in hypertensive COVID-19 patients is associated with reduced mortality rate [14]. This observation is further complicated by the possibility of clinical deterioration due to abrupt cessation of ACEI/ARB [15]; hence, simply changing the medications may also potentially cause more harm than good. Therefore, to investigate the association between the administration of ACEI/ARB and the outcomes of hypertensive COVID-19 patients, a systematic review and meta-analysis were performed.

2. Material and methods

2.1. Search strategy and study selection

We systematically searched PubMed, EuropePMC, ProQuest, and Cochrane Central Databases using the terms "(COVID-19 OR SARS-CoV-2) AND (angiotensin converting enzyme OR angiotensin receptor blocker)". Additional records were retrieved from Google Scholar/Preprints server. After removal of duplicates, the remaining articles were independently screened for relevance by their abstracts with two authors (IH and RP). The full text of the remaining articles was assessed according to the inclusion and exclusion criteria. Initial search was performed on April 26th, 2020, the search was later updated and finalized in June 14th, 2020.

2.2. Eligibility criteria

All studies (original studies and research letters) reporting COVID-19 patients with hypertension, in which data for ACEI/ARB administration on the clinically validated definition of mortality and/or severe COVID-19 were available were included. Review articles, non-research letters, commentaries, and articles in non-English language were excluded.

2.3. Data extraction

Data were extracted independently by two authors (IH and RP); we used standardized forms that include author name, year, study design, age, gender, hypertension, diabetes, chronic kidney diseases, coronary artery/cardiovascular diseases, chronic obstructive pulmonary diseases, ACEI/ARB use, severe COVID-19, and mortality.

The primary outcome was mortality (non-survivor) in patients with COVID-19 pneumonia. The secondary outcome was severe COVID-19, which was defined as patients WHO-China Joint Mission definition of severity [16], the need for intubation/mechanical ventilation, and transfer to intensive unit care (ICU).

2.4. Statistical analysis

To perform a meta-analysis, we used Review Manager 5.3 (Cochrane Collaboration) and Stata version 16 (College Station, TX: StataCorp LLC). Outcomes were reported as Odds Ratios (ORs), which were calculated using the Generic-Inverse Variance formula by inserting the log[OddsRatio] or events/total. Random-effects models were used for pooled analysis, regardless of heterogeneity. P-value was two-tailed, and the statistical significance was set at ≤ 0.05. Inter-study heterogeneity was assessed using Cochran's Q test and I^2 statistic; I^2 values > 50% and p-value <0.10 indicated statistically significant heterogeneity. Sensitivity analysis by leave-one-out was performed to single out heterogeneity and evaluate statistical robustness. Subgroup analyses were performed for ACEI use and ARB use. For the subgroups analyses, we used Mantel-Haenszel Formula with a random-effects model to calculate ORs, regardless of heterogeneity. Funnel-plot analysis was used to assess publication bias. To assess the small-study effect, we performed regression-based Egger's test. Random-effects restricted maximum likelihood was performed to evaluate whether the association between ACEI/ARB and mortality were affected by age and gender, other comorbidities were not included due to insufficient data.

3. Results

The initial search yielded 1232 records and an additional 4 were acquired from Google Scholar/Preprints server. 225 duplicates were removed, and 1005 records were then screened by assessing the title/abstracts. There were 27 potential records, and their eligibility was assessed by reading the full-text articles. We excluded 12 full-text articles because 1) no information of ACEI/ARB was available on the outcome of interest (n = 9), 2) prior home medication (n = 1), 3) the outcome was composite of mortality + severity (n = 1), and 4) retracted paper (n = 1). There was 15 eligible studies [14,17–30] for systematic review and meta-analysis, comprising retrospective observational studies (Fig. 1).

There were 7410 patients from 15 studies. Assessment using Newcastle Ottawa Scale showed a moderate-high quality of studies. Baseline characteristics of the included studies are displayed in Table 1. Zhang P et al. (14). and Reynolds et al. (30). studies includes propensity-matched cohort, whose result we used for the analysis. Yang et al. (22). included patients that remained in the hospital for their outcome measurement. Meanwhile, other studies only accounted discharge and death for their total patients. Hence, in the analysis for mortality, we the remaining in-hospital patients were excluded, causing discrepancies in the total patients analyzed on the mortality and severity. outcome.

3.1. Mortality

Individually, only Felice et al. (28). Zhang P et al. (14). showed the benefit of ACEI/ARB on mortality. Pooled analysis showed that the use of ACEI/ARB was associated with a significantly reduced mortality (OR 0.73 [0.38, 1.40], p = 0.34; I^2: 81%, p < 0.001) [Fig. 2a]. Sensitivity analysis showed that removal of Jung et al. (23) leads to a significantly lower mortality with ACEI/ARB use (OR 0.63 [0.45,

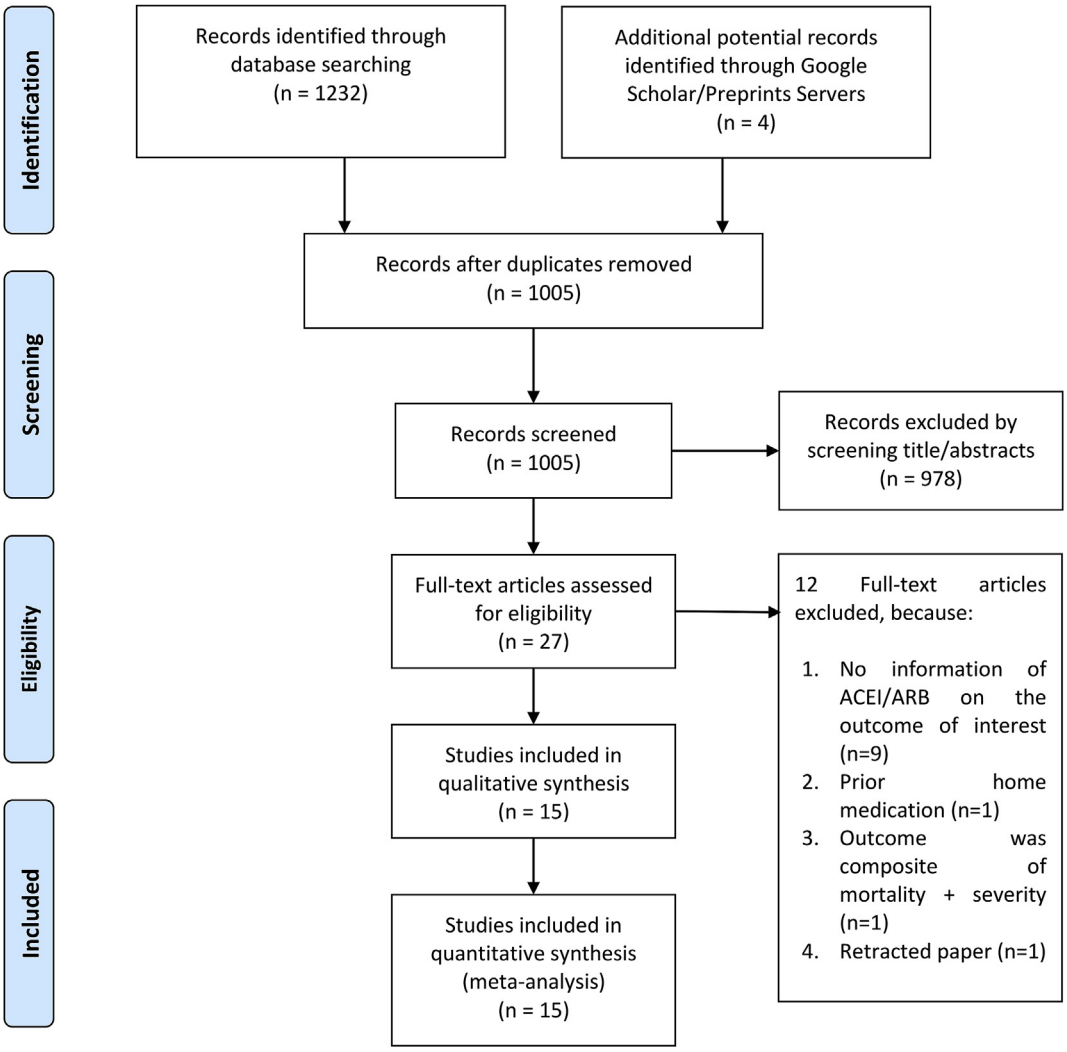

Fig. 1. PRISMA flowchart.

0.88], p = 0.006; I^2: 12%, p < 0.33), indicating lack of statistical robustness.

Pooled adjusted OR of Felice et al. (28), Gao C et al. (29), and Jung et al. (23). showed no risk/benefit associated with ACEI/ARB use in terms of mortality (OR 0.83 [0.54, 1.27], p = 0.38; I^2: 0%, p = 0.79).

3.2. Severity of COVID-19

Pooled analysis showed that the severity of COVID-19 was not affected by the use of ACEI/ARB (OR 1.03 [0.73, 1.45], p = 0.87; I^2: 65%, p = 0.004) [Fig. 2b]. Sensitivity analysis showed that removal of a single study did not affect the heterogeneity or outcome, indicating statistical robustness.

3.3. Subgroup analysis

Subgroup analysis showed that the use of ARB was associated with reduced mortality (OR 0.51 [0.29, 0.90], p = 0.02; I^2: 22%, p = 0.28) [Fig. 3a]. However, no mortality benefit was demonstrated by ACEI subgroup (OR 0.68 [0.39, 1.17], p = 0.16; I^2: 0%, p = 0.62) [Fig. 3b].

3.4. Meta-regression

Meta-regression showed that the association between ACEI/ARB use and mortality in patients with COVID-19 do not varies by gender (p = 0.104). However, the association was shown to vary with age (−0.817, p < 0.001), after removing Jung et al. (23). study, an outlier with the largest weight in the study, the effect become non-significant (p = 0.160). ACEI/ARB users in Jung et al. (23) study are much older compared to non-users (62.5 vs 41.5).

3.5. Publication bias

Funnel-plot analysis showed a qualitatively asymmetrical shape for both mortality [Fig. 4a] and severity [Fig. 4b]. There are more studies contributing to the favorable effect, indicating possibility of publication bias. Regression-based Egger's test showed no indication of small-study effects for mortality (p = 0.14) and a significant small-study effects for severity (p = 0.034).

3.6. GRADE assessment

Grading of Recommendations Assessment, Development and Evaluation (GRADE) showed a very low certainty of evidence for

Table 1
Characteristics of the included studies.

Authors	Study Design	Sample Size (ACEI/ ARB vs Non)	Male (%)	Overall Age (Mean vs. Median) (years)	ACEI[a]/ARB[b]/Outcome	HTN[c] (%)	DM[d] (%)	CKD (%)	CAD/CVD[e] (%)	COPD[f] (%)	Outcome	NOS[h]
Conversano (27) 2020	Observational Retrospective	68 vs 28	76.3	70.6	21/68 vs 13/28	100	N/A	N/A	N/A	N/A	Mortality COVID-19	9
Felice (28) 2020	Observational Retrospective	82 vs 51	72 vs 53	70.9 vs 76.2	ICU: 21/82 vs 25/51 Mortality: 15/ 82 vs 18/51	100	24.3 vs 27.5	N/A	35.8 vs 52.9	8.5 vs 13.7	Mortality and Need for ICU COVID-19	9
Feng (20) 2020	Observational Retrospective	16 vs 49	62.5 vs 46.9	57 vs 63	1/16 vs 16/49	100	12.5 vs 36.7	6.3 vs 2.0	0 vs 16.3	0 vs 2.0	Severe COVID-19	7
Gao C (29) 2020	Observational Retrospective	183 vs 527	67.8 vs 50.5	62.64 vs 62.84	Severe: 74/183 vs 179/527 Mortality: 4/183 vs 19/527	100	30.1 vs 26.6	1.1 vs 1.9	17.5 vs 15.2 (Myocardial angina)	0.6 vs 1.5	Mortality and Severe COVID-19	9
Jung (23) 2020	Observational Retrospective	719 vs 438	52 vs 43	62.5 vs 41.5	Mortality: OR 3.88 [2.48, 6.07]	100	N/A	N/A	N/A	N/A	Mortality COVID-19	8
Li (19) 2020	Observational Retrospective	115 vs 247	59.1 vs 49.0	65 vs 67	Severe: 57/115 vs 116/247 Mortality: 21/115 vs 56/247	100	36.5 vs 34.4	11.3 vs 8.9	23.5 vs 14.2	7.0 vs 4.0 (CLD)[g]	Mortality and Severe COVID-19	6
Liabeuf (24) 2020[i]	Observational Retrospective	52 vs 64	63 vs 55	73 vs 73	Severity: OR 2.28 [1.17, 4.44]	62 vs 53	18 vs 18	9 vs 6	19 vs 7	13 vs 7	Mortality and Need for ICU COVID-19	9
Liu Yingxia (22) 2020	Observational Retrospective	12 vs 34	55.1	65.2	4/12 vs 24/34	N/A	N/A	N/A	N/A	N/A	Severe COVID-19	9
Mehta (25) 2020	Observational Retrospective	211 vs 1494	55 vs 55	63 vs 63	Mortality: OR 1.69 [0.77, 3.71]	93 vs 93	46 vs 46	N/A	22 vs 22	14 vs 14	Mortality COVID-19	7
Meng (21) 2020	Observational Retrospective	17 vs 25	52.9 vs 60.0	64 vs 65	Severe: 4/17 vs 12/25 Mortality: 0/17 vs 1/25	100	11.8 vs 16.0	0 vs 0	11.8 vs 24.0	0 vs 0	Mortality and Severe COVID-19	7
Reynolds (30) 2020	Observational Retrospective	1019 vs 986	52 vs 52	64.9 vs 65.3	Severe: 252/1019 vs 249/986	100	44 vs 40	25 vs 26	11 vs 11	23 vs 23	Severe COVID-19	9
Yang G (22) 2020	Observational Retrospective	43 vs 83	48.8 vs 49.4	65 vs 67	Severe: 15/43 vs 35/83 Mortality: 2/43 vs 11/83	100	30.2 vs 30.1	3.6 vs 0 (Kidney Disease)	19.3 vs 16.3 (Cardiopathy)	3.6 vs 7.0 (CLD)[g]	Mortality and Severe COVID-19	7
Zeng Z (17) 2020	Observational Retrospective	28 vs 47	43 vs 49	64 vs 69	Severe: 15/28 vs 15/47 Mortality: 2/28 vs 5/47	100	31.0	5.0	21.0	9.0	Mortality and Severe COVID-19	7
Zhang P (14) 2020	Observational Retrospective Propensity-matched 1:2	174 vs 348	54 vs 56	64 vs 64	Mortality: OR 0.37 [0.15, 0.89]	100	23.0 vs 24.7	4.0 vs 3.2	13.8 vs 13.2	0.6 vs 0.3	Mortality COVID-19	9
Zhou X (26) 2020	Observational Retrospective	15 vs 21	60 vs 47.6	58.5 vs 69.2	2/15 vs5/21	100	25	N/A	19.4	N/A	Mortality COVID-19	9

Data is presented stratified by those with ACEI/ARB use vs. those without ACEI/ARB use.
[a] ACEI: Angiotensin Converting Enzyme Inhibitor;
[b] ARB: Angiotensin Receptor Blocker; [c]HTN: Hypertension;
[d] DM: Diabetes Mellitus; [e]CAD/CVD: Coronary Artery Disease/Cardiovascular Disease;
[f] COPD: Chronic Obstructive Pulmonary Disease;
[g] CLD: Chronic Lung Disease/Respiratory Disease;
[h] NOS: Newcastle-Ottawa Scale.
[i] Liabeuf 2020; comparing positive composite endpoint vs negative composite endpoint.

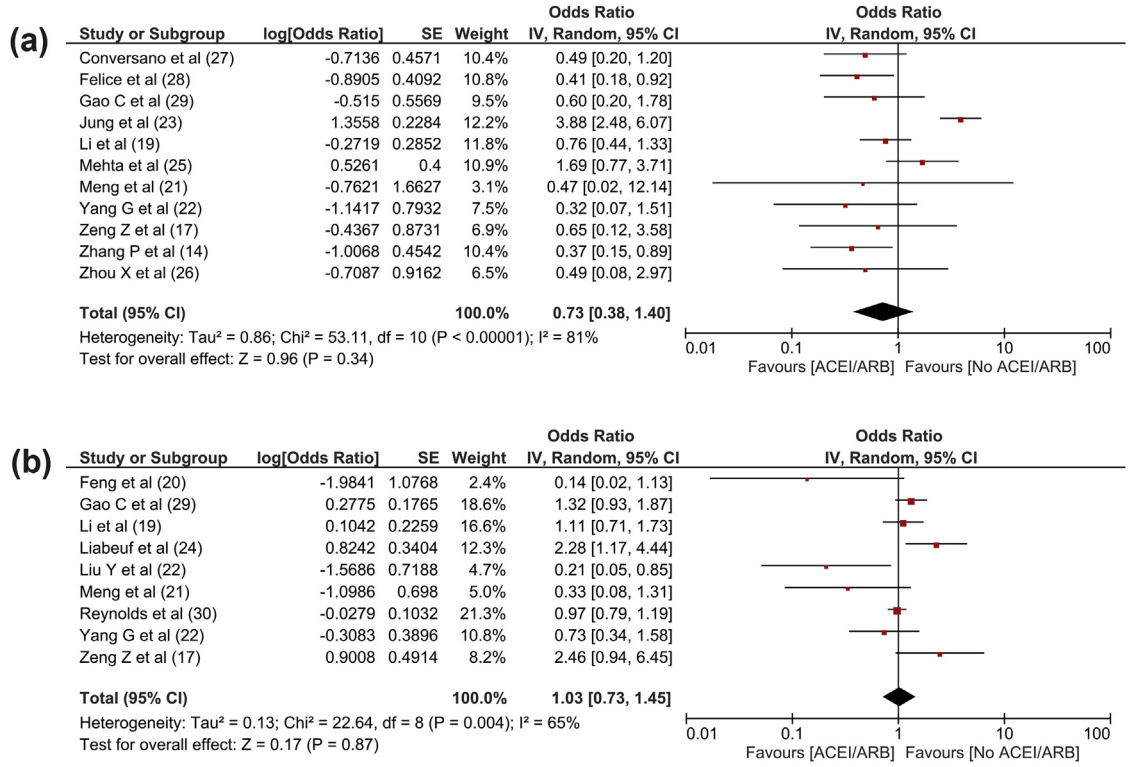

Fig. 2. Pooled analysis showed the association of ACEI/ARB was not associated with increase/decreased mortality [a] and severe COVID-19 [b].

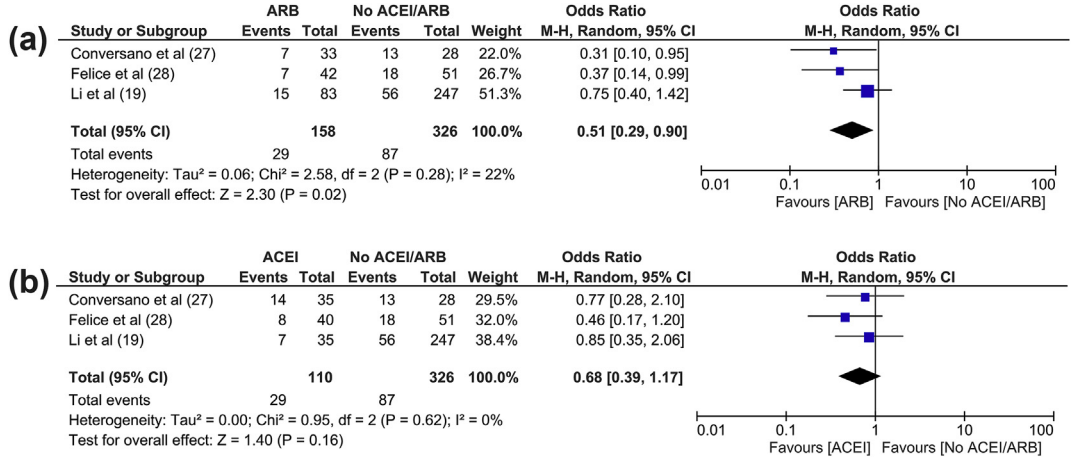

Fig. 3. Pooled analysis showed the association of ARB [a] but not ACEI [b], reduces mortality in COVID-19 patients.

effect of ACEI/ARB on mortality and severity. The certainty of evidence was very low for both ACEI and ARB subgroups (Table 2).

4. Discussion

The present meta-analysis showed that the use of ACEI/ARB was associated with neither increased nor decreased mortality rate in hypertensive COVID-19 patients. Although a significant benefit can be seen if Jung et al. (23). study was excluded. Jung et al. (23) study showed that ACE/ARB was associated with increased mortality in an unadjusted model, which became non-significant after adjustment to several covariates. ACEI/ARB users in their study were much older compared to non-users in their study. Jung et al. (23). study was the only study that showed increased mortality with ACEI/ARB use. Subgroup analysis showed that the use of ARB was associated with reduction in mortality, albeit a very low certainty of evidence.

As mentioned in the methods, we excluded two studies that, although potentially eligible, did not fulfil the inclusion criteria. The first was by Richardson et al. [31]., in which the use of ACEI/ARB in their study was defined as prior home medication. The home medication was later continued or discontinued at the discretion of the attending physician; hence, it might not reflect the in-hospital use of ACEI/ARB. The rate of ACEI/ARB cessation was approximately 50% in the aforementioned study. Another excluded study was by Bean et al. [32]., in which data on mortality and severity were not available separately, but as a composite endpoint. Hence, this study was not suitable for our analysis. Nevertheless, the authors

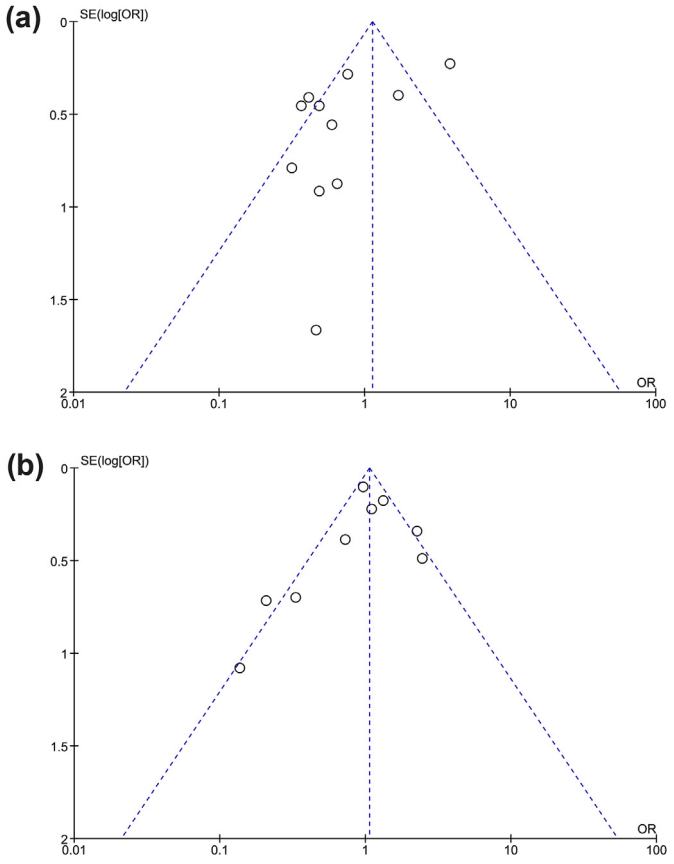

Fig. 4. Funnel-plot analysis showed a qualitatively asymmetrical shape for both mortality [a] and severity [b].

reported that ACEI/ARB was associated with reduced mortality or need for intensive care unit (ICU) care within 7 days in patients on an ACE-inhibitor (OR 0.29 [0.10–0.75], $p < 0.01$) after adjustment for several patient characteristics including age, gender, hypertension, diabetes mellitus, ischemic heart disease, and heart failure [32].

In the pooled analysis for the association of ACEI/ARB use on mortality and severity, there was no statistically significant association between the use of ACEI/ARB in hypertensive patients and severe COVID-19. The heterogeneity for the effect estimates was high. The certainty of evidence was very low due to the high risk of bias and inconsistencies. Although Liu et al. (22) did not find a statistically significant difference in terms of COVID-19 severity, their subgroup analysis showed a reduction in elderly patients who were >65 years old and used ARB [22]. Even though the current meta-analysis demonstrated no benefit/harm in terms of mortality and severity, integrating adjustments of several confounding variables is crucial, especially factors that may affect the RAS, including age, gender, and DM. Adjustment to these confounding factors might result in a different conclusion.

In our previous study, we found that hypertension was associated with a poor outcome, including higher mortality rate, ARDS, disease progression, and severe COVID-19 [5]. It seems that one of the underlying mechanisms was mediated by ACE2 in the renin-angiotensin-aldosterone system (RAS) [33]. ACE2 is a gateway for SARS-CoV-2 cell infiltration; it is present not only in lung epithelial cells, but also in other extra-pulmonary sites such as the heart, kidney, and intestinal tissues [33–35]. ACE2 reduces interleukin-6 (IL-6) through the conversion of angiotensin II to angiotensin 1-7, which subsequently promotes antioxidant function, increases the

Table 2
GRADE Assessment of the outcomes.

Certainty assessment								No of patients		Effect		Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		ACEI/ARB	No ACEI/ARB	Relative (95% CI)	Absolute (95% CI)	
Mortality												
11	observational studies	serious[a]	serious[b]	not serious	serious[c]	all plausible residual confounding would reduce the demonstrated effect		5353	3633	**OR 0.73** (0.38–1.40)	**N/A**[d]	⊕◯◯◯ VERY LOW
Severity												
9	observational studies	serious[a]	serious[b]	not serious	serious[c]	all plausible residual confounding would reduce the demonstrated effect		1485	2062	**OR 1.03** (0.73–1.45)	**N/A**[d]	⊕◯◯◯ VERY LOW
Mortality ACEI Subgroup												
3	observational studies	serious[a]	not serious	not serious	serious[c]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect[e]		29/110 (26.4%)	87/326 (26.7%)	**OR 0.68** (0.39–1.17)	**68 fewer per 1000** (from 143 fewer to 32 more)	⊕◯◯◯ VERY LOW
Mortality ARB Subgroup												
3	observational studies	serious[a]	not serious	not serious	not serious	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect[e]		29/158 (18.4%)	87/326 (26.7%)	**OR 0.51** (0.29–0.90)	**110 fewer per 1000** (from 171 fewer to 20 fewer)	⊕◯◯◯ VERY LOW

CI: Confidence interval; **OR:** Odds ratio Explanations.
[a] Mostly retrospective studies, inadequately adjusted for confounders.
[b] High heterogeneity.
[c] Important benefit or important harm cannot be excluded.
[d] Not every studies report their events/total.
[e] Studies that show difference between ACEI/ARB, ACEI, and ARB subgroup are more likely to report the subgroup analyses.

concentration of alveolar surfactants, and triggers vasodilation [36,37]. The aforementioned mechanism was thought to protect the lung from ARDS [38]. Furthermore, the use of ACEI/ARB was linked with increased CD3 and CD8 T cell numbers and a decreased peak viral load, compared to other antihypertensive drugs [21]. Interestingly, SARS-CoV-2 was shown to downregulate ACE2 expression that eventually resulted in an unregulated angiotensin-2 activity [39], which is proposed as one of the underlying pathomechanisms that potentially leads to multiple organ injury [40,41,46].

Regular use of ARB and/or ACEI increases ACE2 expression, hence the hypothesis that its use facilitates SARS-CoV-2 entry [33,36]. Albeit the overexpression of ACE2 supposedly offers lung protection, it may increase susceptibility to COVID-19. Theoretically speaking, medication that reduces angiotensin-2 activity, such as ACEI and/or ARB, might decrease the lethality of inflammatory-related injury in COVID-19. Our result denies this hypothesis, wherein we found that the use of ACEI/ARB did not reduce mortality, in COVID-19 patients. However, subgroup analysis showed that ARB use might reduce mortality, which may be in line with the hypothesis. Nevertheless, further prospective cohort studies and randomized controlled trials are needed to confirm this possible benefit. Richardson et al. (31). showed an increasing trend (but not statistically significant) in mortality in patients with ACEI/ARB, which is in contrast to the finding of this meta-analysis; this might be due to the fact that around 50% of the patients in their study used ACEI/ARB as home medication, which was discontinued during the course of hospitalization. While it may support the hypothesis that abrupt cessation of ACEI/ARB may lead to deterioration, further information and dedicated analysis are needed before a conclusion can be drawn.

We previously discussed the complex correlation between ACE2, renin-angiotensin system (RAS) signaling, hypertension, DM, and age, with COVID-19 severity [5–7,42]. As pointed out in our previous meta-analysis, the association between DM and a poor outcome was interdependent from age and hypertension [6]. The rationale behind these factors in COVID-19 may be linked in RAS as the central core. As in the hypothesis of AlGhatrif et al. [43], the differences of ACE2 levels and RAS signaling between older individuals with hypertension and younger people might hypothetically explain the severity of COVID-19 in the elderly. This is a plausible explanation of a more pronounced protective effect of ACEI/ARB in the elderly, and is in line with the results of Liu et al. [22]. It was unfortunate that we could not do the meta-regression analysis for the comorbidities due to the limited number of studies.

4.1. Implication for clinical practice

Regardless of the potential benefit or harm associated with ACEI/ARB, controlling blood pressure is still important to prevent cardiovascular complications. Although the result showed a protective benefit of using ARB in COVID-19, until further studies showed more evidences, we only recommend continuing ACEI/ARB in hypertensive patients with those regular blood pressure medications. This is in line with the current recommendation by the American Heart Association (AHA), the Heart Failure Society of America (HFSA), the American College of Cardiology (ACC), and International Society of Hypertension (ISH) on COVID-19 [44,45].

4.2. Limitations

The limitation of this systematic review and meta-analysis is the possibility of publication bias demonstrated by asymmetrical funnel plot. These studies were mostly retrospectively observational in design and was not adequately matched/adjusted for confounders. Hence, the result may be subjected to multiple confounders.

5. Conclusion

Administration of a RAS inhibitor, was not associated with mortality or severity in COVID-19 with hypertension. However, ARB use was associated with lower mortality. Prospective cohorts with methodologically sound matching/adjustment of the analysis or randomized controlled trials are needed before a definite conclusion can be drawn.

Data availability

The data used to support the findings of this study are included within the article.

Funding statement

None.

Ethics approval and consent to participate

Not Applicable.

Consent for publication

Not Applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. The corresponding author (R.P) can be contacted for more information.

Declaration of competing interest

The authors declared no conflict of interest.

Acknowledgments

None.

Abbreviations

ACE2	Angiotensin Converting Enzyme 2
ARB	Angiotensin Receptor Blocker
ARDS	Acute Respiratory Distress Syndrome
COVID-19	Coronavirus Disease 2019
DM	Diabetes Mellitus
FiO2	Fractional Concentration of Oxygen Inspired Air
ICU	Intensive Care Unit
MOF	Multiple Organ Failure
PaO2	Partial Pressure of Arterial Oxygen
RAS	Renin Angiotensin System
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

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