Original research

Renin-angiotensin system blocker and outcomes of COVID-19: a systematic review and meta-analysis

Hyun Woo Lee,[1] Chang-Hwan Yoon,[2] Eun Jin Jang,[3] Chang-Hoon Lee[4]

ABSTRACT

Background The association of ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) with disease severity of patients with COVID-19 is still unclear. We conducted a systematic review and meta-analysis to investigate if ACEI/ARB use is associated with the risk of mortality and severe disease in patients with COVID-19.

Methods We searched all available clinical studies that included patients with confirmed COVID-19 who could be classified into an ACEI/ARB group and a non-ACEI/ARB group up until 4 May 2020. A meta-analysis was performed, and primary outcomes were all-cause mortality and severe disease.

Results ACEI/ARB use did not increase the risk of all-cause mortality both in meta-analysis for 11 studies with 12 601 patients reporting ORs (OR=0.52 (95% CI=0.37 to 0.72), moderate certainty of evidence) and in 2 studies with 8577 patients presenting HRs. For 12 848 patients in 13 studies, ACEI/ARB use was not related to an increased risk of severe disease in COVID-19 (OR=0.68 (95% CI=0.44 to 1.07); I^2=95%, low certainty of evidence).

Conclusions ACEI/ARB therapy was not associated with increased risk of all-cause mortality or severe manifestations in patients with COVID-19. ACEI/ARB therapy can be continued without concern of drug-related worsening in patients with COVID-19.

Key messages

What is the key question?

- Is there a statistical significance in clinical outcomes, including all-cause mortality and severe disease between ACE inhibitors/angiotensin II receptor blocker (ACEI/ARB) group and non-ACEI/ARB group in patients with COVID-19?

What is the bottom line?

- For 21 178 patients in 13 studies, ACEI/ARB use did not increase the risk of all-cause mortality of patients with COVID-19.
- For 12 848 patients in 13 studies, ACEI/ARB use was not related to an increased risk of severe disease in those with COVID-19.

Why read on?

- Our study supports the current recommendations favouring the continuation of ACEI/ARB use during the COVID-19 pandemic.

INTRODUCTION

As of 9 May 2020, SARS-CoV-2 has infected >3.7 million people and killed >259 000 patients worldwide.[1] However, knowledge of this new virus remains sparse, which is a major hindrance to overcoming the current pandemic. One of the main issues to resolve is whether the use of the renin-angiotensin system blockers, including ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), may be associated with the severity of COVID-19 caused by SARS-CoV-2.

Preclinical studies demonstrated an increase in the expression level of ACE2 in the heart[2] and kidney[3] of rats treated with ARBs, as well as in human intestine biopsies treated with ACEIs.[4] ACE2 was identified as a functional receptor through which SARS-CoV-2 enters host cells.[5 6] Therefore, it is reasonable to be concerned that treatment with ACEI/ARB could facilitate virus entry due to increased ACE2 expression, leading to more severe disease. If this is the case, ACEI/ARB should be discontinued in patients who are being treated with these drugs on the confirmation of COVID-19 diagnosis.[7] This issue is important, given that the duration of the SARS-CoV-2 pandemic remains unclear,[8] and ACEI/ARBs are among the most commonly prescribed drugs.[9 10] Although several professional societies have recommended the continuation of ACEI/ARBs in the current situation,[11] uncertainty remains owing to a lack of supporting clinical data. Although several observational studies have been published recently,[12–21] they reported somewhat different results. For example, Zhang *et al* showed that ACEI/ARB treatment was associated with a reduced risk of mortality in patients with COVID-19,[21] but Mancia *et al* showed a higher proportion of ACEI/ARB use among critical patients than among those with mild-to-moderate infection.[14]

To help resolve this issue, we conducted a systematic review and meta-analysis on recently published studies to investigate the effects of ACEI/ARBs on the risk of mortality and severe disease in patients diagnosed with COVID-19.

METHODS

Protocol and registration

This systematic review was reported according to the guidelines of the Meta-analysis of Observational Studies in Epidemiology[22] and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement.[23] The protocol of the systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020179780) on 17 April 2020.

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Eligibility criteria

The eligibility criteria for studies included in the systematic review were as follows: (1) the study subjects were diagnosed with COVID-19 by high-throughput sequencing or real-time reverse transcription-PCR assay using upper or lower respiratory tract specimens, (2) the subjects could be classified into ACEI/ARB user and non-ACEI/ARB user groups, (3) the severity of disease or all-cause mortality was evaluated according to the use of ACEI/ARB and (4) any human clinical comparative study except for those with a cross-sectional design.

Information sources and search strategy

The Medline, Embase, Cochrane Central Register of Controlled Trials, MedRxiv, Social Science Research Network and Peer J databases were searched for potentially eligible published and unpublished studies up to 4 May 2020. The search strategy was designed by experienced researchers (HWL and C-HL) based on The Peer Review of Electronic Search Strategies checklist.[24] Manual searches were conducted for references cited in recent articles, systematic reviews and meta-analyses to complement the search strategy. When unpublished or forthcoming papers were found, we contacted the authors to obtain all available data, but none replied. There was no restriction on study period, ethnicity or language in the search strategy. The details of the search strategy are outlined in online supplemental appendix 1. The searched references from retrieved articles were imported into a reference management software (Endnote X7, Thomson Reuters, Philadelphia, Pennsylvania, USA) and shared with the other authors.

Study selection

The study selection was conducted by two individual reviewers (HWL and C-HL) based on the PRISMA flow diagram.[25] Duplicated studies were censored based on the study title and name of the first author. The two independent reviewers (HWL and C-HL) individually screened the titles, abstracts and keywords to select potentially eligible studies. The independent reviewers (HWL and C-HL) then conducted a full-text review to check for conformance with the prespecified eligibility criteria. In case of any conflict or disagreement, eligibility was discussed by all authors until a consensus was reached.

Data extraction and quality assessment

Data were extracted using a standardised format.[26] HWL and C-HL extracted data on the study characteristics (first author, published or preprinted year, region, eligibility criteria, exposure to intervention and definition of severe disease) and the baseline characteristics of the patients (number of analysed patients, age, sex and comorbidities, including hypertension, diabetes mellitus, cardiovascular disease, pulmonary disease, cerebrovascular disease, chronic liver disease, chronic kidney disease and cancer). Two dichotomous variables (number of patients who died during the observation period and number of patients with severe disease) were used as clinical outcomes. We extracted adjusted risk ratios, including the OR and HR, when data were available. If the use of ACEI/ARB was evaluated only in the subpopulation with hypertension, the extraction process was conducted with a focus on the subpopulation, along with the collection of data for the whole population to determine any relevant differences.

The risk of bias (ROB) of eligible studies was assessed using the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool,[27] as recommended by the Cochrane Scientific Committee in 2017. If a study was assessed to have a critical level of ROB in any domain in ROBINS-I tool, a sensitivity analysis was planned after excluding the biassed study.

Outcomes

The primary outcomes were all-cause mortality and severe disease. *The definition of severe disease was according to individual study definitions*.

Data synthesis and analysis

The outcomes were conservatively analysed using a random-effects model because heterogeneity was detected among the included studies regarding the study method and patient characteristics. Risk of all-cause mortality or severe disease events was calculated as the OR with a 95% CI in terms of summary statistics. The overall results of the meta-analysis were visualised with forest plots. The I^2 statistic and the Cochran's Q test were used to evaluate statistical heterogeneity among the effect sizes of the included studies.

Meta-regression analysis was conducted by using different variables including baseline characteristics, whether confounders were adjusted or not, and the definition of outcome, as a covariate. Subgroup analysis was also performed according to categorical covariates.

Funnel plot asymmetry and Egger's and Begg's tests were used for qualitative and quantitative evaluation of publication bias, respectively.[26] If publication bias was suspected, the trim-and-fill method was planned to calculate a corrected OR by estimating the number of missing studies.[28] All the analyses were performed using Stata software V.14.2 (StataCorp, College Station, Texas, USA), using the commands named "metan", "metafunnel", "metabias" and "metareg" and using R V.3.4.0 statistical computing software (R Foundation for Statistical Computing, Vienna, Austria) with the metafor and meta packages.[29] Two-tailed $p<0.05$ was considered to indicate statistical significance.

Certainty of evidence

The certainty of evidence was rated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[30]

RESULTS

Study selection

After removing duplicates, 404 studies were screened, and 35 potentially relevant articles were retrieved for full-text review (figure 1). Twenty studies met the eligibility criteria. The reasons for excluding 15 articles are described in online supplemental appendix 2. Three studies were excluded because the data could be overlapped with other included data sources.[31] The details of data sources of included studies are described in online supplemental appendix 3. All 20 studies were observational studies, and there was no randomised controlled trial reporting relevant results. All-cause mortality was reported in 13 studies,[13 15–17 19–21 32–37] and severe disease was reported in 13 studies.[12–14 16–18 20 34 35 38–41] Mortality was evaluated during hospitalisation in nine studies,[13 15–17 19 20 32 33 35] at 28 days during hospitalisation in two studies,[21 34] during hospitalisation in about 87% of patients in one study,[36] and at 60 days in one study.[37] Severe disease was evaluated during hospitalisation in 12 studies,[12 13 16–18 20 34 35 38–41] and during hospitalisation in severe cases in 1 study,[14] where about half of mild-to-moderate cases were not hospitalised.

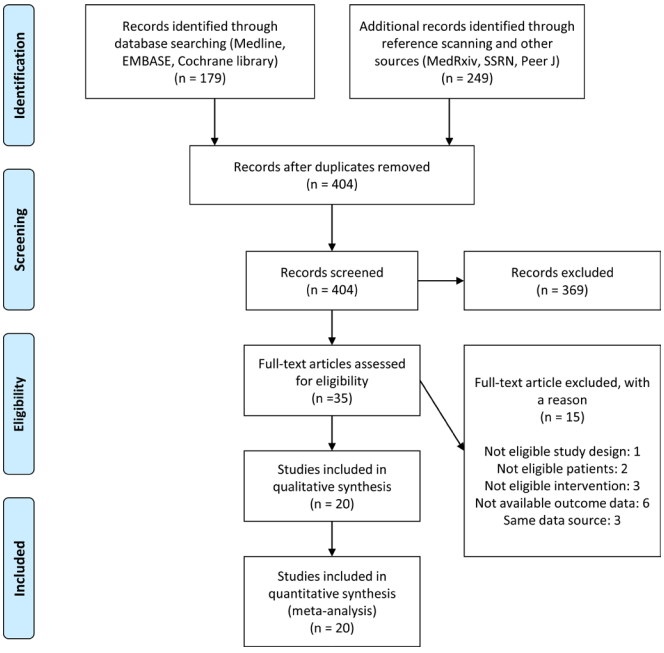

Figure 1 Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow diagram for the systematic review and meta-analysis. In PRISMA flow diagram, the information of different phases of a systematic review are summarised. PRISMA flow diagram maps out the number of records identified, included and excluded, and the reasons for exclusion.

Baseline characteristics of the included studies and patients

The baseline characteristics of the included studies and patients are summarised in table 1 and online supplemental appendix 4. All studies were conducted in 2020; nine in China, four in the USA, three in Italy, one in Iran, one in South Korea, one in the UK and one other study across multiple countries. All the 36 108 patients with a confirmed diagnosis of COVID-19 were hospitalised or isolated. Among these patients, data for 30 766 patients with information on the use or non-use of ACEI/ARB were included in the meta-analysis, 8066 of whom were classified in the ACEI/ARB group. The mean age was 54.4 years and 54.5% of the included patients were men. Several comorbidities were reported, including 41.9% patients with hypertension in all 20 studies, 15.3% with cardiovascular diseases in 18 studies, 17.9% with diabetes in 17 studies, 8.8% with chronic respiratory diseases in 14 studies, 3.9% with chronic kidney disease in 12 studies, 9.1% with malignancies in 10 studies, 3.7% with cerebrovascular diseases in 8 studies and 4.6% with chronic liver diseases in 7 studies. The ACEI/ARB group was defined as those with any medication history of treatment with ACEI or ARB based on the electric medical record in 12 studies, those who used ACEI or ARB during hospitalisation in 6 studies, those who used ACEI or ARB at the time of hospitalisation in 1 study and those who were treated with ACEI or ARB within the 7 days before symptoms or during inpatient treatment in 1 study. Definitions of severe disease followed the report of the WHO-China Joint Mission on COVID-19[42] for (1) respiratory rate (RR) ≥30, (2) O_2 saturation at rest ≤93% and (3) PaO_2/FiO_2 ratio ≤300 in seven studies[12 13 16 17 20 38 41]; the criteria for severe disease as intensive care, mechanical ventilation or death in four studies[14 18 39 40]; the criteria for severe disease as (1) reduced consciousness, (2) RR ≥30/min, (3) blood pressure <90/60, (4) multilobar infiltration and (5) hypoxaemia in one study[35] and the severe community-acquired pneumonia definition in the clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America[43] in one study.[34]

ROB assessment within studies

The ROB assessment is summarised in online supplemental appendix 5. In general, the studies had low ROB in patient selection, classification of interventions and deviations from intended interventions, but showed moderate ROB in missing data and selection bias. Many studies did not provide sufficient information on confounding variables. The majority of studies were assessed to be vulnerable to ROB in the measurement of outcomes, which was attributed to the innate nature of a retrospective study in that the outcome assessors were aware of the intervention status, rather than to a serious or critical defect in the study design.

All-cause mortality

We found 21 178 patients in 11 studies reporting OR and 2 studies reporting HR. The risk of all-cause mortality was significantly decreased in the ACEI/ARB group compared with non-ACEI/ARB group with a heterogeneity (OR=0.52 (95% CI=0.37 to 0.72), I^2=87%, p value for heterogeneity <0.01, figure 2) (moderate level of evidence, online supplemental appendix 6). To identify factors affecting the heterogeneity, we conducted meta-regression and subgroup analyses. A meta-regression analysis showed whether confounders were adjusted or not affected the effect size (test of moderator p<0.01). However, ACEI/ARB group had significantly lower risks of all-cause mortality than non-ACEI/ARB group in both subgroup analyses where confounders were adjusted (OR=0.30 (95% CI=0.22 to 0.40); I^2=61%, p value for heterogeneity=0.11, figure 3) and where confounders were not adjusted (OR=0.52 (95% CI=0.37-0.72); I^2=0%, p value for heterogeneity=0.59, figure 3). There were no other factors affecting the effect size in meta-regression analyses by using the following covariates: 'including hypertensive patients only or not' (test of moderator p=0.92), 'the age of participants aged ≥60 or <60 years' (test of moderator p=0.19) or 'male proportion ≥50% or <50%' (test of moderator p=0.89). ACEI/ARB group was associated with decreased risk of all-cause mortality in hypertensive patients-only subgroup (OR=0.53 (95% CI=0.39 to 0.73); I^2=87%, p value for heterogeneity=0.04, online supplemental appendix 7). ACEI/ARB group was associated with decreased risk of all-cause mortality in both subgroups of age ≥60 and <60 years (online supplemental appendix 8) and was also associated with decreased risk of all-cause mortality in both subgroups of male proportion ≥50% and <50% (online supplemental appendix 9). The sensitivity analysis excluding three studies, in which the definition of mortality was not 'in-hospital mortality' but '28 days mortality'[21 34] or not all patients were hospitalised,[36] showed a similar result (online supplemental appendix 10).

There were two studies applying HR to compare the risk of all-cause mortality between ACEI/ARB group and non-ACEI/ARB group. Because those studies included patients with largely different characteristics such as age (44.4[37] vs 76.0 years[19]), male proportion (38.5%[37] vs 72.3%[19]) and the proportion of hypertensive patients (19.0%[37] vs 100%),[19] we did not perform a meta-analysis. Both the study by Lee *et al* (HR=1.07 (95% CI=0.66 to 1.74))[37] and the study by Tedeschi *et al* (HR=0.97 (95% CI=0.68 to 1.38))[19] showed that ACEI/ARB use did not increase the risk of all-cause mortality compared with non-ACEI/ARB group.

Table 1 Characteristics of 20 included observational studies

No.	Study	Region	Eligibility criteria	N	Age, mean	Male, %	Exposure to intervention	Definition of severe disease
1	Ashraf MA. *et al*[35]	Iran	The patients confirmed with COVID-19 who were admitted to hospital	100 ACEI/ARB group: 19	58*	64.6	Medical records on ACEI or ARB was reviewed	One of the following conditions: reduced consciousness, RR ≥30/min, BP <90/60, Multilobular infiltration, hypoxaemia
2	Bean D. *et al*[39]	UK	Patients with COVID-19 symptomatic and requiring inpatient admission	205 ACEI/ARB group: 46	63.0 ACEI/ARB group: 72.7 Non-ACEI/ARB group: 60.1	51.7 ACEI/ARB group: 54.3 Non-ACEI/ARB group: 44.6	Exposure to ACEI or ARB within 7 days before symptoms or during inpatient treatment	Death or admission to a critical care unit for organ-support within 7 days of symptoms onset
3	Benelli G. *et al*[32]	Crema, Italy	The patients diagnosed with COVID-19 who were admitted to hospital	411 ACEI/ARB group: 110	66.8	66.6	Data on medication history of ACEI or ARB was extracted from electric medical record	N/A (although CPAP/NIV use, ICU admission and death was evaluated, those outcomes can be overlapped)
4	Caraballo C. *et al*[36]	USA	The adult patients (aged ≥18 years) with heart failure who were admitted to hospital for the treatment of confirmed COVID-19	206 ACEI/ARB group: 172	78*	45.1	Exposure to ACEI or ARB before and during hospitalisation	N/A
5	Feng Y *et al*[12]	Multicentre, China	All the patients diagnosed with COVID-19 who visited the hospitals designated for the treatment of COVID-19	113 (476) ACEI/ARB group: 33	(53.0)*†	(56.9)†	Data on medication history of ACEI or ARB was extracted from electric medical record	One of the following conditions: RR ≥30/min, O_2 saturation at rest ≤93%, PF ratio ≤300 (WHO-China criteria)
6	Feng Z. et al[38]*	Multicentre, China	All the adult patients with confirmed COVID-19 with available clinical or imaging data who were treated at hospital	65 (564) ACEI/ARB group: 16	61.5 (47)* ACEI/ARB group: 57* Non-ACEI/ARB group: 63*	50.8 (50.4) ACEI/ARB group: 62.5 Non-ACEI/ARB group: 46.9	Data on medication history of ACEI or ARB was extracted from electric medical record	One of the following conditions: RR ≥30/min, O_2 saturation at rest ≤93%, PF ratio ≤300 (WHO-China criteria)
7	Ip A. *et al*[33]	USA	The hypertensive patients diagnosed with COVID-19 who were admitted to hospital	1129 ACEI/ARB group: 460	–	–	Data on medication history of ACEI or ARB was extracted from electric medical record	N/A
8	Lee H. *et al*[37]	South Korea	The patients diagnosed with COVID-19 who were admitted to hospital or isolated	8266 ACEI/ARB group: 977	44.4 ACEI/ARB group: 41.6 Non-ACEI/ARB group: 64.8	38.5 ACEI/ARB group: 56.4 Non-ACEI/ARB group: 37.8	Data on medication history of ACEI or ARB was extracted from electric medical record	N/A (severe disease was not evaluated)
9	Li J. *et al*[1]	Wuhan, China	The hypertensive patients diagnosed with COVID-19 who were admitted to hospital	362 ACEI/ARB group: 115	66* ACEI/ARB group: 65* Non-ACEI/ARB group: 67*	52.2 ACEI/ARB group: 59.1 Non-ACEI/ARB group: 49.0	Use of these drugs at the time of admission that continued through hospitalisation	One of the following conditions: RR ≥30/min, O_2 saturation at rest ≤93%, PF ratio ≤300 (WHO-China criteria)
10	Mancia G. *et al*[14]	Italy	The beneficiaries of the Regional Health Service (aged ≥40 years) diagnosed with COVID-19	6272 ACEI/ARB group: 2896	68	36.7	Data on medication history of ACEI or ARB was extracted from claim data	Assisted ventilation or death
11	Mehra MR. *et al*[15]	International (Asia, Europe and North America)	The patients diagnosed with COVID-19 who were admitted to hospital	8910 ACEI/ARB group: 1326	49.1	59.9	Exposure to ACEI or ARB at the time of hospitalisation	N/A
12	Meng J. *et al*[16]	Shenzhen, China	The hypertensive patients diagnosed with COVID-19 who were admitted to hospital and took antihypertensive drugs	42 ACEI/ARB group: 17	62.0 ACEI/ARB group: 61.9 Non-ACEI/ARB group: 62.1	57.1 ACEI/ARB group: 47.1 Non-ACEI/ARB group: 60.0	Exposure to ACEI or ARB during hospitalisation	One of the following conditions: RR ≥30/min, O_2 saturation at rest ≤93%, PF ratio ≤300 (WHO-China criteria)
13	Peng Y. *et al*[17]	Wuhan, China	The adult patients (aged ≥18 years) with cardiovascular disease who were diagnosed with COVID-19 and treated in hospital The patients with systemic diseases, liver disease or kidney abnormalities were excluded	112 ACEI/ARB group: 22	62.0	47.3	Data on medication history of ACEI or ARB was extracted from electric medical record	One of the following conditions: RR ≥30/min, O_2 saturation at rest ≤93%, PF ratio ≤300 (WHO-China criteria)

Continued

Table 1 Continued

No.	Study	Region	Eligibility criteria	N	Age, mean	Male, %	Exposure to intervention	Definition of severe disease
14	Rentsch CT.*et al*[40]	USA	Among the eligible patients in VA who underwent COVID-19 tests, only patients with a positive test for COVID-19 were evaluated in our study	585 ACEI/ARB group: 255	66.1	95.4	Data on medication history of ACEI or ARB was extracted from electric medical record	Intensive care
15	Reynolds HR. *et al*[18]	USA	Propensity score-matched patients with a positive test for COVID-19	2211 (5894) ACEI/ARB group: 1110	-†	-†	Data on medication history of ACEI or ARB was extracted from claim data	Admission to the intensive care unit, the use of non-invasive or invasive mechanical ventilation or death
16	Tedeschi S. *et al*[19]	Italy	Prospectively enrolled adult patients with hypertension who were hospitalised and diagnosed with a microbiologically confirmed COVID-19	311 ACEI/ARB group: 175	76*	72.3	Patients received antihypertensive medication including ACEI or ARB during hospitalisation	N/A
17	Yan H. *et al*[41]	Zhejiang, China	All adult patients diagnosed with COVID-19	137 (610) ACEI/ARB group: 58	(48.8)†	(51.1)†	Data on medication history of ACEI or ARB was extracted from electric medical record	One of the following conditions: RR ≥30/min, O_2 saturation at rest ≤93%, PF ratio ≤300, respiratory failure requiring mechanical ventilation, shock and requiring ICU admission requirement due to multiple organ failure (WHO-China criteria)
18	Yang G. *et al*[20]	Wuhan, China	The patients diagnosed with COVID-19 who were admitted to hospital	126 (251) ACEI/ARB group: 43	66 (66)* ACEI/ARB group: 65* Non-ACEI/ARB group: 67*	49.2 (49.0) ACEI/ARB group: 48.8 Non-ACEI/ARB group: 49.4	Exposure to ACEI or ARB prior to admission and during hospital stay	One of the following conditions: RR ≥30/min, O_2 saturation at rest ≤93%, PF ratio ≤300 (WHO-China criteria)
19	Zeng Z. *et al*[34]	Wuhan, China	The hospitalised patients suspected and confirmed of patients with COVID-19 who were aged <18 years, whose entire stay in hospital lasted for <48 hours were excluded	75 (274) ACEI/ARB group: 28	67 (60) ACEI/ARB group: 64 Non-ACEI/ARB group: 69	46.7 (54.7) ACEI/ARB group: 42.9 Non-ACEI/ARB group: 48.9	Data on medication history of ACEI or ARB were extracted from electric medical record	One of the following conditions: septic shock, mechanical ventilation Three of the following conditions: RR ≥30/min, PF ratio ≤250, multiple infiltration, altered mentality, BUN ≥20 mg/dL, WBC <4000 cells/μL, platelet <100 000/μL, body temperature <36°C, hypotension requiring fluid resuscitation (ATS/IDSA criteria for severe pneumonia)
20	Zhang P. *et a*[21]	Multicentre, China	The hypertensive adults (aged 18–74 years) diagnosed with COVID-19 who were admitted to hospital The patients with incomplete medical records, pregnancy, lethal organ injury, decompensated or end-stage disease, AIDS or malignancy were excluded	1128 ACEI/ARB group: 188	64* ACEI/ARB group: 64 Non-ACEI/ARB group: 64	53.5 ACEI/ARB group: 53.2 Non-ACEI/ARB group: 53.5	Exposure to ACEI or ARB during hospitalisation	N/A (although acute respiratory syndrome, septic shock, disseminated intravascular coagulopathy and acute kidney injury were evaluated, those outcomes can be overlapped)

Some studies evaluated the association between ACEI/ARB use and severe disease or mortality only in the subgroup patients with hypertension. If the information is available, we described the information of hypertensive patients first, and then the information of all patients in the bracket.
*Only median value was reported.
†Only the values of the whole patient cohort were available; the values of the subjects analysed in the study were not presented.
ACEI, ACE inhibitor; ARB, angiotensin II receptor antagonist; ATS, American Thoracic Society; BP, blood pressure; BUN, blood urea nitrogen; IDSA, Infectious Diseases Society of America; N/A, not available; NIV, non-invasive ventilation; PF ratio, PaO_2/FiO_2; RR, respiratory ratio; WBC, white blood cell.

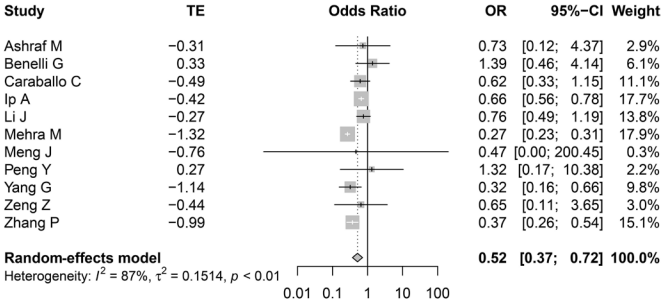

Figure 2 Forest plot of for all-cause mortality using OR. All-cause mortality data of OR and 95% CI from 11 studies were pooled in this meta-analysis using random-effects model and the result of meta-analysis was described as a forest plot. The square and horizontal line indicated the OR and 95% CI of individual study that was also described in the right side of the forest plot. The diamond on the bottom of this forest plot indicated a pooled OR and 95% CI. TE, treatment effect.

Severe disease in COVID-19

For 12 848 patients in 13 studies, ACEI/ARB use was not associated with an increased risk of severe disease manifestation in a meta-analysis using a random-effects model, although there was a significant heterogeneity (OR=0.68 (95% CI=0.44 to 1.07); I^2=95%, p value for heterogeneity <0.01, figure 4) (low level of evidence, online supplemental appendix 6). We conducted a various meta-regression, but did not identify a contributor of heterogeneity among the following covariates: 'confounders were adjusted or not' (test of moderator p=0.99), 'including hypertensive patients only or not' (test of moderator p=0.35), 'the age of participants ≥60 or <60 years' (test of moderator p=0.21) or 'male proportion ≥50% or <50%' (test of moderator p=0.58). Whether the definition for severe disease followed the WHO-China criteria or not also did not affect the effect size (test of moderator p=0.17). ACEI/ARB group did not have a higher risk of severe disease than ACEI/ARB group both in subgroup of studies defining severe disease according to WHO-China criteria (OR=0.51 (95% CI=0.30 to 0.87)) and in

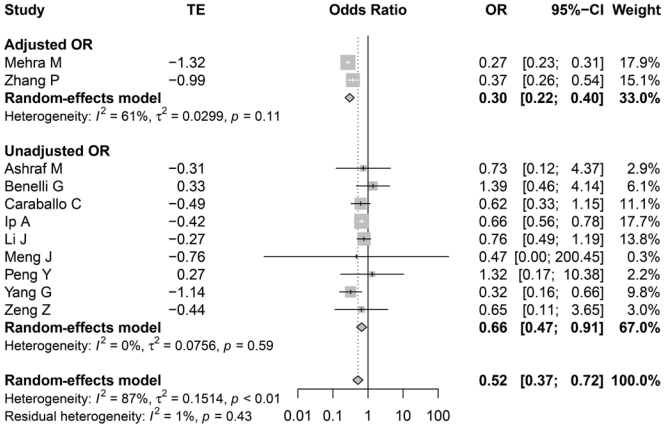

Figure 3 Forest plot for all-cause mortality in adjusted OR and unadjusted OR. Subgroup analysis for all-cause mortality was conducted according to adjusted or unadjusted OR. The square and horizontal line indicated the OR and 95% CI of individual study that was also described in the right side of the forest plot. The diamond of this forest plot indicated a pooled OR and 95% CI in each subgroup analysis and in overall population. Meta-regression analysis performed using 'unadjusted versus adjusted' as the covariate affected the effect size (test of moderator, p<0.001). TE, treatment effect.

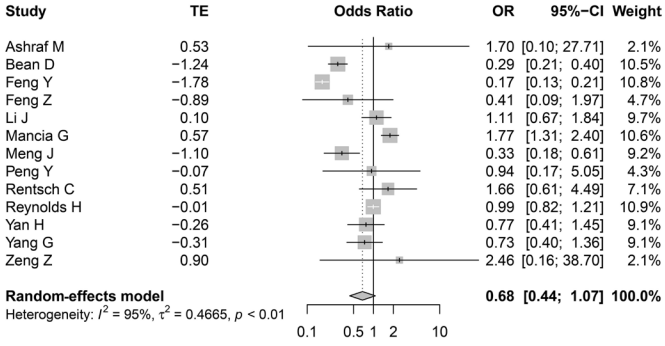

Figure 4 Forest plot for severe disease using OR. Severe disease data of OR and 95% CI from 13 studies were pooled in this meta-analysis using random-effects model and the result of meta-analysis was described as a forest plot. The square and horizontal line indicated the OR and 95% CI of individual study that was also described in the right side of the forest plot. The diamond on the bottom of this forest plot indicated a pooled OR and 95% CI. TE, treatment effect.

subgroup of studies defining severe disease according to other criteria (OR=0.99 (95% CI=0.51 to 1.90)) (figure 5). ACEI/ARB was not associated with increased risk of severe disease in all other subgroup analyses, although there were statistical heterogeneities in majority of subgroup analysis (online supplemental appendices 11–14. The sensitivity analysis excluding one study,[14] in which not all patients were hospitalised, showed a similar result (online supplemental appendix 15).

Publication bias

Observation of funnel plots supported by Egger's and Begg's tests indicated no significant publication bias for the associations with mortality and severe disease (online supplemental appendix 16).

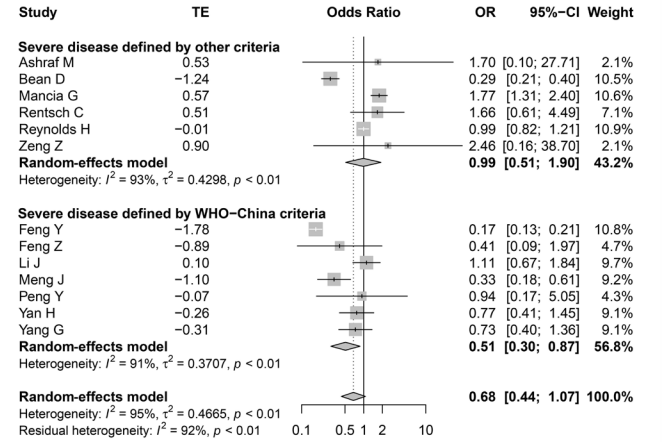

Figure 5 Forest plot for severe disease according to the definition of severe disease. Subgroup analysis for severe disease was conducted according to whether the definition of severe disease followed WHO-China criteria or not. The square and horizontal line indicated the OR and 95% CI of individual study that was also described in the right side of the forest plot. The diamond of this forest plot indicated a pooled OR and 95% CI in each subgroup analysis and in overall population. Meta-regression analysis performed using 'defined by WHO-China criteria versus other criteria' as the covariate did not affect the effect size (test of moderator, p=0.1657). TE, treatment effect.

DISCUSSION

To our knowledge, this is the systematic review and meta-analysis investigating the association between ACEI/ARB treatment and the risk of mortality and severe disease in patients with COVID-19 first registered in PROSPERO. ACEI/ARB use was significantly associated with a decreased risk of all-cause mortality in meta-analysis for studies using ORs. Two studies using HR did not show an increased risk of all-cause mortality in ACEI/ARB group compared with non-ACEI/ARB group. Thus, we concluded that ACEI/ARB did not increase the risk of all-cause mortality in patients infected with SARS-CoV-2. ACEI/ARB use was not associated with an increased risk of severe disease, although there was a significant heterogeneity. We rated moderate certainty of evidence for all-cause mortality and low certainty of evidence for severe disease, mainly rated down due to the limitation of retrospective study design. Overall, the continuation of ACEI/ARB use during the COVID-19 pandemic can be a suitable strategy as current guidance suggested.[11]

Hypertension, cardiovascular diseases and diabetes are the most common comorbidities of patients with severe disease in COVID-19,[44] which are commonly treated with ACEI/ARBs. Researchers have postulated that ACEI/ARB use could be a link between more frequent cases of severe disease symptoms in patients with comorbidities.[44–47] This is based on the fact that ACEI/ARBs were found to upregulate ACE2 expression in rats and human intestinal cells.[2–4] Since ACE2 is the receptor for SARS-CoV-2 entry in the host cell,[5 6] ACEI/ARB use could facilitate worse symptoms in patients with COVID-19.[44–47]

However, our study does not support this speculation; it even suggests a potential benefit of ACEI/ARB for some COVD-19 patients given that a decreased risk of all-cause mortality was observed in the meta-analysis for studies using ORs. The biological mechanism of these beneficial effects with ACEI/ARB could be explained from two perspectives.[48] First, ACEI/ARBs inhibit the activity of angiotensin II, which increases blood pressure, retention of sodium and water,[49] inflammation[50] and tissue injury.[51] Thus, these drugs attenuate lung and cardiovascular insults, which could prevent severe disease and death.[52] In fact, serum angiotensin II levels were found to be markedly elevated and linearly associated with viral load and lung injury in patients with COVID-19.[53] Second, ACEI/ARBs upregulate ACE2, which is expressed in the heart, lung, intestine and kidneys.[54] Human coronaviruses downregulate ACE2 expression on cell membranes after invading cells,[55 56] thereby enhancing neutrophil infiltration in the lungs.[57] Since angiotensin II is the main substrate of ACE2, the increase in ACE2 levels by ACEI/ARBs could mitigate the harmful effects of angiotensin II. ACE2 also degrades angiotensin I to angiotensin-(1-9), inducing anti-inflammatory, antioxidative and vasodilating effects through binding to the Mas receptor.[11] In fact, some previous studies suggested that ACEI/ARBs may have a beneficial effect in preventing pneumonia[58 59] and in improving the outcomes of patients with acute respiratory distress syndrome.[60] The study of Meng *et al*,[16] which was included in our meta-analysis, demonstrated no difference in viral load at baseline, although the peak viral load was significantly lower in the ACEI/ARB group than in the non-ACEI/ARB group (p=0.03).

Our study has limitations. First, the interpretation of the results from our systematic review and meta-analysis should be careful because of high ROB from observational studies. According to GRADE approach, we attenuated the certainty of our conclusions. Second, the definition of severe disease was heterogeneous among studies. Seven studies defined severe disease based on the WHO-China criteria, and six studies used other different criteria. The heterogenous definition for severe disease may have led to a significant statistical heterogeneity in the meta-analysis (I^2=91%, p value for heterogeneity <0.01). Although ACEI/ARB group did not increase the risk of severe disease both in subgroup of studies defining severe disease according to WHO-China criteria and in subgroup of those using other criteria, the results should be cautiously interpreted considering the heterogeneity of outcome definition and the statistical heterogeneity. Third, there were a little bit different time points when the outcomes were evaluated. Most studies evaluated severe disease and mortality during hospitalisation. However, in the study by Mancia *et al*, half of patients with non-severe disease were not hospitalised, although all patients with severe disease were hospitalised. In the study by Caraballo *et al*, about 87% of patients with COVID-19 were hospitalised and in-hospital mortality was evaluated. We postulated the patients with COVID-19 who were not hospitalised as those with mild disease who recovered spontaneously without hospitalisation. The studies by Zeng *et al* and Zhang *et al* used 28 days mortality. However, we performed sensitivity analysis, excluding those studies, which showed similar results. Fourth, we found significant interstudy heterogeneities in meta-analyses for all-cause mortality and severe disease. To identify factors contributing on interstudy heterogeneity, we conducted meta-regression analysis and subgroup analysis. We identified whether confounders were adjusted or not significantly affect the effect size for all-cause mortality and conducted subgroup analysis according to confounders were adjusted or not. However, both subgroup analysis showed that ACEI/ARB group did not have a higher risk of all-cause mortality than non-ACEI/ARB group as described above. Fifth, although all the included studies fulfil the eligibility criteria stipulated in the present systematic review, there were several inconsistent participant criteria because of eligible age (all adults vs ≥40 years old), comorbidities (general population vs specific disease cohort) and indications to exclude specific comorbid diseases.

CONCLUSIONS

The ACEI/ARB treatment does not increase the risk of all-cause mortality in patients with COVID-19. ACEI/ARB use does not increase the risk of severe disease, although the heterogeneous outcome definition and the statistical heterogeneity should be considered. Physicians can prescribe ACEI/ARB without concern of drug-related worsening in patients with COVID-19.

Contributors Study concept and design: HWL and C-HL. Acquisition of data: HWL and C-HL. Analysis and interpretation of data: HWL and C-HL. Manuscript drafting: HWL and C-HL. Critical revision of the manuscript and important intellectual content: EJJ and C-HY. Study supervision: C-HL.

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Competing interests None declared.

Patient consent for publication Not required.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. The data are available by accessing the published studies listed in table 1.

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Supplementary Appendix 1. Search strategy for the systematic review and meta-analysis

COVID-19 AND (ACEI or ARB)

Pubmed

#1. COVID-19

((((novel[Title/Abstract]) AND (((corona[Title/Abstract]) AND virus[Title/Abstract]) OR (coronavirus[Title/Abstract]))) OR ((COVID[Title/Abstract]) OR (COVID-19[Title/Abstract]) OR (nCoV[Title/Abstract]) OR (2019-nCoV[Title/Abstract]) OR (Novel Coronavirus Pneumon.ia[Title/Abstract]) OR (NCP[Title/Abstract]) OR (severe acute respiratory infection[Title/Abstract]) OR (SARI[Title/Abstract]) OR (SARS-CoV-2[Title/Abstract])))

#2. ARB

(("Angiotensin Receptor Antagonists"[Mesh]) OR (((angiotensin receptor blocker[Title/Abstract]) OR angiotensin receptor blockers[Title/Abstract]) OR ARB.*[Title/Abstract]) OR (((angiotensin[Title/Abstract]) AND receptor[Title/Abstract]) AND (antagonist.*[Title/Abstract] OR inhibitor.*[Title/Abstract] OR blocker.*[Title/Abstract]))) OR (ARB[Title/Abstract])

OR

(olmesartan[Title/Abstract]) OR (valsartan[Title/Abstract]) OR (eprosartan[Title/Abstract]) OR (irbesartan[Title/Abstract]) OR (candesartan[Title/Abstract]) OR (losartan[Title/Abstract]) OR (telmisartan[Title/Abstract]) OR (azilsartan[Title/Abstract]) OR (tasosartan[Title/Abstract]) OR (embusartan[Title/Abstract]) OR (forasartan[Title/Abstract]) OR (milfasartan[Title/Abstract]) OR (saprisartan[Title/Abstract]) OR (zolasartan[Title/Abstract])

#3. ACE inhibitor

("Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR ((angiotensin converting enzyme inhibitor[Title/Abstract]) OR ACE inhibitor[Title/Abstract]) OR ((((angiotensin[Title/Abstract]) AND converting[Title/Abstract]) AND enzyme[Title/Abstract]) AND (antagonist.*[Title/Abstract] OR inhibitor.*[Title/Abstract] OR blocker.*[Title/Abstract]))

OR

(alacepril[Title/Abstract] OR altiopril[Title/Abstract] OR ancovenin[Title/Abstract] OR benazepril[Title/Abstract] OR captopril[Title/Abstract] OR ceranapril[Title/Abstract] OR ceronapril[Title/Abstract] OR

cilazapril[Title/Abstract] OR deacetylalacepril[Title/Abstract] OR delapril[Title/Abstract] OR enalapril[Title/Abstract] OR epicaptopril[Title/Abstract] OR foroxymithine[Title/Abstract] OR fosinopril[Title/Abstract] OR idrapril[Title/Abstract] OR imidapril[Title/Abstract] OR indolapril[Title/Abstract] OR libenzapril[Title/Abstract] OR lisinopril[Title/Abstract] OR moexipril[Title/Abstract] OR moveltipril[Title/Abstract] OR pentopril[Title/Abstract] OR perindopril[Title/Abstract] OR pivopril[Title/Abstract] OR quinapril[Title/Abstract] OR ramipril[Title/Abstract] OR rentiapril[Title/Abstract] OR nitrosocaptopril[Title/Abstract] OR spirapril[Title/Abstract] OR temocapril[Title/Abstract] OR trandolapril[Title/Abstract] OR utibapril[Title/Abstract] OR zabicipril[Title/Abstract] OR zofenopril[Title/Abstract] OR teprotide[Title/Abstract])

#1 AND (#2 OR #3)

N= 80 (2020.5.4)

EMBASE

#1. COVID-19

'novel':ab,ti AND ('corona':ab,ti AND 'virus':ab,ti OR 'coronavirus':ab,ti OR 'coronavirus pneumonia':ab,ti) OR 'covid':ab,ti OR 'covid 19':ab,ti OR 'ncov':ab,ti OR '2019 ncov':ab,ti OR 'ncp':ab,ti OR 'sari':ab,ti OR 'sars cov 2':ab,ti

#2. ARB

'angiotensin receptor antagonist'/exp

OR

'angiotensin receptor blocker':ti,ab,kw OR 'angiotensin receptor blockers':ti,ab,kw OR arb.*:ti,ab,kw OR (angiotensin:ti,ab,kw AND receptor:ti,ab,kw AND (antagonist.*:ti,ab,kw OR inhibitor.*:ti,ab,kw OR blocker.*:ti,ab,kw)) OR arb:ti,ab,kw

OR

(olmesartan:ti,ab,kw) OR (valsartan:ti,ab,kw) OR (eprosartan:ti,ab,kw) OR (irbesartan:ti,ab,kw) OR (candesartan:ti,ab,kw) OR (losartan:ti,ab,kw) OR (telmisartan:ti,ab,kw) OR (azilsartan:ti,ab,kw) OR (tasosartan:ti,ab,kw) OR (embusartan:ti,ab,kw) OR (forasartan:ti,ab,kw) OR (milfasartan:ti,ab,kw) OR (saprisartan:ti,ab,kw) OR (zolasartan:ti,ab,kw)

#3. ACE inhibitor

'dipeptidyl carboxypeptidase inhibitor'/exp

OR

'angiotensin converting enzyme inhibitor':ti,ab,kw OR 'ace inhibitor':ti,ab,kw OR (angiotensin:ti,ab,kw AND converting:ti,ab,kw AND enzyme:ti,ab,kw AND (antagonist.*:ti,ab,kw OR inhibitor.*:ti,ab,kw OR blocker.*:ti,ab,kw))

OR

(alacepril:ti,ab,kw OR altiopril:ti,ab,kw OR ancovenin:ti,ab,kw OR benazepril:ti,ab,kw OR captopril:ti,ab,kw OR ceranapril:ti,ab,kw OR ceronapril:ti,ab,kw OR cilazapril:ti,ab,kw OR deacetylalacepril:ti,ab,kw OR delapril:ti,ab,kw OR enalapril:ti,ab,kw OR epicaptopril:ti,ab,kw OR foroxymithine:ti,ab,kw OR fosinopril:ti,ab,kw OR idrapril:ti,ab,kw OR imidapril:ti,ab,kw OR indolapril:ti,ab,kw OR libenzapril:ti,ab,kw OR lisinopril:ti,ab,kw OR moexipril:ti,ab,kw OR moveltipril:ti,ab,kw OR pentopril:ti,ab,kw OR perindopril:ti,ab,kw OR pivopril:ti,ab,kw OR quinapril:ti,ab,kw OR ramipril:ti,ab,kw OR rentiapril:ti,ab,kw OR nitrosocaptopril:ti,ab,kw OR spirapril:ti,ab,kw OR temocapril:ti,ab,kw OR trandolapril:ti,ab,kw OR

utibapril:ti,ab,kw OR zabicipril:ti,ab,kw OR zofenopril:ti,ab,kw OR teprotide:ti,ab,kw)

#1 AND (#2 OR #3)

N=99 (2020.5.4)

Cochrane

#1. COVID-19

(novel:ti,ab,kw AND (corona:ti,ab,kw AND virus:ti,ab,kw OR coronavirus:ti,ab,kw OR (coronavirus pneumonia:ti,ab,kw)))

OR

(COVID-19:ti,ab,kw OR SARS-CoV-2:ti,ab,kw)

#2. ARB

MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees

OR

(angiotensin receptor blocker:ti,ab,kw) OR (angiotensin receptor blockers):ti,ab,kw OR arb.*:ti,ab,kw OR (angiotensin:ti,ab,kw AND receptor:ti,ab,kw AND (antagonist.*:ti,ab,kw OR inhibitor.*:ti,ab,kw OR blocker.*:ti,ab,kw)) OR arb:ti,ab,kw

OR

(olmesartan:ti,ab,kw) OR (valsartan:ti,ab,kw) OR (eprosartan:ti,ab,kw) OR (irbesartan:ti,ab,kw) OR (candesartan:ti,ab,kw) OR (losartan:ti,ab,kw) OR (telmisartan:ti,ab,kw) OR (azilsartan:ti,ab,kw) OR (tasosartan:ti,ab,kw) OR (embusartan:ti,ab,kw) OR (forasartan:ti,ab,kw) OR (milfasartan:ti,ab,kw) OR (saprisartan:ti,ab,kw) OR (zolasartan:ti,ab,kw)

#3. ACE inhibitor

MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees

OR

(angiotensin converting enzyme inhibitor:ti,ab,kw) OR (ace inhibitor:ti,ab,kw) OR (angiotensin:ti,ab,kw AND converting:ti,ab,kw AND enzyme:ti,ab,kw AND (antagonist.*:ti,ab,kw OR inhibitor.*:ti,ab,kw OR blocker.*:ti,ab,kw))

OR

(alacepril:ti,ab,kw OR altiopril:ti,ab,kw OR ancovenin:ti,ab,kw OR benazepril:ti,ab,kw OR captopril:ti,ab,kw OR ceranapril:ti,ab,kw OR ceronapril:ti,ab,kw OR cilazapril:ti,ab,kw OR deacetylalacepril:ti,ab,kw OR delapril:ti,ab,kw OR enalapril:ti,ab,kw OR epicaptopril:ti,ab,kw OR foroxymithine:ti,ab,kw OR fosinopril:ti,ab,kw OR idrapril:ti,ab,kw OR imidapril:ti,ab,kw OR indolapril:ti,ab,kw OR libenzapril:ti,ab,kw OR lisinopril:ti,ab,kw OR moexipril:ti,ab,kw OR moveltipril:ti,ab,kw OR pentopril:ti,ab,kw OR perindopril:ti,ab,kw

OR pivopril:ti,ab,kw OR quinapril:ti,ab,kw OR ramipril:ti,ab,kw OR rentiapril:ti,ab,kw OR nitrosocaptopril:ti,ab,kw OR spirapril:ti,ab,kw OR temocapril:ti,ab,kw OR trandolapril:ti,ab,kw OR utibapril:ti,ab,kw OR zabicipril:ti,ab,kw OR zofenopril:ti,ab,kw OR teprotide:ti,ab,kw)

#1. AND (#2. OR #3.)

N=0 (2020.5.4)

MedRxiv

(abstract or title "COVID-19" or "SARS-Cov-2" or "nCov" or "coronavirus" (match any words))

AND

(full text or abstract or title "angiotensin" (match all words))

AND

Posted date: Since 2020.01.01

N=216 (2020.5.4)

Social Science Research Network (SSRN)

((COVID-19 AND angiotensin) OR (SARS-Cov-2 AND angiotensin) OR (nCov AND angiotensin) OR (coronavirus AND angiotensin))

AND

Posted date: Since 2020.01.01

N=28 (2020.5.4)

Peer J

((COVID-19 AND angiotensin) OR (SARS-Cov-2 AND angiotensin) OR (nCov AND angiotensin) OR (coronavirus AND angiotensin))

AND

Posted date: Since 2020.01.01

N=5 (2020.5.4)

Supplementary Appendix 2. List of excluded references after full-text review

Number	Title	First author	Journal (Year)	Main reason for exclusion
1	Clinical Characteristics and Risk Factors for Fatal Outcome in Patients with 2019-Coronavirus Infected Disease (COVID-19) in Wuhan	Chen M. et al.	SSRN (2020)	data source is likely to be same with the included study of Zhang et al.
2	ACE inhibitors, AT1 receptor blockers and COVID-19: clinical epidemiology evidences for a continuation of treatments. The ACER-COVID study	Dauchet L. et al.	medRxiv (2020)	The use of ACE inhibitor or ARB was not evaluated according to disease severity or mortality.
3	ACE inhibitors, ARBs and other anti-hypertensive drugs and novel COVID-19: An association study from the COVID Symptom tracker app in 2,215,386 individuals	Dooley HC. et al.	SSRN (2020)	Disease severity or mortality data was not available.
4	Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19)	Guo T. et al.	JAMA Cardiol. (2020)	data source is likely to be same with the included study of Zhang et al.
5	The Role of Angiotensin Converting Enzyme 2 in Coronaviruses/Influenza Viruses and Cardiovascular Disease	Li C. et al.	SSRN (2020)	No specific data on COVID-19 was available
6	Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients	Liu Y. et al.	medRxiv (2020)	The data source is likely to be same with the included study of Meng et al.
7	The Effect of Psychological Support for the Relatives of Intensive Care Unit Patients on Cadaveric Organ Donation Rate	Liu Y. et al.	Sci China Life Sci. (2020)	Disease severity or mortality data was not available.
8	Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury	Liu Y. et al.	Sci China Life Sci. (2020)	Disease severity or mortality data was not available.
9	Clinical presentation and initial management critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brescia, Italy	Piva S. et al.	J Crit Care (2020)	The use of ACE inhibitor or ARB was not evaluated according to disease severity or mortality.
10	Outcomes in Patients with COVID-19 Infection Taking ACEI/ARB	Rico-Mesa JS. et al.	Curr Cardiol Rep. (2020)	The use of ACE inhibitor or ARB was not evaluated according to disease severity or mortality.
11	Clinical characteristics associated with COVID-19 severity in California	Samuel R. et al.	medRxiv (2020)	The use of ACE inhibitor or ARB was not evaluated according to disease severity or mortality.
12	Comorbidities in COVID-19: Outcomes in hypertensive cohort and controversies with renin angiotensin system blockers	Singh AK. et al.	Diabetes Metab Syndr. (2020)	This is a pooled analysis using results from other studies.
13	Chronic Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers Is High Among Intensive Care Unit Patients With Non–COVID-19 Sepsis but Carries a Moderately Increased Risk of Death	Sunden-Cullberg J. et al.	Hypertension (2020)	The patients diagnosed with COVID-19 were not evaluated.
14	Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients	Xiaoping C. et al.	medRxiv (2020)	Although researchers found that angiotensin-converting enzyme 2 was related with delayed viral clearance, the data on effect of ACE inhibitor or ARB was not available.
15	The Role of Angiotensin Converting Enzyme 2 in the Gastrointestinal Infection Risk and Potential Fecal Oral-Transmission Route of 2019-nCoV	Xing yong C. et al.	SSRN (2020)	The use of ACE inhibitor or ARB was not evaluated according to disease severity or

mortality.

Supplementary Appendix 3. The details of the data source of studies included in the meta-analysis.

No	Author	Study data source details
1	Ashraf MA[1]	YAS hospital of Tehran University of Medical Sciences
2	Bean D[2]	King's College Hospital and Princess Royal University Hospital
3	Benelli G[3]	The Hospital of Crema
4	Caraballo C[4]	Yale Heart Failure Registry
5	Feng Y[5]	Jinyintan Hospital in Wuhan Shanghai Public Health Clinical Center in Shanghai Tongling People's Hospital in Anhui
6	Feng Z[6]	Third Xiangya Hospital of Central South University Changsha Public Health Treatment Center First Hospital of Yueyang Junshan People's Hospital of Yueyang, Central Hospital of Shaoyang Central Hospital of Xiangtan, Second Hospital of Changde Central Hospital of Loudi First Affiliated Hospital of University of South China
7	Ip A[7]	Hackensack Meridian Health network
8	Lee H[8]	Korea Centers for Disease Control and Prevention
9	Li J[9]	Central Hospital, Wuhan
10	Mancia G[10]	Database on residents in Lombardy who were beneficiaries of the Regional Health Service
11	Mehra MR[11]	International (169 hospitals located in 11 countries in Asia, Europe, and North America)
12	Meng J[12]	Shenzhen Third People's Hospital*
13	Peng Y[13]	West Hospital of Wuhan Union Hospital
14	Rentsch CT[14]	Veterans Affairs Birth Cohort
15	Reynolds HR[15]	New York University (NYU) Langone Health
16	Tedeschi S[16]	A prospective cohort from ten Italian hospitals including Policlinico di Sant'Orsola
17	Yan H[17]	Database on citizens of in Gulin town, a suburban area of Ningbo City, in Zhejiang province (14 hospitals)
18	Yang G[18]	Hubei Provincial Hospital of Traditional Chinese Medicine
19	Zeng Z[19]	Hankou Hospital, Wuhan

20	Zhang P[20]	Renmin Hospital of Wuhan University, Zhongnan Hospital of Wuhan University, Wuhan First Hospital, Wuhan Third Hospital, Wuhan Seventh Hospital, Wuhan Ninth Hospital, Thunder Mountain Hospital, Huanggang Central Hospital, and the Central Hospital of Enshi Tujia and Miao Autonomous Prefecture

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19. Zeng Z, Sha T, Zhang Y, et al. Hypertension in patients hospitalized with COVID-19 in Wuhan, China: A single-center retrospective observational study. 2020.
20. 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. Circulation research 2020.

Supplementary Appendix 4. The details of comorbidities of the included patients in the meta-analysis

No.	Author (year)	Hypertension, %	Diabetes mellitus, %	Cardiovascular comorbidities, %	Pulmonary comorbidities, %	Cerebrovascular disease, %	Chronic liver disease, %	Chronic kidney disease, %	Cancer, %
1	Ashraf MA. (2020)	26.0	26.0	19.0	13.0	-	-	-	-
2	Bean D. (2020)	Total: 51.2, ACEI/ARB group: 82.6 Non-ACEI/ARB group: 42.1	Total: 30.2 ACEI/ARB group: 50.0 Non-ACEI/ARB group: 24.5	Total: 14.6 ACEI/ARB group: 28.3 Non-ACEI/ARB group: 10.7	-	-	-	-	-
3	Benelli G. (2020)	47.0	16.3	22.6	11.7	-	-	5.3	8.0
4	Caraballo C. (2020)	79.6	-	35.4	32.5	-	-	38.3	-
5	Feng Y (2020)	100 (23.7)	(10.3)[a]	(8.0)[a]	(4.6)[a]	(3.6)[a]	-	(0.8)[a]	(2.5)[a]
6	Feng Z. (2020) [a]	100 (14.5)	Total: 30.8 (8.0), ACEI/ARB group: 12.5, Non-ACEI/ARB group: 36.7	Total: 12.3 (3.9), ACEI/ARB group: 0, Non-ACEI/ARB group: 16.3	Total: 1.5 (21.3), ACEI/ARB group: 0, Non-ACEI/ARB group: 2.0	Total: 4.6 (0.9), ACEI/ARB group: 0, Non-ACEI/ARB group: 6.1	Total: 3.1 (1.6), ACEI/ARB group: 0, Non-ACEI/ARB group: 4.1	Total: 3.1 (0.5), ACEI/ARB group: 6.3, Non-ACEI/ARB group: 2.0	-
7	Ip A. (2020)	100	-	-	-	-	-	-	-
8	Lee H. (2020)	19.0 ACEI/ARB group: 97.3 Non-ACEI/ARB group: 8.6	17.1 ACEI/ARB group: 50.0 Non-ACEI/ARB group: 12.6	5.7 ACEI/ARB group: 19.7 Non-ACEI/ARB group: 3.8	14.3 ACEI/ARB group: 25.7 Non-ACEI/ARB group: 12.8	2.9 ACEI/ARB group: 12.3 Non-ACEI/ARB group: 1.6	-	1.0 ACEI/ARB group: 4.3 Non-ACEI/ARB group: 0.6	4.4 ACEI/ARB group: 9.0 Non-ACEI/ARB group: 0.6
9	Li J. (2020)	100	35.1 ACEI/ARB group: 36.5 Non-ACEI/ARB group: 34.4	17.1 ACEI/ARB group: 23.5 Non-ACEI/ARB group: 14.2	5.0 ACEI/ARB group: 7.0 Non-ACEI/ARB group: 4.0	18.8 ACEI/ARB group: 23.5 Non-ACEI/ARB group: 16.6	-	9.7 ACEI/ARB group: 11.3 Non-ACEI/ARB group: 8.9	3.0 ACEI/ARB group: 1.7 Non-ACEI/ARB group: 3.6
10	Mancia G. (2020)	57.9	19.1	30.1	10.4	-	-	5.0	17.4
11	Mehra MR. (2020)	26.3	14.3	11.3	2.5	-	-	-	-
12	Meng J. (2020)	100	Total: 14.3 ACEI/ARB group: 11.8 Non-ACEI/ARB group: 16.0	Total: 19.0 ACEI/ARB group: 11.8 Non-ACEI/ARB group:24.0	-	-	-	-	Total: 4.8 ACEI/ARB group: 0 Non-ACEI/ARB group: 8.0
13	Peng Y. (2020)	82.1	20.5	55.4	-	-	0	0	-
14	Rentsch CT. (2020)	72.3	44.4	27.9	15.4	-	10.3	19.0	14.2
15	Reynolds HR. (2020)	43.7	-[a]	-[a]	-	-	-	-	-
16	Tedeschi S. (2020)	100	23.8	42.1	15.8	-	-	-	-
17	Yan H. (2020)	(22.5)[a]	(9.8)[a]	(2.6)[a,b]	-	(2.6)[a,b]	(5.6)[a]	-	(1.8)[a]
18	Yang G. (2020)	100 (50.2)	30.2 (21.9) ACEI/ARB group: 30.2 Non-ACEI/ARB group: 30.1	18.3 (14.0) ACEI/ARB group: 16.3 Non-ACEI/ARB group: 19.3	4.7 (4.6) ACEI/ARB group: 7.0 Non-ACEI/ARB group: 3.6	7.9 (6.0) ACEI/ARB group: 9.3 Non-ACEI/ARB group: 7.2	6.3 (5.2) ACEI/ARB group: 7.0 Non-ACEI/ARB group: 6.1	2.4 (1.6) ACEI/ARB group: 0 Non-ACEI/ARB group: 3.6	-
19	Zeng Z. (2020)	100 (27.4)	30.7 (15.3)	21.3 (11.3)	9.3 (5.5)	14.7 (8.0)	4.0 (3.6)	5.3 (1.8)	2.7 (2.9)
20	Zhang P. (2020)	100	21.3 ACEI/ARB group: 23.4 Non-ACEI/ARB group: 20.9	11.7 ACEI/ARB group: 15.4 Non-ACEI/ARB group: 10.9	0.5 ACEI/ARB group: 0.5 Non-ACEI/ARB group: 0.5	3.6 ACEI/ARB group: 2.7 Non-ACEI/ARB group: 3.8	1.9 ACEI/ARB group: 2.1 Non-ACEI/ARB group: 1.8	3.1 ACEI/ARB group: 3.7 Non-ACEI/ARB group: 3.0	0

ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor antagonist

Some studies evaluated the association between ACEI/ARB use and severe disease or mortality only in the subgroup patients with hypertension. If the information is available, we described the information of hypertensive patients first, and then the information of all patients in the bracket.

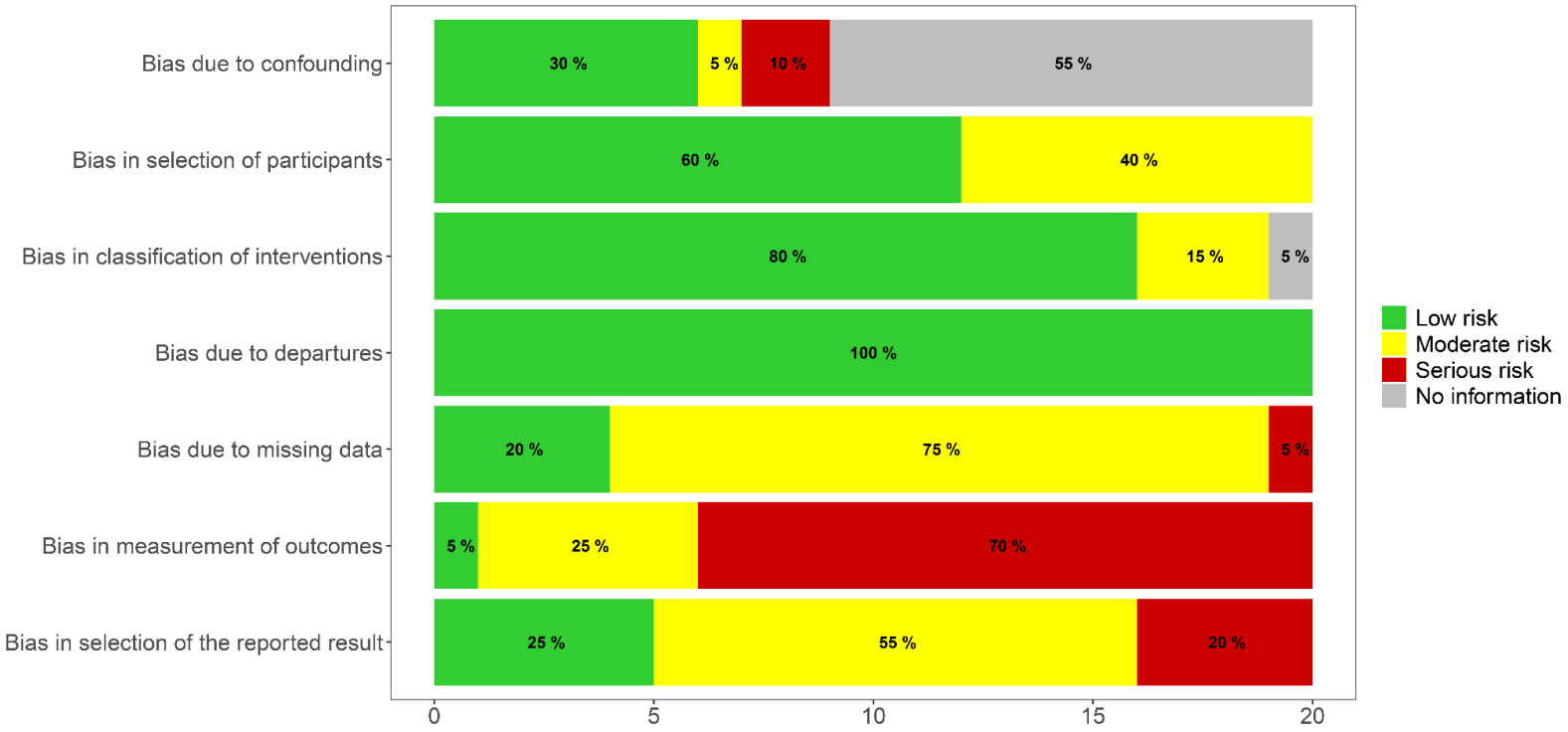
[a] Only the values of the whole patient cohort were available; The values of the subjects analyzed in the study were not presented.

[b] Cardiovascular and cerebrovascular disease were reported as a combined value.

Supplementary Appendix 5. The risk of bias assessment for the included nonrandomized studies and reasons for judgement

Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Ashraf MA. et al. (2020)	No information	Low	Low	Low	Moderate	Serious	Moderate
Bean D. et al. (2020)	Serious	Low	Low	Low	Moderate	Serious	Moderate
Benelli G. et al. (2020)	No information	Low	Low	Low	Low	Serious	Serious
Caraballo C. et al. (2020)	No information	Low	Low	Low	Moderate	Moderate	Moderate
Feng Y. et al. (2020)	Serious	Moderate	Low	Low	Moderate	Serious	Moderate
Feng Z. et al. (2020)	Moderate	Low	Moderate	Low	Low	Serious	Moderate
Ip A. et al. (2020)	No information	Moderate	Low	Low	Moderate	Moderate	Serious
Lee H. et al. (2020)	Low	Low	Low	Low	Moderate	Moderate	Moderate
Li J. et al. (2020)	Low	Moderate	Low	Low	Moderate	Serious	Low
Mancia G. et al. (2020)	No information	Low	Moderate	Low	Moderate	Serious	Moderate
Mehra MR. et al. (2020)	No information	Low	Low	Low	Moderate	Moderate	Moderate
Meng J. et al. (2020)	Low	Moderate	Low	Low	Moderate	Serious	Low
Peng Y. et al. (2020)	No information	Low	Low	Low	Moderate	Serious	Serious
Rentsch CT. et al. (2020)	No information	Moderate	Low	Low	Low	Serious	Moderate
Reynolds HR. et al. (2020)	Low	Low	Moderate	Low	Moderate	Serious	Moderate
Tedeschi S. et al. (2020)	No information	Low	No information	Low	Low	Low	Serious
Yan H. et al. (2020)	No information	Low	Low	Low	Serious	Serious	Moderate
Yang G. et al. (2020)	Low	Moderate	Low	Low	Moderate	Serious	Low
Zeng Z. et al. (2020)	No information	Moderate	Low	Low	Moderate	Serious	Low
Zhang P. et al. (2020)	Low	Moderate	Low	Low	Moderate	Moderate	Low

Interpretation of risk of bias	No information	Low	Moderate	Serious	Critical


Bias due to confounding
Bias in selection of participants
Bias in classification of interventions
Bias due to departures
Bias due to missing data
Bias in measurement of outcomes
Bias in selection of the reported result
30 %
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20
Low risk
Moderate risk
Serious risk
No information

Author (year) Study name	Domain	Review author's assessment and reason for judgment
Published studies (n=10)		
Feng Y. et al. (2020)	Bias due to confounding	Serious risk. Underlying chronic diseases were more likely to be found in severe to critical group. These kinds of underlying condition can affect the severity of COVID-19 or mortality risk
	Bias in selection of participants into the study	Moderate risk. All the patients newly diagnosed with COVID-19 were included. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, ACEI or ARB use was analyzed in hypertensive patients, not all the patients.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Li J. et al. (2020)	Bias due to confounding	Low risk. Underlying chronic diseases and other confounding factors were similar between ACEI/ARB group and non-ACEI/ARB group.
	Bias in selection of participants into the study	Moderate risk. Hypertensive patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that selection of hypertensive patients may impact on our results.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Low risk. All the variables were analyzed whether there is any difference between ACEI or ARB user group and non-user group
Mancia G. et al. (2020)	Bias due to confounding	No information. Main analysis was conducted to know the risk factors for COVID-19 development. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use.
	Bias in selection of participants into the study	Low risk. All the patients who received COVID-19 test were included. Medical records were reviewed retrospectively and patients were classified according to COVID-19 positivity. Analysis was conducted to evaluate the risk of severe COVID-19 according to anti-hypertensive drugs. In the process of inclusion and analysis, selection bias would hardly intervene in this study.
	Bias in classification of interventions	Moderate risk. Although claim data were reviewed retrospectively, operational definition was not clearly described (eg. minimum treatment days, when treatment starts and ends). There may be a risk of misclassification of interventions.

	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Mehra MR. et al. (2020)	Bias due to confounding	No information. Main analysis was conducted to know the risk factors for all-cause mortality. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use
	Bias in selection of participants into the study	Low risk. Hospitalized COVID-19 patients were included internationally. Medical records were reviewed retrospectively and the patients were classified according to mortality.
	Bias in classification of interventions	Low risk. Medical records were reviewed retrospectively, and ACEI or ARB use at the time of hospital admission was identified.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Moderate risk. This study was conducted retrospectively. Therefore, investigators knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment can be suggested. However, only mortality was analyzed in this study, that cannot be biased even though the investigators knew the patient data before analysis.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Meng J. et al. (2020)	Bias due to confounding	Low risk. Underlying chronic diseases and other confounding factors were similar between ACEI/ARB group and non-ACEI/ARB group.
	Bias in selection of participants into the study	Moderate risk. Hypertensive patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that selection of hypertensive patients may impact on our results.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in ACEI or ARB use. However, the patient data without available information on the use of ACEI or ARB may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Low risk. All the variables were analyzed whether there is any difference between ACEI or ARB user group and non-user group.
Peng Y. et al. (2020)	Bias due to confounding	No information. Main analysis was conducted to know the risk factors for mortality in COVID-19 patients upon admission. However, it is

		not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use.
	Bias in selection of participants into the study	Low risk. All the hospitalized patients diagnosed with COVID-19 were included. Medical records were reviewed retrospectively and patients were classified according to mortality, which was clearly defined in Methods section. Therefore, selection bias would hardly intervene in this study.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in ACEI or ARB use. However, the patient data without available information on the use of ACEI or ARB may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Serious risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but the possibility of bias in selective reporting is strongly suggested because other hypertensive or cardioprotective drugs were not described (eg. beta-blocker) and any other intervention (eg. antibiotics or antiviral agents) which may impact on prognosis were not evaluated at all.
Reynolds HR. et al. (2020)	Bias due to confounding	Low risk. Propensity score-matched patients with a positive test for COVID-19 were evaluated according to anti-hypertensive treatments.
	Bias in selection of participants into the study	Low risk. Both matched patients with hypertension and all matched patients were evaluated. Medical records were reviewed retrospectively analyzed according to anti-hypertensive treatments. Selection bias would hardly intervene in this study.
	Bias in classification of interventions	Moderate risk. Although claim data were reviewed retrospectively, operational definition was not clearly described (eg. minimum treatment days, when treatment starts and ends). There may be a risk of misclassification of interventions.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in ACEI or ARB use. However, the patient data without available information on the use of ACEI or ARB may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Tedeschi S. et al. (2020)	Bias due to confounding	No information. Main analysis was conducted to know the different mortality according to hypertension or hypertensive drugs in COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use.
	Bias in selection of participants into the study	Low risk. All the hospitalized patients diagnosed with COVID-19 were prospectively enrolled. Patients were classified according to hypertension, which hardly makes selection bias in this study.
	Bias in classification of interventions	No information. There was no description how the researchers coded the use of anti-hypertensive drugs when a patient who started or stopped ACEI or ARB during hospitalization. We think there may be a few patients who changed anti-hypertensive medication during hospitalization. However, the information of classification of interventions was not described in the manuscript.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether

		ACEI or ARB was used or not.
	Bias due to missing data	Low risk. There would be no missing data because all the patients were hospitalized and followed up.
	Bias in measurement of outcomes	Low risk. As COVID-19 patients were enrolled prospectively in 10 hospitals, investigators independently assessed outcomes and were independent to the researchers who analyzed outcomes.
	Bias in selection of the reported result	Serious risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but the possibility of bias in selective reporting is strongly suggested because other hypertensive or cardioprotective drugs were not described (eg. beta-blocker) and any other intervention (eg. antibiotics or antiviral agents) which may impact on prognosis were not evaluated at all.
Yang G. et al. (2020)	Bias due to confounding	Low risk. Underlying chronic diseases and other confounding factors were similar between ACEI/ARB group and non-ACEI/ARB group.
	Bias in selection of participants into the study	Moderate risk. Hypertensive patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that selection of hypertensive patients may impact on our results.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Low risk. All the variables were analyzed whether there is any difference between ACEI or ARB user group and non-user group.
Zhang P. et al. (2020)	Bias due to confounding	Low risk. Although underlying chronic diseases and other confounding factors were significantly different between ACEI/ARB group and non-ACEI/ARB group, adjusted effect size was calculated.
	Bias in selection of participants into the study	Moderate risk. Hypertensive patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that selection of hypertensive patients may impact on our results.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Moderate risk. This study was conducted retrospectively. Therefore, investigators knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment can be suggested. However, only mortality was analyzed in this study, that cannot be biased even though the investigators knew the patient data before analysis.
	Bias in selection of the reported result	Low risk. All the variables were analyzed whether there is any difference between ACEI or ARB user group and non-user group.
Unpublished study (n=10)		
Ashraf MA. et al. (2020)	Bias due to confounding	No information. Main analysis was conducted according to non-critically ill and critically ill COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use

	Bias in selection of participants into the study	Low risk. All the hospitalized patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to ACEI/ARB use, which was clearly defined in Methods section. Selection bias was not suspected.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Bean D. et al. (2020)	Bias due to confounding	Serious risk. There were significant differences in underlying diseases between ACEI or ARB user group and non-user group.
	Bias in selection of participants into the study	Low risk. All the symptomatic and hospitalized patients diagnosed with COVID-19 were included. Medical records were reviewed retrospectively and patients were classified according to recent ACEI or ARB use, which was clearly defined in Methods section. Therefore, selection bias would hardly intervene in this study.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Benelli G. et al. (2020)	Bias due to confounding	No information. Main analysis was conducted to know the risk factors for in-hospital death, ICU admission, and CPAP/NIV use in COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use
	Bias in selection of participants into the study	Low risk. All the suspected patients admitted to hospital underwent diagnostic SARS-COV-2 real-time polymerase chain reaction assay. Among the COVID-19 positive patients were included. Medical records were reviewed retrospectively and patients were classified according to recent ACEI or ARB use, which was clearly defined in Methods section. Therefore, selection bias would hardly intervene in this study.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Low risk. Researchers reported 8 missing cases. The number of missing data occupied small proportion of total included patients.

	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Serious risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but the possibility of bias in selective reporting is strongly suggested because other hypertensive or cardioprotective drugs were not described (eg. beta-blocker) and any other intervention (eg. antibiotics or antiviral agents) which may impact on prognosis were not evaluated at all.
Caraballo C. et al. (2020)	Bias due to confounding	No information. Main analysis was conducted to know the risk factors for death in COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use
	Bias in selection of participants into the study	Low risk. All the hospitalized patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to ACEI/ARB use, which was clearly defined in Methods section. Selection bias was not suspected.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Moderate risk. This study was conducted retrospectively. Therefore, investigators knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment can be suggested. However, only mortality was analyzed in this study, that cannot be biased even though the investigators knew the patient data before analysis.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Feng Z. et al. (2020)	Bias due to confounding	Moderate risk. Underlying chronic diseases, medications, and other conditions were not significantly different between ACEI/ARB group and non-ACEI/ARB group, but the small number of included patients may contribute to insufficient statistical power.
	Bias in selection of participants into the study	Low risk. Hypertensive patients diagnosed with COVID-19 were included. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. Researchers rigorously evaluated medical history of the included patients and selections bias was not suspected.
	Bias in classification of interventions	Moderate risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). However, 17 patients with available or irregular anti-hypertensive therapy were not classified and excluded from analysis. More clear definition for classification was needed.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Low risk. Researchers reported missing data in Figure 1. The number of missing data occupied small proportion of total included patients.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Ip A. et al. (2020)	Bias due to confounding	No information. Main analysis was conducted to know the risk factors for death in COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use

	Bias in selection of participants into the study	Moderate risk. Hypertensive patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that selection of hypertensive patients may impact on our results.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Moderate risk. This study was conducted retrospectively. Therefore, investigators knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment can be suggested. However, only mortality was analyzed in this study, that cannot be biased even though the investigators knew the patient data before analysis.
	Bias in selection of the reported result	Serious risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but the possibility of bias in selective reporting is strongly suggested because other hypertensive or cardioprotective drugs were not described (eg. beta-blocker) and any other intervention (eg. antibiotics or antiviral agents) which may impact on prognosis were not evaluated at all.
Lee H. et al. (2020)	Bias due to confounding	Low risk. Although underlying chronic diseases and other confounding factors were significantly different between ACEI/ARB group and non-ACEI/ARB group, adjusted effect size was calculated.
	Bias in selection of participants into the study	Low risk. All the COVID-19 patients who were hospitalized or isolated were included in this study.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Moderate risk. This study was conducted retrospectively. Therefore, investigators knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment can be suggested. However, only mortality was analyzed in this study, that cannot be biased even though the investigators knew the patient data before analysis.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Rentsch CT. et al. (2020)	Bias due to confounding	No information. Confounding factors were compared between COVID-19 positive and negative patients. However, it is not possible to know whether there is any difference in confounding factors between the patients who used ACEI or ARB and those who did not use.
	Bias in selection of participants into the study	Moderate risk. All the patients who were registered in VA Birth cohort and took COVID-19 tests were included. Medical records were reviewed retrospectively and patients were classified according to COVID-19 positivity. There may a selection bias in those who took COVID-19 tests among the VA Birth cohort patients and this may impact on our results.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for anti-hypertensive or protective effect on heart, kidney, or other vascular diseases. Therefore, it is difficult to think that there would be a different management according to whether

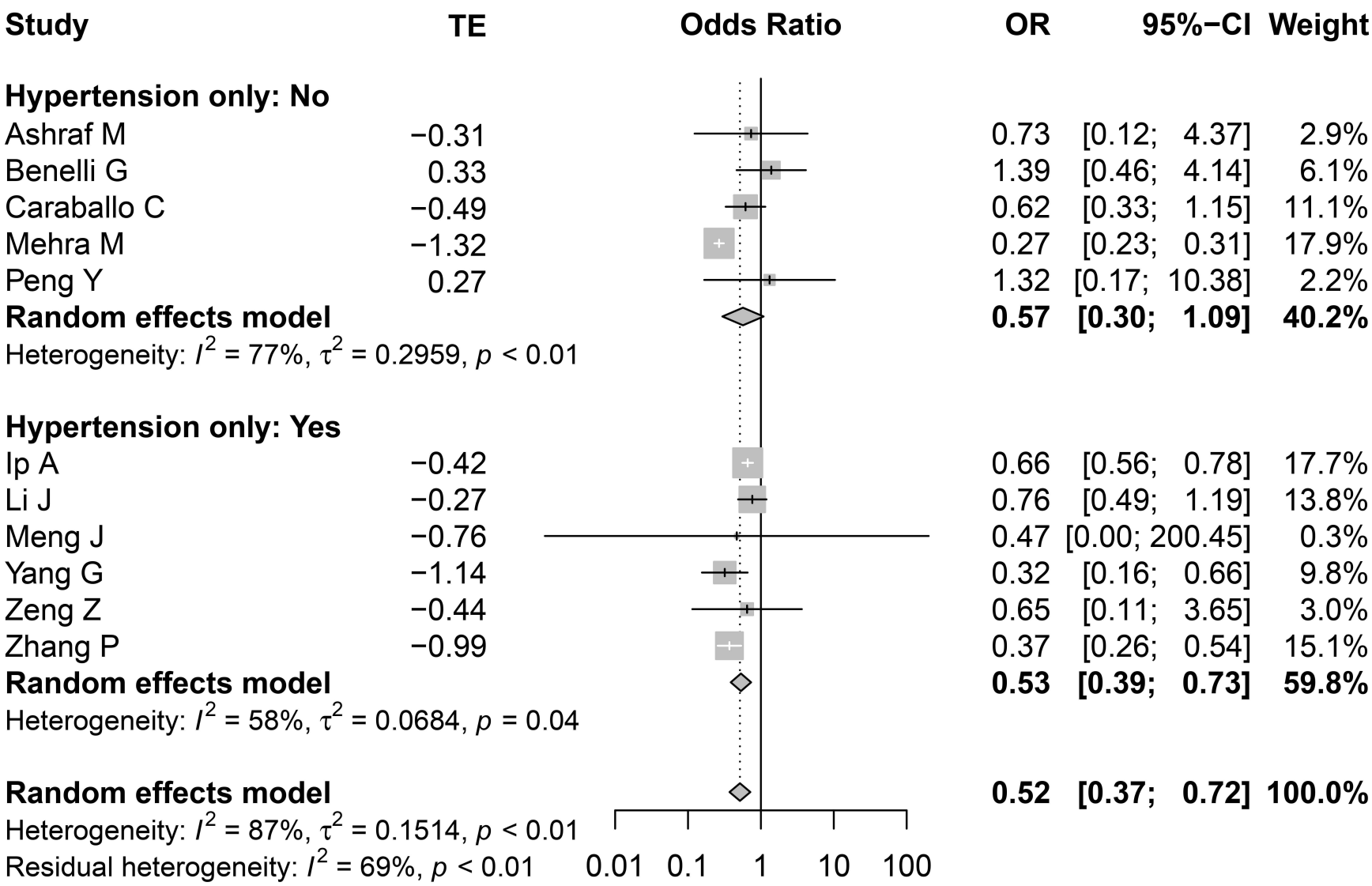
		ACEI or ARB was used or not.
	Bias due to missing data	Low risk. Missing data on ACEI/ARB use was not found.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Yan H. et al. (2020)	Bias due to confounding	No information. Main analysis was conducted according to severity in COVID-19 patients. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use
	Bias in selection of participants into the study	Low risk. All the hospitalized patients diagnosed with COVID-19 were included for analysis. Medical records were reviewed retrospectively and patients were classified according to ACEI/ARB use, which was clearly defined in Methods section. Selection bias was not suspected.
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Moderate risk. Reported results may be prespecified by registered protocol before intervention classification was conducted, but still the possibility of bias in selective reporting cannot be ignored because this study was conducted retrospectively.
Zeng Z. et al. (2020)	Bias due to confounding	No information. Subgroup analysis was conducted to know the impact of ACEI or ARB on disease severity and all-cause mortality in the patients with hypertension. However, it is not possible to know whether there is any difference in underlying diseases between the patients who used ACEI or ARB and those who did not use.
	Bias in selection of participants into the study	Moderate risk. Hypertensive patients diagnosed with COVID-19 were included. Medical records were reviewed retrospectively and patients were classified according to disease severity, which was clearly defined in Methods section. However, there is a still possibility that other hypertensive drug may impact on our results (eg. calcium channel blocker).
	Bias in classification of interventions	Low risk. As medical records were reviewed retrospectively, there is no misclassification of intervention (ACEI or ARB). Even though misclassification existed, it would be a systematic error.
	Bias due to deviations from intended interventions	Low risk. The use of ACEI or ARB was not intended for antiviral treatment, bur for treating hypertension. Therefore, it is difficult to think that there would be a different management according to whether ACEI or ARB was used or not.
	Bias due to missing data	Moderate risk. Missing data was not reported in terms of severity and mortality according to use of ACEI or ARB. However, the patient data without information on the use of ACEI or ARB or severity of COVID-19 may be excluded in initial stage of this study.
	Bias in measurement of outcomes	Serious risk. This study was conducted retrospectively. Therefore, investigator knew patient data including group and intervention classification before initiation of analysis. The possibility of bias in outcome assessment is strongly suggested.
	Bias in selection of the reported result	Low risk. All the variables were analyzed whether there is any difference between ACEI or ARB user group and non-user group.

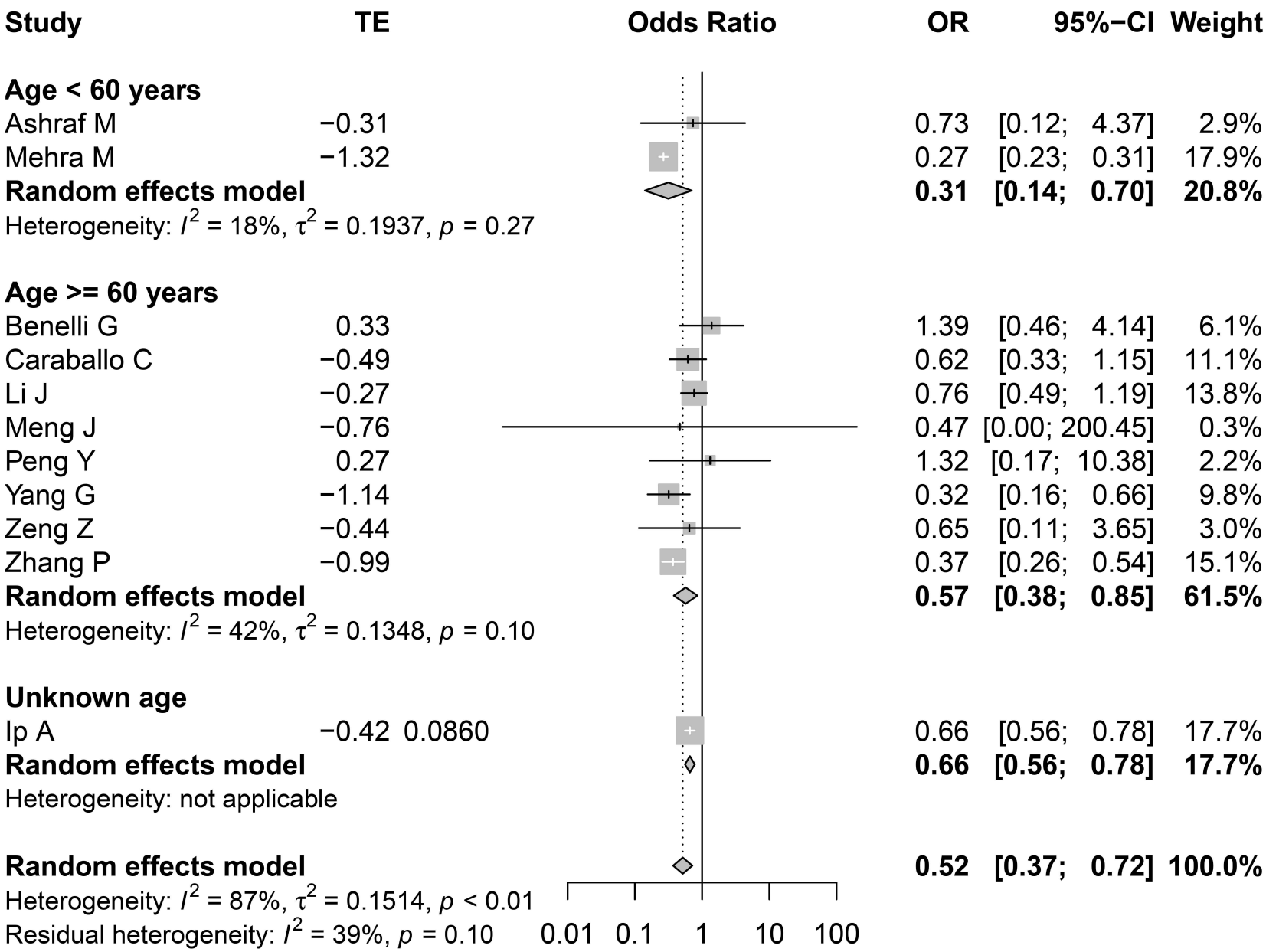
Supplementary Appendix 6. GRADE approach to rate the quality of evidence on the effects of ACEI/ARB on the outcomes of COVID-19 from systematic review and meta-analyses

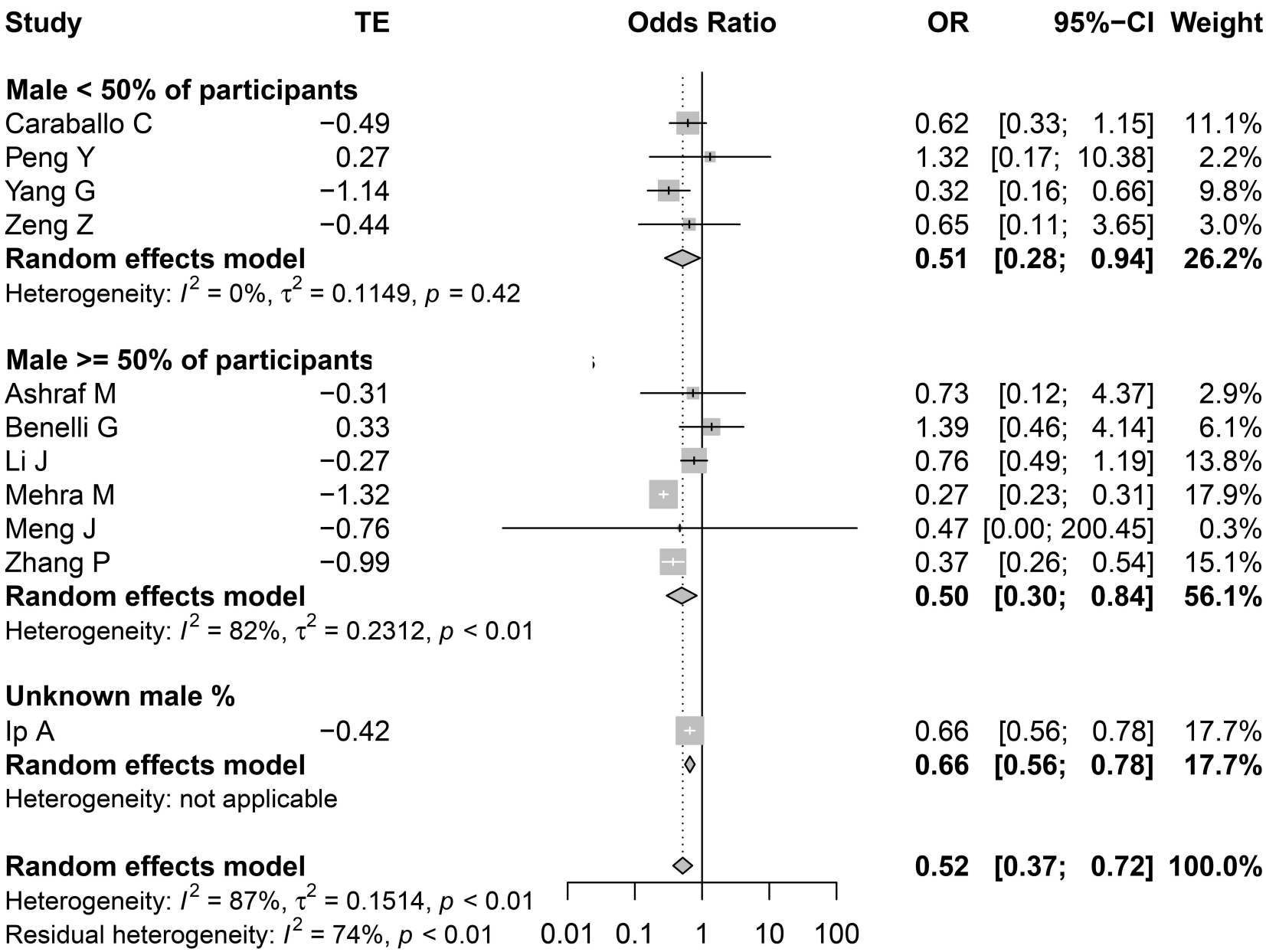
Outcome	The GRADE domains	Rating the quality of evidence and reasons for judgement
All-cause mortality; Odds ratio (11 studies, 12,601 patients)	**Risk of bias**	Serious limitations; Although all-cause mortality can be assessed objectively in retrospective studies, we cannot exclude study limitations such as failure to adequately control confounding and selective outcome reporting. These limitations are based on the retrospective study design.
	Imprecision	No serious imprecision; Our results were based on the pooled estimates from 12,601 patients in 11 studies reporting odds ratio. Optimal information size was met. We found satisfactory narrow 95% confidence interval excludes no effect.
	Inconsistency	Serious inconsistency; We found similar trends of pooled estimates in unadjusted and adjusted odds ratios and confidence intervals. However, statistical heterogeneity was found based on the effect size, not the effect direction, of ACEI/ARB use on all-cause mortality.
	Indirectness	No serious indirectness; The effect of ACEI/ARB was directly compared and study outcome (mortality) measurement was identical. All the study subjects were diagnosed with COVID-19 by RT-PCR test using upper respiratory specimen.
	Publication bias	No serious publication bias; We searched and included unpublished studies in our meta-analysis. Egger's and Begg's tests indicated no significant publication bias
	Certainty of evidence	Moderate certainty of evidence (◯⊕◯⊕⊕)
Severe COVID-19 (13 studies, 12,848 patients)	**Risk of bias**	Serious limitations; We found several study limitations such as failure to adequately control confounding, selective outcome reporting, and bias in measurement of outcomes. These limitations are based on the retrospective study design.
	Imprecision	No serious imprecision; Our results were based on the pooled estimates from 15,757 patients in 13 studies reporting odds ratio. As 95% confidence interval appears satisfactory narrow and overlaps no effect, we concluded that ACEI/ARB use did not affect severe COVID-19. Therefore, there is no risk of imprecision in our conclusion.
	Inconsistency	Serious inconsistency; Our study showed pooled estimates with statistically heterogeneity in both unadjusted and adjusted odds ratios and confidence intervals.
	Indirectness	Serious indirectness; All the study subjects were diagnosed with COVID-19 by RT-PCR test using upper respiratory specimen, However, different definitions of severe disease were used as study outcome. Although the included COVID-19 patients showed reportedly similar clinical severity across the studies, indirectness still

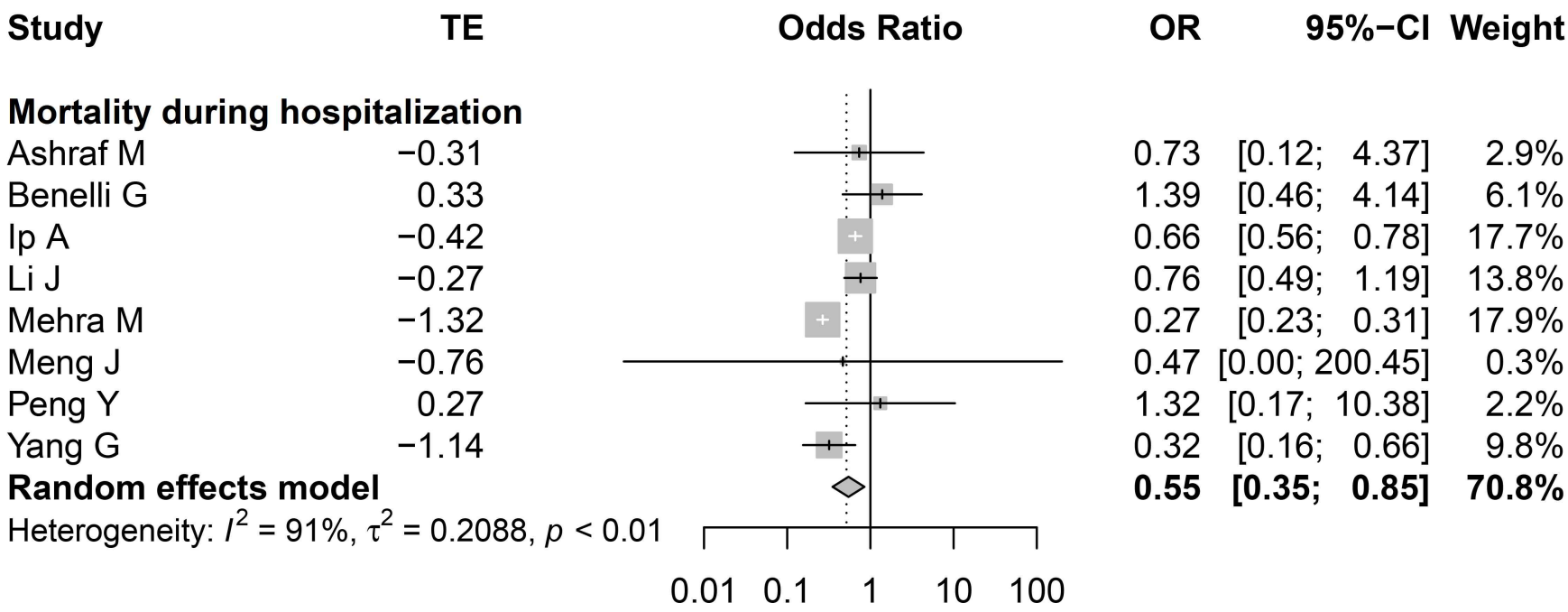
		cannot be excluded.
	Publication bias	No serious publication bias; We searched and included unpublished studies in our meta-analysis. Egger's and Begg's tests indicated no significant publication bias
	Certainty of evidence	Low certainty of evidence (◯⊕◯◯⊕)

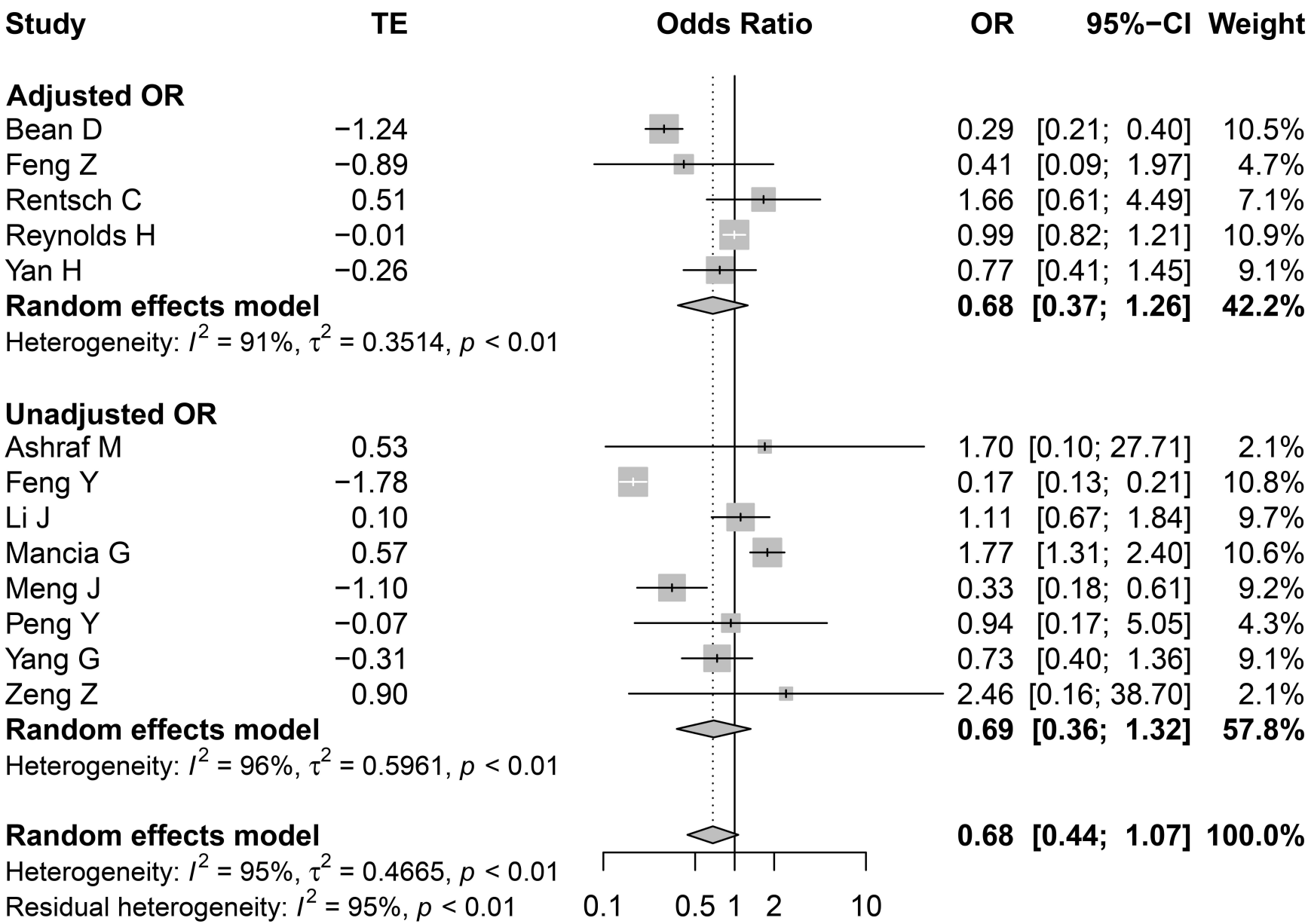
ACEIs, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; COVID-19, coronavirus disease-19; RT-PCR, real-time reverse transcription-polymerase chain reaction

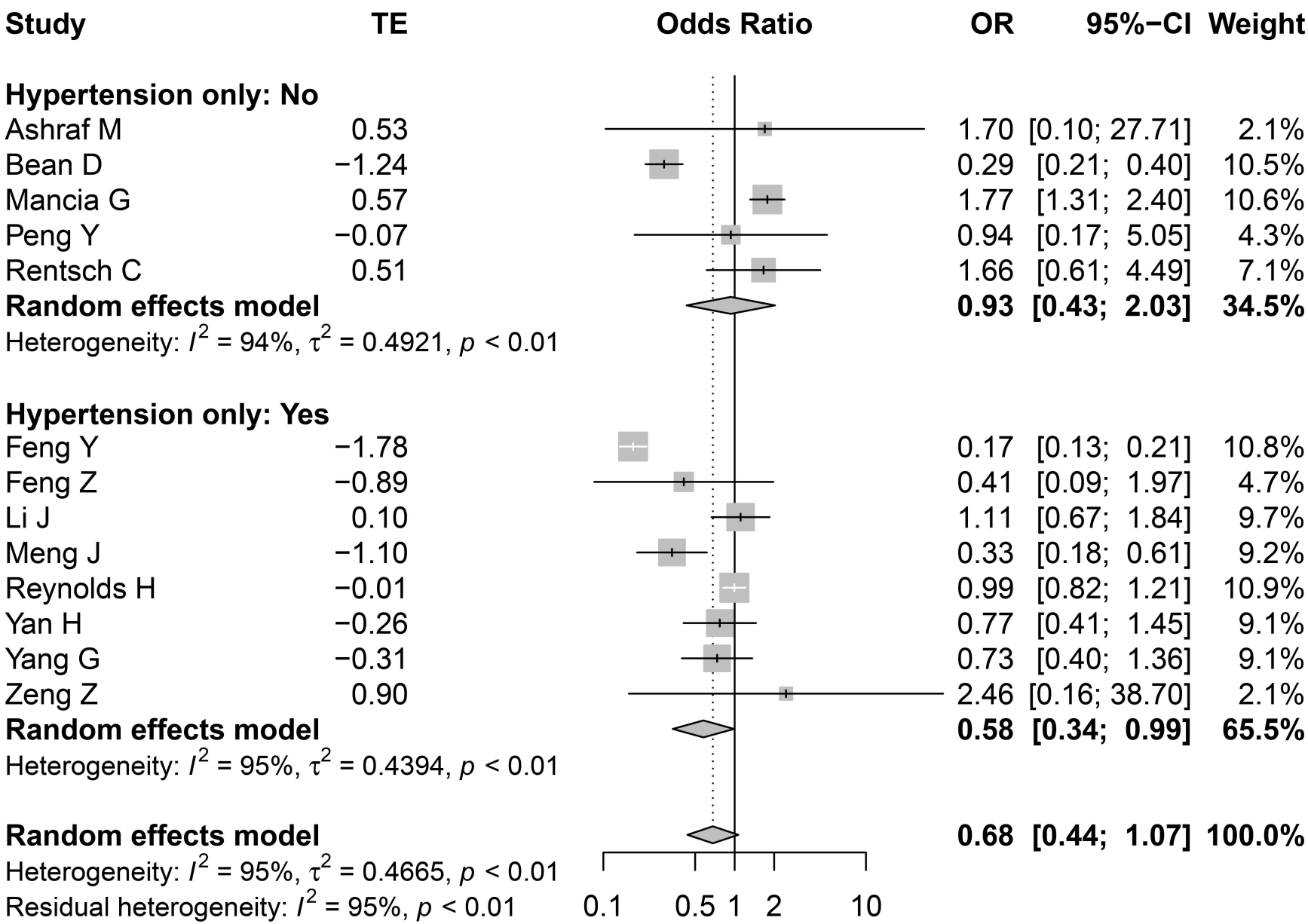

Study
TE
Odds Ratio
OR
95%−CI
Weight
Hypertension only: No
Ashraf M −0.31 0.73 [0.12; 4.37] 2.9%
Benelli G 0.33 1.39 [0.46; 4.14] 6.1%
Caraballo C −0.49 0.62 [0.33; 1.15] 11.1%
Mehra M −1.32 0.27 [0.23; 0.31] 17.9%
Peng Y 0.27 1.32 [0.17; 10.38] 2.2%
Random effects model 0.57 [0.30; 1.09] 40.2%
Heterogeneity: I^2 = 77%, τ^2 = 0.2959, p < 0.01
Hypertension only: Yes
Ip A −0.42 0.66 [0.56; 0.78] 17.7%
Li J −0.27 0.76 [0.49; 1.19] 13.8%
Meng J −0.76 0.47 [0.00; 200.45] 0.3%
Yang G −1.14 0.32 [0.16; 0.66] 9.8%
Zeng Z −0.44 0.65 [0.11; 3.65] 3.0%
Zhang P −0.99 0.37 [0.26; 0.54] 15.1%
Random effects model 0.53 [0.39; 0.73] 59.8%
Heterogeneity: I^2 = 58%, τ^2 = 0.0684, p = 0.04
Random effects model 0.52 [0.37; 0.72] 100.0%
Heterogeneity: I^2 = 87%, τ^2 = 0.1514, p < 0.01
Residual heterogeneity: I^2 = 69%, p < 0.01
0.01 0.1 1 10 100

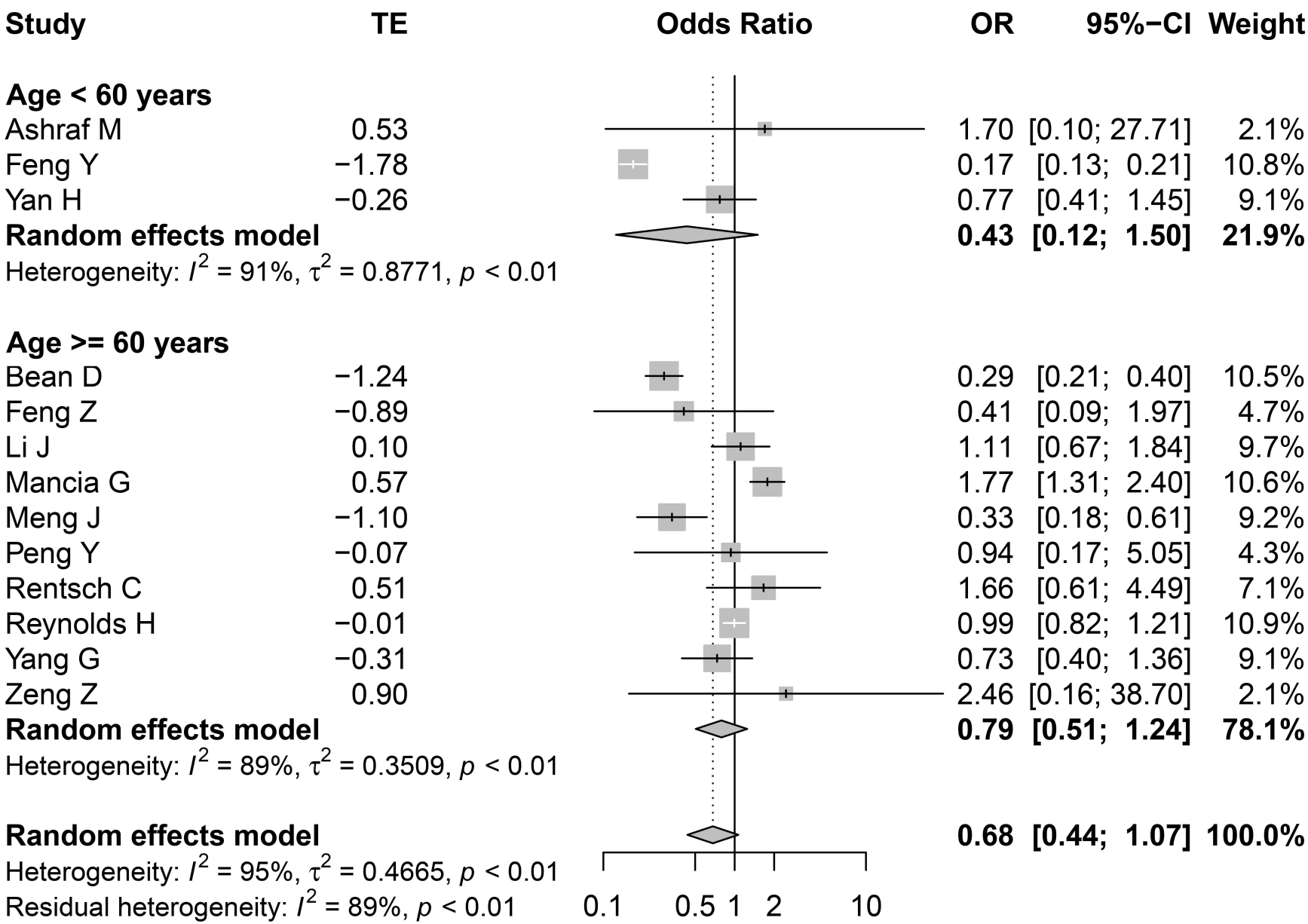

Study
TE
Odds Ratio
OR
95%−CI
Weight
Age < 60 years
Ashraf M −0.31 0.73 [0.12; 4.37] 2.9%
Mehra M −1.32 0.27 [0.23; 0.31] 17.9%
Random effects model 0.31 [0.14; 0.70] 20.8%
Heterogeneity: I^2 = 18%, τ^2 = 0.1937, p = 0.27
Age >= 60 years
Benelli G 0.33 1.39 [0.46; 4.14] 6.1%
Caraballo C −0.49 0.62 [0.33; 1.15] 11.1%
Li J −0.27 0.76 [0.49; 1.19] 13.8%
Meng J −0.76 0.47 [0.00; 200.45] 0.3%
Peng Y 0.27 1.32 [0.17; 10.38] 2.2%
Yang G −1.14 0.32 [0.16; 0.66] 9.8%
Zeng Z −0.44 0.65 [0.11; 3.65] 3.0%
Zhang P −0.99 0.37 [0.26; 0.54] 15.1%
Random effects model 0.57 [0.38; 0.85] 61.5%
Heterogeneity: I^2 = 42%, τ^2 = 0.1348, p = 0.10
Unknown age
Ip A −0.42 0.0860 0.66 [0.56; 0.78] 17.7%
Random effects model 0.66 [0.56; 0.78] 17.7%
Heterogeneity: not applicable
Random effects model 0.52 [0.37; 0.72] 100.0%
Heterogeneity: I^2 = 87%, τ^2 = 0.1514, p < 0.01
Residual heterogeneity: I^2 = 39%, p = 0.10
0.01 0.1 1 10 100

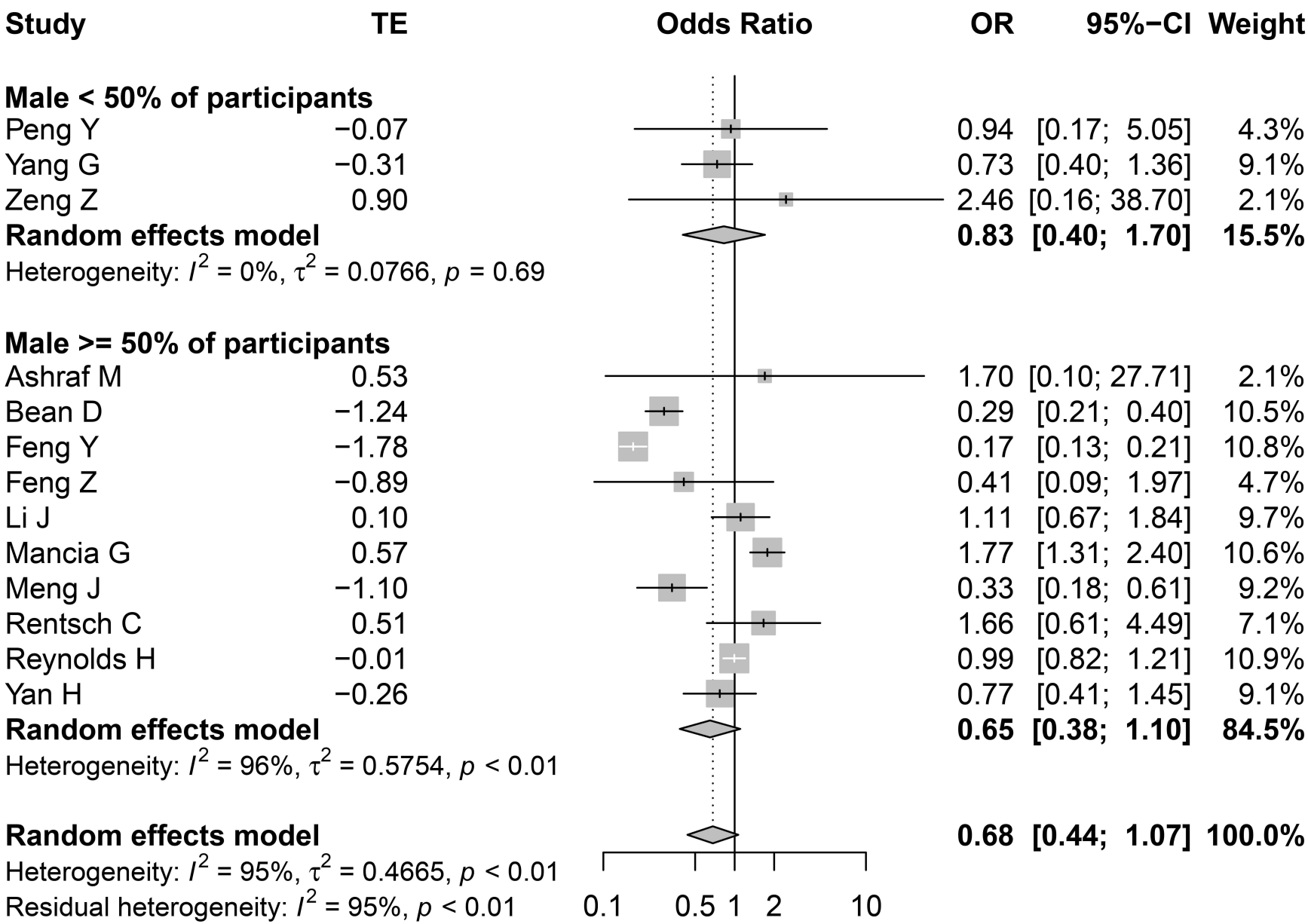

Study
TE
Odds Ratio
OR
95%−CI
Weight
Male < 50% of participants
Caraballo C −0.49 0.62 [0.33; 1.15] 11.1%
Peng Y 0.27 1.32 [0.17; 10.38] 2.2%
Yang G −1.14 0.32 [0.16; 0.66] 9.8%
Zeng Z −0.44 0.65 [0.11; 3.65] 3.0%
Random effects model 0.51 [0.28; 0.94] 26.2%
Heterogeneity: I^2 = 0%, τ^2 = 0.1149, p = 0.42
Male >= 50% of participants
Ashraf M −0.31 0.73 [0.12; 4.37] 2.9%
Benelli G 0.33 1.39 [0.46; 4.14] 6.1%
Li J −0.27 0.76 [0.49; 1.19] 13.8%
Mehra M −1.32 0.27 [0.23; 0.31] 17.9%
Meng J −0.76 0.47 [0.00; 200.45] 0.3%
Zhang P −0.99 0.37 [0.26; 0.54] 15.1%
Random effects model 0.50 [0.30; 0.84] 56.1%
Heterogeneity: I^2 = 82%, τ^2 = 0.2312, p < 0.01
Unknown male %
Ip A −0.42 0.66 [0.56; 0.78] 17.7%
Random effects model 0.66 [0.56; 0.78] 17.7%
Heterogeneity: not applicable
Random effects model 0.52 [0.37; 0.72] 100.0%
Heterogeneity: I^2 = 87%, τ^2 = 0.1514, p < 0.01
Residual heterogeneity: I^2 = 74%, p < 0.01
0.01 0.1 1 10 100

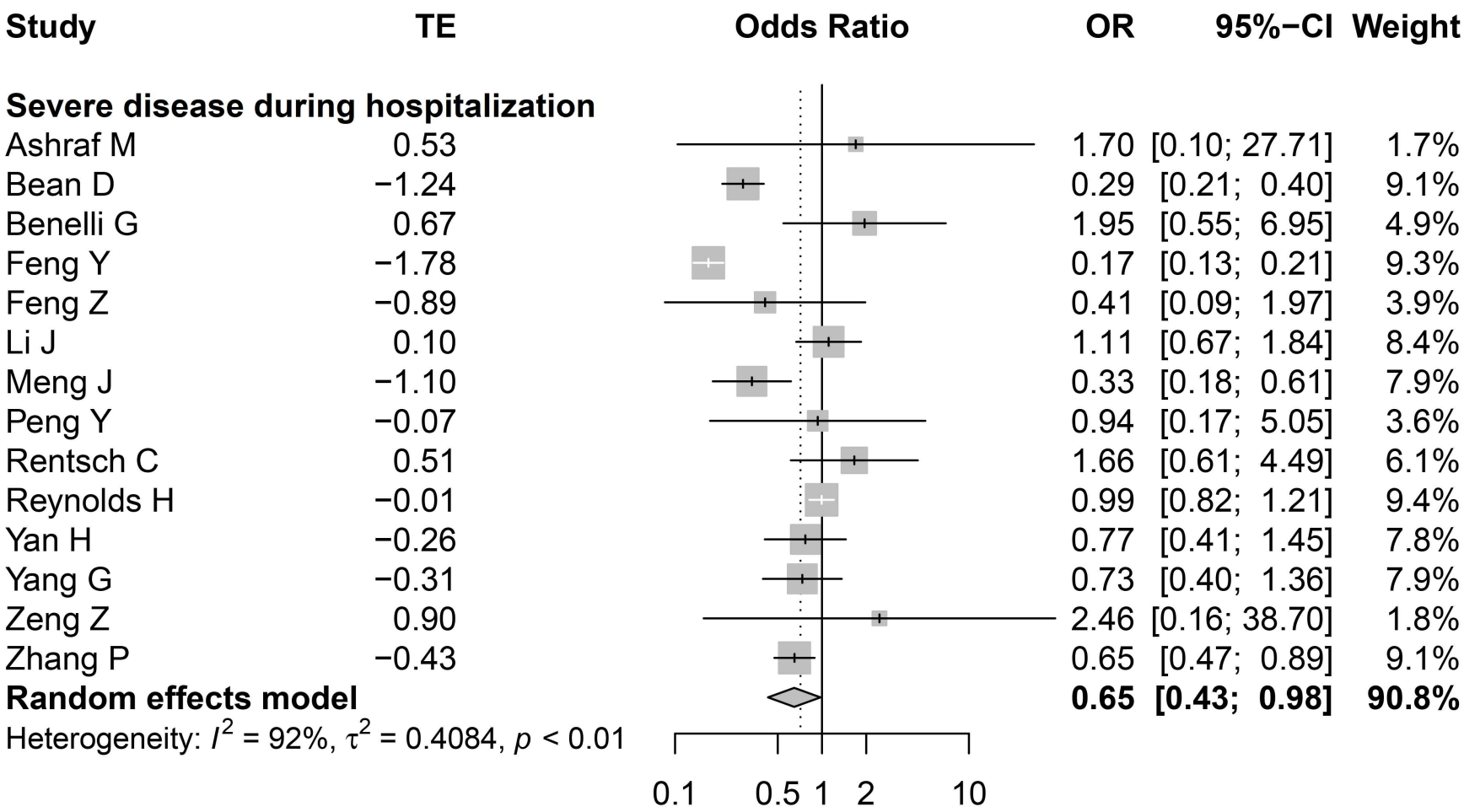

Study
TE
Odds Ratio
OR
95%−CI
Weight
Mortality during hospitalization
Ashraf M −0.31 0.73 [0.12; 4.37] 2.9%
Benelli G 0.33 1.39 [0.46; 4.14] 6.1%
Ip A −0.42 0.66 [0.56; 0.78] 17.7%
Li J −0.27 0.76 [0.49; 1.19] 13.8%
Mehra M −1.32 0.27 [0.23; 0.31] 17.9%
Meng J −0.76 0.47 [0.00; 200.45] 0.3%
Peng Y 0.27 1.32 [0.17; 10.38] 2.2%
Yang G −1.14 0.32 [0.16; 0.66] 9.8%
Random effects model 0.55 [0.35; 0.85] 70.8%
Heterogeneity: I^2 = 91%, τ^2 = 0.2088, p < 0.01
0.01
0.1
1
10
100


Study
TE
Odds Ratio
OR
95%−CI
Weight
Adjusted OR
Bean D −1.24 0.29 [0.21; 0.40] 10.5%
Feng Z −0.89 0.41 [0.09; 1.97] 4.7%
Rentsch C 0.51 1.66 [0.61; 4.49] 7.1%
Reynolds H −0.01 0.99 [0.82; 1.21] 10.9%
Yan H −0.26 0.77 [0.41; 1.45] 9.1%
Random effects model 0.68 [0.37; 1.26] 42.2%
Heterogeneity: I^2 = 91%, τ^2 = 0.3514, p < 0.01
Unadjusted OR
Ashraf M 0.53 1.70 [0.10; 27.71] 2.1%
Feng Y −1.78 0.17 [0.13; 0.21] 10.8%
Li J 0.10 1.11 [0.67; 1.84] 9.7%
Mancia G 0.57 1.77 [1.31; 2.40] 10.6%
Meng J −1.10 0.33 [0.18; 0.61] 9.2%
Peng Y −0.07 0.94 [0.17; 5.05] 4.3%
Yang G −0.31 0.73 [0.40; 1.36] 9.1%
Zeng Z 0.90 2.46 [0.16; 38.70] 2.1%
Random effects model 0.69 [0.36; 1.32] 57.8%
Heterogeneity: I^2 = 96%, τ^2 = 0.5961, p < 0.01
Random effects model 0.68 [0.44; 1.07] 100.0%
Heterogeneity: I^2 = 95%, τ^2 = 0.4665, p < 0.01
Residual heterogeneity: I^2 = 95%, p < 0.01
0.1
0.5
1
2
10

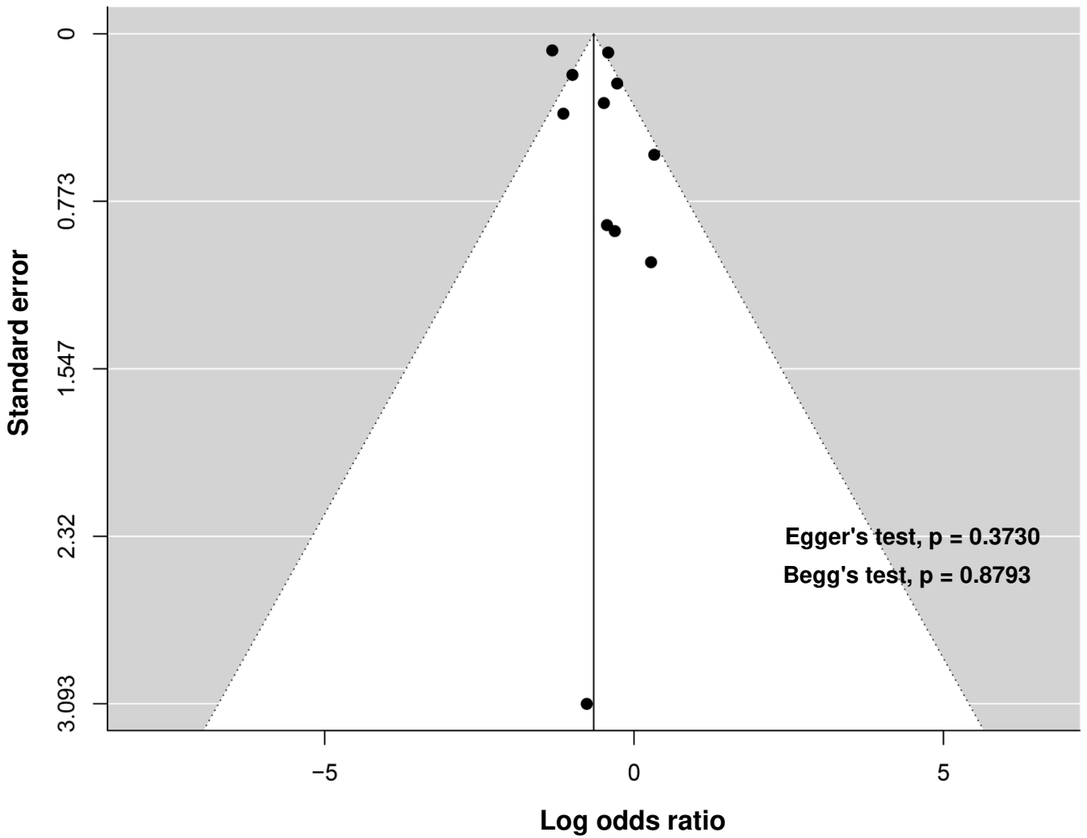

Study
TE
Odds Ratio
OR
95%−CI
Weight
Hypertension only: No
Ashraf M 0.53 1.70 [0.10; 27.71] 2.1%
Bean D −1.24 0.29 [0.21; 0.40] 10.5%
Mancia G 0.57 1.77 [1.31; 2.40] 10.6%
Peng Y −0.07 0.94 [0.17; 5.05] 4.3%
Rentsch C 0.51 1.66 [0.61; 4.49] 7.1%
Random effects model 0.93 [0.43; 2.03] 34.5%
Heterogeneity: I^2 = 94%, τ^2 = 0.4921, p < 0.01
Hypertension only: Yes
Feng Y −1.78 0.17 [0.13; 0.21] 10.8%
Feng Z −0.89 0.41 [0.09; 1.97] 4.7%
Li J 0.10 1.11 [0.67; 1.84] 9.7%
Meng J −1.10 0.33 [0.18; 0.61] 9.2%
Reynolds H −0.01 0.99 [0.82; 1.21] 10.9%
Yan H −0.26 0.77 [0.41; 1.45] 9.1%
Yang G −0.31 0.73 [0.40; 1.36] 9.1%
Zeng Z 0.90 2.46 [0.16; 38.70] 2.1%
Random effects model 0.58 [0.34; 0.99] 65.5%
Heterogeneity: I^2 = 95%, τ^2 = 0.4394, p < 0.01
Random effects model 0.68 [0.44; 1.07] 100.0%
Heterogeneity: I^2 = 95%, τ^2 = 0.4665, p < 0.01
Residual heterogeneity: I^2 = 95%, p < 0.01
0.1
0.5
1
2
10


Study
TE
Odds Ratio
OR
95%−CI
Weight
Age < 60 years
Ashraf M 0.53 1.70 [0.10; 27.71] 2.1%
Feng Y −1.78 0.17 [0.13; 0.21] 10.8%
Yan H −0.26 0.77 [0.41; 1.45] 9.1%
Random effects model 0.43 [0.12; 1.50] 21.9%
Heterogeneity: I^2 = 91%, τ^2 = 0.8771, p < 0.01
Age >= 60 years
Bean D −1.24 0.29 [0.21; 0.40] 10.5%
Feng Z −0.89 0.41 [0.09; 1.97] 4.7%
Li J 0.10 1.11 [0.67; 1.84] 9.7%
Mancia G 0.57 1.77 [1.31; 2.40] 10.6%
Meng J −1.10 0.33 [0.18; 0.61] 9.2%
Peng Y −0.07 0.94 [0.17; 5.05] 4.3%
Rentsch C 0.51 1.66 [0.61; 4.49] 7.1%
Reynolds H −0.01 0.99 [0.82; 1.21] 10.9%
Yang G −0.31 0.73 [0.40; 1.36] 9.1%
Zeng Z 0.90 2.46 [0.16; 38.70] 2.1%
Random effects model 0.79 [0.51; 1.24] 78.1%
Heterogeneity: I^2 = 89%, τ^2 = 0.3509, p < 0.01
Random effects model 0.68 [0.44; 1.07] 100.0%
Heterogeneity: I^2 = 95%, τ^2 = 0.4665, p < 0.01
Residual heterogeneity: I^2 = 89%, p < 0.01
0.1
0.5
1
2
10


Study
TE
Odds Ratio
OR
95%−CI
Weight
Male < 50% of participants
Peng Y −0.07 0.94 [0.17; 5.05] 4.3%
Yang G −0.31 0.73 [0.40; 1.36] 9.1%
Zeng Z 0.90 2.46 [0.16; 38.70] 2.1%
Random effects model 0.83 [0.40; 1.70] 15.5%
Heterogeneity: I^2 = 0%, τ^2 = 0.0766, p = 0.69
Male >= 50% of participants
Ashraf M 0.53 1.70 [0.10; 27.71] 2.1%
Bean D −1.24 0.29 [0.21; 0.40] 10.5%
Feng Y −1.78 0.17 [0.13; 0.21] 10.8%
Feng Z −0.89 0.41 [0.09; 1.97] 4.7%
Li J 0.10 1.11 [0.67; 1.84] 9.7%
Mancia G 0.57 1.77 [1.31; 2.40] 10.6%
Meng J −1.10 0.33 [0.18; 0.61] 9.2%
Rentsch C 0.51 1.66 [0.61; 4.49] 7.1%
Reynolds H −0.01 0.99 [0.82; 1.21] 10.9%
Yan H −0.26 0.77 [0.41; 1.45] 9.1%
Random effects model 0.65 [0.38; 1.10] 84.5%
Heterogeneity: I^2 = 96%, τ^2 = 0.5754, p < 0.01
Random effects model 0.68 [0.44; 1.07] 100.0%
Heterogeneity: I^2 = 95%, τ^2 = 0.4665, p < 0.01
Residual heterogeneity: I^2 = 95%, p < 0.01
0.1
0.5
1
2
10


Study
TE
Odds Ratio
OR
95%−CI
Weight
Severe disease during hospitalization
Ashraf M 0.53 1.70 [0.10; 27.71] 1.7%
Bean D −1.24 0.29 [0.21; 0.40] 9.1%
Benelli G 0.67 1.95 [0.55; 6.95] 4.9%
Feng Y −1.78 0.17 [0.13; 0.21] 9.3%
Feng Z −0.89 0.41 [0.09; 1.97] 3.9%
Li J 0.10 1.11 [0.67; 1.84] 8.4%
Meng J −1.10 0.33 [0.18; 0.61] 7.9%
Peng Y −0.07 0.94 [0.17; 5.05] 3.6%
Rentsch C 0.51 1.66 [0.61; 4.49] 6.1%
Reynolds H −0.01 0.99 [0.82; 1.21] 9.4%
Yan H −0.26 0.77 [0.41; 1.45] 7.8%
Yang G −0.31 0.73 [0.40; 1.36] 7.9%
Zeng Z 0.90 2.46 [0.16; 38.70] 1.8%
Zhang P −0.43 0.65 [0.47; 0.89] 9.1%
Random effects model 0.65 [0.43; 0.98] 90.8%
Heterogeneity: I^2 = 92%, τ^2 = 0.4084, p < 0.01
0.1
0.5
1
2
10

A. Mortality



B. Severe disease