

SUPPLEMENTARY DATA

Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers and the risk of COVID-19 infection or severe disease: Systematic Review and meta-analysis of observational studies

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Supplementary Table 1 – Search Strategy

#	Searches using OVID
1	exp angiotensin-converting enzyme inhibitors/
2	(angiotensin-converting enzyme inhibitor or ACE-inhibitor* or acei or ace inhibitor or alacepril or benazepril or benazeprilat or captopril or ceranapril or cilazapril or cilazaprilat or delapril or enalapril or enalaprilat or fosinopril or fosinoprilic acid or imidapril or libenzapril or lisinopril or moexipril or omapatrilat or perindopril or perindoprilat or quinapril or quinaprilat or ramipril or ramiprilat or rentiapril or spirapril or temocapril ortrandolapril or zofenopril).af.
3	exp Angiotensin Receptor Antagonists/
4	(ARB* or angiotensin?receptor?blocker or (angiotensin adj2 receptor adj2 (antagonist or blocker)) or candesartan or eprosartan or enoltasosartan or irbesartan or Losartan or olmesartan or sapisartan or tasosartan or telmisartan or valsartan).af.
5	1 or 2 or 3 or 4
6	("2019 nCoV" or 2019nCoV or "2019 novel coronavirus" or "COVID 19" or COVID19 or "new coronavirus" or "novel coronavirus" or "SARS CoV-2" or (Wuhan and coronavirus) or "COVID 19" or "SARS-CoV" or "2019-nCoV" or "SARS-CoV-2 SARS-CoV2").af.
7	5 and 6
8	remove duplicates from 7

Supplementary Table 2: Key studies excluded at full-text appraisal stage, with reasons.

Study	Reason for exclusion
Murray 2020 Cardiovasc Res	Wrong publication type: Background/narrative review article
Piva 2020 J Crit Care	Wrong outcome: no data between exposure and outcomes of interest
Rothlin 2020 Drug Devel Res	Wrong publication type: Background/narrative review article
Sommerstein 2020 J Am Heart Assoc	Wrong publication type: Background/narrative review article
Morfeld 2020 Gesundheitswesen	Wrong outcome: no data between exposure and outcomes of interest
Rico-Mesa 2020 Curr Cardiol Rep	Wrong publication type: Background/narrative review article
Slawinski 2020 Kardiol Pol	Wrong publication type: review article
Speth 2020 J Travel Med	Wrong publication type: Background article/comment
Sriram K 2020 Clin Pharmacol Ther	Wrong publication type: review of basic science studies about ACE
Liu Y 2020 Sci China Life Sci.	Wrong intervention: No data about ACEi/ARB exposure
Ciulla 2020 Eur Heart J	Wrong outcome: not enough data to establish the risk of exposure and outcomes of interest
Aronson 2020 BMJ	Wrong publication type: Editorial
Cure 2020 Diabetes Metab Syndr.	Wrong publication type: review of pathophysiology
Guo 2020 Zhonghua nei ke za zhi	Wrong control: case series of 4 patients treated with aliskiren for blood pressure control during hospitalization for severe COVID-19; no comparator
Zangrillo 2020 Crit Care	Wrong intervention: Angiotensin II (agonist) as treatment; also no comparator
Vaduganathan 2020 NEJM	Wrong publication type: review
Lopes 2020 Am Heart J	Wrong publication type: Study rationale/protocol
Sama 2020 Eur Heart J	Wrong population: patients without SARS-CoV-2 infection / COVID-19
Di Castelnuovo 2020 Hypertension	Wrong publication type: Study rationale
Furuashi 2020 Hypertens Res	Wrong publication type: Editorial
Snyder 2020 Pharmacogenomics	Wrong publication type: Background/narrative review article
Canata 2020 Eur Heart J Cardiovasc Pharmacother	Wrong intervention – continuation vs. discontinuation ACEi/ARB
Turgeon 2020 Can J Cardiol	Wrong publication type: Editorial
Sunden-Cullberg 2020 Hypertens	Wrong population: non-COVID
De Vries 2020 Neth Heart J	Wrong publication type: review
Bobkova 2020 Med Hypotheses	Wrong publication type: review
Chen 2020 J Med Virol	Wrong intervention: Arbidol (hemagglutinin)
Mehra 2020 New Eng J Med	Retracted paper
NCT04353596	Ongoing trial - ARB/ACEi
NCT04311177	Ongoing trial - ARB
NCT04318418	Ongoing case-control study; same as Di Castelnuovo [Hypertension]
NCT04312009	Ongoing trial - ARB

Supplementary Table 3 – Risk of bias for each study, *per* outcome.

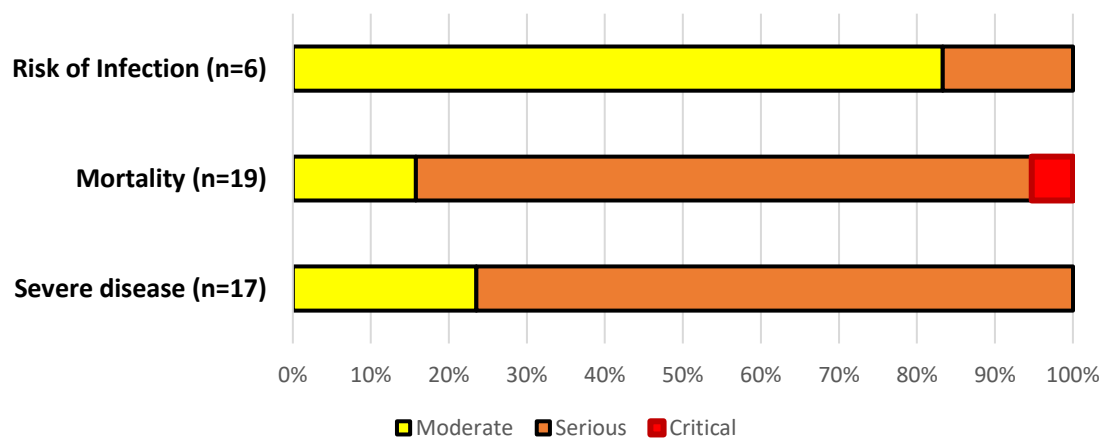
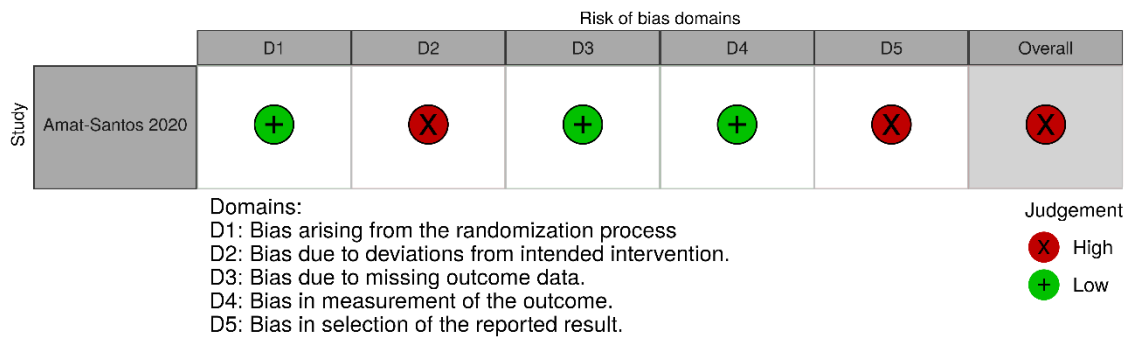
STUDY (FIRST AUTHOR SURNAME) / OUTCOME	RISK OF INFECTION	RISK OF MORTALITY	RISK OF SEVERE DISEASE
AMAT-SANTOS	Moderate*	Serious*	-
ARGENZIANO	-	-	Serious
BEAN	-	Serious	Serious
CHODICK	Moderate	-	-
CHEN	-	Serious	-
DE ABAJO	Moderate	-	Moderate
FELICE	-	Serious	Serious
FENG	-	-	Serious
GAO	-	Moderate	Serious
GNAVI	Serious	-	-
HU	-	Serious	Serious
HUANG	-	Serious	Serious
IMAM	-	-	-
JUNG	-	Moderate	Moderate
LI	-	Serious	Serious
MANCIA	Moderate	Moderate	-
MEHRA	-	Serious	-
MEHTA	Moderate	-	Moderate
MENG	-	Serious	Serious
MILLION	-	Serious	-
MONTASTRUC	-	Critical	-
PENG	-	Serious	Serious
REYNOLDS	Moderate	-	Moderate
TAN	-	Serious	Serious
TEDESCHI	-	Serious	-
YANG	-	Serious	Serious
ZHANG	-	Serious	Serious
ZHOU	-	Serious	Serious
UNPUBLISHED			
IP**	-	Critical	-
KHERA**	-	Critical	-
LIU**	-	-	Critical
RENTSCH**	Critical	-	Critical
ROSSI**	-	Critical	-
YAN**	Critical	-	Critical
ZENG**	-	Critical	-

* Using the Cochrane Risk of Bias Tool; The remaining studies were evaluated with ROBINS-I.

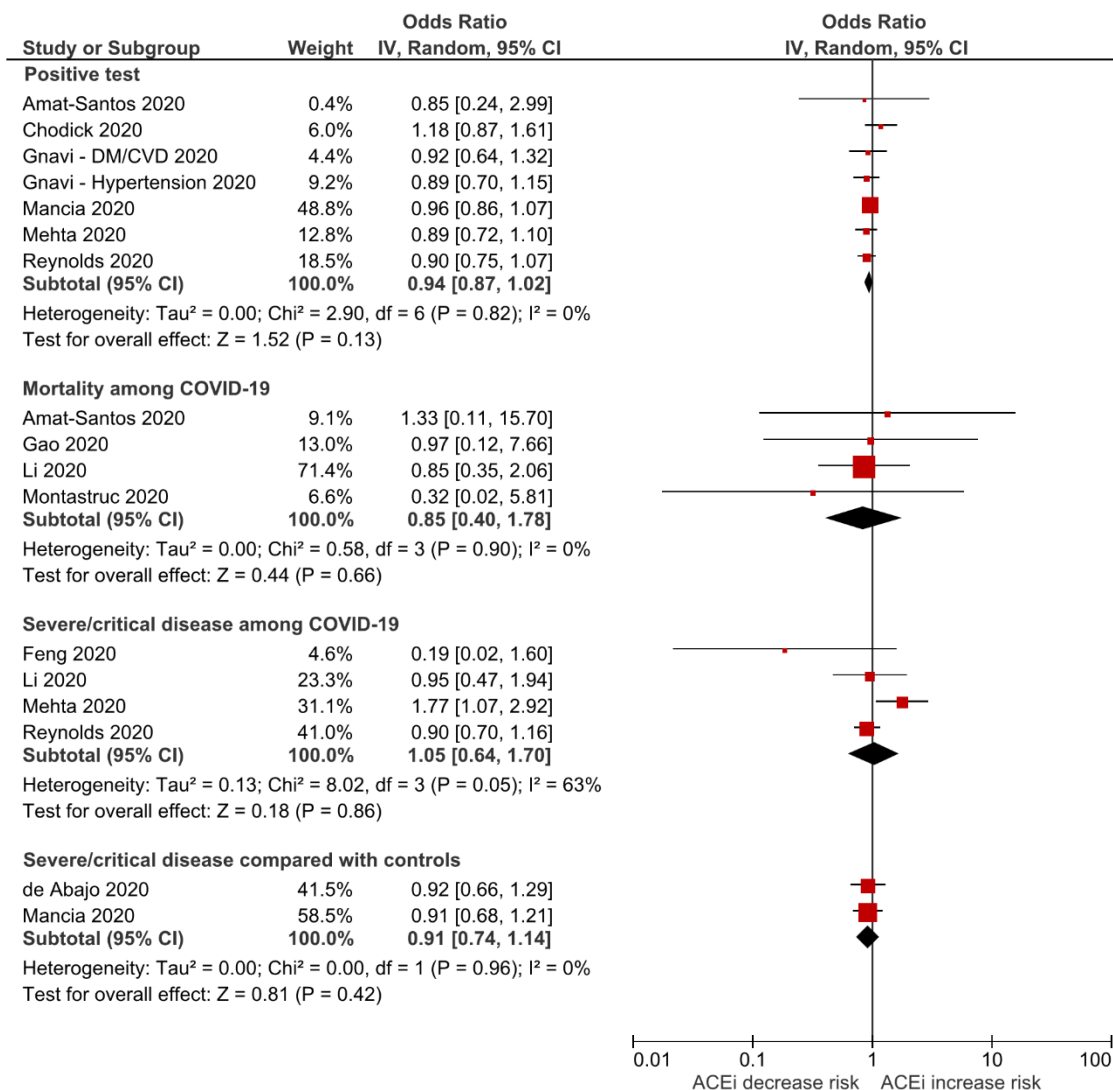
**Unpublished studies were classified by the reviewers as having critical risk of bias due to this status.

Supplementary Table 4 – References of unpublished studies included.

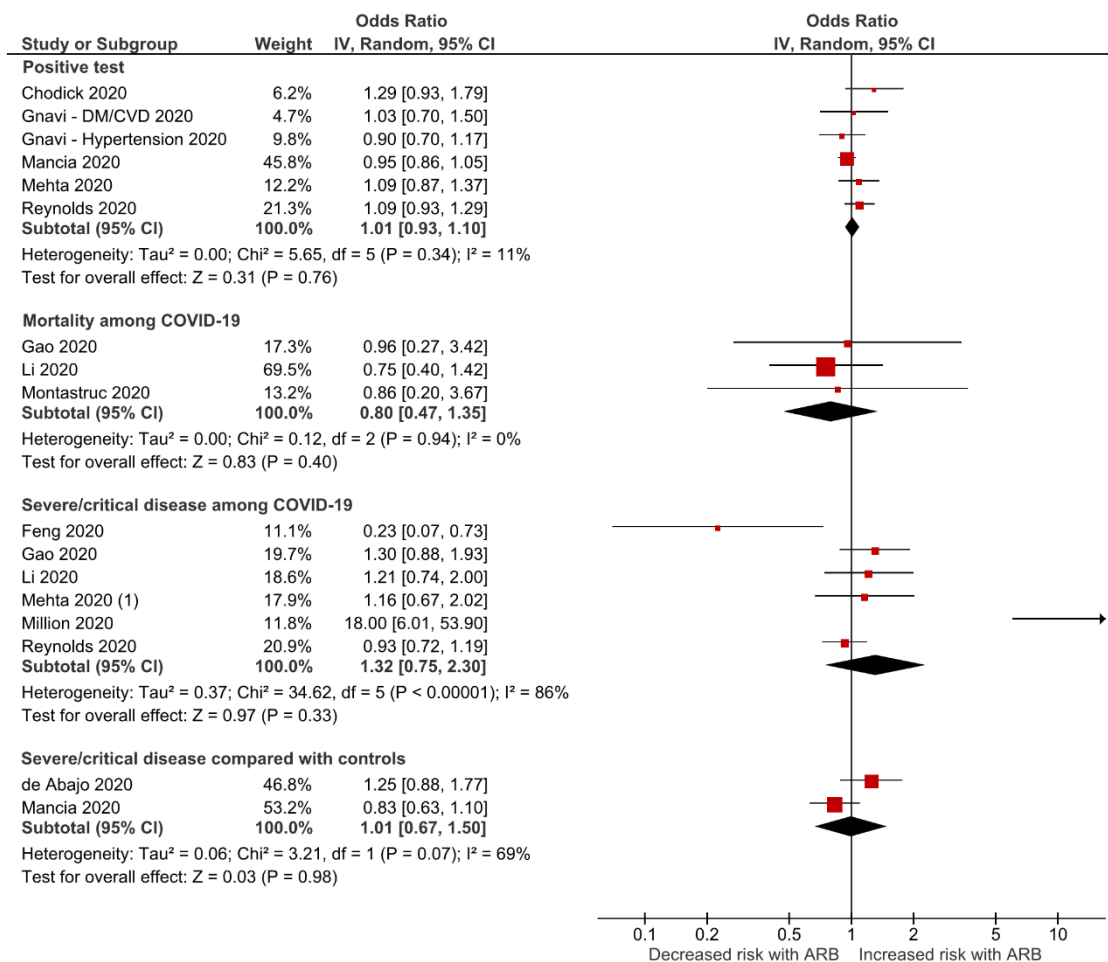
References of unpublished studies
Rossi PG, Marino M, Formisano D, Venturelli F, Vicentini M, Grilli R, et al. Characteristics and outcomes of a cohort of SARS-CoV-2 patients in the Province of Reggio Emilia, Italy. medRxiv 2020
Ip A, Parikh K, Parrillo JE, Mathura S, Hansen E, Sawczuk IS, et al. Hypertension and Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. medRxiv 2020
Liu Y, Huang F, Xu J, Yang P, Qin Y, Cao M, et al. Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. medRxiv 2020
Rentsch CT, Kidwai-Khan F, Tate JP, Park LS, King JT, Skanderson M, et al. Covid-19 Testing, Hospital Admission, and Intensive Care Among 2,026,227 United States Veterans Aged 54-75 Years. medRxiv 2020
Yan H, Valdes AM, Vijay A, Wang S, Liang L, Yang S, et al. Role of Drugs Affecting the Renin-Angiotensin-Aldosterone System on Susceptibility and Severity of COVID-19: A Large Case-Control Study from Zhejiang Province, China. medRxiv 2020
Zeng Z, Sha T, Zhang Y, Wu F, Hu H, Li H, et al. Hypertension in patients hospitalized with COVID-19 in Wuhan, China: A single-center retrospective observational study. medRxiv 2020
Khera R, Clark C, Lu Y, Guo Y, Ren S, Truax B, et al. Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with the Risk of Hospitalization and Death in Hypertensive Patients with Coronavirus Disease-19. medRxiv 2020



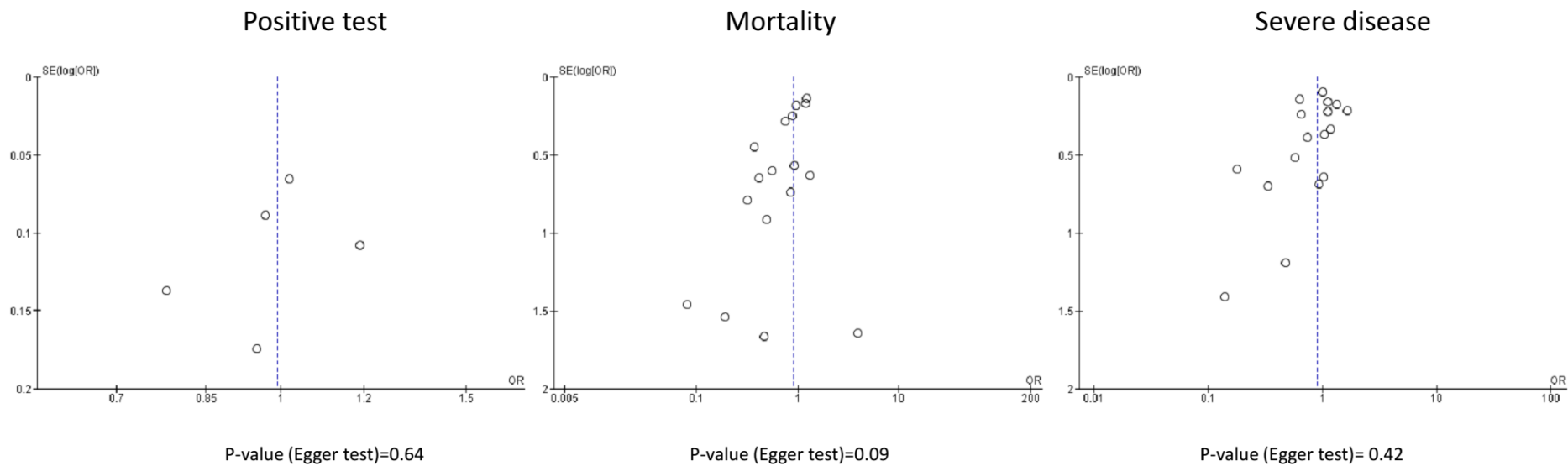
Supplementary Figure 1 – Overview of risk of bias classification; Upper figure for randomized controlled trial with risk of bias tool; and lower figure for observational studies with ROBINS-I



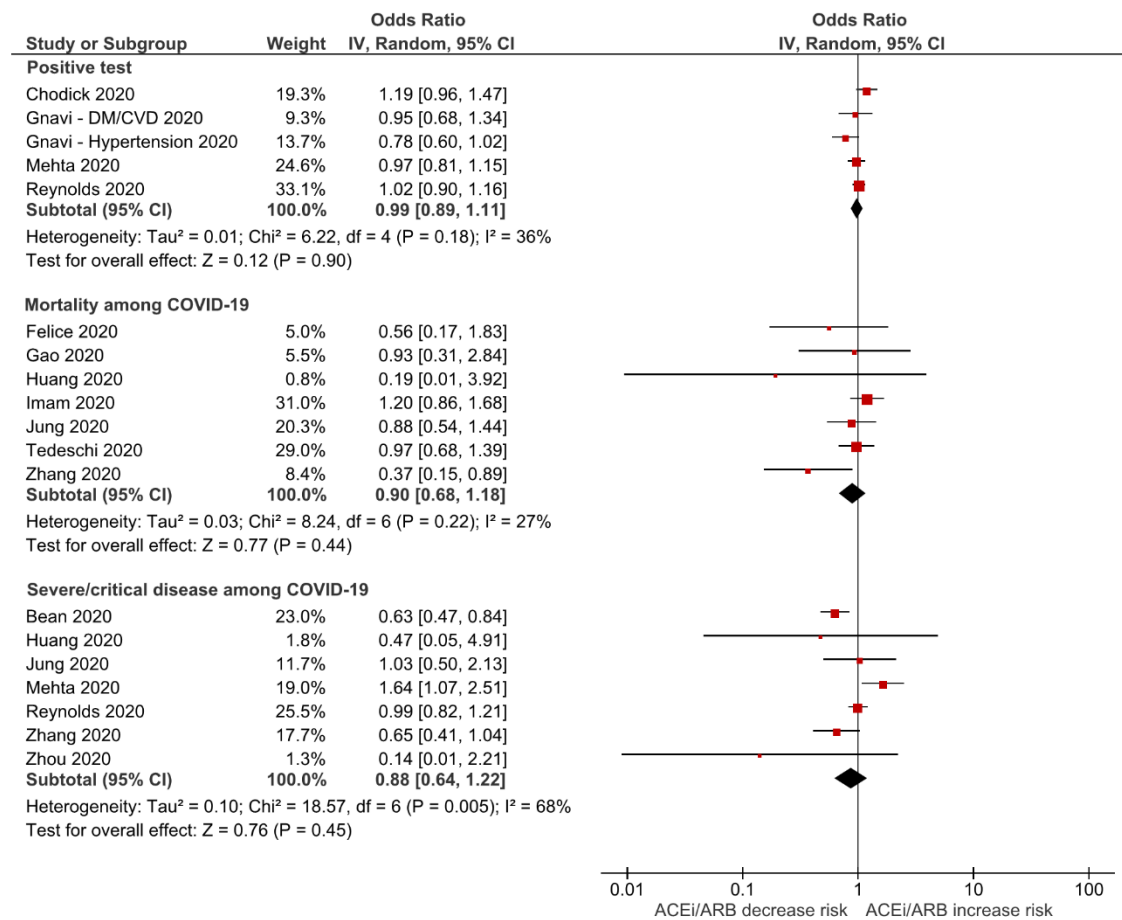
Supplementary Figure 2: Forest plots of ACEi association with the risk of COVID-19 infection and disease severity.



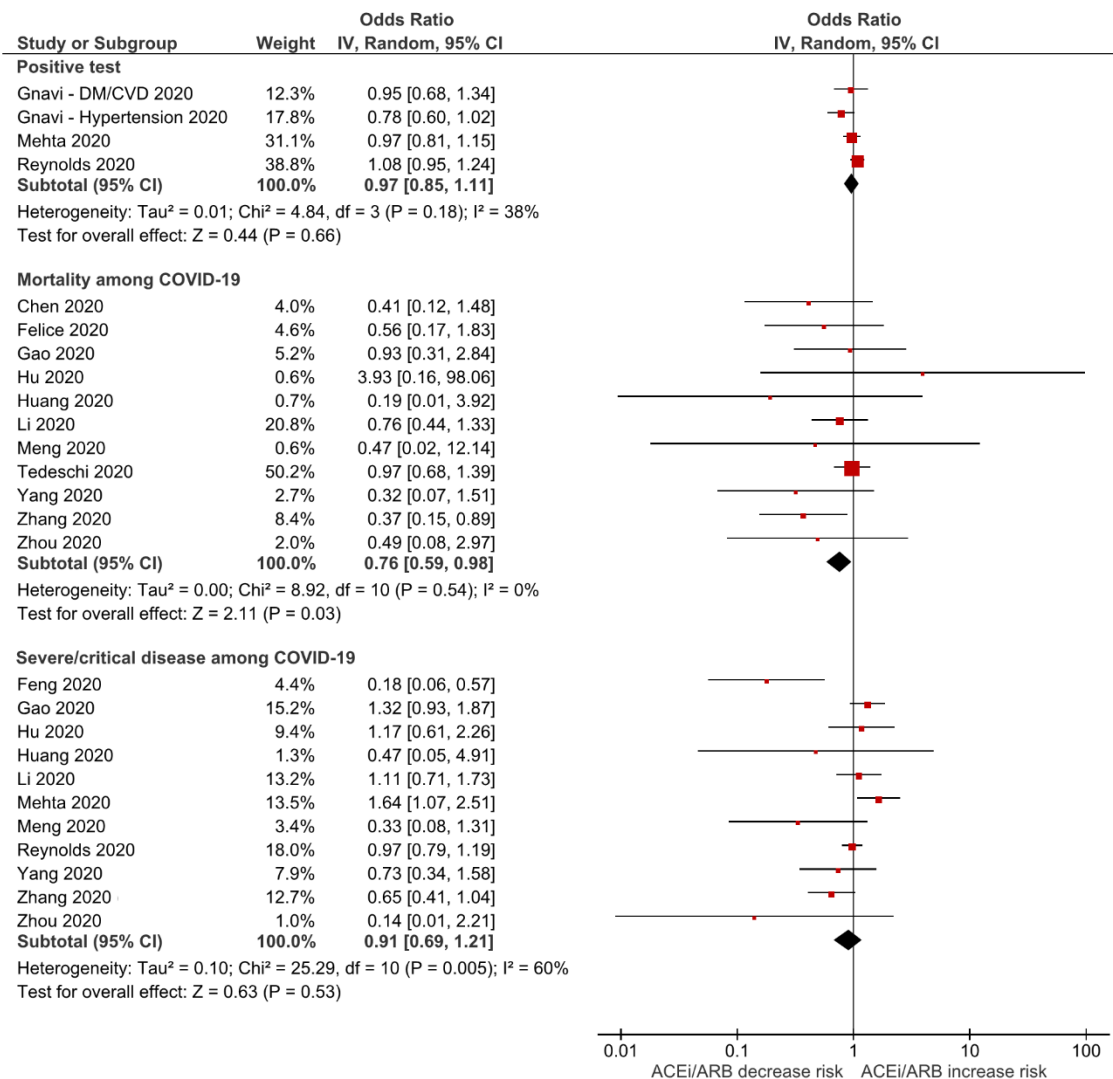
Supplementary Figure 3: Forest plots of ARB association with the risk of COVID-19 infection and disease severity.



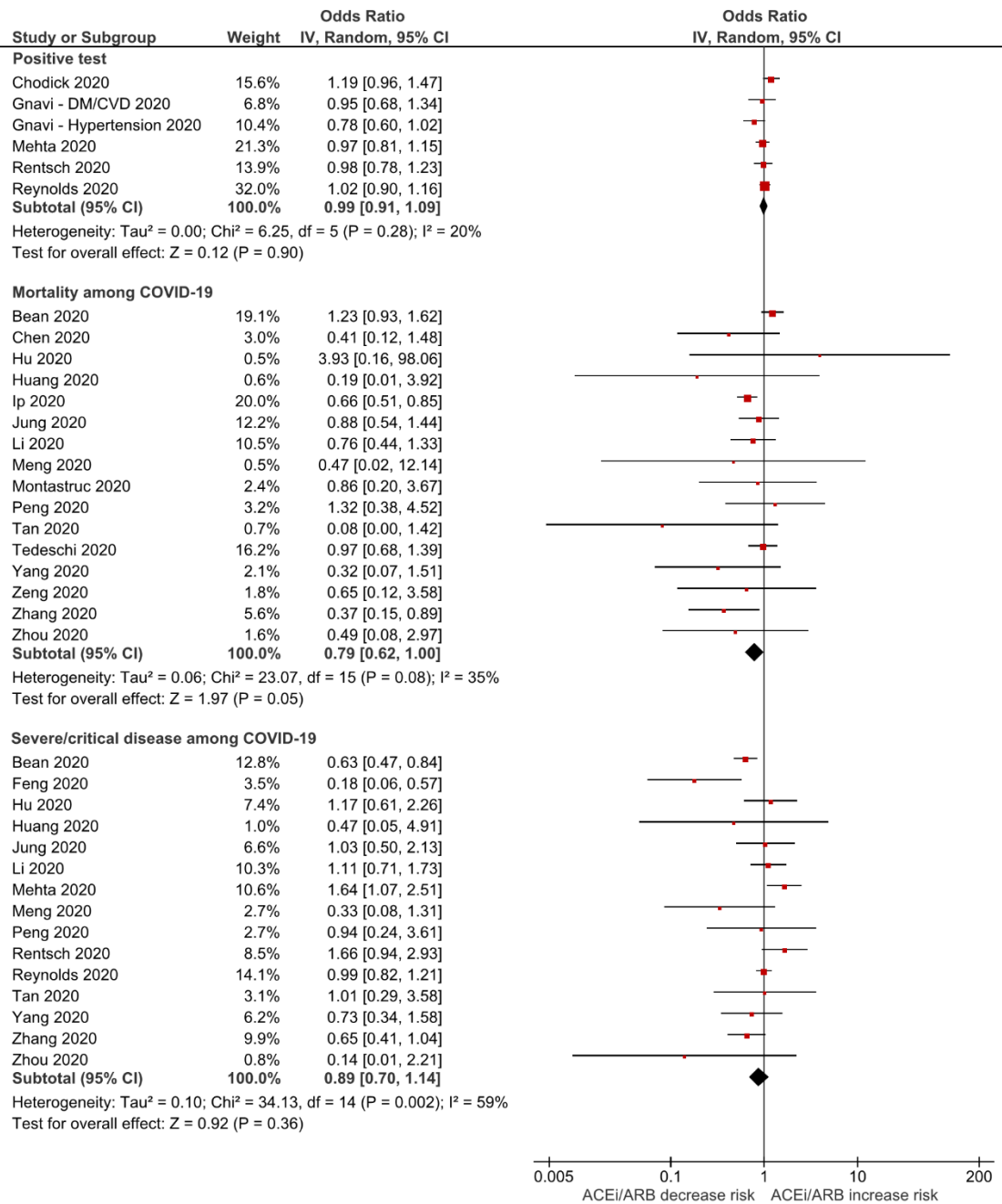
Supplementary Figure 4: Funnel plots for grouped ACEi/ARB evaluations and respective outcomes.



Supplementary Figure 5: Forest plots of ACEi/ARB association in studies with **adjusted estimates** with the risk of COVID-19 infection and disease severity.



Supplementary Figure 6: Forest plots of ACEi/ARB association with the risk of COVID-19 infection and disease severity, in studies including only patients with **hypertension**.



Supplementary Figure 7: Forest plots of ACEi/ARB association with the risk of COVID-19 infection and disease severity, **including unpublished data from medRxiv.**