



Supplementary Online Content

Table S1. Corpus of studies included in meta-analysis (search closing date of 4 July 2020.

Appendix to Table S1: Publications included in the meta-analysis

Fig. S1: PRISMA flowchart.

Fig. S2: Funnel plots (A) mortality, (B) severity of COVID-19 disease, and (C) hospitalization.

Table S1. Corpus of studies included in meta-analysis (search closing date of 4 July 2020; citations in Appendix to this Table).

Study	Country	Design	Study	ACEI/ARB	Non-	Outcomes of	Statistical	NOS
			Period		ACEI/ARB	interest	adjustments	
Bean et al ¹	UK	Multi-center	1st Mar to	399	801	Mortality	Mortality: none	7
		retrospectiv	13th Apr,			Severity (death or	Severity: age, sex,	
		e study	2020			organ support	comorbidities	
						within 21-days of		
						symptom onset)		
Bravi et al ²	Italy	Population-	Up to 24th	450	1152	Severity (requiring	Severity: age,	7
		based	Apr, 2020			ICU or causing	gender, diabetes,	
		case-				death)	major	
		control					cardiovascular	
		retrospectiv					diseases, COPD,	
		e study					cancer, renal	
							diseases	
Chen et al ³	China	Single-	1st Jan to	32	39	Mortality	None	5
		center	Mar 17th,					
		retrospectiv	2020					
		e study						
Conversano	Italy	Single-	27th Feb	-	-	Mortality	None	5
et al4		center	to 17th Mar,					
		retrospectiv	2020					
		e study						
Felice et al⁵	Italy	Single-	9th Mar to	82	51	Mortality	Mortality, severity,	8
		center	31st Mar			Severity (requiring	hospitalization:	
		retrospectiv	2020			semi ICU or ICU)	age, gender, BMI,	
		e study				Hospitalization	days with	
							symptoms,	
							previous	
							cardiovascular	
Feng et al ⁶	China	Multi-center	1st Jan to	35	62	Severity (National	None	5
		retrospectiv	15th Feb			Health Commission		
		e study	2020			of China definition)		

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Fosbøl et al ⁷	Denmark	National	1st Feb to	895	3585	Mortality	Mortality, severity:	9
		registry	4th May,			Severity (unclear	age, sex,	
		retrospectiv	2020			definition)	comorbidities	
		e cohort						
		study						
Gao et al ⁸	China	Single-	5th Feb to	183	527	Mortality	Mortality, severity:	8
		center	15th Mar,			Severity (unclear	propensity score	
		retrospectiv	2020			definition)	matched for age,	
		е					sex, diabetes,	
		observation					insulin-treated	
		al study					diabetes,	
							myocardial	
							infarction,	
							underwent	
							PCI/CABG, renal	
							failure, stroke,	
							heart failure,	
							COPD.	
Guo et al ⁹	China	Single-	23th Jan	19	168	Mortality	None	4
		center	to 23th Feb,					
		retrospectiv	2020					
		e study						
Huang et al10	China	Single-	7th Feb to	20	30	Mortality	None	4
		center	3rd Mar,			Severity (National		
		retrospectiv	2020			Health Commission		
		e study				of China definition)		
Jung et al ¹¹	Korea	Retrospecti	Up to 8th	377	1577	Mortality (in-	Mortality: age, sex,	7
		ve	Apr, 2020.			hospital death)	Charlson	
		observation					Comorbidity Index,	
		al data from					immunosuppressio	
		nationwide					n	
		database						
Li et al ¹²	China	Single-	15th Jan to	115	247	Mortality	None	4
		center	15th Mar,			Severity (National		
		retrospectiv	2020			Health Commission		
		e case				of China definition)		
		series						
Liabeuf et	France	Single-	Feb 28th to	96	172	Mortality	Mortality: none	4
al ¹³		center	30th Mar,			Severity (admission	Severity:	
Ci.		retrospectiv	2020			to ICU)	comorbidities	
		•				,		

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Li Xiaochen	China	Single-	Jan 26th to	42	503	Severity (IDSA	None	4
et al ¹⁴		center	Feb 5th,			Pneumonia		
		ambispectiv	2020			severity)		
		e cohort						
		study						
Liu Y et al ¹⁵	China	Multi-center	Jan 11th to	12	34	Severity (National	Severity: sex	6
		retrospectiv	Feb 5th,			Health Commission		
		e study	2020			of China definition)		
Lopez-	Spain	Single-	Mar 10th to	210	755	Mortality	Mortality, severity:	8
Otero ¹⁶		center	April 6th,			Severity (ICU	propensity score	
		retrospectiv	2020			admissions)	matching	
		e study						
Mancia et	Italy	Population-	Feb 21th to	2896	12506	Severity (defined	Severity:	9
al ¹⁷		based	Mar 11th,			as critical or fatal	propensity score	
		case-	2020			disease)	matching	
		control						
		study						
Mehta et al ¹⁸	USA	Multi-center	Mar 8th to	211	1494	Mortality	Mortality: none	8
		retrospectiv	Apr 12th,			Severity (admission	Severity,	
		e study	2020			to ICU)	hospitalization:	
						Hospitalization	propensity score	
							matching	
Meng et al ¹⁹	China	Single-	Jan 11th to	17	25	Mortality	None	4
		center	Feb 23rd,			Severity (National		
		retrospectiv	2020			Health Commission		
		e study				of China definition)		
Richardson	USA	Population-	Mar 1st to	413	953	Mortality	None	4
et al ²⁰		based	Apr 4th,			Severity (ICU care)		
		retrospectiv	2020					
		e case						
		series study						
Rentsch et	USA	Population-	Feb 8th and	1532	2247	Severity (ICU	Severity,	9
al ²¹		based	Mar 30th,			admission)	hospitalization:	
		retrospectiv	2020			Hospitalization	age, race,	
		e cohort					comorbid	
							conditions, and	
							Veterans Aging	
							Cohort Study Index	
							of physiologic injury	

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Reynolds et	USA	Multi-center	Mar 1st to	1774	439	Severity (defined	Propensity score	9
al ²²		retrospectiv	Apr 15th,			as intensive care,	matching	
		e cohort	2020			mechanical		
		study				ventilation, or		
						death)		
Rossi et al ²³	Italy	Population-	Feb 27th	818	4488	Mortality	Mortality, severity:	8
		based	Up to Apr			Hospitalization	age, sex, Charlson	
		prospective	8th				Comorbidity Index	
		cohort						
		study						
Tedeschi et	Italy	Multi-center	Feb 1st to	175	136	Mortality	Mortality: age,	8
al ²⁴		prospective	Apr 4th,				gender, presence	
		cohort	2020				of comorbidities	
		study						
Yang et al ²⁵	China	Single-	Jan 5th to	43	83	Mortality	None	4
3		center	Feb 22nd,			Severity (National		
		retrospectiv	2020			Health Commission		
		e study				of China definition)		
Yan et al ²⁶	China	Population-	Jan 10th to	_	_	Severity (National	Severity: age, sex,	4
		based	Feb 28th,			Health Commission	BMI	
		retrospectiv	2020			of China definition)		
		e case-				,		
		control						
		study						
Yu et al ^{27*}	China	Multi-center	Jan 17th to	103	173	Mortality	Mortality: sex, age,	9
		retrospectiv	Feb 19th,				smoking,	
		e cohort	2020				symptoms, chronic	
		study					diseases	
Zeng et al ²⁸	China	Single-	Jan 5th to	28	47	Mortality	None	4
		center	Mar 8th,			Severity (IDSA		
		retrospectiv	2020			Pneumonia		
		e study				severity)		
						Hospitalization		
Zhang et al ²⁹	China	Multi-center	Dec 31st to	174	348	Mortality	Mortality, severity:	9
		retrospectiv	Feb 20th,			Severity (ARDS)	propensity score	
		e study	2020				matching	
Zhou et al ³⁰	China	Single-	Jan 25th to	15	21	Mortality	None	4
	-	center	Feb 20th,			,		
		retrospectiv	2020					

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* Data were not reported separately but merged into the Zhang et al (2020) meta-analysis. Data included here are as reported in the meta-analysis.

Abbreviations

ACEI: angiotensin converting enzyme inhibitors

ARB: Angiotensin II receptor blockers

ARDS: Acute respiratory distress syndrome

BMI: Body mass index

CABG: Coronary artery bypass surgery

COPD: Chronic obstructive pulmonary disease

ICU: Intensive care unit

IDSA: Infectious Diseases Society of America PCI: Percutaneous coronary intervention

NOS: Newcastle-Ottawa Scale

Appendix to Table S1: Publications included in the meta-analysis

References:

- 1. Bean DM, Kraljevic Z, Searle T, et al. ACE-inhibitors and Angiotensin-2 Receptor Blockers are not associated with severe SARS-COVID19 infection in a multi-site UK acute Hospital Trust. *Eur J Heart Fail*. 2020.
- 2. Bravi F, Flacco ME, Carradori T, et al. Predictors of severe or lethal COVID-19, including Angiotensin Converting Enzyme inhibitors and Angiotensin II Receptor Blockers, in a sample of infected Italian citizens. *PLoS One.* 2020;15(6):e0235248.
- 3. Chen Y, Yang D, Cheng B, et al. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. *Diabetes Care*. 2020;43(7):1399-1407.
- 4. Andrea C, Francesco M, Antonio N, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Outcome in Patients With SARS-CoV-2 Pneumonia: A Case Series Study. *Hypertension*. 2020;76(2):e10-e12.
- 5. Felice C, Nardin C, Di Tanna GL, et al. Use of RAAS inhibitors and risk of clinical deterioration in COVID-19: results from an Italian cohort of 133 hypertensives. *Am J Hypertens*. 2020.
- 6. Feng Y, Ling Y, Bai T, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. *Am J Respir Crit Care Med.* 2020;201(11):1380-1388.
- 7. Fosbøl EL, Butt JH, Østergaard L, et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. *JAMA*. 2020.
- 8. Gao C, Cai Y, Zhang K, et al. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *Eur Heart J.* 2020;41(22):2058-2066.
- 9. Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020.
- 10. Huang Z, Cao J, Yao Y, et al. The effect of RAS blockers on the clinical characteristics of COVID-19 patients with hypertension. *Ann Transl Med.* 2020;8(7):430.
- 11. Jung SY, Choi JC, You SH, Kim WY. Association of renin-angiotensin-aldosterone system inhibitors with COVID-19-related outcomes in Korea: a nationwide population-based cohort study. *Clin Infect Dis.* 2020.
- Li J, Wang X, Chen J, Zhang H, Deng A. Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China. JAMA Cardiol. 2020
- 13. Liabeuf S, Moragny J, Bennis Y, et al. Association between renin-angiotensin system inhibitors and COVID-19 complications. *Eur Heart J Cardiovasc Pharmacother*. 2020.
- 14. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol*. 2020;146(1):110-118.
- 15. Liu Y, Huang F, Xu J, et al. Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. *medRxiv*. 2020;2003.2020.20039586.
- 16. López-Otero D, López-Pais J, Cacho-Antonio CE, et al. Impact of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on COVID-19 in a western population. CARDIOVID registry. *Rev Esp Cardiol (Engl Ed)*. 2020.
- 17. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19. *New England Journal of Medicine*. 2020;382(25):2431-2440.

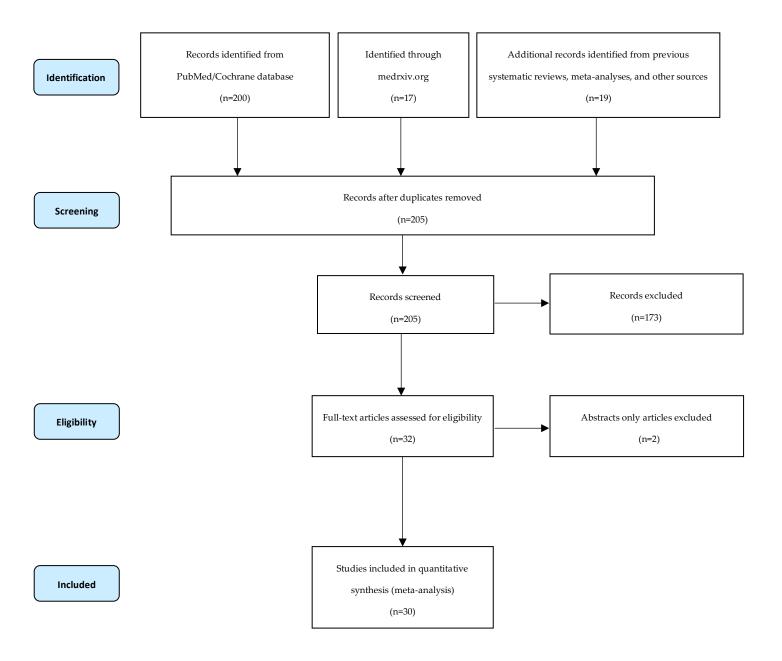
Healthcare **2021**, 9, 127 6 of 10

18. Mehta N, Kalra A, Nowacki AS, et al. Association of Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Testing Positive for Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol.* 2020.

- 19. Meng J, Xiao G, Zhang J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. *Emerg Microbes Infect*. 2020;9(1):757-760.
- 20. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 2020.
- 21. Rentsch CT, Kidwai-Khan F, Tate JP, et al. Covid-19 Testing, Hospital Admission, and Intensive Care Among 2,026,227 United States Veterans Aged 54-75 Years. *medRxiv*. 2020.
- Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. N Engl J Med. 2020;382(25):2441-2448.
- Giorgi Rossi P, Marino M, Formisano D, Venturelli F, Vicentini M, Grilli R. Characteristics and outcomes of a cohort of SARS-CoV-2 patients in the Province of Reggio Emilia, Italy. *medRxiv*. 2020;2020.2004.2013.20063545.
- 24. Tedeschi S, Giannella M, Bartoletti M, et al. Clinical Impact of Renin-angiotensin System Inhibitors on In-hospital Mortality of Patients With Hypertension Hospitalized for Coronavirus Disease 2019. *Clinical Infectious Diseases*. 2020.
- Yang G, Tan Z, Zhou L, et al. Effects of Angiotensin II Receptor Blockers and ACE (Angiotensin-Converting Enzyme)
 Inhibitors on Virus Infection, Inflammatory Status, and Clinical Outcomes in Patients With COVID-19 and Hypertension: A Single-Center Retrospective Study. *Hypertension*. 2020;76(1):51-58.
- Yan H, Valdes AM, Vijay A, et al. Role of Drugs Affecting the Renin-Angiotensin-Aldosterone System on Susceptibility and Severity of COVID-19: A Large Case-Control Study from Zheijang Province, China. medRxiv. 2020:2020.2004.2024.20077875.
- 27. Zhang X, Yu J, Pan LY, Jiang HY. ACEI/ARB use and risk of infection or severity or mortality of COVID-19: A systematic review and meta-analysis. *Pharmacol Res.* 2020;158:104927.
- 28. Zeng Z, Sha T, Zhang Y, et al. Hypertension in patients hospitalized with COVID-19 in Wuhan, China: A single-center retrospective observational study. *medRxiv*. 2020:2020.2004.2006.20054825.
- 29. Zhang P, Zhu L, Cai J, et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19. *Circ Res.* 2020;126(12):1671-1681.
- 30. Zhou X, Zhu J, Xu T. Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on reninangiotensin system inhibitors. *Clin Exp Hypertens*. 2020;42(7):656-660.

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Fig. S1: PRISMA flowchart

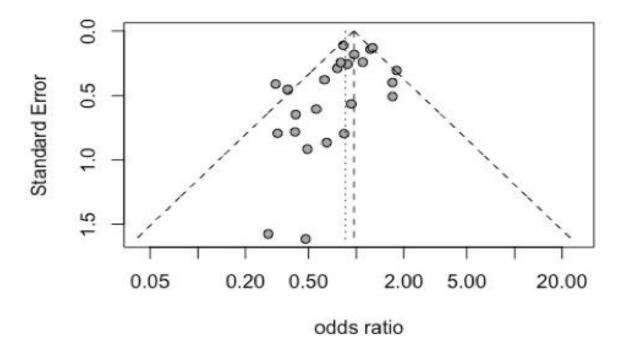


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Figure Legend

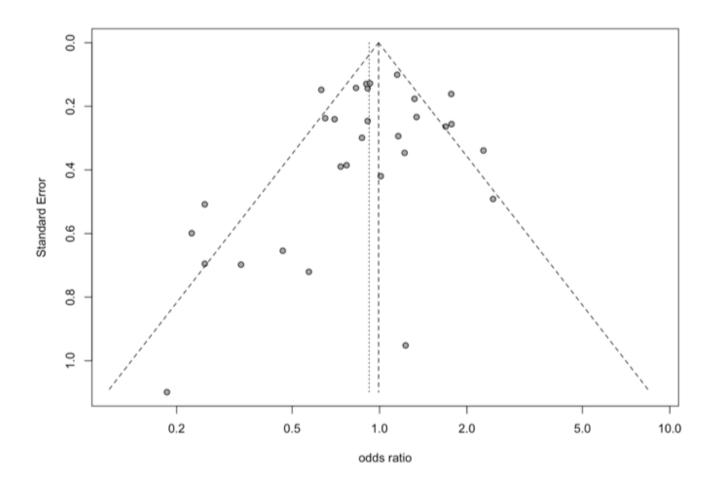
Figure. S2: Funnel plots (A) mortality, (B) severity of COVID-19 disease, and (C) hospitalization.

Panel A: Mortality



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Panel B: Severity



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Panel C: Hospitalization

