Supplemental Materials

P Zhang, L Zhu, J Cai *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

This supplementary material has been provided by the authors to give readers additional information about their work.

Online Table I Diagnostic criteria of COVID-19 (Exclusive for patients from Hubei Province) and septic shock in the study

COVID-19 diagnosis: Any a positive result on below, irrespective of clinical signs and symptoms	
(1) Typical CT manifestations of viral pneumonia	Primary reported findings on CT: 1. bilateral, subpleural or peripheral ground-glass opacities; 2. lobular septal thickening; 3. air space consolidation; 4. bronchovascular thickening in the lesion; 5.traction bronchiectasis
(2) RT-PCR* for COVID-19 nasal and pharyngeal swab specimens or blood sample	+
Septic shock definition: Any a positive result on below	
(1) Persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg	Hypotension: 1. systolic blood pressure <90 mmHg; 2. MAP < 65 mmHg; 3. a drop of > 40 mmHg of systolic blood pressure from baseline
(2) Serum lactate level > ULN† and using vasoactive drug (excluding single rescue medication)	+

SBP <90 mm Hg, or mean arterial pressure <65 mm Hg, or SBP decrease >40 mm Hg from baseline, or serum lactate >2.0 mmol/L

*The laboratory RT-PCR procedures and cycle threshold (Ct) denoted positive findings varied from suppliers. PCR positive defined as a Ct of less than indicated threshold in each instruction.

†ULN, upper limit of normal. The ULN was defined according to the criteria by the laboratory standards in each hospital.

Online Table II The normal range of serum CRP, procalcitonin, creatinine, D-dimer, and platelet test in study hospitals

	Normal Range for Serum Test				
	CRP	**Procalcitonin**	**Creatinine**	**D-dimer**	**Platelets**
Site 1	0-10(mg/L)	0-0.05(ng/ml)	64-104(umol/L)	0-500(ng/ml)	0.50-2.50(mmol/L)
Site 2	0-10(mg/L)	0-0.10(ng/ml)	41-81(umol/L)	0-0.55(mg/L)	0.50-1.50(mmol/L)
Site 3	0-5(mg/L)	0-5.00(ug/L)	53-106(umol/L)	0-0.55(mg/L) /0-1(mg/L)	1.65-2.90(mmol/L)
Site 4	0-5(mg/L)	0-0.05(ng/ml)	40-105(umol/L)	0-0.50(mg/L)	1.65-2.90(mmol/L)
Site 5	0-10(mg/L)	0-0.10(ng/ml)	57-97(umol/L)	0-0.24(mg/L)	0.50-2.20(mmol/L)
Site 6	0-3(mg/L)	0-0.50(ng/mL)	57-111(umol/L)	0-1(ug/mL)	0.50-2.20(mmol/L)
Site 7	0-4(mg/L)	0-0.05(ng/ml)	64-104(umol/L)	0-0.55(mg/L)	0.50-2.50(mmol/L)
Site 8	0-10(mg/L)/0-5(mg/L)	0-0.10(ng/ml) /0-0.50(ng/mL)	38-120(umol/L)	0-243(ng/ml)	0.00-3.00(mmol/L)
Site 9	0-10(mg/L)	0-0.50(ng/mL)	35-110(umol/L)	0-0.24(ug/ml)	0.50-2.20(mmol/L)

Abbreviations: CRP, C-reactive protein. Site 1, Zhongnan Hospital of Wuhan University; Site 2, Renmin Hospital of Wuhan University; Site 3, Wuhan First Hospital; Site 4, Wuhan Third Hospital; Site 5, Wuhan Seventh Hospital; Site 6, Wuhan Ninth Hospital; Site 7, Thunder Mountain Hospital; Site 8, Huanggang Central Hospital; Site 9, Central Hospital of Enshi Tujia and Miao Autonomous Prefecture.

Online Table III Clinical characteristics, laboratory data and CT features of patients on admission

Parameters	Total (n=3430)	Hypertension† (n=1128)	Non-hypertension‡ (n=2302)	*P* value§
Clinical characteristics				
Age, median(IQR), y	57(45-65)	64(56-69)	52(40-62)	1.40E-107
Male gender, n (%)	1675(48.8)	603(53.5)	1072(46.6)	1.73E-4
Female gender, n (%)	1755(51.2)	525(46.5)	1230(53.4)	1.73E-4
Heart rate, median(IQR), bpm	82(76-93)	84(78-96)	81(76-92)	5.21E-4
Respiratory rate, median(IQR)	20(19-21)	20(19-22)	20(19-21)	0.004
SBP, median(IQR), mmHg	126(119-136)	132(120-145)	124(117-132)	1.70E-42
DBP, median(IQR), mmHg	78(70-83)	80(72-87)	77(70-81)	2.06E-15
Days from symptom onset to hospitalization, median(IQR)	10(7-15)	10(7-15)	10(6-14)	1.26E-4
Fever, n(%)	2534(73.9)	826(73.2)	1708(74.2)	0.57
Cough, n(%)	2331(68.0)	775(68.7)	1556(67.6)	0.54
Fatigue, n(%)	1228(35.8)	428(37.9)	800(34.8)	0.07
Dyspnea, n(%)	719(21.0)	298(26.4)	421(18.3)	5.01E-8
Comorbidities				
Diabetes, n(%)	388(11.3)	240(21.3)	148(6.4)	9.76E-38
Coronary heart disease, n(%)	178(5.2)	131(11.6)	47(2.0)	4.34E-32
Chronic liver disease, n(%)	62(1.8)	21(1.9)	41(1.8)	0.98
Cerebrovascular diseases, n(%)	50(1.5)	41(3.6)	9(0.4)	2.99E-13
Chronic renal diseases, n(%)	52(1.5)	35(3.1)	17(0.7)	2.28E-7
COPD, n(%)	19(0.6)	6(0.5)	13(0.6)	1.00
Chest CT				
Unilateral lesion, n/N(%)	326/3216(10.1)	58/1068(5.4)	268/2148(12.5)	6.70E-10
Bilateral lesions, n/N (%)	2721/3216(84.6)	941/1068(88.1)	1780/2148(82.9)	1.30E-4
Laboratory examination				
Leukocytecount>9.5, 10^9/L, n/N (%)	267/3191(8.4)	123/1066(11.5)	144/2125(6.8)	6.35E-6
Neutrophil count > 6.3, 9.5 10^9/L, n/N (%)	442/3186(13.9)	211/1065(19.8)	231/2121(10.9)	9.25E-12
Lymphocyte count < 1.1, 9.5 10^9/L, n/N (%)	1361/3187(42.7)	508/1066(47.7)	853/2121(40.2)	7.27E-5
C-reactive protein increase>ULN*, n/N (%)	1361/2226(61.1)	521/774(67.3)	840/1452(57.9)	1.59E-5
Procalcitonin level increase> ULN*, n/N (%)	633/2503(25.3)	277/871(31.8)	356/1632(21.8)	5.70E-8
ALT increase> 40 U/L, n/N (%)	555/3141(17.7)	203/1056(19.2)	352/2085(16.9)	0.12
AST increase> 40 U/L, n/N (%)	718/3144(22.8)	287/1056(27.2)	431/2088(20.6)	4.53E-5
Creatinine>ULN*, n/N (%)	178/3009(5.9)	106/1011(10.5)	72/1998(3.6)	7.70E-14
D-dimer> ULN*, n/N (%)	1055/2567(41.1)	459/892(51.4)	596/1675(35.6)	9.77E-15
Platelets < ULN, n/N (%)	316/3192(9.21)	188/2126(8.5)	128/1066(12.0)	0.005
K^+ < 3.5 mmol/L, n/N (%)	690/3132(22.0)	284/1052(27.0)	406/2080(19.5)	2.33E-6
LDL-c, mmol/L, median (IQR)	2.3 (1.9-2.8) [n=2311]	2.3 (1.8-2.8) [n=872]	2.3(1.9-2.8) [n=1439]	0.10
SaO2, <95%, n/N (%)	398/2442(16.3)	176/830(21.2)	222/1612(13.8)	3.27E-6
Blood glucose, median (IQR), mmol/L	5.7(4.9-7.3) [n = 2797]	6.2(5.2-8.3) [n = 966]	5.5(4.8-6.8) [n = 1831]	8.89E-24

Abbreviations: SBP, Systolic blood pressure; DBP, Diastolic blood pressure; COPD, Chronic obstructive pulmonary disease; ALT, alanine transaminase; AST, Aspartate transaminase; IQR, Interquartile range.

*Upper limit of normal (ULN) was defined according to criteria in each hospital and normal ranges of tests in each hospital were provided in Online Table 2.

†1128 participants with a history of hypertension enrolled in the hypertension cohort.

‡2302 participants without a history of hypertension enrolled in the non-hypertension cohort.

§The *P* values were calculated by Mann-Whitney U test for continuous variables, while categorical variables were compared by Fisher's exact test or Chi-square test between Hypertension and Non-hypertension group.

Online Table IV Characteristics of ACEI/ARB and non-ACEI/ARB groups among patients with hypertension taking antihypertensive drugs before and after propensity score-matching.

	Unmatched			Matched [a]		
Parameters	**ACEI/ARB[†] (n = 188)**	**Non-ACEI/ARB[‡] (n = 557)**	**SD[§]**	**ACEI/ARB[†] (n = 181)**	**Non-ACEI/ARB[‡] (n = 181)**	**SD[§]**
Clinical characteristics on admission						
Age, median(IQR)	64 (55-68)	64 (57-68)	-0.061	64(56-68)	64(57-69)	-0.056
Male gender, n (%)	100(53.2)	277(49.7)	0.069	95(52.5)	92(50.8)	0.033
Female gender, n (%)	88(46.8)	280(50.3)	-0.069	86(47.5)	89(49.2)	-0.033
Heart rate, median(IQR)	82.0(76.0-95.3)	82.0(78.0-94.8)	-0.014	82(76.3-95.0)	80(76.3-94.0)	0.036
Respiratory rate, median(IQR)	20.0(19.0-21.0)	20.0(19.0-22.0)	-0.022	20(19.0-21.0)	20(19.0-21.8)	0.081
SBP, median(IQR)	132.5(123.0-145.8)	134.0(121.0-145.0)	0.019	133.5(124.0-147.3)	132(120.0-145.0)	0.045
DBP, median(IQR)	80.0(72.0-87.8)	80.0(73.0-86.0)	-0.010	80(72.0-88.0)	80(73.8-88.0)	-0.025
Symptom onset to admission, median(IQR), day	10.0(7.0-15.0)	10.0(7.0-15.0)	-0.078	10(7-15)	9.5(6-15)	-0.031
Fever, n(%)	126(67.0)	411(73.8)	-0.149	125(69.1)	119(65.8)	0.071
Cough, n(%)	122(64.9)	379(68.0)	-0.067	118(65.2)	113(62.4)	0.058
Fatigue, n(%)	65(34.6)	216(38.8)	-0.087	62(34.3)	70(38.7)	-0.092
Dyspnea, n(%)	38(20.2)	148(26.6)	-0.151	37(20.4)	38(21.0)	-0.014
Comorbidities on admission						
Diabetes, n(%)	44(23.4)	118(21.2)	0.053	42(23.2)	42(23.2)	0.000
Coronary heart disease, n(%)	29(15.4)	56(10.1)	0.162	25(13.8)	28(15.5)	-0.047
Chronic renal diseases, n(%)	7(3.7)	19(3.4)	0.017	7(3.9)	8(4.4)	-0.028
Cerebrovascular diseases, n(%)	5(2.7)	18(3.2)	-0.034	5(2.8)	5(2.8)	0.000
Chronic liver disease, n(%)	4(2.1)	7(1.3)	0.068	4(2.2)	4(2.2)	0.000
Chronic obstructive pulmonary disease, n(%)	1(0.5)	3(0.5)	-0.001	1(0.6)	1(0.6)	0.000
Chest CT on admission						
Unilateral lesion, n/N(%)	16/173(9.3)	27/525(5.1)	0.159	14(8.4)	12(7.1)	0.050
Bilateral lesions, n/N (%)	146/173(84.4)	474/525(90.3)	-0.178	143(86.1)	150(88.8)	-0.079
Laboratory examination on admission						
Leukocyte count > 9.5, 10^9/L, n/N (%)	22/183(12.0)	55/527(10.4)	0.050	22/177(12.4)	17/175(9.7)	0.087
Neutrophil count > 6.3, 9.5 10^9/L ,n/N (%)	32/183(17.5)	100/527(19.0)	-0.039	32/177(18.1)	38/175(21.7)	-0.091
Lymphocyte count <1.1, 9.5 10^9/L, n/N (%)	82/183(44.8)	228/527(43.3)	0.031	81/177(45.8)	77/175(44.0)	0.035

	Unmatched			Matched [a]		
Parameters	**ACEI/ARB[†] (N = 188)**	**Non-ACEI/ARB[‡] (N = 557)**	**SD**	**ACEI/ARB[†] (N = 181)**	**Non-ACEI/ARB[‡] (N = 181)**	**SD**
C-reactive protein increase>ULN[*], n/N (%)	78/133(58.7)	242/374(64.7)	-0.125	78/129(60.5)	70/119(58.8)	0.033
Procalcitonin level increase> ULN[*], n/N (%)	40/144(27.8)	135/432(31.3)	-0.076	39/140(27.9)	48/142(33.8)	-0.129
ALT increase> 40 U/L, n/N (%)	33/179(18.4)	100/523(19.1)	-0.018	32/173(18.5)	31/173(17.9)	0.015
AST increase> 40 U/L, n/N (%)	40/179(22.4)	133/523(25.4)	-0.072	39/173(22.5)	41/173(23.7)	-0.027
Creatinine>ULN[a], n/N (%)	14/166(8.4)	49/504(9.7)	-0.045	14/160(8.8)	19/166(11.5)	-0.090
D-dimer> ULN[a], n/N (%)	67/149(45.0)	240/445(53.9)	-0.180	67/144(46.5)	76/145(52.4)	-0.118
K^+ < 3.5 mmol/L, n/N (%)	51/179(28.5)	135/522(25.9)	0.059	50/173(28.9)	45/174(25.9)	0.068
Platelets < ULN, n/N (%)	22/183(12.02)	50/477(9.49)	0.058	22/177(12.43)	18/175(10.29)	0.048
LDL-c, mmol/L, median (IQR)	2.2(1.8-2.8) [n = 151]	2.3(1.9-2.8) [n = 426]	-0.069	2.23(1.8-2.8) [n = 146]	2.34(1.8-2.8) [n = 142]	0.011
SaO2, <95%, n/N (%)	30/138(21.7)	84/413(20.3)	0.034	29/132(22.0)	28/134(20.9)	0.026
Blood glucose, median (IQR), mmol/L	6.0(5.1-8.3) [n = 163]	6.2(5.2-8.2) [n = 483]	0.028	6.05(5.1-8.3) [n = 158]	6.14(5.2-8.2) [n = 163]	0.036

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; COPD, Chronic obstructive pulmonary disease; ALT, alanine transaminase; AST, Aspartate transaminase; IQR, Interquartile range.

[*]Upper limit of normal (ULN) was defined according to criteria in each hospital and normal ranges of tests in each hospital were provided in Online Table 2.

[†]Patients with hypertension who taking ACEI and/or ARB during hospitalization were enrolled in the ACEI/ARB cohort. Patients discontinued treatment of hypertension due to inability to take medications or hypotension were not excluded from the cohort.

[‡]Patients with antihypertension drug who never taking ACEI and ARB during hospitalization were enrolled in the non-ACEI/ARB cohort.

[§]SD, Standardized differences be used to compare the mean of baseline covariate between ACEI/ARB and non-ACEI/ARB group.

Online Table V Hazard ratio and incidence rate ratios for association between ACEI/ARB and COVID-19 outcomes among patients with hypertension taking antihypertensive drugs in mixed-effect Cox model after propensity score-matching

	Mixed-effect Cox Model After PSM in patients taking antihypertensive drugs (1:2) *		
ACEI/ARB vs non-ACEI/ARB	**IRD**	**HR(95%CI)**	***P* value†**
All-cause mortality	-0.36(-0.60,-0.12)	0.29(0.12,0.69)	0.005
Septic shock	-0.31(-0.54,-0.09)	0.24(0.10,0.63)	0.003
ARDS	-0.27(-0.64,0.10)	0.73(0.44,1.19)	0.21
DIC	-0.14(-0.25,-0.03)	-‡	-‡
Acute kidney injury	-0.06(-0.28,0.16)	0.83(0.36,1.87)	0.65
Acute heart injury	-0.16(-0.47,0.14)	0.81(0.44,1.47)	0.49

Abbreviations: HR, Hazard ratio; CI, Confidence interval; IRD, incidence rate differences, an absolute difference in the incidence between two groups.

*In the mixed-effect Cox model after propensity score matching, age, gender, cough, dyspnea, comorbidities (diabetes, coronary heart disease and chronic renal disease), CT-diagnosed lung lesions, and incidence of increased CRP and creatine were matched. Modeled center as a random effect in the multivariate analyses followed by adjustment for antiviral drug and lipid lowering drug.

†The *P* values were calculated by Fisher's exact test or $\chi 2$ test.

‡The incidence of DIC was 0 in the ACEI/ARB cohort. HR in DIC was not calculated.

Online Table VI In-hospital management of participants

Management	Total (N=3430)	Hypertension* (n=1128)	Non-hypertension† (n=2302)	*P* value‖
Traditional Chinese medicine%	2921(85.2)	978(86.7)	1943(84.4)	0.08
Antiviral drug, n (%)	2872(83.7)	935(82.9)	1937(84.1)	0.38
Antibiotics drug, n (%)	2524(73.6)	862(76.4)	1662(72.2)	0.01
Nasal cannula Oxygen inhalation‡, n (%)	2436(71.0)	887(78.6)	1549(67.3)	7.87E-12
Systemic corticosteroids, n (%)	1185(34.6)	446(39.5)	739(32.1)	2.00E-5
Immunoglobin, n (%)	918(26.8)	330(29.3)	588(25.5)	0.02
Antidiabetic drug, n (%)	486(14.2)	281(24.9)	205(8.91)	2.85E-36
Lipid lowering drug, n (%)	214(6.2)	137(12.2)	77(3.3)	2.89E-23
Vasoactive drug, n (%)	220(6.4)	124(11.0)	96(4.2)	3.25E-14
Noninvasive ventilation§, n (%)	206(6.0)	122(10.8)	84(3.7)	1.99E-16
Invasive ventilation§, n (%)	96(2.8)	60(5.3)	36(1.6)	7.54E-10
Antifungal medications, n (%)	81(2.4)	47(4.2)	34(1.5)	1.99E-6
Renal replacement therapy,n(%)	19(0.6)	15(1.3)	4(0.2)	5.33E-5
Extracorporeal membrane oxygenation§, n (%)	7(0.2)	4(0.4)	3(0.1)	0.23
Anti-hypertensive drug, n (%)				
ACEI, n (%)	31(0.9)	31(2.8)	0(0)	6.29E-15
ARB, n (%)	157(4.6)	157(13.9)	0(0)	2.62E-74
CCB, n (%)	592(17.3)	592(52.5)	0(0)	1.12E-318
Diuretic, n (%)	300(8.8)	178(15.8)	122(5.3)	3.57E-24
beta-blocker, n (%)	334(9.7)	221(19.6)	113(4.9)	6.38E-42
alpha-blocker, n (%)	35(1.0)	25(2.2)	10(0.4)	2.63E-6

Abbreviations: CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

*1128 participants with a history of hypertension enrolled in the hypertension cohort.

†2302 participants without a history of hypertension enrolled in the non-hypertension cohort.

‡Nasal cannula oxygen inhalation was taken in isolation.

§Noninvasive ventilation, invasive ventilation, and extracorporeal membrane oxygenation are at mutually exclusive.

‖ The *P* values were calculated by Mann-Whitney U test for continuous variables, while categorical variables were compared by Fisher's exact test or Chi-square test.

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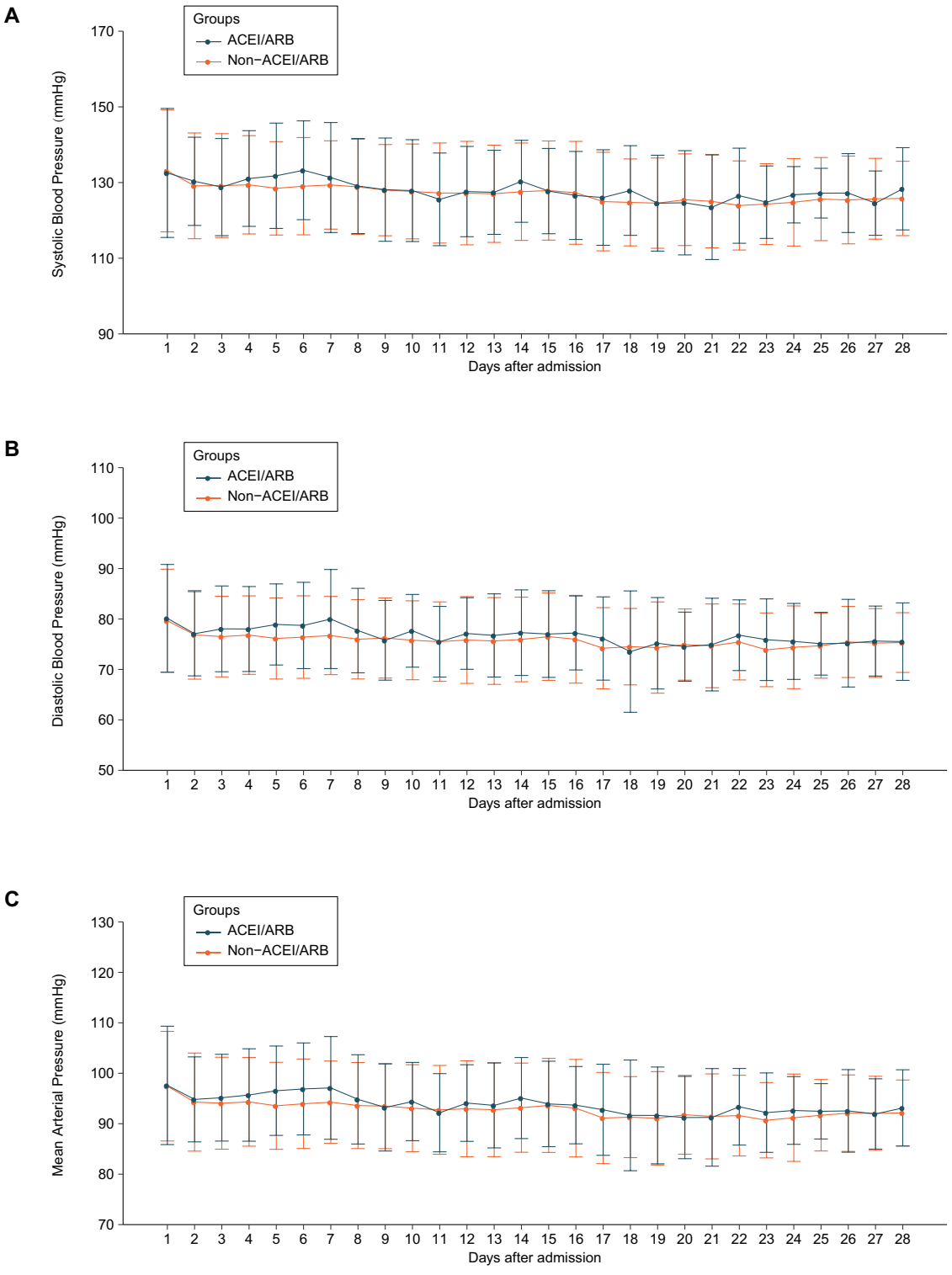
Online Table VII Hazard Ratio for primary and secondary outcome in hypertension and non-hypertension group

	Unadjusted		Adjusted*	
Hypertension vs non-hypertension	HR(95%CI)	*P* value†	HR(95%CI)	*P* value†
All-cause mortality	2.612(1.95,3.51)	0.000	1.41(1.03,1.94)	0.03
Septic shock	3.51(2.47,5.01)	0.000	1.95(1.33,2.85)	0.001
ARDS	2.42(2.01,2.91)	0.000	1.61(1.32,1.97)	0.000
DIC	5.84(2.60,13.11)	0.000	2.74(1.15,6.54)	0.02
Acute kidney injury	4.08(2.62,6.34)	0.43	2.55(1.58,4.12)	0.000
Acute heart injury	3.05(2.34,3.96)	0.000	1.68(1.26,2.23)	0.000

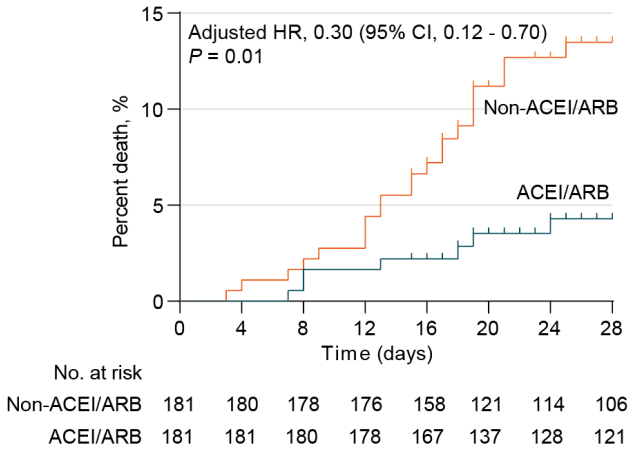
Abbreviations: ARDS, Acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; HR, Hazard ratio; CI, Confidence interval.

*The adjusted variables included age, gender, comorbid diabetes, cerebrovascular diseases, and chronic renal disease.

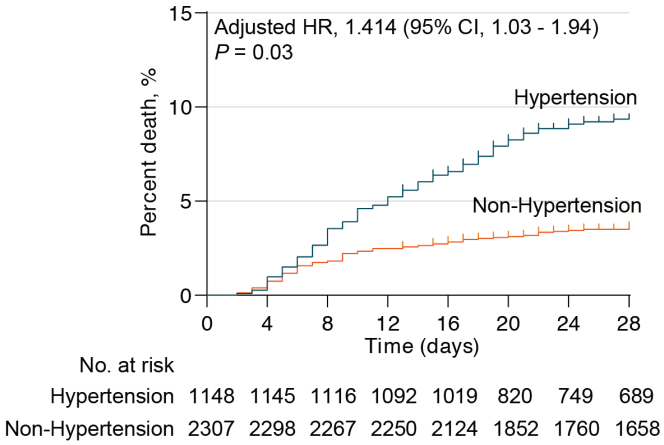
†The *P* values were calculated based on Cox proportional hazard model.



Online Figure I Dynamic change of blood pressure and mean arterial pressure of patients with hypertension treated with ACEI/ARB or without ACEI/ARB. (A-C) The systolic pressure (A), diastolic pressure (B), and mean arterial pressure (C) of patients with hypertension in a 28-day follow-up duration from admission.



Online Figure II. Kaplan-Meier Curves for cumulative probability of COVID-19 mortality among individuals with inpatient use of ACEI/ARB (ACEI/ARB cohort) or taking other antihypertensive drugs (non-ACEI/ARB cohort) in propensity score-matched analysis. The blips indicate censoring. The median (IQR) observation time was 28 (20-28) in ACEI/ARB cohort and 28 (18-28) in non-ACEI/ARB cohort.



Online Figure III. The 28-day Kaplan-Meier Curves of hypertensive and non-hypertensive cohort. The blips indicate censoring. Patients with hypertensive status were identified according to their electronic medical record and disease history.