


Hypertension as an independent risk factor for severity and mortality in patients with COVID-19: a retrospective study

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ABSTRACT

Purpose of the study Hypertension is one of the most common comorbidities in COVID-19 pneumonia. However, whether it is an independent factor on the severity and mortality of COVID-19 has not been studied.

Study design In this study, 736 patients with a PCR-confirmed diagnosis of COVID-19 were included from 12 January 2020 to 25 March 2020. All patients were divided into two groups according to whether or not they were hypertensive. After propensity score matching (PSM) to remove the interference of mismatches in the baseline data, the clinical characteristics and outcomes of angiotensin II receptor blocker (ARB)/ACE inhibitors application were analysed.

Results A total of 220 (29.9%) patients were hypertensive, and 516 (70.1%) patients were not hypertensive. PSM eliminated demographic and comorbidity differences between the two groups. Of all participants, 32 patients died (4.3% mortality), including 17 out of 220 in the hypertension group (7.7%) and 15 out of 516 in the non-hypertension group (2.9%). The incidence of intensive care unit (ICU) stay in the hypertension group (12.8%) was higher than in the non-hypertension group (5.3%) ($p < 0.05$). Logistic regression analysis showed that hypertension was an independent risk factor for death, not other comorbidities. Kaplan-Meier analysis showed that mortality was higher in the hypertension group than in the non-hypertension group before and after PSM ($p < 0.05$). There was no statistically significant difference in ICU therapy, mortality and hospitalisation time between hypertensive patients with or without ARBs/ACE inhibitors ($p > 0.05$).

Conclusion Hypertension was an independent risk factor for the severity and mortality of patients with COVID-19. ARBs/ACE inhibitors should not be discontinued in hypertensive patients with COVID-19.

is no direct evidence that hypertension increases the risk of new infections, several recent clinical studies have shown that hypertension is one of the most prevalent comorbidities of COVID-19 and a risk factor for severe COVID-19 infection.^{3–5} Another major concern between hypertension and COVID-19 is the viral invasion pathway. The COVID-19 virus belongs to the β genus coronavirus, and the first step of human infection with coronavirus is the contact of the virus with ACE2 on the cell surface.⁶ ACE2, one of the components of the renin-angiotensin system, on the other hand, is one of the targets of antihypertensive drugs. Many patients with COVID-19 are hypertensive, which has caused a lot of discussion on the treatment of hypertensive patients. The use of angiotensin II receptor blocker (ARB)/ACE inhibitors has also become a hot topic in patients with COVID-19.

To date, studies on the systematic and comprehensive epidemiology and clinical features of hypertensive patients with COVID-19 are still lacking. More evidence for the epidemiology and clinical information should be collected and analysed. In addition, investigating whether hypertension affects the clinical outcomes of patients with COVID-19 deserves further attention. This study aimed to investigate the clinical characteristics and outcomes of hypertensive and non-hypertensive patients with COVID-19. Furthermore, the relationship between ARBs/ACE inhibitors and clinical outcomes in patients with COVID-19 was analysed to provide clinical evidence to address the question of whether or not ARBs/ACE inhibitors should be discontinued during COVID-19 infection.

METHODS

Participants

In this study, we included 736 hospitalised patients with a PCR-confirmed diagnosis of COVID-19 from the Hubei Provincial Hospital of Integrated Traditional Chinese and Western Medicine between 12 January and 25 March 2020. COVID-19 was diagnosed according to the WHO's interim guidance. A total of 220 hypertensive and 516 non-hypertensive patients were randomly selected. In accordance with the guidelines for prevention and treatment of hypertension in China (2018 edition), hypertension was defined as: clinical systolic blood pressure (BP) ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg without the use of antihypertensive medications at three visits

INTRODUCTION

As of 27 April 2021, a cumulative total of 147 539 302 cases and 3116444 deaths have been caused by COVID-19 since the start of the outbreak.¹ Although its mortality rate has been decreasing by 3% per week until now, its incidence rate continues to increase by 1% in the number of cases per week. COVID-19 poses a great challenge to public health and the global economy.

It was estimated that almost 1.39 billion adults worldwide were hypertensive.² Hypertension causes a variety of diseases that greatly increase the mortality rate in the population. Although there



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on different days; with a BP <140/90 mm Hg but having hypertensive history and currently are taking antihypertensive medication.

Data collection and procedures

Information on demographics, past history, symptoms and signs, laboratory data, radiological features, treatments, complications, and outcome data of admitted patients was extracted from electronic medical records. Incomplete data would be directly obtained by contacting attending doctors or other healthcare providers; finally, missing data would describe the reasons. Clinical outcomes were followed up until 25 March 2020.

Laboratory confirmation was conducted in the Hubei Provincial Hospital of Integrated Traditional Chinese and Western Medicine. The confirmation of 2019-nCoV was done via high-throughput sequencing or real-time reverse-transcriptase PCR (RT-PCR) assay of nasal and pharyngeal swab specimens in accordance with the protocol established by WHO. Other laboratory indicators include complete blood count, coagulation testing, and kidney and liver function tests. The radiological examination results of the included patients were also collected according to documentation or description in inspection report charts.

All patients were divided into two groups according to whether or not they were hypertensive. After propensity score matching (PSM) to remove the interference of mismatches in the baseline data, their clinical characteristics and outcomes were analysed. The covariates included in the propensity score model were the patient's age, sex and past history (including diabetes, coronary heart disease, stroke, malignant tumour, chronic kidney disease, chronic obstructive pulmonary disease, asthma, heart failure, arrhythmia, bronchiectasis and systemic lupus erythematosus). Matching was performed with the use of a 1:1 matching protocol without replacement, with a calliper width equal to 0.01 of the SD of the logit of the propensity score. Logistic regression was used to clarify the effects of independent variables on mortality of patients with COVID-19. The survival rates of COVID-19-positive patients during the observation period were analysed using Kaplan-Meier plots and compared using the log-rank test. In addition, the clinical outcome of ARBs/ACE inhibitors in hypertensive patients has also attracted attention. According to their antihypertensive medication, patients were retrospectively allocated to the ARBs/ACE inhibitor and non-ARBs/ACE inhibitor groups.

Statistical analysis

The Statistical Package for the Social Sciences V.26.0 software was used for statistical analyses. To reduce the effect of potential confounding factors other than hypertension, PSM was used to match hypertensive and non-hypertensive patients when we evaluated the associations between hypertension and outcome variables. The association of ARBs/ACE inhibitor exposure and clinical outcome was assessed using Kaplan-Meier regression analysis in all hypertensive patients.

Continuous variables were expressed as medians (IQRs), while categorical variables as counts and percentages. Normally distributed data were compared using t-tests or one-way analysis of variance. Non-normally distributed data were compared using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test when necessary. The threshold for significance was set at $p < 0.05$.

RESULTS

Demographics and comorbidities of participants

A total of 736 patients with confirmed COVID-19 was included in this study. Among the patients, 344 (46.7%) were men and 392 (53.5%) were women (table 1). The median age was 59 years (IQR 48–69 years). A total of 220 (29.9%) of these patients had a history of hypertension (hypertension group) and 516 (70.1%) patients were without hypertension (non-hypertension group). The median ages in the hypertension and non-hypertension groups were 67 years (IQR 58–76 years) and 56 years (IQR 43–65 years) ($p = 0.000$), respectively. The average age of the hypertensive group was higher than that of the non-hypertensive group. The number of male patients was 107 (48.6%) in the hypertension group and 237 (45.9%) in the non-hypertension group ($p = 0.501$). There were no significant differences between the two subgroups underlying comorbidities, including cancer ($p = 0.327$), chronic kidney disease ($p = 0.163$), chronic kidney disease ($p = 0.848$), asthma ($p = 0.280$), heart failure ($p = 0.280$), arrhythmia ($p = 0.059$), bronchiectasis ($p = 0.534$), systemic lupus erythematosus ($p = 0.513$), diabetes ($p = 0.007$), coronary heart disease ($p = 0.000$) and stroke ($p = 0.000$), which demonstrated that hypertensive patients had a higher comorbidity rate than non-hypertensive patients with glucolipid metabolic disease, which is consistent with the results of previous studies.³⁷ After PSM, the differences in demographic data and comorbidities between the two groups were removed (table 1).

Clinical symptoms and signs

On admission and during hospitalisation, the body temperature of hypertensive patients was similar to that of non-hypertensive patients ($p = 0.396$). Obviously, hypertensive patients had significantly higher BP values than non-hypertensive patients ($p < 0.05$). The common symptoms of patients with COVID-19 were fatigue (67.3%), cough (56.0%), shortness of breath (27.2%), chest tightness (23.4%), sputum (19.4%), myalgia or arthralgia (12.5%), chills (8%), diarrhoea (7.3%), nausea or vomiting (4.3%), dyspnoea (4.3%), and headache (3.5%) (table 1). There were no statistically significant differences in any of the symptoms at baseline between the two groups ($p > 0.05$). After PSM, there was still no significant difference in the main symptoms such as cough, fatigue, shortness of breath, chest tightness, and sputum between the two groups.

Laboratory indices and radiological features

The laboratory test (including routine blood tests, blood biochemistry and coagulation markers) and radiological data of all patients and the propensity score-matched subpopulations between the two groups are shown in table 1. Of all participants, the patients in the hypertension group had a higher white cell count, aspartate aminotransferase, globulin, cystatin C, total bilirubin, creatinine and blood urea nitrogen than those in the non-hypertension group ($p < 0.05$). On the contrary, the lymphocyte count and albumin levels were lower in the hypertension group than in the non-hypertension group ($p < 0.05$). Leucocytosis and lymphopenia indicate different immune functions in hypertensive patients with COVID-19 and in non-hypertensive patients. However, there were no significant differences in platelet count, haemoglobin, alanine aminotransferase, prothrombin time, international normalized ratio, activated partial thromboplastin time and thrombin time levels ($p > 0.05$). These findings indicate that hypertensive patients with COVID-19 are more likely to show abnormal liver and kidney functions in clinical practice. After PSM, there was no statistically significant difference

Table 1 Clinical characteristics of patients with COVID-19

	Total patients				Unmatched		PSM (1:1)	
	(n=736)	Hypertension (n=220)	Non-hypertension (n=516)	P value	Hypertension (n=188)	Non-hypertension (n=188)	P value	
Demographic, median (IQR) or count (%)								
Age, years	59 (48–69)	67 (58–76)	56 (43–65)	0	65 (56–72)	65 (57–72)		0.793
Gender, male	344 (46.7%)	107 (48.6%)	237 (45.9%)	0.501	92 (48.9%)	95 (50.5%)		0.757
Comorbidities, count (%)								
Diabetes	36 (4.9%)	18 (8.2%)	18 (3.5%)	0.007	11 (5.9%)	15 (8%)		0.416
CHD	44 (6.0%)	27 (12.3%)	17 (3.3%)	0	14 (7.4%)	14 (7.4%)		1
Stroke	19 (2.6%)	14 (6.4%)	5 (1%)	0	7 (3.7%)	5 (2.7%)		0.557
Cancer	20 (2.7%)	4 (1.8%)	16 (3.1%)	0.327	4 (2.1%)	4 (2.1%)		1
CKD	3 (0.4%)	2 (0.9%)	1 (0.2%)	0.163	2 (1.1%)	1 (0.5%)		0.562
COPD	11 (1.5%)	3 (1.4%)	8 (1.6%)	0.848	3 (1.6%)	3 (1.6%)		1
Asthma	6 (0.8%)	3 (1.4%)	3 (0.6%)	0.28	2 (1.1%)	1 (0.5%)		0.562
Heart failure	6 (0.8%)	3 (1.4%)	3 (0.6%)	0.28	3 (1.6%)	2 (1.1%)		0.653
Arrhythmia	18 (2.4%)	9 (4.1%)	9 (1.7%)	0.059	4 (2.1%)	1 (0.5%)		0.177
Bronchiectasis	2 (0.3%)	1 (0.2%)	1 (0.5%)	0.534	0 (0.0%)	0 (0.0%)		-
SLE	1 (0.1%)	0 (0.0%)	1 (0.2%)	0.513	0 (0.0%)	0 (0.0%)		-
Symptom-sign, median (IQR) or count (%)								
Admission temperature	36.7 (36.5–37.0)	36.7 (36.4–37.0)	36.7 (36.5–37.0)	0.396	36.7 (36.4–37.0)	36.6 (36.4–37.0)		0.159
Maximum temperature	37.1 (36.9–37.7)	37.2 (36.9–37.8)	37.1 (36.9–37.6)	0.069	37.2 (36.9–37.9)	37.1 (36.9–37.5)		0.272
Systolic pressure (mm Hg)	124 (110–134)	130 (118–143)	121 (110–131)	0	130 (119–141)	127 (119–136)		0.128
Diastolic pressure (mm Hg)	80 (71–90)	81 (76–90)	80 (70–89)	0	81 (77–90)	80 (70–86)		0.001
Chills	59 (8%)	17 (7.7%)	42 (8.1%)	0.85	15 (8.0%)	27 (14.4%)		0.049
Cough	412 (56.0%)	118 (53.6%)	294 (57.0%)	0.403	108 (57.4%)	115 (61.2%)		0.462
Sputum	143 (19.4%)	38 (17.3%)	105 (20.3%)	0.334	34 (18.1%)	37 (19.7%)		0.693
Haemoptysis	3 (0.4%)	2 (0.9%)	1 (0.2%)	0.163	2 (1.1%)	0 (0.0%)		0.156
Sore throat	20 (2.7%)	5 (2.3%)	15 (2.9%)	0.628	5 (2.7%)	5 (2.7%)		1
Nasal congestion	6 (0.8%)	1 (0.5%)	5 (1%)	0.477	1 (0.5%)	1 (0.5%)		1
Headache	26 (3.5%)	8 (3.6%)	18 (3.5%)	0.921	6 (3.2%)	9 (4.8%)		0.429
Shortness of breath	200 (27.2%)	61 (27.7%)	139 (26.9%)	0.826	51 (27.1%)	63 (33.5%)		0.178
Dyspnoea	32 (4.3%)	9 (4.1%)	23 (4.5%)	0.823	8 (4.3%)	9 (4.8%)		0.804
Chest tightness	172 (23.4%)	54 (24.5%)	118 (22.9%)	0.623	47 (25.0%)	40 (21.3%)		0.392
Chest pain	22 (3.0%)	7 (3.2%)	15 (2.9%)	0.841	6 (3.2%)	4 (2.1%)		0.521
Nausea or vomiting	32 (4.3%)	9 (4.1%)	23 (4.5%)	0.823	9 (4.8%)	8 (4.3%)		0.804
Diarrhoea	54 (7.3%)	19 (8.6%)	35 (6.8%)	0.377	18 (9.6%)	12 (6.4%)		0.253
Myalgia or arthralgia	92 (12.5%)	29 (13.2%)	63 (12.2%)	0.715	23 (12.2%)	25 (13.3%)		0.757
Fatigue	495 (67.3%)	154 (70.0%)	341 (66.1%)	0.3	132 (70.2%)	115 (61.2%)		0.065
Routine blood test, median (IQR)								
White cell count, $\times 10^9/L$	5.6 (4.5–7.1)	6.0 (4.8–7.8)	5.5 (4.3–6.8)	0.002	6.0 (4.7–7.7)	5.7 (4.5–6.9)		0.253

Continued

Table 1 Continued

	Total patients (n=736)			Unmatched			PSM (1:1)			
		Hypertension (n=220)		Non-hypertension (n=516)		P value	Hypertension (n=188)		Non-hypertension (n=188)	
Lymphocyte count, ×10 ⁹ /L	1.3 (0.9–1.8)	1.2 (0.8–1.7)	1.4 (0.9–1.8)	0.014	1.3 (0.9–1.7)	1.3 (0.9–1.8)	0.324			
Platelet count, ×10 ⁹ /L	222 (171–274)	219 (163–281)	223 (173–271)	0.923	222 (166–282)	227 (170–263)	0.513			
Haemoglobin, g/L	128 (116–137)	127 (117–137)	128 (116–138)	0.28	128 (117–137)	126 (116–133)	0.296			
Blood biochemistry, median (IQR)										
ALT, U/L	21 (11–37)	22 (13–37)	21 (11–37)	0.239	22 (14–38)	27 (14–40)	0.311			
AST, U/L	23 (17–33)	25 (18–36)	23 (17–32)	0.045	24 (17–37)	24 (18–37)	0.889			
Albumin, g/L	37.8 (34.4–41.2)	37.1 (34.0–40.2)	38.2 (34.7–41.5)	0.023	37.5 (34.8–41.1)	36.5 (33.4–38.6)	0.001			
Globulin, g/L	25.9 (22.7–29.1)	26.3 (23.8–29.9)	25.6 (22.3–28.8)	0.004	26.2 (23.7–29.0)	26.8 (23.4–30.0)	0.453			
Cystatin C, mg/L	0.8 (0.1–1.0)	0.9 (0.7–1.1)	0.8 (0.7–0.9)	0	0.9 (0.7–1.1)	0.8 (0.7–1.0)	0.563			
TB, µmol/L	11.2 (8.4–14.7)	12.0 (8.7–15.8)	11.0 (8.3–14.3)	0.023	11.4 (8.5–15.1)	11.2 (9.0–14.4)	0.593			
Creatinine, µmol /L	66.9 (57.1–81.4)	73.5 (61.3–88.2)	65.0 (55.3–78.4)	0	72.5 (61.3–84.5)	66.4 (57.1–80.5)	0.012			
BUN, mmol/L	4.8 (3.8–6.1)	5.2 (4.1–6.7)	4.6 (3.7–5.8)	0	5.2 (4.0–6.5)	5.3 (4.1–6.5)	0.594			
Coagulation marker, median (IQR)										
PT, s	12.1 (11.4–13.1)	12.2 (11.3–13.1)	12.1 (11.4–13.1)	0.911	12.0 (11.2–12.9)	12.0 (11.3–13.1)	0.54			
INR	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (1.0–1.1)	0.808	1.0 (0.9–1.1)	1.0 (1.0–1.1)	0.205			
APTT, s	30.1 (28.1–32.1)	29.5 (27.8–32.1)	30.3 (28.4–32.1)	0.039	29.1 (27.5–31.1)	29.7 (27.5–31.3)	0.729			
TT, s	15.8 (14.9–17.1)	15.9 (15.0–17.0)	15.7 (14.9–17.1)	0.718	15.8 (15.0–17.0)	16.7 (15.7–17.8)	0			
Radiological features, count (%)										
Ground-glass opacity	423 (61.6%)	130 (63.1%) 18 (8.7%)	293 (60.9%) 45 (9.4%)	0.588 0.797	115 (64.6%) 15 (8.4%)	121 (65.8%) 11 (6.0%)	0.818 0.367			
Unilateral patchy shadowing	63 (9.1%)	18 (8.7%)	45 (9.4%)	0.797	15 (8.4%)	11 (6.0%)	0.367			
Bilateral patchy shadowing	410 (60.0%)	132 (64.1%)	278 (57.8%)	0.124	115 (64.6%)	107 (58.2%)	0.207			
Hydrothorax	34 (5.0%)	20 (9.7%)	14 (2.9%)	0	15 (8.4%)	6 (3.3%)	0.036			
Complications, count (%)										
Septic shock	8 (1.1%)	1 (0.5%)	7 (1.4%)	0.28	0 (0.0%)	4 (2.1%)	0.044			
Heart failure	12 (1.6%)	6 (2.7%)	6 (1.2%)	0.125	4 (1.1%)	3 (0.8%)	0.703			
ARDS	44 (6.0%)	11 (5.0%)	33 (6.4%)	0.465	8 (4.3%)	12 (6.4%)	0.358			
ARF	7 (1.0%)	2 (0.9%)	5 (1.0%)	0.939	2 (1.1%)	2 (1.1%)	1			
DIC	2 (0.3%)	1 (0.5%)	1 (0.2%)	0.534	1 (0.5%)	1 (0.5%)	1			
Rhabdomyolysis	1 (0.1%)	0 (0.0%)	1 (0.2%)	0.513	0 (0.0%)	1 (0.5%)	0.317			
Treatments, count (%)										
Antiviral medication	549 (74.6%)	172 (78.2%)	377 (73.1%)	0.144	146 (77.7%)	128 (68.1%)	0.037			
Antibacterial medication	450 (61.1%)	143 (65.0%)	307 (59.5%)	0.161	120 (63.8%)	107 (56.9%)	0.17			
Antifungal medication	12 (1.6%)	5 (2.3%)	7 (1.4%)	0.369	4 (2.1%)	1 (0.5%)	0.177			
Glucocorticoids	232 (31.5%)	79 (35.9%)	153 (29.7%)	0.094	64 (34.0%)	45 (23.9%)	0.031			
Oxygen therapy	631 (85.7%)	195 (88.6%)	436 (84.5%)	0.141	165 (87.8%)	153 (81.4%)	0.087			
Immunoglobulin	177 (24.0%)	63 (28.6%)	114 (22.1%)	0.057	52 (27.7%)	41 (21.8%)	0.189			

Continued

Table 1 Continued

	Total patients (n=736)		Unmatched		PSM (1:1)		P value
	Hypertension (n=220)	Non-hypertension (n=516)	Hypertension (n=188)	Non-hypertension (n=188)	PSM (1:1)		
					Hypertension (n=188)	Non-hypertension (n=188)	
Mechanical ventilation							
Invasive	11 (1.5%)	8 (1.6%)	2 (1.1%)	5 (2.7%)	0.848	0.252	0.252
Non-invasive	60 (8.2%)	36 (7.0%)	17 (9.0%)	16 (8.5%)	0.074	0.855	0.855
TCM	625 (84.9%)	443 (85.9%)	157 (83.5%)	151 (80.3%)	0.278	0.421	0.421
Acupuncture	132 (17.9%)	85 (16.5%)	37 (19.7%)	40 (21.3%)	0.113	0.701	0.701
Antihypertensive	264 (35.9%)	100 (19.4%)	140 (74.5%)	41 (21.8%)	0	0	0
Antidiabetic	50 (6.8%)	28 (5.4%)	14 (7.4%)	23 (12.2%)	0.024	0.119	0.119

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; ARF, acute renal failure; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DIC, disseminated intravascular coagulation; INR, international normalized ratio; PSM, propensity score matching; PT, prothrombin time; SLE, systemic lupus erythematosus; TB, total bilirubin; TCM, traditional Chinese medicine; TT, thrombin time. It should be noted that there were 49 (35 hypertensive patients and 14 non-hypertensive patients) cases of missed chest radiation data in 736 patients with COVID-19.

in the laboratory test results for the matched subpopulations of patients between the hypertension and non-hypertension groups (almost all $p > 0.05$).

According to radiological results, except for 49 (6.7%) cases without inspection, most patients had ground-glass opacity and bilateral patchy shadowing, accounting for 61.6% and 60.0%, respectively. Additionally, hydrothorax occurred in 34 (5.0%) patients, and 63 (9.1%) patients reported unilateral patchy shadowing. It should be noted that whether or not propensity matching was performed, the radiological data showed that the incidence of hydrothorax in the hypertension group was significantly higher than that in the non-hypertension group ($p < 0.05$), although hydrothorax is less common in COVID-19.

Complications and treatments

The common serious complications in patients with COVID-19 included acute respiratory distress syndrome (ARDS), heart failure, septic shock and acute renal failure (table 1). No significant difference in the rate of occurrence of complications was observed between the hypertension and non-hypertension groups ($p > 0.05$). Once diagnosed with COVID-19, all patients received standard treatments according to the Clinical Guideline for COVID-19 Diagnosis and Treatment published by the National Health Commission of China (National Health Commission of the People's Republic of China, 2020). Table 1 demonstrates that antiviral medication (74.6%), antibacterial medication (61.1%), traditional Chinese medicine (84.9%), oxygen therapy (85.7%), glucocorticoids (31.5%), immunoglobulins (24.0%) and anti-hypertensive medication (35.9%) were the most common treatments. There was no statistically significant difference in management between the hypertension and non-hypertension groups, except for antihypertensive therapy ($p < 0.05$).

Outcomes

In table 2, among the 736 patients with COVID-19, a total of 32 patients died (mortality 4.3%), including 17 out of 220 in the hypertension group (7.7%) and 15 out of 516 in the non-hypertension group (2.9%, $p = 0.003$). After PSM, there was still a statistically significant difference in mortality between the hypertension and non-hypertension groups ($p = 0.006$). The hypertension group had a higher mortality rate than the non-hypertension group. In addition, the rate of intensive care unit (ICU) stay in the hypertension group (12.8%) was higher than that in the non-hypertension group (5.3%) ($p < 0.05$). There was no statistically significant difference between the two groups in terms of median hospital stay ($p = 0.931$).

Logistic regression was used to clarify the effects of independent variables on mortality of patients with COVID-19. Results showed that hypertension was an independent risk factor for death ($p < 0.05$), not other comorbidities before and after PSM (table 3). Kaplan-Meier plots and comparison using the log-rank test was used to analyse the influence of hypertension on survival rates. The results (figure 1) showed that the survival rates were higher in the non-hypertension group than in the hypertension group ($p < 0.05$). By the log-rank test, the mean survival times for patients with COVID-19 with non-hypertension were longer than for those with hypertension before ($\chi^2 = 7.912$, $p = 0.005$) and after ($\chi^2 = 7.228$, $p = 0.007$) PSM. In the observation period, the mean survival time for all patients with COVID-19 with or without hypertension was 80.52 days (range=78.01–83.03 days) and 87.71 days (range=86.57–88.85 days), respectively. After further adjustments for age, sex and past history (including diabetes, coronary heart disease, stroke, malignant tumour,

Table 2 Comparison of clinical outcome of patients between the hypertension and non-hypertension groups

	Total patients (n=736)	Unmatched			PSM (1:1)		
		Hypertension (n=220)	Non-hypertension (n=516)	P value	Hypertension (n=188)	Non-hypertension (n=188)	P value
Outcomes, count (%) or median (IQR)							
ICU during stay	78 (10.6%)	28 (12.7%)	50 (9.7%)	0.224	24 (12.8%)	10 (5.3%)	0.012
Mortality	32 (4.3%)	17 (7.7%)	15 (2.9%)	0.003	14 (7.4%)	3 (1.6%)	0.006
Hospitalisation time (days)	13 (9–19)	14 (10–22)	13 (8–18)	0.002	13 (9–21)	13 (9–20)	0.931

ICU, intensive care unit; PSM, propensity score matching.

chronic kidney disease, chronic obstructive pulmonary disease, asthma, heart failure, arrhythmia, bronchiectasis, systemic lupus erythematosus), non-hypertensive patients still had a significantly higher survival rate than hypertensive patients ($p < 0.05$); the mean survival time for patients with COVID-19 with or without hypertension was 72.28 days (range=69.89–74.67 days) and 78.91 days (range=77.68–80.14 days), respectively.

The relationship between ARB/ACE inhibitor exposure and clinical outcomes of hypertensive patients with COVID-19 were further analysed and compared. Table 4 shows that there was no significant difference in mortality among hypertensive patients with or without ARBs/ACE inhibitors ($p = 0.260$). Otherwise, ICU therapy and hospitalisation time were analysed and showed no statistical significance ($p > 0.05$).

The influence of ARBs/ACE inhibitor exposure on the mortality of hypertensive patients with COVID-19 was also analysed by Kaplan-Meier regression. The results showed that the risk of mortality in the ARBs/ACE inhibitor group did not differ significantly from that in the non-ARBs/ACE inhibitor group ($\chi^2 = 1.217$, $p = 0.270$).

DISCUSSION

In this retrospective study, we evaluated the association between hypertension and adverse clinical outcomes in patients with COVID-19. Our results showed that hypertension was associated with significantly increased mortality, and a similar association was observed in different subgroups after PSM removed

the interference of mismatches in the baseline data (age, sex and comorbidities). Furthermore, ARBs/ACE inhibitor treatment had no significant effect on the severity of COVID-19 and the mortality of hypertensive patients with COVID-19.

Hypertension is the leading cause of cardiovascular disease and death worldwide. Although the global average BP has decreased due to the widespread use of antihypertensive drugs, the prevalence of hypertension is still on the rise. Hypertension is also a common comorbidity in patients with COVID-19. Clinical studies have shown that it has a high incidence (30.6%–49.6%) among patients with COVID-19.^{8,9} In our study, 220 (29.9%) of these patients had a history of hypertension, which is in line with the overall trend. Although there is no reliable evidence that hypertension is associated with the risk of infection with COVID-19, several studies have suggested that it increases the risk of COVID-19 severity and COVID-19-related mortality, which is always associated with age, obesity, diabetes mellitus, cardiovascular and cerebrovascular diseases, and chronic respiratory disease.^{9,10} Our results also showed that hypertension, diabetes, coronary heart disease and stroke were common comorbidities. Among the 736 patients, the prevalence of hypertension was closely related to age and other comorbidities such as diabetes, stroke and coronary heart disease ($p < 0.05$). All of these comorbidities were found to be associated with worse clinical outcomes in patients with COVID-19, although not as independent risk factors.^{11,12} To clarify the effect of hypertension as an independent factor on COVID-19-related mortality, PSM was used to eliminate age and other comorbidities from our study.

Common symptoms of COVID-19 include fever, cough, fatigue, sputum, myalgia, headache, haemoptysis, vomiting and diarrhoea.¹³ Except for BP, there were no clinical symptoms to distinguish between hypertensive patients and non-hypertensive patients among the participants. Consistent with the report, patients with COVID-19 usually experience immune function and abnormal coagulation function imbalances.^{14,15} Compared with the non-hypertension group, impaired liver and kidney functions in the hypertension group may indicate severity and poor clinical outcomes. Studies have shown that the imaging features of COVID-19 could help in the initial diagnosis of highly suspicious cases by supplementing the results of RT-PCR. However, radiological characteristics could be used as the basis for determining the severity of pneumonia.¹⁶ Previous chest CT studies have shown typical features of pneumonia, such as peripheral ground-glass opacity, usually bilateral, with adjacent and multilobed expansion, depending on the severity of the disease.^{17–19} Our results also stated that ground-glass opacity and bilateral patchy shadowing were prevalent in radiological studies of COVID-19.

The lungs are in direct contact with the external environment, so they are the main hosts of many airborne pathogens, including coronaviruses. ARDS is the most common and severe complication of COVID-19. Mechanical ventilation (invasive or non-invasive)

Table 3 The effect of variables on mortality in the logistic regression equation

	Unmatched		PSM (1:1)	
	P value	Exp(B)	P value	Exp(B)
Age	0.325	1.014	0.553	1.014
Gender	0.240	0.645	0.095	0.393
Diabetes	0.491	1.580	0.278	2.480
Hypertension	0.034	2.329	0.009	5.554
CHD	0.449	1.578	0.212	2.465
Stroke	0.537	0.507	0.999	0.000
Cancer	0.131	3.295	0.999	0.000
CKD	0.999	0.000	0.999	0.000
COPD	0.999	0.000	0.999	0.000
Asthma	0.999	0.000	0.999	0.000
Heart failure	0.999	0.000	0.999	0.000
Arrhythmia	0.229	2.689	0.999	0.000
Bronchiectasis	0.999	0.000	–	–
SLE	1.000	0.000	–	–

CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; PSM, propensity score matching; SLE, systemic lupus erythematosus.

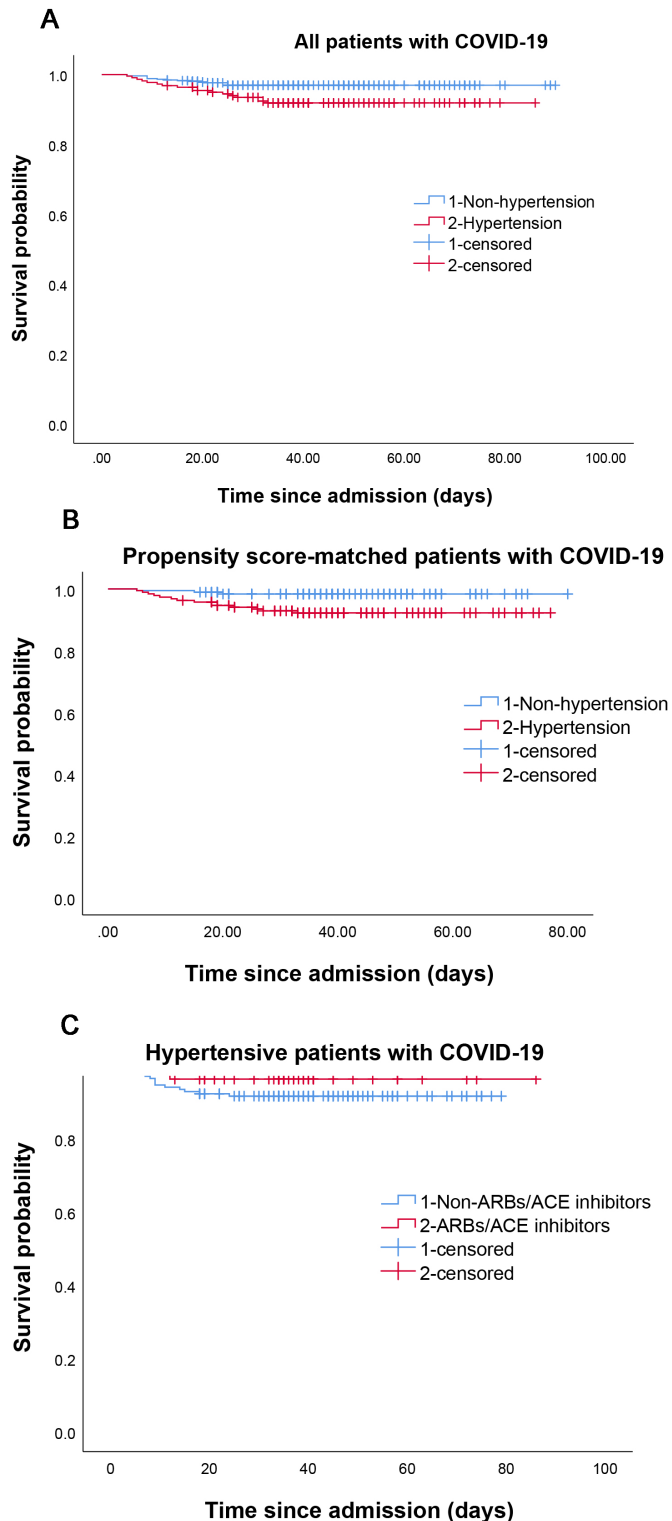


Figure 1 Kaplan-Meier regression curve analysing the relationship between hypertension or ARBs/ACE inhibitors and death due to COVID-19. (A,B) The relationship between hypertension and the risk of mortality due to COVID-19 before (A) and after (B) propensity score matching. (C) The effects of ARBs/ACE inhibitors on the risk of mortality due to COVID-19. ARB, angiotensin II receptor blocker.

is a suitable management method for respiratory failure and provides an opportunity for the treatment of critically ill patients. All patients received standard treatment according to the clinical guidelines once diagnosed with COVID-19. Traditional Chinese

Table 4 Comparison of clinical outcomes of hypertensive patients between ARBs/ACE inhibitors and non-ARBs/ACE inhibitors

	Hypertension (n=220)	ARBs/ACE inhibitors (n=53)	Non-ARBs/ACE inhibitors (n=167)	P value
Age, years	67 (58–76)	67 (59–73)	68 (58–77)	0.648
Gender, male	106 (48.4%)	28 (52.8%)	78 (47.0%)	0.459
ICU during stay	28 (12.7%)	3 (1.4%)	25 (11.4%)	0.076
Mortality	16 (7.3%)	2 (3.8%)	14 (8.4%)	0.260
Hospitalisation time (days)	14 (9–22)	14 (11–21)	14 (9–22)	0.643

ARBs, angiotensin II receptor blockers; ICU, intensive care unit.

medicine has been widely used in SARS-CoV-2 (COVID-19) as in SARS-CoV-1 and has been reported to inhibit the replication, transcription, and invasion of viruses and attenuate cytokine storms and the immune deficiency caused by infection with the virus.^{20 21} In terms of complications and treatment, there was no significant difference between the hypertension and non-hypertension groups, except for antihypertensive treatment.

To identify and treat critically ill patients as soon as possible, the factors associated with the COVID-19 severity and COVID-19-related mortality in clinical practice are of great importance. Advanced age, high sequential organ failure assessment score, medical comorbidities (hypertension, diabetes, cardiovascular disease and so on), morbid obesity, and abnormally elevated D-dimer levels were reported to help clinicians identify patients with poor prognoses at an early stage.^{22–24} To some extent, most risk factors have a combined effect on the adverse outcomes of COVID-19 rather than independent risk factors. This study aimed to analyse the role of hypertension as an independent factor in the clinical process and outcome of COVID-19. In view of the poorer baseline well-being in patients with coexisting comorbidities, it is necessary to balance the baseline data (including age and major comorbidities) of hypertensive and non-hypertensive patients. PSM reduced the effects of the potential confounding factors. Our results demonstrated that hypertension was an independent risk factor for severity and increased mortality due to pneumonia.

In addition, the administration of ARBs/ACE inhibitors to patients with COVID-19 has become an issue that requires attention. SARS-CoV-2 binds to the ACE2 receptor, which is highly expressed in lung epithelial cells and other tissues.^{25 26} Increased expression of ACE2 can facilitate viral infection and pathological inflammation. ARBs/ACE inhibitors, extensively used in hypertensive patients and patients with other cardiovascular conditions, were found to upregulate the expression of ACE2.²⁷ The continued use of ARBs/ACE inhibitors in hypertensive patients with COVID-19 has become a hot topic. Our results indicated that ARBs/ACE inhibitors had no effect on the severity and clinical outcome of patients with COVID-19, indicating that patients with COVID-19 should not discontinue ARBs/ACE inhibitors.

Our study has several limitations. As a retrospective study, it was a single-centre study, and all patients were from a hospital in Wuhan, which might have produced sample bias and narrowed down the interpretation of the conclusion. To reduce this bias, we included as many eligible cases as possible. In addition, we hope to conduct larger cohort studies or prospective randomised controlled trials to further verify our conclusions. Based on only 220 hypertensive patients among the participants, the sample size of the study on the effect of ARBs/ACE inhibitors in patients with COVID-19 was limited. Therefore, the results require further verification through future large-sample studies. Much information

about inflammatory factors and immune function was incomplete, so we could not explore the mechanism of adverse prognosis in hypertensive patients with COVID-19. Although the mechanism is still unclear, our study provides an important cautionary note for clinicians.

In conclusion, apart from age and other comorbidities, hypertension was an independent risk factor for severity and mortality in patients with COVID-19. ARBs/ACE inhibitors do not increase the risk of severity and mortality in patients with COVID-19; thus, the drugs should not be discontinued.

Main messages

- ▶ Hypertension was an independent risk factor for the severity and mortality of patients with COVID-19.
- ▶ Angiotensin II receptor blockers (ARBs)/ACE inhibitors should not be discontinued in hypertensive patients with COVID-19.

Current research questions

- ▶ Is hypertension an independent factor for the severity and mortality of COVID-19?
- ▶ Do ARBs/ACE inhibitors increase the risk of severity and mortality in patients with COVID-19?

What is already known on the subject

- ▶ In our study, the hypertensive patients with COVID-19 had a higher mortality rate than the non-hypertensive patients with COVID-19.
- ▶ The incidence of intensive care unit stay in the hypertensive patients with COVID-19 (12.8%) was higher than in the non-hypertensive patients with COVID-19 (5.3%).
- ▶ There was no significant difference in the mortality rate among hypertensive patients with COVID-19 with or without ARBs/ACE inhibitors.

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