Risk Factors and Blood Pressure Control Targets Associated With the Clinical Outcome of Elderly COVID-19 Patients With Hypertension: a Retrospective Cohort Study

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Abstract

Background: COVID-19 is a global pandemic, especially among the elderly. Our study aimed to explore the risk factors and identify the blood pressure control targets associated with the clinical outcome of elderly COVID-19 patients with hypertension.

Methods: In this retrospective cohort study, elderly COVID-19 patients who were admitted to Wuhan Huoshenshan Hospital from February 8 to 17, 2020 was included. Demographic, medical history, clinical data, and laboratory test data were collected from medical records. The adverse clinical outcomes were intensive care unit (ICU) admission and death. Difference between hypertension and non-hypertension groups were compared. Hypertension group were further divided into 3 subgroups according to their maximum blood pressures. Kaplan–Meier (K–M) method was used to find the differences both between hypertension and non-hypertension groups, and among the 3 hypertension subgroups. Univariable and multivariable Cox proportional hazards regression model were used to find risk factors.

Results: All 133 elderly COVID-19 patients (79 patients with hypertension) were included. (1) Univariate analysis between hypertension and non-hypertension patients showed most laboratory tests were significantly ($P < 0.05$, or $P < 0.01$), particularly in adverse clinical outcomes (32.91% vs 7.41% at 30 days, $P < 0.05$). (2) Multivariate Cox proportional hazards models confirmed hypertension (HR 3.202, 95% CI: 1.164 - 8.807) were the most important independent risk factors of outcomes in elderly patients, as well as low lymphocyte count, while the statistical difference of other values diminished. (3) Hypertension group were further divided into 3 subgroups according to their maximum blood pressures. K-M analysis showed maximum systolic blood pressure (SBP) ≥ 160 mmHg subgroup ($P < 0.01$) and maximum blood pressure (DBP) ≥ 90 mmHg subgroup ($P < 0.05$) experienced more adverse outcomes than others. (4) Multivariate Cox-proportional hazard model confirmed that maximum SBP ≥ 160 mmHg and maximum DBP ≥ 90 mmHg were risk factors (HR 8.279, 95% CI: 1.346, 50.914; HR 5.080, 95% CI: 1.606, 16.071; respectively).

Conclusions: Hypertension is the most important independent risk factor of adverse outcomes in elderly COVID-19 patients, controlling the maximum blood pressure levels under 160/90 mmHg will decrease large part risks of adverse outcomes, the first week are key treatment period for patient prognosis.

Background

Coronavirus disease-2019 (COVID-19) is a life-threatening infection caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus(1). It has caused billions infections and millions deaths(2, 3). Based on the global pandemic of COVID-19, it has become critical to study the risk factors of clinical prognosis.

It has been previously reported that patients with older age and chronic underlying conditions might have a high risk of experiencing intensive care and death. Moreover, current clinical data suggest that, in COVID-19 patients, hypertension can worsen outcomes and increase the risk of admission to intensive

care unit (ICU) (4). Previous clinical trials showed that SARSCoV-2 enters cells through angiotensin-converting enzyme 2 (ACE2) receptors(5); high blood pressure is likely to increase COVID-19 mortality by affecting lung function and impairing oxygen delivery(6). As the COVID-19 pandemic progresses, the high incidence of hypertension makes this problem particularly worrying. However, it is not clear whether the mortality of COVID-19 patients with hypertension is related with the level of blood pressure control(7); there is a lack of detailed prognosis studies of hypertension at different blood pressure levels; even not to say few studies have explicitly identified blood pressure control cut-off points in hypertension comorbidities(8).

Thus, in this study, we aim to report the correlation between hypertension and COVID-19 adverse outcomes in elderly hypertensive population, and try to found the risk factors and the control cut-off value for elderly hypertension population.

Methods

Study design and participants

This single-center, retrospective cohort study was conducted at the Huoshenshan Hospital in Wuhan, which was approved by the Institutional Ethics Committee of Huoshenshan Hospital (HSSLL030). Considering the urgency of the COVID-19 pandemic, the need for informed consent forms were waived by the ethics board of the hospitals. All participants included in the study were diagnosed with COVID-19 who were hospitalized at Huoshenshan Hospital from February 8 to 17, 2020. According to the World Health Organization's temporary guidelines, COVID-19 was diagnosed based on SARS-CoV-2 nucleic-acid swab test and/or chest computed tomography (CT) scanning (the criteria of the New Coronavirus Pneumonia Prevention and Control Program, sixth edition, National Health Commission of China, 2020(9)).

Data collection

By reviewing electronic medical records, we obtained medical history, demographic data, signs and symptoms, laboratory tests, and chest CT scans. The outcomes were followed up until March 29, 2020. The adverse clinical outcomes were intensive care unit (ICU) admission and death. The clinical characteristics, laboratory tests, incidence of complications were monitored. All data were checked by another researcher to ascertain their accuracy and were analysed by an integrated research team which includes physicians and statisticians.

Definitions

All patients with COVID-19 met the following criteria: (1) fever and/or other typical respiratory symptoms, (2) typical CT image manifestations of viral pneumonia, and (3) positive SARS-COV-2 RNA by reverse

transcription-polymerase chain reaction (RT-PCR) and/or gene diagnosis. And severe COVID-19 patients met the following criteria: (1) respiratory distress, with respiratory rate ≥ 30 beats/min, (2) finger oxygen saturation $\leq 93\%$ at rest, and (3) ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ($\text{PaO}_2:\text{FiO}_2$) ≤ 300 mmHg.

Hypertension was designated based on the patient's medical history and guideline for diagnosis according to their blood pressure level at admission (higher than 140/90 mmHg). Patients with transient hormone-induced hypertension in the ICU were not included in the hypertension group. Blood pressure of patient were all measured and recorded several times depending on the patient's condition, the classification of hypertension made depending the 2020 International Society of Hypertension Global Hypertension Practice Guidelines(10). Maximum blood pressure, minimum blood pressure, pulse pressure and mean arterial pressure were all extracted based from the above data. Diabetes, cardiac injury, acute liver injury, and acute kidney injury status were designated based on the patient's medical history and guideline for diagnosis(11).

Statistical analysis

Our statistical analyses were conducted with SPSS (version 26.0) and GraphPad Prism (version 8.0) software. We made no assumptions regarding missing data. Categorical variables are described as frequency rates and percentage (%). Continuous variables are described as mean $\pm$ standard deviation (SD) or median (interquartile range (IQRs)). We used the Student's t-tests (normally distributed) or Mann Whitney test (non-normally distributed) for continuous variables between two groups, and used the Fisher's exact test or χ^2 test for categorical variables between two groups. To explore the risk factors associate with adverse clinical outcomes, univariable and multivariable Cox proportional hazards regression model was performed. All the variables included in the final models were based on clinical and scientific understanding, previous findings, and the results of univariable analyses. We divided the hypertension group into different blood pressure subgroups according to the latest guideline and analyzed the composition ratio of each subgroup. Kaplan–Meier (K–M) method was further used to find the best blood pressure control level in the COVID-19 hypertension group. A two-sided P value ,0.05 was considered statistically significant.

Results

Population

A total of 180 patients were initially screened for the study, and 47 patients younger than 60 years old were excluded. According to the clinical diagnosis and/or medical history on admission, the 133 patients were divided into two groups: hypertension patients (n = 79) and non-hypertension patients (n = 54) (Fig. 1). A total of 36 (27.1%) patients were defined as adverse clinical outcomes, including ICU admission (n = 34, 25.6%) and in-hospital death (n = 16, 12.0%, of which 14 had overlapping with ICU patients).

The difference of general conditions between hypertension and non-hypertension patients

The median age was 68 years (IQR, 64–73 years) and 68 cases (51.1%) were male in this study (Table 1). Hypertension (n = 79, 59.4%), diabetes (n = 57, 42.9%), and coronary atherosclerotic heart disease (n = 18, 13.5%) were the three most common comorbidities. Cough (n = 114, 85.7%), fever (n = 109, 82.0%), and shortness of breath (n = 88, 66.2%) were the three most common symptoms (Table 1).

Table 1
Demographics and symptomatic characteristics of patients with COVID-19

	Total (n = 133)	Hypertension (n = 79)	Non-hypertension (n = 54)	P value
Age, median (IQR)	68(64–73)	69(64–75)	67(63–71)	0.122
Gender				0.221
Male	68(51.1%)	44(55.9%)	24(44.4%)	
Female	65(48.9%)	35(44.3%)	30(55.6%)	
Smoking history	9(7.1%)	8(10.8%)	1(1.9%)	0.062
Cluster disease	11(8.3%)	7(8.9%)	4(7.4%)	0.765
Diagnosis method				0.119
RT-PCR	114(85.7%)	65(82.3%)	49(90.6%)	
Gene	1(0.8%)	0(0.0%)	1(1.9%)	
Clinical diagnosis	18(13.5%)	14(17.7%)	4(7.4%)	
Comorbidities				
Hypertension	79(59.4%)	79(100.0%)	0(0.0%)	/
Diabetes	57(42.9%)	41(51.9%)	16(29.6%)	0.013
CHD	18(13.5%)	13(16.5%)	5(9.3%)	0.233
Cerebrovascular disease	10(7.5%)	8(10.1%)	2(3.7%)	0.168
Liver disease	3(2.3%)	2(2.5%)	1(1.9%)	0.795
Kidney disease	5(3.8%)	4(5.1%)	0(0.0%)	0.407
COPD	4(3.0%)	2(2.5%)	2(3.7%)	0.698
Malignancy	7(5.3%)	4(5.1%)	3(5.6%)	0.901
Signs and symptoms				
Fever	109(82.0%)	62(78.5%)	47(87.0%)	0.255
Cough	114(85.7%)	70(88.6%)	44(81.5%)	0.249
Expectoration	23(17.3%)	19(24.1%)	4(7.4%)	0.013
Rhinorrhoea	3(2.3%)	1(1.3%)	2(3.7%)	0.325
Haemoptysis	1(0.8%)	1(1.3%)	0(0.0%)	0.407
Shortness of breath	88(66.2%)	54(68.4%)	34(63.0%)	0.519

	Total (n = 133)	Hypertension (n = 79)	Non-hypertension (n = 54)	P value
Fatigue	86(64.7%)	46(58.2%)	40(74.1%)	0.060
Myalgia	52(39.1%)	24(30.4%)	28(51.9%)	0.013
Diarrhoea	13(9.8%)	9(11.4%)	4(7.4%)	0.447
Nausea and vomiting	12(9.0%)	8(10.1%)	4(7.4%)	0.447
Arrhythmias	8(6.0%)	6(7.6%)	2(3.7%)	0.354
Palpitation	4(3.0%)	2(2.5%)	2(3.7%)	0.698
Dizziness	5(3.8%)	4(5.1%)	1(1.9%)	0.339
Headache	4(3.0%)	1(1.3%)	3(5.6%)	0.155
Abbreviation: IQR, interquartile range; RT-PCR, reverse transcription-polymerase chain reaction; CHD, coronary atherosclerotic heart disease; COPD, chronic obstructive pulmonary diseases				

There was no difference in age, gender, smoking history and diagnostic methods between hypertension and non-hypertension patients ($P > 0.05$). Among all comorbidities, only diabetes had a statistically significant difference between hypertension and non-hypertension patients ($P < 0.01$). Of all the symptoms recorded, only expectoration and myalgia had statistically significant differences between hypertension and non-hypertension patients ($P < 0.01$) (Table 1).

The difference of clinical laboratory between hypertension and non-hypertension patients

Except c-reactive protein (CRP) and D-dimer, mean levels of other indices of the 133 patients were in normal range (Table 2). All BG indices, kidney function (urea nitrogen, BUN), nutrition (albumin), myocardial enzyme (creatine kinase-MB, lactate dehydrogenase), inflammatory indices (CRP, white blood cell count, neutrophil percentage, neutrophil count, lymphocyte percentage), hemoglobin, coagulation indices (prothrombin time, PT) were significantly higher in hypertension patients than non-hypertension patients ($P < 0.05$). Other blood routine examination (lymphocyte count et al.) and biochemical detection (liver function et al.) in the hypertension group were inferior to the non-hypertension group ($P < 0.05$) (Table 2).

Table 2

Laboratory parameters of patients with COVID-19

	Reference values	Total (n = 133)	Hypertension (n = 79)	Non-hypertension (n = 54)	P value
Blood glucose					
Maximum BG, median (IQR), mmol/L	3.9–6.11	5.61(4.93-14.40)	9.06(5.06-17.20)	5.16(4.80-7.28)	0.001
Average BG at the day of admission, median (IQR), mmol/L	3.9–6.11	5.38(4.80-8.86)	7.07(4.84-11.04)	5.06(4.71-7.28)	0.005
Biochemical detection					
Total protein, median (IQR), g/L	65–85	61.10(57.35-65.65)	60.90(57.20-63.90)	61.40(58.35-67.15)	0.245
ALT, median (IQR), IU/L	7–40	23.95(16.55-41.00)	23.90(17.40-41.00)	24.20(15.40-41.05)	0.753
AST, median (IQR), IU/L	7–45	23.30(16.75-34.15)	24.60(18.40-37.05)	21.90(15.25-28.20)	0.070
Albumin, median (IQR), g/L	40–55	33.40(30.30-36.60)	32.90(29.40-36.30)	34.15(30.96-37.55)	0.042
BUN, median (IQR), mmol/L	2.6–7.5	5.12(4.05-6.85)	5.75(4.33-8.34)	4.60(3.82-5.62)	□ 0.001
Creatinine, median (IQR), μmol/L	41–73	67.45(56.78-80.75)	68.90(58.13-83.53)	64.15(54.05-74.28)	0.080
Uric acid, median (IQR), μmol/L	142–340	258.00(190.50-329.00)	273.00(180.00-341.00)	233.00(199.00-303.50)	0.410
Total bile acid, median (IQR), μmol/L	0–10	3.75(2.53-5.60)	4.30(2.50-6.05)	3.50(2.70-5.50)	0.331
Creatine kinase, median (IQR), IU/L	24–170	43.20(29.15-72.80)	44.60(31.30-74.70)	40.60(26.60-65.80)	0.171
Creatine kinase-MB, median (IQR), IU/L	0–24	10.00(7.05-12.95)	10.80(8.15-14.25)	7.95(6.13-11.65)	□ 0.001
LDH, median (IQR), IU/L	120–250	212.80(173.93-326.55)	257.80(185.05-382.50)	190.70(167.15-250.45)	□ 0.001
Inflammatory indices					
CRP, median (IQR), mg/L	0–4	8.97(2.41-53.58)	16.03(2.71-81.70)	6.37(1.96-21.00)	0.021
Blood routine examination					

White blood cell count, median (IQR), $\times 10^9/L$	3.5–9.5	6.35(4.70-8.35)	6.90(5.20-9.00)	5.70(4.15-7.25)	0.011
Neutrophil percentage, mean $\pm$ SD, %	40–75	70.15 $\pm$ 14.67	70.97 $\pm$ 15.05	65.95 $\pm$ 12.98	0.021
Lymphocyte percentage, mean $\pm$ SD, %	20–50	20.85 $\pm$ 12.02	19.90 $\pm$ 11.91	23.99 $\pm$ 11.78	0.023
Neutrophil count, median (IQR), $\times 10^9/L$	1.8–6.3	4.55(2.85-6.77)	5.15(3.30-7.21)	3.63(2.32-5.45)	□ 0.001
Lymphocyte count, median (IQR), $\times 10^9/L$	1.1–3.2	1.18(0.75-1.64)	1.08(0.65-1.60)	1.24(0.94-1.67)	0.170
Monocyte count, mean $\pm$ SD, $\times 10^9/L$	0.1–0.6	0.47 $\pm$ 0.23	0.47 $\pm$ 0.20	0.47 $\pm$ 0.20	0.920
Eosinophil count, median (IQR), $\times 10^9/L$	0.02–0.52	0.06(0.03-0.12)	0.05(0.02-0.12)	0.06(0.03-0.11)	0.689
Hemoglobin, mean $\pm$ SD, g/L	130–175	121.59 $\pm$ 17.75	125.19 $\pm$ 18.49	120.03 $\pm$ 12.95	0.025
Platelet count, mean $\pm$ SD, $\times 10^9/L$	125–350	242.02 $\pm$ 94.16	228.30 $\pm$ 92.87	242.39 $\pm$ 93.06	0.195
Coagulation indices					
PT, median (IQR), seconds	9.2–15	13.32(12.44-14.38)	13.73(12.61-14.99)	13.12(12.10-13.85)	0.012
APPT, median (IQR), seconds	21–37	27.96(25.60-30.19)	28.15(25.59-30.15)	27.65(25.65-30.38)	0.586
D-dimer, median (IQR), mg/L	0–0.55	0.78(0.45-2.90)	0.82(0.50-2.76)	0.70(0.37-2.91)	0.384
Abbreviation: IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, urea nitrogen; LDH, lactate dehydrogenase; CRP, C-reactive protein; PT, prothrombin time; APPT, activated partial thromboplastin time					

The difference of adverse clinical outcomes between hypertension and non-hypertension patients

There were 49.4% hypertension patients with mild to moderate symptoms and 50.6% with severe symptoms, compared to the 88.9% non-hypertension patients with mild to moderate symptoms and 11.1% with severe symptoms (Fig. 2A a-b). K-M analysis were performed to calculate the percent of clinical outcomes between hypertension group and non-hypertension group. At the last follow-up visit, 31 patients in the hypertension group (39.2%, in which 24.0% of on death in ICU and 15.2% of death) and 5 in the non-hypertension group (9.3%, in which 1.9% of on death in ICU, 7.4% of death) had adverse clinical

outcomes (Fig. 2A c-d), and the overall clinical outcomes rates in the two groups differed significantly on the basis of the stratified log-rank test. It showed 32.91% (at 30 days) and 39.24% (at 60 days) adverse clinical outcomes in hypertension patients, compared to the 7.41% (at 30 days) and 9.26% (at 60 days) in non-hypertension patients. The adverse event in hypertension patients began to increase sharply at about 5 days and relaxed after 30 days. And it reached the platform at about 45 days (Fig. 2B).

Risk factors of adverse clinical outcomes in elderly COVID-19 patients

Univariate Cox hazard analysis was used to screen for statistically significant variables associated with adverse clinical outcomes. In the total population, hypertension (HR 4.937) and diabetes (HR 5.821) were the most significantly two risk factors related with adverse clinical outcomes. Average BG, BUN, neutrophil percentage, neutrophil count, maximum BG, white blood cell count, PT were the following 8 risk factors with HR range from 1.085–1.154 (Table 3). The Cox hazard analysis also showed that the top 10 risk factors of univariate Cox analysis in hypertension group were the same with that of total population only different in rank order (Table 3). Multivariate Cox-proportional hazard model analysis was conducted to further certify whether above variables got from univariate Cox affected patient clinical outcomes independently. The results demonstrated hypertension was the most important independent factor that relates with higher adverse clinical outcomes (HR 3.202, 95% CI:1.164–8.807; Fig. 3); and other significantly risk factors include low lymphocyte count, hemoglobin, CRP, LDH and platelet count.

Table 3. Univariate Cox hazard analysis to further certify whether variables affected patient clinical outcomes (Only if P < 0.05 is listed in the table)

Factors	Total (N=133)			Hypertension (N=79)			Non-hypertension (N=54)		
	Rank	HR	P value	Rank	HR	P value	Rank	HR	P value
Age	11	1.051	0.017	/	/	/	8	1.180	0.024
Hypertension	2	4.937	0.001	/	/	/	/	/	/
Diabetes	1	5.821	<0.001	1	3.863	0.002	1	10.904	0.033
Cerebrovascular disease	/	/	/	/	/	/	18	0.105	0.044
[Average BG]	3	1.154	<0.001	5	1.103	0.005	5	1.302	0.010
Maximum BG	8	1.116	<0.001	7	1.085	<0.001	7	1.182	0.007
Maximum SBP	14	1.032	<0.001	13	1.022	0.005	10	1.052	0.020
Maximum DBP	13	1.037	<0.001	11	1.024	0.044	/	/	/
Total protein	21	0.943	<0.001	19	0.953	0.010	15	0.915	0.008
AST	16	1.019	0.002	14	1.016	0.012	/	/	/
Albumin	22	0.904	<0.001	20	0.922	<0.001	16	0.816	0.060
BUN	5	1.136	<0.001	2	1.125	0.003	/	/	/
Creatine kinase	19	1.003	<0.001	17	1.002	0.013	11	1.028	0.015
Creatine kinase-MB	12	1.049	<0.001	10	1.032	0.021	9	1.168	0.007
LDH	18	1.007	<0.001	16	1.006	<0.001	13	1.009	0.001
CRP	17	1.014	<0.001	15	1.011	<0.001	11	1.028	<0.001
White blood cell count	9	1.097	<0.001	9	1.069	0.005	3	1.416	0.009
Neutrophil percentage	6	1.128	<0.001	4	1.104	<0.001	4	1.305	0.008
Lymphocyte percentage	23	0.862	<0.001	21	0.884	<0.001	17	0.639	0.031
Neutrophil count	7	1.121	<0.001	6	1.092	<0.001	2	1.501	0.001
Lymphocyte count	24	0.069	<0.001	22	0.134	<0.001	19	0.002	0.003
Hemoglobin	15	1.025	0.012	11	1.024	0.025	/	/	/
Platelet count	20	0.993	<0.001	18	0.995	0.010	14	0.983	0.009
PT	10	1.085	<0.001	8	1.078	<0.001	/	/	/
D-dimer	4	1.143	<0.001	3	1.123	<0.001	6	1.186	0.007

Abbreviation: BG, blood glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, urea nitrogen; LDH, lactate dehydrogenase; CRP, C-reactive protein; PT, prothrombin time

The cut-off value of blood pressure related with adverse clinical outcomes in elderly hypertension COVID-19 patients

The hypertension population were divided into 3 subgroups according to their blood pressure level. 40.5% had a maximum SBP of higher than 160mmHg; and 49.4% had a maximum DBP of higher than 90mmHg. (Fig. 4A).

Significant difference of clinical outcomes could be seen among different SBP subgroups in the hypertensive group. The difference of overall clinical outcomes was not statistically between the SBP (1) subgroup and the SBP (2) subgroup ($P = 0.412$ by the log-rank test), but was statistically between the SBP (1) subgroup and the SBP (3) subgroup ($P = 0.002$ by the log-rank test). There were 11.11% (at both 30 days and 60 days) cases with adverse clinical outcomes in SBP subgroup (1), 13.79% (at 30 days) and 20.69% (at 60 days) cases in SBP subgroup (2), 53.12% (at 30 days) and 71.87% (at 60 days) cases in SBP subgroup (3). At the same time, the difference of overall clinical outcomes between the DBP (1) subgroup and the DBP (2) subgroup ($P = 0.005$ by the log-rank test) or the DBP (3) subgroup ($P = 0.02$ by the log-rank test) was statistically. There were 17.50% (at 30 days) and 22.50% (at 60 days) patients with adverse clinical outcomes in the DBP subgroup (1), 47.83% (at 30 days) and 52.17% (at 60 days) patients in the DBP subgroup (2), 37.5% (at 30 days) and 62.5% (at 60 days) patients in the DBP subgroup (3). The difference among maximum SBP and DBP subgroups all increased sharply at about 5 days and continued over time, the increase was most pronounced at 30 days, and reached the platform at about 45 days (Fig. 4B).

The results of multivariate Cox-proportional hazard model analysis showed that maximum SBP (3), maximum DBP (2) and maximum BG were the independent risk factors of adverse clinical outcomes in hypertension population (Fig. 4C).

Discussion

Our study provides the clinical characteristics of elderly concerning the role of comorbidities in the setting of COVID-19. Similar to the previously reported results, hypertension, diabetes, and cardiovascular diseases are the most frequent comorbidities(7, 11, 12). However, in our cohort, patients with hypertension reach 59.4% (79 of 133), 27.1% of total patients and 39.2% of the hypertension group have adverse clinical outcomes, which are higher than other studies(13). This might because the Huoshenshan Hospital prefers to treat severely ill patients and all enrolled cases are elderly in our study.

K-M analyze, univariate and multivariate Cox hazard analysis in the total patients confirmed that hypertension is the most independent risk factor of developing adverse clinical outcome in elderly COVID-19 patients, which consistent with previous research(14, 15). The pathophysiologic mechanisms are generally believed to be the following two aspects: a critical interaction between SARS-CoV-2 and the angiotensin-converting enzyme 2(ACE2) (16, 17); the hypotension medicines which act on ACE2(18, 19). Our study shows that the percentage of good outcomes in hypertension decreases 50% and the risk of adverse outcomes increases more than 3 times. COVID-19 patients with hypertension should be given additional attention to prevent worsening of their clinical outcomes(4, 18). Instruction of blood pressure control in hypertensive patients is very important for clinical treatment of COVID-19.

We identify that among the many blood pressure indexes, the maximum systolic and diastolic blood pressure are independent risk factors. Further multivariate Cox-proportional hazard model indicates that maximum blood pressure $\geq 160/90$ mmHg is associated with increased adverse clinical outcomes in

hypertension group. Former studies also suggest that low and stable BP are optimal to achieve a favorable prognosis for COVID-19 patients with coexisting hypertension(19–21), but no exact treatment target was put forward. Only a Spanish study showed that admission SBP < 120 and ≥ 140 mmHg was a predictor of higher all-cause mortality compared to SBP between 120-140mmHg(8). Our study shows a brand-new evidence for hypertension COVID-19 patients' treatment: it is no more benefit to strictly control blood pressure lower than 160/90 mmHg to the completely normal range.

The other highlight of our study is the treatment time point in COVID-19 patients with hypertension. The good outcomes in higher hypertension group of $\geq 160/90$ mmHg decrease sharply after the first week, then reached about 50% at one month, 50–70% at the second month, the effect of SBP plays more important role than DBP. Thus, we believe that early blood pressure control in elderly COVID-19 cases with hypertension was important for the clinical prognosis of disease.

Our research reveals several other prognostic factors in elderly COVID-19 patients with hypertension. (1) In addition to blood pressure, the most effective factor in the progression of COVID-19 hypertension patients in this cohort was maximum BG value, which was out of our expectation. This may be because the maximum BG value presents the worst pancreatic conditions and makes infection difficult to control(11, 22). (2) PT level was also an important risk factor for clinical outcome of elderly COVID-19 cases with hypertension, while D- dimer is not mentioned in our study. Some studies suggest mild increases in PT are reminiscent of thrombotic microangiopathy(23–25). (3) CRP level was related to the adverse outcomes of COVID-19 patients, which associated with cytokine storms caused by virus invasion. In the systemic hyperinflammation phase of COVID-19, there is a significant elevation of inflammatory cytokines and biomarkers, which may lead to cardiopulmonary collapse and multi-organ failure(26, 27). (4) Hemoglobin level and platelet count were related to the adverse outcomes of COVID-19 patients. Thrombocytopenia was resulting from the consumption and/or the reduced production of platelets in damaged lungs. Anemia was not observed notably, but the decrease in hemoglobin was frequent(28, 29). (5) In this analysis, age was not included in the risk factors after adjustment for confounders, which might be because patients were all elderly, and the age span was relatively small.

Our study has the following limitations. First, the sample size of the study was small, especially in the non-hypertensive group. Second, due to the retrospective study design, the absence of ambulatory blood pressure monitoring results in all patients has limited the analysis of blood pressure control. Third, we did not have access to the data of patients before admission, so we were unable to evaluate the patient's previous blood pressure control. Fourth, patients admitted to Huoshenshan hospital were generally more serious, which made our study had an unavoidable selective bias.

Conclusions

In summary, hypertension is the most important independent risk factor of adverse outcomes in elderly COVID-19 patients, controlling the maximum blood pressure levels under 160/90 mmHg will decrease large part risks of adverse outcomes, the first week are key treatment period for patient prognosis.

Abbreviations

COVID-19 = coronavirus disease 2019

HR = hazard ratio

CI = confidence interval

SBP = systolic blood pressure

DBP = diastolic blood pressure

SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2

ACE2 = angiotensin-converting enzyme 2

RAAS = renin-angiotensin-aldosterone system

CT = computed tomography

RT-PCR= reverse transcription-polymerase chain reaction

ICU = intensive care unit

SD = standard deviation

IQR = interquartile range

CRP = C-reactive protein

BUN = blood urea nitrogen

LDH = lactate dehydrogenase

PT = prothrombin time

BG= blood glucose

ACE = angiotensin-converting enzyme

ACEI = angiotensin-converting enzyme inhibitors

ARB = angiotensin receptor blockers

Declarations

1. Ethics approval and consent to participate

Our study was conducted at the Huoshenshan Hospital in Wuhan, which was approved by the Institutional Ethics Committee of Huoshenshan Hospital (HSSLL030).

2. Consent for publication

Not applicable.

3. Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

4. Competing interests

Not applicable.

5. Funding

Not applicable.

6. Authors' contributions

MW responded to the care of the patient. MW, LW, and YG were involved in the diagnosis, management, and treatment. MW and LW collected the data. TL, PZ and YW explained the data. YG, TL and CL designed the study. JZ and YW conducted the analysis. JZ and TL reviewed the relevant papers. YG, TL, and CL wrote the first draft. All authors contributed equally to writing the manuscript.

7. Acknowledgements

Not applicable.

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Figures

Figure 1

Diagram of study inclusion criteria

A

B

Figure 2

The difference of adverse clinical outcomes between hypertension and non-hypertension patients. A a: clinical classification in hypertension, b: clinical classification in non-hypertension, c: clinical outcomes in

hypertension, d: clinical outcomes in non-hypertension B: Kaplan-Meier Analysis of the percent of good clinical outcomes between hypertension and non-hypertension cases. Abbreviation: ICU, intensive care unit

Figure 3

The multivariate Cox-proportional hazard model analysis to further certify whether variables affected patient clinical outcomes in the total population

Figure 4

The cut-off value of blood pressure related with adverse clinical outcomes in elderly hypertension COVID-19 patients. A a: the hypertension population were divided into 3 subgroups according to their maximum SBP, b: the hypertension population were divided into 3 subgroups according to their maximum DBP. B Kaplan-Meier Analysis of the percent of good clinical outcomes between different blood pressure subgroups. a: Maximum SBP in the hypertension group, b: Maximum DBP in the hypertension group. C

The multivariate Cox-proportional hazard model analysis to further certify whether variables affected patient clinical outcomes in the hypertension group