Blood Pressure Control and Adverse Outcomes of COVID-19 Infection in Patients with Coexisting Hypertension in Wuhan, China

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Abstract

Hypertension was a common comorbidity in hospitalized patients with COVID-19 infection. This study aimed to estimate the risks of adverse events associated with in-hospital blood pressure (BP) control and the effects of angiotensin II receptor blockers (ARB) prescription, in COVID-19 patients with coexisting hypertension. In this retrospective cohort study, the anonymized medical records of COVID-19 patients were retrieved from an acute field hospital in Wuhan, China. Clinical data, drug prescriptions, and laboratory investigations were collected for individual patients with diagnosed hypertension on admission. Cox proportional hazards models were used to estimate the risks of adverse outcomes associated with BP control during the hospital stay. Of 803 hypertensive patients, 67 (8.3%) were admitted into ICU, 30 (3.7%) had respiratory failure, 26 (3.2%) heart failure, and 35 (4.8%) died. After adjustment for confounders, the significant predictors for heart failure were average systolic blood pressure (hazard ratios (HR) per 10 mmHg 1.89, 95% CI: 1.15, 3.13) and pulse pressure (HR per 10 mmHg 2.71, 95% CI: 1.39, 5.29). The standard deviations of systolic and diastolic blood pressure were independently associated with mortality and ICU admission. The risk estimates of poor BP control were comparable between patients receiving ARB and those without, with the only exception of a high risk of heart failure in the non-ARB group. Poor BP control was independently associated with higher risks of adverse outcomes of COVID-19. ARB drugs did not increase the risks of adverse events in hypertensive patients.

Keywords: COVID-19; hypertension; heart failure; intensive care unit; mortality

Introduction

Early investigations on clinical characteristics of patients with COVID-19 infection have found that comorbidities significantly increased the risk of clinical severity such as mortality, ICU admission and mechanical ventilation [1-5]. One of the most common comorbidities in COVID-19 patients was hypertension, with the range of 16.9-31.2% in the hospitalized patients in China [3,5,6]. Hypertension was also the most common comorbidity in ICU patients in Lombardy, Italy (49%) and hospitalized COVID-19 patients in New York, the US (56.6%) [7,8]. The mechanism of exacerbation of underlying conditions remains unclear, and the experts worldwide have called for in-depth analysis on blood pressure control of hypertension patients during clinical course of COVID-19 [9].

The mechanisms of exacerbation of underlying cardiovascular conditions after COVID-19 infection remain unclear. One of the most cited hypotheses is over expression of angiotensin converting enzyme II (ACE2) in arterial endothelial and smooth muscle cells. A recent experiment study demonstrated the elevated levels of ACE2 in the cardiomyocytes of patients with heart diseases [10]. Similar to SARS-CoV, the causal pathogen of COVID-19, SARS-CoV-2 virus, also targeted on ACE2 receptors as entry points to human host cells [11,12]. ACE2 and ACE2 receptors play important roles in the renin–angiotensin–aldosterone system (RAAS), and the RAAS inhibitors have been widely used as anti-hypertension drugs. Two of these RAAS inhibitors, angiotensin II receptor blockers (ARB) and ACE inhibitors (ACEI), have caused great concerns due to their direct interactions with ACE2 and ACE2 receptors [13]. ARB/ACEI have been widely recommended as antihypertensive drugs in patients with both hypertension and diabetes mellitus (DM). It is of note DM was the second most common comorbidity found in hospitalized patients with COVID-19 [3]. As a result,

concerns have been raised that ARB and ACEI drugs could result in overexpression of ACE2 to facilitate virus entry, and thereby increasing the susceptibility and clinical severity of COVID-19 infection [14]. However, theoretically ACE2 could also degrade angiontensin II to protect the host from severe lung injury, based on the animal experiments of SARS-CoV [15]. To date, evidence is rather limited to support the harmful effects of ARB and ACEI drugs on COVID-19 patients with hypertension.

Besides average levels of systolic and dialytic blood pressure, blood pressure variability (BPV) has also been positively associated with high risks of morbidity and mortality in patients with hypertension. Recent studies also suggested high BPV could predict a high risk of organ damages, cardiovascular events, all-cause and cardiovascular mortality independent of mean BP, in patients with hypertension or cerebrovascular disease [16,17]. Taken together, there is an urgent need to evaluate the optimal control of blood pressure and the effect of ARB and ACEI drugs in hypertensive patients with COVID-19 infection.

Material and Methods

Data sources

In this retrospective cohort study, the anonymized individual medical records during 4 February (admission of the first patient) to 31 March 2020 were retrieved from the electronic database of the Huoshenshan hospital, an acute field hospital built in Wuhan in response to the COVID-19 outbreak [18].

COVID-19 infection diagnosis and classification

The diagnosis and classification of COVID-19 infection followed the guideline by the National Health Commission of China [19]. Patients were confirmed with COVID-19 infection if tested positive in the RT-PCR for SARS-CoV-2 virus in throat or nasal swabs, or tested positive for both IgM and IgG in serum SARS-CoV-2 antibody tests.

The tests were conducted using standard kits by the Sansure Biotech Inc., Hunan, China. COVID-19 patients were divided into four types by their symptoms and chest CT imaging according to the national guideline: 1) mild cases, with mild respiratory symptoms but no signs of pneumonia in chest X-ray or CT imaging; 2) moderate cases, with respiratory symptoms and signs of pneumonia in chest X-ray or CT imaging; 3) severe cases, with one of the following symptoms: respiratory rate $\geq$ 30/min, $SpO_2 \leq$ 93%, $PaO_2/FiO_2 \leq$ 300 mmHg; 4) critical cases, with one of the following symptoms: respiratory failure in the need of mechanical ventilation; shock; ICU admission for other organ failures.

Hypertension definition and measurements for blood pressure

Hypertension status was defined according to the self-reported medical history for each patient. Their blood pressure was also measured by nurses using mercury blood pressure monitor, usually twice per day (in mornings and afternoons) after admission. The target of hypertension control during hospitalization was set to systolic blood pressure (SBP)/diastolic blood pressure (DBP) < 140/90 mmHg, according to the 2018 ESC/ESH guideline and the 2020 ISH guideline [20,21]. Patients were classified as poor BP control if either the average in-hospital SBP $\geq$ 140 mmHg or the average in-hospital DBP $\geq$ 90 mmHg. Patients were classified as good BP control if both the average in-hospital SBP < 140 mmHg and the average in-hospital DBP < 90 mmHg. Blood pressure variability (BPV) was calculated by standard deviation (SD) of daily mean SBP/DBP during hospitalization [16]. Mean arterial pressure (MAP) and pulse pressure (PP) were derived from average SBP and DBP using standard formulas.

Outcomes and confounding factors

We retrieved from the medical records for the incidence and dates of disease outcomes of individual patients. The selected adverse outcomes include mortality, ICU

admission, respiratory failure, heart failure. The confounding factors were also retrieved, including age, sex, disease severity status, smoking (current smoker *vs* ever/never/unknown), drinking (current drinker *vs* ever/never/unknown), comorbidities such as cancer, diabetes, coronary heart disease, cerebrovascular disease, chronic obstructive pulmonary diseases (COPD), chronic liver disease and chronic kidney disease. Respiratory failure was defined as arterial partial pressure of oxygen < 60 mmHg and/or arterial partial pressure of carbon dioxide > 50 mmHg during rest. The diagnosis of heart failure followed the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [22]. The diagnosis of heart failure could be made, if patients fulfilled one of the following conditions: 1) having typical symptoms (shortness of breath, oedema and fatigue), and reduced left ventricular ejection fraction (LVEF<40%); 2) LVEF >40%, but having symptoms and elevated natriuretic peptide, and also showing abnormal heart structures and/or diastolic dysfunction in ultrasound.

Statistical analysis

Descriptive statistics were calculated for patients with poor and good control of SBP and DBP, respectively. Between-group differences were compared by Student's t test, Mann-Whitney U test, ANOVA for continuous variables, and by Chi-square test, Fisher's exact test for categorical variables. Survival analysis was conducted by fitting univariate Cox proportional hazards (PH) models to estimate the associations of adverse outcomes with mean and SD of SBP, mean and SD of DBP, MAP, and PP during hospitalization. Multivariate models were built by adding all the confounding factors as covariates, together with SBP and DBP on admission. We depicted dose-response relationships of outcomes with the six BP variables by the natural spline regression with two degrees of freedom that yielded the minimal Akaike information criterion (AIC) in model selection. The linearity assumption was checked by the Chi-square test between

linear and spline regression models. We also stratified patients into two subgroups by ARB prescriptions (ever *vs* never in hospitalization) to estimate the effect modification of ARB on the associations of outcomes with each BP variable in the univariate model. Then we utilized Z-test to check the statistical significance of difference between these subgroups.

Several sensitivity analyses were conducted by 1) replacing the Cox PH model with the logistic regression model; 2) replacing continuous BP variables with categorical BP variables: good *vs* poor SBP, good *vs* poor DBP, as well as binary variables of SBP/DBP variability, MAP and PP (overall median as a cutoff point); 3) replacing the SD of SBP/DBP by the coefficient of variation (CV), an alternative measurement for BP variability; 4) excluding patients who entered ICU or died with at least one record of hypotension (SBP<90 mmHg and DBP<60 mmHg). We calculated crude and adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) associated with per 10 mmHg increase in average SBP, average DBP, MAP and pulse pressure, and per 1 mmHg increase in the SD of SBP or DBP to estimate the effects of risk factors (HR>1) and beneficial factors (HR<1). All analyses were carried out in the R software (version 3.6.1) using the 'survival' package.

Ethical approval and consent of patients

The ethical approval was obtained from the No. 923 Hospital of Joint Service Supporting Force in China, which led the military medical team in the Huoshenshan hospital and officially kept the databased of electronic medical records with all personal information removed, after this hospital was closed on 15 April 2020.

Results

Descriptive statistics of patients

A flow chart of data screening procedure is shown in **Figure 1**. A total of 3023 patients were admitted into the Huoshenshan hospital from February 4 to March 23, 2020 and followed up till March 31, 2020. After excluding 2135 patients without coexisting hypertension, 10 suspected COVID-19 cases, 72 cases without multiple blood pressure measurements during hospitalization (< 3 times), and 3 cases without BP measurement on admission, a total of 803 patients were included into analysis. Of 803 hypertensive patients, 67 (8.3%) were admitted into ICU, 30 (3.7%) had respiratory failure, 26 (3.2%) heart failure, and 35 (4.8%) died. Their average follow-up time is about 39 days.

Of 803 patients in our study, 609 had BP measurements on admission and 295 (48.4%) had normal BP on admission (SBP/DBP < 140/90 mmHg). The mean SBP and DBP on admission were 137.0 mmHg (± 19.7) and 84.2 mmHg (± 12.8), respectively (**Table 1**). There were 82.4% (662/803) of COVID-19 patients who had good BP control and 17.6% (141/803) who had poor BP control during hospitalization (**Table 1**). Compared to those with good BP control, the patients with poor BP control had higher average of SBP and DBP, higher SD of SBP and DBP, higher MAP and PP during the period. The patients with poor BP control were more likely to have COPD and chronic kidney disease.

Laboratory profile, clinical courses, and disease outcomes

Laboratory investigations on admission were similar between patients with good and poor BP control, except that the latter had higher albumin and lower total bilirubin. Patients with poor BP control less likely to have alanine aminotransferase > 40 U/L and more likely to have creatinine > 133 μmol/L on admission (**Table 2**). Treatment during hospitalization was generally comparable between the patient groups (good *vs* poor BP control). During hospitalization, there were 581, 199, 100, and 33 patients who received

calcium antagonists, beta-blockers, ARB, and thiazide diuretics, respectively (**Table 2**). Patients with poor BP control were more likely prescribed with calcium antagonists, ARB, or three types combined of antihypertensive drugs during their hospital stay.

Hazard ratio (HR) of adverse outcomes

Correlations coefficients between BP variables and outcomes were low to moderate (**Supplementary Tables 1-3**). Crude and adjusted HR estimated from univariate and multivariate Cox PH models are shown in **Table 3**. In the univariate models, average SBP was positively associated with heart failure, whereas average DBP and MAP was negatively associated with mortality, ICU admission, and respiratory failure. Higher SBP/DBP variability and PP were associated with higher hazards of all critical events. After adjustment for confounding factors (SBP and DBP on admission, age, sex, smoking, drinking, and comorbidities), the remaining significant predictors for heart failure were average SBP (HR per 10 mmHg: 1.89, 95% CI 1.15 to 3.13) and PP (HR per 10 mmHg: 2.71, 95% CI 1.39 to 5.29), and increase in SBP variability was also marginally associated to the escalating hazards of heart failure (HR per 1 mmHg: 1.09, 95% CI: 0.99, 1.20). Increased SBP or DBP variability was significantly associated with higher risks of mortality and ICU admission, respectively ($p<0.05$). These BP variables had high discriminability associated with the critical events, as indicated by the area under the receiver operating characteristic curve (AUC) > 0.8 in all multivariate models (**Supplementary Table 4**).

Dose-response curves show a clear trend of higher mortality hazards associated with the increasing SD of SBP/DBP and MAP, and a similar pattern was found in the hazards of heart failure associated with average SBP, MAP and PP (**Figure 2**). A linear relationship was observed for the hazards of ICU admissions associated with increased SD of SBP/DBP. The Chi-square tests show that the assumption of a linear relationship

with the outcomes held for most BP variables (**Supplementary Table 5**). Sensitivity analyses yielded similar effect estimates, suggesting the robustness of the main results (**Supplementary Tables 6-8**). The results were also consistent after excluding 8 ICU/death patients with at least one record of hypotension. (**Supplementary Tables 9**).

ARB medication

Crude and adjusted HR estimates associated with ARB prescriptions are shown in **Supplementary Table 10**. After adjustment, ARB users had a significantly lower risk of ICU admission (HR: 0.21, 95% CI 0.06 to 0.73). We further did a stratified analysis by estimating HRs of critical events with average BP and BP variability to patients with and without ARB prescriptions, respectively. Similar HR estimates of average SBP were found between the patients with and without ARB prescriptions, in all critical events except heart failure (Z-test P=0.01) (**Figure 3**). A significantly higher risk of heart failure was associated with SBP in the subgroup without ARB (HR=1.73, 95% CI 1.19 to 2.51), compared to the ARB group (HR=0.53, 95% CI 0.23 to 1.24). For the SD of SBP/DBP, significant HRs were found for all critical events in the subgroup without ARB prescriptions. Similar estimates were found in those with ARB prescriptions, though none were statistically significant. The protective effects of mean DBP were found in all outcomes.

Discussion

Hypertension was the most common comorbidity found in hospitalized patients with COVID-19 infection. Previous studies have reported a higher risk of all-cause mortality in COVID-19 patients with coexisting hypertension [2,23]. Our findings suggest that high SBP and PP, and instability of SBP/DBP control, were independently associated with greater risks of adverse outcomes, including mortality, ICU admission and heart failure, in COVID-19 patients. To our best knowledge, this study is the first to

comprehensively evaluate the impact of BP control and stability on prognosis of COVID-19 infection in hypertensive patients. The findings shall provide important evidence for clinical management of COVID-19 patients with hypertension.

Safety and efficacy of ARB and ACEI drugs as antihypertensive drugs in COVID-19 patients have caused debates in literature. Some researchers raised a hypothesis that ARB and ACEI drugs could elevate ACE2 in these patients, which could potentially increase entry points for SARS-CoV-2 virus [24]. While others argued that there was no evidence to suggest these drugs increased ACE2 levels in lung epithelial cells [25]. It also remains controversial whether ACE2 plays a protective or detrimental role in lung injury associated with COVID-19 infection [26,27]. Concerns have also been raised that discontinuation of routine antihypertensive treatment could increase the risk of cardiovascular events and mortality in COVID-19 patients with coexisting hypertension [28]. A recent study in the US found that ARB/ACEI use did not increase the infection risk of COVID-19 [29]. In our study, we found ARB users had a lower risk of ICU admission, but did not significantly differ from non-ARB users in other outcomes. We compared the risk estimates associated with different BP variables between two ARB groups. There was no significant difference in these estimates, except a relatively smaller HR of heart failure associated with SBP in the ARB group. Our findings echo the study by Zhang *et al*. that the in-hospital use of ARB/ACEI was associated with a lower mortality risk in hypertensive patients with COVID-19 [23]. Our analysis further revealed that the adverse effects of poor BP control did not significantly differ between the patients, regardless of receiving ARB in hospitalization. Therefore our findings support the current statements from both the European Society of Cardiology and the American Heart Association, which suggested patients with hypertension shall continue ARB and ACEI treatment if they already had these drugs as

their usual regimens [30,31]. Unfortunately, none of the patients used ACEI as antihypertensive drug in our study, therefore we were unable to assess the effect of this type of drugs. Future studies from other countries are warranted to investigate the adverse or beneficial effects of ARB and ACEI given the potential ethnicity difference.

The mortality rate of our patients (66/803, 8.2%) was comparable to that reported for inpatients with coexisting hypertension in other hospitals in China (8.8%) [23]. In consistent with the previous findings on cardiovascular risks of hypertension [32], we found that the risks of adverse outcomes of heart failure significantly increased in patients with high SBP, but such a trend was less evident in the risks associated with DBP. This incidates that high BP is the significant predictor for unfavorable prognosis of COVID-19 and SBP is the primary target of BP control in COVID-19 patients. However, high SBP/DBP variability was associated with high risks of mortality and ICU admissions, suggesting the importance of maintaining stable in-hospital BP in these patients. High BPV might reflect arterial stiffness and endothelial dysfunction which increased the risk of cardiovascular events [33-35]. Another possibility was the sudden BP decrease due to rapid deterioration of underlying conditions. We did a sensitivity analysis by excluding the patients with at least one record of hypotension (both SBP/DBP < 90/60 mmHg). The estimates of BPV were consistent with the main results (Supplementary Table 9). The underlying mechanism between high BPV and severe outcomes in COVID-19 patients warrants further investigations.

Our study has a few caveats. First, the data were from one hospital in Wuhan, which might not be generalized to all COVID patients in China and other countries. Second, due to the overwhelmed healthcare system in Wuhan, most patients in our study were admitted two-three weeks after symptom onset. Therefore, the impact of blood pressure variability on early progression of COVID-19 cannot be assessed. Third,

there was no data on baseline BP or antihypertensive drugs taken before hospital admissions, hence the long-term intake of ACEI or ARB was not available in these patients, which could have some residual effects on cardiovascular events in this retrospective cohort. Fourth, BP monitor probably has been enhanced in those with high BP and complicated by disease progression, which could have resulted in biased effect estimates. Nevertheless, in sensitivity analysis we also used CV of SBP as exposure in our model, which was believed to partially address this bias. This sensitivity analysis yielded similar but slightly more conservative estimates, suggesting that SBP/DBP variability had significant adverse effects on clinical outcomes of COVID-19 infection, independently from average BP. Last but not least, the disease outcomes of ICU admission, respiratory failure and heart failure might not be objective. Nevertheless, the diagnosis criteria were strictly followed and clinical decision involved at least one senior and one junior doctors.

Conclusion

In this retrospective study of 803 COVID-19 patients with coexisting hypertension, we found high average SBP and high SBP/DBP variability in hospitalization was independently associated with in-hospital mortality, ICU admission and heart failure. The findings suggest low and stable BP are optimal to achieve a favorable prognosis for COVID-19 patients with coexisting hypertension. Another finding of clinical implications is that ARB drugs did not cause higher risks of adverse outcomes in hypertensive patients, and even a benefit in heart failure was observed. This supports the continuation of ARB drugs in COVID-19 patients.

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Author Responsibility

LY is the guarantor of the manuscript including its content, data, and analysis. JR, YS, ZZ, SZ, and LY originated and designed the study. YS and YG contributed to data collection. JR, ZZ, SZ, LH, PC contributed to data clean. JR, ZZ, SZ and LH conducted data analysis. JR, LX and LY interpreted the findings and drafted the manuscript. JR, SZ, LH, LX, LX, DH, FW, JQ and LY reviewed and edited the manuscript. All the authors proved the final version of this manuscript.

Conflict of interest and Source of Funding

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Data sharing

All data and materials used in this work were available based on request.

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Table and figure legends:

Table 1. Demographic characteristics, presenting symptoms on admission and coexisting comorbidities in patients with good or poor BP control during hospitalization.

Table 2. Laboratory profile on admission, clinical courses, and outcomes of COVID-19 patients with good BP control and poor BP control during hospitalization.

Table 3. Crude and adjusted hazard ratio (HR) for critical events of COVID-19 infection associated with the average and SD of SBP/DBP, MAP, and PP in models. All the BP variables were continuous variables.

Figure 1. Flow chart of patients included in analysis.

Figure 2. Dose-response relationships of mortality, ICU admission, and heart failure associated with mean and standard deviation (SD) of SBP/DBP, MAP and PP in 803 COVID-19 patients with coexisting hypertension.

Figure 3. Crude hazard ratio (HR) for critical events associated with BP control in COVID-19 patients with ARB prescriptions (red triangle) and those with other anti-hypertensive medication or without any (blue square). Vertical bars indicate 95% confidence intervals.