Clinical characteristics of coronavirus disease 2019 (COVID-19) patients with hypertension on renin–angiotensin system inhibitors

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ABSTRACT
In December 2019, COVID-19 outbreak in Wuhan, China. The current study aimed to explore the clinical characteristics of COVID-19 complicated by hypertension. In this retrospective, single-center study, we recruited 110 discharged patients with COVID-19 at Wuhan Fourth Hospital in Wuhan, China, from January 25 to February 20, 2020. All study cases were grouped according to whether they had a history of hypertension. Then, a subgroup analysis for all hypertensive patients was carried out based on whether to take ACEI or ARB drugs. The mean age of 110 patients was 57.7 years (range, 25–86 years), of which 60 (54.5%) were male patients. The main underlying diseases included hypertension [36 (32.7%)] and diabetes [11 (10.0%)]. Compared with the non-hypertensive group, the lymphocyte count was significantly lower in the hypertensive group (average value, 0.96 × 10^9/L vs 1.26 × 10^9/L), and analysis of clinical outcomes showed that the crude mortality rate was higher in the hypertensive group [7/36 (19.4%) vs 2/74 (2.7%)]. Patients treated with ACEI or ARB, compared with the control group, were younger (average age, 58.5 years vs 69.2 years), but there was no statistical difference in the crude cure rate [10/15 (66.7%) vs 15/21 (71.4%)] and the crude mortality rate [2/15 (13.3%) vs 5/21 (23.8%)]. In conclusions, the COVID-19 patients with a history of hypertension had a significantly lower lymphocyte count on admission. The elderly and comorbidities such as hypertension may together constitute risk factors for poor prognosis in patients with COVID-19. Taking ACEI or ARB drugs may not change the prognosis of COVID-19 patients with hypertension.

Background
Since December 2019, Wuhan City, Hubei Province has successively discovered multiple cases of patients with pneumonia infected by a novel type of coronavirus. With the spread of the epidemic, other cases in China and abroad have also been found. As of March 21, 2020, a total of 81,054 COVID-19 cases in China have been confirmed.

The new coronavirus belongs to the beta-type coronavirus, which has an envelope and is round or oval, usually polymorphic, and 60–140 nm in diameter. Its genetic characteristics are significantly different from SARSr-CoV and MERSr-CoV. Current research shows that it has more than 85% homology with bat SARS-like coronavirus (bat-SL-CoVZC45). Recently, the International Virus Classification Commission had proposal named the novel coronavirus as “SARS-CoV-2”(1), and the World Health Organization has officially named the novel coronavirus pneumonia as “COVID-19.”

At present, it has been confirmed that receptor-binding mechanism in infection of host cells by novel coronavirus is the binding of the coronavirus S protein to the human angiotensin-converting enzyme 2 (ACE2) protein, which involves in the regulation of blood pressure in the human body (2). It is widely present in the lungs, heart, kidneys, and intestines. Additionally, studies had reported that a considerable number of patients with COVID-19 were complicated by underlying diseases such as hypertension and the proportion of patients with hypertension was high. Peng et al. showed that among 138 COVID-19 patients, the proportion of patients with hypertension was the highest (43/138, 31.2%) (3). Huang et al. also found that 15% of patients with COVID-19 had hypertension, ranking second among all comorbidities (4). In addition, there were reports that most of the deaths disclosed during the early stage of the COVID-19 epidemic were complicated by hypertension. However, at present, there were no researches about the clinical characteristics of COVID-19 patients with hypertension and the effects of taking ACEI or ARB drugs on patients’ prognosis. Therefore, we selected hypertension as a case–control retrospective study to investigate the clinical characteristics of hypertensive patients exposed to the COVID-19.

Methods
Study design and patient population
This case series was approved by the institutional ethics board of Wuhan Fourth Hospital (KY2020-027-01). All study cases were from confirmed patients with COVID-19 at Wuhan Fourth Hospital discharged from January 25 to February 20, 2020. Wuhan Fourth Hospital is located in Wuhan, Hubei Province, which is one of the first batch of COVID-19
diagnosis and treatment hospitals requisitioned by the Wuhan Municipal Government. All patients included in the study were diagnosed and treated in accordance with the COVID-19 diagnosis and treatment program issued by the Chinese National Health Committee.

The medical records of patients were collected and analyzed by the research team of the Department of Critical Care Medicine, Wuhan Fourth Hospital. The clinical data included demographic data, medical history, underlying comorbidities, symptoms, signs, laboratory findings, treatment measures, and clinical outcomes. All study cases were grouped according to whether they had a history of hypertension. Then, hypertensive patients were further divided into two groups based on whether to take ACEI or ARB.

**Statistical analysis**

Prism 5 (GraphPad Software, La Jolla, CA, USA) and SPSS 23.0 (SPSS, Inc., Chicago, IL, USA) were used to perform statistical analysis. Means of two groups were tested for the statistical difference using unpaired Student’s t-test. The distribution of categorical variables was evaluated using Chi-square test. *P* < .05 was considered statistically significant. The association between whether to take ACEI or ARB and prognosis in COVID-19 patients with hypertension was examined by logistic regression analysis performed by SPSS.

**Results**

**Baseline characteristics**

The study included 110 patients with COVID-19 who had been discharged. The mean age of all patients was 57.7 years (range, 25–86 years), of which 60 (54.5%) male patients. The most common symptoms at onset of illness were fever [94 (85.5%)], dry cough [71 (64.5%)], fatigue [38 (34.5%)], and dyspnea [25 (22.7%)]. Less common symptoms were pharyngalgia, anorexia, nausea, vomiting, diarrhea, dizziness, headache, and myalgia. Patients with fever were mainly moderate fever [66 (60.0%)]. Common underlying diseases included hypertension [36 (32.7%)], diabetes [11 (10.0%)], and cardiovascular disease [10 (9.1%)] (Table 1).

**Clinical features of COVID-19 patients with hypertension**

As shown in Table 2, compared to the non-hypertensive group, patients in the hypertensive group were significantly older (average age, 64.8 vs 54.3) and showed a significantly higher occurrence of dyspnea [15 (41.7%) vs 10 (13.5%)], diabetes [9 (25.0%) vs 2 (2.7%)], and cardiovascular disease [7 (19.4%) vs 3 (4.1%)]. Remarkably, the lymphocyte count on admission was significantly lower in the hypertensive group (average value, 0.96 × 10^9/L vs 1.26 × 10^9/L). There was no statistical difference in the time from onset to hospitalization between the two groups. Clinical outcomes showed the two groups had no significant differences for crude cure rate, the rate of referral to high-level hospitals, and length of stay, but the crude mortality rate was higher in the hypertensive group than that in the control group [7 (19.4%) vs 2 (2.7%)]. Taking ACEI or ARB drugs may not change the prognosis of COVID-19 patients with hypertension.

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**Table 1. Baseline characteristics of patients diagnosed with COVID-19.**

| No. of patients | N = 110 |
|----------------|---------|
| Age, years, mean (SD) | 57.7(14.2) |
| Sex |  |
| Female | 50(45.5%) |
| Male | 60(54.5%) |
| Signs and symptoms, n(%) |  |
| Fever | 94(85.5%) |
| 39°C < T < 40°C | 6(5.5%) |
| 38°C < T ≤ 39°C | 66(60.0%) |
| 37.3°C < T ≤ 38°C | 22(20.0%) |
| T < 37.3°C | 16(14.5%) |
| Dry cough | 71 (64.5%) |
| Fatigue | 38(34.5%) |
| Dyspnea | 25(22.7%) |
| Pharyngalgia | 3(2.7%) |
| Diarrhea | 10(9.1%) |
| Anorexia | 10(9.1%) |
| Nausea | 1(0.9%) |
| Vomiting | 1(0.9%) |
| Dizziness | 21(18.2%) |
| Headache | 1(0.9%) |
| Myalgia | 6(5.5%) |
| Comorbidities, n (%) |  |
| Hypertension | 7(19.4%) |
| Cardiovascular disease | 10(9.1%) |
| Diabetes | 11(10.0%) |
| Cerebrovascular disease | 3(2.7%) |
| Epilepsy | 1(0.9%) |
| COPD | 3(2.7%) |
| Asthma | 1(0.9%) |
| Chronic kidney disease | 2(1.8%) |
| Chronic liver disease | 4(3.6%) |
| Malignancy | 4(3.6%) |
| Rheumatoid arthritis | 1(0.9%) |

**Table 2. Comparison of clinical features in hypertensive and non-hypertensive patients diagnosed with COVID-19.**

|          | Hypertension (n = 36) | Non-hypertension (n = 74) | P Value |
|----------|-----------------------|--------------------------|---------|
| Age, years, mean (SD) | 64.8(10.1) | 54.3(14.8) | <.001 |
| Sex |  |
| Female | 17(47.2%) | 33(44.6%) | .795 |
| Male | 19(52.8%) | 41(55.4%) | |
| Major signs and symptoms |  |
| Fever | 30(83.3%) | 64(86.5%) | .660 |
| Dry cough | 26(72.2%) | 45(60.8%) | .240 |
| Fatigue | 14(38.9%) | 24(32.4%) | .504 |
| Dyspnea | 15(41.7%) | 10(13.5%) | <.001 |
| Major Comorbidities |  |
| Cardiovascular disease | 7(19.4%) | 3(4.1%) | .022 |
| Diabetes | 9(25.0%) | 2(2.7%) | <.001 |
| Laboratory Findings |  |
| White blood cell count, ×10^9/L, mean (SD) | 6.5(5.0) | 4.9(1.85) | .070 |
| Lymphocyte count, ×10^9/L, mean (SD) | 0.96(0.38) | 1.26(0.59) | <.01 |
| Hypersensitive c-reactive protein or c-reactive protein increased | 29(80.6%) | 54(72.8%) | .386 |

**Prognosis**

|          | Hypertension | Non-hypertension | P Value |
|----------|-------------|-----------------|---------|
| Clinical cure | 25(69.4%) | 62(83.8%) | .083 |
| Transfer to mobile cabin hospital | 0 | 11(1.3%) | |
| Transfer to high-level hospital | 4(11.1%) | 9(12.2%) | .877 |
| Clinical death | 7(19.4%) | 2(2.7%) | <.01 |
| Onset of symptom to hospital admission, days, mean (SD) | 9.0(4.7) | 9.0(5.9) | .978 |
| Hospital stay, days, mean (SD) | 11.1(5.6) | 11.9(6.5) | .464 |

*P* values indicate differences between hypertensive and non-hypertensive patients. *P* < .05 was considered statistically significant. Means of two groups were tested for statistical difference using unpaired Student’s t-test. The distribution of categorical variables was evaluated using Chi-square test.
Clinical features of COVID-19 patients taking ACEI or ARB

The COVID-19 patients with a history of hypertension were divided into two groups according to whether to take ACEI or ARB drugs, of which 15 patients had previously taken ACEI or ARB were divided into ACEI or ARB group, and other patients were divided as control group. The patients in ACEI or ARB group were younger than that in the control group and the difference was statistically significant (average age, 58.5 vs 69.2). While there were no significant differences in lymphocyte counts, crude cure rate, crude mortality rate, onset time, and length of hospital stay between the two groups (Table 3). We classify patients transfer to high-level hospital and clinical death as a poor prognosis, and the prognosis between the two groups was examined by logistic regression analysis with adjustment for age, sex, hospitalization time, time from onset to hospital admission, and whether to take ACEI or ARB. As shown from Table 4, whether to take ACEI or ARB was not significantly associated with prognosis.

Discussion

In this report, we recruited 110 patients with COVID-19. From the results, we found that fever was the commonest symptom during the early stage, besides, the patient also showed other symptoms such as dry cough, fatigue, and dyspnea, and so on. In terms of underlying diseases, hypertension was the commonest comorbidity (32.7%). For the first time, this report showed that compared to the non-hypertension group, the hypertension group had significantly lower lymphocyte count. In addition, we grouped the COVID-19 patients with a history of hypertension based on whether to take ACEI or ARB for antihypertensive treatment, and found that there was no difference in clinical outcomes between the two groups.

As reported by other researchers (4–6), for most patients with COVID-19, the common symptoms were fever, dry cough, and fatigue, but we should be alert to the clinical manifestations of a few patients without fever at the time of consultation. Besides, we also should be wary of a few patients without clinical manifestations of the respiratory tract, such as anorexia, nausea, vomiting, diarrhea, and other clinical manifestations of the digestive system, as well as clinical manifestations of the nervous system such as dizziness and headache.

We observed about one-third of patients with COVID-19 were complicated by hypertension. This result was consistent with Peng et al. results which showed that 31% of 138 COVID-19 cases had hypertension (3). Until now, there were no effective drugs for the treatment of COVID-19. We observed that most patients used antiviral drugs (Arbidol Tablets or Lopinavir and Ritonavir Tablets) and antibiotics, and some patients used low-dose hormones (methylprednisolone) and immune globulin, and some critically ill patients had used oxygen therapy. In studies with limited conditions and data, it can be seen that there was no difference in cure rate between the hypertension group and the non-hypertension group, while the mortality rate in the hypertension group was higher, and the prognosis seems to be worse. However, it should be noted that the patients in the hypertension group were older and had a higher proportion of major comorbidities, which indicates that the elderly and comorbidities together constitute risk factors for poor prognosis to a certain extent.

Blood pressure is affected by many molecules, such as endothelin-1 (7), AngII, etc. (8,9). Like AngII, ACE2 belongs to the renin–angiotensin–aldosterone system and kallikrein–bradykinin system family and is also a blood pressure regulating protein (10,11), which can degrade AngII to form Ang1-7 and degrade Des-Arg (9) bradykinin (DABK) to an active peptide (12). As we all know, AngII and DABK can bind to corresponding receptors and play physiological roles such as constricting blood vessels, promoting value-added, inflammation, neutrophil infiltration, and pulmonary fibrosis (12,13). While Ang1-7 can bind to specific Mas receptors and exert diastolic blood vessels, anti-inflammatory, anti-proliferative, anti-fibrotic, and anti-alveolar epithelial cell apoptosis. Therefore, ACE2 indirectly exerts anti-inflammatory and anti-lung injury effects. Animal experiments show that ACE2 expression in hypertensive rats is decreased (14,15). ACE2 is also the binding protein of novel coronaviruses (16) like severe acute respiratory syndrome (SARS) (17). In studies on SARS, researchers found that coronavirus can cause ACE 2 levels to decline or even be absent (18,19), but the expression of ACE remains unchanged, and the balance of ACE2 and ACE in lung is broken (20), leading to AngⅠ elevation and activation of the DABK-BK1 receptor pathway work.

Table 3. Comparison of clinical features of hypertensive patients taking different antihypertensive drugs.

| Variable                        | ACEI or ARB (n = 15) | Other antihypertensive drugs (n = 21) | P Value* |
|---------------------------------|----------------------|--------------------------------------|----------|
| Age, years, mean (SD)           | 58.5(10.1)           | 69.2(7.5)                            | .001     |
| Sex                             |                      |                                      |          |
| Female                          | 6(40.0%)             | 11(52.4%)                            | .516     |
| Male                            | 9(60.0%)             | 10(47.6%)                            |          |
| Lymphocyte count, ×109/L, mean (SD) | 0.87(0.33)           | 1.02(0.17)                           | .237     |
| Prognosis                       |                      |                                      |          |
| Clinical cure                   | 10(66.7%)            | 15(71.4%)                            | >.099    |
| Transfer to high-level hospital | 3(20.0%)             | 1(4.8%)                              |          |
| Clinical death                  | 2(13.3%)             | 1(4.8%)                              |          |
| Onset of symptom to hospital admission, days, mean (SD) | 9.6(4.0)           | 8.6(5.2)                            | .528     |
| Hospitalization time, days, mean (SD) | 10.1(5.2)           | 11.7(6.0)                           | .405     |

*p values indicate differences between ACEI or ARB group and other antihypertensive drug groups. P < 0.05 was considered statistically significant. Means of two groups were tested for statistical difference using unpaired Student’s t-test. The distribution of categorical variables was evaluated using Chi-square test.

Table 4. Logistic regression analysis to detect the relationship between taking ACEI or ARB and prognosis.

| Variables                        | OR    | (95% CI)    | p value |
|----------------------------------|-------|-------------|---------|
| Age                              | 0.864 | 0.753 – 0.990 | .036   |
| Sex                              | 0.139 | 0.016 – 1.200 | .073   |
| Hospital stay                    | 1.127 | 0.961 – 1.322 | .251   |
| Time from onset to hospital admission | 1.14  | 0.920 – 1.413 | .231   |
| ACEI or ARB                       | 0.140 | 0.009 – 2.208 | .162   |

The association between whether to take ACEI or ARB and prognosis in COVID-19 patients with hypertension was examined by logistic regression analysis performed by SPSS with adjustment for age, sex, hospitalization time, time from onset to hospital admission, and whether to take ACEI or ARB.
together to cause lung inflammation, apoptosis, and accelerated lung injury. Because novel coronavirus and SARS both use ACE2 as a receptor, we speculate that novel coronavirus and SARS have similar mechanisms of action (Figure 1).

Reduced lymphocyte count is one of the diagnostic criteria in the National Health Commission’s diagnosis and treatment program. The results of this study show that COVID-19 patients with a history of hypertension had lower lymphocyte count. In reports by Peng et al., a persistent decline in lymphocyte counts was observed in death cases (3). Chen et al. also reported that patients with COVID-19 who were over 50 years of age, and low lymphocyte counts can easily turn into severe cases (21). Maybe the lymphocyte count could reflect the severity of the condition in patients with a history of hypertension. Whether lymphopenia can easily turn into severe cases requires further basic experimental research.

After scientists announced that novel coronavirus enters target cells through the receptor ACE2, many experts in the cardiovascular field began to discuss whether COVID-19 patients with a history of hypertension should continue to use ACEI or ARB as antihypertensive drugs. Some scholars believe that ACEI should be discontinued, while other scholars believe that the recommendations to discontinue ACEIs have no scientific basis.

In our data analysis, we saw that a considerable number of cases were complicated by hypertension, so we further collected the patient’s previous medication situation, and grouped them according to whether they were taking ACEI or ARB drugs. Statistical analysis under limited data showed that the prognosis of the two groups was not statistically different, but we need to note that there was a statistical difference in the age of the two groups. Further logistic regression analysis showed that patients whether had a history of taking ACEI or ARB were not correlated with prognosis. Studies show that both ACEI and ARB can cause increased expression of ACE2 (22,23). As the angiotensin type I receptor, ARB can increase Ang2, and then compensatingly increasing ACE2 expression. ACEI prevents Ang1 from forming Ang2, which in turn promotes ACE2 expression. But whether both types of drugs will affect COVID-19 patients with hypertension require further research.

This study has several limitations. First, some patients had been referred to other hospitals, so we can only calculate a crude cure rate and a crude mortality rate. Second, this is only a single-center study, and the sample size was also limited, especially for patients with hypertension. Therefore, it is difficult to accurately assess the risk factors for poor outcomes.

**Conclusions**

In general, our current work demonstrated that in 110 discharged patients with confirmed COVID-19 in Wuhan,
China, hypertensive patients had a significantly lower lymphocyte count on admission, the elderly and comorbidities such as hypertension may together constitute risk factors for poor prognosis. Taking ACEI or ARB drugs may not change the prognosis of COVID-19 patients with hypertension. However, as mentioned above, the sample size of the hypertensive patients we collected is small, and more researches are needed to confirm it.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
ZX, ZJK, and XT conceived and designed the study. ZX collected all clinical data. ZX and ZJK did statistical analysis. ZX and ZJK wrote the paper. XT reviewed and edited the manuscript. All authors read and approved the manuscript.

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