Hypertension May Reduce the Infection Risk but Increase the Severity of COVID-19: Based on the Current Data in China

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Increasing evidence has shown an unusual relationship between hypertension and COVID-19, which may not be as simple as previously thought. The purpose of our study was to determine the association of hypertension with the onset and development of COVID-19. A meta-analysis was performed to summarize the prevalence of hypertension in COVID-19 patients, as well as the usage of ACEIs/ARBs. Metaregression analyses were used to evaluate the association of hypertension with disease severity and mortality. PubMed and Google Scholar were searched for relevant studies. A total of 42 studies including 14138 patients were enrolled in the study. The proportion of hypertension in COVID-19 patients in China was 17.7% according to the enrolled studies, while it was 6.0% in a study containing 72314 confirmed cases, which are both much lower than in the general population. All of the data from the 11 provinces in China showed the same tendency. The proportions of hypertension were higher in severe/ICU patients and nonsurvivors than in nonsevere/ICU patients and survivors. The metaregression analyses suggested that both disease severity and risk of death were associated with the incidence of hypertension. A total of 27.6% of COVID-19 patients with hypertension received ACEI/ARB therapy. The proportion of deaths in COVID-19 patients with hypertension treated with ACEIs/ARBs was significantly lower than that in nonuse patients treated with ACEIs/ARBs. In conclusion, hypertension may reduce the infection risk of COVID-19 but increase the risk of developing worse clinical outcomes. The use of ACEIs/ARBs may benefit COVID-19 patients with hypertension.
1. Introduction

With the publication of several studies concerning the epidemiological and clinical features of coronavirus disease 2019 (COVID-19), a growing amount of evidence is emerging about the relationship between cardiovascular complications and COVID-19. According to early published data in Wuhan, hypertension was associated with a high prevalence and an increased risk of morbidity and mortality.

In Wang’s study, 31.2% of the 138 confirmed COVID-19 cases had hypertension [1]. Another study included 140 COVID-19 patients, of whom 42 patients (30%) had hypertension [2]. The prevalence of hypertension in fatal patients was extremely high (42.57%–60%) [3–5]. Thus, patients with hypertension seemed to be more likely to be infected with SARS-CoV-2 and face a greater risk of developing severe conditions [6, 7].

However, emerging evidence shows the reported prevalence of hypertension is gradually decreasing. In our previous study, the 6 earliest studies about COVID-19 were summarized, and the results suggested that the proportion of hypertension in patients with COVID-19 was 17.1% [8]. A study that included 1099 patients with confirmed COVID-19 reported that 14.9% of patients had hypertension comorbidities [9]. In another study, among 44672 individuals with confirmed COVID-19, 2683 patients (12.8%) had hypertension [10]. Even more surprising was that in the largest study ever conducted in China thus far, including 72314 confirmed cases, only 6.0% of patients had hypertension [11]. Because the total number of infections in China was 84414 as of May 7th, the study was very representative of the total population. The incidence of 6.0% was much lower than that of the general population, which reported a 27.9% overall crude prevalence of hypertension according to the Summary of the 2018 report on cardiovascular diseases in China [12]. This information indicated that individuals with underlying hypertension seemed to be less susceptible to COVID-19. This discovery is very different from all others that have been made thus far. Thus, it is urgent to determine the relationship between hypertension and the virus.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are the main antihypertensive drugs recommended in the current guidelines. However, angiotensin-converting enzyme 2 (ACE2) has been identified as a receptor for SARS-CoV-2, which infects humans by binding to ACE2 in host respiratory epithelial cells [13]. Therefore, the application of ACEIs/ARBs to control blood pressure in patients with COVID-19 complicated with hypertension has been a matter of intense debate [14, 15]. Therefore, we will conduct an analysis on the incidence and prognosis of patients with COVID-19 complicated with hypertension, as well as the use of ACEIs/ARBs in infected patients and their impact on prognosis.

2. Methods

This meta-analysis was conducted following the Preferred Reporting Items for the Systematic Review and Meta-Analysis (PRISMA) statement [16].

2.1. Search Strategy and Selection Criteria. A literature search was conducted in MEDLINE via the PubMed database, Cochrane Library, Web of Science, EMBASE and EMBASE Classic databases, and Google Scholar from inception through April 23, 2020. The following terms (MeSH) were used: “2019-nCoV,” “COVID-19 virus,” “2019 novel coronavirus,” “SARS-CoV-2,” and “hypertension.” The included articles met the following eligibility criteria: (1) RCTs or non-RCTs; (2) patients were diagnosed with 2019 novel coronavirus infection; (3) sample size ≥10 in each study population; and (4) comorbidities of hypertension and the outcome of hypertension were given. Studies not meeting these criteria, non-clinical studies, incompatible or repeated studies, case reports, and studies without complete data were excluded.

2.2. Data Management and Quality Assessment. Clinical data, including age, sex, prevalence of hypertension, clinical outcome, and interventions for hypertension, were collected from the identified studies. The primary outcomes were to analyse the prevalence of hypertension and the impact of hypertension on the severity of the disease and mortality. The secondary outcomes were to analyse the use of ACEIs/ARBs in COVID-19 and the impact of ACEIs/ARBs on prognosis. Two reviewers assessed the eligibility of the included reports, extracted data with a standardized report form, and evaluated the quality of reports independently. All discrepancies were solved by discussion until a consensus was reached.

2.3. Statistical Analysis. The statistical analysis was performed using OpenMeta Analyst version 10.10 (https://www.cebm.brown.edu/open_meta) and Review Manager (RevMan) software version 5.3. Forest plots were used to illustrate the prevalence of hypertension in 2019-nCoV infection from the selected studies as well as the impact of 2019-nCoV infection and therapeutic interventions on hypertension. Heterogeneity among studies was assessed by $I^2$ statistics. In the pooled analysis, a fixed-effects model was applied when the heterogeneity $I^2$ was less than 50%; otherwise, a random-effects model was used [17, 18]. Metaregression analyses were used to evaluate the associations between disease severity, risk of death, and incidence of hypertension. Cochrane Collaboration’s tool was followed to assess the risk of bias.

3. Results

3.1. Selected Studies and Baseline Characteristics. We searched all the databases and websites using the search words described above, and 21052 total records were...
3.2. Primary Outcomes. Forty-two studies, including 14138 COVID-19 patients with hypertension, were collected in the study. Meta-analysis of the identified studies showed that the prevalence of hypertension was 17.7% (95% CI: 15.1–20.4%) (Figure 2(a)). There was significant heterogeneity (Cochran’s Q) in the estimates of hypertension among the identified studies with an $I^2$ index of 93.3%. Next, 26 studies including 4458 patients outside of Hubei were also analysed, showing that the prevalence of hypertension was 14.3% (95% CI: 13.3–15.3%) (Figure 2(b)). Then, 14 studies including 6991 patients in Hubei Province were analysed, and the data showed that the prevalence of hypertension was 24.7% (95% CI: 19.4–30.1%) (Figure 2(c)).

Furthermore, we compared the prevalence of hypertension in COVID-19 patients with data from the China Hypertension Survey, 2012–2015 [19]. The results demonstrated the differences in all 11 provinces outside of Hubei. All studies with the data from the China Hypertension Survey, 2012–2015 [19] showed that the prevalence of hypertension was 24.7% (95% CI: 19.4–30.1%) (Figure 3). The results demonstrated the differences in all 11 provinces outside of Hubei. All studies with the data from the China Hypertension Survey, 2012–2015 [19]. The results demonstrated the differences in all 11 provinces outside of Hubei. All studies with the data from the China Hypertension Survey, 2012–2015 [19]. The results demonstrated the differences in all 11 provinces outside of Hubei. All studies with the data from the China Hypertension Survey, 2012–2015 [19]. The results demonstrated the differences in all 11 provinces outside of Hubei. All studies with the data from the China Hypertension Survey, 2012–2015 [19]. The results demonstrated the differences in all 11 provinces outside of Hubei. All studies with the data from the China Hypertension Survey, 2012–2015 [19]. The results demonstrated the differences in all 11 provinces outside of Hubei. All studies with the data from the China Hypertension Survey, 2012–2015 [19]. The results demonstrated the differences in all 11 provinces outside of Hubei. All studies with the data from the China Hypertension Survey, 2012–2015 [19].

4. Discussion

A growing number of studies on the epidemiological and clinical characteristics of COVID-19 suggest a relationship between cardiovascular complications and COVID-19. Hypertension is one of the most important complications in patients with COVID-19. According to earlier data in Wuhan, there was a high proportion of hypertension among confirmed cases, reaching more than 30%. However, in a study covering 72314 confirmed cases, only 6.0% of patients had hypertension [11]. In the present study, we collected all of the published data involving provinces outside Hubei. We compared the prevalence of hypertension in COVID-19 patients with the data from the China Hypertension Survey, 2012–2015 [19]. The results demonstrated the differences in all 11 provinces whose data could be currently obtained. All of the incidences of hypertension in COVID-19 patients were lower than those in the general population. We do not believe this is just a coincidence. We hypothesized that hypertension might reduce the risk of SARS-CoV-2 infection. However, in Hubei Province, the result was the opposite. One possible reason why the incidence of hypertension in COVID-19 patients was higher than that of the general population in Hubei was that many people with mild illnesses might have gone undiagnosed in the face of a collapsed healthcare system, which would reduce the accuracy of the data. However, when the healthcare system is healthy, milder and even asymptomatic patients can be diagnosed, which might result in a lower prevalence of hypertension outside of Hubei. If the above hypothesis and interpretation can be accepted, there must be a premise as follows: the incidence of hypertension in mild patients is low, but it is high in severe patients. To test this premise, we analysed the prevalence of hypertension between severe and nonsevere patients and
nonsurvivors and survivors. We found that patients with hypertension were more likely to develop severe cases or be nonsurvivors after SARS-CoV-2 infection. The total proportion of hypertension in severe/ICU patients was approximately 1.78-fold that in nonsevere/ICU patients, while in nonsurvivors, it was 2.50-fold that in survivors, both of which showed significant differences. In metaregression analyses in patients with COVID-19, the disease severity and risk of death were both statistically associated with the incidence of hypertension.

Although the underlying mechanism is unknown, further investigation of the expression and activity of ACE2 is worthwhile. ACE2 is a carboxypeptidase that can hydrolyse Ang I to Ang-(1–9) and Ang II to Ang-(1–7) without being

| References | Date | Number of patients | Area | Age | Sex (male, %) | Hypertension (%) |
|------------|------|-------------------|------|-----|--------------|-----------------|
| Chaolin Huang | As of 2020.1.2 | 41 | Wuhan | 49 | 73.2 | 14.6 |
| Youbin Liu | 2020.1.10–2020.2.24 | 291 | Guangzhou | 48.1 | 45.7 | 18.6 |
| Jie Li | 2020.1.22–2020.2.10 | 17 | Dazhou | 45 | 52.9 | 5.9 |
| Guyi Wang | As of 2020.2.20 | 242 | Changsha | 45 | 49.2 | 14.9 |
| Yafei Wang | 2020.1.1–2020.2.10 | 110 | Wuhan | — | 43.6 | 20.9 |
| Xiaowei Xu | 2020.1.10–2020.2.26 | 62 | 7 hospitals in Zhejiang | 41 | 56.5 | 8.1 |
| Wabo Zhu | 2020.1.24–2020.2.20 | 32 | Hefei | 46 | 46.9 | 21.9 |
| Xu Chen | 2020.1.23–2020.2.14 | 291 | Changsha and Loudi | 46 | 49.8 | 13.4 |
| Qingxian Cai | 2020.1.11–2020.2.6 | 298 | Shenzhen | 47 | 50 | 12.8 |
| Dawei Wang | 2020.1.1–2020.1.28 | 138 | Wuhan | 56 | 54.3 | 31.2 |
| W. Guan | 2019.1.11–2020.1.29 | 1099 | 552 hospitals | 47 | 58.1 | 15.0 |
| Fei Zhou | 2019.12.29–2020.1.31 | 191 | Wuhan | 56 | 62.3 | 30.4 |
| Guoqing Qian | 2020.1.20–2020.2.11 | 91 | 7 hospitals in Zhejiang | 50 | 40.7 | 16.5 |
| Guqin Zhang | 2020.1.2–2020.1.20 | 221 | Wuhan | 55 | 48.9 | 24.4 |
| Pengfei Cui | 2020.1.28–2020.2.18 | 35 | Wuhan | 61.5 | 0 | 34.3 |
| Yu Lei | 2020.1.4–2020.2.28 | 67 | Daofu | 39.3 | 58.2 | 11.9 |
| Lei Liu | 2020.1.20–2020.2.3 | 51 | Chongqing | 45 | 62.7 | 7.8 |
| Lei Wang | 2020.1.21–2020.2.5 | 18 | Zhenguangzhou | 39 | 55.6 | 27.8 |
| Penghui Yang | 2019.12.27–2020.2.18 | 55 | Beijing | 44 | 60 | 20 |
| Jinjin Zhang | 2020.1.16–2020.2.3 | 140 | Wuhan | 57 | 50.7 | 30 |
| Jie Liu | 2020.1.16–2020.2.15 | 64 | Wuhan | 35 | 35.9 | 4.7 |
| Min Cao | 2020.1.20–2020.2.15 | 198 | Shanghai | 50.1 | 51.0 | 21.2 |
| Chengfeng Qiu | 2020.1.22–2020.2.12 | 104 | Huaihua | 43 | 47.1 | 14.4 |
| Rui Huang | 2020.1.22–2020.2.10 | 221 | 10 hospitals in Jiangsu | 45 | 57.0 | 14.5 |
| Zhijun Xie | 2020.1.22–2020.2.15 | 60 | Hangzhou | 45 | 45 | 15 |
| Pengqin Zhang | 2020.1.30–2020.2.15 | 81 | Jinzhou | — | 55.6 | 13.6 |
| Songqiao Liu | 2020.1.10–2020.2.18 | 620 | 24 hospitals in Jiangsu | 44.48 | 52.6 | 15.5 |
| Weijie Guan | 2019.12.11–2020.1.31 | 1590 | 575 hospitals | 48.9 | 57.3 | 17.0 |
| Peng Zhang | 2019.12.31–2020.2.20 | 3430 | 9 hospitals in Hubei | 42.9 | 32.9 | 32.9 |
| Juan Meng | 2020.1.11–2020.2.23 | 417 | Shenzhen | 64.5 | — | 12.2 |
| Sijiao Wang | 2020.1.22–2020.2.16 | 165 | Fuzhou | 44 | 55.8 | 14.5 |
| Shijiao Yan | 2020.1.22–2020.3.13 | 168 | Haikou | 51 | 48.2 | 14.3 |
| Xiufeng Jiang | 2020.1.23–2020.2.16 | 55 | Wuxi | 45 | 49.1 | 30.9 |
| Yu Shi | 2020.1.16–2020.2.17 | 487 | 5 hospitals in Zhejiang | 46 | 53.2 | 20.3 |
| Huisi He | 2020.2.8–2020.3.16 | 94 | Wuhan | 69.2 | 57.4 | 59.6 |
| Caizheng Yu | 2020.1.14–2020.2.28 | 1663 | Wuhan | 64 | 50.4 | 20.9 |
| Lin Fu | 2020.1.1–2020.1.30 | 200 | Wuhan | — | 49.5 | 50.5 |
| Zhenhua Zeng | 2020.1.5–2020.3.8 | 274 | Wuhan | 60 | 54.7 | 27.4 |
| Xin Chen | 2020.2.11–2020.2.29 | 208 | Xiaogang | 50.5 | 51.4 | 19.7 |
| Xingwei Ge | 2020.2.3–2020.2.24 | 54 | Wuhan | 68 | 63.0 | 44.4 |
| Bo Hu | 2020.1.8–2020.2.9 | 50 | Wuhan | 62 | 68 | 36 |
| Suxin Wan | 2020.1.23–2020.2.8 | 135 | Chongqing | 47 | 53.3 | 9.6 |
| Yimei Yin | As of 2020.2.15 | 112 | Wuhan | 66 | 68.8 | 43.8 |
| Zhongbao Zuo | 2020.1.20–2020.2.28 | 70 | Hangzhou | 43 | 41.4 | 12.9 |
| Wei Chen | 2020.1.19–2020.2.7 | 74 | Nanjing | 48.1 | 58.1 | 13.5 |
| Jiaxi Chen | 2020.1.22–2020.2.26 | 137 | Taizhou | — | 52.6 | 12.4 |
| Wentao Xu | 2020.1.10–2020.2.18 | 87 | Suzhou | — | 52.9 | 6.9 |
| Ye Xia | 2020.1.31–2020.2.20; | 78 | Wuhan | — | — | 100 |
| Yingxia Liu | 2019.12.27–2020.2.27 | 100 | Beijing | — | — | 100 |
| Kun Wang | 2020.1.7–2020.2.11 | 305 | Wuhan | 47.8 | 46.6 | 14.8 |
| Fei Zhou | 2019.12.29–2020.1.31 | 191 | Wuhan | 56 | 62.3 | 30.4 |
inhibited by selective ACE inhibitors. ACE2 has more favourable kinetics for the hydrolysis of Ang II than Ang I [36]. A previous study suggested that the ACE2 expression level was significantly downregulated in the kidneys of three hypertensive rat strains [37]. In a clinical study, hypertension status was also confirmed as an independent confounding determinant of the ACE to ACE2 ratio, leading to the relative downregulation of ACE2 [38]. SARS-CoV-2 binds to its target cells through ACE2, which is expressed in epithelial cells, type 2 pneumocytes, and macrophages in the lungs. Studies have speculated that high expression of ACE2 in patients with hypertension might facilitate SARS-CoV-2 entry into targeted cells in the respiratory system [13]. One of the main reasons why hypertension could reduce SARS-CoV-2 infection might be the loss of ACE2 in hypertensive subjects. ACE2 has a strong cardiovascular protective effect, which could also explain why patients with hypertension had a worse prognosis once they were infected with the virus. The downregulated expression of ACE2 after infection with SARS-CoV leads to excessive activation of the RAS [39], which activates peripheral sympathetic neuron release of catecholamine mediated by activation of multiple signalling pathways causing vasoconstriction and bronchial contraction [40]. It has been shown that the binding of coronavirus to ACE2 leads to the downregulation of ACE2, which in turn causes an ACE/ACE2 imbalance and an excessive production of angiotensin II by the related ACE enzyme. Excessive activation of the RAS also promotes inflammation, causes cytokine storms [41], generates ROS by activating the NADH/NADPH oxidase system [42], and induces cell apoptosis, thus promoting the progression of coronavirus-related lung injury [43].

ACEIs and ARBs are the major RAS inhibitors commonly used in clinical practice and the main
| Studies                        | Estimate (95% C.I.) | Ev/Trt |
|-------------------------------|---------------------|--------|
| Chaolin Huang 2020            | 0.146 (0.038, 0.255)| 6/41   |
| Youbin Liu 2020               | 0.186 (0.141, 0.230)| 54/291 |
| Jie Li 2020                   | 0.059 (0.000, 0.171)| 1/17   |
| Guyi Wang 2020                | 0.149 (0.104, 0.194)| 36/242 |
| Xiaowei Xu 2020               | 0.081 (0.013, 0.148)| 5/62   |
| Wanbo Zhu 2020                | 0.219 (0.076, 0.362)| 7/32   |
| Xu Chen 2020                  | 0.134 (0.095, 0.173)| 39/291 |
| Qingsxian Cai 2020            | 0.128 (0.090, 0.165)| 38/298 |
| Dawei Wang 2020               | 0.312 (0.234, 0.389)| 43/138 |
| W. Guan 2020                  | 0.150 (0.129, 0.171)| 165/1099 |
| Guoqing Qian 2020             | 0.165 (0.089, 0.241)| 15/91 |
| Guqin Zhang 2020              | 0.244 (0.188, 0.301)| 54/221 |
| Pengfei Cui 2020              | 0.343 (0.186, 0.500)| 12/35 |
| Yu Lei 2020                   | 0.119 (0.042, 0.197)| 8/67   |
| Lei Liu 2020                  | 0.078 (0.005, 0.152)| 4/51   |
| Lei Wang 2020                 | 0.278 (0.071, 0.485)| 5/18   |
| Penghui Yang 2020             | 0.200 (0.094, 0.306)| 11/55 |
| Jie Liu 2020                  | 0.047 (0.000, 0.099)| 3/64   |
| Jinjin Zhang 2020             | 0.300 (0.224, 0.376)| 42/140 |
| Min Cao 2020                  | 0.212 (0.155, 0.269)| 42/198 |
| Chengfeng Qiu 2020            | 0.144 (0.077, 0.212)| 15/104 |
| Rui Huang 2020                | 0.145 (0.098, 0.191)| 32/231 |
| Zhijun Xie 2020               | 0.150 (0.060, 0.240)| 9/60   |
| Fengjun Zhang 2020            | 0.136 (0.061, 0.210)| 11/81 |
| Songqiao Liu 2020             | 0.155 (0.126, 0.183)| 96/620 |
| Weijie Guan 2020              | 0.169 (0.151, 0.188)| 269/1590 |
| Peng Zhang 2020               | 0.329 (0.313, 0.343)| 112/3430 |
| Jueun Meng 2020               | 0.122 (0.091, 0.154)| 51/417 |
| Sijiao Wang 2020              | 0.145 (0.092, 0.199)| 24/165 |
| Shijiao Yan 2020              | 0.143 (0.090, 0.196)| 24/168 |
| Yu Shi 2020                   | 0.203 (0.168, 0.239)| 99/487 |
| Caizheng Yu 2020              | 0.209 (0.189, 0.228)| 347/1663 |
| Lin Fu 2020                   | 0.505 (0.436, 0.574)| 101/200 |
| Zhenhua Zeng 2020             | 0.274 (0.221, 0.327)| 75/274 |
| Xin Chen 2020                 | 0.197 (0.143, 0.251)| 41/208 |
| Suxin Wan 2020                | 0.096 (0.047, 0.146)| 13/135 |
| Zhongbao Zuo 2020             | 0.129 (0.050, 0.207)| 9/70 |
| Wei Chen 2020                 | 0.135 (0.057, 0.213)| 10/74 |
| Jiaxi Chen 2020               | 0.124 (0.069, 0.179)| 17/137 |
| Wentao Xu 2020                | 0.069 (0.016, 0.122)| 6/87 |
| Kun Wang 2020                 | 0.148 (0.108, 0.187)| 45/305 |
| Fei Zhou 2020                 | 0.304 (0.238, 0.369)| 58/191 |

Overall (I^2=93.3 % , P< 0.001) 0.177 (0.151, 0.204) 3070/14138

(a)

Figure 2: Continued.
Figure 2: Meta-analysis for the proportion of hypertension in COVID-19 cases. Weights were calculated from binary random-effects model analysis. Values represent the proportion of hypertension in COVID-19 patients and 95% CI. Heterogeneity analysis was carried out using the Q test among the studies variation ($I^2$ index). (a) The proportion of hypertension in data from all of China. (b) The proportion of hypertension outside Hubei. (c) The proportion of hypertension in Hubei.
Figure 3: Comparison of the incidence rates of hypertension in COVID-19 patients with that from the China Hypertension Survey, 2012–2015, in 11 provinces and all of China.

| Study or Subgroup       | Severe Events | Severe Total | Non-Severe Events | Non-Severe Total | Weight (%) | Risk Ratio M-H, Random, 95% CI | Risk Ratio M-H, Random, 95% CI |
|-------------------------|---------------|--------------|-------------------|------------------|------------|--------------------------------|--------------------------------|
| Caizheng Yu 2020        | 205           | 864          | 142               | 799              | 6.7        | 1.34 [1.10, 1.62]               |                                |
| Chaolin Huang 2020      | 2             | 13           | 4                 | 28               | 2.0        | 1.08 [0.23, 5.15]               |                                |
| Dawei Wang 2020         | 21            | 36           | 22                | 102              | 5.7        | 2.70 [1.70, 4.29]               |                                |
| Fei Zhou 2020           | 32            | 137          | 26                | 54               | 5.9        | 0.49 [0.52, 0.73]               |                                |
| Fengqin Zhang 2020      | 7             | 35           | 4                 | 46               | 2.9        | 2.30 [0.73, 7.24]               |                                |
| Guojin Zhang 2020       | 26            | 55           | 28                | 166              | 5.8        | 2.80 [1.81, 4.34]               |                                |
| Guozi Wang 2020         | 14            | 37           | 22                | 205              | 5.2        | 3.53 [1.99, 6.24]               |                                |
| Jinlin Zhang 2020       | 22            | 58           | 20                | 82               | 5.5        | 1.56 [0.94, 2.57]               |                                |
| Lei Liu 2020            | 1             | 7            | 3                 | 44               | 1.2        | 2.10 [0.25, 17.42]              |                                |
| Min Cao 2020            | 6             | 19           | 36                | 179              | 4.3        | 1.57 [0.76, 3.24]               |                                |
| Rui Huang 2020          | 4             | 25           | 28                | 196              | 3.5        | 1.12 [0.43, 2.93]               |                                |
| Shijiao Yan 2020        | 11            | 36           | 13                | 132              | 4.5        | 3.10 [1.52, 6.33]               |                                |
| Songqiao Liu 2020       | 18            | 53           | 78                | 567              | 5.8        | 2.47 [1.61, 3.79]               |                                |
| Suxin Wan 2020          | 4             | 40           | 9                 | 95               | 3.0        | 1.06 [0.34, 3.23]               |                                |
| W. Guan 2020            | 41            | 173          | 124               | 926              | 6.3        | 1.77 [1.29, 2.42]               |                                |
| Weijie Guan 2020        | 38            | 99           | 231               | 1491             | 6.4        | 2.48 [1.88, 3.27]               |                                |
| Xiufeng Jiang 2020      | 3             | 8            | 14                | 47               | 3.4        | 1.26 [0.46, 3.41]               |                                |
| Xu Chen 2020            | 19            | 50           | 20                | 241              | 5.3        | 4.58 [2.64, 7.93]               |                                |
| Yafei Wang 2020         | 15            | 38           | 8                 | 72               | 4.3        | 3.55 [1.66, 7.62]               |                                |
| Yu Shi 2020             | 26            | 49           | 73                | 438              | 6.2        | 3.18 [2.27, 4.46]               |                                |
| Zhenhua Zeng 2020       | 30            | 117          | 45                | 157              | 6.0        | 0.89 [0.60, 1.33]               |                                |
| **Total (95% CI)**      | 1949          | 6067         | 100.0             |                  | 1.91 [1.48, 2.48] |                                |

Total events: 545
Total (95% CI)

Heterogeneity: $\tau^2 = 0.25; \chi^2 = 112.65, df = 20 (P < 0.00001); I^2 = 82%$

Test for overall effect: $Z = 4.90 (P < 0.00001)$

(a)

Figure 4: Continued.
antihypertensive drugs recommended in current guidelines. Although ACE is not directly inhibited by ACE inhibitors, ACE2 is affected by chronic treatment with these drugs, which leads to an increase in ACE2 expression in several tissues [44]. Interestingly, this feature is also shared by another drug, angiotensin receptor-1 blocker (ARB).

According to the circulating level of the ACE2 product angiotensin 1–7, long-term administration can also increase the expression level and activity of ACE2 [45]. The use of ACEIs/ARBs in COVID-19 patients with hypertension has caused great controversy. We performed a meta-analysis on the application of ACEIs/ARBs in patients with COVID-19...

| Study or Subgroup | Non-Survivors | Survivors | Weight (%) | Risk Ratio (M-H, Random, 95% CI) | Risk Ratio (M-H, Random, 95% CI) |
|------------------|--------------|-----------|------------|---------------------------------|---------------------------------|
| Bo Hu 2020       | 8            | 16        | 34         | 9.0                             | 1.70 [0.83, 3.48]               |
| Fei Zhou         | 26           | 54        | 32         | 137                             | 11.7                            | 2.06 [1.37, 3.11]               |
| Huisi He 2020    | 25           | 42        | 52         | 92                              | 12.3                            | 1.00 [0.71, 1.40]               |
| Kun Wang         | 10           | 22        | 35         | 283                             | 10.4                            | 3.68 [2.11, 6.39]               |
| Lin Fu 2020      | 22           | 34        | 79         | 166                             | 12.6                            | 1.36 [1.01, 1.83]               |
| Wei jie Guan 2020| 28           | 50        | 241        | 1540                            | 12.8                            | 3.58 [2.73, 4.70]               |
| Xingwei He 2020  | 12           | 26        | 12         | 28                              | 10.0                            | 1.08 [0.59, 1.95]               |
| Yimei Yin 2020   | 27           | 52        | 22         | 60                              | 11.6                            | 1.42 [0.93, 2.16]               |
| Zhenhua Zeng 2020| 7            | 21        | 68         | 253                             | 9.6                             | 1.24 [0.66, 2.35]               |
| **Total (95% CI)**| **317**      | **2553**  | **100.0**  | **1.71 [1.19, 2.46]**           |                                 |

Total events: 165
Non-Survivors 530

Heterogeneity: $\tau^2 = 0.25; \chi^2 = 53.11, df = 8 (P < 0.00001); I^2 = 85%$

Test for overall effect: $Z = 2.91 (P = 0.004)$

Figure 4: (a) Forest plots depict the comparison of the incidences of hypertension in severe/ICU and nonsevere/ICU patients. (b) Forest plots depict the comparison of the incidences of hypertension in nonsurvivors and survivors. Forest plots depict the comparison of the incidences of cardiac injury in ICU/severe and non-ICU/severe patients.

Figure 5: (a) Bubble plots for the association of hypertension with severe/ICU rates in COVID-19 cases. (b) Bubble plots for the association of hypertension with mortality in COVID-19 cases.
and hypertension and found that 27.6% (95% CI: 15.8–39.4%) of patients received ACEI/ARB therapy. The proportion of nonsurvivors or severe patients with hypertension and COVID-19 treated with ACEIs/ARBs was lower than that of survivors or nonsevere patients. The use of ACEIs/ARBs upregulated the expression of ACE2, which might increase susceptibility to COVID-19 and in turn reduce the severity of the disease. In Zhang’s study, among hospitalized COVID-19 patients with hypertension, the use of ACEIs/ARBs was associated with a lower risk of all-cause mortality. The upregulation of ACE2 induced by long-term intake of AT1R and ACE inhibitors may play a protective role through the following two mechanisms, first, by blocking the increase of angiotensin 1–7 and, second, by reducing the production of angiotensin II [46].

There were several limitations in the present study. First, there was a difference in the proportion of hypertension among the included cohorts, which may account for the heterogeneity. Occasionally, a small number of samples were reused, which might lead to bias; however, they cannot be excluded crudely in order to avoid bias caused by incomplete data inclusion. Second, the differences in sample size and study design in different studies may be one of the reasons for the heterogeneity. Third, in different studies, severe patients are defined according to different criteria. To simplify the conclusions and improve readability, we combined the severe patients and ICU patients into one category for analysis. In addition, confounding factors (such as sex, smoking, drinking, and history of other comorbidities) in studies may have impacted the outcomes of the patients.

**Data Availability**

The data supporting the findings of this study are included within the article.

**Additional Points**

Notwithstanding these limitations, our pooled analysis showed that patients with hypertension might be less susceptible to SARS-CoV-2. However, patients with previous

| Studies               | Estimate (95% C.I.) | Ev/Trt |
|-----------------------|--------------------|--------|
| Peng Zhang 2020       | 0.167 (0.145, 0.188) | 188/1128 |
| Juan Meng 2020        | 0.333 (0.204, 0.463) | 17/51  |
| Zhenhua Zeng 2020     | 0.373 (0.264, 0.483) | 28/75  |
| Yingxia Liu 2020      | 0.261 (0.134, 0.388) | 12/46  |
| **Overall (I^2=85.28 % , P< 0.001)** | 0.276 (0.158, 0.394) | 245/1300 |

**Figure 6:** (a) Prevalence of usage of ACEIs/ARBs in COVID-19 patients with hypertension. (b) Comparison of mortality in ACEI/ARB and non-ACEI/ARB patients. (c) Comparison of the incidences of the severe/ICU rate in ACEI/ARB and non-ACEI/ARB patients.
hypertension may be at increased risk of developing worse clinical outcomes and even death. ACEIs/ARBs can control the blood pressure of COVID-19 patients with hypertension, which may improve the prognosis and reduce mortality.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
Bo Li and Lu Zeng contributed equally to this work.

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