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A STUDY ON CORRELATION BETWEEN SYSTEMIC HYPERTENSION IN COVID-19

General Medicine

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ABSTRACT

Coronavirus 2019 (COVID-19) causing severe acute respiratory syndrome. (SARS-CoV-2), has affected more than seven million people worldwide. The virus enter the cell through angiotensin-converting enzyme (ACE)-2 receptor . Hypertension as well as cardiovascular disease coexist with COVID-19 have generated discussion on the management of patients with hypertension. Here we discuss the pathophysiology of SARS-CoV-2 infection with ACE2 receptors, the cardiovascular system, and the kidney. Result showing evidence on the use of antihypertensive medication such as ACE inhibitors and angiotensin receptor blockers in SHTN patients with COVID-19.

KEYWORDS

Prevalence of hypertension among COVID-19 patients

Although emerging reports have demonstrated a high prevalence of hypertension among patients with COVID-19 , evidence is still insufficient For example, 58 of 191 patients with COVID-19 (30.4%; median age, 56.0 years) had hypertension, and investigators in these studies [4, 5] reported a high prevalence of hypertension among patients with COVID-19. However, nationwide survey showed that 44.6% of the population aged 55–64 years had hypertension . Furthermore, it should be noted that demographic data among patients, including comorbidities, were collected by different methods (by electronic medical records [4, 6] or by phone [5]). Most importantly, none of the currently available epidemiological studies regarding COVID-19 and hypertension clearly state the diagnostic methodology used or the criteria for hypertension, e.g., BP values based on office or out-of-office measurement, as well as self-reported or testimony of a family in serious situations. These variations would make the comparison of reported incidence with that in the general population inaccurate. Taking the high proportion of individuals with hypertension who are not aware of their condition [10] into account, it would be a reasonable assumption that the prevalence of hypertension in these reports [4–6] may be underestimated. Nevertheless, no supporting report was found that shows a higher rate of hypertension among patients with COVID-19, and there have been no reliable reports demonstrating an increased risk of SARS-CoV-2 infection in the presence of hypertension

Impact of hypertension on the severity and mortality of COVID-19

Comparisons of COVID-19 patients with mild and severe clinical symptoms can be used to evaluate whether hypertension is a risk factor for aggravation of the disease. According to a retrospective study consisting of 487 COVID-19 patients ,the prevalence of hypertension was higher in the 49 severe cases than in the 438 mild cases (53.1% vs. 16.7%, $p < 0.0001$) [11]. Further multivariable-adjusted analysis revealed that male sex, age ≥50 years old, and hypertension were independent factors for COVID-19 severity on admission (odds ratio, 2.71; 95% confidence intervals 1.32–5.59) [11]. In another study involving 548 inpatients in the first COVID-19 outbreak occurred in December 2019 [12], the prevalence of hyper- tension was significantly higher in patients with severe COVID-19 than in nonsevere cases (38.7% vs. 22.2%, $p < 0.001$). In a logistic model with adjustment for age, high lactate dehydrogenase (LDH), and D-dimer, hypertension was independently associated with the severity of COVID- 19 on admission (odds ratio, 2.01; 95% confidence inter- vals, 1.27–3.17) [12].

However, it should be noted that hypertension is commonly accompanied by many comorbidities that are major determinant factors for the severity of COVID-19. The study [12] also reported that male sex, age ≥65 years old, high white blood cell count, LDH, cardiac injury, hyperglycemia, and high dose corticosteroid were independent predictive factors for death in a multivariable-adjusted Cox proportional hazard model. Nonetheless, hypertension was not included as a candi- date explanatory factor in the multivariate analysis. A French single-center study [13] reported that hyperten- sion was not significantly associated with progression of COVID-19, as defined as the requirement of invasive mechanical ventilation during hospitalization (OR, 2.29; 95% CI, 0.89–5.84; $p = 0.08$), even though the associa- tion was significant in a univariate model. In these and other studies, hypertension was not selected as an inde- pendent factor for COVID-19 severity based on multivariable-adjusted analysis, despite being identified as a risk factor by univariate [4, 12–14] or bivariate [15] survival analysis. Although some studies report that hypertension can be an independent risk factor for severe COVID-19 [11, 12], it would be plausible to interpret that the high prevalence of hypertension among patients with severe and fatal COVID-19 may be attrib- uted to the vulnerability of older individuals to SARS- CoV-2 infection. At present, there is no clear epide- miological evidence supporting that hypertension itself is an independent risk factor for developing severe dis- ease in patients with COVID-19. We, therefore, agree with the conclusion of the Centers for Disease Control and Prevention (CDC), which does not include hypertension in the list of risk factors for COVID-19 severity [16

Key comorbidities of hypertension in relation to COVID-19

As mentioned above, age is the essential risk factor for increased severity and mortality in COVID-19. In COVID-19 patients aged 70–79 and ≥80 years were 6.8% and 14.8%, respectively, whereas COVID-19 mortality in all age groups was 2.6% as of 7 May 2020 [17]. In addition to age, available reports have suggested a variety of underlying medical conditions to be associated with COVID-19 disease severity and mortality[4–6, 11, 12, 15, 16]. Furthermore, the majority of these risk factors are observed in patients with hypertension [9, 18]. In clinical practice, one may not always have enough time to assess comorbidities in acute-phase patients with COVID-19. In such situations, hypertension diagnosed by various methods might be regarded as a marker of the severity of the disease.

COVID-19 and ACE2

ACE2 as the entry receptor for SARS-CoV-2

The first step of SARS-CoV-2 infection in humans is con- tact of the virus with cell-surface ACE2 (Fig. 1). ACE2 interacts with external SARS-CoV-2 by binding to the receptor-binding domain (RBD) of the viral spike protein [23]. This process is followed by proteolytic cleavage of the spike protein, which allows fusion to cells, and transmem- brane protease serine 2 (TMPRSS2) has been identified as a protease responsible for the reaction (Fig. 1) [24]. Although SARS-CoV, which was responsible for SARS outbreaks in 2002–2004, uses the same ACE2 and TMPRSS2 for entry, our understanding of the differences between SARS-CoV and SARS-CoV-2 with regard to their cell entry mechanism

has been rapidly developed by recent studies, including structural analysis of these viruses [25–29]. Interestingly, ACE2 binds with higher affinity to the RBD of SARS-CoV- 2 than that of SARS-CoV. Paradoxically, however, the affinity of ACE2 for the entire SARS-CoV-2 spike protein is comparable to that of SARS-CoV, suggesting that the SARS-CoV-2 RBD is less exposed than is the SARS-CoV RBD [26].

Antihypertensive agents during the COVID- 19 pandemic

Use of ACE inhibitors and ARBs in patients with COVID-19

Because ACE inhibitors and ARBs may increase the amount of ACE2, whether these drugs should be discontinued during the COVID-19 pandemic has been a topic of discussion [152, 153]. The role of ACE2 in the pathophysiology of COVID-19 as well as experimental evidence for ACE2 and RAS inhibitors are reviewed in detail in the previous sections. In the following sections, we discuss the clinical evidence for COVID-19 and antihypertensive agents.

Although several reports in an early phase of the COVID-19 pandemic have suggested the relationship between COVID-19 and ACE inhibitors or ARBs [154, 155], it is possible that the association between COVID-19 and hypertensive medication results from reverse causality because older patients, who are at the highest risk for COVID-19, tend to have multiple comor- bidities, including hypertension and CVD. Moreover, adjustments for age and other possible confounding factors were not performed in most of the early studies [156–158]. Several recent reports analyze the effect of ACE inhibitors and ARBs on clinical outcomes in patients with COVID-19 and hypertension [159, 160]. A retrospective, single-site, cohort study from Wuhan compared clinical outcomes among 126 COVID-19 patients with pre-existing hypertension (43 of whom were taking either ACE inhibitors or ARBs; 83 of whom were not taking these agents) and 125 age- and sex- matched COVID-19 control patients without hypertension [159]. In that study, it was found that ACE inhibitors or ARBs did not increase the risk of morbidity or mortality in patients with SARS-CoV-2 infection. Moreover, the study showed a nonsignificant trend toward marginally lower cri- tical illness and death rates in patients taking ACE inhibitors or ARBs compared to those taking other antihypertensive agents. In a study from Spain, a case-population study (1139 cases and 11,390 population controls) showed that users of ACE inhibitors or ARBs had an adjusted odds ratio for COVID-19 requiring admission to hospital of 0.94 (95% CI 0.77–1.15) compared to users of other antihypertensive drugs, with no increased risk for ACE inhibitors or ARBs [160]. This study concluded that ACE inhibitors or ARBs do not increase the risk of COVID-19 requiring admission to the hospital, including fatal cases and those admitted to ICU, and that these agents should not be discontinued to prevent the development of severe COVID-19 [160].

Two other retrospective cohort studies from China comparing disease severity and mortality rates between hypertensive patients taking ACE inhibitors or ARBs and those not taking these agents are available [161, 162]. One, a single-center study, showed that the percentage of patients taking ACE inhibitors and ARBs did not differ between those with severe and nonsevere infections or between survivors and nonsurvivors [161]. In the other, a multicenter cohort study, hypertensive patients with COVID-19 who were taking ACE inhibitors or ARBs were compared with those who were taking antihypertensive drugs other than ACE inhibitors and ARBs as well as patients with COVID- 19 without hypertension [162]. The risk for 28-day all-cause mortality was lower in the ACE inhibitor/ARB group than in the control group (adjusted HR 0.42, 95% CI 0.19–0.92; $P = 0.03$) and in matched subgroup analysis (adjusted HR 0.30, 95% CI 0.12–0.70; $P = 0.01$).

In addition, two clinical studies from northern Italy and from New York provide further evidence on the association between antihypertensive medication and COVID-19 [163, 164]. In the case-control study in Italy, which inclu- ded 6272 patients with COVID-19 and 30,759 controls matched for age, sex, and municipality of residence, after adjustment for drugs and coexisting conditions, the odds ratios for the use of ACE inhibitors and ARBs were 0.96 (95% CI 0.87–1.07) and 0.95 (95% CI 0.86–1.05), respectively, among all patients and 0.91 (95% CI 0.69–1.21) and 0.83 (95% CI 0.63–1.10), respectively, among patients who had a severe or fatal course of the disease [163]. In the New York study, none of the major classes of antihypertensive drugs, including ACE inhibitors and ARBs, were associated with a positive SARS-CoV-2 test or disease severity [164].

Taken together, the data from these six studies, although retrospective, from different countries [159–164] provide evidence for continuing treatment with ACE inhibitors or ARBs in patients with hypertension during the COVID-19 pandemic. Moreover, a recent meta-analysis showed the potential benefit of ACE inhibitors or ARBs in patients with hypertension [165]. In nine studies comprising 3936 patients with hypertension and COVID-19, ACE inhibitors or ARB treatment was not associated with disease severity but was related to lower mortality from COVID-19 com- pared with other antihypertensive drugs. Although future well-designed randomized controlled trials are needed, these results suggest that treatment with ACE inhibitors or ARBs should be continued in COVID-19 patients with hypertension Current conclusion regarding the use of antihypertensive agents during the COVID-19 pandemic In the early phase of the COVID-19 pandemic, there was considerable confusion regarding whether ACE inhibitors The aforementioned two studies on RAS inhibitors also address the association of COVID-19 with other classes of antihypertensive agents [163, 164]. In one study, the adjusted odds ratios for COVID-19 associated with the use of calcium-channel blockers, beta-blockers, thiazide diure- tics, loop diuretics, and MRA were 1.03 (95% CI 0.95–1.12), 0.99 (95% CI 0.91–1.08), 1.03 (95% CI0.86–1.23), 1.46 (95% CI 1.23–1.73), and 0.90 (95% CI 0.75–1.07), respectively [163]. Thus, none of the anti- hypertensive agents except loop diuretics were associated with an increased risk of COVID-19 in multivariate ana- lysis. In the study population, loop diuretics were used more frequently in patients with COVID-19 than controls (13.9% versus 7.8%; relative difference, 43.6%) [163], and their use may reflect the existence of severe comorbidities such as heart failure and renal dysfunction, the severities of which were not appropriately quantified [163]. In another study, calcium-channel blockers, beta-blockers, and thiazide diuretics were not associated with an increased likelihood of a positive SARS-CoV-2 test

Areas of uncertainty and future perspectives

In this article, we review recent studies on COVID-19 in the context of hypertension and related diseases. As discussed in detail, there are no reliable reports on whether SARS- CoV-2 infection risk is increased in patients with hyper- tension. Hypertension is known to be associated with endothelial injury, especially in the elderly [175], and recent evidence suggests that thromboembolism triggered by endothelial injury is one of the important complications that influence disease outcome in COVID-19. At this time, it is unclear whether pre-existing endothelial injury increases the severity of COVID-19; however, hypertensive patients with atherosclerotic diseases may need to be carefully monitored for the occurrence of new-onset CVDs during SARS-CoV-2 infection.

Given that hypertension is the leading contributor to the development of cardiovascular and kidney diseases and given that myocardial injury and advanced CKD are asso- ciated with an increased risk of severe disease following SARS-CoV-2 infection, optimal management of hyperten- sion can contribute to a better prognosis of COVID-19 by mitigating the progression of these disorders. Regardless, amajor challenge is to achieve target BP control in the "New Normal" lifestyle, in which health care workers may have areduced opportunity for in-person clinical examination of patients. In the Great East Japan Earthquake in 2011, medical care for patients with hypertension was compro- mised ("disaster hypertension") [176]. After the recognition of BP increases following the disaster, which may have contributed to the increased cardiovascular events [176, 177], the remote BP monitoring system using infor- mation and communication technology (ICT) was intro- duced and was indeed useful in achieving target BP control [178, 179]. Therefore, in the post-COVID-19 era, medical practice using ICT may need to be widely implemented for the management of hypertension. In addition, the COVID- 19 pandemic may increase the risk of mental disorders

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