COVID-19 Comorbidities: How Do Underlying Hypertensive and Cardiovascular Conditions Affect the Prognosis and Therapies of COVID-19?

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Abstract: The coronavirus disease 2019 (COVID-19), a contagious disease caused by the SARS-CoV-2 virus, spread worldwide in a short period and affected the lives of billions of people. Recent studies have found that many COVID-19 patients have underlying comorbidities that lead to acute disease prognosis and more severe complications of COVID-19 symptoms. Among all common comorbidities, hypertension and cardiovascular-related diseases appear more frequently in patients. In this review, we investigate the bidirectional interaction between COVID-19 and the cardiovascular system by clarifying the effects of SARS-CoV-2 infection on underlying hypertension conditions and cardiovascular disorders and how hypertension and cardiovascular diseases affect the mortality and prognosis COVID-19. Combined with analysis of promising but currently controversial remedies for COVID-19, such as anti-hypertensive therapies that use ARBs and ACE inhibitors and other treatments of acute COVID-19 cardiovascular syndrome, we could better understand the interactions between SARS-CoV-2 virus and hypertensive-cardiovascular related comorbidities to develop safer and more effective treatments for COVID-19.

1 INTRODUCTION

COVID-19 is a contagious disease caused by SARS-CoV-2. Researchers have found that SARS-CoV-2 has numerous similar biological characteristics to SARS-CoV, which caused the 2002 outbreak. SARS-CoV-2 binds the viral spike protein to ACE2 for cell entry into human bodies (Allen, Altae-Tran, Briggs, Jin, McGee, Shi, Lin, Bansal, Bosso, Thanaraj, Abu-Farha, Alanbaei, Abubaker, & Al-Mulla 2020)

Comorbidities increase the severity of COVID-19 symptoms, prolong the viral clearance time, and deteriorate acute disease prognosis, thus leading to more severe forms and complications of COVID-19 in patients (De Cauwer, Ejaz, Alsrhani, Zafar, Javed, Junaid, Abdalla, Younas, Esakandari, Nabi-Afjadi, Fakkari-Afjadi, Farahmandian, Miresmaeili, & Bahreini, Fang, Karakiulakis, & Roth 2020). Among these factors, we found that hypertension and cardiovascular diseases are associated with cardio-cerebrovascular systems. The exceeding frequency of COVID-19 patients with hypertension and cardiovascular diseases implies the crucial role they played in the prognosis of COVID-19 patients and thus need to be investigated comprehensively.

This review will collect common comorbidities found by various studies and evaluate the substantial incidence of COVID-19. We will investigate the mechanisms of how the SARS-CoV-2 virus affects hypertension and cardiovascular conditions of patients. The impacts of underlying hypertension and cardiovascular diseases on the progression and prognosis of COVID-19 will be collected as well, especially factors that affect the morbidity and mortality of COVID-19 (Fox, Akmatbekov, Harbert, Li, Quincy Brown, & Vander Heide 2020), we also analyze current treatments toward COVID-19 induced comorbidities in line with ACE2 expression mechanism. There are debates about whether using RAAS inhibitors (ARBs and ACEI) in COVID-19 patients is effective, with some studies claiming they could alleviate inflammatory responses (Fujihashi, & Jones 2020) while other studies were arguing that they would rise the severity of COVID-19 symptoms instead (Garg, Kim, Whitaker, O'Halloran, Cummings, Holstein, Fry 2020). The treatments toward acute myocardial injury, a representative acute

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respiratory syndrome associated with high mortality of hospitalized COVID-19 patients, are also investigated to show that current treatments toward COVID-19 induced comorbidities involve complex factors, and the efficacy of many treatments are still uncertain.

2 COVID-19 CLINICAL CHARACTERISTICS

COVID-19 patients could report various symptoms ranging from mild symptoms to severe illness and even death. COVID-19 symptoms usually begin between 2 and 14 days after being infected, and the incubation period is estimated to be approximately 5 days after exposure to the SARS-CoV-2 virus, similar to SARS (Garg, S). The virus can be spread to others from someone infected with the coronavirus but is in the pre-symptomatic or asymptomatic state (Gasmi, Peana, Pivina, Srinath, Gasmi Benahmed, Semenova, Menzel, Dadar, & Bjørklund 2021, Gold, Guo, Fan, Chen, Wu, Zhang, He, Lu 2020).

According to information from CDC as shown in Figure 1, it would be necessary to seek emergency medical attention if patients manifest severe symptoms, (Guo, Fan, Chen, Wu, Zhang, He, Lu 2020, Hancox, Hasnain, Vieweg, Crouse, & Baranchuk 2013). Based on 3,661,716 total responses about COVID-19 symptoms collected in the United States, the common symptoms reported by most users (73%) (Hendren, Drazner, Bozkurt, & Cooper 2020).

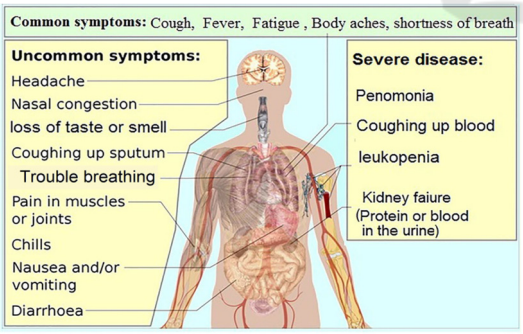

Figure 1. The systemic disorders caused by COVID-19 (Lauer, Grantz, Bi, Jones, Zheng, Meredith, Lessler 2020).

COVID-19 could be especially life-threatening to older adults and young children. The severity of COVID-19 varies dramatically for patients of different ages. Age as a risk factor seems to be independent of common comorbidities (Liu, Huang, Xu, Yang, Qin, Cao, Jiang 2020). Additionally, old adults with severe underlying medical conditions seem to have higher risks of developing more serious COVID-19 symptoms (Hancox, Hasnain, Vieweg, Crouse, & Baranchuk 2013). Children infected with COVID-19 usually have a milder illness than adults. Additionally, these children may also tend to experience very rare complications of the coronavirus, such as having abdominal symptoms like skin changes or rashes (Maragakis 2021).

3 PROFILE OF COMORBIDITIES

Current studies have revealed that the severity of COVID-19 is highly related to comorbidities (Mayo Clinic Staff 2021). Comorbidities contribute to acute disease prognosis, and increased risk of severe symptoms and more comorbidities were found in severe cases compared to non-severe cases (Bosso, Thanaraj, Abu-Farha, Alanbaei, Abubaker, & Al-Mulla 2020). In a research study, over 50% of patients reported having at least one comorbidity, and around 70% of ICU patients have been observed to have comorbidities (De Cauwer 2020). Another study conducted among 178 adult patients about underlying conditions shows that 89.3% of patients had one or more underlying conditions (McGonagle, Plein, O'Donnell, Sharif, & Bridgewood 2020). To be specific, different types of comorbidities need to be investigated.

A study among 225 patients with severe COVID-19 symptoms who were hospitalized in eight Georgia hospitals during March 2020 reported comorbidities including hypertension (67.5%), diabetes (39.7%), cardiovascular disease (25.6%), chronic lung disease (20.3%), severe obesity (BMI ≥40, 12.7%) (Mayo Clinic Staff 2021). The percentage of each type of comorbidity is shown in Figure 2. These studies show that hypertension, obesity, and cardiovascular diseases are the top 3 comorbidities of COVID-19. We have noticed that two of the three most common commodities are related to a heart condition and blood pressure (Meng, Xiao, Zhang, He, Ou, Bi, Zhang 2020). This suggests that people with preexisting high blood pressure may be at higher risk of becoming severely ill with COVID-19 and may induce further hypertensive heart conditions and high blood pressure. The exceeding frequency implies a causal relationship between hypertension and COVID-19, leading to more severe complications of COVID-19 in patients (Mueller, McNamara, & Sinclair 2020). Therefore, this review will mainly focus on hypertension and cardiovascular problems, investigating how the SARS-CoV-2 virus interacts with these underlying

conditions and how these conditions impact the progression and prognosis of COVID-19 (Muhamad, Ugusman, Kumar, Skiba, Hamid, &amp, Aminuddin 2021).

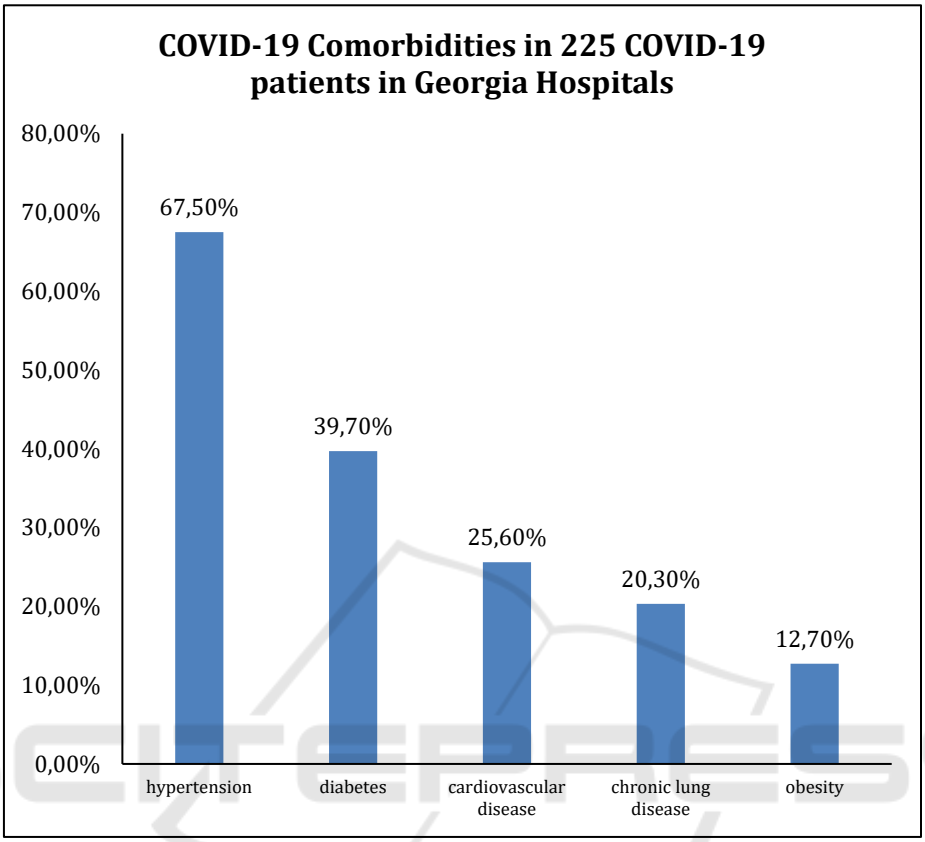

Figure 2. Common comorbidities associated with COVID-19 infection collected from clinical outcomes of adult patients hospitalized in Georgia (Mayo Clinic Staff 2021).

4 THE MECHANISM OF COVID-19-INDUCED DETERIORATION OF HYPERTENSION AND CARDIOVASCULAR DISEASE

The mechanisms underlying this interaction need to be figured out to clarify the bidirectional interaction between COVID-19 and the cardiovascular system. Figure 3 shows how COVID-19 interacts with underlying comorbidities and leads to cardiovascular complications.

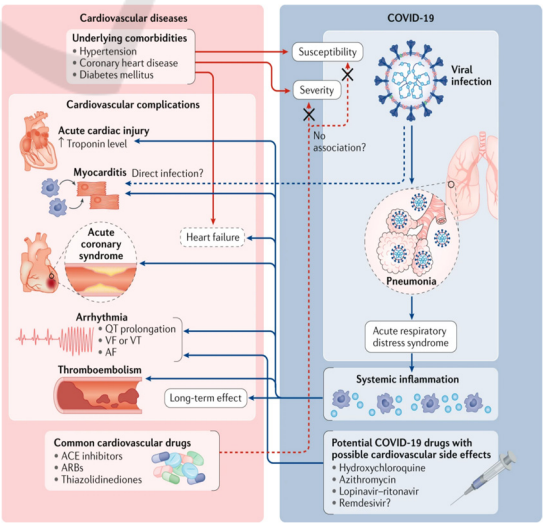

Figure 3. Bidirectional interaction between cardiovascular diseases and COVID-19 (Allen, Altae-Tran, Briggs, Jin, McGee, Shi, Lin 2020).

The mechanisms and pathophysiology underlying the development of COVID-19-related cardiovascular injury are currently unclear, but ACE2, a surface protein for SARS-CoV-2 virus entry and part of RAAS, is known to be a significant factor involved in the biological mechanism of COVID-19 infection (Nishiga, Wang, Han, Lewis, & Wu 2020). It would be possible that SARS-CoV-2 could directly infect multiple cardiovascular cell types. However, since the expression of ACE2 in itself is not sufficient for the virus to enter the cell, the interaction is more likely to affect the cardiovascular system in an indirect manner (Allen, Altae-Tran, Briggs, Jin, McGee, Shi, Lin 2020).

The factors that trigger the impact of the SARS-CoV-2 virus on hypertension conditions are controversial. Some studies mentioned that that originally target the Renin-Angiotensin System (RAS) for anti-hypertensive purposes. In certain studies, they are demonstrated to increase ACE2 expression and thus increase the severity of COVID-19 symptoms (Garg, Kim, Whitaker, O'Halloran, Cummings, Holstein, Fry 2020). In contrast, in other studies, the use of ACEi/ARB drugs attenuates inflammatory responses of COVID-19 patients by inhibiting IL-6 cytokine levels (Osibogun, Balogun, Abayomi, Idris, Kuyinu, Odukoya, Akinroye, Pettersson, Manley, & Hernandez 2021).

5 IMPACTS OF HYPERTENSION AND CARDIOVASCULAR DISEASES CONDITIONS ON THE PROGNOSIS OF COVID-19

Many studies evaluating COVID-19 prognosis demonstrated that cardiovascular diseases and hypertension conditions significantly increase the severity and mortality rate of COVID-19 patients (Garg, Kim, Whitaker, O'Halloran, Cummings, Holstein, Fry 2020). The impacts could be best manifested in mortality rate data (Preventing the spread of the coronavirus. 2021). Accordingly, the case fatality rate (CFR) was also significantly higher for patients with hypertension and CVD (Meng, Xiao, Zhang, He, Ou, Bi, Zhang 2020). Additionally, a research study suggested that hypertension and cerebro-cardiovascular diseases could be critical factors that lead to the higher mortality of COVID-19 patients.

To evaluate factors that cause the high mortality rates for COVID-19 patients with hypertension and cerebro-cardiovascular diseases, Sharon Fox el. from the Lancet Respiratory Medicine demonstrates that the high mortality rates could be attributed to severe lung involvement, diffuse alveolar damage, and pulmonary tissue destruction (Public Health Agency of Canada. 2021). The infected alveolar ACE2+ (angiotensin-converting enzyme 2) cells with extensive pulmonary vasculature lead to pulmonary hypertension development due to a pulmonary intravascular coagulopathy. Therefore, ACE2 expression on endothelial cells could cause virally mediated endothelins linked to increased mortality (Riphagen, Gomez, Gonzalez-Martinez, Wilkinson, & Theocharis, Ruan, Yang, Wang, Jiang, & Song, Sanyaolu, Okorie, Marinkovic, Patidar, Younis, Desai, Altaf 2020). In another study in the scope of 150 patients, 32% of patients were reported to have an acute myocardial injury with heart failure as a contributing factor (Schiffrin, Flack, Ito, Muntner, & Webb 2020). These data demonstrate that pulmonary-related diseases and acute myocardial injury could be the commonly observed complications leading to the higher mortality of COVID-19 patients with hypertension and cardiovascular diseases.

Some studies use the cardiac troponin T level as a predictive prognosis parameter (Shi, Qin, Shen, Cai, Liu, Yang, Huang 2020). Combined with other studies, acute myocardial injury is an essential factor in the death of COVID-19 patients, and the markers of myocardial injury could be used to predict the risk of in-hospital mortality in patients with severe COVID-19.

6 TREATMENTS TOWARD COVID-19 INDUCED COMORBIDITIES

Among widely known treatments, many targeted the mechanism of the interaction between SARS-CoV-2 virus and ACE2 molecules to alleviate hypertension-related COVID-19 symptoms. Combined with other studies that revealed the elevated expression of ACE2 in blood samples from COVID-19 patients (Symptoms of covid-19. (2021), Turner, Hiscox, & Hooper 2004, Wan, Shang, Graham, Baric, & Li 2020). While ACEIs/ARBs are proven to be effective in preventing and treating COVID-19 infections in some animal studies, limited clinical data in humans could show that ACE-inhibitors or ARBs affect the severity of COVID-19 patients with CVD comorbidity, either improve or deteriorate (Wu, & McGoogan 2020). By contrast, another retrospective

study was conducted among 511 COVID-19 patients with hypertension comorbidity to compare the severity of SARS-CoV-2 infection for those who used one of the anti-hypertension drugs and those who used none (Yang, Tan, Zhou, Yang, Peng, Liu, He 2020). The implication of this study recommends using treatments with ACEI and ARBs are continuously in patients with hypertension or CVD to reduce the morbidity and mortality of SARS-CoV-2 infection, especially in elderly COVID-19 patients (Fujihashi, & Jones 2020). Therefore, anti-hypertensive therapies such as ARBs or ACEI could be a possible solution to COVID-19 patients with hypertensive-related comorbidities, but the efficacy and potential effects still need further investigation.

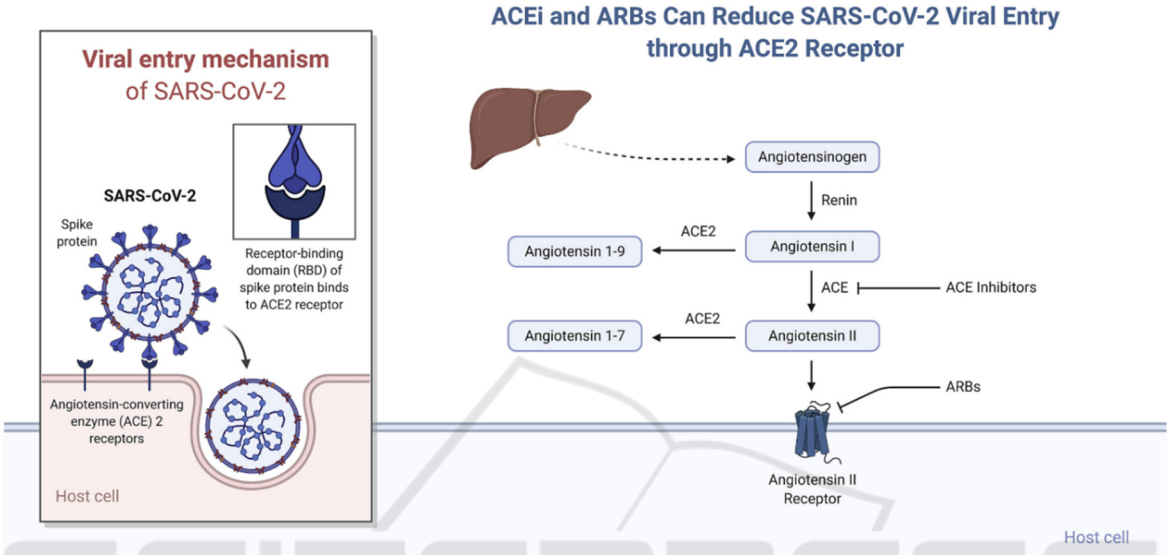

Figure 4. ACE2 in the Entry of SARS-CoV-2 into the Host Cell and the function of ACEi and ARBs to reduce SARS-CoV-2 viral entry (Pettersson, Manley, & Hernandez 2021).

Besides treatments that aim to reduce hypertension-related comorbidities exacerbated by the SARS-CoV-2 virus, other treatments focused on managing the acute COVID-19 cardiovascular syndrome (Allen, Altae-Tran, Briggs, Jin, McGee, Shi, Lin 2020). Due to the contagious nature of COVID-19, the priorities in the diagnosis stage include reducing staff/patient exposures by limiting testing and patient transfer to avoid the delay of diagnostic procedures, though this would reduce the certainty of diagnosis. Therefore, it is essential to minimize the staff/patient exposure for testing while not changing clinical management that recognizes syndromes when the most effective intervention.

One focus among acute respiratory syndromes would be an acute myocardial injury, the comorbidity that appears to complicate the symptoms of hospitalized patients and is associated with high mortality, as mentioned in the earlier paragraph (Ruan, Yang, Wang, Jiang, & Song 2020). In some cases, patients diagnosed with myocarditis relating to COVID-19 were treated with extracorporeal membrane oxygenation, steroids, intravenous immunoglobulins, and antiviral therapy and subsequently recovered.

Treatments need to vary according to the special situations of patients. In multiple COVID-19 clinical studies, Hydroxychloroquine and azithromycin, drugs that show improved clinical recovery time, body temperature recovery time, cough remission time, and pneumonia-related symptoms compared to traditional treatments, are also known to induce arrhythmias, prolong the QT interval, and more likely to have cardiac arrest (Allen, Altae-Tran, Briggs, Jin, McGee, Shi, Lin, Zeng, Liu, Yuan, Wang, Wu, Li, Liu, Zhang, Dong, Cao, Yuan, Yang, Yan, Gao 2020). Another drug combination Lopinavir–ritonavir, should be carefully used in COVID-19 patients (Allen, Altae-Tran, Briggs, Jin, McGee, Shi, Lin 2020). In sum, acute COVID-19 cardiovascular syndrome management needs to consider complex factors (Ruan, Yang, Wang, Jiang, & Song 2020).

7 CONCLUSIONS

Current studies have revealed that comorbidities and underlying conditions are strongly associated with the severity of COVID-19 symptoms, contributing to more acute disease prognosis and increased risk of severe symptoms. Among the most influential comorbidities, hypertension and cardiovascular diseases appear with exceeding frequency in COVID-19 patients. The interaction between the expression of ACE2 protein and the SARS-CoV-2 virus is a significant factor involved in the biological mechanism of COVID-19 viral entry and infection and then affects the cardiovascular system. Hypertension and cardiovascular diseases also impact the progression and prognosis of COVID-19, which are manifested in higher mortality rates and longer viral clearance time. Major factors contributing to high mortality rates of COVID-19 patients with cardiovascular conditions include pulmonary tissue destruction and acute myocardial injury. Potential remedies for COVID-19 include ARBs (angiotensin II receptor blockers) or ACE (angiotensin-converting enzyme) inhibitors, which are anti-hypertensive therapies, but the efficacy and further effects of these treatments are still controversial. Other treatments that focus on the management of the acute COVID-19 cardiovascular syndrome, especially for acute myocardial injury, need to vary according to different situations of patients and consider complex factors. Some treatments of COVID-19 have some known or unknown cardiovascular adverse effects to be noticed. Learned from imperfections of current COVID-19 treatments, researchers may have a clearer direction of drug development that improves efficacy while reducing side effects.

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