Impact of COVID-19 on Cardiovascular Patients and Review of Current COVID-19 Treatment Strategies

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Authors’ contributions

This work was carried out in collaboration among all authors. Author DAA designed the study and wrote the final draft of the manuscript. Author MA managed the literature searches and wrote the COVID-19 and the cardiovascular system section. Author AMA wrote the introduction section. All authors read and approved the final manuscript.

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ABSTRACT

Coronavirus disease of 2019 (COVID-19) has severely affected global health and caused a significant health burden worldwide, particularly in patients with cardiovascular insult. Worldwide, the COVID-19 confirmed cases number reached 81,658,440 cases with 1,802,206 deaths stated to the world health organization by January 1, 2021. Many risk factors, such as the elderly, diabetes, chronic kidney disease (CKD), and cardiovascular illness, like coronary disease, cardiomyopathy, and hypertension; put people at high vulnerability with COVID-19 infection. Many cardiovascular insults directly occur because of COVID-19 infection as myocarditis, pericarditis, heart failure, myocardial infarction, thromboembolic events, or arrhythmias. This review aims to shed light on different management modalities for COVID-19 and discuss the impact of COVID-19 on underlying cardiovascular comorbidities. Our hope lies in the COVID-19 vaccine as the best promising plan against the pandemic with the antiviral medications. Till the availability of antiviral agents and...
Keywords: COVID-19; SARS-CoV-2; cardiovascular; treatment; review.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), known previously as novel coronavirus 2019 (nCoV-19). The number of confirmed cases of COVID-19 reached 81,658,440 cases by January 1, 2021, worldwide, with 1,802,206 deceased cases stated to WHO [1]. The SARS-CoV-2 belongs to the β-coronavirus category; round or elliptic pleomorphic structure and has a small size range from sixty to one hundred-forty nm in diameter. The external morphology of SARS-CoV-2 has multiple nucleoproteins, membranous proteins, and poly-proteins, such as spike glycoproteins S [2]. The latter includes homotrimers that project away from the virus’s exterior, producing a halo-like shape. The virus consists of 6 open-reading frames, common coronaviruses, and some other accessory genes [3]. The genome of SARS-CoV-2 RNA encompasses 29,891 nucleotides, composing around 9860 amino acids. Although we do not entirely comprehend its origin, its genomic analysis proposed the possibility it developed from a species existed in bats [4, 5].

The external membrane thorn glycoprotein of SARS-CoV-2 is the chief protein that targets the host cell receptors (like angiotensin-converting enzyme 2 (ACE2), cyclophilins), essential for cell virulence and adhesion [6]. SARS-CoV-2 causes damage to host cells by attachment to human ACE2, a membrane-bound enzyme found in the pharynx, heart, lungs, neuron, intestine, liver, and kidneys (and also found in other organs). Although pericytes within the heart express the highest levels of ACE2 [7, 8], endothelial and cell cardiomyocytes also express ACE2 [9]. Receptor down-regulation occurs just after the virus attachment to ACE2 and entrance the cell. This is believed to be the host defense process to restrain more viral infiltration or provoke viral mechanisms to escape the immune system. Once endocytosis of the virus occurs, it leaves the endosome and begins its replication. During this process, ACE2 receptor down-regulation markedly reduces the physiological functions of ACE2 in degrading ANG-II into (ANG1-7). ACE2 inhibits the conversion of angiotensin I and II to angiotensin (1-9) and (1-7) [10]. Angiotensin II enforces sympathetic tone, fibrosis, and water and sodium retention across the angiotensin type 1 receptor. While angiotensin 1-7 binds to the receptor, thus counters all these events [10]. A significant number of COVID-19 infected cases have mild to moderate conditions. Yet severe conditions happen in 14% of cases in the form of hypoxia, dyspnea, or 50% of the lung appeared affected on imaging in 24 to 48 hrs. At the same time, critical conditions happen in 5% of the cases, including multiorgan failure, shock, or respiratory failure. The mortality rates extend from 0.09% up to 12%, regarding the population sample in the study [11,12]. Severe conditions and elevated mortality have been linked with diabetes, cardiovascular insults, dyslipidemia, hypertension, smoking, cancer, chronic kidney and lung disease, and obesity [13,14]. In this review, we aimed to direct the main focus on the various management techniques for COVID-19 and discuss how COVID-19 impacts coexisting cardiac comorbidities.

2. COVID-19 AND THE CARDIOVASCULAR SYSTEM

2.1 Pathogenesis

SARS-CoV-2 produces enormous damage to the heart’s tissues and muscles and directs critical myocarditis [15]. Therefore, many severe myocarditis cases with decreased systolic function have been reported after infection with SARS-CoV-2 [16]. All mechanisms by which the virus involves the myocardium are still unclear; however, they are probably related to direct infection by the viral particles, cytokine storm caused by cell damage, and hypoxia-induced by apoptosis [17]. Severe inflammation (TNFα, IL-1, and IL6) can also adapt to the role of numerous cardiac ion channels, particularly Ca++ and K + channels, which may cause inflammatory cardiac channelopathies [18].

Lethal consequences appear due to the myocardial injuries in patients infected with COVID-19, highly evident by the TnT [19]. This
may be explained by several mechanisms, mostly myocardial insult driven by cytokines, microangiopathy, and infectious viral myocarditis. Yet, none of them helped recognize the key for either the myocardial injury or troponin increase. The elevation in TnT is not counted as proof for acute myocardial infarction (MI), as it might happen due to many factors; on the contrary, it’s less to be increased because of athero-thrombosis of the coronary arteries [20]. Relatively satisfactory outcomes rose in 60% of cardiovascular cases with within-range TnT [21]. Information on cardiac biomarkers’ role reinforced the function of assessing TnT and natriuretic peptides (NT-proBNP and BNP) for evaluating cardiac hazard and prognosis of subjects with serious COVID-19 [22]. Based on the incidence of myocardial insults and complications of the cardiovascular system, the care provided amongst COVID-19 cases might need some adjustments, and the infection risk reduction might be achieved with some limitations [23]. However, other new biomarkers are necessitated for risk stratification, diagnosis, and COVID-19 management in CV patients.

2.2 The ACE2 Implication in Cardiovascular Comorbidities and Complications

We still have no idea about SARS-CoV-2 infectivity and its probable impact on myocarditis despite the reported case reports [16]. Among COVID-19 patients treated and hospitalized in Wuhan, 25% of them had cardiovascular morbidities [24]. ACE2 has been useful in COVID-19 [25]. Cardiovascular diseases, including hypertension, worsened the outcomes in patients with COVID-19 [26]. A few studies showed abnormal pathological features like acute cardiac injury (12%) as one of the clinical features of COVID-19 [27]. Clinical data of COVID-19 patients show that 2.5% to 15% of cases present with coronary heart disease, and 15% to 30% of them present with hypertension [24, 28]. Cardiac injury in these patients is most probably due to the systemic inflammation and the viral involvement of cardiomyocytes [29]. And this potentiates the suggestion that the inflammatory process may be a potential mechanism for MI.

ACE2 improves cardiac function in patients with cardiac diseases [30]. Activation of Renin-Angiotensin system (RAS) and downregulation of ACE2 expression on the cell surface accelerate the pathogenesis of CVDs [31]. The possible effect of ACE2 expression on cardiac function and the susceptibility to heart failure makes it a suitable target for genetic manipulation [25, 32]. ACE2 expression on the cell surface is lower in patients with established heart failure, but ACE2 shows higher activity and higher levels in their circulation than in normal individuals [32, 33]. The higher endogenous ACE2 activity may be due to detaching the membrane-bound ACE2 in COVID-19 patients [34]. Due to its low or non-detectable levels in the circulation, soluble ACE2 is not expected to have an efficient role in SARS-CoV-2 sequestration or to guard against its dissemination [25]. However, we do not know precisely how far ACE2 can competitively bind to SARS-CoV-2 to reduce viremia and tissue injury.

3. TREATMENT

Because no definitive treatment is available, supportive treatment measures are the only used treatment for COVID-19. There are many ongoing treatment strategies. We recommend more clinical trials to investigate the relationship between COVID-19 treatment and CVDs.

3.1 Antiviral Drugs

The use of Antiviral drugs for COVID-19 treatment aims mainly to decrease the infectious shedding and the replication of SARS-CoV-2 [35-43].

Remdesivir is the most frequently used antiviral agent. It is a nucleoside analog used mainly to prevent viral replication, and it was proven clinically as a successful agent in managing many viral infections [44]. Many studies were done to investigate its efficacy; the first one was a randomized controlled trial (RCT), but without any proven virological or clinical benefit in minimizing deaths or recovery time than the placebo group. Furthermore, it has led to severe adverse events, so the trial was early terminated [45]. Initial data from an international multicenter RCT suggest the effectiveness of remdesivir in minimizing the time of recovery from fifteen to eleven days in hospitalized patients [46]. On April 29, 2020, the National Institute of Allergy and Infectious Diseases in the United States stated that remdesivir accelerates the recovery in COVID-19 hospitalized patients – based on the results of the Adaptive COVID-19 Treatment Trial [47]. Recent studies investigate remdesivir specifically for the treatment of COVID-19, and the drug has been approved for use in patients with severe symptoms in the U.S. as an emergency condition [48].
Favipiravir, recently licensed in Japan for treating influenza virus [49-51], is a purine nucleic acid analog taken orally. It acts against a broad spectrum of RNA viruses in vitro. In a trial, better therapeutic effects happened with favipiravir in the progression of the disease and clearing the virus [52]. Comparing favipiravir with arbidol for the treatment of COVID-19, an RCT included 116 subjects for taking favipiravir and 120 subjects for taking arbidol. Within seven days, the clinical presentation’s healing rate reached 71.43% and 55.86% in the favipiravir and the arbidol groups, respectively (p = 0.0199) [53]. In Thailand, an observational retrospective study, including 247 hospitalized COVID-19 adult patients at five tertiary care hospital, found that the group taking favipiravir had better clinical presentation’s healing rate of 71.4% within seven days, which was 67.7% in the group not receiving it. In the meanwhile, the clinical presentation’s healing rate within 28 days was 83.3% with favipiravir. Almost all subjects with COVID-19 (92.6%) who did not need oxygenation clinically improved within their first seven therapy days. This study concluded that favipiravir is a promising treatment for COVID-19, although it was slower to affect more severe patients [54].

### 3.2 Chloroquine / Hydroxychloro-Quine

Chloroquine and hydroxychloroquine increase the endosome’s PH by rapidly protonation and concentration within the endosome, inhibiting viral S protein’s cathepsin-induced priming. Two issues have delayed using chloroquine and hydroxychloroquine. The first one is its mechanism of action; they are more effective when used before or with the onset of the disease as they prevent invading the human cells by the virus. A study stated that the chronic use of hydroxychloroquine protects against SARS-CoV-2 infection [55]. The second one is their documented side effects, including proarrhythmia and Torsade de Pointes [56]. A study has overlooked this issue and has noted these medications may cause QT prolongation, yet physicians seldom needed to stop the treatment [56]. Till now, hydroxychloroquine studies gave the impression of no benefit from hydroxychloroquine administration in COVID-19 cases [57-62]. It was not effective as prophylaxis against COVID-19; it did not prevent the COVID-19 infection within four days of exposure [63]. Generally, its beneficial effect is in question, and until it is determined, clinicians should not use hydroxychloroquine in the therapeutic course of COVID-19.

### 3.3 Anticoagulant

Coagulopathy may develop with significant SARS-CoV-2 infection, mostly a state of hypercoagulopathy, which led to pre-emptive anticoagulant treatment [64]. Despite the reported thrombotic cases, many COVID-19 cases may have hemorrhagic complications [64-68]. A pooled analysis of 35 observational clinical records showed 4,685 incidents of venous thromboembolism, with no previous prophylaxis of 41.9%, with the standard dose of prophylaxis of 19.8%, with the intermediate dose of prophylaxis of 11.9%, and with the therapeutic dose of anticoagulants of 10.5%. The whole arterial thrombosis has incidence levels (No. = 1,464) pooled in this study, which were: with no previous prophylaxis of 11.3%, with the standard dose of prophylaxis of 2.5%, with the intermediate dose of prophylaxis of 2.1%, and with the therapeutic dose of anticoagulants of 1.3%. The bleeding insults rates (No. = 6,393) pooled in this study showed no significant increase with the therapeutic dose than the standard prophylactic dose of the anticoagulants (6.3% against 1.7%, with p = 0.083). The study found that thromboprophylaxis drugs lower thrombosis rates in hospitalized COVID-19 patients. There was no difference between bleeding and thrombosis rates in patients taking intermediate thromboprophylaxis/therapeutic doses than patients taking standard thromboprophylaxis [69].

### 3.4 Amiodarone

It is an ion channel inhibitor used to treat arrhythmias. A retrospective review by Wang et al. in China of 138 COVID-19 cases found that 17% (23 cases) experienced cardiac arrhythmia with a significantly higher incidence, especially with ICU-requiring cases (44.4% against 6.9%, p < 0.001) [24]. In addition, a study found that critical cases of COVID-19 have a higher incidence of arrhythmias than non-critical cases [70]. The previous studies concluded that amiodarone helps in inhibiting SARS-CoV by changing the late endosome [71] and that SARS-CoV-2 is highly similar to SARS-CoV [72]. As a result, amiodarone might be beneficial by a similar mechanism in suppressing SARS-CoV-2 replication. Amiodarone, in many studies, has displayed activity against the virus, while some other studies discovered its ability to prevent the ebola virus from entering in vitro using the mechanism of interfering with the endocytosis pathway and hindering proteolysis [73, 74].
3.5 Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

The enzyme ACE2 is present on the surface of type 2 alveolar epithelial cells within the lung and many other tissues. Additionally, it functions as a spike protein receptor for the SARS-CoV. The SARS-CoV-2 has a higher affinity to ACE2 than that of SARS-CoV by 10 to 20-folds. ACE2 counters the RAAS regulatory component and is approximately 60% homology share with ACE. After angiotensin receptor blockers (ARBs) and ACE inhibitors (ACEIs) administration, ACE2 quantity increases, which in turn its using may cause an increase in the severity of COVID-19, especially with cardiac patients.

On the contrary, the clinical and experimental data have contradicted the results [75, 76]. A recently published meta-analysis, including 68 records with 103,317 hypertensive cases showed that the treatment with ACEIs or ARBs was not related to the increase of SARS-CoV-2 infection in 60,141 cases, 5,925 cases hospitalization, 7,218 cases ITU, 13,163 cases ventilation (or ventilation/ITU/death) or 18,735 cases fatality with the incidence of 2,893 deaths. All in all, a general conclusion that ARBs and ACEIs are safe within the SARS-CoV-2 and have no need to be discontinued [77].

3.6 Colchicine

For the treatment of pericarditis, colchicine is extensively utilized [78]. Increased inflammatory mediators, involving IL-6, IL-8, IL-10, were associated with COVID-19, in addition to tumor necrosis factor-α (TNF-α) [79]. The SARS-CoV-2 has been assumed to stimulate the activation of the NLRP3 inflamasome while the action of colchicine as anti-inflammatory hypothetically inhibits NLRP3. An ongoing RCT in phase 3 evaluates what 30-day therapy with colchicine affect mortality rate and COVID-19 pulmonary complications. This trial’s results would focus the light on the possibility of using colchicine for COVID-19 [80]. A high beneficial result of colchicine has appeared on IL-1b, IL-1b, and CRP in conditions with chronic inflammation in the previously conducted studies [79]. A randomized experimental clinical trial of open-label kind assessed the colchicine’s role in the treatment of COVID-19 by evaluating the colchicine and control groups for clinical deterioration progression time, time to increasing CRP, and varieties in the highest recorded high-sensitivity cardiac troponin (hs-cTn). The authors discovered that CRP and hs-cTn levels were equivalent in both groups. However, an improvement was recorded in clinical deterioration progression time (control 14% versus colchicine 1.8% with an odds ratio (OR) of 0.11, 95% CI 0.01–0.96; p = 0.046) [81]. A systematic review was recently conducted, involving 19 records, examined the use of colchicine in infections. It showed evidence that colchicine might manage COVID-19 by decreasing clinical deterioration progression time, mortality rate, and stay length in hospital [82].

3.7 Statins and PCSK9 Inhibitors

Proprotein convertase subtilisin/Kexin type 9 (PCSK9) inhibitors and statins affect many COVID-19 pathophysiological pathways. Statins have a direct antiviral effect by inhibiting SARS-CoV-2 main protease. ACE2 up-regulation induced by statins might be of great use, while reducing cholesterol may considerably inhibit SARS-CoV-2 by blocking its entry in the host-cell throughout lipid rafts disruptions or suppressing its replications. They may immunomodulate in covid-19 and guard against significant complications, as cytokine release syndrome and ARDS. Regarding their antithrombotic, anti-arrhythmic, antioxidative qualities and beneficial impact on the dysfunction of the endothelium, in addition to a high mortality rate of the cases with elevated cardiovascular risk disease with COVID-19, PCSK9 inhibitors and statins might show effectiveness in the face of the thromboembolic and cardiovascular complications with COVID-19 [12, 24, 83-87]. A meta-analysis of 13 observational clinical studies, recently published, involved 10,829 cases using statins and 31,893 who did not reveal non-critical outcomes. After the univariate analysis, no considerable declines in either severity of COVID-19 or mortality rate in the hospital were stated amongst statin-takers compared with non-takers; such diminutions were detected after regulating the confounding factors. These observational results were highly heterogeneous, which needs confirmation by ongoing experimental randomized trials [88].

3.8 Vaccines

Globally, a total of 164 COVID-19 vaccines in diverse phases of experimental clinical trials, while about 48 vaccines achieved a very decisive stage of trials on humans and all by November 12, 2020. And around 280,000 contributors enrolled from 470 places at least, from 34
various countries [89]. On December 11, 2020, the FDA released its first emergency use authorization (EUA) for a vaccine produced to protect against COVID-19 caused by SARS-CoV-2 in 16 years and older [90]. This EUA permits the Pfizer-BioNTech COVID-19 Vaccine’s distribution in the U.S. After that, the FDA allowed EUA of Moderna (mRNA-1273) for COVID-19 prevention in 18 years and older on December 18, 2020 [91]. The nucleoside-modified mRNA in the Pfizer-BioNTech Vaccine and the Moderna Vaccine for Covid-19 is expressed in the lipid units, allowing RNA release in the cell of the host to make the S antigen of SARS-CoV-2 expressed and that helps the immune system to provoke an immune response fighting Covid-19. Oxford University and AstraZeneca developed a vaccine for COVID-19 using adenovirus. Researchers created the vaccine by genetically altering this virus to hold a gene of a coronavirus protein, which in turn, by theory, would guide the immune system to identify the actual coronavirus. The Pfizer-BioNTech COVID-19 Vaccine got approval by health officials almost four weeks earlier, and it does not have the best effect. A clinical trial in stage three proposed that it prevents the development of the COVID-19 symptoms in 70% of the cases compared to 95% for Moderna (which is distributed in the U.S., not the U.K.) and an approximate one from the Pfizer vaccine.

4. CONCLUSION

Despite the high severity of the COVID-19 pandemic, the current treatments are not explicitly created against SARS-CoV-2. Remdesivir and favipiravir showed good initial results on COVID-19 severe cases, yet they are still under investigation. As a result, the search to find efficient antiviral drugs exclusive to SARS-CoV-2 is still ongoing. Our complete understanding of its diagnosis, spreading, and management is quickly developing. Our hope lies in the COVID-19 vaccine as the best promising plan against the pandemic with the antiviral medications. Developing novel antiviral medications tailored for SARS-CoV-2 will effectively help in the management of COVID-19. At the same time, effective antiviral agents and vaccine development require multidisciplinary collaboration. Till the availability of antiviral agents and effective vaccines, repurposing drugs therapy would continue to be the mainstream. Early-phase cases may benefit from drugs suppressing the virus. Anti-inflammatory agents may help the critically ill COVID-19 cases with cytokine release syndrome features while administering antiviral drugs. Anticoagulants and colchicine showed positive effects on COVID-19, while RAAS use appeared to be safe with COVID-19. Hydroxychloroquine should not be used for COVID-19. In the meanwhile, statins showed a non-significant effect on COVID-19. CVDs may be incident complications or precedent factors in COVID-19 patients. The physicians and the medical staff should be up-to-date regarding probable complications with COVID-19.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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