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Cardiovascular Complications in COVID-19 Pandemic and Its Management

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Authors' contributions

This work was carried out in collaboration among all authors. Author VA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SA and SKP managed the analyses of the study. Author AA managed the literature searches. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Pneumonia like the pandemic COVID-19 is a virus disease, first time came into light in December 2019 in the Wuhan city of China. As of today, more than two million deaths from more than 210 countries have been confirmed. This disease has modeled a great threat to human mental health, physical health, and forcefully stuck the routine life with psychosocial consequences globally. The COVID-19 disease is caused by SARS-CoV-2 which leads to acute respiratory distress. The pathogenesis of the disease started from virus entry to the host cell where it controlled the cellular

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system of the patient directly or indirectly. Population having cardiovascular, immunosuppressive, AIDS, and diabetes-like complications are thought to be very risky for mortality caused by the SARS-CoV-2 virus. The correlation to Noncommunicable diseases like cardiovascular disorders and diabetes has led our attention towards the management of these diseases in the corona outbreak. Thus, this review aimed to better understand the threats modeled by the disease COVID-19 to the cardiovascular system, and the medical community should share their experiences promptly. It is concluded that both published research and real-time experiences shared on social media by world experts will act as a valuable tool and will help to learn more about this disease. Several preventive and therapeutic measures including drug therapy are suggested to manage the disease in comorbidities conditions.

Keywords: SARS-CoV-2; noncommunicable diseases; comorbidities; cardiovascular.

ABBREVIATIONS

Here : the Definitions section;
This : an optional section;
Term : Definition for the term.

1. INTRODUCTION

The Wuhan city of China was first to see the patients of pneumonia, in December 2019, of unknown cause [1]. The pathological reports of various laboratories indicated the causative agent of the disease as a novel coronavirus [2-4]. The name SA§RS-CoV-2 is severe acute respiratory syndrome coronavirus-2, which was allocated to the virus by the WHO and the disease was named coronavirus disease 2019 (COVID 19). WHO declared the disease as pandemic when it started to spread in Europe, Asia, Australia, and then to the USA and Canadian countries [5-7]. As per the current status of the disease on 19 June 2021, there are 177 108 695patients affected with COVID19, and the number of deaths is 3 840 223, in different countries, areas, or territories from all over the world. The disease mainly affects the respiratory system characterized by the symptoms like difficulty in breathing, fever, fatigue, and cough [8,9]. Other systems have also been reported to be affected by the disease like the cardiovascular system, gastrointestinal system. The present study focuses on a high risk of mortality & morbidity of a patient suffering from cardiovascular disease especially in elder patients. In Washington State**,** cardiovascular arrest was reported as the second most common standard comorbidity (42.9%)and it is with the increase in the rate of spread of disease. Moreover, it was acknowledged that individuals with underlying cardiac diseases as well as diabetics may also be inexplicably affected [10-13]. Several cardiovascular problems like cardiomyopathy, cardiac arrhythmia, cardiac arrest, coronary artery disease have a higher incidence of occurrence during seasonal influenza, or in COVID 19 outbreaks [Fig. 1; Table 1].

All these events suggest that severe respiratory infections may reveal the progression or activation of endothelial cell dysfunction, proinflammatory effects, and coagulation pathway [21,22]. Despite these facts, little effort has been rewarded to the cardiac liability of respiratory viruses and influenza pandemics [23].

In a metastatic study, it was primarily reported with 99 patients who were treated in Jinyintan hospital of Wuhan city in Jan 2020 that 40% of the patients had reported pre-existing cerebrovascular disease or complications [24]. It was further reported in a report of 1099 COVID-19 patients observations that patients with concomitant diseases like diabetes, ischemic, hypertension, cerebrovascular heart disease, were more prone to the severity of disease (38.7% vs 21.0%) [25]. Consequently, study analysis of COVID-19 disease generally characterized by pneumonia-like symptoms not only in the patient but also in patients with cerebrovascular disease and diabetes. The prevalence was much higher and nearly 15-20% of patients required treatment with intensive care [26].

2. ESTABLISHMENT OF A VIRUS INSIDE THE HOST AND CONSEQUENCES OF ENTRY

Previously conducted studies represented that COVID-19 disease pathogenicity involved with protease, spike protein, and Angiotensin-Converting Enzyme-2 (ACE-2) that facilities the entry of the virus into the host cell [27].

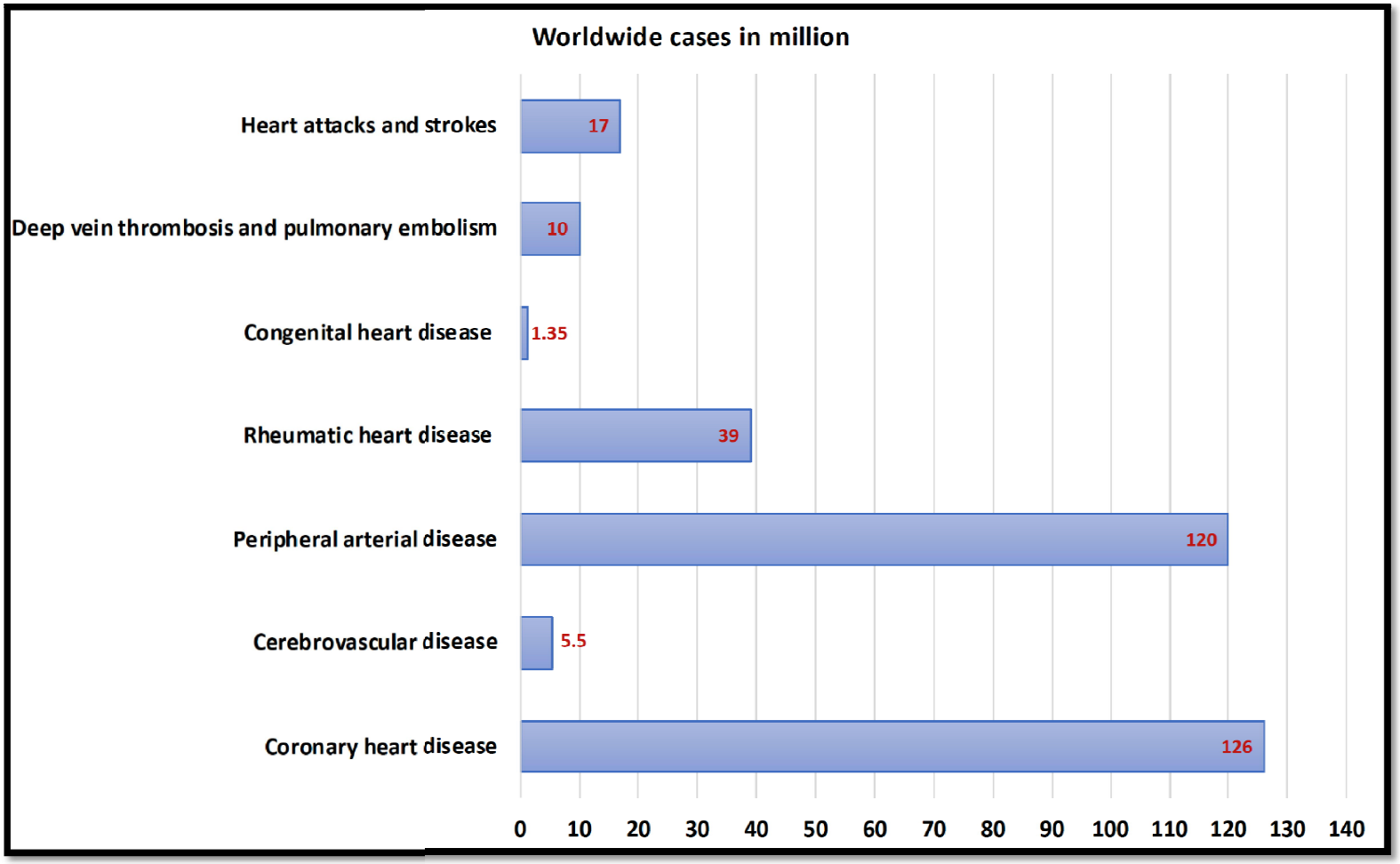

Fig. 1. Horizontal bar graph showing the worldwide total number of cases of different types of cardiovascular diseases

Table 1. Showing worldwide cases of types of cardiovascular diseases

Cardiovascular Diseases	Worldwide cases in million	References
Coronary heart disease	126	Khan MA et al.[14]
Cerebrovascular disease	5.5	WHO [15]
Peripheral arterial disease	120	Fowkes FG et al. [16]
Rheumatic heart disease	39	World Heart Federation [17]
Congenital heart disease	1.35	Indian Academic of Pediatrics [18]
Deep vein thrombosis and pulmonary embolism	10	International Society on Thrombosis and Haemostasis, Inc.[19]
Heart attacks and strokes	17	WHO [20]

Initially, the virus enters through the nasal inhalation, targeted to the nasal epithelial cell where it binds and starts its replication. At this stage, the patient remains asymptomatic for 1-2 days. In the next few days, the virus proliferates and moves down the respiratory tract, triggers the immune responses, and releases inflammatory cytokines. Nearly 80% of the infected patients reported infection in the upper respiratory tract with mild symptoms. Severe symptoms like hypoxia and pulmonary infiltration were reported in 20% of the infected patients.

ACE-2 is a membrane subordinated monocarboxypeptidases frequently distributed in humans and synthesize predominantly in the intestine, heart, pulmonary alveolar (type II) cells, and kidney [28-30]. The ACE-2 augments the catalysis of Angiotensin-II generated through ACE-1 and converts it to Angiotensin [1-7], which results in anti-inflammatory vasodilators, antigrowth, and ant fibrotic actions [31]. In an experiment on the heart of rats, the use of ACE-2 blockers and Angiotensin receptor blockers (ARBs) increased the manifestation of ACE-2 and in this manner confers susceptibility to high severity of the infection and other adverse consequences during COVID-19 virus infection [32,33] but no significant association has been described in a recently a metanalysis conducted on 10 studies on the use of these drugs in covid-19 infected patients and normal patients.

3. CARDIAC BIOMARKER AND ACUTE CARDIAC INJURY

The present report emphasizes the relation between an elevated cardiac biomarker and acute cardiac injury in patients suffering from COVID-19. The prevalence of rising in, analyzed from 191 patients admitted in two hospitals in China was 17% and it was significantly much more among no survivor (46% versus 1%, $p<0.001$) [34] and concluded that the amount of cardiac troponin I (cTnI) was considerably much higher in COVID-19 patient, those have pre-existing other disease complications than those not have other disease and calculated standardized mean difference described was 25.6 ng/l; 95% CI {6.8-44.5}) [35]. Moreover, the person who suffers from this virus infection was reported with a mild increase in cTnI, and values crossing the upper reference boundary can only be described with 8-12% of positive cases [36]. Therefore, it is practical to propose that preliminary screening of biomarkers for cardiac function at the time of hospital admission, and also longitudinal remarking at the hospital stayed timing of the patient, may help to detect a subgroup of a person with proof of worse prognosis and acute cardiac injury and. However, the exact mechanism of the increased level of biomarkers among these persons has yet not been known and needs to be explored.

4. USE OF ALTERNATIVE NONINVASIVE TECHNIQUE IN COVID-19 PATIENTS

Moreover, we have to consider the risk and advantages of adopting noninvasive and invasive testing that can significantly be explored the contaminate equipment and the capability of COVID-19 pathogen to persist on the surfaces for many days. The previously conducted studies have reported that the virus survives 6.8 hours on plastic and 5-6 hours on stainless steel and [37]. Moreover, for a person having suspected acute coronary syndrome (ACS), an increase in cardiac biomarkers is a key principle of etiology, the thrombolytic may be suggested and it could be significant substituted management of the disease to primary percutaneous coronary intervention to diminish infection of the catheterization laboratory.

5. CARDIAC PROBLEMS IN COVID-19 PATIENTS

5.1 Cardiac Arrhythmia

In his study, Wang et al noted that out of 138 COVID-19 patients admitted to a hospital in China, 23 were suffering from cardiac arrhythmias [8]. It was observed that among the patients with cardiac arrhythmias need intensive care unit (ICU) care was much higher (44.4% versus 6.9%, p<0.001), than the patients without arrhythmias [8]. Another study reported that cardiac arrhythmias were significant among patients with a critical form of the disease as compared to patients with mild and moderate conditions [38].

Clinical conditions like atrioventricular block, sinus bradycardia, atrial flutter, atrial fibrillation, supraventricular tachycardia, ventricular fibrillation are classified as patients with cardiac arrhythmias. It has been described commonly in COVID-19 patients, but the nature and its mechanism of incidence have not been well known and could be the results of systemic consequences. The researchers reported that the patient those died in COVID-19, are generally associated with atrial arrhythmias, or ventricular arrhythmias and bradyarrhythmias condition were common and it could be due to the cardiac conduction and/or repolarization properties, hypoxia, myocarditis, inflammation by increasing cytokines like IL-2, IL-6, IL-IL-8, IL-17, 1β, GM-CSF, G-CSF, IP10, MCP1, CCL3, and TNF-α, cardiac injury, cardiac hemodynamics, ACE2-related signaling pathways, direct viral endothelial damage, QT-prolonging medications, and metabolic imbalances in COVID-19 illness. The cardiac injury is diagnosed by the increased level of cardiac biomarker troponin [39] an independent risk factor in COVID-19 death. Many repurposing antimicrobials drugs like ritonavir, chloroquine, azithromycin, hydroxychloroquine benefit, and yet may induce electrocardiographic QT prolongation with potential ventricular pro-arrhythmic effects. Another study conducted on 3416 patients during a pandemic, reported the high rate of new atrial fibrillation followed by Atrial flutter (AFL) and Ventricular arrhythmias. prior heart failure, AFL, dyslipidemia, ritonavir/ lopinavir, and combined azithromycin and hydroxychloroquine were individually linked with NAEs [40]. Thus, patients with COVID-19 disease could be benefited from extra clinical and supportive care to manage the disease.

The spreading and transmission of SARS coronavirus can be reduced by the use of Amiodarone. It is an anti-arrhythmic drug that controls irregular heartbeats Moreover, intravenously administered amiodarone has been reported to reduce the sudden cardiac arrest death of SARS-COV-2 infected persons [41]. Amiodarone is a commonly used antiarrhythmic drug to manage the condition of supraventricular, ventricular arrhythmias, and also it is the choice of drug in arterial fibrillation. The drug amiodarone reduces the oxidative stress, inhibits ion channel, control the viral replication, and reduces the level of inflammatory cytokines IL-6, IL-1β, TNFα, and 8-iso-prostaglandin F2α levels in lung tissue in rats treated with 25–50 mg/kg Amiodarone and also in human peripheral blood mononuclear cells.

5.2 Myocarditis

The incidence of myocarditis in a person infected with COVID-19 disease is not yet clear. The disease is reported much closure to Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV), which has been reported with heart failure and acute myocarditis [42]. Thus, it is assumed that cardiovascular complication arises in those patients who are infected with Coronavirus infection is related. It has been expected to increase in acute myocarditis with COVID-19.

5.3 Acute Heart Failure and Cardiogenic Shock

In many cases of this disease patients, acute heart failure incidence was reported in 44 patients out of 191 (23%), and the ratio was reported was much more between non-survivors (52% versus 21%, p<0.0001) [28]. Multiple precipitating etiologies, stress-induced cardiomyopathy, cardiac arrhythmias, acute coronary syndrome, and fulminant myocarditis, might result in cardiogenic shock or heart failure. Coronary CT angiogram may offer a valuable non-invasive evaluation and identification of disease might be complex in guiding further therapies for the management of the disease.

5.4 Coagulation Abnormalities and Thrombosis

The coagulation abnormalities have been studied with many patients diagnosed with severe symptoms of COVID-19. The abnormalities of systemic coagulopathies have also been reported to associate with severe infections like thrombotic micro antipathy or disseminated intravascular coagulation (DIC). Moreover, a high risk of death has been reported due to an increase in the risk of Coagulopathy in COVID-19 patients [42-44]. Moreover, coagulation abnormalities have also been reported to cause arterial thromboembolic and venous, complications in COVID-19 disease persons [45,46]. The symptoms of coagulopathy like extension in the prothrombin time and decline platelet counts and improved dimer concentration have also been observed with COVID-19 patients [47]. The increased amount nearly more the 0.5 mg/L of D-dimer level has been observed with 505 Chinese patients out of 1099 COVID-19 patients [44]. The increased concentration of D-dimer in the range 0·77–5·27,(2·12 mg/L) were observed with non-survivors patients also supported the above-described research. Moreover, in the study conducted in 183 covid-19 patients, the amount of D-dimer in survivors was reported to be in the limit of 0·61 mg/L (0·35–1·29). Moreover, the patients in the critical stage, supported by (ICU) the intensive care unit also have reported with elevated median D-dimer level as compared to patients not supported by ICU((2·4 mg/L, IQR 0·6–14·4: 0·5 mg/L, 0·3–0·8) [48]. In another research, D-dimer on admission more than 1 mg/L associated with an 18-times elevated risk of death (95% CI 2·6–128·6; p=0·0033) [49]. Recently published hypothesis described the link of elevated D-dimer which is thought to be due to the life cycle of the virus and triggered coagulopathy operated due to apoptotic mechanism, targeting the endothelial cells of the vascular structure.

The patient with coronary heart disease, hypertension, cerebrovascular disease, and diabetes, became reported with elevated D-dimer value and are higher risk of death. Therefore, It is significant to dynamically monitor D-dimer levels, to test thrombotic difficulties as fast as possible, and should take preventive measures to minimize hemorrhage in DIC secondary fibrinolysis and thromboembolism, thus minimizing the mortality rate of COVID-19 [50,51].

6. CONCOMITANT USE OF CARDIO-VASCULAR DRUGS IN COVID 19 PATIENTS

6.1 ACE Inhibitors: Angiotensin Receptor Blockers (ARBs) and Angiotensin-Converting Enzyme Inhibitors (ACEIs)

The ACE inhibitors have the potential to regulate the activity of angiotensin-converting enzyme inhibitors (ACE2). A study conducted in mice with lung injury due to infection with coronavirus has reported improved conditions when treated with losartan, an angiotensin receptor blocker [52,53]. The death rate was also reported to reduce the death rate particularly in those patients who were treated with ACE inhibitors [54].

Though, an inconsistent view is that raised synthesis of ACE2 could hypothetically elevate the risk of SARS CoV-2 infection. This could be an apprehension for those patients who suffer from diabetes and are thought to be at high risk of SARS CoV-2 infections. However, there is no report or mechanism has been reported that favors this hypothesis. A retrospective study completed on 112 Wuhan's city patients infected with SARS CoV-2 virus, reported no substantial difference in the amount of ACEIs/ARBs medication between survivors and non-survivors [54]. In the light of the lack of strong suggestion for either harm or benefit, it is sensible for patients to prescribe ARBs and ACEIs to COVID-19 infected patients. The European Society of Hypertension, the European Society of Cardiology Council on Hypertension, and the American Heart Association have also suggested the use of ACEIs to cardiovascular patients who suffer from viruses [55-58].

6.2 Statins, Calcium Channel Blockers, and Aspirin

Previously conducted research has reported the caring consequences of statins in pneumonia patients. It is established that statins raise levels of ACE-2 and may protect the virus entry to progress the pathogenicity of SARS-Co-V2. It is established that statins prevent the activation of nuclear factor kappa B (NFκB) that could help to lower cytokine storm [59-61]. By obstructing the entry of calcium flow into the cell, calcium channel blockers (CCBs) may lower the disease severity and weakness in pneumonia patients [62]. Although, the exact role of statins in COVID-19 is yet to be studied; however the use of these drugs in the management of blood pressure in

hypertensive patients does not seem to pose any danger. Since CCBs do not affect ACE2 expression, some clinicians have preferred to use them in patients with COVID-19 and hypertension [63]. The continuation of aspirin in patients with circulated intravascular coagulation and sepsis is contraindicated. However, if not contraindicated, it should be continued as an anticoagulant in patients with original coronary artery disease.

6.3 Antiviral Drugs

The ritonavir and lopinavir combination is an established HIV/AIDS therapy to treat the virus. This combination was trumpeted to treat SARS infections and therefore, is believed to be significant in the handling of the SARS-CoV-2 virus [64]. Xu et al., published a scientific study on 62 COVID-19 patients, out of whom 46 patients were kept on lopinavir/ritonavir therapy [9]. They received this treatment strategy either alone or in conjunction with other therapies. The significance was reported as one patient had been discharged from the hospital and no death of the patient was reported till the time of the publication [9]. One more case series has also been reported from China that included this combination as a part of the treatment algorithm to manage the COVID-19 disease [34]. Nevertheless, the results of an in recent times reported open-label randomized controlled trial that found no difference between this combination therapy(lopinavir/ritonavir,400 mg, and 100 mg respectively), and standard care in COVID-19 patients [65]. Another antiviral drug, Oseltamivir has also been reported to manage the COVID-19 disease [8].

Hyperlipidemia (hypertriglyceridemia and hypercholesterolemia), is one of the common side effects caused by lopinavir/ritonavir. In 2009, FDA(the US Food and Drug Administration) notified prolong QT and PR intervals as some of the side effects caused by these drugs. FDA recommended the cautious use of these drugs in persons who suffer from structural heart disease. So, COVID-19 patients who are at therapy with these drugs should be monitored for cardiac symptoms, especially patients with pre-existing cardiac co-morbidities. Oseltamivir drug in animals has been described to lessen the risk of ventricular and atrial arrhythmias and is considered as cardio-benign [66,67].

6.4 Anti-Malarial Drugs

Chloroquine, which is extensively used to treat malaria and autoimmune disease, is being described as a possible broad-spectrum drug against the virus [66-69]. Chloroquine is renowned for blocking viral infection by raising the pH of the endosomal environment and interrupt the glycosylation required for cellular receptors of the virus SARS-CoV [70]. Hydroxychloroquine possesses a similar mode of action but with a better safety profile and makes it the preferred option. Recently, the clinical significance of both Chloroquine and Hydroxychloroquine molecules have been evaluated using Vero cells infected with the SARS-CoV-2 virus [71]. The study results proved hydroxychloroquine stronger at inhibiting SARS-CoV-2 in vitro. Resulted, off-label use of hydroxychloroquine sulfate was recommended to treat the infection caused by the SARS-CoV-2 virus. A loading dose for the first day was 400 mg twice daily and subsequently maintained 200 mg dose two times a day for 4 days. Although the cardiac adverse events related to the usage of Hydroxychloroquine are rare, at the times can be life-threatening. A recent study described that cardiac symptoms appeared mostly on those patients who were on this medication for a time (median 7 years), and had been treated with large (median 1,235 g) cumulative doses [72]. The most common side effect which showed up in 85% of such patients was conduction abnormalities (prolonged QT and PR intervals). Hence, it is suggested that patients with COVID-19 infection being treated with drugs should be monitored for cardiac arrhythmias.

6.5 Extracorporeal Membrane Oxygenation (ECMO) and Heart Transplantation

In COVID-19 patients experiencing respiratory failure and refractory cardiac, venovenous (VV) and veno-arterial (VA), extracorporeal membrane oxygenation (ECMO) may both be enormously appreciated. Nearly 15–30% of patients with COVID-19 infection suffer from acute respiratory distress syndrome (ARDS) [8,73,74]. In China, ECMO was used in some patients with COVID-19 and ARDS, yet the results of this are still unknown [8]. According to the provisional guidelines provided by the WHO, patients with severe refractory ARDS should be admitted to centers providing ECMO support [75]. Criteria for the start of VV and VA ECMO are the same for COVID-19 and non-COVID-19 patients. Reports from, Japan, South Korea, China and, Italy about the outcomes of ECMO treatment are not conclusive. It is noteworthy, that ECMO is very expensive and needs specialized care. There are

high chances of significant complications. Thus, its usage should exclusively be for truly refractory cases. As it is a limited resource, so should be used sensibly. The pandemic has made immunocompromised people more susceptible to the infection. Similar is the case with the patients requiring heart transplantations. Both transplant candidates and orthotopic heart transplant recipients are at risk. Due to the immunocompromised state, the risk for later is more. To reduce such risks, health institutions should adopt strict measures. Suspected or confirmed patients of COVID-19 should not share ICU settings with transplant patients. Potential transmission risk from the donor to the recipient has jeopardized the safety of transplant patients. Moreover, until fast testing for SARS-CoV-2 turns out to be promptly accessible, there will be no real way to completely affirm the negative status of the donors. It is rational to assume that we might see an increase in establishments of robust left ventricular assist devices as a link to transplantation until we find a definitive treatment of the COVID-19 or until the pandemic is over [73-75].

6.6 Use of Corticosteroids in COVID-19

The used corticosteroids like double-edged swords have been described with significant benefits as well as problems in COVID-19. The duration of their prescription to the patients is an important consideration and 10 days are reported to be safe to use them. However, later on, a longer duration is also given which was reported to be reduced the mortality and increased survival rate of COVID-19 patients.

Moreover, with higher doses, some risks are associated and in selected patients, pulmonary fibrosis might be seen with longer therapy of corticosteroid in COVID-19 patients. The thrombotic complications, another problem of their use, and use of corticosteroids in such conditions could be considered. Dexamethasone suggested giving 6 mg once daily to the patient with respiratory support, increased the concentration of fibrinogen and clotting factors. Moreover, the safer use of corticosteroid result in neuromuscular weakness, myopathy, and psychiatric symptoms might be complex. The use of methylprednisolone might increase mortality in the condition of acute respiratory distress syndrome. Thus, OP/AFOP features in CT scans of severe COVID-90 patients must be analyzed and the use of higher systemic corticosteroid doses should be under the supervision of expert physicians [76,77].

6.7 COVID-19 and Diabetes

Analysis of patients with COVID-19 suggests that people who also suffer from diabetics are susceptible to severe pulmonary illness. The high mortality rate with COVID-19 has been reported in a patient with diabetic's condition as compared to the non-diabetics patient. The mortality rate with SARS and MERS was also high, with 8000 patients from Asia and 2000 from Saudi Arabia with hyperglycemic conditions. Moreover, greater weight loss, macrophage infiltrates, and more lung inflammation have also been reported in diabetic rats. Thus, diabetics person infected with the coronavirus have a worse prognosis, this could be due to the involvement of multiple factors. The type 1 and type 2 both diabetic patient has more susceptibility but more death rate has been reported with type 2 diabetic patients. The researches have shown that multiple factors including dipeptidyl peptidase IV (DPP-IV) and angiotensin-converting enzyme 2 expressions in human lungs cell are linked to the severity of the disease. In diabetics patients, these molecules might have more expression that increased the vulnerability in diabetics patients but no conclusive scientific proof to support the hypothesis is yet available. Thus it is concluded that diabetes persons should be more alert than non-diabetics to self-defensive planning and implementation, particularly physical distancing and personal hygiene like handwashing. An acceptable intake of insulin and self-protective supplies is important when sheltering at home. The health systems and Medical suppliers can assist by promising reliable access to tools for the self-management of diabetes. The health care worker must be aware that pulmonary severity is more in the diabetic patient so that extra attention is proved to save the life of patients and remotely monitoring the glycemic condition of the patient could be uniquely helpful [78,79].

6.8 Safety of Using ACEIs, Statins, and Gliptins

Statins are lipid-lowering drugs with good pleiotropic effects and their safety profile is well explored. Significant wound healing effects in the lung, as well as antiviral effects of statins, are recently reported. Moreover, it has also been described that pleiotropic modes of action of

statin, mediate improvement of endothelial function, antithrombotic effects, and anti-inflammatory, and it could be medicinally precious for COVID-19 patients. The regulation of proteinaceous molecules like dipeptidyl peptidase 4 DPP4 and renin-angiotensin–aldosterone system (RAAS) component ACE2 are imbalanced in diabetes and exert lethal vascular effects. The DPP4 has been described as a receptor through which viruses bind and interact to initiate the pathogenicity in human cells. Thus, research has been accelerated to search for the drugs effective against RAAS and DPP4 to manage the COVID-19-derived diabetics and vascular complications [80].

ACE2 is the receptor, by which coronaviruses enter human cells, replicates there, and propagate the disease. The drugs of class ACEIs and ARBs are generally used to treat the patient suffering from cardiovascular diseases including hypertension and diabetes. Pharmacologically, they increase the level of ACE2 and ARBs that are undesirable to treat the COVID-19 patient due to the increased risk of viral infection as well as mortality. However, it has also been reported to form an anti-inflammatory/anti-oxidative molecule; angiotensin(1-7) with contrasting functions. That indicated uncertainty in existed pharmacology of these drugs. The recently published meta-analysis studies reported that prescribing ACEIs/ARBs is not associated with an increased risk and could be safely prescribed to treat the COVID-19 patients. For definitive clarity, further clinical and mechanistic studies are more needed to explore the clinical safety of ACE2 drugs [81]. The regulation of proteinaceous molecules like dipeptidyl peptidase 4 DPP4 and renin-angiotensin-aldosterone system (RAAS) component ACE2 are imbalanced in diabetes and exert lethal vascular effects. The DPP4 has been described as a receptor through which viruses bind and interact to initiate the pathogenicity in human cells. Thus, research has been accelerated to search for the drugs effective against RAAS and DPP4 to manage the COVID-19-derived diabetics and vascular complications. The DPP4 inhibitor is generally used to treat diabetes by preventing the proteolytic degradation of incretins. Gliptins is DPP4i used to control diabetes by prolonging the life of incretins and cardiovascular complications. The clinical trial reports its safe use like no effect on body weight, no hypoglycemic episode, and a substantial drop of HbA1c, which are significant issues that are associated with reduced CV risk and mortality. Thus, Gliptins can store endothelial function due to their anti-inflammatory, anti-oxidant, and potentially protective effects on the cardiac system, which are beneficial aspects to manage the cardiovascular and diabetes condition in COVID-19 patients [81,82].

7. CONCLUSION

Cardiovascular problems like microvascular damage, myocardial injury, cellular hypoxia, the release of cytokines, and diabetics problems both are associated with the risk of COVID-19. There is much scientific evidence that suggested the effect of diabetes and CVD on viral entry into the host cell and mediates the inflammatory responses to initiate the infection. Thus, it is very important to control cardiac conditions and have better glycemic control in COVID-19 patients. Treatment of these conditions with lockdown restrictions imposed makes it more challenging. Better usage of technological innovations can prove to be valuable in these difficult times. Surely, the question, whether the drug given in cardiovascular complications like ACE inhibitors and DPP4 inhibitors for diabetes, gliptins, will appear as a “holy grail” or just an additional dead-end in COVID-19 research, may be important not only for cardiovascular complication and diabetes patients. Efforts are continuously going on to developed effective molecules that effectively be used in such complicated conditions and completely eradicate the virus. In such complex conditions vaccine is preferred choice and attenuated, antigen vaccine and mRNA vaccines successfully have been developed with significant efficacy and vaccination program in many countries are going on. To better understand the threats modeled by the disease COVID-19 to the cardiovascular system, the medical community should share their experiences promptly. Both published research and real-time experiences shared on social media by world experts will act as a valuable tool and will help to learn more about this disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wuhan Municipal Health Commission. Report of clustering pneumonia of unknown etiology in Wuhan City. Wuhan: Wuhan Municipal Health Commission; 2019.
2. Lu R, Zhao X, Li J et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395:565–74.
3. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 2020;579:270–3.
4. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382:727–33.
5. Kuiken T, Fouchier RA, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D et al Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet. 2003;362: 263-70.
6. Available:http://www.who.int/emergencies/mers-cov/en/
7. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-1741.
DOI: 10.1111/all.14238
8. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069.
DOI: 10.1001/jama.2020.1585.
Erratum in: JAMA. 2021;325(11):1113.
PMID: 32031570; PMCID: PMC7042881.
9. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL et al.Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. BMJ. 2020;368:m606;368:m606.
DOI: 10.1136/bmj.m606
Erratum in: BMJ. 2020;368:m792.
PMID: 32075786; PMCID: PMC7224340.
10. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA. 2020;323(16):1612-1614.
DOI: 10.1001/jama.2020.4326
PMID: 32191259; PMCID: PMC7082763.
11. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(5):846-848.
DOI: 10.1007/s00134-020-05991-x
12. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-810.
DOI: 10.1001/jamacardio.2020.0950
PMID: 32211816; PMCID: PMC7097841
13. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):811-818.
DOI: 10.1001/jamacardio.2020.1017
Erratum in: JAMA Cardiol. 2020;5(7):848.
PMID: 32219356; PMCID: PMC7101506.
14. Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi SKBM, AlKatheeri R et al. Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study. Cureus. 2020;12(7): e9349.
DOI: 10.7759/cureus.9349.
PMID: 32742886; PMCID: PMC7384703.

15. Available:https://www.who.int/healthinfo/statistics/bod_cerebrovasculardiseasestroke.pdf
16. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382(9901):1329-40.
DOI: 10.1016/S0140-6736(13)61249-0
Epub 2013 Aug 1. PMID: 23915883.
17. Available:https://world-heart-federation.org/what-we-do/rheumatic-heart-disease/
18. Available:https://www.indianpediatrics.net/dec2018/dec-1075-1082.htm
19. Available:https://www.worldthrombosisday.org/issue/vte/
20. Available:https://www.who.int/cardiovascular_diseases/resources/atlas/en/
21. Eastin C, Eastin T. Characteristics and Outcomes of 21 Critically Ill Patients with COVID-19 in Washington State: Arentz M, Yim E, Klaff L, et al. *JAMA*. Published online March 19, 2020. doi:10.1001/jama.2020.4326. J Emerg Med. 2020;58(4):710.
DOI: 10.1016/j.jemermed.2020.04.002
Epub 2020 Jun 3. PMCID: PMC7266755.
22. Nguyen JL, Yang W, Ito K, Matte TD, Shaman J, Kinney PL. Seasonal influenza infections and cardiovascular disease mortality. JAMA Cardiol. 2016;1: 274-81.
23. Madjid M, Casscells SW. Of birds and men: cardiologists' role in influenza pandemic. Lancet. 2004;364:1309.
24. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395(10223):507-13.
25. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J et al. China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med; 2020.
26. Guan W-jie, Liang W-hua, Zhao Y, Liang H-rui, Chen Z-sheng, Li Y-min, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. European Respiratory Journal. 2020;55(5):2000547.
27. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-280.e8.
DOI: 10.1016/j.cell.2020.02.052
Epub 2020 Mar 5. PMID: 32142651; PMCID: PMC7102627.
28. Nicin L, Abplanalp WT, Mellentin H, Kattih B, Tombor L, John D et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. Eur Heart J. 2020;41(19):1804-1806.
DOI: 10.1093/eurheartj/ehaa311
PMID: 32293672; PMCID: PMC7184464.
29. Rice GI, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. Biochem J. 2004;383(Pt 1):45-51.
DOI: 10.1042/BJ20040634
PMID: 15283675; PMCID: PMC1134042.
30. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020;181(2):281-292.e6.
DOI: 10.1016/j.cell.2020.02.058
Epub 2020 Mar 9.
Erratum in: Cell. 2020;183(6):1735.
PMID: 32155444; PMCID: PMC7102599.
31. Li XC, Zhang J, Zhuo JL. The vasoprotective axes of the renin-angiotensin system: Physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. Pharmacol Res. 2017;125(Pt A):21-38.
DOI: 10.1016/j.phrs.2017.06.005
Epub 2017 Jun 12. PMID: 28619367; PMCID: PMC5607101.
32. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111(20):2605-10.
DOI:
10.1161/CIRCULATIONAHA.104.510461
Epub 2005 May 16. PMID: 15897343.
33. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8(4): e21.
DOI: 10.1016/S2213-2600(20)30116-8
Epub 2020 Mar 11.

Erratum in: Lancet Respir Med. 2020;8(6):e54.
PMID: 32171062; PMCID: PMC7118626.

34. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-1062.
DOI: 10.1016/S0140-6736(20)30566-3
Epub 2020 Mar 11. Erratum in: Lancet. 2020;395(10229):1038.
Erratum in: Lancet. 2020;395(10229):1038.
PMID: 32171076; PMCID: PMC7270627.

35. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. Prog Cardiovasc Dis. 2020;63(3):390-391.
DOI: 10.1016/j.pcad.2020.03.001
Epub 2020 Mar 10. PMID: 32169400; PMCID: PMC7127395.

36. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med. 2020;382(16):1564-1567.
DOI: 10.1056/NEJMc2004973
Epub 2020 Mar 17. PMID: 32182409; PMCID: PMC7121658.

37. Hui H, Zhang Y, Yang X, Wang X, He B, Li L et al. Clinical and radiographic features of cardiac injury in patients with 2019 novel coronavirus pneumonia; 2020.
Available:https://www.medrxiv.org/content/10.1101/2020.02.24.20027052v1

38. Stadler K, Ha HR, Ciminale V, Spirli C, Saletti G, Schiavon M et al. Amiodarone alters late endosomes and inhibits SARS coronavirus infection at a post-endosomal level. Am J Respir Cell Mol Biol. 2008;39(2):142-9.
DOI: 10.1165/rcmb.2007-0217OC
Epub 2008 Feb 28. PMID: 18314540.

39. Chen L, Hu W, Guo X, Zhao P, Tang J, Gu Y, et al. Association of coagulation dysfunction with cardiac injury among hospitalized patients with COVID-19. Sci Rep. 2021;11(1):4432.
DOI: 10.1038/s41598-021-83822-9
PMID: 33627696; PMCID: PMC7904824.

40. Merino JL, Caro J, Rey JR, Castrejon S, Martinez-Cossiani M. Cardiac arrhythmias in COVID-19: Mechanisms, outcomes and the potential role of proarrhythmia. EP Europace. 2021;23(Supplement_3).
Available:https://doi.org/10.1093/europace/euab116.115

41. Sanchis-Gomar F, Lavie CJ, Morin DP, Perez-Quilis C, Laukkanen JA, Perez MV. Amiodarone in the COVID-19 Era: Treatment for Symptomatic Patients Only, or Drug to Prevent Infection? Am J Cardiovasc Drugs. 2020;20(5):413-418.
DOI: 10.1007/s40256-020-00429-7
PMID: 32737841; PMCID: PMC7394926.

42. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. Eur Heart J. 2021;42(2):206.
DOI: 10.1093/eurheartj/ehaa190
Erratum in: Eur Heart J. 2021;42(2):191.
PMID: 32176300; PMCID: PMC7184348.

43. Levi M, Scully M. How I treat disseminated intravascular coagulation. Blood. 2018;131(8):845-854.
DOI: 10.1182/blood-2017-10-804096
Epub 2017 Dec 18. PMID: 29255070.

44. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847.
DOI: 10.1111/jth.14768
Epub 2020 Mar 13. PMID: 32073213; PMCID: PMC7166509.

45. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099.
DOI: 10.1111/jth.14817
Epub 2020 Apr 27. PMID: 32220112.

46. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-1026.
DOI: 10.1111/jth.14810
Epub 2020 Apr 27. PMID: 32338827.

47. Guan W-jie, Ni Z-yi, Hu Y, Liang W-hua, Ou C-quan, He J-xing, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-1720.

48. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
DOI: 10.1016/S0140-6736(20)30183-5

Epub 2020 Jan 24. Erratum in: Lancet; 2020.
PMID: 31986264; PMCID: PMC7159299.

49. Zhou S, Mi S, Luo S, Wang Y, Ren B, Cai L, et al. Risk Factors for Mortality in 220 Patients With COVID-19 in Wuhan, China: A Single-Center, Retrospective Study. Ear Nose Throat J. 2021;100(2_suppl):140S-147S.
DOI: 10.1177/0145561320972608
Epub 2020 Nov 6. PMID: 33155834.
50. Guler N, Siddiqui F, Fareed J. Is the Reason of Increased D-Dimer Levels in COVID-19 Because of ACE-2-Induced Apoptosis in Endothelium?. Clin Appl Thromb Hemost. 2020;26: 1076029620935526.
DOI:10.1177/1076029620935526.
51. He X, Yao F, Chen J, Wang Y, Fang X, et al. The poor prognosis and influencing factors of high D-dimer levels for COVID-19 patients. Sci Rep. 2021; 11(1):1830.
DOI: 10.1038/s41598-021-81300-w
PMID: 33469072; PMCID: PMC7815913.
52. Basu A, Slama MQ, Nicholson WT, Langman L, Peyser T, Carter R, et al. Continuous Glucose Monitor Interference With Commonly Prescribed Medications: A Pilot Study. J Diabetes Sci Technol. 2017;11(5):936-941.
DOI: 10.1177/1932296817697329
Epub 2017 Mar 23. PMID: 28332406; PMCID: PMC5950984.
53. Yang P, Gu H, Zhao Z, Wang W, Cao B, Lai C, et al. Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. Sci Rep. 2014;4:7027.
DOI: 10.1038/srep07027
PMID: 25391767; PMCID: PMC4229671.
54. Henry C, Zaizafoun M, Stock E, Ghamande S, Arroliga AC, White HD. Impact of angiotensin-converting enzyme inhibitors and statins on viral pneumonia. Proc (Bayl Univ Med Cent). 2018; 31(4):419-423.
DOI: 10.1080/08998280.2018.1499293
PMID: 30948970; PMCID: PMC6414001.
55. Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Zhonghua Xin Xue Guan Bing Za Zhi. 2020;48(0):E004.
DOI: 10.3760/cma.j.cn112148-20200220-00105
56. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers; 2020.
Available:https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-aceinhibitors-and-ang
57. ESH Statement on COVID-19; 2020.
Available:https://www.eshonline.org/spotlights/esh-statement-on-covid-19/
58. HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19.
Available:https://www.acc.org/latest-incardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concernsre-using-raas-antagonists-in-covid-19.
59. Batais MA, Khan AR, Bin Abdulhak AA. The Use of Statins and Risk of Community-Acquired Pneumonia. Curr Infect Dis Rep. 2017;19(8):26.
DOI: 10.1007/s11908-017-0581-x
60. Fedson DS, Opal SM, Rordam OM. Hiding in Plain Sight: An Approach to Treating Patients with Severe COVID-19 Infection. mBio. 2020;11(2).pii:e00398-20.
DOI: 10.1128/mBio.00398-20
61. Yuan S. Statins May Decrease the Fatality Rate of Middle East Respiratory Syndrome Infection. mBio. 2015;6(4):e01120.
DOI: 10.1128/mBio.01120-15
62. Zheng L, Hunter K, Gaughan J, Poddar S. Preadmission Use of Calcium Channel Blockers and Outcomes After Hospitalization With Pneumonia: A Retrospective Propensity-Matched Cohort Study. Am J Ther. 2017;24(1):e30-e38.
DOI: 10.1097/MJT.0000000000000312.
63. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020; published online March 11.
Available:https://doi.org/10.1016/S2213-2600(20)30116-8.
64. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;382(19):1787-1799.
DOI: 10.1056/NEJMoa2001282
Epub 2020 Mar 18. PMID: 32187464; PMCID: PMC7121492.
65. Kitahara K, Nakamura Y, Tsuneoka Y, Adachi-Akahane S, Tanaka H, Yamazaki

H, et al. Cardiohemodynamic and electrophysiological effects of anti-influenza drug oseltamivir in vivo and in vitro. Cardiovasc Toxicol. 2013;13(3):234-43.
DOI: 10.1007/s12012-013-9202-6
PMID: 23420508.

66. Frommeyer G, Mittelstedt A, Wolfes J, Ellermann C, Kochhäuser S, Leitz P, et al. The anti-influenza drug oseltamivir reduces atrial fibrillation in an experimental whole-heart model. Naunyn Schmiedebergs Arch Pharmacol. 2017;390(11):1155-1161.
DOI: 10.1007/s00210-017-1415-y
Epub 2017 Aug 6. PMID: 28780600.
67. Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. Lancet Infect Dis. 2006;6(2):67-9.
DOI: 10.1016/S1473-3099(06)70361-9
PMID: 16439323; PMCID: PMC7129107.
68. Yan Y, Zou Z, Sun Y, Li X, Xu KF, Wei Y, et al. Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model. Cell Res. 2013;23(2):300-2.
DOI: 10.1038/cr.2012.165
Epub 2012 Dec 4. PMID: 23208422; PMCID: PMC3567830.
69. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2:69.
DOI: 10.1186/1743-422X-2-69
PMID: 16115318; PMCID: PMC1232869.
70. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71(15):732-739.
DOI: 10.1093/cid/ciaa237
PMID: 32150618; PMCID: PMC7108130.
71. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers YM. Cardiac Complications Attributed to Chloroquine and Hydroxychloroquine: A Systematic Review of the Literature. Drug Saf. 2018;41(10):919-931.
DOI: 10.1007/s40264-018-0689-4
PMID: 29858838.
72. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. Biochem Biophys Res Commun. 2020;525(1):135–40.
DOI: 10.1016/j.bbrc.2020.02.071
Epub ahead of print. PMID: 32081428; PMCID: PMC7092824.
73. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected: Interim Guidance; 2020.
Available:https://www.who.int/publications-detail/clinical-management-of-severe-ac...(ncov)-Infection-is-suspected
(Accessed March 23, 2020).
74. Jamal QMS, Khan S, Khan M, Ansai AA, Ashraf JM, Habibullah M, Farasani A, Madkhali AM, Lohani M. Smoking May Increase the Risk of COVID-19 Infection: Evidence from In Silico Analysis. JPRI [Internet]; 2021. [cited 30Apr. 2021]; 33(22B):12-21.
Available:https://www.journaljpri.com/index.php/JPRI/article/view/31394
75. Rosenbaum L. Facing Covid-19 in Italy - Ethics, Logistics, and Therapeutics on the Epidemic's Front Line. N Engl J Med. 2020;382(20):1873-1875.
DOI: 10.1056/NEJMp2005492
Epub 2020 Mar 18. PMID: 32187459.
76. Mishra GP, Mulani J. Corticosteroids for COVID-19: the search for an optimum duration of therapy. Lancet Respir Med. 2021;9(1):e8.
DOI: 10.1016/S2213-2600(20)30530-0
Epub 2020 Nov 26. PMID: 33248469; PMCID: PMC7836750.
77. Chaudhuri D, Sasaki K, Karkar A, Sharif S, Lewis K, Mammen MJ, et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: A systematic review and meta-analysis. Intensive Care Med. 2021;47(5):521-537.
DOI: 10.1007/s00134-021-06394-2
Epub 2021 Apr 19. PMID: 33876268; PMCID: PMC8054852.
78. Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. JCI Insight. 2019; 4(20):e131774.
DOI: 10.1172/jci.insight.131774
PMID: 31550243; PMCID: PMC6824443.
79. Riddle MC, Buse JB, Franks PW, Knowler WC, Ratner RE, Selvin E, et al. COVID-19 in People with Diabetes: Urgently Needed Lessons From Early Reports. Diabetes Care. 2020;43(7):1378-1381.
DOI: 10.2337/dci20-0024

Epub 2020 May 14. PMID: 32409505; PMCID: PMC7305002.

80. Valencia I, Peiró C, Lorenzo Ó, Sánchez-Ferrer CF, Eckel J, Romacho T. DPP4 and ACE2 in Diabetes and COVID-19: Therapeutic Targets for Cardiovascular Complications? Front Pharmacol. 2020;11:1161.
DOI: 10.3389/fphar.2020.01161
PMID: 32848769; PMCID: PMC7426477.

81. Akhtar S, Benter IF, Danjuma MI, Doi SAR, Hasan SS, Habib AM. Pharmacotherapy in COVID-19 patients: a review of ACE2-raising drugs and their clinical safety. J Drug Target. 2020;28(7-8):683-699.
DOI: 10.1080/1061186X.2020.1797754
Epub 2020 Aug 12.
PMID: 32700580.

82. Wang W, Zhao X, Wei W, Fan W, Gao K, He S, et al. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) may be safe for COVID-19 patients. BMC Infect Dis. 2021;21(1):114.
DOI: 10.1186/s12879-021-05821-5
PMID: 33494713;
PMCID: PMC7829637.

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