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COVID-19 AND HEART DISEASES

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AUTHORS' CONTRIBUTIONS

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Review Article

ABSTRACT

The virus that caused the COVID-19 pandemic, SARS-CoV-2, has had a profound impact on cardiovascular healthcare. Patients having a history of cardiovascular disease are more likely to experience morbidity and mortality. The virus can harm the heart in both direct and indirect ways, causing clinical syndromes such as acute myocardial injury, myocarditis, acute coronary syndromes, heart failure, and arrhythmias, some of which can last for months after the original infection, resulting in long-term problems. Drug-drug and drug-disease interactions have an impact on the therapy of COVID-19-related cardiac problems. Furthermore, several COVID-19 treatment drugs can have negative cardiac consequences. Because the Renin-Angiotensin-Aldosterone System (RAAS) is involved in viral entry, it's important to evaluate the adverse effects of drugs that target this system. For optimal patient care and disease outcome, adequate information on COVID-19's unique cardiovascular manifestations and the guidelines established for their management is essential. The goal of this study is to look at the pathophysiology of SARS-CoV2 infection and related cardiac problems, as well as how to treat them. It also highlights the influence it has on individuals with pre-existing cardiac disorders, as well as long-term problems and heart-related side effects of COVID-19 drugs.

Keywords: Cardiovascular diseases; COVID-19; pandemics; severe acute respiratory syndrome coronavirus.

1. INTRODUCTION

Coronavirus disease (COVID-19), also known as 2019 new coronavirus, is caused by an infection with SARS Coronavirus 2. (SARS-CoV-2): It was originally discovered in a group of patients with pneumonia in Wuhan, Hubei Province, China, in December 2019. The World Health Organization (WHO) designated it a pandemic on March 11, 2020, and as of December 27, 2020, more than 79 million cases had been documented worldwide, with more than 1.7 million deaths [1]. COVID-19 presents with asymptomatic infection, mild upper respiratory tract sickness, severe viral pneumonia with respiratory failure, systemic inflammatory syndrome, and mortality in a wide range of individuals. SARS-CoV-2 primarily targets the respiratory system, however, cardiovascular involvement has been documented in 40% of individuals dying from COVID-19 illness [2]. SARS-CoV-2 infection increases the risk of cardiac consequences such as myocarditis and myocardial damage, heart failure and cardiomyopathy, arrhythmias, and acute coronary syndrome in patients with pre-existing cardiovascular disorders and the

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elderly. Patients with pre-existing comorbidities had a higher risk of death, with a reported mortality rate of 10.5 percent [3].

2. REVIEW OF LITERATURE

2.1 Pathophysiology of COVID-19

Spike is one of four structural proteins found in SARS-CoV-2 (S). Spike is a transmembrane glycoprotein that protrudes from the viral surface and controls coronavirus diversification and host tropism [4]. The functional receptor for SARS-CoV-2 has been identified as angiotensin-converting enzyme 2 (ACE2). The spike for SARS-CoV-2 is also linked to ACE2, boosting its entrance into host cells, according to structural and functional analyses [5]. ACE2 is highly expressed in the lungs, heart, ileum, kidneys, and bladder. When the virus enters the cells, it activates the immune system of the host [6].

2.2 The Host Response to SARS-CoV-2 Infection is Divided into 3 Phases

The first phase of infection involves virus distribution and growth in lung tissues, as well as innate immune activation and recruitment of antigen-presenting cells such as monocytes and macrophages [7]. The patient exhibits modest constitutional symptoms such as fever, tiredness, and headache during this stage. Mild respiratory symptoms may occur in certain symptomatic patients, necessitating the use of supplementary oxygen. The initial infection phase may be followed by an adaptive immunity stage with lowering viral titers and remission of symptoms in a patient with a favorable immune response [8]. The second stage involves a number of mechanisms that lead to pulmonary tissue injury, vasodilation, endothelial permeability, and leukocyte recruitment, all of which contribute to additional pulmonary damage, hypoxemia, and cardiovascular stress [9]. The third stage is hyperinflammation: 10% of patients in the second stage may experience a further exacerbation of the immune response with the formation of a cytokine storm, becoming critically ill with ARDS, acute cardiac injury, multi-organ failure, secondary bacterial infections, sepsis, and requiring intensive care [10] (Fig. 1).

2.2.1 Impact of COVID-19 in pre-existing cardiovascular disease

Patients with chronic medical co-morbidities experience more intense symptoms and have poorer results. According to a comprehensive study of 1527 individuals, the prevalence of hypertension, cardiac and cerebrovascular disease, and diabetes was 17.1%, 16.4%, and 9.7%, respectively. Patients with pre-existing cardiovascular illness had a mortality rate of up to 10.5 percent, compared to a normal mortality rate of 2.3 percent [12]. Diabetes and dyslipidemia, as well as age, are substantial risk factors for cardiovascular disease. All of these factors are linked to a weakened immune system. Furthermore, patients with underlying hypertension and cardiovascular illness may have higher ACE-2 receptor expression, making them more susceptible to SARS-CoV-2 infection; however, this notion has to be investigated further [13].

2.2.2 Myocarditis and myocardial injury

Serial cardiac troponin assays with quantitative levels >99th percentile of the upper reference limit obtained in a normal reference population [14] are used to detect acute myocardial damage, which is the most prevalent cardiovascular consequence in COVID-19. The symptoms of fulminant myocarditis range from minor chest pain, dyspnea, and fatigue to more severe symptoms such as left and right ventricular failure, cardiogenic shock, arrhythmia, and sudden cardiac death. COVID-19-induced myocarditis can mimic an acute coronary syndrome by causing ST-segment elevation and increased enzymes as a result of abrupt cardiac damage [15]. Early in the course of the disease, up to 36% of patients have increased troponin levels, according to a study conducted in the United States. Myocardial damage was more prevalent in those with pre-existing cardiovascular diseases. During hospitalization, elevated troponin levels are linked to an increased risk of needing ventilation, fatal cardiac arrhythmias, and a 59.6% mortality risk [16].

The precise process that causes heart damage is unknown. Acute myocardial damage, on the other hand, could be caused by either of these mechanisms: Myocardial damage that occurs directly: The binding of SARS-CoV-2 to ACE2 for viral entry into cardiomyocytes has the potential to modify ACE2 signaling pathways, resulting in acute myocardial and lung injury, however, this pathway has yet to be proven. Myocardial infarction can be caused in one of two ways [17]. Inflammatory reaction that is too strong: Myocardial damage may be exacerbated by a cytokine storm mediated by T-helper-1. The inflammatory response has been linked to specific cytokines, such as interleukin-6 (IL-6). Multiple organ failure results from this cytokine storm. Several investigations have found that individuals with critical COVID-19 disease had high levels of proinflammatory cytokines [18]. Acute respiratory damage can cause severe hypoxia, which can lead to oxidative stress and increased metabolic demand, which can lead to acute myocardial injury [18] (Fig. 2).

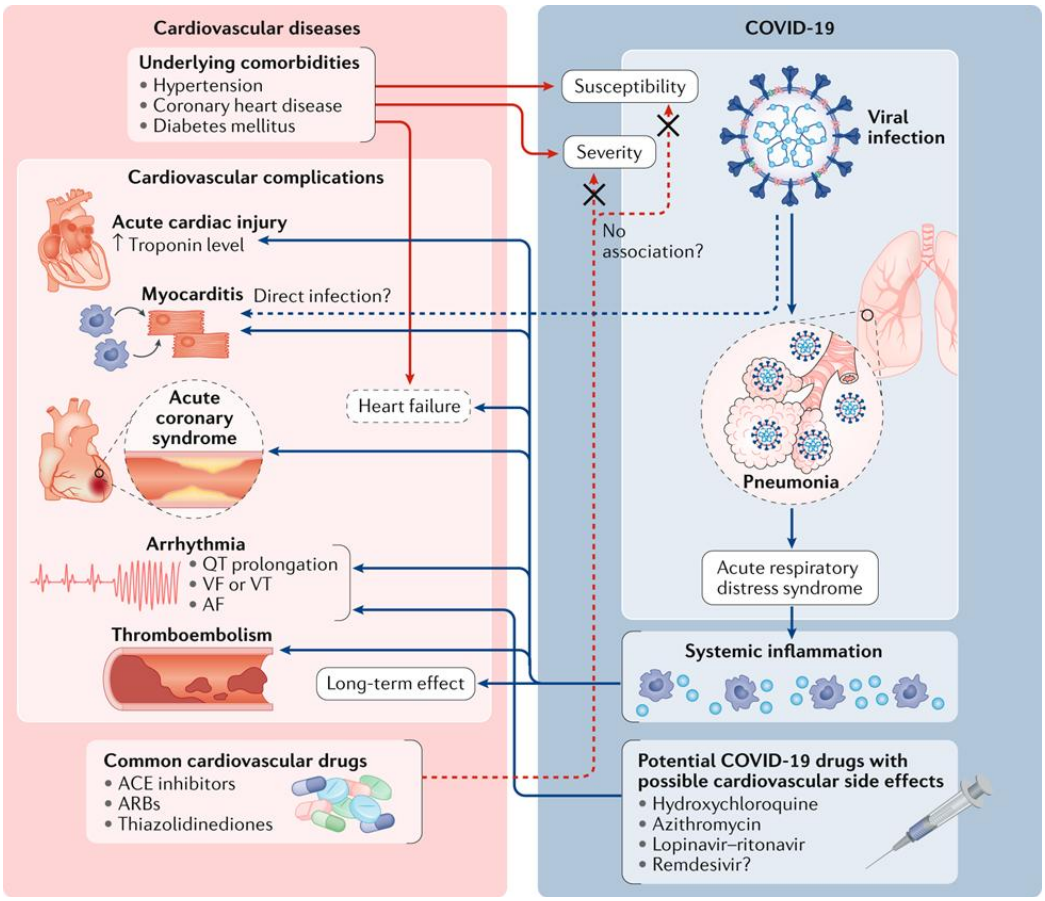

Fig. 1. Pathophysiology of COVID-19 [11]

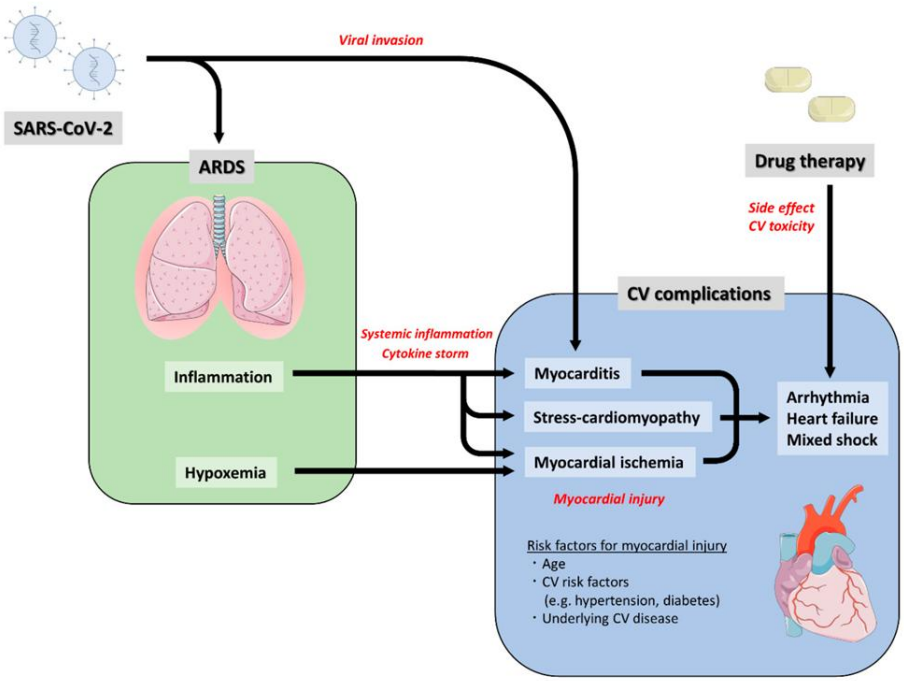

Fig. 2. Mechanism of myocardial injury in COVID-19 [18]

The therapy of COVID-19–related myocarditis is primarily supportive, based on data derived from cases with myocarditis as a result of other viral infections. Antiviral medication, as well as immunomodulators, may be beneficial [19].

2.2.3 Arrhythmias

A common complication found in 16.7% of COVID-19 patients in a Chinese hospital was arrhythmia. It was more common in patients who needed ICU hospitalization than in those who did not. A substantial increase in mortality was found in patients hospitalized for COVID-19 who developed acute malignant arrhythmias such as ventricular tachycardia, ventricular fibrillation, or atrioventricular block [20]. Symptomatic/asymptomatic tachycardia is the most commonly observed arrhythmia in COVID-19 disease. There have also been reports of bradycardia. Myocarditis, myocardial ischemia, and severely unwell patients with hypoxia and shock can all cause arrhythmia [21].

Arrhythmias in COVID 19 individuals have been linked to a number of processes. Electrolyte disruption is one of the possible causes. Hypokalemia is a consequence of SARS-CoV-2 infection that predisposes to arrhythmias due to its interaction with RAAS [22]. Proinflammatory cytokines like IL-6, IL-1, and TNF- have been demonstrated to affect the expression and/or function of K+ and Ca2+ ion channels in cardiomyocytes, which could lead to arrhythmias. Other causes include the side effects of drugs that prolong the QT interval (e.g., chloroquine/hydroxychloroquine and azithromycin), which can lead to polymorphic ventricular tachycardia (VT) and fever, which can reveal cases of cardiac channelopathies like Brugada syndrome and long QT syndrome [23].

2.2.4 Acute Coronary Syndrome (ACS)

The incidence of ST-segment elevation myocardial infarction (STEMI) caused by intracoronary plaque rupture or obstruction in COVID 19 patients is unknown, however, it is likely minimal [24]. SARS-CoV-2 is thought to cause an overwhelming acute systemic inflammatory response, resulting in endothelial dysfunction and activation of complement pathways, platelets, von Willebrand factor, and tissue factor pathways, all of which can lead to venous and arterial thrombosis [25]. In COVID-19 individuals, there has also been a documented rise in factor VIII and neutrophil extracellular traps (NETs), all of which could lead to a hypercoagulable state, Increased NETs levels, which are pro-inflammatory and pro-thrombotic, could explain thrombotic events in the coronary circulation [26]. The systemic inflammation may cause an increase in metabolic demand, which cardiomyocytes may not be able to meet, resulting in an ACS. It may also hasten the rupture of coronary plaques and raise the risk of stent thrombosis. In COVID-19 patients, there was an increase in IL-6 levels. It's possible that IL-6 interacts with NETs to cause thrombosis [27].

Since the COVID-19 pandemic began, the number of patients seeking medical advice for STEMI has decreased noticeably. This was ascribed to patients' unwillingness to seek medical counsel for fear of infection, as well as a delay in examination following arriving at the hospital due to measures. When taken together, these factors may cause the patient's transfer to the catheterization laboratory to be delayed, resulting in an increase in the STEMI case fatality rate to 13.7 percent in 2019 [28]. Although primary Percutaneous Coronary Intervention (PCI) is the gold standard of therapy for STEMI patients within the time frame, it is not always achievable due to the risk of virus transmission and exposure. Instead, fibrinolytic treatment may be used. If primary PCI is being contemplated, sufficient catheterization protection equipment must be available [29].

2.3 Anti-platelets

In the treatment of ACS, an efficient antiplatelet regimen is essential. The best antiplatelet regimen is determined by the treatment plan and the presence of COVID-19. Clopidogrel is the P2Y12 inhibitor of choice if fibrinolytic drugs are utilized in patients who are not on active COVID-19 therapy, according to current guidelines. Prasugrel and ticagrelor are suggested for individuals undergoing primary PCI [30]. Anti-platelet medications have been used with COVID-19, although there have been concerns about drug-drug and drug-disease interactions. Low-dose aspirin has a negligible anti-inflammatory impact in ACS and hence has little influence on the immune system's response to the virus. Interactions between P2Y12 inhibitors and protease inhibitors are also a concern. Because the suppression of the CYP3A4 pathway by lopinavir can enhance the risk of bleeding when combined with ticagrelor, it is not recommended to use them together [31].

2.4 Anticoagulants

Low Molecular Weight Heparin (LMWH) may offer advantages over Unfractionated Heparin (UF) in patients with coagulopathy, making it the agent of choice. UFH remains the best option in facilities where angiography is routinely performed within 24 hours following fibrinolytic therapy. There are no

known interactions between parenteral antithrombotic medicines and the COVID-19 drugs now available [32].

2.5 Thrombolytics

In stable patients with no contraindications, thrombolytic reperfusion treatment is a viable choice. Because of its high success rate, low bleeding risk, and single-dose administration method, tenecteplase, the most fibrin-specific drug, is a wise choice in patients with COVID-19 [33].

2.6 Statins

Regardless of COVID-19, statins have favorable vascular and cardiac effects that are linked to their anti-inflammatory properties. Every patient with ACS should be given a high-intensity statin (atorvastatin or rosuvastatin) [34].

2.7 Beta-Blockers

Beta-1 selective beta-blockers may be preferable over nonselective medications, according to ACS guidelines. Unlike metoprolol, which is metabolized by CYP2D6, and bisoprolol, which is metabolized primarily by CYP3A4 and CYP2D6, atenolol is not metabolized by CYP450 [35].

2.8 ACEIs and ARBs

There is conflicting evidence on the benefits and drawbacks of using ACEIs and ARBs in COVID-19 patients. It was discovered that ACE2 was increased in individuals on long-term RAAS inhibitors, perhaps increasing their risk of SARS-CoV-2 infection. Losartan medication, on the other hand, has been shown in some animal experiments to have a potentially protective impact on the lungs [36]. There are now three large trials on ACEIs and ARBs in COVID-19 patients, all of which have found no harm in using RAAS blockers in COVID-19 patients. Almost all worldwide societies have advised against discontinuing ACEIs and ARBs owing to COVID-19 [37] due to conflicting studies on the subject. The potential pharmacological interaction between lopinavir and ARBs is the most pressing concern here. Losartan and irbesartan may have a reduced ability to change into their respective active moieties when given with ritonavir and, as a result, lose their efficacy [38]. Unfortunately, erroneous fears that RAAS inhibitors increase the risk of infection have led to some patients discontinuing treatment, which can lead to decompensated HF, especially since plasma levels of angiotensin II, aldosterone, cortisol, norepinephrine, and left ventricular end-diastolic and end-systolic volumes return to pre-treatment levels when these drugs are stopped [39].

2.9 Heart Failure

The prevalence of left ventricular systolic dysfunction, abrupt left ventricular failure, and cardiogenic shock is unknown. COVID-19 infection can cause underlying heart failure to decompensate, resulting in a mix of septic and cardiogenic shock [40]. In China, heart failure (HF) was found in 23% of COVID-19 positive inpatients. In a retrospective analysis of 113 deceased patients, heart failure was found to be present in over half of them. Those with underlying cardiovascular co-morbidities were also more likely to develop heart failure. Thromboembolic events, ARDS, severe hypotension, and death were observed to be more common in HF patients. In a hospital in Spain, COVID-19 positive patients who had acute HF had a 46.8% mortality rate [41] (Fig. 3).

2.10 Long-term Complications

COVID-19 signs and symptoms that last 4 to 12 weeks after the acute infection are referred to as long COVID, as are signs and symptoms that last more than 12 weeks after the infection. However, it has yet to be fully defined and requires further investigation. Dyspnea, chest pain, palpitations, cough, weariness, arthralgia, anosmia, and psychological distress are some of the most prevalent signs and symptoms [42]. Understanding the cardiovascular involvement and alterations in Long COVID has been aided by the use of imaging technologies. Myocardial edema and late gadolinium enhancement (LGE) were found in 58 percent of 26 Chinese patients with Long COVID cardiac symptoms, according to the study. In the UK, 27 percent of patients had myocarditis-like LGE up to a month after infection [43].

A prospective observational cohort study comparing the recovery of 100 persons with severe COVID-19 to healthy volunteers of the same age and sex was done. The duration between diagnosis and cardiac MRI was 71 days on average. High sensitivity troponin was found in 75 percent of individuals during cMRI. Patients recovering from COVID-19 exhibited a lower left ventricular ejection percentage, greater left ventricular volumes, higher left ventricular mass, and elevated T1 and T2 weighted images compared to the control group [44]. cMRI abnormalities were found in 78 out of 100 people, including elevated myocardial native T1 and T2, late gadolinium enhancement of the myocardium, and pericardial enhancement [45]. After that, patients with the most aberrant cMRI findings were given an endomyocardial biopsy, which confirmed lymphocytic inflammation. Finally, the

study discovered that 80% of patients with severe COVID-19 have cardiac involvement, with approximately 25% showing indications of continuing myocardial inflammation three months following diagnosis [46].

2.11 Cardiac Implications of COVID-19 Medication

Antiviral medicines such as hydroxychloroquine (HCQ), azithromycin, lopinavir/ritonavir, and remdesivir have been utilized and studied as COVID-19 treatment alternatives [47]. Chloroquine and hydroxychloroquine (CQ/HCQ) are considered to change endosomal pH and diminish ACE2 receptor glycosylation, blocking virus entrance. By inhibiting the hERG K+ channel, they can potentially extend QT intervals, which can lead to torsade de pointes or abrupt cardiac death [48]. Chloroquine/hydroxychloroquine may build in the kidneys after a COVID-19 infection, causing additional QT prolongation. Because azithromycin has the potential to cause QTc prolongation, it should not be taken with HCQ [49].

HCQ also inhibits the enzyme CYP2D6, which metabolizes beta-blockers and raises their levels. As a result, individuals on beta-blockers must have their heart rate and blood pressure monitored and their doses re-adjusted. As a result, these medicines should be avoided in patients with a QTc interval of more than 500 milliseconds. It is not suggested to utilize QTc interval–prolonging drugs at the same time, and a baseline ECG must be conducted first [50]. CQ/HCQ can also promote lysosomal dysfunction and glycogen and phospholipid buildup, both of which are cardiotoxic and can lead to HF [51]. Lopinavir also causes QTc and PR intervals to lengthen, especially in patients who already have a long QT. It also inhibits CYP3A4, lowering serum concentrations of P2Y12 inhibitors' active metabolites, such as clopidogrel, which can lead to thrombosis [52].

Although no significant cardiovascular events have been linked to remdesivir, one instance of abrupt hypotension and cardiac arrest following a loading dosage was recorded during the Ebola outbreak. In a recent study with remdesivir in severe COVID-19 patients, 5.6 percent had atrial fibrillation and 11.3 percent developed hypotension [53]. Immunomodulating steroids (methylprednisolone and dexamethasone) can cause fluid retention, electrolyte imbalance, and hypertension, all of which contribute to cardiovascular morbidity. Tocilizumab has not been linked to any cardiac side effects [54].

2.12 Management of Cardiac Patients during the COVID-19 Pandemic

2.12.1 Outpatient management of cardiac patients

To avoid infection, all medical personnel should wear suitable PPE (gloves, protective suits, N95 masks, work caps, and goggles/protected screens).

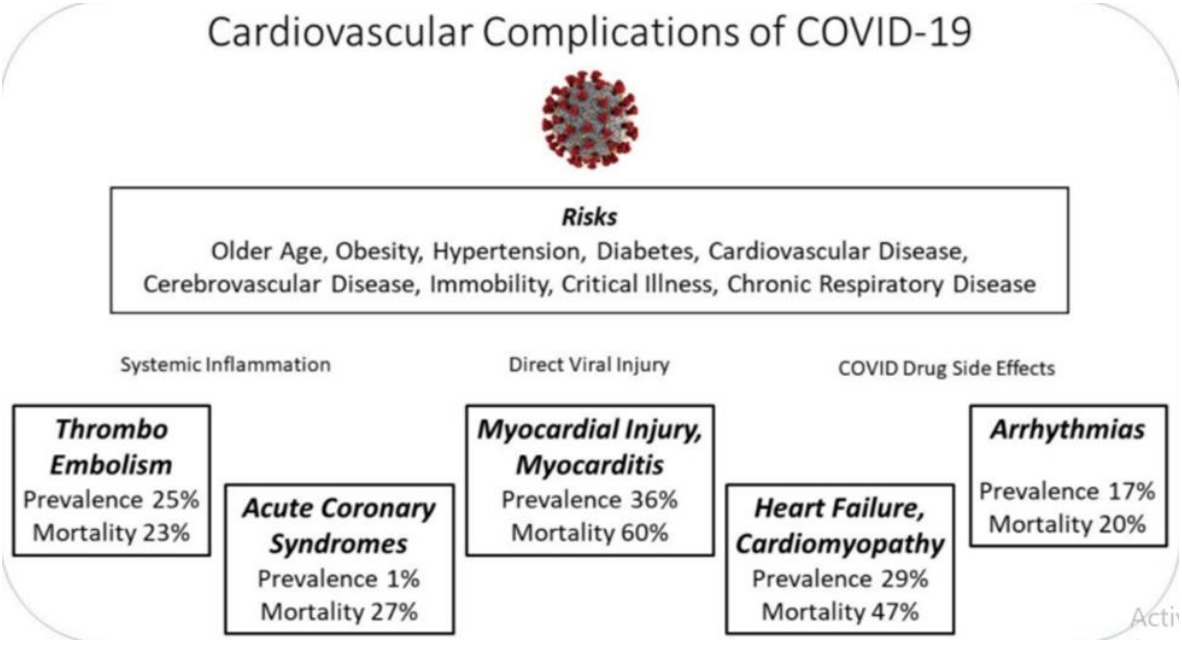

Fig. 3. cardiovascular complications of covid-19 [41]

It is critical to take the patients' temperatures and only admit those with normal temperatures into the waiting area, where they should be seated at least 1 meter apart. The hospital should enforce a "one doctor, one patient, and one consultation room" policy during the consultation, with no attendants permitted. Patients and their families should wear surgical masks and remain a safe distance from the procedure. Medical personnel performing ECGs or other noninvasive imaging are in close proximity to patients and should be adequately protected. COVID-19 testing should be done on all patients very away [55].

2.12.2 ER management of cardiac patients

All patients should be screened for COVID-19, and the requirement for hospital admission should be determined. No or mild symptoms, 14-day home isolation, and no need for hospitalization. Symptoms ranging from mild to severe, hospitalization, and isolation If the patient tests positive for COVID-19, he or she must be taken to a specified hospital and evaluated by a cardiologist. If an urgent cardiac procedure is required, it should be carried out with extreme caution to avoid infection. If COVID-19 cannot be ruled out, the patient should be admitted to an infectious disease isolation ward and treated. If COVID-19 was temporarily ruled out, the patient is sent to the emergency buffer ward for treatment and reexamination to determine whether SARS-CoV-2 infection was a possibility. If COVID-19 is still negative, the patient will be sent to the Cardiology Department's Coronary Care Unit (CCU), which follows a stringent single-room admission policy. A full COVID-19 assessment should be performed after 5-7 days of observation in the CCU. If the patient's cardiovascular system is stable and they are SARS-CoV-2 negative, they may be shifted to a conventional medicine floor ward with shared rooms [56].

2.12.3 Catheterization lab management of COVID-19 patients

Patients should wear surgical masks before entering the lab and be questioned about symptoms that could indicate SARS-CoV-2 infection. The lab is only open to key personnel. Patients should wear a surgical mask, and operators should put on the appropriate PPE. COVID-19 carts should be stocked with the necessary materials for invasive procedures such as pericardiocentesis and intra-aortic balloon pumping. A mask should be worn over a nasal cannula or oxygen mask if oxygen is necessary. Avoid using a high-flow nasal cannula, noninvasive positive pressure breathing, or an Ambu bag. To reduce aerosolization, endotracheal intubation should be performed prior to transfer to the lab. All items must be discarded after the treatment, and the area must be thoroughly cleaned with a disinfectant such as sodium hypochlorite at a concentration of 1000 parts per million [57].

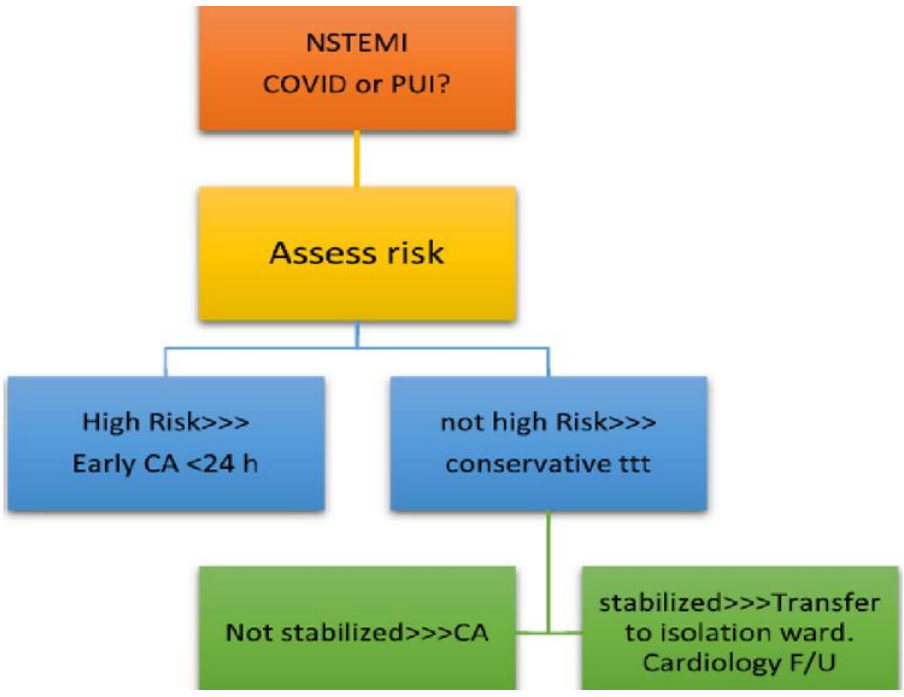

Fig. 4. Management of emergent cardiovascular diseases during COVID-19 [59]

2.12.4 Management of emergent cardiovascular diseases during COVID-19 pandemic

All STEMI patients should be brought to primary PCI if the facility is not overburdened. However, thrombolytic treatment may be used if COVID-19 patients are overburdened. Except in the case of anterior STEMI and cardiogenic shock, other specialists recommend employing fibrinolytic treatment. These patients, on the other hand, will need to be in the ICU for a lengthy time. Primary PCI, on the other hand, is reserved for high-risk patients with anterior STEMI [58]. Most specialists agree that NSTEMI patients should be triaged based on their risk classification. STEMI when thrombolytic therapy is necessary, acute pulmonary embolism, and abrupt exacerbation of HF are examples of patients who require hospitalization and conservative medical treatment for serious cardiovascular illness. Hemodynamic instability in patients with acute STEMI, bradyarrhythmia, and pulmonary embolism, on the other hand, necessitates immediate intervention or surgery [59] (Fig. 4).

3. CONCLUSION

Finally, COVID-19 is a disease produced by the SARS-CoV-2 virus, which has a wide range of symptoms and can damage a variety of organs in the body, including the heart. When SARS-CoV-2 infects a body, it enters the host cells by binding to ACE2 receptors, and the resulting inflammation progresses through three stages: early, second, and hyper inflammation, which is characterized by a cytokine storm and leads to a variety of complications, including cardiac complications. Patients with pre-existing co-morbidities have poorer clinical results and are more likely to develop illness complications. The most prevalent cardiac consequence caused by COVID-19 is myocardial damage and myocarditis. ACS, arrhythmias, and heart failure are some of the other cardiac problems. Several therapy drugs used to treat COVID-19 have been shown to have negative effects on the heart, such as HCQ-induced QTc prolongation and Lopinavir-induced QTc prolongation. During the COVID-19 pandemic, healthcare personnel must follow the rules for managing cardiac patients in hospitals.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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