Review Article

Cardiovascular Complications in COVID-19 and Its Vaccines

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The COVID-19 pandemic due to SARS-CoV-2 has proven to be a tremendous challenge to the medical community. The greatest challenge since the turn of the century. The authors summarized the main cardiovascular (CV) complications and mechanisms of COVID-19 and its vaccines. COVID-19 has lung tropism, but it has been reported to affect the CV system as well. The presence of comorbidities such as hypertension, CV disease, diabetes, and chronic obstructive pulmonary disease increased the risk of developing serious complications and in turn mortality significantly. The common CV complications include cardiac arrhythmia, myocardial infarction, myocarditis, and cardiac failure, which occurred in around 20% of all COVID-19 patients. The present difficulty in the diagnosis of CV complications were that COVID-19 symptoms often mimic CV events. Furthermore, the rapid diagnosis and management of serious CV events are sometimes overlooked due to COVID-19. Access to medical treatments were sometimes restricted due to the limited healthcare resources during the pandemic. The advent of various covid vaccines have reduced the number of these complications. However, CV events following mRNA vaccines or adenoviral vector vaccines are recognized as well as myocarditis and vaccine-induced immune thrombotic thrombocytopenia. With increasing experience in managing covid patients with CV complications, physicians are becoming better equipped in preventing, detecting, and treating these complications.

Keywords: COVID-19; Cardiovascular complication; Myocardial infarction; Myocarditis; COVID-19 vaccine

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The ongoing global pandemic of coronavirus (COVID-19) was first reported in Wuhan (Hubei, China) as a local outbreak of pneumonia. The pathogen was promptly identified as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Websites for case tracking were released to closely monitor the situation around the world[2,3]. The current situation as of the 11 of May 2022 has cumulative cases of over 516 million cases worldwide with more than six million deaths[4]. In Thailand, the total number of cases were over four million with almost 30,000 deaths[5]. Over the course of the pandemic, SARS-CoV-2 mutated into five variants of concern, Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1)[6,7], Delta (B.1.617.2)[8], Omicron (B.1.1.529)[7,9]. Since the beginning of April 2022, data indicated that the variant of concern Omicron had been spreading rapidly[10]. The common symptoms are fever, cough, dyspnea, fatigue, and headache[11].

A large study done in the United Kingdom (UK) found that almost half of hospitalized COVID-19 patients had at least one complication. Moreover, elderly will also be more likely to develop complications including cardiovascular (CV), renal, complex respiratory, systemic, neurological, gastrointestinal, or liver[12]. The presence of comorbidities gravely increases the mortality rate of COVID-19, inducing multiple cardiovascular disease (CVD) complexities. The pathophysiology and etiology of COVID-19 induced CVD complications had not reached a meaningful understanding[13].

The rapid global response to the COVID-19 pandemic had resulted in ten vaccines approved for use by the World Health Organization (WHO)[14]. An emergence of a new vaccine technology is the messenger ribonucleic acid (mRNA) vaccine that has shown great phase 3 results in the efficacy of the vaccine, specifically BNT162b2 (Pfizer/BioNTech)[15]. The CVD adverse effects of the mRNA vaccine[16] and other vaccines[17] had been reported. The mechanisms and clinical outcomes of vaccine induced CVD complications are also poorly understood. In the present review, the authors summarized the current understanding of COVID-19 and its vaccines' CVD

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complications.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

SARS-CoV-2 gene is about 30K nucleotides long, belonging to the β-coronavirus genus[18]. The genome shares about 80% of the severe acute respiratory syndrome coronavirus (SARS-CoV) BJ01 sequence, which is from the previous outbreak of severe acute respiratory syndrome (SARS) in 2003[19,20]. The virus spreads directly via fomites and droplets from infected hosts, both symptomatic and asymptomatic, to the uninfected in close proximity, especially those without protection. Another mode of transmission is an indirect method where the contaminated surface comes into contact with the mucous membrane of the mouth, nose, and eyes. The virus has been found to survive for up to nine days on inanimate surfaces but disinfectants like 70% ethanol are effective in inactivating the virus[21]. The virus has a longer survival period on the inanimate surface in the low temperature and humidity conditions[22]. The early epidemic doubling time was 6.4 days[23]. Studies have found the median incubation period to be 5 to 6.4 days and the period before the patient becomes symptomatic is 11.1 to 14 days[24,25]. The highest viral load in the upper respiratory tract samples were found to be in the first week[26]. Patients commonly develop symptoms such as pyrexia, tussis, dyspnea, fatigue, disorientation, cephalgia, and pharyngitis[11].

The mechanism of infection of SARS-CoV-2 is the viral cell entry via viral spike (S) protein binding to cellular receptors. Direct contact with Angiotensin-Converting Enzyme 2 receptors (ACE2) is mediated by a receptor-binding domain on the spike. The virus uses SARS-CoV receptors and transmembrane protease serine 2 (TMPRSS2) for S protein priming, enabling cell entry[27]. The virus also shows lung tropism due to ACE2 enriched ciliated bronchial epithelial cells. Type II pneumocytes expressed these receptors, which is a major target for SARS-CoV-2. Besides, Neuropilin 1 is another factor that acts in tandem with ACE2 to mediate the viral entry. A study indicates that the SARS-CoV-2 entry is a four-step process of cell surface attachment, receptor engagement, proteolytic cleavage, and membrane fusion that involves S protein[28]. After viral entry, it uses RNA-dependent RNA polymerase (RdRp) for viral replication. The virus then induces ER-derived double membrane vesicles, allowing encapsidation of transition of RNA strands in the cytosol. The assembly, release, and cell-to-cell spread of SARS-CoV-2 is still not fully understood but its cellular tropism of the respiratory system is clear[29]. For the virus to thrive, it must be able to evade the immune system, in which interferons (IFNs) are the primary target of evasion[30]. SARS-CoV-2 is able to drastically suppress type I, III IFNs and elevate chemokines and expression of IL-6. A paper proposed that the suppression and stimulation of parts of the immune response is responsible for defining features of COVID-19[31].

CV injury pathogenesis of COVID-19

Many papers reported CV complications to be common among COVID-19 patients with the prevalence of about 12.3% to 17%[12,32]. The mechanism of entry and injury has been proposed that SARS-CoV-2 utilizes the ACE2 to enter the cell, presenting an explanation for the pericytes with high expression of ACE2 as their target cardiac cell. The viral infection of pericytes might cause capillary endothelial cells dysfunction, leading to microvascular dysfunction[33] as shown in Figure 1. A study suggested that the association between the CVD comorbidities and worse prognosis was due to the positive feedback between CVD and ACE2 levels. As a result, a presence of CVD increased the ACE2 level, raising the virulence of SARS-CoV-2 within the heart and lungs[34]. The damage to the cardiac cells from the SARS-CoV-2 was both direct and indirect. The SARS-CoV-2 shares a similar viral entry to the human SARS-CoV infection of the myocardium as they both depend on ACE2. The direct damage that SARS-CoV mediates myocardial inflammation and damage associated with downregulation of myocardial ACE2 system. Both of which increase tumor necrosis factor (TNF) alpha. The TNF alpha causes inflammatory response as a common inflammatory cytokine, damaging the myocardial[35]. A study showed the evidence of myocardial injury as indicated by elevated Troponin T level (TnT) in COVID-19 patients. Patients without CVD comorbidities and elevated TnT exhibited a high mortality rate of 37.5% but the mortality rate of those with CVD comorbidity and elevated TnT skyrocketed to 69.44%[36].

The indirect damage to the myocardium can be attributed to inflammation caused by cytokine storm, which is induced by factors such as rapid viral replication and cellular damage, ACE2 downregulation and shedding, and anti-spike IgG. These may have different specific circumstances induced by the virus but they all release proinflammatory cytokines and chemokines[37]. For example, in a rapid viral

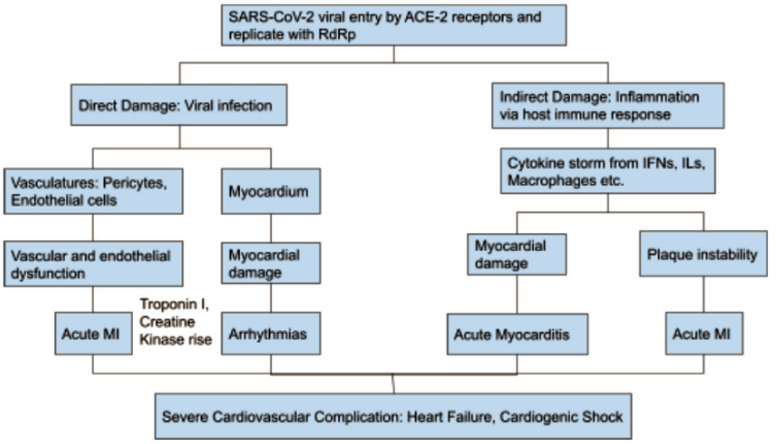

Figure 1. Cardiovascular complications manifestation proposed pathway in COVID-19 patients. Damages to the CV system are categorized into direct and indirect. The hyperstimulation of immune cells (macrophages, etc.) produce cytokine storms of IFNs, and ILs, leading to systemic inflammation.

replication and cellular damage pathway, SARS-CoV-2 may cause pyroptosis in macrophages and lymphocytes, triggering inflammatory response[38]. In SARS-CoV, NOD-like receptor protein 3 (NLRP3) inflammasome is activated by viroporin 3a. The interleukin 1 beta is also secreted[39], causing enormous release of proinflammatory factors.

CV risk factors and worsen prognosis of COVID-19

The association between age and the poor prognosis of COVID-19 has been well documented for patients older than 55 years old, who had significantly worse outcomes[40-43]. Studies have found that comorbidities greatly impact the risk of serious complications and the mortality rate such as hypertension (HTN), CVD, diabetes, and chronic obstructive pulmonary disease (COPD)[32,44]. A meta-analysis study found that patients with CVD and HTN (OR 4.58, 2.95, respectively) are among the highest at risk of developing serious complications from COVID-19. However, COVID-19 patients with COPD are at the greatest risk of having serious events (OR 6.66) and CVD comorbidities increase the risk of mortality in COVID-19[45].

CV risk factors and adverse event following COVID-19 immunization

There is limited available data of long-term adverse events and comorbidities of COVID-19 vaccines due to its rapid development and administration. The phase 3 trial of BNT162b2 vaccine (Pfizer/BioNTech) reveals high efficacy rate (95%) and very few adverse reactions. Although two of the BNT162b2 recipients died from arteriosclerosis, and cardiac arrest, respectively, it was not considered to be related to the vaccine by the investigator[15]. Soon after, a large study in Israel found that BNT162b2 vaccine was associated with myocarditis at a rate of one to five per 100,000 persons or risk ratio (RR) 3.24[46]. Myocarditis and pericarditis are rare complications of COVID-19 mRNA vaccines as the occurrence rate is estimated to be 12.6 cases per million doses of second-dose mRNA vaccine among younger individuals aged 12 to 39 years[16]. The serious adverse events are not limited to the mRNA vaccine as the adenoviral vector vaccine was also found to cause adverse events. A case report revealed a rare and intriguing event after the ChAdOx1 nCoV-19 vaccine (Oxford, AstraZeneca vaccine). All five cases developed a condition referred to as vaccine-induced immune thrombotic thrombocytopenia (VITT), which is a rare vaccine complication that mimics heparin-induced thrombocytopenia with no previous exposure to heparin[47]. Another recent study reveals that VITT may present from the first dose of ChAdOx1 nCoV-19 vaccine with the median presentation of 14 days. The mortality rates were high, depending on the sites of the thrombosis with the overall mortality rate of 22%[17].

COVID-19 CV complications/manifestation

The clinical symptoms of COVID-19 are similar to the symptoms from CV complications such as chest pain and dyspnea. The underlying pneumonia from COVID-19 often leads to dyspnea. Following dyspnea, significant hypoxemia coupled with tachycardia can result in myocardial ischemia and is presented as chest pain and electrocardiographic

(ECG) changes. Elevated biomarkers such as cardiac troponin and BNP, with ECG morphologies are suggestive of myocardial infarction (MI).

Myocardial infarction

Patients with COVID-19 have an increased risk of developing acute myocardial infarction (AMI) as a study in Sweden found significant increased risk (OR 6.61) in two weeks following COVID-19[48]. Another study found an incidence ratio of AMI among COVID-19 patients to be 5.9[49]. This may be due to the systemic inflammatory response from the viral infection, leading to destabilization of the atherosclerotic plaques[50]. A recent study reported that type 2 MI is the most common subtype, limiting the value of invasive management such as coronary revascularization[51].

Traditionally, diagnosis of MI is based on ST elevation on ECG. However, this could be problematic due to various concurrent ECG abnormalities in COVID-19 patients. The most common ECG morphology is a sinus tachycardia (90%) but others also include atrial fibrillation, ventricular tachycardia, and T wave deviations[52,53]. Another report showed that 40% of intensive care unit (ICU) patients had ST-T abnormalities and 38% had arrhythmias[54], meaning that emergency physicians must consider ST-elevated myocardial infarction (STEMI), myocardial injury, and myocarditis with COVID-19 patients[52]. Furthermore, the percutaneous coronary intervention (PCI) remains the gold standard for treatment of STEMI within 120 minutes, operating under the assumption that all unknown COVID-19 infection status patients are positive for COVID-19 to prioritize healthcare workers safety[55,56].

Laboratory tests for biomarkers such as creatine kinase-myoglobin binding (CK-MB), and high-sensitivity cardiac troponin I (hs-cTnI) have a predictive effect for AMI and prognosis of COVID-19 patients. The CK-MB level is higher in patients in ICU than non-ICU patients. Moreover, myocardial injury of COVID-19 patients is associated with an increase in the hs-cTnI of more than 28 pg/mL[57]. Clinicians should adopt high-sensitivity cardiac troponin T (hs-cTnT) instead of hs-cTnI due to a higher prognostic accuracy[58,59]. In fact, many cohort studies revealed that patients who died from COVID-19 had elevated troponin and are associated with poorer prognosis and higher mortality than survivors[60].

N terminal pro B-type natriuretic peptide (NT-proBNP) indicates a presence of hemodynamic myocardial stress and heart failure (HF). It has high diagnostic accuracy in identifying the cause of dyspnea to be HF. COVID-19 patients have elevated NT-proBNP in 27.5% of the cases, suggesting cardiac injury. However, NT-proBNP concentration alone cannot be used to make a definitive diagnosis and it should be used as a supplemental test. Besides, the presence of the NT-proBNP is associated with right ventricular hemodynamic stress[51,60-62].

Cardiogenic shock

Patients may eventually present with cardiogenic shock (CS) partly due to the delay in seeking medical attention from healthcare system overload and anxiety over the virus. Although the exact incidence of CS is largely unknown, the increase in CS and mixed shock in COVID-19 patients both with and without AMI is observed[63-65]. Severe COVID-19 patients with risk factors such as AMI, and HF may precipitate into CS[60]. To diagnose CS, non-invasive testing must be utilized. All CS patients should undergo ECG, chest X-ray, and echocardiogram to find the dominant cause of acute hemodynamic instability. CS patients must be given supportive care such as resuscitation, reperfusion, and revascularization in tandem with treating the underlying condition. For patients requiring mechanical circulatory support (MCS), extracorporeal membrane oxygenation (ECMO) is preferred due to its oxygenation capabilities[66,67].

Out-of-hospital cardiac arrest (OHCA) has been increasing[68] during the COVID-19 pandemic, both the incidence and mortality rate. As OHCA is very time-sensitive, a late presentation due to healthcare system overcrowding and anxiety over COVID-19 infection may have delayed the time taken for patients to seek medical attention. Although the exact incidence of OHCA and CS are unknown, they are medical emergencies with a high mortality rate. Treatments should follow the current guidelines and evidence[55,69-71].

Myocarditis

The majority of COVID-19 patients showed signs of increased interstitial macrophages and multifocal lymphocytic myocarditis in a small proportion of patients[72]. The current data indicates that viral myocarditis is less likely than myocarditis induced from cytokine storm[73]. Myocarditis complication has been reported to be prevalent in 8% to 27.8% of COVID-19 patients with deadly prognosis, with a mortality of 51.2% to 97%[44,74,75]. COVID-19 patients have a higher risk of developing myocarditis (RR=18.28) than other CV complications[46]. Although patients are

hemodynamically stable, clinical presentation ranges from fever, dyspnea, and angina. Moreover, fulminant myocarditis may occur in mild COVID-19 patients[76]. Myocarditis should be considered in COVID-19 patients with angina as it could precipitate into sudden HF and CS even without comorbidities[56].

The diagnostic tool of choice for myocarditis is cardiac magnetic resonance imaging (CMRI) and in severe cases, endomyocardial biopsy is indicated. If CMRI was not feasible, cardiac CT angiography might exclude significant coronary artery disease and identify myocardial inflammatory patterns[77]. A combination of ECG, TnT, and transthoracic echocardiography may be used to include the diagnosis of myocarditis[77-79]. A study reported that CMRI abnormalities were detected in 46% of COVID-19 patients and some highlighted the use of late-gadolinium enhancement (LGE) to evaluate the severity of myocarditis[80].

Studies are suggesting that glucocorticoids and other agents such as Interleukin-6 inhibitors are effective treatment of myocarditis in COVID-19 patients. MCS, mechanical ventilation (MV), and vasopressors might be needed in severe myocarditis COVID-19 patients[56,76]. Studies found that dexamethasone or other systemic corticosteroids with MV can reduce all causes of mortality, 28-day mortality, and ventilator days[78,81-83]. Endomyocardial biopsy may be able to refine the treatment risks of systemic immunosuppression[77]. However, there is no evidence or established recommendations or guidelines on the treatment using corticosteroids on myocarditis related COVID-19 patients, meaning that decisions about this treatment must be made on an individual level.

CV involvement in COVID-19 vaccines

The rapid emergence of mRNA vaccines had prompted the public to be skeptical of its adverse effects. A nationwide study in Israel reported that BNT162b2 is associated with the risk of myocarditis (RR=3.24) and minor risk increase of MI and pericarditis[46]. Interestingly, myocarditis induced from mRNA vaccines are prevalent in the young population aged between 12 and 39 years old[84,85] with the rates of 12.6 cases per million[16]. In addition, apart from mRNA vaccines, adenoviral vector vaccine, ChAdOx1 nCoV-19, had a rare complication of VITT[86-88]. VITT is similar to heparin-induced thrombocytopenia but without heparin exposure where patients may develop intracranial hemorrhage with high mortality. The estimated incidence of VITT was at least 1 in 100,000 in 50 years or older patients and 1 in 50,000 among younger than 50 years old patients[17,47]. Nevertheless, vaccines reduce death, and severe cases of COVID-19 patients[89], which substantially reduces risk of serious complications. For instance, the risk of myocarditis from SARS-CoV-2 infection is RR=18.28 but BNT162b2 vaccination reduces it to RR=3.24. Thus, the data strongly indicates that potential serious complications from vaccines are significantly less than SARS-CoV-2 infection, advocating for a widespread vaccine administration[46].

Conclusion

CV complications such as arrhythmias, fulminant myocarditis, and MI in COVID-19 patients are not rare in patients with or without preexisting CVD. This is due to myocardial damage, and atherosclerotic plaque instability either by direct viral infection with or without cytokine storm induced by SARS-CoV-2 infection. Comorbidities such as hypertension, CVD, and chronic obstructive pulmonary disease, and age are independent risk factors for developing serious complications and worsening the prognosis. The vital rapid diagnostic tools to detect CV complications are ECG, hs-cTnT, echocardiogram, and clinical presentations. The gold standard to treat MI is still PCI but it has limited value in treating type 2 MI, which has been reported in COVID-19 cases. Additionally, cardiac magnetic resonance imaging with late-gadolinium enhancement may be used in severe COVID-19 patients to evaluate the severity of myocarditis. Patients suffer out-of-hospital cardiac arrest and develop cardiogenic shock due to late presentation to the healthcare system. Lastly, vaccines reduce the risks of developing severe COVID-19 infection, CV complications, and mortality from SARS-CoV-2 infection, emphasizing its importance in the hindrance of the pandemic.

Further research

There is a need for consensus and specific guidelines on the management of CV complication arising from COVID-19. Through further research, physicians may eventually have a viable antiviral drug and effective treatment of COVID-19. This pandemic is most probably not the last and the world needs to answer these questions with the utmost quality and ethical research to end the pandemic.

What is already known on this topic?

There are reports of CV complications in

COVID-19 patients and there are theories, diagnostic methods, and treatments that have been proposed.

What this study adds?

The authors summarize the current knowledge of CV complications, pathogenesis, diagnostic methods, and treatments in a clear and concise article.

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Conflicts of interest

Authors declare that they have no conflict of interest.

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