

## REVIEW ARTICLE

# COVID-19 AND IT'S IMPACT ON CARDIOVASCULAR SYSTEM

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Received: 16.06.2021

Accepted: 09.11.2021

DOI: <https://doi.org/10.3329/bjm.v33i1.56794>

**Citation:** Akanda MAK, Rahman MHNA, Alam MS. COVID-19 and It's Impact on Cardiovascular System. *Bangladesh J Medicine* 2022; 33: 76-84.

### Introduction:

The Severe Acute Respiratory Syndrome (SARS) Coronaviruses (CoVs), namely SARS-CoV2 (COVID-19), pandemic has pushed global health system to its limit. Till 27 August 2021, total cases of COVID-19 infection crossed 214 million; with over 4.4 million deaths since the beginning of the pandemic.<sup>1</sup> Evidence suggests that adults with cardiovascular disease (CVD) are at a higher risk of in-hospital mortality with COVID-19 infection.<sup>2</sup> Evidence suggests that higher age, male sex, black or African American ethnicity, underlying health conditions including CVD and cardiovascular risk factors (e.g. hypertension, diabetes mellitus, and chronic kidney disease) increase risk of severe COVID-19 or mortality with COVID-19.<sup>3-11</sup> Although, COVID-19 mainly affects respiratory system, severe COVID-19 may involve multiple organs including cardiovascular system. There is a both way relationship between covid 19 and CVS risk factors. Covid19 can adversely affect CVS directly or indirectly by various mechanisms and on the other hand, patients having CVS risk factors when infected by covid19 are at higher risk of poor outcome. Meta analysis by Harrison SL et al. showed that the cardiovascular complications in hospitalized covid19 infected patients were acute heart failure (2%), myocardial infarction (4%), deep vein thrombosis (7%), myocardial injury (10%), angina

(10%), arrhythmias (18%), pulmonary embolism (19%), and venous thromboembolism (25%).<sup>12</sup> Research is going on for better understanding of the impact of covid19 in different systems of human body and finding better clinical solution to reduce the morbidity and mortality.

### Pathophysiological effects of covid on CVS:

Entry of Covid19 virus into the body is mediated by binding of viral spike proteins with the angiotensin converting enzyme-2 (ACE-2) receptor expressed on type 2 pneumocytes and ciliated bronchial epithelial cells.<sup>13-16</sup> ACE-2 is expressed also in other tissues like lung, gut, kidney epithelial cells, cardiomyocytes, arterial and venous endothelial cells, testis and to lesser extent in the breast, skin and on cells of haematopoietic origin.<sup>17</sup> ACE-2 enzyme is a negative regulator of RAAS (Renin-Angiotensin-Aldosterone system) that serves as a protective mechanism against heart failure, myocardial infarction, lung disease, hypertension, vascular permeability by its beneficial effects like anti-inflammatory (reducing vascular inflammation and plaque destabilization), anti-fibrotic (preventing ventricular remodeling), vasodilatation effect<sup>18,19</sup>. Following Covid19 binding, the activity of ACE-2 is reduced due to endocytosis and proteolytic cleavage.<sup>20</sup> There is increase in the level of Angiotensin II in these patients which accelerates

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the accumulation of inflammatory cells in the endothelium, rendering to endothelial inflammation/injury, vasoconstriction, pro-inflammatory and pro-oxidative state<sup>21</sup>.

### **CARDIAC EFFECTS:**

COVID-19 is associated with a wide spectrum of cardiovascular sequelae, including myocardial injury<sup>22</sup>, myocarditis<sup>23</sup>, ischemic injury caused by cardiac microvascular dysfunction, small vessel cardiac vasculitis<sup>24</sup>, endotheliitis<sup>25</sup> or epicardial coronary artery disease (with plaque rupture or demand ischemia), oxygen supply and demand imbalance, acute-onset heart failure, arrhythmias, cardiac arrest, stress (takotsubo) cardiomyopathy<sup>26,27</sup>, right heart strain (acute cor pulmonale, with causes including pulmonary embolism<sup>28</sup>, adult respiratory distress syndrome<sup>29</sup> and pneumonia); and systemic inflammatory response syndrome (cytokine storm)<sup>30,31</sup>.

Most patients with Covid19 with cardiac abnormalities have typical symptoms of Covid-19, including cough, fever, myalgia, fatigue, headache and dyspnea. A minority of patients present with symptoms suggestive of heart disease (such as palpitations<sup>31</sup> or chest pain<sup>33</sup>). These symptoms may or may not be accompanied by prior or concurrent symptoms typical of COVID-19 infection<sup>30,34</sup>. Dyspnea and chest pain are non-specific, symptoms which may occur due to non-cardiac and/or cardiac causes. Approximately 20% of patients admitted with Covid-19 have clinically significant cardiac involvement<sup>35</sup>, occult involvement may be even commoner<sup>36</sup>. Various pathophysiological mechanisms have been proposed, including viral infiltration, inflammation and microthrombi, and down-regulation of ACE-2 receptors.

#### **a. Type I Myocardial infarction (MI) :**

The incidence of MI is high in this group of patients. The large amount of inflammatory mediators eg. Interleukins (IL-1, IL-6, and IL-8), tumor necrosis factor-alpha (TNF- $\alpha$ ) generated due to covid19 infection stimulates the release of macrophages and T-cells inside the atherosclerotic plaques<sup>37</sup>. These cells activate matrix metalloproteinase and peptidase causing degradation of extracellular matrix and oxidative burst occurs and releasing phospholipids, tissue factor, collagen and platelet-adhesive matrix elements which contribute to plaque instability and thrombus formation. Besides this, COVID produces a hypercoagulable state, increased thrombus burden in culprit arteries, increased need for heparin and GP IIb/IIIa inhibitors and increased morbidity and mortality in the patients with MI with COVID19<sup>38</sup>.

The diagnosis of MI may go unnoticed in critically ill patients with acute respiratory failure<sup>39</sup>.

#### **b. Type II Myocardial Infarction:**

Type 2 MI can be induced by imbalance between oxygen supply and demand provoked by different clinical etiologies such as hypoxemia due to Covid19 associated respiratory failure and sepsis<sup>40,41</sup>. The risk of myocardial ischemia is 17 folds higher in patients with acute respiratory infections, mainly due to disruption in ventilation-perfusion ratios, loss of hypoxic vaso-constrictive reflex, activation of the sympathetic nervous system which all together puts stress on myocardial oxygen demand leading to myocardial infarction<sup>42</sup>. Moreover, respiratory viruses have been associated with an increased risk of MI due to susceptible gene expression that stimulates platelet activation<sup>39</sup>. The clinical manifestations of type 2 MI include atypical signs and symptoms such as dyspnea<sup>43</sup>.

#### **c. Myocarditis:**

Covid19 has been found to cause myocarditis and myopericarditis. Lindner and colleagues performed autopsies on 39 decedents (median age 85 years) who died of covid19 infection and 24 of them (61.5%) had SARS-CoV-2 in their cardiac tissues. Viral loads above 1000 copies per iq RNA were documented in 16 cases (41.0%). Proinflammatory gene upregulation was present in each decedent with high viral loads<sup>44</sup>. Clinical feature of myocarditis is variable ranging from minimal symptoms to fulminant heart failure, cardiogenic shock and arrhythmias. Subclinical myocarditis may portend a particularly high risk for sudden. Puntmann and colleagues showed that approximately 80% of patients with severe COVID-19 have cardiac involvement and nearly 25% have evidence of ongoing myocardial inflammation three months after diagnosis. So these patients would require careful monitoring and follow up.

#### **d. Arrhythmia:**

Cardiac arrhythmias are common in COVID-19 infected patients. It may occur during the ongoing covid19 infection or after recovery. This may be due to preexisting cardiac illness, newly developed MI i, myocarditis, pericarditis, hypoxia, drug interaction or electrolyte imbalance<sup>45</sup>. Patients taking remdesivir may experience sinus bradycardia<sup>46</sup> and those treated with hydroxychloroquine and azithromycin may experience ventricular arrhythmia due to their QT prolonging effect. Fever due to covid19 can unmask cases of cardiac channelopathies such as Brugada syndrome and long QT syndrome<sup>47,48</sup>. Study from Italy revealed nearly 60 percent increase in the rate of

out-of-hospital cardiac arrest during the peak of the 2020 COVID-19 pandemic (when compared with the same time frame from 2019)<sup>49</sup>.

#### **e. TakoTsubo syndrome:**

Stress (takotsubo) cardiomyopathy has been reported in patients with COVID-19<sup>50</sup>. During the COVID-19 pandemic, the incidence of TakoTsubo syndrome (TTS) has risen 4.5-fold<sup>51</sup>. Even individuals without covid 19 infection are at increased risk of TTS. This is probably due to increased emotional stress. TTS associated with COVID 19 is known as secondary TTS and this secondary TTS has got worse prognosis than primary TTS<sup>52</sup>. Patients with TTS are at risk for a repeat episode of stress-induced cardiomyopathy; the largest study reported a recurrence rate of 1.8% per patient-year<sup>53,54</sup>.

#### **f. Nonischemic myocardial injury:**

Non ischaemic myocardial injury may occur in covid19 infected patients for various reasons such as hypoxia, acute RV strain as a result of pulmonary embolism, covid pneumonia, ARDS, systemic inflammatory response syndrome (cytokine storm), direct myocardial damage by virus, small vessel inflammation. In a retrospective study on 416 COVID-19-affected patients, myocardial injury (transient increase of hs-T-troponin values) was associated with significantly higher mortality than the subgroup without myocardial injury (51% vs 4.4%, respectively;  $p < 0.001$ )<sup>55</sup>.

#### **g. DVT/ Thrombosis:**

A high frequency of thrombosis and thromboembolism has been reported in COVID-19-affected patients<sup>56-58</sup>. Arterial and venous endothelial cells express ACE-2 receptor which makes them prone to get infected by covid19 with subsequent development of endotheliitis, endothelial cell damage, systemic vasculitis and disseminated intravascular coagulation (DIC). COVID-19-affected patients present a severe hypercoagulability rather than consumptive coagulopathy with massive endothelial stimulation and damage with release of von Willebrand Factor from Weibel-Palade bodies<sup>59</sup>. Significantly higher levels of D-dimer and fibrin degradation products along with longer prothrombin and activated thromboplastin times were observed in covid19 infected subjects<sup>59</sup>. Unlike acute DIC, COVID-19 patients have high fibrinogen and high factor VIII activity, suggesting that major consumption of coagulation factors does not occur<sup>61</sup>.

#### **h. Multisystem inflammatory syndrome in adults (MIS-A):**

Multisystem inflammatory syndrome (MIS) was initially described in children (MIS-C) with recent COVID-19 infection which presents as a Kawasaki-like illness (fever, gastrointestinal symptoms, shock, LV systolic dysfunction, and elevated inflammatory markers). Similar cases of MIS have been described in young to middle-aged adults (MIS-A)<sup>62,63</sup>. Many of these patients had history of recent COVID-19 and had positive covid19 antibody tests, with fewer having positive covid19 rt-PCR tests. MIS-A should be considered in young adults presenting with inflammatory shock. This syndrome seems to be highly responsive to parenteral steroids.

#### **Management implications:**

The overall management principles for patients presenting with COVID-19 who develop CV complications or who have pre-existing CVD are same as for any other patient without COVID-19. However, there are a few important points that need consideration.

1. All healthcare personnel involved in the care of COVID-19 patients should use personal protective equipment (PPE) and they should be trained for proper donning, usage and doffing of PPEs according to practice guidelines.
2. The cardiology ward should be arranged into a COVID-free zone, a COVID-19 zone and a grey zone hosting suspected of having COVID-19. The cardiology department should develop and rehearse working protocols for rapid diagnosis, triage, isolation, and management of COVID-19 patients with CV complications.
3. Patients with acute MI need rapid assessment followed by transfer from emergency room to CCU or cath lab to avoid the risk of acquiring infection as well as minimizing delay. There are reports of delays in acute cardiac care due to extra precautions taken in view of COVID-19<sup>64</sup>.
4. Patients with COVID-19 who present with ST-segment elevation myocardial infarction (STEMI) within 12 hours of symptom onset, may be managed by primary PCI if there is a dedicated cath lab for covid19 positive cases. Where dedicated cath lab is not available, a fibrinolysis-first strategy is recommended. National Clinical Guidance for the management of cardiac patients in the COVID-19 pandemic, Bangladesh,<sup>65</sup> also supported conservative management by fibrinolysis with tenecteplase for STEMI presenting within 12 hours in the absence of

dedicated cath lab and if the risk of transmission is greater than the patient's possible benefit.<sup>66</sup>

5. Unwarranted diagnostic tests (e.g. cardiac troponin, natriuretic peptides, echocardiography, etc.)<sup>67</sup> should be avoided in these patients. The American College of Cardiology has urged clinicians to perform these assays only when they would meaningfully add to the management of the patients with COVID-19. The American Society of Echocardiography has also issued a similar advisory regarding the use of echocardiography in these patients<sup>68</sup>.
6. Thrombo-prophylaxis with heparin has been recommended for all hospitalized patients of COVID-19. It prevents pulmonary vascular thrombo-embolism, decrease dead space ventilation and mortality. International Society on Thrombosis and Hemostasis recommend at least six weeks of anticoagulation in high risk patients following discharge<sup>57</sup>.
7. Heart failure (HF) patients may be treated with guideline directed HF therapy including beta-blockers, ACEI/ARB/ARNI and aldosterone antagonists<sup>69</sup>. There was theoretical concerns regarding increased levels of ACE2 and the risk of acute COVID-19 with the use of RAAS inhibitors but they are now shown to be safe and should be continued in those with stable cardiovascular disease<sup>70,71</sup>. Instead, abrupt cessation of RAAS inhibitors may be potentially harmful<sup>72</sup>.
8. Patients with postural orthostatic tachycardia syndrome (POTS) can be managed by adequate hydration, betablocker and minimizing the dose of drugs which can exaggerate the condition<sup>73</sup>. Inappropriate sinus tachycardia may benefit from a low-dose beta blocker for heart rate management and reducing adrenergic activity<sup>73</sup>. Attention is warranted to the use of drugs such as anti-arrhythmic agents (for example, amiodarone) in patients with fibrotic pulmonary changes after COVID-19<sup>74</sup>.

#### **Discharge and Follow-Up:**

ACS patients during pandemic who have tested negative for COVID-19 disease should be discharged as early as the condition of the patient allows.<sup>75</sup> It is recommended for very early discharge for NSTEMI cases within less than 24 hours and less than 48 hours for ST elevation myocardial infarction patients. ACS patients who have tested positive for COVID-19 disease with mild illness can be discharged within the same timeframes. After discharge, patients should self-isolate for at least 14 days or until full recovery from COVID-19, whichever is longer.<sup>76</sup> Patients with positive COVID-19 and ACS who have a moderate to severe presentation such as pneumonia, severe pneumonia, Acute Respiratory Distress Syndrome,

or even sepsis with or without septic shock should be managed primarily for the viral illness as inpatients for as long as the condition requires.<sup>75</sup> All face-to-face follow-up appointments in outpatient department should be postponed.<sup>76</sup> To avoid unnecessary patient contamination tele-consultation services for follow-up should be established and encouraged.<sup>77</sup>

#### **Cardiac presentation of Post COVID-19 Syndrome**

Evidence is evolving on the long-term effects of COVID-19, which can affect multiple organ systems.<sup>78</sup> Persistence of symptoms such as fatigue, palpitations, dyspnea, chest pain, cognitive disturbances etc. beyond 4 weeks from the onset of acute symptoms of covid19 is defined as post covid syndrome<sup>79,80</sup>. Long-term CV sequelae may include increased cardiometabolic demand, myocardial fibrosis or scarring (detectable via cardiac MRI), arrhythmias, stress cardiomyopathy<sup>81</sup> and autonomic dysfunction. Management of post covid syndrome includes serial clinical and imaging evaluation with electrocardiogram and echocardiogram at 4–12 weeks, identification and treatment of the CVS pathology<sup>82,83</sup>. Current evidence does not support the routine utilization of advanced cardiac imaging, and this should be considered on a case-by-case basis. Recommendations for competitive athletes with cardiovascular complications related to COVID-19 include abstinence from competitive sports or aerobic activity for 3–6 months until resolution of myocardial inflammation by cardiac MRI or troponin normalization<sup>69,84</sup>.

#### **Conclusion:**

COVID-19 is more of a systemic disease than respiratory disease. Cardiovascular disease and certain cardiovascular risk factors are associated with severe COVID-19 and /or increased mortality with COVID-19. Heart disease management scenario is changed in COVID era. Diagnostic dilemma limits the therapeutic plan. International global registry and randomized trials from a global perspective can help to develop a standardized approach for diagnosis and treatment to optimize the early morbidity and mortality along with documentation of actual prevalence of ACS and other cardiac complications. Clinicians and policy makers should consider primary and secondary prevention strategies to improve cardiovascular health and outcomes for people following COVID-19.

#### **Declaration of interest:**

The authors report no conflict of interest.

**Funding:**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Ethics Committee Approval:** Not applicable

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