"COVID-19 – Current Status and Trends: A Comprehensive Review

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Abstract

The current global pandemic of COVID-19 is caused by a virus of corona family named SARS-CoV-2. Cardiovascular manifestations of COVID-19 are varied and complex and include myocarditis, acute coronary syndrome, heart failure, pericarditis and pericardial effusion. Those with cardiac comorbidites are at higher risk of severe infection and death. SARS-CoV-2 may infiltrate and injury the heart directly or may cause Myocardial infarction, LV dysfunction secondary to myocarditis, congestive cardiac failure, rhythm abnormalities and pulmonary and other vascular embolisms. The medications used to treat COVID-19 may also have serious cardiac side effects. A through understanding of the cardiac involvement of COVID-19 and its varied presentation is needed for management of COVID-19 infection and its complications.

Keywords *COVID-19, myocarditis, myocardial injury*

Introduction

Coronavirus disease 2019 (COVID-19) is a disease syndrome caused by the novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a single stranded positive sense RNA virus belonging to the family *Coronaviridae*[1, 2]. The current pandemic of COVID-19 is one of the greatest threats faced by humanity in the 21st century. This disease, identified by Dr Zhang Jixian from Hubei Provincial Hospital had started initially in Wuhan, China in December 2019[1]but has then spread rapidly and on March 11 was declared a pandemic. As of October 1st , 2020 the virus has spread to countries with 33 million cases and one million deaths of COVID-19 have now been reported globally. [3]COVID-19 is extremely contagious and if precautions not taken can infect 60-80% of the population.[4]

COVID-19 can have variable presentation ranging from asymptomatic infection, Mild sore throat to severe pneumonia with Acute Respiratory Distress Syndrome, Multi Organ Dysfunction to death.[5] The lungs have been the main involvement seen in COVID-19infection, however in 27-40%cases, cardiac involvement is also seen and has a worse prognosis in them .[6-8]Earlier studies have shown cardiac involvement in previous influenza and coronavirus epidemics, including myocarditis, acute myocardial infarction, and worsening of heart failure leading to significant morbidity and mortality.[9]COVID related myocarditis has been described with varied electrocardiographic changes, rise in troponin and echocardiographic evidence of systolic dysfunction. Patients with pre-existing comorbidities are thought to be at an increased risk of infection with SARS-CoV2 and also tend to have worse clinical outcomes[8]. Myocardial injury is associated with cardiac dysfunction and arrhythmias and death compared to those without cardiac injury .[10].

In this article we have reviewed available literature to describe cardiac involvement in COVID-19 with respect to the risk factors, comorbidities, pathophysiology

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and complications associated with the infection. This review aims for physicians and cardiologists to update the knowledge of the pandemic and assist them in management of the same.

CARDIOVASCULAR INVOVLEMENT IN COVID-19

Epidemiology

Age

The severity of COVID infection and complications increase with age.[11].In the elderly age group of 75 to 84 years the rate of admission to ICU was 11 to 31% while in less than 20 years of age the risk of hospitalization was 2 to 3%[12]. Increasing age was also associated with increased mortality with death rate up to 27.3% in the elderly age group and 0.1 to 0.2% in the younger age group[13]. There have also been reports of increased incidence of Kawasaki disease noticed in children with COVID-19 infection .[14]

Sex

Higher Hospitalization rates, more complications and mortality was noted in males compared to females[11]. Studies have shown male preponderance ranging from 52.9% to 60% of the hospitalized patients[11, 15]. The mortality rate in men was higher than women for every age group. The pathophysiology and significance of male predominance of COVID-19 disease is uncertain.

Comorbidities

Patients with pre-existing co-morbidities are at an increased risk of infection with SARS-CoV2 and tend to have worse clinical outcomes[16]. In a study by Wang et al it was reported that in patients with severe disease 25% had cardiovascular diseases, 44% had arrhythmia, and58% had hypertension.[17]Notably a high complication rate with mortality rate of 10.5% was reported in cardiac patients while hypertensive patients had 6.0% death rates and diabetic patients had 7.3% death rates.[6] In a review of 1590 patients by Zhou et al, those with comorbidites of hypertension, diabetes, heart disease had severe COVID-19 disease requiring ICU care and increased mortality.[18]Recent studies have suggested that obesity may also be a risk factor for severe COVID-19 disease.[15, 19]

Virology and entry into human host cell

Coronaviridae (CoV) are so called because of their crown like appearance. The COVID-19 pathogen belongs to the β-CoV group. CoV has four major structural proteins: the nucleocapsid (N) protein, envelope (E) protein, the membrane (M) protein, and the spike (S) protein which allows attachment and fusion with the host receptor.[20]The animal reservoir of COVID-19 is presently uncertain , but the viral genome was found to be approximately 88% similar to Bat coronavirus and distant to the previously known SARS and Middle East respiratory syndrome viruses.[2]The entry of virus into the human cell followed by the pathophysiology of COVID infection is demonstrated in figure 1.

Mechanism of cardiovascular Involvement

SARS-CoV-2 can bind to the angiotensin-converting enzyme 2 (ACE2) receptor and enter the host cell.[21] These receptors are highly expressed in the heart and lungs, and they have been confirmed to be the functional receptors for the novel coronavirus.[22] Hence The virus infiltrates the human cells through angiotensin-converting enzyme 2 (ACE2) receptors which leads to ARDS, myocarditis and cardiac failure.[23]This receptor may be upregulated in people taking ACE inhibitors and ARBs, thus theoretically providing more targets for the virus' spike protein, which binds to the ACE-2 receptor. Due to this pathway there has been a lot of discussion on use of ACE inhibitors for hypertension whether they make patients susceptible to SARS-CoV-2 infection. However, there is no clear evidence that ACEIs or ARBs may increase the odds of virus entry into host cells. Hence updates from the American heart association, European Society of Cardiology and European Society of Hypertension suggest that ACE inhibitors should be maintained or initiated as per need in patients with myocardial infections, heart failure, or hypertension.[24]

COVID-19 and myocarditis

Acute myocarditis is a known complication of any acute viral infection. Cardiac muscle autopsy specimens have shown signs of myocarditis such as mononuclear cell infiltrates and myocardial necrosis.[25, 26]Acute myocardial injury is the most common cardiovascular complication inCOVID-19manifested by elevation of high-sensitivity cardiac troponin I and the incidence of

acute myocardial injury has been reported to be around 8% to 12%.[27]These studies suggest that fulminant myocarditis is an important cause of the acute cardiac injury in COVID- 19 patients. The symptoms may vary from angina, breathlessness on exertion, tiredness to cardiac failure, shock, rhythm disturbance and sudden cardiac death. Varied arrythmias ranging from AV blocks to atrial and ventricular tachyarrhythmias. Transient ECG changes are common and may even mimic a ST Elevation MI but coronary angiogram is usually not showing any obstructive lesion. Up to two to three times elevation of cardiac troponin levels is suggestive of previous cardiac conditions or mild cardiac injury cardiac condition and/or acute injury related to COVID-19 whereas more than five times elevations is suggestive of myocarditis, myocardial infarction secondary to plaque rupture and systemic thrombosis.[3]Serum high-sensitivity troponin, High BNP/NT-proBNPand Hs CRP levels correlates with the extent of ventricular stress and also the severity of illness.[26] Elevations of DDimer have been associated with poor outcome. The rise in Tn-I does not occur in isolation but alongside the rise of other inflammatory markers, such as ferritin, c-reactive protein, interleukin-6 [IL-6], interferon-γ, tumor necrosis factor-α, and lactate dehydrogenase possibly representing a cytokine storm syndrome.[28]Echocardiography may help to assess for global and regional wall motion abnormalities and also demonstrating thickened interventricular septum with associated enlarged left ventricular diastolic diameter, decreased left ventricular ejection fraction, and increased pulmonary arterial pressure [29].MRI may confirm acute myocarditis and myocardial injury.[30] Endomyocardial biopsy (EMB), long considered the gold standard diagnostic test, can directly demonstrate myocyte necrosis and mononuclear cell infiltrates. EMB will detect evidence of a viral cause in some cases, though in others an immunologically autoimmune-mediated cause of the myocarditis is suspected.[31] However EMB and MRI may be cumbersome and not practical during the current situation but can be considered for research purpose in an appropriate setting.

The various distinct mechanisms for non-ischemic myocardial injuries that have been published in the literature are – [i] inflammation and cytokine storm mediated through pathologic T-cells and monocytes leading to myocarditis and documented by significantly raised inflammatory markers [ii] secondary to hemophagocytic lymphohistiocytosis, [iii] viral myocarditis with reports of progression to fulminant myocarditis, [iv] stress cardiomyopathy, [v] hypercoagulability and development of coronary microvascular thrombosis [vi] respiratory failure and hypoxemia

induced cardiac myocyte apoptosis.[8, 23, 32] COVID-19 induced cardiac injury leads to activation of the innate immune response with release of proinflammatory cytokines. Proteins released through cell lysis like Myosin heavy chain, a cardiac sarcomere protein, appears to be a prime example of 'molecular mimicry'. Myocarditis appears in COVID-19 patients after a prolonged period (up to 10–15 days) after the onset of infection. Together, the data suggest that a delay in myocardial inflammation is consistent with at least two pathogenic mechanisms: first, that the 'cytokine storm' unleashes a subclinical autoimmune myocarditis, and secondly that myocardial damage and/or molecular mimicry initiate a de novo autoimmune reaction.[33]

There is no specific treatment option for myocarditis and need to be managed by supportive therapy like antivirals and early application of interferon, corticosteroids, tocilizumab, anakinra, intravenous immunoglobulin, statin, and active mechanical life support.[26, 34]

Arrythmias

Viral infections are associated with myocardial inflammation, metabolic imbalances and activation of the sympathetic nervous system, all of which predispose to cardiac arrhythmia.[10, 35]The incidence of arrythmias has been reported in COVID-19 patients up to 16.7%. [17]The commonest rhythm abnormality noted is tachycardia, uncommonly bradycardia has been noted in some patients.[17] Arrhythmias were observed in 7% of patients without ICU care as compared to 44% of patients admitted to an ICU.A 5.9% incidence of malignant arrhythmias, with a significantly greater incidence in those with elevated troponin level was found (17.3% vs 1.5%, $p<0.001$). [10]Other arrhythmias seen include atrial fibrillation, conduction block, ventricular tachycardia, and ventricular fibrillation.[13] Others causative factors include dyselectrolytemia, medications affecting QT interval with potential to cause torsades de pointes [32] and fever which may predispose to Brugada syndrome

and long QT syndrome.[6]Even after hospital discharge, we should consider that myocardial injury might result in atrial or ventricular fibrosis s and scarring which may form the substrate for subsequent cardiac arrhythmias. The extent of myocardial scar, as assessed with cardiac magnetic resonance, helps to stratify the arrhythmic risk in patients recovered from COVID-19.[36]

Acute coronary syndrome

Acute ST elevation Myocardial Infarction due to plaque rupture or coronary thrombosis due to hyperinflammation may be seen in patients of COVID-19. Patients with risk factors or existing CV disease have a heightened risk of developing an acute coronary syndrome (ACS) during acute infections, including viral illnesses and other acute inflammatory conditions.[32] However the number of patients presenting with Acute MI in Emergency room has been significantly reduced and this has been attributed to the reluctance of patients to go to a hospital during the COVID-19 outbreak, delays in evaluating patients with STEMI after hospital arrival due to precautions such as detailed travel and contact history, symptomatology, and chest X-ray. SCAI and other Expert groups recommend to consider fibrinolytic therapy in select patients with 'low risk' ST-elevation MI (STEMI).[37] Additional precautions taken in catheterization laboratory such as time needed to wear protective gear may further delay intervention.[38]

Heart Failure

Although data on incidence of left ventricular systolic dysfunction, acute left ventricular failure, and cardiogenic shock is less but available studies have shown heart failure as a complication of COVID-19. ACE2 expression is up-regulated in failing human hearts, which may lead to a higher infectivity of virus and a higher mortality in patients with heart failure. Underlying mechanisms of acute HF in COVID-19 may include acute myocardial ischemia, infarction or inflammation (myocarditis), ARDS, acute kidney injury and hypervolemia, stress-induced cardiomyopathy, myocarditis and tachyarrhythmia. Heart failure has been seen in 23% of COVID patients in a study by Zhen et al. The incidence of significant heart failure in 52% of the non survivors and up to 12% patients who recovered.[18] Also as with any critically ill patients in ICU, they may develop reversible sepsis-related cardiomyopathy with left ventricular dilatation and impaired systolic function. COVID-19 infection can cause decompensation of underlying heart failure and may lead to mixed shock syndrome (combination of septic shock and cardiogenic shock).Significantly elevated BNP/NT-proBNP levels also suggest acute HF.[3]If heart failure is suspected, a limited TTE or focused ECHO can be performed. Invasive hemodynamic monitoring and supportive measures like inotropes and diuresis can be used to treat cardiogenic shock and fluid overload in such cases.

Venous and Arterial Thromboembolism

COVID-19 disease causes a prothrombotic state leading to venous and arterial thrombosis. prolonged immobilization leads to venous stasis and hypercoagulability due to use of glucocorticoid, immunoglobulins as well as vascular endothelial damage due to central venous catheterization and/or ECMO, hypoxia often are a contributing factor for occurrence of VTE. The Exact incidence of thromboembolism is unknown but few case reports have mentioned the occurrence of pulmonary embolism in these patients. Report of occurrence of acute pulmonary embolism in two patients aged 57 and 70 years with elevated D-dimer and multiple filling defects on CT pulmonary angiogram[39]. Multiple studies from China have reported higher D-dimer levels in COVID-19 patients with adverse outcomes[18].D-dimer levels were significantly higher in non survivors than survivors (2.12 μg/ml vs 0.61 μg/ml; $p<0.001$) thus reflecting a worse prognosis [40]. Multiple reasons can be postulated for activation of coagulation cascade in critically ill-patients which include i) pro-inflammatory cytokines lead to activation of coagulation cascade; ii) during inflammatory conditions, the alveolar hemostatic balance is tilted more towards a prothrombotic state; iii) proinflammatory cytokines may itself lead to endothelial injury and activation of coagulation cascade. In such a scenario, levels of D-dimer which serves as marker of fibrinolytic activity is elevated along with other inflammatory cytokines. Critically ill patients with COVID-19 are at an increased risk for venous thrombosis and hence the need for anticoagulation in these patients. A recent study showed that in COVID-19 positive patients with sepsis-induced coagulopathy score <4, administration of heparin led to a reduced 28-day mortality. Anticoagulation with heparin has been recommended for patients with raised D Dimer. [40]

Long term sequel of COVID-19 infection

Since COVID-19 infection is a new disease it is too early to understand the long-term cardiovascular outcome for patients who have recovered from COVID 19. Patients recovered from previous SARS infections and followed over 12 years showed that 40% had cardiovascular abnormalities, 60% with abnormal glucose metabolism and 68% with hyperlipidemia.[38] Patients recovered from pneumonia followed on long term show cardiovascular abnormalities like myocardial infarction, stroke, and fatal coronary artery disease. These are secondary to increased systemic inflammatory and procoagulant state seen in these patients. The hyperlipidemia may be attributed to the high dose methylprednisolone therapy. In addition, these patients had significantly higher lipid levels as compared to controls which had been attributed to the high-dose pulses of methylprednisolone [41].

Social effects and consequences on health care

COVID-19 will lead to a huge burden on developing countries. In a resource limited setup already burdened with existing disease COVID-19 can potentially crash the healthcare system. The focus on COVID-19 treatment has lead to Cardiac diseases taking a back seat. Patients with CVD are not only more susceptible to have COVID-19, the neglect in the care of their primary disease will lead to disastrous consequences. Although control measures like lockdown and curfews are needed due to these restrictions and also fear of contracting disease patients with acute MI delay in coming to hospitals and increasing patients with sequel like LV dysfunction and heart failure are now seen[42]. Hence, strict control measures such as social distancing, lockdown and curfews are the need of the hour to prevent the disease spread. Also, routine follow up and compliance to medications especially in patients from rural areas would be hampered. More emphasis on telemedicine to maintain consultation and follow up with patients and to minimize contact should be encouraged.

Interventions and cardiac implications

There are various medications (new and established ones which are repurposed) that are currently being tested in various ongoing studies. Chloroquine and hydroxychloroquine shown promise in some trials when used early in the disease.[43]. However clinicians need to be watchful for some rare cardiac arrythmias associated with these drugs like polymorphic VT (Torsade de Pointes) as they have potential to prolong the QT interval.[44] Convalescent plasma and tocilizumab (a monoclonal antibody against interleukin-6) are other therapies that have shown some promise in reducing severity of illness.[45]

Although, ACEi might facilitate viral entry into respiratory cells leading to viral mediated cell damage, these same medications might upregulate ACE2 and reduce the acute lung injury caused by COVID-19. As for now, guidelines recommend that patients on ACEi and ARBs should continue taking their medications as usual and should not discontinue them with CoVID-19 disease. Some statins like pitavastatin have shown some effect against COVID but further studies are needed in this regard. [46]NSAIDS have been shown to increase the expression of ACE2 on the cellular membranes and could theoretically increase viral entry into respiratory cells. More studies will be needed on this, but given this concern, many European countries have suggested that in patients with respiratory tract infections, acetaminophen should be used in preference to NSAIDs for control of pain and fever.[47]

Remdesivir an antiviral repurposed from previous used for Ebola has shown to be effective in trials to reduce time to clinical improvement and mortality in patients on oxygen [48] but needs larger studies for efficacy and tolerability . Tocilizumab has shown to cause dyslipidemia in patients treated for rheumatoid arthritis. Following tocilizumab, LDL-C, and HDL-C were increased, while cardiac risk markers like phospholipase A2 and LPa were decreased. .[49]

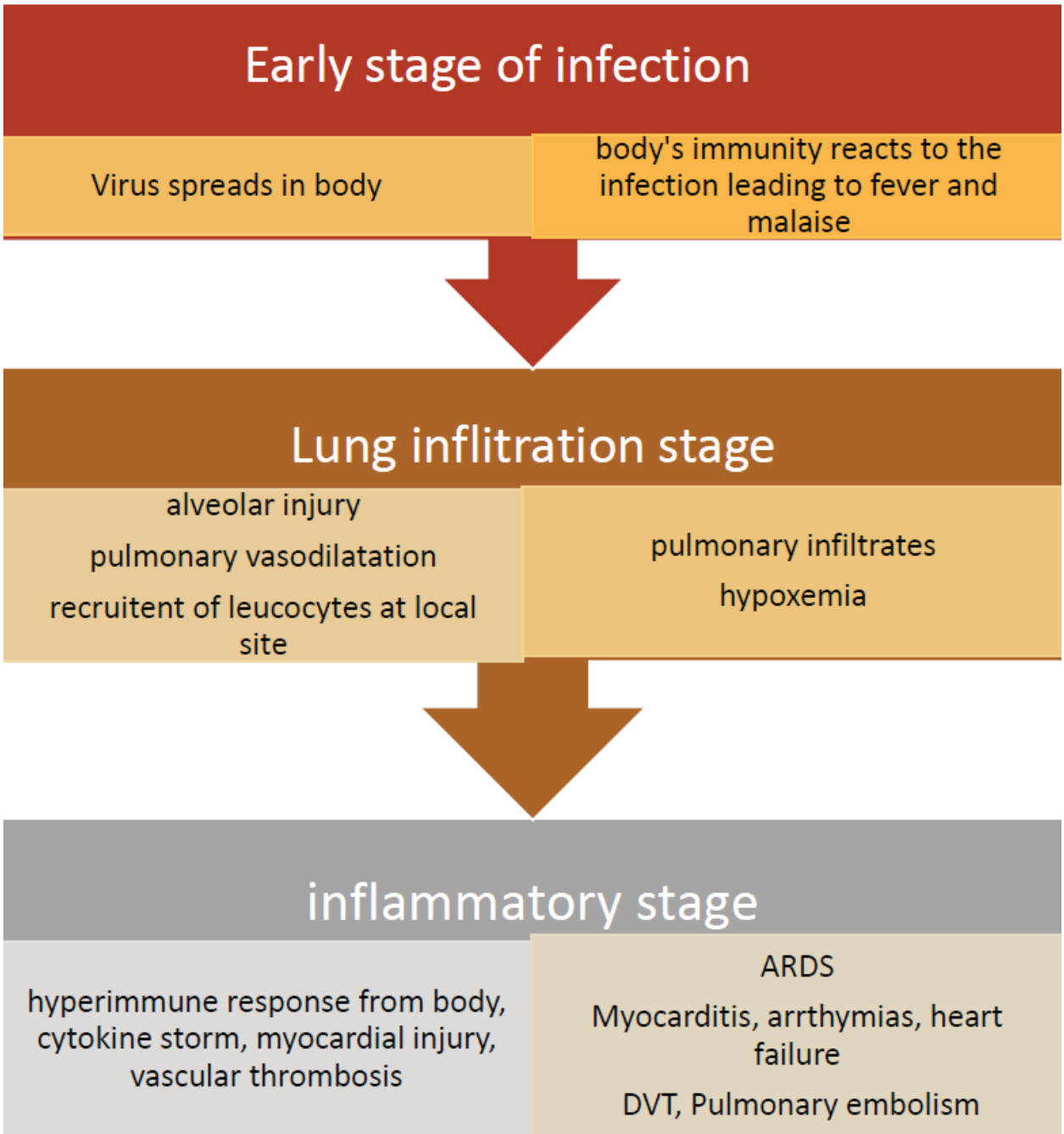

Figure 1. Pathophysiology of COVID infection and cardiac complications.

Conclusion

SARS-CoV-2 with its varied presentation and rapid infectivity has emerged to be the biggest challenge faced by mankind in this century. Cardiac patients are at increased risk of severe COVID-19 infection and it is associated with worse prognosis. COVID-19 infection leads to fulminant myocarditis, acute coronary syndromes, heart failure, arrythmias (Atrial Fibrillation, Ventricular Tachycardia and Fibrillation) etc. all of which are life threatening. Cardiac complications usually appear 10 days after onset of fever and can be detected early using biomarkers. Hence there is need for close monitoring of patients to detect and manage these cardiac complications especially in those with comorbid conditions. Several potential areas of research include pathogenesis and therapeutics; along with randomized control trials are urgently needed which will help in managing this global pandemic.

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