Review Article

Cardiological society of India position statement on COVID-19 and heart failure

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The COVID-19 pandemic has emerged as an unprecedented health emergency which has gripped the world. With nearly 2 million cases and 140,000 deaths reported worldwide as of April 18, 2020, it has shattered the health systems in all the major economies of the world. Mankind is facing a crisis unheard of in its history. Government of India acted early and initiated a nationwide lockdown on 25th March 2020, which has resulted in slowing the spread of the virus, as of April 18th, we have about 11,906 cases and nearly 480 deaths.

Coronavirus, a type of RNA virus causes all the three dreaded new-age virus diseases - COVID-19, SARS and MERS. The virus which causes COVID-19, the SARS-CoV2, (the novel coronavirus) has much lower case fatality rate (3–8%) compared to SARS (10.87%) and MERS (34.77%). The problem is that it has much more infectivity which leads to exponential spread and that is why it is more dangerous than the other two.

The majority (80%) of people with COVID-19 are either asymptomatic or have mild symptoms of a respiratory infection (fever, sore throat and cough) and make a full recovery. The mortality in COVID-19 increases with the age of the patient. Though the mortality is less than 1% in <50 years, it reaches 15% in those >80 years. This could be due to the loss of immunity and the presence of comorbidities in older ages. What has been observed in several affected countries is that people with diabetes, hypertension and heart disease including heart failure are at risk of a more severe illness.

In this position statement we will discuss the current understanding of the inter-relation between heart failure (HF) and COVID-19. There is no large data on patients developing HF as a complication of the viral infection or the effect of COVID-19 on patients with pre-existing heart failure.

The guidance provided in this position statement is based mostly on expert opinion which stands on limited published data, coming mostly from China and Europe. The knowledge on COVID-19 is rapidly evolving and the guidance will need periodic review.

1. Morbidity and mortality in cardiovascular disease (CVD) patients with COVID-19

1. The novel coronavirus — SARS-CoV2 produces a typical flu-like syndrome predominantly affecting the respiratory system. Critical infection, which develops in about 6% of the patients, can lead to bilateral pneumonia, ARDS and circulatory shock, which can be fatal.

2. Like any other viral respiratory tract infection, COVID-19 can cause worse outcomes in patients with pre-existing CVD risk factors or in those with established CVD. This is due to low cardio-respiratory reserve of these patients or by worsening of the underlying CVD due to systemic effects of the illness or by precipitating de novo cardiac complications.

3. The incidences of hypertension, cardio-cerebrovascular diseases and diabetes were about two folds, three folds and two folds, respectively in severe cases compared to the non-severe cases.

4. COVID-19 patients with pre-existing CVD have increased case fatality rates compared to others. Case fatality rates reported are 6% for hypertensives, 7.3% for diabetics and 10.5% among those with CVD, while the overall case-fatality was only 2.3%. However, these are univariate analysis and not adjusted for comorbidities.

2. Mechanisms of cardiac injury

Cardiac injury seems to occur in about 20–30% of hospitalized patients and cardiac complications contribute to 40% of deaths related to COVID-19. The incidence of acute cardiac injury was about 13 folds higher in ICU patients compared to non-ICU patients as reported by Li et al. In a series of 191 patients, acute cardiac injury was seen in 17% of the whole group, while it was 59% among those patients who died and 1% in survivors. The mortality risk attributed to acute cardiac injury was found to be much more significant than that of age, diabetes, COPD or prior CVD history.

1. Acute cardiac injury is defined as elevation of serum levels of cardiac troponin I/T above 99th percentile of the upper reference limit OR if new abnormalities were shown in echocardiography or ECG.

2. Majority of cardiovascular events in patients with COVID-19 are the result of severe immune over-reaction by the body called cytokine storm. The evidence of myocarditis in COVID-19 without any evidence of direct viral infiltration points to the deleterious bystander effects on heart. It is postulated that downregulation of ACE2 occurs due to viral infection, resulting in unopposed action of Angiotensin II with effects such as increased inflammation, hypertension and thrombosis.

3. Second mechanism is the myocardial insult due to hemodynamic stress, respiratory failure and hypoxemia. This produces
supply-demand mismatch which leads to myocardial ischemia—what is termed as Type 2 myocardial infarction. (Type 2 MI).
4. It is known that the risk for acute coronary syndromes (ACS) will be more in patients with viral illnesses due to heightened inflammation and thrombotic milieu. But typical Type 1 MI due to atherosclerotic plaque instability (plaque rupture or erosion) are relatively uncommon. Many of the patients who presented with ST elevation had angiographically normal epicardial coronaries.

5. Another form of cardiac manifestation is myocarditis. It can vary in severity from mild ventricular dysfunction to severe fulminating myocarditis. It is either caused by direct infiltration of the virus into the myocardium but mainly it is attributed to the “cytokine storm” occurring in response to the systemic inflammation.

6. Another mechanism of cardiac injury is similar to Takotsubo cardiomyopathy or stress cardiomyopathy, where intense microvascular dysfunction contributes to ventricular dysfunction.

7. Cardiac injury usually becomes evident in the second week of the illness and manifests as ECG changes, troponin elevation, ventricular dysfunction or arrhythmias.

Any of the above mechanisms which causes cardiac injury can potentially lead to heart failure. Also, the hemodynamic stress and inflammatory milieu can worsen pre-existing heart failure.

3. Heart failure in COVID-19

Zhou et al in a series of 191 patients found that 23% of the overall cohort had heart failure; while HF was present in 52% of those who died, but only in 12% among those who survived. This report points to the fact that HF is an important prognostic marker, but the criteria used to define HF in this study was not provided. In another study of a cohort of 799 patients from China, HF was identified as a complication in 49% of patients who died vs 3% in those who recovered. This patient population had a baseline prevalence of HF <1%, indicating that most of the cases were due to the effect of COVID-19 itself and not due to worsening of pre-existing HF. Patients with HF and COVID-19 are mostly male. Most of the patients with heart failure were noted to have lymphopenia and also high levels of CRP.

4. HFrEF or HfPEF?

Although there are isolated reports of depressed ventricular function in COVID-19, the majority of patients with uncomplicated lymphocytic myocarditis presented with near normal systolic function. Performing echocardiography has technical difficulties and limited by the availability of PPE, hence there is no large data to say whether myocarditis in COVID-19 presents as heart failure with preserved ejection fraction (HfPEF) or reduced ejection fraction (HFrEF). It is possible that the presentation as HfPEF may be more common.

5. Clinical presentation – heart failure and COVID-19

Patients with COVID-19 present with predominantly respiratory symptoms like cough and dyspnoea and can masquerade worsening heart failure or acute decompensated heart failure (ADHF). This is especially true since heart failure patients may not mount a fever. Cardiac symptoms like chest pain and palpitations lack specificity. Fatigue is also reported.

6. Evaluation of patients with COVID-19 and HF

6.1. ECG

A baseline ECG is recommended in COVID-19 patients, especially with cardiovascular comorbidities. This is to have a baseline status and to assess the QTc. QTc may be useful as the patient may be prescribed drugs like chloroquine and azithromycin, both of which increase QT interval. The most common ECG abnormalities reported in patients with COVID-19 with troponin elevation are ST segment depression, T-wave inversion and occasionally Q waves. These changes may not be specific to any coronary territory, but may be diffuse. ST-segment elevation is also reported in patients with myocarditis or Takotsubo (stress) cardiomyopathy. ECG may show arrhythmias like sinus tachycardia and atrial fibrillation. Though AF is the most common arrhythmia, malignant ventricular arrhythmias and bradycardia are also rarely reported. Extensive ST elevation and heart blocks indicate poor prognosis.

6.2. Echocardiography

Since there is significant risk involved to the personnel, echocardiogram should be ordered only if it is expected to change the course of management. Echocardiogram may reveal wall-motion abnormalities and give an idea about the global LV function. Both regional and global LV dysfunction have been reported in patients with COVID-19.

6.3. Cardiac MR findings in COVID myopericarditis

We don’t have large data on MR findings in COVID-19 myocarditis. The following were reported in CMR in one of the patients with myopericarditis who had ventricular systolic dysfunction: increased wall thickness with diffuse biventricular hypokinesis, especially in the apical segments, marked biventricular myocardial interstitial edema, and diffuse late gadolinium enhancement involving the entire biventricular wall.

6.4. Coronary angiography

Type 1 MI due to plaque rupture or erosion is not very common in COVID-19, a few patients who had ST elevation in ECG had angiographically normal coronaries. So, the threshold for doing CAG should be high. Coronary angiogram and PCI may be considered only in selected patients since it involves significant risk to the performing physicians, nurses and technicians. In addition, terminal cleaning is required after catheterization of COVID-19 cases. Most of the professional associations including Cardiological Society of India have come-up with guidelines in this regard. Interventional procedures should only be done in patients having hemodynamic compromise or for those who need rescue PCI. CT coronary angiography can be used to rule out significant obstructive CAD in suspected cases of ACS, as many patients go for chest CT for evaluation of pneumonia. Cardiological Society of India recommends fibrinolytics and pharmacological therapy as treatment of choice in stable STEMI.

6.5. Biomarkers

Biomarkers give important clues to the diagnosis and aid in the management of COVID-19 patients. The most evaluated biomarker is Troponin. Other markers which are being evaluated in COVID-19 include natriuretic peptides, D-dimer, ferritin, interleukin-6 (IL-6), Interleukin-10 (IL-10) and lactate dehydrogenase. Elevated total white blood cell (WBC) count, and decreased lymphocyte and
platelet counts were seen in non-survivors compared to survivors.  

6.6. Troponin

Troponin is the most utilized biomarker in COVID-19. Those patients who had higher values during the hospital stay had higher mortality. Zhou et al reported a particular trend in the levels of troponin. They found that during follow-up, the median hs-cTnI values did not change significantly among survivors whereas it almost doubled every week in non-survivors.

Lippi et al. report that a high initial value and a rising trend of Troponin I in COVID-19 indicates a worsening patient. They hypothesize that an initial measurement as well as longitudinal monitoring, may help to identify a subset of patients with possible cardiac injury and worse prognosis. Such patients can be intervened early and anti-inflammatory agents or steroids or antivirals can be instituted in the beginning itself.

The most common scenario is a mild elevation of troponin – this will persist throughout the course of the illness below the 99th percentile of the normal and such patients have a good prognosis. Progressive elevation as described above carries a worse prognosis. Moderate elevation which tend to show a fall during the course of the illness indicates ACS or myocarditis.

If the rise in hs-cTnI tracks with the other inflammatory biomarkers (D-dimer, ferritin, interleukin-6 (IL-6), lactate dehydrogenase), it reflects a possibility of a cytokine storm more than an isolated myocardial injury where only troponin is elevated.

7. NT pro-BNP/BNP

When HF is clinically suspected, serum natriuretic peptide levels (BNP or NT Pro BNP) should be assessed for aiding diagnosis and also to obtain prognostic information. Elevated NP have been reported in patients irrespective of the presence of objective evidence of HF, and are found to correlate with troponin values. NT-pro BNP levels were significantly higher in patients with elevated troponin levels as compared to the patients without troponin elevation (1689 versus 139 pg/mL).

8. Management of patients with pre-existing CVD

The management principles for patients who have pre-existing CVD and who develop COVID-19 and develop CV complications during coronavirus infection are the same. But there are certain aspects in the management of COVID-19 patients which the physicians and health care providers should consider. It is crucial to identify and isolate known CVD patients with COVID-19 symptoms from other patients. All CVD patients should be advised to practice isolation, especially if they are 60 years or older with meticulous frequent hand washing and social distancing.

Government should ensure that adequate supplies of all essential medicines are available to chronic patients with heart failure. Skipping or discontinuing medications can be catastrophic in patients with heart failure.

Telemedicine links should be established which allows patients to contact health care personnel when there is a lock-down and there are restrictions in public transport. Also, the government should ensure smooth function of emergency services in hospitals which cater to acute coronary syndromes and acute decompensated heart failure.

9. Management of patients with COVID-19 and HF

COVID-19 patients who are diagnosed as having asymptomatic left ventricular systolic dysfunction or clinically overt heart failure should receive standard guideline directed therapy. Careful management of fluid balance, careful monitoring of electrolytes and renal function is very important. Another cardiovascular co-morbidity which can co-exist is venous thromboembolism and adequate prophylactic measures need to be undertaken. NSAIDs like ibuprofen should be avoided and paracetamol may be the preferred analgesic. Drug interactions between repurposed or investigational drugs for COVID-19, especially protease inhibitors and various classes of cardiovascular medications should be checked for when administered concomitantly.

9.1. Personal protection

Caregivers should understand the responsibility of protecting themselves from getting infected. Therefore, it is crucial that all healthcare personnel caring for suspected and known COVID-19 patients must always observe all necessary precautions. All the personnel should be trained in using PPE (personal protective equipment) in accordance with the existing guidelines of MOHFW, Govt. of India.

9.2. Health system preparedness

Health care systems – including hospitals and health department should be prepared to deal with the potential high flow of patients of COVID-19. The necessary isolation wards or ICUs should be identified and kept ready. Necessary PPE should be procured and stocked. The medicines required for prophylaxis and treatment of COVID-19 and cardiac drugs should be stocked adequately. Many of the patients may be needing ventilator support. Adequate number of ventilators and physicians and support staff should be available.

10. Medical management

It is recommended to do only the investigations that are likely to provide decisive information in the management of patients with COVID-19. Routine echocardiography and routine measurement of natriuretic peptides or troponins are discouraged by ACC, ESC and ASE. The medical therapy of HFrEF – the evidence based management using beta blockers, ACEI/ARB/ARNI and Aldosterone blockers should be continued unless there are any contra-indications to these drugs.

Ministry of health and family welfare, Govt. of India (MOHFW) does not recommend any specific antiviral therapy for COVID-19 at the time of preparing this manuscript. In symptomatic patients, they recommend a combination of hydroxy chloroquine and azithromycin with close monitoring of QT interval. Some state government protocols recommend Lopinavir/Ritonavir therapy in those patients who deteriorate to develop MODS/ARDS while on HCQ + Azithromycin.

MOHFW recommends to “closely monitor patients with severe acute respiratory illness (SARI) for signs of clinical deterioration and sepsis, and apply supportive care interventions at the earliest: application of timely, effective, and safe supportive therapies and managing the co-morbidities is the cornerstone of therapy for patients who develop severe manifestations of COVID – 19.”
Indian guidelines by MOHFW recommends short term (3–5 days) glucocorticoid therapy (methyl prednisolone up to 1 – 2 mg/ kg/day) for patients with progressive deterioration of oxygenation, rapid worsening on imaging and excessive activation of the body’s inflammatory response. Many antiviral drugs (eg. remdesivir) and therapies like convalescent plasma therapy are being tested in patients with COVID -19 across the world. Management of ventilation and shock are beyond the scope of this document and readers are recommended to refer to the MOHFW guidelines.

11. Fluid management in acute decompensation

It is imperative to optimize volume status very carefully with less aggressive fluid resuscitation for hypotension in patients with COVID and HF. Diuretics are to be used very carefully. Many a times it will be difficult to differentiate ARDS from pulmonary congestion. Non-invasive ventilation may be avoided as it generates aerosols.

12. ACEI/ARB/ARNI use in COVID-19 patients

SARS-CoV-2 binds to ACE2 before entering human cells, and there is a theoretical potential for worsening of the clinical status in patients who are on ACEI/ARB, due to upregulation of ACE2 induced by these medications. On the other hand, it is also postulated that binding of SARS CoV2 to ACE2 can attenuate the activity of ACE2, thereby increasing the levels of Angiotensin II, resulting in pulmonary vasoconstriction and acute lung injury. At the time of preparation of this manuscript, there is no conclusive major clinical or experimental evidence regarding clinical translation of benefit or harm of ACEI or ARB use in Covid-19. A retrospective, propensity-score matched analysis from Wuhan, China reported lower risk of all-cause mortality with in-patient use of ACEI/ARB among hospitalized Covid-19 patients with hypertension. All major professional societies have issued statements urging medical community and public to continue these medications. We recommend continuing ACE inhibitors/angiotensin receptor blockers and ARNI in patients with COVID-19 when there are no contraindications to their use.

Table 1

| Drug                          | Interactions and effects                        | Action to be considered                                                                 |
|-------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1. Antibiotics                | QT prolongation and arrhythmias                 | Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor  |
| Macrolides (Azithromycin etc.)| QT prolongation and arrhythmias                 | Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor  |
| Quinolones (Ciprofloxacin etc.)| QT prolongation and arrhythmias                 | Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor  |
| 2. Anti-arrhythmic drugs      | QT prolongation and arrhythmias                 | Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor  |
| (Amiodarone, disopyramide     |                                                 | May need to monitor blood sugar levels and may need to reduce dose of antidiabetic drugs |
| procanamid quinidine          |                                                 | Can be continued, but monitoring of BP and heart rate may be needed                     |
| amidarone sotalol)            |                                                 | Can be continued, but monitoring may be needed                                         |
| 3. Anti-diabetic drugs        | HCO lowers blood sugar levels                   | Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor  |
| including Insulin             |                                                 |                                                                                         |
| 4. Betablockers (Metoprolol,  | HCO increases drug levels of BB interfering    |                                                                                         |
| Carvediol, Bisoprolol etc.)   | with its metabolism at higher doses             |                                                                                         |
| 5. Digoxin                    | HCO increases Digoxin levels at high doses       |                                                                                         |
| 6. Lopinavir; Ritonavir        | Lopinavir prolongs QT                           |                                                                                         |
15. Heart transplant and COVID-19

Heart transplant recipients are at high risk of contracting COVID-19 as per one report from China where they followed up 87 heart transplant patients. In another report of two heart transplant recipients who contracted COVID-19, both survived and were treated with antibiotics and antivirals, while the sicker patient required cessation of immunosuppression, along with treatment with methylprednisolone and IVIG. It is recommended to avoid donors with known or suspected COVID-19 and if a donor had COVID-19, they should be tested to be COVID-19 free (by PCR) for at least 14 days.

16. Vaccination

COVID-19 patients are prone to have co-infections with other respiratory pathogens like H1N1. So it is advisable to continue to have routine influenza vaccination for patients with heart failure. Pneumococcal vaccinations may be considered in patients with HF who have specific indications.

17. Long-term cardiovascular effects of COVID-19

Data on the long term sequelae of COVID-19 patients with cardiovascular involvement are emerging. CMR findings in recovered COVID-19 patients with documented cardiac involvement revealed myocardial edema in more than half of the patients. Late gadolinium enhancement and impaired right ventricular function were also observed. One study of survivors of in-hospital COVID-19 revealed that 80% have routine in-hospital infections. CMR findings in recovered COVID-19 patients with documented cardiac involvement revealed myocardial edema in more than half of the patients. Late gadolinium enhancement and impaired right ventricular function were also observed.

18. Conclusions

- The COVID 19 global pandemic has engulfed humanity with a huge impact on health systems across the world.
- Many patients develop myocardial injury which can lead to significant cardiovascular complications including HF. This will require aggressive management strategies, many of them are evolving.
- Guideline directed drug therapy including BB, ACEI/ARB/ARNI and aldosterone blockers is to be continued in patients with pre-existing HF.
- Long-term cardiovascular effects of COVID-19 are yet to be ascertained.
- Protection of health care personnel from contracting the disease should be given high priority.

**Conflicts of interest**

All authors have none to declare.

**List of abbreviations used in the document**

| Abbreviation | Description |
|--------------|-------------|
| ACC/AHA      | American College of Cardiology/American Heart Association |
| ACE          | Angiotensin Converting Enzyme |
| ACEI         | Angiotensin Converting Enzyme inhibitor |
| ACS          | Acute Coronary Syndrome |
| ARB          | Angiotensin type II receptor blocker |
| ARDS         | Acute Respiratory Distress Syndrome |
| ARNI         | Angiotensin receptor – Neprilysin inhibitor |
| ASE          | American Society of Echocardiography |
| BNP          | Brain-type Natriuretic Peptide |
| COPD         | Chronic Obstructive Pulmonary Disease |
| COVID-19     | Coronavirus Disease of 2019 |
| CRP          | C-Reactive Protein |
| CT           | Computerised Tomography |
| CVD          | Cardiovascular Disease |
| ECG          | Electrocardiogram |
| HCQ          | Hydroxychloroquine |
| HFrEF        | Heart Failure with Preserved Ejection Fraction |
| HFrEF        | Heart Failure with Reduced Ejection Fraction |
| ICU          | Intensive Care Unit |
| LV           | Left ventricular |
| MERS         | Middle East Respiratory Syndrome |
| MI           | Myocardial infarction |
| MODS         | Multi-organ dysfunction syndrome |
| MOHFW        | Ministry of Health and Family Welfare |
| MR(1)        | Magnetic resonance (imaging) |
| NSAID        | Non-steroidal Anti-inflammatory Drug |
| NT-Pro BNP   | N terminal Pro hormone Brain-type Natriuretic Peptide |
| PCI          | Percutaneous Coronary Intervention |
| RNA          | Ribonucleic Acid |
| SARS-CoV-2   | Severe Acute Respiratory Syndrome Coronavirus -2 |
| SLE          | Systemic Lupus Erythematosus |

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