Cardiovascular Disease and COVID-19: Issues in Women

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Abstract

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COVID-19, although primarily a respiratory illness, has myriad cardiovascular manifestations. Underlying comorbidities like hypertension, diabetes, and underlying cardiovascular disease are associated with higher mortality. Diabetes confers greater risk in women than men. Myocardial injury is seen in 17 to 36% of patients and is associated with higher mortality. Acute coronary syndromes (ACS) pose diagnostic and therapeutic challenges in the setting of the COVID-19 pandemic. Case reports of myocarditis have been documented. The sex differences in these common presentations have not been disaggregated and such evaluation is warranted to elucidate future interventions.

Introduction

Cardiovascular involvement is reported in COVID-19 and carries a grave prognosis. The mechanisms of cardiac injury include the following:
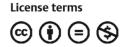
1. Nonischemic myocardial injury: Severe form of COVID- 19 disease can lead to cytokine storm, which can result in multiorgan damage including the heart.
2. Myocardial demand supply mismatch: Increased cardiometabolic demand and hypoxia in the setting of COVID-19 infection can result in myocardial oxygen demand-supply mismatch which, in turn, leads to acute myocardial injury.[1,2]
3. Plaque rupture and coronary thrombosis: Viral infection is associated with a systemic inflammatory state, which creates a prothrombotic milieu that along with the increased shear stress precipitates plaque rupture, resulting in acute coronary syndrome (ACS).
4. Direct viral myocardial injury (viral myocarditis): SARS-CoV-2 binds to the membrane angiotensin-converting enzyme-2 (ACE-2) expressed in heart. The virus replicates in the myocardial cells and causes direct cell damage and activation of T lymphocytes, causing cell-mediated cytotoxicity, which is aggravated by cytokine storm syndrome.[3]
5. Microvascular dysfunction: This can occur from diffuse microthrombi and vascular injury.
6. Stress-related cardiomyopathy: Takotsubo syndrome can cause left ventricular (LV) dysfunction.
7. Various therapies-related adverse effects: Antiviral drugs, corticosteroids (used in higher doses), and other therapies can have deleterious effects on the cardiovascular system. Myocardial injury, electrolyte imbalance from critical illness can precipitate arrhythmia.

Cardiovascular Comorbidities and COVID-19 Infection

Hypertension, diabetes and cardiovascular disease are prevalent among patients with COVID-19 infection and are associated with higher mortality. Wu et al,[4] in an analysis of 18465 patients with confirmed COVID-19 infection, studied the sex-specific differences in the risk of cardiovascular morbidity and COVID-19 mortality. The median age of patient population was 50.5 years and included 47.8% women. As much as 13.87% had hypertension, 5.53% had diabetes, and 4.45% had cerebrovascular disease, 2.51% had lung disease, and 0.81% had chronic liver diseases. Compared with women, men were more likely to have at least one comorbidity (27.37% vs. 24.98%; $p < 0.001$). The prevalence of diabetes (5.81% vs. 5.23%; p 0.092) and cerebrovascular diseases (CBVDs) (4.66% vs. 4.23%; p 0.16) were similar in men and women. Hypertension (14.73% vs. 12.92%; $p < 0.001$), lung diseases (2.92% vs. 2.06% $p < 0.001$), chronic kidney

diseases (0.94% vs. 0.66%; p 0.036), and chronic liver diseases (0.84% vs. 0.49%; p 0.004) were more prevalent in men than in women. Mortality was significantly higher in patients with hypertension (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.35–1.78), diabetes (HR 1.35, 95% CI 1.13–1.62), CBVDs (HR 1.70, 95% CI 1.43–2.02), chronic kidney diseases (HR 2.09, 95% CI 1.47–2.98), and at least two comorbidities (HR 1.84, 95% CI 1.55–2.18) after adjusting for age, gender, and severity of illness. Women with diabetes had a higher mortality than men (HR 1.69, 95% CI 1.27–2.25).

Acute Myocardial Injury and Myocarditis in COVID-19

Cardiovascular involvement can occur at any stage of the COVID-19 infection. Myocardial injury is defined as elevation of cardiac troponin above 99th percentile of upper reference limit. In a retrospective cohort study, Zhou et al[5] analyzed the risk factors for mortality in adult hospitalized patients with COVID-19. Older age, d-dimer greater than 1 µg/mL, and elevated troponin I were associated with higher mortality. They also found elevated troponin I in 46% of nonsurvivors versus 1% in survivors. In an analysis conducted by Shi et al[6] in hospitalized patients, 50.7% of whom were women with a mean age of 64 years, 19.7% had cardiac injury. The same group[7] analyzed 671 eligible hospitalized patients with severe COVID-19, with a median age of 63 years and included 52% women, of whom 9.2% died and more often had myocardial injury (75.8% vs. 9.7%; $p < 0.001$) than survivors. They reported that mortality was 50% (53 of 106) for patients with a cardiac troponin I (cTnI) > 0.026 ng/mL compared with just nine deaths (1.6%) among 565 patients with a lower cTnI. They found no difference in incidence of myocardial injury between men and women. The patients who died were older and more often male than the survivors ($p < 0.001$). Prevalence of hypertension, diabetes, coronary heart disease, chronic renal failure, chronic heart disease, and CBVDs was higher among the patients who died. Lala et al[8] analyzed 2,736 patients with COVID-19 infection admitted to five hospitals in New York, of whom 36% patients had elevated troponin I levels within 24 hours of admission. They concluded that even mild elevation of troponin I levels portended an increased risk of death (HR 1.75, 95% CI 1.37–2.24, $p < 0.001$) and this risk was tripled in patients with a marked elevation in troponin I levels (HR 3.03, 95% CI 2.42–3.80, $p < 0.001$) (►Table 1).

Acute Coronary Syndromes (ACS)

The proinflammatory state in COVID-19 infection triggers ACS by destabilizing plaques which could be further aggravated by the presence of a prothrombotic milieu in the setting of an infection. The largest database of ACS in India is the Kerala ACS registry (only 22.8% women), in which ST-segment elevation myocardial infarction (STEMI) constituted 40% of all ACS patients, with a high mortality rate of 8.2% in the hospital. Delays in presentation were common, with 41% of STEMI presenting more than 6 hours after onset of pain. Fibrinolytic therapy was administered in 41% of STEMI patients.[9] It is accepted that women with ACS have atypical presentations and undergo less aggressive diagnostic and therapeutic measures. There is paucity of data in India to ascertain the gender differences. The current pandemic poses additional challenges in the management of ACS due to further delays in presentation, nonavailability of rapid tests for SARS-CoV-2 which in effect have low sensitivity, lack of personal protection equipment (PPE), and the confounding effect of mild troponin elevations observed in SARS-CoV-2 infection. Numerous studies[5-8] found troponin elevation in COVID-19, which qualifies as non-ST elevation myocardial infarction and is associated with increased mortality. Most of these patients were managed conservatively and the incidence of coronary artery disease (CAD) was lacking in these studies.

In a case series[10] of 18 patients with COVID-19 who had STEMI (17% women), 10 patients (56%) had ST elevation at admission and another 8 developed ST elevation during hospitalization (median 6 days). Only 33% had chest pain at admission. Fourteen (78%) patients had focal ST elevation. Nine patients (50%) underwent coronary angiography, 6 of these patients (67%) had obstructive disease, and 5 underwent percutaneous coronary intervention (1 after fibrinolysis). Patients with myocardial infarction had higher peak troponin and D-dimer levels than the patients with noncoronary myocardial injury. Thirteen patients (72%) died, of whom 4 had myocardial infarction (50%) and 9 sustained noncoronary myocardial injury (90%). This case series reported a high incidence of noncoronary myocardial injury, which was paradoxically associated with a very high mortality of 90%.

Chieffo[11] concluded from a primary analysis performed in Lombardy on 33 patients with COVID-19, who underwent urgent coronary angiography (90.9%) or coronary computed tomography angiography (CCTA) (9.1%), that 60.6% of these patients did not have a culprit lesion requiring treatment. Stefanini et al[12] in a retrospective analysis on 28 COVID-19 patients (28.6% women), who were admitted for STEMI, reported a high incidence (39.3%) of nonobstructive CAD in 11 patients. The status of SARS-CoV-2 test was unknown at the time of coronary angiography in 24 patients (85.7%). STEMI could be the first clinical presentation of COVID-19 and a large proportion had nonobstructive CAD, which could be attributable to a type 2 myocardial infarction, endothelial dysfunction, or a cytokine storm. In another multicenter retrospective study,[13] including 78 patients (63% men), with a median age of 65 years, 59 patients (76%) received fibrinolytic therapy and only 19 patients (24%) were treated with primary percutaneous coronary intervention (PCI). Adverse outcomes in the form of intubation and cardiac resuscitation occurred in 16 patients (84%) treated with primary PCI. As much as 21% had stent thrombosis, which was unacceptably high, and 5 patients (26%) died. Fibrinolytic therapy was successful in 50 patients (85%). Hemorrhagic stroke occurred in 5 patients (9%). Adverse outcomes in the form of intubation and cardiac resuscitation occurred in 11 patients (19%) and death in 4 patients (7%). A high rate of stent thrombosis was

Table 1 Myocardial injury in various studies

Study	*n* women %	Myocardial injury	ACS	In-hospital mortality
Zhou et al[5]	191 38%	17%	Autopsy in one consistent with MI	28.3% With cardiac injury 59%
Shi et al[6]	416 50.7%	19.7%	ECG features consistent with NSTEMI 3.3%	13.7% With cardiac injury 51.2%
Shi et al[7]	671 52%	15.8%	No data	9.2% With cardiac injury 75.8%
Lala et al[8]	2736 40.4%	36% Mild 16.6% severe > 0.09 ng/dL 19.4%	No data	18.5% Mild troponin elevation HR 1.75 severe HR 3.03

Abbreviations: ACS, acute coronary syndrome; HR, hazard ratio; MI, myocardia infarction; NSTEMI, non-ST segment elevation myocardial infarction.

reported in a case series[14] of 4 patients (1 acute and 3 very late). Various case reports of unusual presentations continue to emerge during the pandemic. STEMI mimics in the form of dynamic ST elevations have been reported. ST elevations are predominantly seen in inferior leads. In two of these reports, a diagnosis of myocarditis was entertained in view of constellation of findings, elevated troponins, decrease in ejection fraction, and absence of obstructive coronary artery disease. In a third case report,[15] a 29-year-old morbidly obese, mechanically ventilated patient developed ST elevation in inferior leads, with normal troponin, absence of wall motion abnormalities, and normal ejection fraction on echocardiogram. He was managed conservatively, and his ST-segment changes resolved and were attributed to acute severe right ventricular strain due to acute respiratory distress syndrome. In another report,[16] a 42-year-old man with history of single episode of fever 2 weeks prior presented with STEMI. Angiography revealed left anterior descending (LAD) artery and right coronary artery (RCA) occlusion for which he underwent PCI. In view of multivessel occlusion in a low-risk young patient, SARS-CoV-2 infection was confirmed by reverse transcriptase polymerase chain reaction. STEMI could have been precipitated due to a prothrombotic milieu induced by a viral infection. This case report highlights the need for testing for SARS-CoV-2 in all STEMI patients in the setting of a pandemic, especially in unusual presentations. In another case report,[17] a young woman who was in close contact with COVID-19 patient presented with inferior STEMI, and angiography revealed normal epicardial vessels. SARS-CoV-2 infection was confirmed and she received antiretroviral therapy. She also received inotropes and mechanical ventilation. Repeat ECG revealed diffuse ST elevation and echocardiogram suggested severe LV dysfunction. She had normal white and red cell counts, mild acute kidney and liver injury, and surprisingly only slightly increased high-sensitivity C-reactive protein (hsCRP) (1.4 mg/dl) but markedly elevated troponin I at admission. After deterioration, she had platelet depletion with increased prothrombin time (PTT), international normalized ratio (INR) and marked increase of plasminogen activator inhibitor (PAI-1). Despite immunosuppressive therapy and immunoglobulin, the patient succumbed. Autopsy revealed microthrombi in inferior wall of right and left ventricles. Interestingly, the autopsy showed no evidence of viral infection in any part of heart, possibly due to low overall expression of ACE-2 receptors in heart.

Both American College of Cardiology (ACC) and European Society of Cardiology (ESC) guidelines recommend carefully weighing the balance between healthcare provider's exposure and patient benefit when considering intervention. All efforts should be made to differentiate between type 2 myocardial infarctions and myocarditis versus type 1 myocardial infarctions, and a strategy of fibrinolysis is detrimental, as a significant proportion of patients have nonobstructive CAD. Although fibrinolysis was suggested as the preferred approach in China, American and European studies endorse the role of primary PCI in PCI-capable hospitals factoring in COVID-19 delays.[18] The Indian strategy, which revolves around fibrinolysis, should be continued in non PCI capable hospitals and should be used judiciously, taking into account a constellation of findings which include patient presentation and rapid antigen testing before treatment. Cardiological Society of India (CSI) suggested the use of clinical screening, which may be combined with rapid antigen tests, as they become widely available across the country to rule out myocarditis and noncoronary myocardial injury and divide STEMI patients into confirmed COVID-19, suspected COVID-19 and low probability/non COVID-19. In community transmission stage, both confirmed and suspected COVID-19 should be managed similarly, with primary PCI being preferred option in PCI-capable hospitals and fibrinolysis if there are logistic problems and in non-PCI hospitals. Primary PCI is the preferred strategy in hemodynamically unstable patients, especially if the COVID-19 pneumonia is mild-to-moderate. Rescue PCI is indicated in cases of failed thrombolysis or for a delayed presentation beyond 12 hours, especially if pneumonia is mild-to-moderate. Patients with low probability/non COVID-19 should be managed with PCI following universal precautions as per CSI guidelines.[19]

Myocarditis and Pericarditis

Cardiac manifestations of COVID-19 like myocarditis and pericarditis were documented in single patient case reports.[20-22] Hu et al reported a 37-year-old man who presented with chest pain, dyspnea, and diarrhea, and he had

thousand-fold elevation of cardiac troponin T and NT-proBNP. His LV ejection fraction (LVEF) was markedly decreased to 27% with normal coronaries on CT angiography. He received intravenous (IV) immunoglobulin and methylprednisolone and supportive care with vasopressors. He was diagnosed to have fulminant myocarditis, as his cardiac biomarkers decreased and LV function improved in this report.[20]

In a case report,[21] a 53-year-old woman with SARS-CoV-2 infection, along with fatigue, ECG changes, and elevated cardiac biomarkers, had diffuse hypokinesia with decreased LVEF of 40%. Cardiac MRI revealed diffuse biventricular hypo-kinesia and diffuse late gadolinium enhancement. Her CRP was normal, and she did not have respiratory failure. She received antivirals and high-dose steroids (IV methylprednis-olone 1 mg/kg/day for 3 days). LV function improved partially by the sixth day. In a case report of a 69-year-old woman who presented with COVID-19 disease and cardiogenic shock, endomyocardial biopsy showed Coronavirus particles within the interstitial cells of the myocardium.[23] In another report, a 43-year-old woman with COVID-19 disease presented with ST elevation and mild LV dysfunction. Endomyocardial biopsy revealed diffuse T lymphocytic inflammatory infil-trates, interstitial edema, and limited foci of necrosis. SARS-CoV-2 virus was not detected within the myocardium.[24] In a retrospective study of 112 patients in Wuhan, China, 12.5% presented with abnormalities similar to myocarditis, which is defined as three-fold elevation in cardiac troponin I along with abnormalities on echocardiography and/or electrocar-diogram.[25] A cardiovascular magnetic resonance (CMR)-based study of unselected cohort of 100 patients who recently recovered from COVID-19 infection showed 78% have cardiac involvement, with the most prevalent abnormality being myocardial inflammation in 60% cases, followed by regional (scar 32%) and pericardial enhancement (22%)[26]

Heart Failure

Heart failure and cardiogenic shock are associated with mor-bidity and mortality in COVID-19 disease apart from respi-ratory failure and other organ failure. Potential causes of myocardial dysfunction include type 1 and type 2 myocardial infarction and myocarditis. Nonischemic heart failure is pre-cipitated by cytokine storm syndrome, which is corroborated by markedly elevated inflammatory markers like IL-6, D-dimer, LDH, ferritin, and CRP in patients with severe COVID-19 disease.[27,28] Patients with high NT-proBNP values (>88.64 pg/mL) had a significantly increased risk of death; therefore, it was included as an independent predictor of mortality.[29] From across two Chinese hospitals, a study of 191 patients with COVID-19 disease revealed that 23% had a clinical diagnosis of heart failure. The mortality was 52% in those with heart failure.[5] Another retrospective case series of 150 patients with COVID-19 showed that 33% of deaths were attributed to respiratory failure plus heart failure; additional 7% had heart failure without respiratory failure.[30] Case reports of the use of mechanical circulatory support (venoarterial extracorporeal membrane oxygenation [ECMO]) in patients with cardiogenic shock from COVID-19 were documented.[31]

Takotsubo cardiomyopathy (TTC) is characterized by acute and transient regional LV systolic dysfunction and has been reported in respiratory failure and infections.[32] Women account for 75% of cases. In an analysis of 118 consecutive laboratory-confirmed COVID-19 patients[33] who underwent a clinically indicated TTE, 5 (4.2%) had features consistent with TTC. The median age of patients with TTC was 66 years. Paradoxically, all patients in this series were male. Higher peak levels of troponin and CK-MB were found in patients with TTC myocardial injury than non-TTC myocardial injury, whereas inflammatory and prothrombotic biomarkers were higher among patients with non-TTC myocardial injury. The authors deduced that TTC may be another phenotype of myocardial injury in COVID-19 and should be considered in patients with myocardial injury and new LV dysfunction.

Although sex disaggregated data[34] from 26 countries sug-gest higher case fatality rate in men, paradoxically, the case fatality rate in Indian women is higher, that is, 3.3% of infected women died of the disease compared with 2.9% of men.[35] The possible reasons for sex differences in mortality could be the higher incidence of comorbidities in men and high-risk behaviors like smoking in men. As the X chromosome har-bors immune-related genes, women mount stronger innate and adaptive immune responses than men.[36] This results in faster clearance of pathogens but paradoxically leads to a stronger inflammatory response. Another biologically plau-sible explanation postulated is that as ACE-2 gene is located on the X chromosome, women have higher ACE-2 levels and are protected against more severe disease compared with men.[37] In summary, although the incidence of myocardial injury is equal in men and women, only further investigation into the association of ACE-2 enzyme activity with severe myocardial injury can shed light on sex differences in disease susceptibility and outcomes. Evaluation of hormonal, immu-nologic, inflammatory, and phenotypic differences in myriad presentations like myocarditis, acute myocardial infarction, and heart failure in COVID-19 is warranted for better under-standing of the disease and development of therapeutic targets.

Conflicts of Interest
None declared

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