COVID-19 AND HEART DISEASES

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Abstract

Many patients with Coronavirus Disease 2019(COVID-19) have pre-existing heart disease or develop various cardiac complications during the disease. This review article is aimed to design understanding the relationship between heart disease and COVID-19 is necessary for optimum management of such condition. Literature search done by using PubMed, Medline and Cochrane data bases. Heart involvement occurs in approximately 8-12% of all patients.Acute cardiac injury, as evident by a significant cardiac troponin elevation is the commonest abnormality. Myocarditis, type II myocardial infarction, heart failure, arrhythmia are other cardiac manifestations that are less common.Pre-existing heart disease and/or involvement of the heart by COVID-19 carries worse prognosis. Most of the reports currently available describes cardiac manifestations briefly. Further study may reveal more clearly the various aspects of cardiac manifestations in COVID-19 patients.

Key words : COVID-19; Heart disease; Pandemic.

Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) causes Coronavirus Disease 2019 (COVID-19) which has become a pandemic affecting every country of the world.[1] The number of patients with COVID-19 as on 11 October, 2020 are about 37.11 million in the world with a total death of 1.07 million. Out of these, about three seventy seven thousands are in Bangladesh with 5,500 patients dying (World Health Organization situation report). Cardiac involvement appears to be a prominent feature of the disease, occurring in 20% to 30% of hospitalized patients and contributing to 40% of deaths in China.[2,3] The dominant clinical manifestation of COVID-19 are respiratory, ranging from mild flu like illness to fulminant pneumonia and lethal acute respiratory distress syndrome. Severe COVID-19 is a systemic illness characterized by hyper inflammatory response and cytokine storm. Pre-existing heart disease and it`s risk factors increase vulnerability to COVID-19. Conversely, COVID-19 can worsen underlying heart disease and even precipitate new cardiac malfunction.This review aims at discussing various aspects of cardiac involvement in COVID-19, including the impact of pre-existing and new onset cardiac manifestations.

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Search Strategy

Available studies and abstracts were indentified through PubMed, Medline data bases (From 2001-2020) and Cochrane data bases. Key search topic were "COVID-19 and Heart disease" and relevant articles. The reference list of review articles were also searched. The search term were following key words used in verious combination : COVID-19; Heart disease; Pandemic.

Discussion

Cardiovascular Manifestations

Acute Cardiac Injury

Although lung is the primary target in COVID-19 heart may get involved.[4,5] Acute cardiac injury is the most documented cardiac abnormality, with an incidence of 8-12%.[6] Acute cardiac injury has been defined as significant elevation in cardiac troponin I above 99th percentile upper reference limit. Severe SARS-CoV-2 binds to Angiotensin-Converting Enzyme 2(ACE2) receptor which is abundant in lung and heart. ACE2 converts angiotensin II into angiotensin.It serves a counter balancing role in the renin-angiotensin-aldosterone system.[7,8] This results in alteration of ACE2 signaling pathways, leading to down regulation of ACE2 in the heart which may contribute to myocardial dysfunction.[9] An unopposed action of angiotensin II leads to increased inflammation, hypertension and thrombosis.[10] Use of renin-angiotensin-aldosterone system antagonist may theoretically increase ACE2 expression with increase in susceptibility to infection but no convincing data in humans available.Higher ACE2 levels may be protective, by providing a reservoirs of receptors

to offset those lost in the course of infection.[11] No association of any medication with increase in the risk of severe illness was detected in patients with positive test result.[12] Also, there was no evidence that ACE inhibitors or Angiotensin Receptor Blockers (ARBs) increase the risk of COVID-19.[13] Patients with underlying heart disease are more susceptible to infection by SARS-CoV-2 with marked elevation of troponin I and associated higher mortality.[14] Acute cardiac injury may develop even in patients without underlying heart disease. Besides direct myocardial injury acute systemic inflammatory response and cytokine storm in severe COVID-19 result in injury to multiple organs,including the heart.[15,16] Acute systemic inflammation or cytokine storm is a hallmark of severe COVID-19.[17] It represents advanced stage of the acute illness. Key inflammatory markers are elevated, such as C-Reactive Protein (CRP) ferritin, procalcitonin and IL(Interleukin)-6, IL-2, IL-7 etc.[17,18,19] These inflammatory biomarkers are associated with high mortality. Thus,although the inflammation starts in lung ,the exaggerated inflammatory response exerts it`s deleterious effect on the heart and other organs.In the same way elevated biomarkers of cardiac injury (Troponin I) and electrocardiographic abnormalities correlate with elevated inflammatory markers.[20,21] Increased myocardial O_2 demand induced by systemic infection coupled with hypoxia resulting from lung infection leads to myocardial O_2 demand supply mismatch. This also results in acute myocardial injury. One type of cardiac injury similar to those of Takotsubo cardiomyopathy or stress cardiomyopathy also occur in COVID-19.[22] Here, an intense microvascular dysfunction contributes to ventricular dysfunction. Cardiac injury usually becomes evident in second week of illness and manifests as ECG changes,troponin I elevation, myocardial dysfunction or arrhythmia.[23]

Acute Coronary Syndrome (ACS)

Plaque rupture induced by systemic inflammation and shear stress of increased coronary flow leads to coronary thrombosis and acute Myocardial Infarction (Type I MI). The risk increases further by the prothrombotic state created by systemic inflammation, as evidenced by significantly elevated D-dimer levels.[18,19,24] The hyper inflammatory response leads to endothelial and smooth muscle activation, expression of tissue factor and platelet activation at site of atheromatous plaque in epicardial coronary arteries.[25] But typical Type I MI are relatively uncommon. In approximately 40% of patients with COVID-19 and ST-Elevated MI (STEMI) a culprit lesion is not identifiable by coronary angiography.[26] Thus, COVID-19 can mimic STEMI requiring immediate revascularization. However, angiogam show may show no blockage. Myocardial oxygen supply demand mismatch may lead to Type II MI. This may be related to ischemic cardiac injury secondary to hypoxia, thrombosis of the microvascular vessels or myopericarditis. The diagnosis of STEMI in COVID-19 patient may sometimes be difficult with similar presentation of chest pain and respiratory distress.

Myocarditis

Case reports of myopericarditis in COVID-19 have been reported although the underlying mechanism is poorly defined.[27] Autopsy showed mononuclear infiltration associated with regions of cardiomyocyte necrosis, which by Dallas criteria defines myocarditis.[28] Few cases of myocarditis due to direct cardiac damage have recently been reported,with detection of coronavirus in histological slides of myocytes, highlighting a marked cardiac tropism. Recently, Tavazzi et al described a case of acute cardiac injury directly linked to myocardial localization of the virus, with an endomyocardial biopsy demonstrating viral particles.[29] Several reports show that patients at greater risk of developing acute carditis already have increased troponin values at first contact in the emergency room with higher in-hospital mortality.[30]

Heart Failure

Acute cardiac injury, acute coronary syndrome, myocarditis may cause myocardial dysfunction and features of acute Heart Failure (HF). Also, increased metabolic demand arising from COVID-19 can cause acute decompensation of pre-existing stable HF. In a study, HF was present in 52% of those dying of COVID-19. It was found in 12% of those who recovered and discharged.[15] Recognition of signs and symptoms of HF in patients with COVID-19 pneumonia is a challenging clinical scenario. One may mask the other and HF may be exacerbated by COVID-19. A reduction in hospitalization of HF was observed in the acute phase of the pandemic as many such patients avoided hospital

visit out of fear of being infected by COVID-19.In the plateau phase of the disease many complicated cases are observed and need to be managed. Thromboembolism in COVID-19 has received widespread attention. The incidence was reported to be 20% to 30% in COVID-19 ICU patients.[31,32] Venous Thromboembolism (VTE) and pulmonary thromboembolism in critically ill patients may develop right heart failure and shock along with sudden onset of O_2 desaturation.[29] Acute pulmonary embolism is a life-threatening manifestation of COVID-19. Left sided HF and cardiogenic shock in COVID patients is rare. The inflammatory damage incurred by the virus causes pulmonary endothelial damage and formation of microthrombi.Fibrin degradation fragment (D-dimer) spills into blood in an attempt to clear thrombi by vigorous fibrinolysis as lung has high fibrinolytic capacity. A strong association between D-dimer levels, disease progression and prognosis is evident. Low-Molecular-Weight Heparin (LMWH) might potentially improve the outcome by prevention of VTE as well as suppression of microthrombosis.[33]

Arrhythmia

Both tachyarrhythmia and bradyarrhythmia can occur in COVID-19 The overall incidence was 16.7% with 44.4% in severe cases and 8.9% in mild cases.[18] Myocarditis, electrolyte imbalance and drugs are responsible in most cases. Hypokalemia may occur due to interaction of SARS-CoV-2 with rennin-angiotensin-aldosterone system predisposing to tachyarrhythmias.[7] Hydroxychloroquine and azithromycin are two common drugs used to treat COVID-19 patients. Both can cause life-threatening arrhythmias by QT prolongation.[34] Bradycardia may be a sign of severe cardiac or neurological impairment since it is associated with lymphopenia that seems to reflect the severity of COVID-19 infection.

Cardiovascular (CV) Comorbidities and COVID-19

The negative impact of pre-existing heart disease and it`s risk factors on COVID-19 has drawn awareness of medical community since the start of the pandemic in China. Patients with pre-existing Cardiovascular Disease (CVD) have heightened vulnerability to develop COVID-19.They also tend to have more severe disease and worse outcome.[18,35,36] This is due to cardio-respiratory embarrassment, worsening of underlying disease due to systemic effect of COVID-19 or by development of new cardiovascular complications.[37] A significantly higher prevalence of cardiovascular disease was found in a meta analysis of six published study from China including 1527 COVID-19 patients.[5] Prognostic importance of CV comorbidities is revealed by a significantly higher mortality among 44672 confirmed cases of COVID-19 in China showing Case Fatality Rate (CFR) of 6%,7.3% and 10.5% in patients with hypertension, diabetes and CVD respectively with 2.3% in the entire cohort.[38] The CFRs are much higher in some European countries and Washington, USA but it is lower in China outside Hubei province and many other countries are due to higher comorbidities among them.[39,40] In particular, a greater risk of having a more severe clinical picture and a fatal outcome in elderly people with CV comorbiditis, including a history of heart disease.[41]

Cardiac Evaluation of COVID-19 Patients

Those investigations that are likely to decide management strategy are to be done.

ECG: Commonly detected abnormalities are diffuse ST segment depression, T-wave inversion and occasional Q waves.[2] ST-segment elevation is reported in some patients with myocarditis and Takotsubo cardiomyopathy.[42] In patients with CV comorbidities a baseline ECG is recommended.

Biomarkers: Besides providing diagnostic clues, these aid in management of COVID-19 patients.Commonly evaluated biomarkers are troponin I, natriuretic peptides (NT pro BNP/BNP) D-dimer, ferritin, interleukin-6 (IL-6) and Lactate Dehydrogenase (LDH). Troponin I are the most elevated biomarkers. A mildly elevated troponin below the 99th percentile of the normal is commonly seen and carries good prognosis. Progressive elevation carries a worse prognosis. If the rise is accompanied by rise of other inflammatory biomarkers (D-dimer, ferritin, IL-6, LDH) it raises possibility of cytokine storm. A moderate rise that falls during the course of disease indicates myocarditis or acute coronary syndrome.[43] Serum natriuretic peptides are significantly elevated in patients with elevated troponin levels.[2] The American College of Cardiology discouraged random measurement of cardiac biomarkers such as troponins and natriuretic peptides.[44]

Echocardiography: Performing echocardiography has technical difficulties and limited by availability of Personal Protection Equipments (PPE). To avoid risk of exposure to infection and further straining the already stressed healthcare resources echocardiography should be reserved for circumstances in which it would add to the management of patients with COVID-19.The American Society of Echocardiography (ASE) and National Clinical Guidance for the Management of Cardiac Patients in the COVID-19 Pandemic, Bangladesh have issued advisories regarding the use of echocardiography in COVID-19 patients.[45,46]

Coronary Angiography (CAG) : Coronary Angiography and Percutaneous Coronary Intervention (PCI) may be considered only in selected cases since it involves significant risk to performing physicians, nurses and technicians. In addition, terminal cleaning is required after doing CAG of COVID-19 cases. Most professional associations and their guidelines including the National Clinical Guidance for the Management of Cardiac Patients in the COVID-19 Pandemic, Bangladesh recommend a conservative strategy in absence of dedicated cath lab.[46] CAG and interventional procedures are recommended for those who need rescue PCI or those having hemodynamic compromise.[47,48] However, 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 their lung involvement.

Long Term Consequences

Long term CV effects of patients recovering from COVID-19 are yet to be learned. Abnormalities of lipid metabolism and alteration in glucose metabolism among patients recovering from similar illness has been reported. Patients with acute myocardial injury and myocarditis in COVID-19 are advised to abstain from competitive sports for 3-6 months following recovery.

Management

The principles of management for COVID-19 patients with pre-existing CVD and COVID-19 patients with CV complications are same. Certain aspects need consideration:

COVID-19 is highly contagious, the caregivers should protect themselves from getting infected while treating these patients. Hospital healthcare staff should be trained in donning, usage and doffing of Personal Protective Equipment (PPE) in accordance with the existing guidelines. It is crucial to identify and isolate known cardiac patients with COVID-19 symptoms from other patients.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 but whose first RT-PCR test was negative (nasopharyngeal swab test may be false negative in about 30% cases)[49]. At the beginning of the pandemic a significant reduction in the absolute number of admission in cardiology ward was observed. It was also the case in the Bergama province of Italy. With subsequent increase in patient flow during the plateau phase cardiology need to ensure preparedness to deal with the increasing patient load. Protocol for rapid identification,triage, isolation,and management of COVID-19 patients with heart disease or cardiac complications should be developed and practiced. Patients with acute MI need a fast track from emergency room to CCU or cath lab to avoid the risk of acquiring infection as well as minimizing delay. Delay in delivering acute cardiac care in COVID-19 era has been reported[50]. Patients with COVID-19 presenting with STEMI, the choice of revascularization depends on risk-benefit ratio of primary PCI vs fibrinolysis. In resource-constraint environment where dedicated cath lab for COVID-19 positive cases are not available, a fibrinolysis-first strategy is recommended. National Clinical Guidance for the management of cardiac patients in the COVID-19 pandemic, Bangladesh, also supported conservative management by fibrinolysis with tenectaplase 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.[46,51,52] Thrombo-prophylaxis with heparin has been recommended for all hospitalized patients of COVID-19. It prevents pulmonary vascular thromboembolism and decrease dead space ventilation and decreases mortality. International Society on Thrombosis and Hemostasis recommend at least six weeks of anticoagulation in high risk patients following discharge.[53] COVID-19 related myocardial dysfunction may be treated with guideline directed HF therapy including beta-blockers, ACEI/ARB/ARNI and aldosterone antagonists. However, in hemodynamically unstable cases it should be

delayed till recovery phase and hemodynamic status is stable.[54] Previous treatment with Angiotensin Converting-Enzyme (ACE) inhibitors and Angiotensin. Receptor Blockers (ARB) upregulate ACE2, to which SARS-CoV-2 binds, raising concern of potential increased risk of developing COVID-19. However, no such association has been found.[12] On the contrary, the risk of discontinuing these drugs are well established. Therefore, continuing these drugs in clinically-indicated situations are strongly recommended by the professional bodies.[55,56]

Conclusion

Large number of patients with COVID-19 have pre-existing heart disease or develop new-onset cardiac manifestations during the course of illness. Being a new disease we have few certainties and several doubts around heart disease and COVID-19. In this COVID-19 era cardiologists have to learn to adapt to an altered, worrisome working environment. Although a large number of articles are produced in a short period current understanding of heart disease and COVID-19 is grossly inadequate. Before drawing conclusions on COVID-19 and heart disease further studies regarding incidence, clinical presentation and outcome are warranted.

Disclosure

The author declared no competing interest.

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