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Cardiovascular diseases in COVID -19: A Narrative Review

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ABSTRACT

COVID-19 was reported in late December 2019. Since then it has been announced as a global pandemic affecting more than 200 countries, with an unwanted effect on social, economic and public health. Cardiovascular disease has been reported in COVID -19 patients. Most probably, cardiovascular complications of COVID-19 are the combination of direct viral injury and host's immune response resulting in vascular inflammation and myocardial inflammation. Additionally, COVID-19 can cause cardiac complications through several ways such as increased release of Cytokines causes indirect cardiac injury direct invasion of cardiac myocytes. Respiratory damage causes hypoxia, supply - demand mismatched in myocardial tissue, followed by oxidative stress and injury in cardiomyocytes.

Cardiac manifestations of COVID-19 include cardiogenic shock, fatal Arrhythmias, myocarditis and acute heart failure. Early findings from China reported that CVD, hypertension and diabetes mellitus, were common preexisting conditions in COVID-19 patients. High prevalence of these comorbidities was confirmed in other studies too. It's important to notice that prevalence of these comorbidities were higher in severe ICU admitted patients. In other words, pre- existing cardiovascular disease seems to be key factor that worsen the outcome and increased risk of death in severe cases of COVID-19. Several clinical studies also reported a relation between COVID-19 and cardiovascular diseases. Moreover, recent studies also confirmed that cardiac injury and cardiomyopathy (CMPs) were common in COVID-19 patients.

In this Review, we focus our research to combine the facts and findings of several studies about current knowledge of cardiac manifestation during COVID-19. Once, we able to know complete facts of cardiomyopathy in COVID-19, we may be able to develop a correct therapeutic algorithm and cut down the mortality rate to the least in severe COVID-19 cases.

Keywords: Cardiovascular diseases, Coronavirus, Cardiomyopathy, Diabetes mellitus

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INTRODUCTION

Coronavirus disease 2019 was first reported in Wuhan, China, during late December 2019.Causative organism for COVID-19 is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a member of genus Beta coronavirus like the two other coronaviruses that were responsible for pandemic diseases SARS-CoV and MERS-CoV. All these viruses like SARS-CoV and MERS - CoV, SARS- CoV -2 causes a respiratory infection, which leads ti viral pneumonia and Acute Respiratory Distress Syndrome (ARDS) in some patients. Several studies made efforts to characterize the features of this novel coronavirus through genomic sequencing [1-3]. It was officially declared a pandemic by WHO in March 2020. While maximum number of cases is suffered from pulmonary complications, it is important for emergency clinicians to be aware about cardiovascular complications, which can be associated with the mortality of the patients of COVID-19 [4-9].

Mortality and morbidity risk in COVID-19 cases created a horrible situation globally and causes a huge transformation in the mode of work, education, examinations, and medical education. During COVID-19 pandemic most of the medical institutions are running online lectures. However, online lectures are not substitute of face- to -face classroom lectures (FFCL) [10].

Exact Reason behind prevalence of CVD in COVID-19 patients is not clear, but Preexisting CVD may be associated with a more severe COVID -19 infections.

Studies have reminded that cardiovascular metabolic comorbidities made patients more prone towards COVID-19. On the other hand, COVID-19 can aggravate the heart damage, development of myocardial injury, Arrhythmias, Acute Coronary Syndrome (ACS) and venous thromboembolism [11-15]. Preexisting CVD has been notified among the patients with COVID-19, and these comorbidities are associated with high mortality [16-18]. Age is the strongest risk factors associated with severe COVID-19; individuals over 80 have 20 fold higher risk of mortality than those of 50-59 year old , after adjustment of other risk factors.

Interestingly, hypertension does not appear to be concerned with risk of death even though it is highly prevalent among the patients admitted with COVID-19 [19].

MATERIAL AND METHODS

We searched PubMed, Google Scholar, Semantic Scholar, Springer using the key words "COVID-19"," SARS-CoV-2","Coronavirus disease", "Cardiomyopathy", "Arrhythmias", "Complications of Coronavirus Disease". We included several types of studies like, case reports, retrospective studies, prospective studies, meta-analysis, narrative reviews, and clinical guidelines for focusing our research on cardiac related complications in COVID-19 patients. We include the studies published in English language only. After reviewing 80 articles, only 35 articles were selected for inclusion.

DISCUSSION

Analysis of Cardiac Function

Echocardiography is widely used in the bedside evaluation of patients with COVID-19 infection, and echocardiographic anomalies have commonly been detected. In COVID-19 patients, myocardial injury takes place from acute coronary syndrome, myocarditis and takotsubo cardiomyopathy [20,21].

Frequently described cardiac abnormalities in COVID-19 are Adverse right ventricular remodeling [22,23] and abnormal RV Longitudinal strain [24] and have been associated with increased mortality. Study concluded that bedside Doppler evaluation of RSVP may be a useful predictive measure for short term risk stratification of hospitalized COVID-19 patients undergoing clinically indicated echocardiography. Pre-existing echocardiographic anomalies were present in 78%.These data should be used with caution in attributing such anomalies to the COVID-19 infection in this population with comorbidities [25]. Chen, et al reported a series of 25 patients who underwent CMR imaging within 10 days of acute COVID-19 diagnosis and found minor left ventricular dysfunction and myocardial Edema as compared to healthy controls.

Major limitations are that control group was not matched for preexisting comorbidities and study design can't demonstrate whether such findings might also be found in other critical diseases [26]. Together, these CMR(Cardiac Magnetic Resonance imaging) Studies have not sufficiently reflect the possible cardiac abnormalities in patients with acute severe COVID-19 but are common with a component of detected anomalies concerned with preexisting cardiovascular disease [27].

Cardiovascular Complications in Covid-19 Infected Children

Majority of COVID-19 infected children may develop very mild symptoms or may be a asymptomatic. A meta-analysis shows the evidence that children of age 10-14 have lower susceptibility towards COVID-19 infection. However, a very small population of children develop multi system inflammatory syndrome (MIS-C). This condition takes place after few weeks of acute COVID-19 and may have predilection towards black and Hispanic background [28-31]. Interestingly, meta- analysis of 16 studies about Cardiovascular involvement in children with PMIS (Pediatric Multi Inflammatory Syndrome) showed that PMIS affects mostly previously healthy schools - aged children and adolescents presenting with Kawasaki disease like symptoms and MOF (Multiple Organ Failure) with a focus on the heart, responsible for most of Pediatric mortality. They frequently presented cardiogenic shock (53%), ECG alterations (27%), myocardial dysfunction (52%), and coronary artery dilation (15%). Almost all of the children recovered with PICU care, ionotropic support and extra corporeal oxygenation. Only 2 % mortality reported in this scenario.

Remarkably, children (with or without pre-existing heart disease) with acute Covid-19 required hospital admission should undergo close cardiovascular monitoring to identify the life threatening cardiac complication timely [32].

The Cardiovascular System and Covid-19 Vaccination

9.03 million doses of the mRNA COVID-19 vaccines by Pfizer - BioNTech and Moderna have been administered and 4.46 million people were fully vaccinated in Singapore. 42 studies reported with cardiac side effects after COVID-19 vaccination .These CVS-AEs (Cardiovascular system Adverse effects) were mainly myocarditis, pericarditis, most commonly seen in adolescent and young adult male individuals after mRNA vaccination. Other adverse events such as stress cardiomyopathy, acute myocardial infarction, Arrhythmia were rare. In this clinical scenario, outcomes of post - vaccine myocarditis and pericarditis were good .Efficacy of vaccination was good, death and high numbers of cases were prevented [33]. In the COVID-19 vaccine safety update by Advisory Committee on Immunisation Practices (ACIP), the Centre for Disease Control and prevention (CDC) and the FDA as of Jan 27, 2021, reported s single event of acute myocardial infarction [34]. Biovin, et al. reported myocardial infarction in 96 years old female and no known cardiac history with the Moderna COVID-19 vaccine, but association of this

adverse event with vaccine could not be proven, it could be a coincidence simply [35].

Vaccines were also concerned with supra ventricular tachycardia, sinus tachycardia, palpitations paroxysmal tachycardia, etc. Peripheral circular failure was also found to have connection with vaccination. 1763 events of palpitations, 622 events of tachycardia, 78 events of fibrillation, 43 events of arrhythmia ,34 events of sinus tachycardia, 21 events extra systoles, eight events each of tachyarrhymia and supra ventricular tachycardia and 6 events of unstable angina reported in case of AstraZeneca vaccine against COVID-19 [36].

There were 792 events of increased heart rate, 61 events of irregular heartbeat, 24 events of decreased heart rate, 16 events of abnormal heart rate, one event of ECG T wave inversion, two events of abnormal ECG, three events of increased C- reactive protein, one event of abnormal C- reactive protein and one event of increased fibrin D -dimer reported in the same report of AstraZeneca vaccine.

Data of various studies showing that global population is already prone to develop many cardiovascular diseases .Henceforth, the data analysis reported as adverse effects following COVID-19 vaccination to the Vigibase can't be considered purely true. Moreover, baseline cardiovascular characteristics of the patients are taken in to consideration to get a conclusion. Meylan et al , reported a case series of nine patients with stage III hypertension after mRNA - based COVID-19 vaccine, later, eight out of nine patients had a history of hypertension and were taking medications[37]. It's essential to review these adverse effects to notice the number of mortality in population [38].

Medication Interactions and Cardiovascular Complications

Many newly introduced medications interact with other cardiovascular drugs, including anti platelets, anticoagulant, antihypertensive, statins.

Lopinavir/ritonavir may cause QT and PR prolongation, particularly in those with baseline QT prolongation or in those taking medication that may cause QT prolongation. These medications can also affect anticoagulant medications , anti-platelet agents , and statins [39]. Chloroquine , Hydroxychloroquine may interact with anti-arrhythmic agents and even these anti-malarial medications can result in electrolyte abnormalities , cardio toxicity and prolonged QT intervals [40,41]. Methyl prednisolone can cause electrolytic imbalance, fluid retention, hypertension [42]. It is important for emergency clinicians to be aware of these complications and interactions of medications to minimize the medication generated adverse effects and cardiovascular complication during the treatment of COVID-19 patient [43].

Myocardial Injury with DIC

DIC is dangerous complication present in 71.4% and 0.6% among non-survivors and survivors of COVID-19 [44]. Marker of severe sepsis, DIC indicates multi organ damage through thrombosis, bleeding and reduced perfusion [45]. Myocardial injury with DIC has been reported in critically ill patients with COVID-19. Troponin and brain natriuretic peptide level elevated significantly, which became normal after treatment with heparin, antiviral agent and mechanical ventilation [46].

Myocarditis and Stress - Induced Cardiomyopathy

it's challenging to differentiate myocarditis and stress induced cardiomyopathy, since cardiovascular magnetic resonance/or biopsy are not available in most cases . Fried et al and Sala et al each reported mild left ventricular or basal to mild LV hypo kinesis , a pattern of mild ventricular, or reverse Takotsubo stress cardiomyopathy in COVID-19 patient, respectively [47,48]. The incidence of acute heart failure was 33% in critically ill patients without a past history of LV systolic dysfunction [49]. Interestingly, COVID-19 patients can develop cardiomyopathy with mild or absent respiratory symptoms [50].

Therapeutics against COVID-19

Stem cell therapy

Stem cell therapy can be a better substitute for metallic hardware or arthroplasty, where we use metallic implants. Furthermore, no single method or approach is ideal for all types of scenarios (fractures). Each spine surgery (ACDF, ACDR) has its own risk and benefits. Hence, stem cell therapy provides better options with least risk and complications [51-55].

Risk and benefits both associated with stem cell therapy. The potential risks are multiplication of mesenchymal stem cells in to inappropriate cell types, product contamination, and growth of tumours, infections, administration site infection and thrombus formation.

MSCs can exert their immunomodulatory effects through multiple mechanisms as these cells have paracrine effects in lung regeneration .MSCs release extracellular vesicles, micro vesicles and exosomes. Exosomes contain a variety of chemokine's messenger RNA, & micro RNA .Products of extracellular vesicles has immunomodulatory and anti- inflammatory qualities and hence regulates the immune system [56, 57]. Recently, we lack any better therapeutic option for severe COVID-19, MSCs may provide a better option [58].

Anticoagulant Therapy

Because of high rate of arterial thromboembolism and VTE, prophylactic anticoagulation is essential in management of hospitalized COVID-19 patients, although optimal thromboprophylaxis regimen is not clear [59,60]. Low molecular weight heparin is likely preferred in critically ill patients with COVID-19, if anticoagulant is required.

ACE Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARBs)

Antihypertensive drugs (ACEI & ARBs) may be used to

treat hypertension patient with COVID-19 [61].

Contrarily, some studies suggested that administration of antihypertensive such as ACEI & ARBs to COVID-19 patients can aggravate the existing disease (COVID-19) [62]. Based on observation, researchers advocated the use of RAS inhibitors such as ACEI & ARBs for alleviating pneumonia injury induced by COVID-19 [63]. Interestingly, other studies raised the concern that RAS inhibitors increase ACE2 expression [64]; therefore the use of RAS inhibitors may aggravate the disease in COVID-19 [65-66].

There is need for further investigation regarding impact of antihypertensive, especially RAS inhibitors, in the treatment of COVID-19.

Hydroxychloroquine / Chloroquine and Azithromycin. Both chloroquine and hydroxychloroquine increases the endosomal pH, which inhibits fusion between COVID-19 and the host cell membrane. Chloroquine inhibits glycosylation of the cellular angiotensin -converting enzyme 2 (ACE2) receptor, which may interfere with binding of SARS- CoV to the cell receptor. Chloroquine and hydroxychloroquine may block the transport of COVID-19 from early endosomes to endolysosomes, may prevent the release of viral genome. Additionally, Azithromycin has antiviral and anti- inflammatory properties, when used in combination with hydroxychloroquine, it has shown synergistic effect on SARS-CoV-2 in vitro and in molecular modeling studies .On the other hand, several additional large randomized controlled trials have failed to show a benefit for hydroxychloroquine with or without Azithromycin or Azithromycin alone in hospitalized adults with COVID-19 [67].

Immunosuppressive Therapy

Dexamethasone use was associated with a lower 28 - day mortality rate in subgroups of patients requiring oxygen or invasive mechanical ventilation at randomization. Besides Six retrospective cohort studies also reported that steroids use was associated with beneficial outcomes in COVID-19 patients [68]. Moreover, Methylprednisolone demonstrated better results than dexamethasone.

Mechanical Cardiopulmonary Support Variable survival rates reported in case of Mechanical cardiopulmonary support in respiratory failure. In cardiogenic Shock related to COVID-19, intra- aortic balloon pump, or veno-arterial ECMO (extra corporeal membrane oxygenation) should be considered. A case has been reported of a patient with COVID-19 without respiratory symptoms presented with cardiogenic shock successfully treated with IABP support. Possibly, a similar scenario is the conversion of venous ECMO for ARDS to veno- arterial - venous ECMO on the development of cardiogenic shock. Regardless of the mode of mechanical support, comorbidities, age, gender and complications and severity of COVID-19 should be considered for patient selection.

There is limited information regarding cardiomyopathy during COVID-19, currently we lack strong data based on Multi-centre clinical trials and Randomized Controlled Trials (RCT). Secondly, adverse drug reaction isn't studied regarding safety of MSC administration, corticosteroid therapy, etc. Thirdly, we may miss some important information published in other languages. Last but not the least, Studies included in this review is dissimilar in nature.

CONCLUSION

Cardiovascular complications can't be avoided in any severe cases of COVID-19. With above therapeutics, we may be able to minimize complications and number of mortalities. As we review the rapidly changing clinical scenario of pandemic COVID-19. Notably, this is living knowledge, which will be transformed and updated with due course of time, as additional research and understanding emerges.

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