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REVIEW ARTICLE **OPEN ACCESS**

Covid-19 Impact On Cardiovascular System And Cardiac Biomarkers

Adeel Ahmed Khalil[1], Syed Arshad Ullah[1], Faisal Malik[2], Ashfaq Ahmad[3], Fawad Khalil[4], Jafar Iqbal[1], Anees Muhammad[5]
1Department of Cardiology, College of Medical Technology, Bacha Khan Medical College, Mardan, Pakistan
2Department of Cardiology, Medical Teaching Institution, Lady Ready Hospital, Peshawar, Pakistan
3Department of Cardiology, Prime Teaching Hospital, Peshawar Medical College, Peshawar, Pakistan
4Medical delegate at Abbott nutrition LRH base Peshawar, Pakistan
5Department of MLT, College of Medical Technology, Bacha Khan Medical College, Mardan, Pakistan
Corresponding Author's Email: aneesafridi15295@yahoo.com

ABSTRACT
The coronavirus disease-2019 (COVID-19) is aviral infectious disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This study was designed to determine the COVID-19 impact of patients having cardiovascular diseases (CVD). The literature review showed that COVID-19 patients having previous CVD disease are more prone to severe morbidity and mortality. Moreover, it was observed that COVID-19 infected patients have been associated with several cardiac complications such as arrhythmias, myocardial infarctions (MI), myocarditis, and thromboembolism. In addition, the treatment used during cardiovascular disease along with COVID-19 infection has a more adverse effect as compared to non-infected patients. The treatment response to the infection of COVID-19 can go through the quick sorting of COVID-19 non-infected patients along with cardiovascular complications. Conclusively, it was evaluated that patients having a history of CVD are a higher risk to COVID-19 as compared to healthy patients. It is suggested to take an additional precautionary measurement for patients having both COVID-19 infection and CVD.
Keywords: *COVID-19,SARS-CoV-2, Cardiovascular diseases, Cardiac biomarkers*

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INTRODUCTION

Many novel coronaviruses have been identified in the last decade in various types of bat species all over America, Europe, Africa, and Asia. In the genera of the coronavirus, there are Alpha and Beta coronaviruses**,** the target host of which are mammals, in bats seven out of fifteen currently identified coronaviruses have been found. Bats have been found the main hosts for alpha and beta coronaviruses which play a major role in the gene evolution of all these coronavirus genera. Among the coronaviruses found in bats, some species pay special research interests, as two of the species were found to cause two high profile human disease outbreaks, Middle East Respiratory Syndrome (MERS), and Severe Acute Respiratory Syndrome (SARS) [1].

SARS first started outbreaks in the Guangdong Province of China, in late 2002 as an unknown clinical severe disease called "atypical pneumonia" which was featured by headache and fever followed by the start of respiratory system symptoms which include dry cough, shortness of breath and pneumonia. Due to its highly spreading infectious nature among humans, SARS quickly reach Hong Kong and other various provinces of China and after that, it spread to the other twenty-eight countries. It has caused 8096 confirmed cases of disease infection in twenty-nine countries by July 2003, of which fatal were 774 (9.6 %) (http://www.who.int/csr/sars/). Only four infections were reported with no mortality and no further transmission was reported in the second outbreak in 2004 [1].

The MERS outbreak started in the middle of 2012 in the Kingdom of Saudi Arabia (KSA), having a similar clinical picture as that of SARS but it was less infectious relatively.Along with respiratory disease, the kidney's failure was recognized in various severe cases. Unlike SARS which was spread to twenty-nine countries majority of MERS cases were independent clusters and were mainly confined to the Middle East

countries, mainly in KSA. Few cases of MERS were reported in the European and African countries and in the USA, but mostly with traveling history from the Middle East. Few of the cases were reported to have an epidemiological link with camels whereas many other cases lacked this link. The second epidemic of MERS which was reported in Korea in the year of 2015 was directly linked to a person who had a travel history to the Middle East. This was the second-largest epidemic of MERS which caused 185 confirmed cases and a total of 36 deaths. A total of 1413 laboratory-confirmed cases of MERS, together with 502 related deaths were reported worldwide by 18 August 2015 with a median age of 50 years. The mortality rate of MERS is also higher (35%) related to SARS (10%) [1,2].

In November 2019, a group of pneumonia cases with unidentified causes emerge in the Hubei Province of China, Wuhan. After that, outbreak and random human infection occur with more than 83,221 confirmed cases (update on June 17, 2020, PST 2:00 AM) in China. After the analysis of its clinical sequence, this unidentified pneumonia was considered to be caused by a novel coronavirus (CoV) named 2019-nCoV. Later on, according to its nomenclature, on 11th February 2020, the World Health Organization announced the name for this disease as Coronavirus Disease-2019 (COVID-19), for this novel coronavirus pneumonia. The International Committee on Taxonomy of Viruses (ICTV) gives name this novel coronavirus as (SARS-CoV-2) on the same day. This novel coronavirus poses a serious threat to public health as it is still spreading [3].

CLASSIFICATION

After the sequence and gene evolutionary analysis, SARS-CoV-2 was identified and it was confirmed that this virus is a member of beta coronaviruses (β-CoVs). The coronavirus group is a class of positive-sense single-stranded enveloped RNA viruses. These viruses can cause neurologic, respiratory, hepatic, and enteric diseases. They are serologically and genotypically classified into four subfamilies: Alpha, Beta, Gamma, and Delta coronavirus respectively. Only Alpha and Beta coronaviruses cause human coronavirus infection. SARS-CoV and MERS-CoV are the members of the Beta coronavirus. On Genome-wide phylogenetic analysis, the genetic sequence of SARS-CoV-2 is 79.5% similar to SARS-CoV and having a 50% similarity with MERS-CoV. Nevertheless, there is a 94.6% sequence identity of SARS-CoV and SARS-CoV-2 between the seven conserved replicase domains of ORF1ab, and there is almost 90% sequence identity between SARS-CoV-2 and other β-CoVs, which implicate that SARS-CoV-2 belong to the lineage B (Sarbecovirus) of β-CoVs [3,4].

Structure of COVID 19

SARS-CoV-2 virion with a genome size of 29.9 kb like other Beta coronaviruses (β-CoVs) constitutes of a nucleocapsid which contains SARS-CoV-2 genomic RNA and phosphorylated nucleocapsid protein [3]. The nucleocapsid of SARS-CoV-2 is surrounded by phospholipid bilayers and enclosed by two distinct kinds of proteins called spike proteins: these are the spike glycoprotein trimmer (S) and hemagglutinin-esterase (HE). The (S) exists in every coronavirus and the (HE) is present in some coronaviruses. The envelope protein (E) and the membrane protein (M) lies in the middle of the S proteins in the viral envelope [5].

Current status (June 11, 2020)

According to the WHO report published on June 11, 2020, total coronavirus confirmed cases globally are 7,273,958 & total deaths 413,372. In Eastern Mediterranean Region there are 696 841 confirmed cases of which the total deaths are 15 581. In our country, Pakistan, the trends of COVID 19 cases are increasing day by day, till June 11, 2020 total confirmed cases in Pakistan according to WHO are 119 536 including 5 834 new cases, of which total deaths are 2 356 including 101 new deaths [6].

The situation in numbers (by WHO Region)

Globally according to WHO report by region, on June 11, 2020, are a total of 7,273,958 cases including 128,419 deaths in the last 24 hours. In Africa total, active cases are 150 102 and total deaths 3,593. The USA is on the top of the list having a total of 3,485,245 cases and 189 544 deaths. Eastern Mediterranean region constitutes a total of 696,841 cases and 15,581 deaths. Europe stands second on the list having a total of 2,339,145 cases and 186,326 deaths. In South-East Asia 407,414 cases and 11,171 deaths are reported. The Western Pacific region constitutes a total of 194,470 cases and 7,144 deaths [6].

Table No.1: WHO report by region on June 11, 2020

Total number of new and old cases by region (11 June 2020)		
Region	Total Cases	Total deaths
Africa	150 102 cases (4 815)	3 593 deaths (100)
America	3 485 245 cases (70 071)	189 544 deaths (3 681)
Eastern Mediterranean	696 841 cases (19 503)	15 581 deaths (335)
Europe	2 339 145 cases (17 998)	186 326 deaths (789)
South-East Asia	407 414 cases (14 740)	11 171 deaths (430)
Western Pacific	194 470 cases (1 292)	7 144 deaths (12)

2019-nCoV genetic map

In the middle of November 2019, a number of patients having clinical symptoms of severe pneumonia across the City of Wuhan were brought in to the hospitals. The causative virus was then genetically mapped, its genetic sequence suggested that it is a strain of beta coronavirus and it was found that most of its sequence was interrelated to SARS-like bat coronaviruses (bat-SL-CoVZC45 and bat-SL-CoVZXC21) with 88% similarity, 50% homology with MERS 79.5% with SARS [7].

The SARS-CoV-2 genome comparison at GenBank revealed 99.9% similarity with two already sequenced genomes, available at GenBank (NC_045512 and MN988668) and, 99.9% with seven, more additional, sequences (MN975262.1, MN938384.1, MN988713.1, MN985325.1, and MN997409.1, MN994467.1, MN994468.1). SARS-CoV-2 final genome, sequenced constitute of 29,811 nucleotides long, a single stranded RNA which is broken down, as: 8,903 (29.86%), adenosines, 5,852 (19.63%) guanines, 9,574 (32.12%) thymines and 5,482 (18.39%) cytosines [8].

SARS-CoV-2 source and transmission

Rising evidence shows the link between the SARS-CoV-2 and other analogous known coronaviruses (CoV) found in bats, and specifically, the bat sub-species. the Rhinolophus bat sub-species. These sub-species are plentiful and broadly present across Asia and Southern China, Africa, the Middle East, and Europe. new studies point out that more than 500 CoVs have been known in bats in China. Well-known serological studies which were conducted in a rural population living close to the caves, bats natural habitat discovered a 2.9% bat coronavirus seroprevalence, signifying that humans exposure to bat coronaviruses might be common [9].

However, the specific route of transmission to humans at the beginning of this outbreak is still not clear. Bats are uncommon in open markets of China but are hunted and then sold directly to the restaurants, for foodstuff. The most recent hypothesis suggests that there is an intermediate host, an animal which has played a key role in virus transmission [9].

2019-nCoV symptoms

Covid-19 infection can cause mild symptoms such as fever (>90% cases), fatigue, rhinorrhea, sore throat, dry cough (80%), shortness of breath (SOB) (20%) and in severe condition, respiratory distress (15%). It can be proved more severe especially for someone having comorbidities and can lead to pneumonia or breathing problem. If the infection is more severe it can lead to pneumonia, severe acute respiratory syndrome, (SARS), myocarditis, myocardial injury, and kidney failure. The disease can be fatal but it is rare. People with pre-existing comorbidities (such as diabetes, hypertension, and heart disease) and Older people, appear to be more susceptible to becoming severely ill with the virus [9,10].

Prevention of COVID- 19

WHO and European Centre for Disease Prevention, and Control (ECDC) suggested a few guidelines. Based on WHO, some overall guidelines were printed for example implementation of touch and droplet precaution, airborne precaution, etc. ECDC also released to the individuals, the data leaflet i.e. stop contacting sick persons, specifically those who have a cough. stop visiting areas and markets where live or dead animals are sold, use an alcohol-based disinfectant solution, or clean your hands properly before eating, after any contact, with animals, after using the restroom and stop contact with animals, their droppings and/or excretions [11].

The following are infection prevention and control (IPC) guidelines to Stop or control transmission in healthcare settings:[12]

- ✓ Recognition of suspected cases, triage system, and source management isolating COVID-19 patients and suspected individuals, Implementing standard precautions.
- ✓ Implementing normal safety measures for every patient.

- ✓ Implementing further empiric safety measures i.e. droplet, touch and airborne, precautions) for suspected, cases of, COVID-19.
- ✓ Implementation of administrative, controls.
- ✓ Environmental, controls, and utilizing technology.

1) Early recognition, triage, and source management

It constitutes a process for scrutinying patients at admission, which allows the health care provider for early detection of possible COVID-19 cases and instant isolation of persons with suspected infection in a place different from other patients.

2) Implementing normal precautions for all patients

Standard Precautions comprise of respiratory and hand hygiene, using proper personal protective, equipment (PPE) based on the exposure assessment, safety practices, appropriate clean up of the environment, safe management of the waste materials, and sterilization of all patient-care gears.

3) Implementing empiric further precautions

a. **Contact and droplet preventive measurements**

Beside usual precautions, droplet, and contact precautions should be practiced by all individuals, including family members and relatives before entering or leaving the room of confirmed COVID-19 patients or suspected cases.

b. **Airborne precautions, for aerosol-generating procedures**

Some procedures, for example, cardio-pulmonary resuscitation(CPR), bronchoscopy, tracheal Intubation, noninvasive venting and venting before intubation, have been associated with a high risk of spread of coronaviruses.

Make to ensure the following before performing aerosol-generating procedures:

- ✓ Carry out the procedure in an area of natural ventilation with an airflow of at least 160 L/s per individual·
- ✓ Put on clean long-sleeved gloves and gear.
- ✓ Limit the number of individuals to a minimum in the area for patient care and support.

4) Implementing administrative controls

Different ways of administrative support and controls for the prevention and control of the spread of COVID-19 inside the healthcare setting include: establish sustainable disease control and prevention (IPC) infrastructures and actions; instructing the caregivers of patients; discovering policies about the early detection of severe exacerbation of respiratory disease by COVID-19 virus, assuring access to the laboratory testing for the diagnosis of the virus, preventing congestion, mainly in emergency departments, dedicate waiting for the area for symptomatic patients, properly separating hospitalized patients, ensuring adequate supplies of personal protective equipment (PPE).

5) Utilizing technology and environmental controls

These controllers deal with the basic healthcare services, infrastructure, and try to make sure sufficient ventilation in every region from the healthcare facility, as well as sufficient cleaning of the environment [12].

Treatment and outcome of COVID-19

Isolation remains the only measure of prevention of COVID-19. Still, there is no absolute therapy, and no vaccine available for COVID-19. All the treatment is symptomatic and oxygen is needed for those patients who have a severe infection and cannot maintain their saturation. In case of respiratory failure, mechanical ventilation may be needed. For handling septic shock hemodynamic assistance is important [13.]

The pharmacological choices are: Glucocorticoids, Baraticinib, Tocilizumab, Chloroquine, and hydroxychloroquine, Angiotensin-converting enzyme inhibitor (ACEI) and azithromycin [13.]

Glucocorticoids are prohibited in those patients having COVID-19 with symptoms like pneumonia until and unless if there is any other associated respiratory disease i.e. exacerbation of COPD [14].

Glucocorticoids have increased rates in patients with influenza and also postponed viral clearance, in patients with (MERS-CoV) disease. However they were broadly used in the control of (SARS), there wasn't any positive indication for the benefit [15].

Interestingly, one hypothesis says that there is an association between COVID-19 and ACE inhibitors. SARS-CoV-2 use ACE2 receptors for the entrance into the human body, and the experiments done on some animals shows that the two drugs losartan and lisinopril can increase, the mRNA expression and hence numbers of ACE2 receptors. By replacing these drugs we might have a chance to decrease the risk of dangerous COVID-19 in various patients [13].

Importance of this review

SARS-CoV-2, which causes COVID-19 is now at a pandemic stage, and this coronavirus can directly affect the cardiovascular system and cardiac biomarkers. We review the basics of coronaviruses, with the main

focus on COVID-19, along with that we have reviewed the effect of coronavirus on the cardiovascular system and cardiac biomarkers.

MATERIAL AND METHODS

Strategy of searching

A broad and systematic search was done using Google Scholar, PubMed up to 18 April 2020 & WHO website up to 11 June 2020. Medical Subject Heading (MeSH) terms and keywords were used so as to gather as several likely documents as possible.

The following search terms or keywords were used alone or in combination: 'corona viruses','novel coronavirus','COVID-19', 'SARS-Cov', 'SARS-Cov-2', 'pneumonia', 'influenza,' 'diabetes', 'hypertension', 'cardiovascular disease,' 'cardiac injury,' 'troponin', myocardial infarction", and "heart failure."

Inclusion and exclusion of articles

Inclusion & exclusion criteria are as follows

i. **Relative studies:** Non-randomized controlled trials or RCTs published in English language in national and/or international journals are included.
ii. **Study population:** Collectively from all published studies, more than ten participants were included in this study.
iii. **Study intervention:** All the patients included in this study were positive for COVID-19.
iv. **Parameters:** The literature which shows the comorbidities of metabolic and cardiovascular disease and its outcome were included.
v. Studies lacking sufficient information, and studies written in languages other than English were excluded from this study.

LITERATURE REVIEW AND DISCUSSION

Cardiac manifestations and its relationship with (SARS, MERS and 2019-nCoV)

After reviewing and analyzing the literature, myocarditis, cardiac injury, heart failure, arrhythmias, cardiomyopathy, and hypotension have been reported in all mentioned strains of coronaviruses infections (SARS, MERS, and 2019-nCoV) in the past literature (1,18,23,28). Some cases of sudden cardiac death have also been reported in SARS. Myocarditis and heart failure appeared to be the most common Cardiac manifestation among all mentioned coronaviruses infections (23,28). Among all cardiac manifestations, myocarditis and heart failure (right ventricular, left ventricular, and biventricular) appeared to be the most common. The electrocardiography (ECG) changes and cardiac biomarkers level were consistent with the cardiac injury in the majority of the studies.

i) Epidemiology of Cardiac patients in SARS

The SARS-CoV is the member of β-CoVs which attaches to zinc peptidase ACE2 receptor, a particle that, is present on the inner surface of respiratory tract epithelium i.e. endothelial cells surface, veins and, arteries, the smooth muscles of the arteries, the epithelia, of the small intestine, and immune cells. During SARS- CoV infection, suppression of ACE2 expression has been anticipated to play a basic role in the abnormal changes that occur in the lungs and contribute to cause pneumonia and then lung failure [16].

In the year of 2003, in 29 countries a total of 8096 SARS-CoV cases was reported, of which 774 was died (about 10%). In the US, there were a total of 8 labs confirmed and other 19 suspected cases of SARS, with zero, fatalities [16].

SARS-CoV also may have caused cardiovascular (CVS) complications(**Table 1.2**), but the majority of the data was unreliable in the lack of systematic, studies. However, it was reported that myocardial infarction and Acute coronary syndrome may occur after SARS [17].

One of the studies of 75 SARS patients who were admitted to hospital, the cause of death was acute myocardial infarction (AMI) in 2 of 5 lethal cases. The conclusion from this incomplete study has not been confirmed in other studies [18].

Another prospective study of 46 confirm SARS cases without pre-existing cardiac disease revealed no significant change in the left ventricular systolic function. Although, left ventricle diastolic dysfunction was reported during the infection, which was resolve on follow-up [19].

One study of 121 SARS confirmed patients with a mean age of 37.5±13.2 years revealed that 12 out of 121 patients had underlying CVS diseases, common finding, was tachycardia (72%), and other complications included hypotension (50%), cardiomegaly (11%), bradycardia (15%), and atrial fibrillation was detected in 1 patient. The majority of these individuals were, asymptomatic, with the self-limiting disease [20].

ii) Epidemiology of Cardiac patients in MERS

The epidemic of MERS-CoV emerged in June 2012 in Saudi Arabia.The virus transmitted from the intermediate host, the infected Arabian camels, to humans during close contact [21].

On November 30, 2019; a total of 2494 laboratory-confirmed cases of MERS-CoV, have been reported in 26 countries with 858 deaths (CFR: 34.4%). The majority of cases were from Saudi Arabia i.e. a total of 2102 cases with a case-fatality rate of 37.1% [21].
A systematic review analysis on 637 MERS-CoV cases revealed that 16% had underlying obesity, 50% had diabetes, 50 % had hypertension, and 30% of cases have cardiac diseases [22].
Hypotension, occasional shock were also reported in some studies. In one case elevated troponin-I consistent with severe global left ventricular systolic dysfunction on echocardiography was documented. Through an unusual outbreak eight children having ages from 5 months, to 15 years, died due to myocarditis and cardiogenic shock in the Havana city of Cuba in July-August 2005 [23].

iii) Epidemiology of Cardiac patients in COVID-19

The prevalence of cardiovascular diseases in patients with COVID-19 isn't reported yet as the majority of the research studies focus on those patients who are admitted to the hospital and who are more likely to have comorbid conditions than those having the asymptomatic or mildly symptomatic disease. Pooling information from the six studies (n=1527) shows the prevalence of hypertension/diabetes mellitus in 9.7% and cardiovascular disease in 17.1% in those patients who are positive for COVID-19 [24].
Those patients having a severe illness or those patients admitted to the intensive care unit (ICU) had two to three-fold higher rates of cardiac disorders than non-severe/ICU patients. (24) For example, 5.8% of severe illness were from those patients who were having coronary heart disease (CHD) and only 1.8 % were those having no severe illness. Similarly, 2.3% of patients with severe disease were those with having a history of cerebrovascular disease and 1.2% were those with mild to moderate disease [25]. Myocarditis has been reported in numerous literature [26].
In another review of twenty-one, critical patients with COVID-19, percentages of diabetes mellitus, heart failure, and chronic kidney disease were 33.3%, 42.9%, and 47.6%, respectively [27]. Comorbid patients have elevated rates of in-hospital mortality, with CAD (OR=21.4, P =0.0001), diabetes (OR 2.85, P=0.0062) show relationship with increased fatality rates in a univariable, analysis [28,29].

Table No. 2: Coronaviruses infection and its Cardiac manifestation

Year	Strains	Region of Origin	Common Cardiac Manifestation	References
2002	SARS	China	Myocarditis, Myocardial Injury Hypotension, Heart Failure, Tachycardia, Bradycardia, Arrhythmia, or even Sudden Cardiac Death	1,17,18, 19,20,23, 28
2012	MERS	Saudi Arabia	Hypotension, occasional shock, Myocarditis, left ventricular systolic dysfunction & cardiogenic shock	22, 23, 28
2019	COVID-19	China	Myocarditis, Acute cardiac injury,& arrhythmias, Cardiomyopathy	23, 24, 25, 26 27, 28

VARIOUS CLINICAL CARDIAC DISEASES IN COVID-19

i) Myocarditis in COVID-19

SARS-CoV-2 seems to cause myocarditis. Random autopsy case reports propose the infiltration of myocardium by, inflammatory cells [30]. In parallel, cases of decreased left ventricular systolic function followed by myocarditis have been reported, after COVID-19 [31]. Various cardiac biomarker studies suggest a high prevalence of cardiac injury in those patients who were admitted to hospitals [19,30]. Myocardial injury is likely to occur with myocarditis or ischemia related to severe infection and is an important, prognostic factor in COVID-19 [23,36,29].

ii) Cardiac injury in COVID-19

Shi et al revealed the significance of myocardial injury in COVID-19 mortality in 416 patients with COVID-19, he reported that 57 out of these 416 died. In these patients, 5.3% had a cerebrovascular disease, 4.1% had heart failure and 10.6% had CHD. Almost 20% of patients have a cardiac injury with high sensitive troponin I(hs-TNI) greater than the 99% percentile, upper reference, elevated leukocytes levels, C-reactive protein, N- terminal pro-brain natriuretic peptides, and procalcitonin, but lower lymphocyte counts [19]. Patients having a myocardial injury, have a higher occurrence of respiratory system problems and a high mortality rate than those having no myocardial injury [19,23,26,29].

iii) Hypertension, coronary artery disease and cardiomyopathy in COVID-19

Guo et al reported the factors that linked with the outcomes in 187 in hospital patients with COVID-19 in which 43 patients died and 144 was discharged in Wuhan city, China. In this particular study, 28% of patients revealed confirmation of acute myocardial injury i.e. elevated troponin T [TnT] level, and 35% of patients had underlying cardiovascular disease i.e. hypertension, cardiomyopathy or coronary artery disease) [32]. The mortality rate was reported and it was significantly higher in those patients having

elevated TnT as compare to those with normal TnT levels i.e. 59.6 % vs 8.9 %, respectively (P < .001). All those patients whose TnT was higher, were older in age and it was common in men as compared to women, and also had higher clinical comorbidities which include hypertension, coronary artery diseases, cardiomyopathies, and CKD along with elevated leukocyte counts, higher levels of C-reactive protein, D-dimer, procalcitonin, and N-terminal pro-brain natriuretic peptides and lymphocyte counts were decreased [32]. The presence of both a high level of TnT and CVD was linked with the higher mortality rate, on the other hand, the patients whose TnT was normal and having CVD had a minor mortality risk [23,29,32].

IV) Arrhythmias and conduction system disease in COVID-19

In a study of 137 cases in Hubei province, China, palpitation was noted in 10 patients (7.3 percent) [33]. In another study of in-hospital 138 patients from Wuhan with COVID-19 induced pneumonia, arrhythmias were noted in 17% of the general cohort and in 44% of patients admitted to ICU [34]. From both of these studies, the specific cause of the type of arrhythmia or palpitations were not specified. Electrolyte imbalance and hypoxia, both were known to contribute in the development of acute arrhythmias, have been commonly reported in the acute phase of severe COVID-19 illness; therefore, the exact role of COVID-19 infection in the development of arrhythmias in asymptomatic, mildly ill, severely ill, and recovered patients is not known [35].

Cell receptor gene ACE2 for COVID-19 or SARS

The 2019 novel coronavirus uses ACE2 as a target host cell, receptor. Tissues of the small intestine, heart, thyroid, testis, kidney, and adipose tissue had the highest number of ACE2 expression levels, while bone marrow, blood vessel, blood, brain, spleen, and muscle had the lowest ACE2 expression levels. In the lungs, the liver, adrenal gland, bladder, and colon ACE2 showed the average expression, levels. These results explain that the expression of ACE2 is not only present on the lungs but also present in a large number of other human tissues[6-8]. The Human Protein Atlas (HPA) database, (http://www.proteinatlas.org/) expressed that the ACE2 protein has comparatively higher expression levels in the small intestine, duodenum, colon, rectum, gallbladder, kidney, adrenal glands, testis, and seminal vesicles. The HPA, database, shows that the male tissues i.e. testis and seminal vesicles, kidney, GIT including the small intestine, duodenum, colon, and rectum and gallbladder have higher expression levels of both protein and ACE2 gene. Collectively all these data show that: i) This 2019 novel coronavirus not only infects lung but it can also infect other tissues as well. ii) Males can be infected more as compared to females [36,37,38].

Holshue e*t al*. discovered that stool of a COVID-19 infected patient was positive for the 2019-nCoV virus, suggesting that 2019-nCoV may infect GIT [39]. Huang et al. revealed 2019-nCoV related cardiac injury in five patients [36]. Another study of 99 patients of 2019-nCoV pneumonia discovered the increased, vulnerability of males to virus infection [37]. Another study shows that 2019-nCoV can infect males and females equally, but males are considered to have a higher mortality risk as compared to females [40].

ECG findings in COVID-19

Myocardial injury or myocardial infarction is present in greater than 25 percent of severe cases. COVID-19 infections are linked with increased cardiac biomarker levels and fresh ECG changes due to myocardial injury. Mostly reports of patients who present with cardiac symptoms suggest a different pattern, like stress cardiomyopathy or viral myocarditis. For example, one case which is recently published described that a man presenting with chest pain and his ECG shows significant ST-segment elevation, but his angiography shows no coronary obstruction [41]. Another study revealed a 64 years old woman who came to the hospital with chest pain. Her ECG showed diffuse ST-segment elevations with sinus tachycardia having no CAD diagnosed after coronary angiography [42].One of the studies revealed ST elevation in II, III & aVF leads in a 29 years old man with a diagnosis right ventricular strain due to acute respiratory distress [43]. Some COVID-19 cases revealed AV blocks and S1Q3T3 pattern which suggests acute pulmonary embolism and some patients,s ECG revealed ST elevation with episodes of multifocal ventricular tachycardia [44]. Arrhythmias of fatal and non-fatal types are also reported in some studies [16,35,45,46].Some critical cases were suspected with non-ST segment elevation myocardial infarction, (NSTEMI) pattern but later on, diagnosed as myocarditis only [47]. Another study suspected prolonged QT interval with no episode of torsades de pointes in covid 19 patients but it was suggested that this QT prolongation may be due to electrolytes imbalance and QT-prolonging drugs (azithromycin, chloroquine, and hydroxychloroquine) [48].

Echocardiography findings in COVID-19

Right ventricular dilatation and the impairment of its systolic function are common in patients having COVID-19 related pneumonia, and the presence of this RV dilatation and systolic function impairment is associated with the pro-thrombotic, inflammatory state, reflected in elevated D-dimer, and CRP levels. On the other hand, the left ventricle size is normal and LV function is mostly hyperdynamic, and significant

valvular abnormalities are absent [49]. One study revealed cardiac tamponade in a COVID-19 patient which progressed with the passage of time pericardiocentesis was routinely done in the said patient [50]. In another study 37% of patients had only left ventricular dysfunction, 17% had biventricular dysfunction, 17% patients had only right ventricular dysfunction, and the remaining 29% patients had preserved biventricular systolic function. Regional LV dysfunction appears to be the most common Echocardiographic, finding in some literature [51]. One study conducted in Chinafound Hyperdynamic cardiac function, acute stress-induced (takotsubo) cardiomyopathy, right ventricular (RV) dilatation & acute pulmonary hypertension [52]. Another study revealed Biventricular dysfunction with cardiogenic shock in a patient which was recovered after the patient undergo Intra aortic balloon counter pulsation (IABP) and venoarterial extracorporeal membrane oxygenation (ECMO) through the femoral artery [46].

Table No.3: Cardiac manifestations due to COVID-19 in different literature

Author	I	II	III	IV	V	VI	VII	References
Zheng et al	+	+	+	+	+	+	+	(16)
Shi et al	N/A	+	N/A	+	+	N/A	N/A	(19)
Yu et al	N/A	+	N/A	+	+	+	N/A	(20)
Guo et al	+	+	N/A	+	+	N/A	N/A	(32)
Lakkireddy et al	N/A	+	+	+	+	+	+	(35)
Clerkin et al	N/A	N/A	N/A	+	+	+	N/A	(41)
He et al	N/A	+	N/A	+	+	+	N/A	(44)
ACC guidelines	+	+	+	+	+	+	+	(45)
Scores et al	N/A	+	N/A	N/A	+	+	+	(46)

I: Hypertension, II: Arrhythmia, III: CardiacArrest, IV: Cardiomyopathy, V: HeartFailure, VI: Hypotension, VII: Cardiogenic Shock

Table No.4: Cardiac biomarkers in COVID-19

I	II	III	IV	V	VI	VII	VIII	R
0.19μg/L	N/A	10.2 mg/dL	1689 pg/mL	3.2 ng/mL	N/A	128 ng/mL	Noted	(19)
0.046 μg/L	0.307ng/mL	106 mg/L	245.5 pg/mL	3.2 ng/mL	513 U/L	390.97 ng/mL	Noted	(26)
0.025 μg/L	>10 ng/mL	129.27 mg/L	>21000 pg/mL	> 24 U/L	336 U/L	49·5 ng/mL	Noted	(29)
0.025 μg/L	>10 ng/mL	129.27 mg/L	>21000 pg/mL	> 24 U/L	336 U/L	49·5 ng/mL	Noted	(37)
0.05 μg/L	0.06ng/mL	141 mg/L	189 pg/mL	2.62 ng/mL	556 U/L	111.6 ng/mL	N/A	(53)
0.05 μg/L	0.06ng/mL	141 mg/L	189 pg/ mL	2.62 ng/mL	556 U/L	111.6 ng/mL	N/A	(54)
0.01 μg/L	N/A	12.06 g/dL	364.8 pg/ mL	13 U/L	396.5 U/L	62.1 g/L	N/A	(55)

I: hs-TNI, II: Troponin T, II: CRP, III: NT-pro-B Natriuretic Peptide, IV: Creatine kinase MB, V: LDH, VI: Myoglobin, VII: ECG Changes, R: References

MANAGEMENT OF COVID-19 PATIENTS HAVING CARDIAC DISORDER

- Construct settings for the scrutinizing of cardiovascular disease patients having COVID-19 symptoms from those patients who are asymptomatic.
- It is most important to triage the patients with COVID-19, based on the underlying disease such as cardiovascular, respiratory, diabetic, renal, oncological, or other illnesses for treatment that is prioritized.
- Patients with CVD are at higher risk of contracting COVID-19, so it is necessary to give advice to all of CVD patients about the higher risk, and encourage further, reasonable safety measures in accordance.
- Patients with CVD need to be on pneumococcal and influenza (ACC/AHA guidelines) vaccinations, in order to stop the higher risk of secondary infection from COVID-19.
- In those areas where there are active cases of COVID-19 pandemic, it may be realistic to surrogate telehealth service for stable CVD patients to prevent possible infection.
- Health care providers are warned that signs and symptoms of acute myocardial infarction(AMI) may be surpassed in COVID-19 infection, resulting in under, diagnosis.
- Those patients having volume overload conditions or with heart failure, profuse fluid intake for viral infection must be used suspiciously and cautiously monitored.

RECOMMENDATION/FUTURE DIRECTION

In some human services settings, the CVD care group, (for example, specialists, attendants, and so forth.) may have halfway preparing and involvement in the intense administration of pandemic malady; the typical transmission of COVID-19 to medicinal services staff recommends that regular irresistible ailment improvement safety measures are lacking and social insurance faculty in scourge or pandemic areas must be prepared to receive individual security measures.

In several health care settings, the CVD care team (such as doctors, paramedics, nurses, etc.) may have limited guidance and experience with the acute management of pandemic diseases; the common spreading of COVID-19 to healthcare personnel suggest that everyday infectious diseases improvement safety measures are deficient and health care personnel in epidemic or pandemic localities have to be ready to adopt, personal protection measures.

Special protocols for the disease diagnosis, triage system, isolation of patients, and proper management of COVID-19 patients having CVD complications have to be improved and special strategies must be developed in collaboration with hospital infectious disease response programs and close cooperation with other, medical .specialties.

CVD care staff personnel having less experience and training in personal protective equipment (PPE) donning, consumption and doffing have to be trained, according to CDC guidelines.

The specific protocol has to be established for the proper management of acute myocardial infarction patients in the situation of a COVID-19 pandemic, for those patients having confirmed COVID-19 or suspected.

Special precautions must be taken in conditions like CABG & PCI, including assessing to limit catheterization lab and/or personnel, to a required minimum, pre,-determining requirements, for better personal, protection, and assessing post-procedural sterilization, sufficiency.

CONCLUSION

Our understanding, of COVID-19, its prevention, diagnosis, and treatment is quickly developing. As much literature revealed the COVID-19 can complicate myocarditis, myocardial ischemia, and myocardial infarction. So, it is very important to triage individuals before admitting him/her in the hospital to reduce his/her other risk of getting COVID-19. Secondly, echocardiography is important to scrutinize the patients for angiography to rule out any CAD and for that consultants are suggested to check the website of CDC and ACC/AHA for the latest guidance. As this pandemic disease spreading and multiple new facts appear, it would be wise, to be familiar with the risk factors for the development, of cardiac complications in those patients having COVID-19. A prospective, registry of patients with COVID-19 having a systematic recording, of clinical and cardiovascular, factors for cardiac complications, and to recognize and/or calculate a response to various treatment modalities.

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