
“COVID-19” and its Cardiovascular Complications – Review

Muhammad Saad bin Tahir^a, Muhammad Salman ullah^b, Mahnoor basit^c,
Rohama zahid^{d*}

^{a,c}*Institute of Microbiology and Molecular genetics, University of the Punjab, Lahore 54000, Pakistan.*

^b*King Edward Medical university (KEMU), Lahore 54000, Pakistan.*

^d*School of Biological Sciences, University of the Punjab, Lahore 54000, Pakistan*

^a*Email: iammuhammadsaad32@gmail.com, ^bEmail: salmanullah087@gmail.com, ^cEmail: mahnoor74basit@gmail.com, ^dEmail: rohamazahid856@gmail.com*

Abstract

By the end of December in 2019, the world got trapped under the dark shadow of the deadly novel virus that was given the name as “Severe Acute Respiratory Syndrome-coronaVirus 2 (SARS-CoV-2)”. Due to its rapid spread in all the continents, “Coronavirus disease 2019 (COVID-19)” was announced as the pandemic due to its high potential of infecting the human beings. This viral infection not only become the reason of mortality, but it also lethally effected the the infrastructure of public health care system and the global economic situation. “COVID-19” generally maifestated as the “viral pneumonia”, sporadically leading to “acute respiratory distress syndrome (ARDS)” and death. Frequent clinical studies have depicted an interrelation between this deadly virus and cardiovascular diseases. Precedent cardiovascular disease in a person seems to be linked with adverse consequences and high chances of mortality in patients with (COVID-19 infection), whereas this virus itself has a potential of inducing the arrhythmia, acute coronary syndrome, myocardial injury and venous thromboembolism. One of the most significant point of concern is the drug & disease interactions that affect the patients with viral infection and comorbid cardiovascular diseases. By integrating the data and information regarding the biological features of this contagious novel virus, this review has summarized the pivotal cardiac manifestations, their management, and future implications.

* Corresponding author.

By correlating the facts and figures related to the biological conditions of this lethal virus with the reported clinical findings, we can ameliorate our conceptions regarding the significant mechanisms underlying (COVID-19), ultimately leading towards the control of this viral infection by the progressive development in preventions and treatments.

Keywords: COVID-19; Cardiovascular diseases; Myocardial Infraction; Cardiovascular drugs; Troponin; ACE2; Spike protein.

1. Introduction

Ever since late December, the whole world is confronting the crises of a new pandemic, the severe acute respiratory disorder or Covid 19/ (SARS-CoV-2). Subsequent to arising out of “Wuhan-China”, the Covid disease-2019, immediately disseminated all around the world. Because of all its obscure elements, doctors are going through “Real-time learning methodology”. As the illness spreads, a gigantic flood of data fills up the media as well as research journals [1,2,3]. From that point forward, this viral disease has spread quickly worldwide and has been declared as a pandemic influencing more than 200 nations and regions, with an extraordinary impact on general wellbeing of people, as well as toppling over the socio-economic balance of countries. The dramatic expansion in the quantity of patients with COVID-19 in the previous year, has overpowered medical care frameworks in various nations all over the globe. As of now, preventive antibodies and prophylactic treatments for COVID-19 are underway but not available to infected individuals. “COVID-19” brings about an onset of an extreme intense respiratory condition. (SARS-CoV-2) is an individual from the family β -coronavirus like that of other two coronaviruses that had initiated pandemic infections (SARS-CoV) and (MERS-CoV) [1,2,3,4]. Likewise with “SARS-CoV and MERS-CoV”, (SARS-CoV-2) also the reason of causing a respiratory disease, which prompts viral caused pneumonia and “Acute respiratory distress syndrome (ARDS)” in certain infected people [1]. Other than its key features relating to respiratory distress, extreme proliferation of the viral progeny can initiate a cytokine storm in body of the patient as a result of which there is excessive production of chemokine and cytokines (IL-6, IL-1 β and tnf- α) by innate defense mechanisms of our body. Such elevated levels are the leading cause of multiple organ failure [5]. A significant number of Covid stricken patients, experience coagulation abnormalities that progress towards thromboembolic events [6,7]. Ever since SARS-CoV-2 has surfaced, its protein structure [8,9,10] and genomic sequence has been the focal point of study [11]. Up till now, considerable similarity of about 79.6% has been established of “SARS-CoV-2 with SARS-CoV” as per the identical genomic sequences of both [1,2]. It is worth mentioning that both of them utilize the same entry pathway i.e the attachment of viral spike protein (glycoprotein) to the “Angiotensin-Converting Enzyme (ACE2) receptor” present on the surface of host cell [4]. Among different physiological prospects of severe “Covid-19” infection, cardiovascular issues have arisen as the most serious and lethal complication [12,13,14]. COVID-19 manifests itself with respiratory distress resulting from pneumonia and ARDS. This progresses towards cardiac injury as depicted by the raised troponin levels and ultimately contribute towards having a heart failure [14,15,16]. The increased mortality rate is owing to heart damage [17]. A group study of “416” Covid positive people revealed that 19.7% of them had elevated levels of troponin during the time they were hospitalized. It has been considered as an independent risk factor for the admitted patients in hospitals [17]. People presenting the condition of “Severe Systemic Inflammatory Response

syndrome (SIRS)” had increased occurrence of cardiac injury. This basically underlines the association of immune response with the cardiovascular system and the virus itself. Nevertheless, it is also worth consideration that the infected individuals with an already underlying comorbidity in the form of cardio metabolic disease [18,19], were a subject to severe form of Covid illness and they were also the ones with the highest death rate [20]. In patients of cardiovascular disease, 10.5% fatality rate has been recorded, in diabetic patients it is 7.3% and in patients with hypertension patients it is 6.0%. This rate is 3-4% higher than those patients with no secondary condition [21]. All in All, the high incidence of severe cardiovascular events coupled with Covid-19, along with similar viral diseases like influenza [22], significantly contribute in making the disease lethal for the patients. Though the precise pathogenesis of cardiac issues and Covid has yet not been determined. Myocardial injury results due to inflammation which in turn is directly proportional to the elevated cardiac biomarker, troponin T [23]. However this is just one of the proposed mechanisms. Damaging effects on the heart can be inflicted by the virus itself, directly, respiratory failure can lead to hypoxic injury, indirect damage can result due to cytokines released as a result of systemic inflammatory response and this inflammation also plays its role in Myocardial infarction (MI) that occur due to the plaque rupture. Plenty of mechanisms responsible for the cardiac damage may comprised of following: (1) damaging effect on the myocardium by the virus directly, (2) Hypoxic injury that can happen due to the respiratory failure, (3) Ischemia from myocardial supply demand mismatch, (4) Severe systemic inflammation can be the reason of prothrombic condition (5) Systemic inflammatory response generates the cytokines that can cause the injury indirectly (Fig. 1). Some mechanisms are dependent on receptors for instance the ACE-2 mediated entry of virus into the cells may bring about direct heart damage. This remains a possibility. There is significant expression of ACE2 receptors on endothelial cells and cardiac pericytes and from animal models it has been determined that the viral infection or secondary inflammation can lead to direct dysfunction and may accumulate MI [24,25]. If the biological parameters are understood deeply, it will greatly help with the establishment of suitable and appropriate confirmatory tests, treatment therapies, and vaccines and can add more to out information about tissue tropism. Previous clinical data is indicative of the fact that vulnerability to and turnout of “COVID-19” is strictly linked with “cardiovascular disease (CVD)” [26,27,28]. A high incidence of corona in CVD patients has been noted which further increase mortality rate [29,30]. On top of this, Coronavirus seems to enhance the development of certain conditions like venous embolism, arrhythmias, “acute coronary syndrome” (ACS) and myocardial injury [31,32].

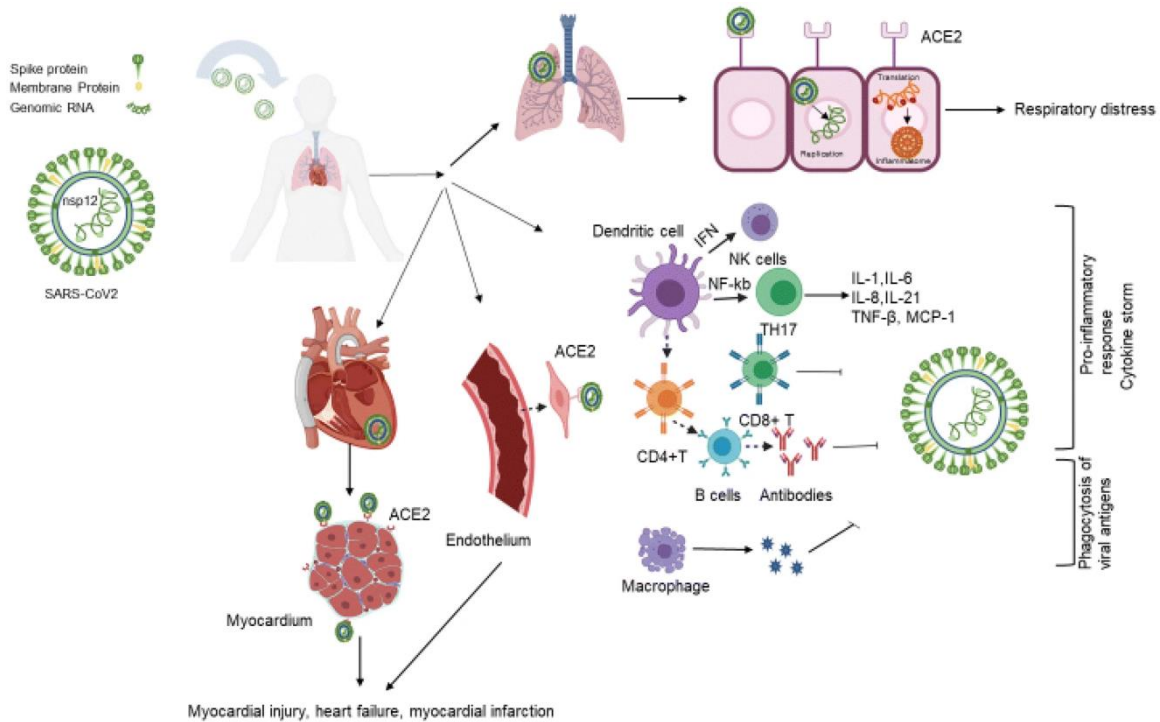


Figure 1: Schematic representation of the COVID-19 structure and route of infection and immune responses (Self made)

Majorly covid related issues have been addressed in adult people but children have the reported cases of developing hyperinflammatory shock with clinical manifestation similar to that of “Kawasaki”, including coronary vessel abnormality and cardiac dysfunction [33]. This data is establishing a two-way link of cardiovascular systems and COVID-19 but the exact mechanism can still not be narrowed down. The excessive systemic inflammation related to COVID-19 has been anticipated to enhance to the establishment of sub-clinical disorders or bring about anew cardiac injury [26,27]. As per the animal models it has also been seen that a part of “renin – angiotensin – aldosterone system” (RAAS), takes part in binding to ACE2 and therefore facilitating the viral entry into the host cells [12]. The swift progression of COVID in nations, countries and our very own community makes it mandatory for the integration of all the previous and the current data to be compiled and be made available to the masses so that better understanding can be developed related to the pathophysiology of this illness and taking a step towards formulating the potential therapies and treatments to cope up. The leading purpose of this review is to summarize the recently known knowledge regarding “SARS-CoV-2” from a biological perspective, focusing on the interaction between the human ACE2 and viral spike protein S. Moreover, the clinical findings regarding the effects of Covid-19 infection on the “cardiovascular system” are reviewed. Lastly, we discuss the most probable links between the frequently used cardiovascular drugs, vulnerability to “Covid-19” and the most viable cardiovascular implications of the drugs being used for treating the “Covid-19 Infection”.

2. Review of Literature

Plenty of current information on SARS-CoV-2 is derived from past authentic pestilences that went before the

current flare-up, as “SARS-CoV, MERS-CoV, and H1N1 flu disorder”. During those viral infection episodes, a critical relationship between fundamental cardiovascular illnesses, myocardial injury were noticed [34]. In 2002, the first case of human infection by this novel virus was notified. During that timeline and situation, it came to our knowledge that in rabbits this viral infection could induce cardiomyopathy subsequent to dilatation of cardiac chambers, simulating other dilated cardiomyopathies and the systolic function impairment [35]. Cardiac arrhythmias, hypotension and even, “Sudden cardiac death (SCD)” were labeled as probable manifestations of “SARS-CoV” [36]. Among the group of “121 patients”, it was confirmed that “sinus tachycardia” is the most common cardiovascular “SARS-CoV” discovery with a general rate of 72 percent. “Persistent tachycardia’s” average span was about 12.7 days and the recorded average heart rate was “117 beats/min” on the other hand, range was about 102 to 150 beats per minute, the tachycardia continued persistently in approximately 40 percent of patients during thirty days after being discharged from the hospital. In the 3rd week of hospitalization, most of the incidences of tachycardia, might be related to the drug mediated treatment, such as “corticosteroid and ribavirin” when most of the infected patients were afebrile. Though, corticosteroid treatment was not linked with the continual “tachycardia” during the follow-up. So, the long-lasting tachycardia might persist due to “autonomic tone changing”. Alternatively, “sinus tachycardia” that is actually secondary to “cardiopulmonary or peripheral deconditioning” since this disease ended up in the lengthened bed rest [37]. Other than these deductions, noteworthy “sinus bradycardia” was realized in 14.9 percent patients. Unlike “tachycardia”, which was tenacious, “bradycardia” was rather temporary with an average heart rate of 43 beats per minutes and the noticed range was 38-49 beats per minute and a mean span of about 2.6 days. In 13 (10.7%) Reversible cardiomegaly was reported, without any clinical indication of heart failure (HF). While, “Transient atrial fibrillation” was detected in just a single patient [37]. Moreover, in accordance with the other researches, it has been elaborated that “palpitation”, in the form of “tachycardia” at rest situation or slight actions, was seen amid patients improving from covid infection. Probable reasons, according to them, were deconditioning, decreased cardiac function, cardiac arrhythmia, autonomic dysfunction, and lessened pulmonary function, anxiety, thyroid dysfunction and anemia [38]. In an urge to explain the incident of cardiac arrest in the fifteen infected people with the virus, some possible mechanisms were suggested by Pan and his colleagues (a) SARS is the reason of causing lung injury , which leads to hypoxemia condition and an unstable condition in myocardial electricity; (b) SARS directly bringing about conduction system or myocardial cells damage; (c) Infection of SARS worsening any already presisting myocardial conditions, or disturbing conductance; (d) severe anxiety induce the release of endogenous catecholamine and results in the “myocardial electrical instability” (Figure 2) [39]. The last viral epidemics have also been correlated with a drastic elevation in the occurrence of MI, HF, myocarditis, arrhythmias, cardiomyopathy and ultimate cardiac death [40,41]. It was therefore not surprising to experience a general increase in the CV events in COVID positive patients. Side by side, an already present cardiac complication aggravates the condition of the patient directly leading to death.

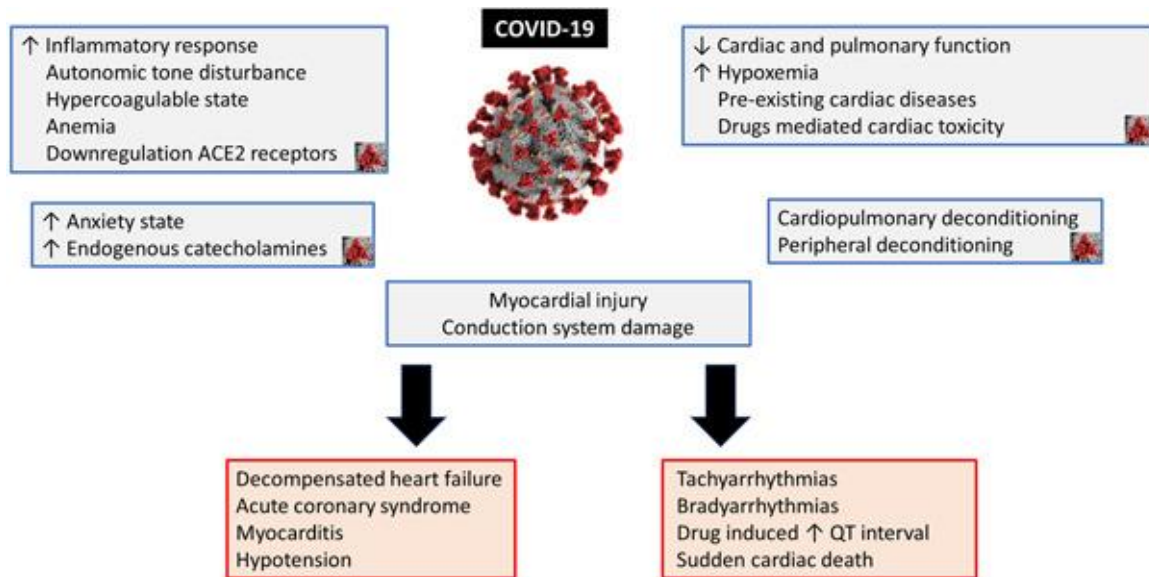


Figure 2: Mechanisms and consequences of COVID-19 myocardial damage. COVID-19, coronavirus disease (Self made)

In non-intensive care unit (ICU), through metanalysis the incidence of CV reported was 16.4% which was thrice as high as those in ICU [42]. Many conducted studies have revealed lower outcomes, including death rate, in patients with raised biomarker levels (such as creatinine kinase, cardiac troponin, “pro-brain natriuretic peptide (BNP)” in ARDS associated with COVID [43,44]. In a concise study of 179 patients with pneumonia during Covid, the level of cardiac troponin ≥ 0.05 ng/mL was observed to be greatly linked to increased mortality (hazard ratio [HR] 4.077, 95% confidence interval [CI] 1.166–14.253; $p < 0.001$) [45]. In another cohort study of 273 patients, “cardiac biomarkers” that are (N-terminal [NT] pro-BNP, cardiac troponin, and myoglobin) were pointedly advanced in critical and severe cases as compared to the moderate cases [46]. An additional study focused on the changes in levels of troponin during pathogenesis of the COVID-19 disease and it was highlighted that 37.5% of individuals had normal troponin levels at the time they were admitted which rose steadily while they continued with hospitalization and reached maximum as they were about to die [47]. In China, these findings were verified in a study of 341 infected people, underlining the importance of measuring troponin levels during the progression of the Covid-19 illness in hospitalized patients. More importantly, if there is an underlying renal malfunctioning, troponin levels can also reach a peak. In this condition, the increase in other cardiac biomarkers will be more dependable while indicating a cardiac injury. Li and his colleagues and Zhou and his colleagues have also established the severity of the illness with increased levels of myoglobin, NT-pro-BNP and creatine kinase-myocardial band (CK-MB) [48,49]. Though the lethality of the virus is low, it is highly contagious. In a published article it was noticed that acute cardiac injury, shock, and arrhythmias were present in 7.2%, 8.7%, and 16.7% of patients and even higher levels in those who were admitted to ICU [50]. Biomarkers levels of the Myocardial injury were recorded high in the covid patients that were admitted in ICU as compared to the non- ICU patients. “Median creatine kinase-MB level” 18 U/l vs 14 U/l; $P < .001$; and high-sensitivity cardiac troponin I [hs-cTnI] level 11.0 pg/mL vs 5.1 pg/mL; $P = .004$, indicating that patients with worsening symptoms often have problems involving acute myocardial injury [50]. Overall, arrhythmia rate had a more frequency in ICU patients (44.4% vs 6.9% ; $P < .001$). Cardiac injury patients more “noninvasive

ventilation” (46.3% vs 3.9%; $P < .001$) and “invasive mechanical ventilation” (22.0% vs 4.2%; $P < .001$), and also had a mortality (51.2% vs 4.5%; $P < .001$) in contrast to those without Cardiac injury. The patients with the increased troponin levels were more ill and older, but after every possible confounding factors was adjusted, it turned out that cardiac injury was a forecaster of mortality (HR: 4.26; 95% CI: 1.92-9.49) [51]. Another study stated that “Myocardial injury” coupled with “SARS-CoV-2” occurred in about five out of forty one patients and he also demonstrated an increase in hs-cTnI levels greater than 28 pg/mL. Out of these five patients, four of them were admitted in ICU indicating the serious progress and harm of Covid-19 [52]. Another study analyzed 187 Covid +ve patients and 27.8% of them had increased troponin levels. With such high levels these patients developed complications at an early stage like acute coagulopathy (65.8% vs 20.0%), (ARDS) Acute respiratory distress syndrome (57.7 percent versus 11.9 percent), Acute kidney injury (36.8 percent versus 4.7 percent), malignant VAs (11.5 percent vs 5.2 percent) as compared to the normal range values. The thing to ponder upon is that death rate was elevated in patients with TnT levels high in plasma than in patients who had normal range values (59.6% vs 8.9%) [53]. Pre-existed CVD in patients led to their increased susceptibility in developing Covid-19 and its complicated clinical outcomes [54]. The parameters related to CV badly impact the prognosis of these infected individuals. Six published studies from China put up the statistics of patients with COVID-19 and reported “9.7%, 16.4% and 17.1%” prevalence of diabetes mellitus, cardio cerebrovascular disease and hypertension respectively [55]. Though the incidence of hypertension and diabetes in these people was similar to the general population of China, cardio cerebrovascular disease prevalence was noticeably greater. More significantly, the diabetes mellitus, cardio-cerebrovascular disease and hypertension is known to be linked with a “2-fold, 3-fold and 2-fold” higher possibility of severe viral pathogenesis and needed to be admitted in intensive care unit (ICU), suggesting extrapolative influence of these underlying diseases. The Chinese Center for Disease Control and Prevention released a much-detailed report describing the clinical outcomes in confirmed cases of about 44672 [56]. The overall fatality rate (CFR) in these infected people was 2.3% and it was much higher in patients with hypertension, diabetes and CVD (6%, 7.3% and 10.5% respectively) (Table 1). Across variable geographical territories the rate of occurrence of different “CV comorbidities” and their clinical outcomes keeps on changing. A small report inclusive of 21 Washington patients, United States of America (USA) exhibited a grave scenario [57]. Comorbidities were usual in this group of patients with 33.3% being diabetic 42.9% suffering from “congestive heart failure”. In 33.3% patients, “acute cardiac dysfunction” occurred and about 52.4% patients died. All in all, 201 deaths out 15219 positive cases indicate CFR in America to be much lower. However, is likely to raise as most of the patients are admitted in hospitals as of this moment and no definitive results are known to us.

Another crucial point to be under discussion is about a promising drug, chloroquine that has been tested in patients with Covid-19 and its cardiovascular side effects. The long term use of the drug enhances Purkinje fiber refractory period and depolarization length duration ultimately leads to the “atrioventricular nodal and/or His system malfunction” [58]. Both the hydroxychloroquine and chloroquine have been used clinically to treat several conditions but these two are equally known to cause “arrhythmias” [59,60]. Azithromycin, was evaluated by being blended with hydroxychloroquine as a therapy for “COVID-19”, has also been recognized to elongate the QT interval [61]. Out of the 90 patients who got azithromycin in combination with and those who got it combined with hydroxychloroquine had larger QT interval than those who were treated with

hydroxychloroquine alone [60].

Table 1: Prevalence of cardiovascular comorbidities in patients with COVID-19 [56]

Country	Number of patients	Prevalence of comorbidity among all patients (among patients who were ventilated or in ICU)			
		Cardiovascular disease (%)	Hypertension (%)	Diabetes (%)	Obesity (%)
China	41	15 (23)	15 (15)	20 (8)	NR
China	138	14.5 (25.0)	31.2 (58.3)	10.1 (22.2)	NR
China	191	8 ^a (24) ^{a,b}	30 (48) ^b	19 (31) ^b	NR
China	150	8.7 (19.1) ^b	34.7 (42.6) ^b	16.7 (17.6) ^b	NR
China	1,099	2.5 ^a (5.8) ^a	15.0 (23.7)	7.4 (16.2)	NR
China	44,672	4.2 (22.7)	12.8 (39.7)	5.3 (19.7)	NR
Italy	1,591	NR (21)	NR (49)	NR (17)	NR
USA	393	13.7 ^a (19.2) ^a	50.1 (53.8)	25.2 (27.7)	35.8 (43.4)
USA	5,700	11.1 ^a (NR)	56.6 (NR)	33.8 (NR)	41.7 (NR)

Additionally, reviewing a group study encompassing 1438 hospitalized patients in New York City, treatment with azithromycin or hydroxychloroquine both were related with neither treatment. In-hospital mortality was not increased in both groups, but the outcome of cardiac arrest was highly likely in patients receiving both medications rather than the ones taking none [62]. Owing to systemic illness and Electrocardiographic evaluation some confirmed cases of Covid-19 might have renal dysfunction. Hence a proper analysis should be done in patients intaking these either of the two medication or both. Despite the total clearance of the virus, some long-term complication might develop in the patients. Previous epidemics can for sure help out in providing indications for any later CV outcomes. For instance, the 2002 SARS epidemic, elevated levels of phosphatidylinositol and lysophosphatidylinositol in the patients recovered from SARS led to metabolic alterations as compared to the normal healthy people. This change was observed owing to impaired glucose metabolism and associated hyperlipidemia. A vascular necrosis has been reported to be a long-term complication for Covid patients to whom corticosteroids were prescribed [63,64]. However the exact mechanism of these metabolic alterations is yet unknown to us. Osteonecrosis is related independently with a high risk of worse CV outcomes in patients to SARS having corticosteroid treatment and warrants further investigation [65,66]. Psychiatric morbidities should also be considered like the chronic fatigue syndrome, which was also observed patients who were recovering from the viral infection [67]. Provided the relation between psychiatric conditions, such as (CFS) chronic fatigue syndrome, depression, and CVD, such as chronic HF and cardiac arrhythmias, the proof backing long-term CV sequelae of this disease seems captivating [68,69,70]. In the US, a recent analysis depicted a 38% decrease in primary PCI during the worldwide pandemic, which is partially in order to avoid visiting the hospital at an early stage in fear of getting infection from the hospital, incorrect diagnosis of STEMI, and increased utilization of fibrinolysis [71]. This would most likely lead to post MI complications, such as the post-MI angina, cardiac rupture, cardiogenic shock and reinfarction, that were not usual before due timely invasive strategy management. There is a possibility that plenty of the complications are enlisted due to the unfortunate deaths at home. Decline in ACS-related hospitalization rates in the “Italy” has been observed [72]. To much surprise, the occurrence of “out-of-hospital cardiac arrest” has become more and more common [73]. Hiding symptoms like chest tightness, shortness of

breath and the poor clinical status of the patient second only to COVID and also the constant dread of availing health care facility might have been the cause of such an elevated rate.

3. Conclusion

SARS-CoV-2 has raised an alarming situation in the world and is a threat to the wellbeing of the people. Among the people with severe infection, high incidence rate of cardiac injury has been reported. Though the pathway of cardiac injury infliction is yet elusive but it most probably includes a coupling of on point viral mediated damage and immune-mediated injury that is due to the “inflammatory cytokines/chemokines” and “cytotoxic immune cell response” at the endmost phases of infection. It has been scrutinized by the bioinformatics tools that the SARS-CoV-2 have many of the alligned similar genetic components with SARS-CoV, so by understanding the pathophysiological mechanistics related to the “SARS” one can be used to comprehend the disease causing mechanisms included in “COVID-19”. The binding of the “S” protein and “ACE2” is most probably to have a significant role in pathogenesis of disease, prominently in cardiovascular indicators, and this link is a possible target for the deterrence & curing of “COVID-19”. Keeping this in mind, the currently existing consideration about the interaction of CVD and COVID-19 is insufficient. Therefore, there must be further research studies on “COVID-19” can precisely define the occurrence, pathways, clinical manifestation and possible results of various CV symptoms in the patients. The investigative and healing trials postured by the correspondence of these two sicknesses are also required to be sufficiently studied. Further researches must be conducted for the better understanding of the spectrum of CV indicators. Doctors should be mindful of this cardiac involvement and must be able to address this situation to minimize the damaging effects. Additionally, we must be cautious regarding the possible adversative effects & connections of prevailing treatments.

4. Conflict of interest

All the authors don't have any conflict of interest regarding this article.

References

- [1]. Zhou P, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579:270–273.
- [2]. Wu F, et al. A new coronavirus associated with human respiratory disease in China. *Nature*. 2020;579:265–269.
- [3]. Lu R, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395:565–574.
- [4]. Hoffmann M, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271–280.
- [5]. Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat. Rev. Immunol*. 2020;20:363–374.
- [6]. Bikdeli B, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J. Am. Coll. Cardiol*.

2020;75:2950–2973.

- [7]. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *J. Thromb. Haemost.* 2020;18:1559–1561. Wrapp D, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science.* 2020;367:1260–1263.
- [8]. Walls AC, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell.* 2020;181:281–292.
- [9]. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J. Virol.* 2020;94:e00127–20.
- [10]. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nat. Med.* 2020;26:450–452.
- [11]. Driggin E, Madhavan M V., Bikdeli B, Chuich T, Laracy J, Bondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. *J Am Coll Cardiol.* 2020.
- [12]. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA.* 2020.
- [13]. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin Hongde. *Eur Heart J.* 2020;1307800.
- [14]. Chen C, Zhou Y, Wang DW. SARS-CoV-2: a potential novel etiology of fulminant myocarditis. *Herz.* 2020;10–2.
- [15]. Zeng JH, Liu Y-X, Yuan J, Wang F-X, Wu W-B, Li J-X, et al. First case of COVID-19 infection with fulminant myocarditis complication: case report and insights. 2020.
- [16]. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* 2020;1–8.
- [17]. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol.* 2020.
- [18]. Liu Y, Li J, Liu D, Song H, Chen C, Lv M, et al. Clinical features and outcomes of 2019 novel coronavirus-infected patients with 1 cardiac injury.
- [19]. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* 2020.
- [20]. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA.* 2020;2019:3–6.
- [21]. Waxman DA, Kanzaria HK, Schriger DL. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med.* 2018;378(26):2538–2541. doi: 10.1056/NEJMc1805679.
- [22]. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2019. <https://doi.org/10.1001/jamacardio.2020.1017>.
- [23]. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res.*

2020;116(6):1097–100.

- [24]. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest.* 2009;39(7):618–25.
- [25]. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol.* 2020 doi: 10.1001/jamacardio.2020.1286.
- [26]. Clerkin KJ, et al. COVID-19 and cardiovascular disease. *Circulation.* 2020;141:1648–1655.
- [27]. Han Y, et al. CSC expert consensus on principles of clinical management of patients with severe emergent cardiovascular diseases during the COVID-19 epidemic. *Circulation.* 2020;141:e810–e816.
- [28]. Huang C, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5.
- [29]. Wang D, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020 doi: 10.1001/jama.2020.1585.
- [30]. Guan WJ, et al. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* 2020;382:1708–1720.
- [31]. Shi S, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur. Heart J.* 2020;41:2070–2079.
- [32]. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet.* 2020;395:1607–1608.
- [33]. Sellers SA, Hagan RS, Hayden FG, Fischer WA 2nd. The hidden burden of influenza: a review of the extra-pulmonary complications of influenza infection. *Influenza Other Respir Viruses.* 2017;11:372-393.
- [34]. Alexander LK, Small JD, Edwards S, Baric RS. An experimental model for dilated cardiomyopathy after rabbit coronavirus infection. *J Infect Dis.* 1992;166:978-985.
- [35]. Xiong TY, Redwood S, Prendergast B, Chen M. Coronaviruses and the cardiovascular system: acute and long-term implications. *Eur Heart J.* 2020. 10.1093/eurheartj/ehaa231.
- [36]. Yu CM, Wong RS, Wu EB, et al. Cardiovascular complications of severe acute respiratory syndrome. *Postgrad Med J.* 2006;82:140-144.
- [37]. Lau ST, Yu WC, Mok NS, Tsui PT, Tong WL, Cheng SW. Tachycardia amongst subjects recovering from severe acute respiratory syndrome (SARS). *Int J Cardiol.* 2005;100:167-169.
- [38]. Pan SF, Zhang HY, Li CS, Wang C. Cardiac arrest in severe acute respiratory syndrome: analysis of 15 cases. *Zhonghua Jie He He Hu Xi Za Zhi.* 2003;26:602-605.
- [39]. Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. *N Engl J Med.* 2018;378(4):345–53.
- [40]. Bandyopadhyay D, Ashish K, Ghosh S, Hajra A, Modi VA. Cardiovascular implications of Zika virus infection. *Eur J Intern Med.* 2018;52:e35–e3636.
- [41]. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, Bi Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol.* 2020;109(5):531–8.
- [42]. Rivara MB, Bajwa EK, Januzzi JL, Gong MN, Thompson BT, Christiani DC. Prognostic significance

- of elevated cardiac troponin-T levels in acute respiratory distress syndrome patients. *PLoS ONE*. 2012;7(7):e40515.
- [43]. Bajwa EK, Boyce PD, Januzzi JL, Gong MN, Thompson BT, Christiani DC. Biomarker evidence of myocardial cell injury is associated with mortality in acute respiratory distress syndrome. *Crit Care Med*. 2007;35(11):2484–90.
- [44]. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J*. 2020;55(5):2000524.
- [45]. Han H, Xie L, Liu R, Yang J, Liu F, Wu K, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. *J Med Virol*. 2020. <https://doi.org/10.1002/jmv.25809>.
- [46]. Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. *Int J Cardiol*. 2020;311:116–21.
- [47]. Zhou B, She J, Wang Y, Ma X. The clinical characteristics of myocardial injury in severe and very severe patients with 2019 novel coronavirus disease. *J Infect*. 2020. <https://doi.org/10.1016/j.jinf.2020.03.021>.
- [48]. Li JW, Han TW, Woodward M, Anderson CS, Zhou H, Chen YD, Neal B. The impact of novel coronavirus on heart injury: a systematic review and meta-analysis. *Prog Cardiovasc Dis*. 2020. <https://doi.org/10.1016/j.pcad.2020.04.008>.
- [49]. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, China. *JAMA*. 2020. 10.1001/jama.2020.1585.
- [50]. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA*. 2020. 10.1001/jamacardio.2020.0950.
- [51]. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506.
- [52]. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020. 10.1001/jamacardio.2020.1017.
- [53]. Wang D., Hu B., Hu C. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *J Am Med Assoc*. 2020.
- [54]. Li B., Yang J., Zhao F. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020.
- [55]. Wu Z., McGoogan J.M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease Control and prevention. *J Am Med Assoc*. 2020.
- [56]. Arentz M., Yim E., Klaff L. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *J Am Med Assoc*. 2020.
- [57]. Ratliff NB, Estes ML, McMahon JT, Myles JL. Chloroquine-induced cardiomyopathy. *Arch Pathol Lab Med*. 1988;112:578.
- [58]. Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for drug interactions on QTc in

- exploratory COVID-19 treatment. *Circulation*. 2020;141:e906–e907.
- [59]. Mercurio NJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19) *JAMA Cardiol*. 2020 doi: 10.1001/jamacardio.2020.1834.
- [60]. Hancox JC, Hasnain M, Vieweg WV, Crouse EL, Baranchuk A. Azithromycin, cardiovascular risks, QTc interval prolongation, Torsade de Pointes, and regulatory issues: a narrative review based on the study of case reports. *Ther. Adv. Infect. Dis*. 2013;1:155–165.
- [61]. Rosenberg ES, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. 2020 doi: 10.1001/jama.2020.8630.
- [62]. Hong N, Du XK. Avascular necrosis of bone in severe acute respiratory syndrome. *Clin Radiol*. 2004;59(7):602–8.
- [63]. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. *Bone Res*. 2020;8:8.
- [64]. Sung PH, Yang YH, Chiang HJ, Chiang JY, Chen CJ, Yip HK, et al. Cardiovascular and cerebrovascular events are associated with nontraumatic osteonecrosis of the femoral head. *Clin Orthop Relat Res*. 2018;476(4):865–74.
- [65]. Kang JH, Lin HC. Increased risk for coronary heart disease after avascular necrosis of femoral head: a 3-year follow-up study. *Am Heart J*. 2010;159(5):803–808e1.
- [66]. Lam MH, Wing YK, Yu MW, Leung CM, Ma RC, Kong AP, et al. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. *Arch Intern Med*. 2009;169(22):2142–7.
- [67]. Das A, Roy B, Schwarzer G, Silverman MG, Ziegler O, Bandyopadhyay D, et al. Comparison of treatment options for depression in heart failure: a network meta-analysis. *J Psychiatr Res*. 2019;108:7–23.
- [68]. Patel N, Chakraborty S, Bandyopadhyay D, Amgai B, Hajra A, Atti V, et al. Association between depression and readmission of heart failure: a national representative database study. *Prog Cardiovasc Dis*. 2020. <https://doi.org/10.1016/j.pcad.2020.03.014>.
- [69]. De Hert M, Detraux J, Vancampfort D. The intriguing relationship between coronary heart disease and mental disorders. *Dialogues Clin Neurosci*. 2018;20(1):31–40.
- [70]. Garcia S, Albaghdadi MS, Meraj PM, Schmidt C, Garberich R, Jaffer FA, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. *J Am Coll Cardiol*. 2020. <https://doi.org/10.1016/j.jacc.2020.04.011>.
- [71]. De Filippo O, D’Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, et al. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in Northern Italy. *N Engl J Med*. 2020. <https://doi.org/10.1056/NEJMc2009166>.
- [72]. Baldi E, Sechi GM, Mare C, Canevari F, Brancaglione A, Primi R, et al. Out-of-hospital cardiac arrest during the Covid-19 outbreak in Italy. *N Engl J Med*. 2020. <https://doi.org/10.1056/NEJMc2010418>.