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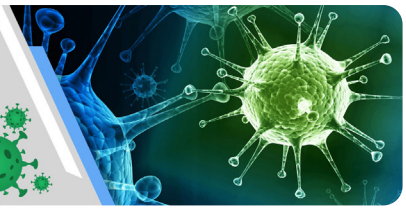

An In-Depth Insight into Clinical, Cellular and Molecular Factors in COVID19-Associated Cardiovascular Ailments for Identifying Novel Disease Biomarkers, Drug Targets and Clinical Management Strategies

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Abstract

COVID-19 was initially identified as a respiratory system disorder, but it has been reported to interact with and influence the cardiovascular system, in addition to many other body systems. Although COVID-19-associated cardiovascular (CV) complications are common, resulting in high acute phase mortality and a large number of morbidities in the chronic phase, thus severely impacting patients' quality of life and health outcomes, yet clinical, cellular, and molecular biological factors underlying the pathophysiology of cardiovascular complications associated with COVID-19 are poorly understood. This review investigates putative underlying clinical factors as well as cellular and molecular biological mechanisms by which COVID-19 leads to acute CV complications, including state-of-the-art genomic sequencing-based findings, and assessing the long-term CV consequences of COVID-19, aiming to shed light on developing strategies for differential diagnosis, risk prognostic stratification, prevention, and clinical management of CV sequels in COVID-19 patients.

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We found that the relationship between COVID-19 and CV risk is complex and multifaceted. Intriguingly, in addition to acute COVID-19 detertriuos effects, COVID-19 survivors may experience long-term CV effects as well that may have long-lasting clinical consequences. Here in this article, we provide a detailed account of a large number of genomic alterations, microRNAs, and novel viral as well as host proteins in CVDs associated with COVID-19, which has helped identify some novel drug targets to treat COVID-19-related cardiovascular complications.

Keywords: Cardiovascular diseases; COVID-19; pathophysiology; molecular pathogenesis; personalized cardiovascular medicine

Introduction

COVID-19 and cardiovascular diseases:

Although COVID-19 primarily affects the respiratory system, yet it also contributes to development of cardiovascular complications as well as onset and progressions of underlying cardiac conditions [1]. The inflammatory response of the body to COVID-19 is quite strong and subsequent inflammation is the major cause of myocardial injury [2]. The plaque buildup in the arteries is usually harmless but can inflate, leading to development of blood thrombi, myocardial infarction (MI), and strokes. There are several potential causes of short-term or long-term heart tissue damage induced by COVID-19 [1,3], as below.

1. A lack of Oxygen: Inflammation and fluid accumulation in the lung air sacs brought on by the virus reduce the amount of oxygen that may enter the bloodstream. When the heart under this stress needs to pump harder to supply sufficient blood and oxygen to the body, it poses a great risk, especially for patients with diagnosed cardiac diseases or with underlying cardiac conditions not diagnosed yet. Thus, overuse of heart tissues can lead to heart failure (HF), and resulting hypoxia can kill cells as well as destroy tissues in the heart and other organs.
2. Cardiac inflammation (myocarditis): Like other viruses, such as the flu, the coronavirus can infect the heart muscle directly and cause inflammation. One the other hand, the body's immunological reactions to COVID-19 infection can cause injury and inflammation to the heart Indirectly.
3. Damage to blood vessels: In addition to damaging the inner linings of veins and arteries, COVID-19 infection also leads to inflamed blood vessels, small vessel damage, and blood clots, all of which contribute to decreased blood flow to the heart and other organs. Endothelial cells, which line the blood vessels, are adversely affected by this infection leading to severe COVID-19.
4. COVID19-triggered Cardiomyopathy: Cardiomyopathy (CM), which is a heart condition caused by stress, impairs the heart's ability to effectively pump blood can be triggered by a viral infection like COVID-19. Thus, due to this viral infection, the body releases an excess of chemicals known as catecholamines, which can temporarily halt the heart.

Long-term CV outcomes of COVID-19 patients were reported in a study including over 11 million participants and published in the journal "Nature Medicine" in February 2022. [1]. The risk of CV illness following COVID-19 infection was reported to be persisting for at least one year after infection, suggesting that the virus's effects last longer than the typical incubation period of two weeks. After 30 days of infection, the risk of CV disorders such as stroke, cardiac disease, pericarditis, myocarditis, HF, and blood thrombi was higher in COVID-19-infected patients, regardless of whether they were hospitalized or not. The patients with COVID-19 infections were 63% more likely to experience cardiac problems within a year of infection as compared to those without COVID-19 infections. Overall, forty-five extra CV incidents were found for every 1,000 persons who tested positive for COVID-19 [1].

Some investigators have recently investigated COVID19-induced damage mechanisms to the CV and cerebrovascular systems [3]. The utilization of state-of-the-art single-cell RNA sequencing has revealed the mechanism of COVID-19 invasion of myocardial tissue, indicating the prospect of utilizing state-of-the-art cell and molecular biological research techniques in exploring the complicated involvement of COVID-19 in CVD and other associated comorbidities [3]. , Other studies have also reported that 26% to 60% of individuals hospitalized due to COVID-19 infection had myocardial complications that were detected by emplying CV magnetic resonance (CMR). [4-6].

The mechanism of long-term CV manifestations of SARS-COV-2 (COVID-19) infections remain unknown [3-7]. Moreover, clinical factors associated with COVID-19-associated pathophysiology and underlying basic cellular molecular biological mechanisms are poorly understood [2-6]. Therefore, this study aimed to provide a comprehensive account of clinical, cellular, and molecular factors associated with COVID19-induced cardiovascular diseases. A thorough analysis of the latest published literature was carried out for this purpose.

Myocardial Injury and COVID-19

Damage or injury to the heart muscle is known as myocardial injury [3]. It can result from MI, surgery, trauma, viral infections, or drug toxicity. Myocardial injuries can range from mild to severe and have significant health implications [6]. CV biomarkers are commonly used to diagnose the

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myocardial injury. These biomarkers include troponin, creatine kinase-MB (CK-MB), and myoglobin, released by damaged heart muscle cells [8]. MI of type I (T1MI) is caused by an acute atherosclerotic plaque rupture. In contrast, type 2 (T2MI) MI results from myocardial oxygen demand and supply mismatches without an acute thrombotic event [9]. Initial definitions of T2MI were included in the universal definition of MI (U.D.M.I.). This term identifies individuals with elevated cardiac troponin (cTn) levels that are not attributed to an ischemic etiology [8,9]. A global task force of cardiology experts published The Fourth UDMI in 2018. It provides updated and standardized criteria to diagnose MI, defined as ischemia-induced myocardial cell death. The Fourth Universal Definition of MI includes five types of MI [9,10]:

5. Type 1 MI: Spontaneous MI resulting from a primary coronary event, such as plaque rupture or erosion, leading to prolonged ischemia.
6. Type 2 MI: MI resulting from an imbalance between myocardial oxygen supply and demand without a primary coronary event and occurring in severe anemia, hypotension, or tachyarrhythmias.
7. Type 3 MI: MI resulting from sudden cardiac death, with symptoms consistent with MI but without diagnostic E.C.G. changes or biomarker elevation.
8. Type 4a MI: MI associated with percutaneous coronary intervention (PCI), where biomarker elevation occurs following PCI.
9. Type 4b MI: MI associated with stent thrombosis, where biomarker elevation occurs associated with angiographic evidence of stent thrombosis.

COVID-19 is a viral respiratory infection caused by the SARS-CoV-2 virus [6]. Since the virus was initially discovered in Wuhan, China, in December 2019, a global pandemic has evolved. Cough, fever, and shortness of breath are the most prevalent COVID-19 symptoms [10]. However, patients also experience fatigue, muscle aches, a sore throat, and a loss of taste or smell. Furthermore, COVID-19 infection can cause severe respiratory disease, pneumonia, acute respiratory distress syndrome (ARDS), and other life-threatening complications may occur [11,12]. According to the latest World Health Statistics from the World Health Organization (WHO), the COVID-19 pandemic reversed the steady rise in life expectancy at birth and healthy life expectancy at birth [12]. This study reports that pandemic erased nearly a decade of life expectancy gains in two years. Global life expectancy fell 1.8 years to 71.4 years in 2019–2021. Global healthy life expectancy fell 1.5 years to 61.9 years in 2021 (back to 2012).

Generally, mild to severe infection may occur due to COVID-19 without proper medical intervention. Some individuals, develop serious conditions that necessitate medical attention, particularly those in older age and with existing illnesses, such as CVD, diabetes, chronic respiratory disease, or cancer [13]. The above-mentioned complications associated with COVID-19 infection can also lead to being seriously ill or leading to death at any age [13,14,15]. The heart function may be affected in some patients, regardless of whether they previously had a CV diagnosis or not.

COVID-19 has been linked to myocardial injury, which can lead to serious cardiovascular complications. Despite the fact that the mechanism of this association is unknown, it is believed to be caused by direct viral invasion of the heart muscle as well as indirect effects such as cytokine release and hypoxia. SARS-CoV-2 penetrates cells through angiotensin-converting enzyme 2 (ACE2), which is a membrane protein that functions as a counterbalance to the adverse effects of the renin–angiotensin– aldosterone system (R.A.A.S.) through converting angiotensin II (Ang II) to Ang-(1–7) and interacting with the ACE2 receptor through the spike (S) protein [16]. The exact mechanism by which SARS-CoV-2 causes myocardial injury remains unclear, but cells expressing high ACE2 levels are more susceptible to SARS-CoV-2 invasion and subsequent organ injury, including cardiomyocytes (C.M.s) [17]. Clinical observations revealed that increased myocardial biomarker levels unrelated to obstructive coronary artery disease (CAD), mostly diagnosed as myocardial injury, occurred in 7.2–40.9% of patients with COVID-19 [18]. Numerous publications have reported a high prevalence of myocardial injury in COVID-19 patients. According to a 2020 research published in J.A.M.A. Cardiology, approximately one-third of hospitalized COVID-19 patients had high troponin levels, indicating myocardial injury. [19]. **Figure 1** depicts the Classification of Myocardial Injury in COVID-19 [20]. It illustrates the potential mechanisms that can result in myocardial injury in COVID-19. In general, for any patient with cTn increases >99th percentile, elevations should be broadly classified as 1) chronic myocardial injury, 2) acute nonischemic myocardial injury, or 3) acute myocardial infarction (MI) [20].

Recent accumulated evidence indicates the myocardial injury among COVID-19 patients manifests with elevated troponin level [21-26]. Stress cardiomyopathy, hypoxic injury, ischemic injury, and systemic inflammatory response syndrome (cytokine storm) may be contributing factors [21-26]. Troponin levels are elevated in a minority of patients with characteristics suggestive of an acute coronary syndrome (A.C.S.) [21-26]. Patients with cardiovascular disease, high blood pressure, obesity, and diabetes have a poor prognosis. In addition, patients with myocardial injury, regardless of cause, have a poorer prognosis [21-26]. The mortality rates of

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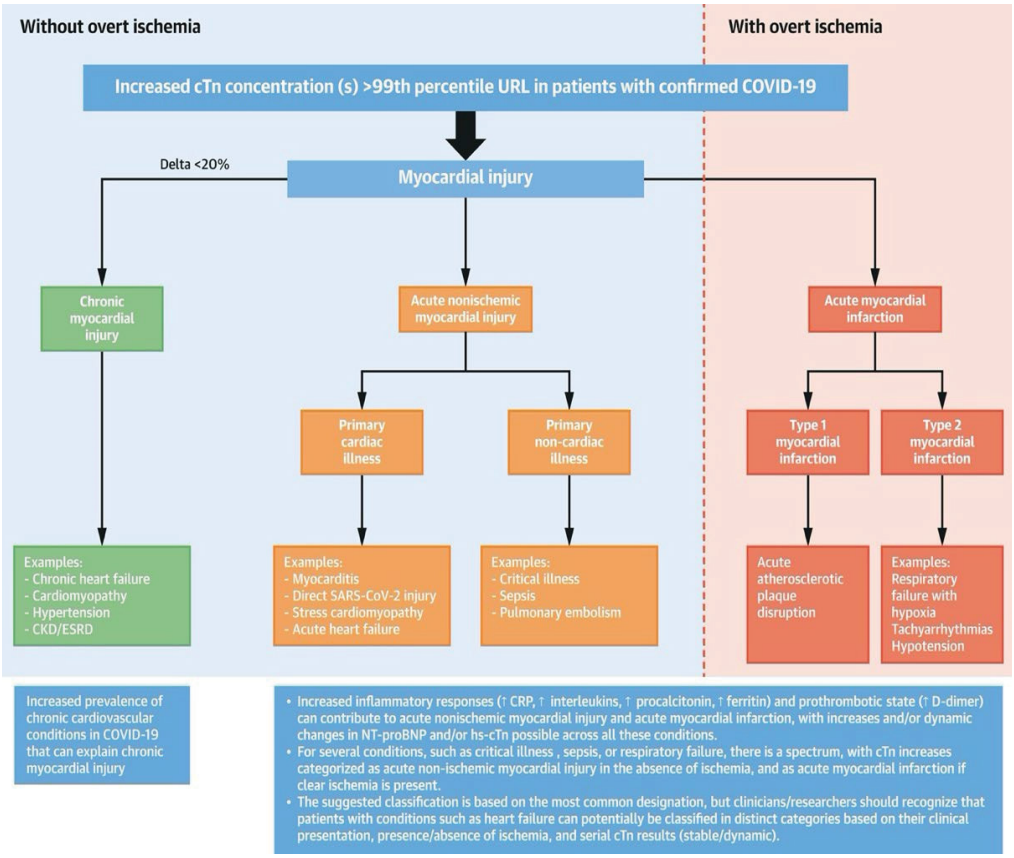

Figure 1: Classification of Myocardial Injury in COVID-19 [20]

patients with Coronavirus disease 2019 (COVID-19) with and without CVD in comparison with patients with and without elevated troponin levels (hs-TNI) are shown in **(Figure 2)** [26]. Cardiac troponin is routinely used to diagnose and treat ACS since it is a sensitive and specific marker of myocardial damage. Patients with COVID-19 who have elevated cardiac troponin levels are at a higher risk of mortality and morbidity. Studies have shown that COVID-19 is associated with myocardial injury and MI [27,28]. As previously stated, SARS-CoV-2 infection is dependent on the ACE2 receptor, which is abundant in diverse tissues and expressed at varying levels in different organs [27,28].

Mechanism of Myocardial Injury and COVID-19

A. Cytokine Storm

Numerous studies have reported that COVID-19 patients with severe illness have significantly increased levels of pro-inflammatory cytokines, including interleukin IL-6, IL-1β, and tumor necrosis factor-alpha (TNF-α), in comparison to patients with mild illness, suggesting the involvement of cytokine storm in COVID-19- induced myocardial injury. A study conducted in Wuhan, China, found that elevated levels of IL-6, C-reactive protein (C.R.P.), and D-dimer were associated with adverse cardiovascular events, including myocardial injury [29]. As a result of cytokine storm, endothelial dysfunction and increased vascular permeability are induced, which eventually trigger capillary dilation, microvascular leakage, and micro-thrombi formation, resulting in myocardial injury. A recent study reported that COVID-19-induced cytokine storm upregulates the expression of ACE2 in the heart, providing an opportunity for ACE2-dependent myocardial infection [29]. The excessive inflammatory response, also known as cytokine storm, can cause collateral damage to different organs and tissues, including the heart, leading to endothelial dysfunction, increased vascular permeability, and myocardial injury [29-30]. Furthermore, the cytokine storm may disrupt the myocardium's balance between oxidative stress and antioxidant defense, causing oxidative damage to cardiac tissues [30].

B. Oxygen supply-demand mismatch

A study explored the host vulnerability to severe COVID-19 and the establishment of a host risk score concluded that mismatch of oxygen supply-demand caused by respiratory failure was a prevalent mechanism underlying severe COVID-19 and was associated with an increased risk of unfavorable outcomes. This study highlighted the importance of monitoring and managing oxygenation in patients with COVID-19 to prevent complications such

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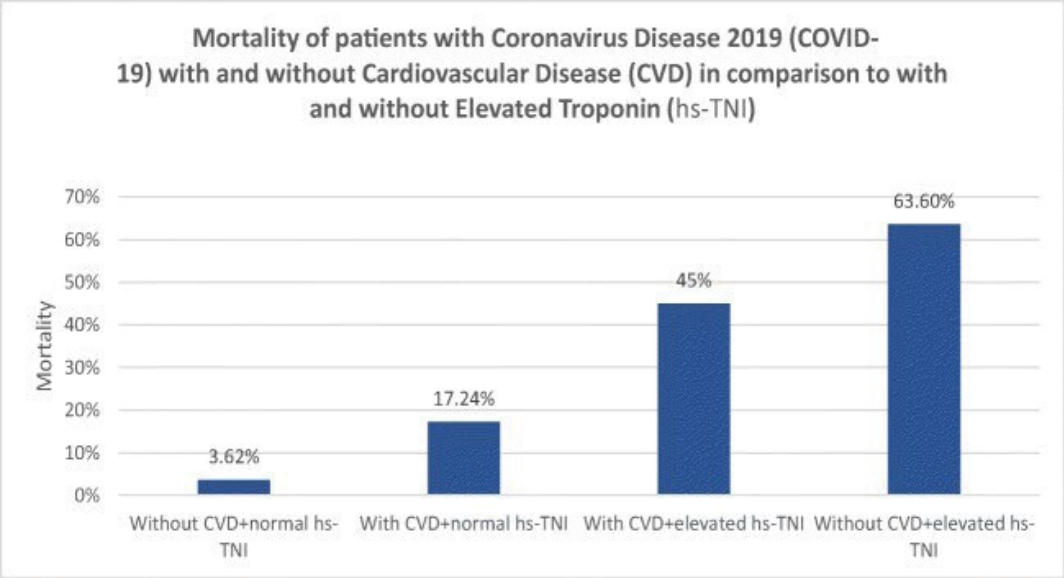

Figure 2: Mortality of patients with coronavirus disease 2019 (COVID-19) with and without cardiovascular disease (CVD) in comparison to those with and without elevated troponin (hs- TNI) [26].

as severe disease and mortality [31]. It was suggested that COVID-19 could cause Oxygen supply-demand mismatch, leading to myocardial injury through various mechanisms, including direct invasion of the virus, respiratory damage causing hypoxia, cytokine storm, and acute plaque rupture.

A direct invasion of the virus leads to damage of the heart tissue, resulting in myocardial injury. Respiratory damage caused by COVID-19 can lead to hypoxia, which increases the oxygen demand of the myocardium and can cause an oxygen supply-demand mismatch, leading to myocardial injury. The cytokine storm caused by COVID-19 can potentially lead to myocardial injury through various pathways, including oxidative stress and inflammation. Acute plaque rupture can also cause an oxygen supply-demand mismatch, leading to myocardial injury [31]. Various studies have reported myocardial injury in COVID-19 patients, one of which observed elevated cardiac troponin levels in 36.1% of COVID-19 patients, associated with a higher mortality risk. In another study, myocardial injury, as defined by elevated cardiac troponin levels, was reported in 19.7% of COVID-19 patients, and these patients were more likely to require mechanical ventilation and have a poor prognosis [30].

C. Stress cardiomyopathy

Stress cardiomyopathy, which is also termed Takotsubo cardiomyopathy, is a reversible left ventricular (LV) dysfunction due to transient wall motion abnormalities in the absence of significant obstructive coronary artery disease (CAD) [32]. The presence of stress cardiomyopathy in individuals affected by COVID-19 has been identified in reports, suggesting that it represents a significant complication of the disease. The pathophysiologic mechanisms of stress cardiomyopathy in patients infected with COVID-19 are not well understood. However, it has been hypothesized that COVID-19 infection can cause a mismatch between oxygen supply and demand, resulting in myocardial injury and stress cardiomyopathy. As a consequence of COVID-19 infection, the manifestation of hypoxemia can reduce the delivery of oxygen to the myocardium; potentially leading to myocardial damage characterized by stress cardiomyopathy (32)(33).

Several studies have reported cases of stress cardiomyopathy in patients infected with COVID-19. In a study of 100 patients with COVID-19, stress cardiomyopathy was identified in five patients, suggesting a prevalence of 5%. Another study found that stress cardiomyopathy was observed in 7.8% of patients with severe cases of COVID-19 [32]. Moreover, it is important to underline that COVID-19 infection has the potential to induce stress cardiomyopathy, which is mainly characterized by LV dysfunction and clinical symptoms resembling acute myocardial infarction. However, some hypothetical frameworks have been postulated including catecholamine surge, direct myocardial injury, and microvascular dysfunction [33]. In another study involving 416 hospitalized patients with COVID-19, 7.2% were diagnosed with stress cardiomyopathy. Patients with stress cardiomyopathy showed higher rates of in-hospital mortality and required mechanical ventilation [34]. Although stress cardiomyopathy is reversible, it can cause significant morbidity and mortality in some patients. Therefore, it is essential to recognize the potential association between COVID-19 infection and stress cardiomyopathy.

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D. Hypoxic injury

Several studies have reported elevated levels of inflammatory markers, such as interleukin-6 (IL 6), in COVID-19 patients, which suggests an underlying inflammatory process. It has been proposed that systemic inflammation may contribute to myocardial injury by releasing inflammatory mediators. These mediators, such as IL-6, can cause endothelial dysfunction and microvascular thrombosis, decreasing oxygen supply to the myocardium [34]. In a study of 416 hospitalized patients with COVID-19, higher levels of IL-6 were observed in those with myocardial injury compared to those without. The study concluded that inflammatory mediators, such as IL-6, may contribute to myocardial injury in COVID-19 patients [19]. Moreover, other increased inflammatory markers including ferritin and C-reactive protein (C.R.P.) have been observed in 19 patients with myocardial injury, which is an indication of a possible role of systemic inflammation in the development of myocardial injury in COVID-19 [29]. In another study, patients with severe COVID-19 were found to have elevated levels of troponin, a biomarker of myocardial injury, which correlated with the levels of inflammatory markers such as IL-6 and C.R.P [19]. The precise mechanism of inflammatory mediator-induced hypoxic injury in COVID-19 patients is unidentified, but systemic inflammation is thought to play a role. Identifying and managing inflammatory mediators may help improve the prognosis of COVID-19 patients with myocardial injury.

E. Endothelial Dysfunction

Endothelial dysfunction and its associated effect on microvascular and epicardial vessels can contribute to many pathological conditions, such as inflammation and thrombosis. In COVID- 19 patients, endothelial damage in the vascular wall can lead to a pro-thrombotic environment and micro-thrombi formation, contributing to myocardial injury [35]. According to recent research, the SARS-CoV-2 virus can infect endothelial cells, causing endothelial dysfunction (E.D.), capillary dilation, and increased vascular permeability. Furthermore, as the inflammatory response is triggered, raising cytokine levels such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) can lead to endothelial dysfunction [35]. A study on inflammatory markers and endothelial dysfunction in COVID-19 patients showed that elevated levels of IL-6, C.R.P, and D-dimer were associated with increased inflammatory activity and endothelial dysfunction, indicating a correlation between COVID-19 severity and endothelial injury. Another study found that damage to epicardial vessels due to endothelial dysfunction could lead to cardiac remodeling and subsequent myocardial injury [36]. In addition, a survey on COVID- 19 patients with acute respiratory distress syndrome (ARDS) found a significant correlation between pulmonary dysfunction and myocardial injury, indicating a possible involvement of microvascular dysfunction in COVID-19-induced myocardial injury [37]. To develop effective preventative and therapeutic techniques, it is critical to understand the influence of COVID-19 on endothelial dysfunction and its association with myocardial injury. Early detection of endothelial dysfunction may aid in the prevention of myocardial injury development in COVID-19 patients. More research is needed to determine the particular mechanism of myocardial injury **(Figure 3)** [16].

Clinical Manifestations of Myocardial Injury

A. Signs and symptoms

The symptoms of myocardial infarction (MI) include chest pain that radiates from the left arm to the neck, shortness of breath, diaphoresis, gastrointestinal symptoms (such as nausea and vomiting), an abnormal heart rate, anxiety, fatigue, weakness, stress, and depression [37]. It has been documented that patients with myocardial infarction may show low blood pressure, fast heartbeat, rapid breathing, signs of low cardiac output, and a third heart sound upon physical examination [38]. MI can be classified by typical symptoms in patients with chest, arm, or jaw pain in the form of dull, heavy, tight, pressure, ache, squeezing, crushing, or gripping in nature. On the other hand, in cases where epigastric back pain is accompanied by symptoms such as burning, stabbing, or indigestion-like sensations, the clinical presentation can be classified as atypical in patients from a medical perspective. However, clinical manifestations encompass pain radiation to different anatomical regions (right arm, left arm, neck, jaw, and back), along with associated symptoms like nausea, vomiting, sweating, dyspnea, and palpitations have been reported as well. [39].

Symptoms of myocardial ischemia include anginal chest pain radiating to the arms, jaw, or epigastric region, which may occur during rest or exercise. Acute myocardial infarction usually causes discomfort for at least 20 minutes. This discomfort is typically diffuse, not localized, not positional, and not exacerbated by movement, and it may be associated with dyspnea, excessive sweating, nausea, or syncope. These symptoms are not diagnostic for myocardial ischemia and may be misdiagnosed as gastrointestinal, neurological, pulmonary, or musculoskeletal disorders. MI symptoms can be atypical or even absent [8]. Diagnosing myocardial injury might be challenging if associated with COVID-19, especially in patients with advanced stages of the disease. Patients with myocardial injury associated with COVID-19 commonly exhibit atypical clinical signs, making challenges for accurate diagnosis. Myocardial injury can manifest in patients with no previous CVD history, even in the absence of chest pain symptoms [40].

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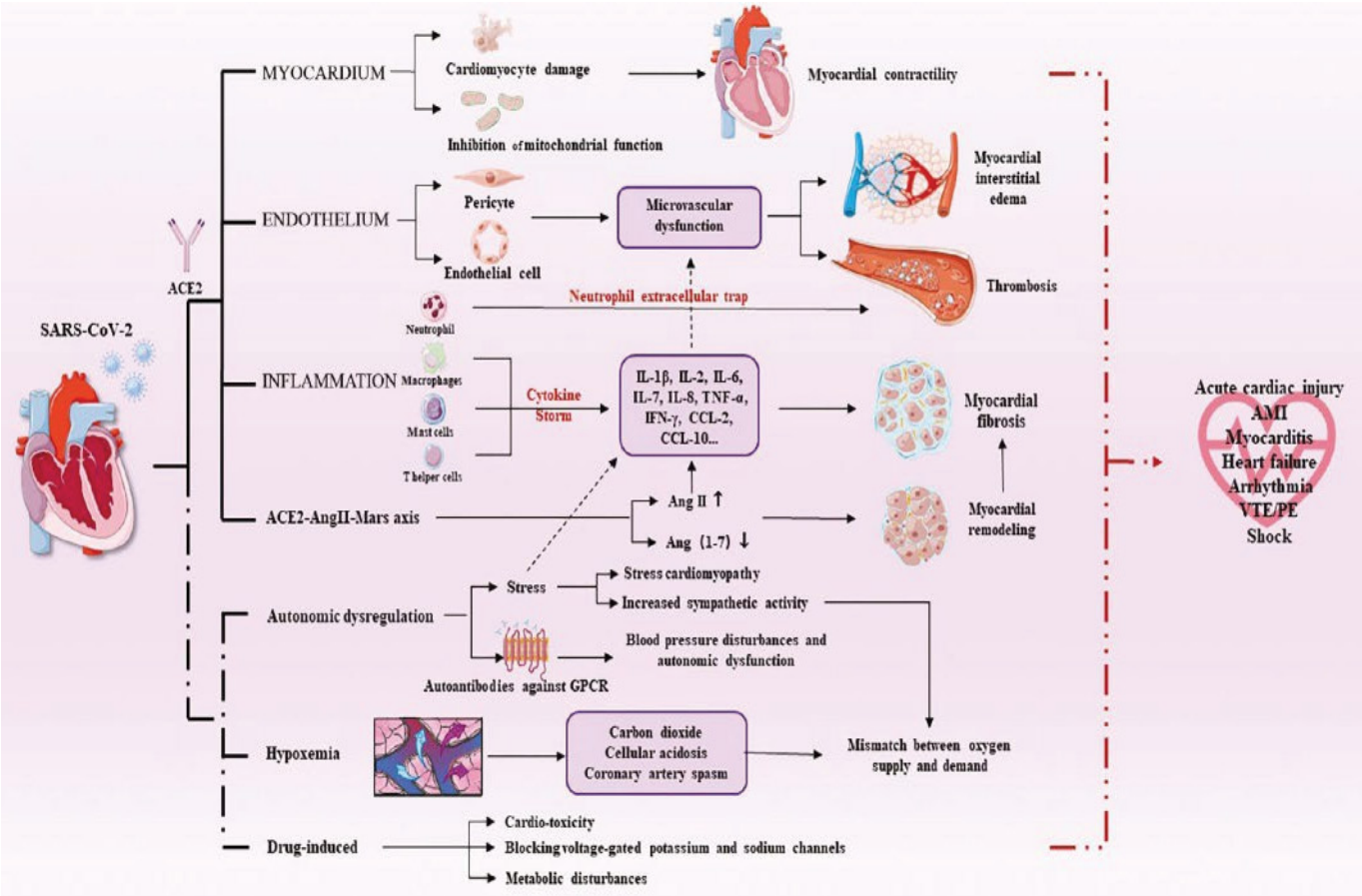

Figure 3: Illustration of the mechanism of myocardial injury [16].

Investigations Cardiac biomarkers, ECG, echocardiography, and CMR are valuable noninvasive investigations for assessing CV involvement and complications in COVID-19 patients [41]. Precautions should be taken to minimize the risk of contagion during these procedures.

Cardiac biomarkers like troponin, C.R.P, D-dimer, and NT-pro BNP are important for diagnosing and predicting the prognosis of COVID-19. Elevated biomarkers indicate a poor prognosis and increased risk of CV complications [42]. Recently, high-sensitive troponin I (hs-TnI), a positive predictor severe COVID-19 infection and subsequent risk of death, and a novel biomarker "soluble suppression of tumorigenicity-2 (sST-2), which is an indicator of severe infection, requirement for ICU care of COVID-19 and resulting mortality, have been reported to be very powerful predictors of cardiovascular complications in long-term survivors of COVID-19 patients with history of COVID19-related hospitalizations [43].

Electrocardiogram (E.C.G.) changes including arrhythmias, conduction defects, and S.T. segment and T-wave abnormalities, are common in COVID-19 patients [44-46]. These changes can resemble those seen in acute myocardial infarction (A.M.I.) and myocarditis, making diagnosis challenging [47-50]. Cardiac arrhythmias, such as ventricular tachycardia and fibrillation, are more prevalent in critically ill COVID-19 patients [51].

Echocardiography is recommended for assessing cardiac structure and function in COVID-19 patients [52]. However, precautions should be taken to minimize the risk of contamination [53, 54]. Transthoracic echocardiography (TTE) and stress echocardiography are preferred, while transesophageal echocardiography (TEE) carries a higher contamination risk [54, 55]. Bedside echocardiography can help diagnose myocarditis in suspected COVID-19 cases [56].

Cardiovascular Magnetic Resonance (CMR) is the gold standard for evaluating myocardial structure and function [57]. Portable C.M.R. devices are recommended for convenience and easier cleaning in COVID-19 settings.

A coronary angiogram is valuable for detecting and assessing CAD, identifying structural anomalies, and measuring hemodynamic parameters [58]. COVID-19-associated coagulopathy has revealed the presence of intracoronary thrombus (I.C.T.) in individuals undergoing

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angiograms for acute coronary syndromes, as coagulation problems are common in COVID-19 affecting venous and arterial Circulation [59, 60]. Liori et al. reported a case of a 39-year-old male with COVID-19 presenting with acute retrosternal chest pain and S.T. segment elevation in leads V4-V6 on the E.C.G. Thrombus aspiration restored flow in the left anterior descending coronary artery (LAD) as confirmed by coronary angiography [60]. Piccolo and Esposito emphasized the higher mortality risk in patients with concomitant coronary artery disease and COVID-19, suggesting avoiding invasive angiography with revascularization [61].

Xie et al. found that invasive coronary angiography (I.C.A.) in stable CAD patients was associated with a higher risk of major adverse cardiovascular events, all-cause mortality, and severe procedure-related complications compared to computed tomography coronary angiography (C.T.C.A.) [62]. COVID-19 and myocardial infarction patients may require a prolonged hospital stay and multiple anticoagulants for severe symptoms [63]. Increased availability of C.T.C.A. was associated with a significantly shorter length of stay for patients with chest pain without increased adverse outcomes [64]. Panjer et al. demonstrated good diagnostic accuracy of dynamic cadmium-zinc-telluride single-photon emission tomography (CZT-SPECT) in coronary artery disease [65].

Cardiac Complications of COVID-19

A. Myocarditis:

One of the cardiac consequences in individuals infected with SARS-CoV-2 and its accompanying systemic inflammation is myocarditis. Regardless of the concurrent viral infection like COVID-19, patients with myocarditis often present with chest discomfort, exhaustion, and dyspnea. Other symptoms may include myalgia, diarrhea, nausea, vomiting, and headaches [66]. Due to lacking of using proper diagnostic tools in the previous studies, the prevalence of myocarditis among COVID-19 patients remains unknown. Yet, myocarditis is claimed to have been a factor in up to 7% of COVID-19-related deaths [67].

B. Arrhythmia:

Cardiac arrhythmias were recognized as one of the potential complications in COVID-19 patients. Indeed, arrhythmia was observed in 7.3% of the total 137 patients in an observational study examining the clinical characteristics of COVID-19 patients in Hubei, China [68]. In addition, Wang et al. found that approximately 44.4% of COVID-19 patients, who were admitted to an intensive care unit, had arrhythmia [21]. After acute COVID-19 infection recovery, researchers have reported a rise in arrhythmic events, and the long-term frequency is still under study. According to recent studies, atrial arrhythmias and bradyarrhythmia, in particular, had an incidence of 13% and 12.8%, respectively, in the acute setting of COVID-19. Furthermore, ventricular arrhythmia was recorded in 5.9% of patients, whereas the prevalence of atrioventricular block was 8.6% [69, 70]. Numerous pathophysiological mechanisms underlie the occurrence of cardiac arrhythmias: 1- Direct injury to cardiomyocytes altering the electrical conduction; 2- Infection of the pericardium causing massive edema; 3- Ischemia from microvascular disease; 4- Re-entrant arrhythmias due to myocardial fibrosis or scars; and 5- Proinflammatory cytokines predisposing to arrhythmogenicity [71, 72].

C. Hypotension

Hypotension following COVID-19 is a serious complication, albeit manifesting less frequently in hypertensive individuals. Frail elderly patients with hypertension have a greater mortality risk and are more susceptible to develop cognitive fragility [73,74]. Koudelka M. et al. conducted a recent case study for five hypertensive elderly patients who were under medications [73]. The study participants shared comparable clinical features, with an age range of 65–85 years, and two out of the five were male. Following the COVID-19 infection, their B.P. was checked in the office, and all patients had well-controlled blood pressure. However, the patients were monitored by A.B.P.M. at home, where they detected multiple episodes of hypotension. **(Figure. 4)** shows the A.B.P.M. home readings for one of the subjects in the study before and after COVID-19 infection, indicating the need for medication adjustments [73]. All five patients showed the same pattern of this phenomenon. Regardless of factors that could contribute to lowering blood pressure, it is crucial to keep monitoring the patient, not only with office measurements. Additional studies and research are needed to elucidate the potential fluctuations in blood pressure readings in this population, as current understanding remains limited.

D. Sudden cardiac death

Sudden cardiac death (S.C.D.) constitutes a significant concern in the context of COVID-19 infection [75, 76]. While the available data suggests a potential association, direct evidence linking cardiac death to COVID-19 remains insufficient. Both community and hospital settings have shown increased S.C.D. incidence [77]. The mechanism of S.C.D. may involve many factors **(Table 1)**. The most prevalent mechanism involved still needs to be determined due to a lack of evidence. According to a study conducted by Yang C et al which included 187 patients, 37.50% (6 of 16) had elevated TnT levels without underlying CVD, while 69.44% (25 of 36) had high TnT levels with underlying CVD. Conversely, 7.62% (8 of 105) of patients with normal TnT levels died in the hospital; therefore, patients with underlying CVD and high TnT levels had the highest mortality (69.44%) and shortest survival times. **(Figure 5)** [78].

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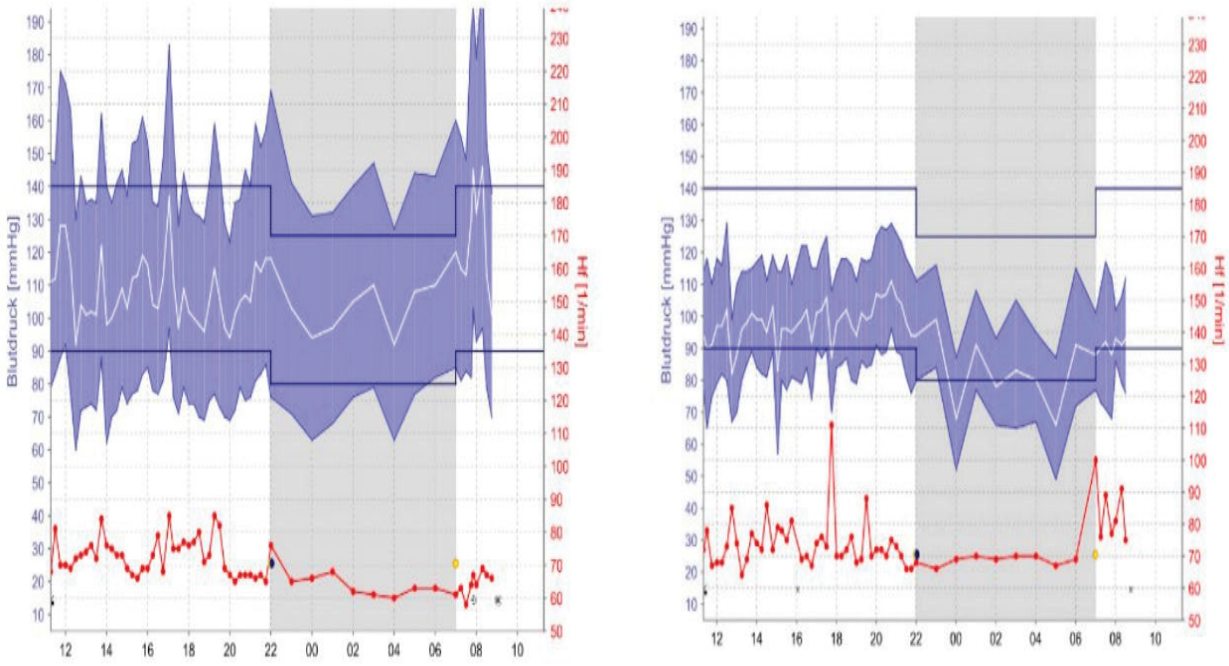

Figure 4: blood pressure (B.P.) values of Patient No.2 before and after COVID-19 [73].

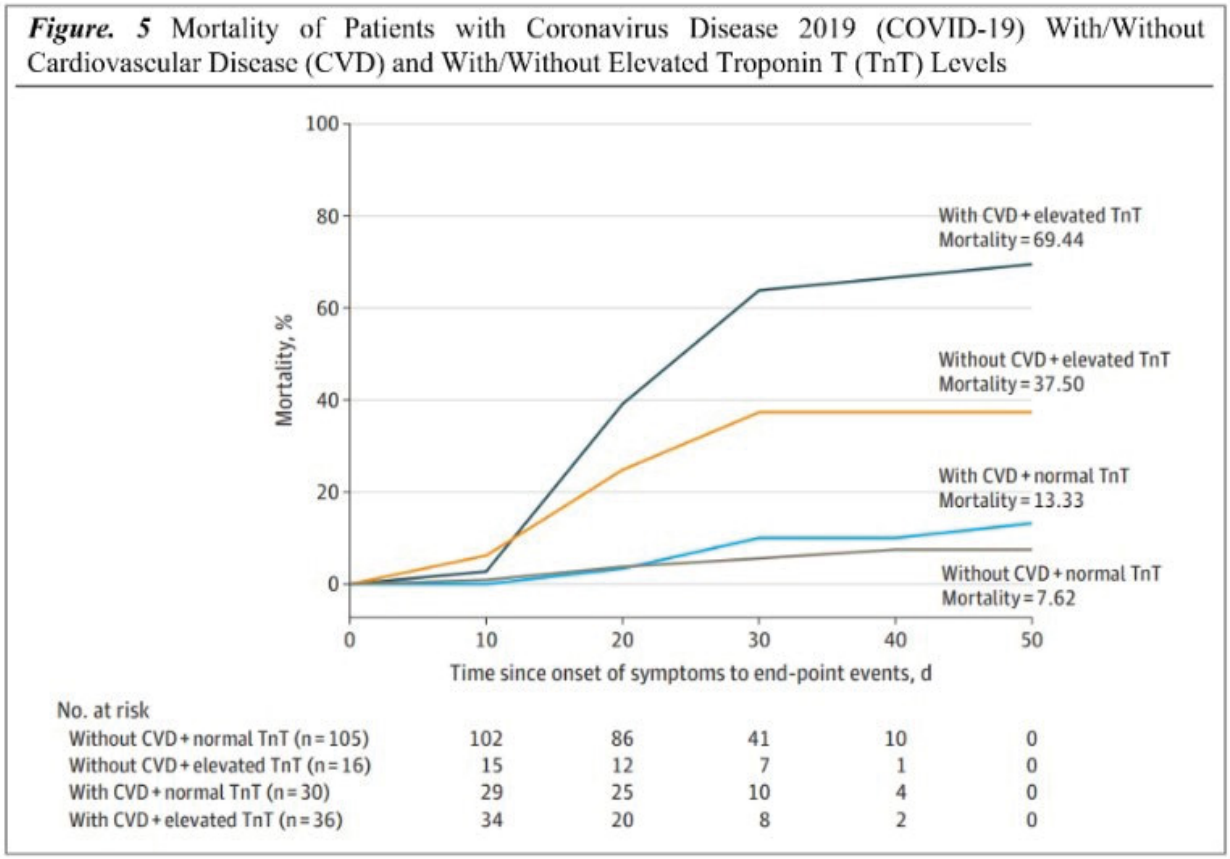

Figure 5: Coronavirus disease 2019 (COVID-19) mortality rates with/without cardiovascular disease and with/without elevated Troponin T levels [78].

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Table 1
Proposed causes of sudden cardiac death in COVID-19.

A	Acute Myocarditis including stress induce Cardiomyopathy
B	Post myocarditis sequel
C	Acute coronary syndrome
D	Hypoxia
E	High-grade systemic inflammatory state
F	Coagulation disorder
1	Pulmonary thromboembolism
2	Coronary thrombosis
3	Stroke
G	Cardiac tamponade
H	Electrolyte imbalance
I	Underlying genetic predisposition
J	Arrhythmiogenesis
1	Drug induce
2	Uncovering of underlying channelopathies
3	Direct arrhythmogenesis by COVID-19

Table 1: A list of presumed causes of sudden cardiac death in COVID-19 [77].

Long-term cardiovascular outcomes of COVID-19

Multiple studies have shown that individuals who have recovered from COVID-19 are at high risk of cardiovascular disease and persisting symptoms. According to a report by Al-Aly Z from June 2021, SARS-CoV-2 post-acute sequelae actively affect both the pulmonary and extrapulmonary components of the cardiovascular system[79]. Nearly a third of hospitalized patients following acute COVID-19 were readmitted, and more than one in ten passed away after discharge [80]. COVID-19 patients had substantially higher rates of respiratory illness, diabetes, and cardiovascular disease (CVD), with 770 diagnoses per 1000 person-years. Those under the age of 70 and individuals from ethnic minority backgrounds showed a higher likelihood towards increased risk. Additionally, in a study led by Huang C et al. with a sample size of 1733 COVID-19 patients, it was identified that the primary issues faced by COVID-19 survivors included weakness of the muscles, sleep disturbances, as well as anxiety and feelings of sadness. Throughout their hospitalization, patients with greater illness severity exhibited abnormal chest imaging findings and significantly reduced pulmonary diffusion capacities compared to less critically ill patients [81].

Furthermore, Carfì A et al. examined 143 individuals for COVID-19 symptoms and found that only 18 patients had no COVID-19-related symptoms. Interestingly, 44.1% of patients experienced a decline in quality of life, with many reporting joint discomfort, chest pain, fatigue, and dyspnea [82]. A research study conducted in May 2021 by Daugherty SE indicates that 14% of adults aged 65 and older developed at least one new clinical sequela following the acute phase of SARS-CoV-2 infection, requiring medical attention. The data revealed a statistically significant increase of 4.95% when compared to the group data of 2020 [83]. The medical conditions examined in the study included chronic respiratory failure, cardiac arrhythmia, hypercoagulability, encephalopathy, peripheral neuropathy, amnesia, diabetes, abnormal liver test results, myocarditis, anxiety, and fatigue. On the other hand, another study included 5,859,411 VHA users without COVID-19 infection and 153,760 US veterans found that those who acquired the virus had higher incidence burdens and risk factors over 12 months as shown in **Figure 6** [84].

COVID-19 can induce an exaggerated activation of the sympathetic nervous system, thereby fostering the development of adverse outcomes such as a cytokine storm, hypercoagulopathy, and inflammation. Even after recovering from COVID-19, these pathways could permanently harm the cardiovascular or respiratory systems. Consequently, the long-term effects of COVID-19, including conditions like congestive heart failure and impaired lung function, is expected to raise the risk of cardiovascular or cerebrovascular disease among those who have recovered from the virus. The National Healthcare Databases (V.H.A.) of the U.S. Department of Veterans Affairs (V.H.A.) provide evidence that hospitalized and non-hospitalized survivors of acute COVID-19 have a high risk of developing CVD and a considerable disease burden within one-year post-infection. This insight is based on data collected from 48 healthcare organizations (HCOs) in the U.S. Collaborative Network (84).

Ultimately, dysrhythmias, pericardial or inflammatory heart disease, and cerebrovascular disorders were observed to be more frequently present in cases of CVD with COVID-19 compared to the current control group. Furthermore, based on the Kaplan-Meier curve in Figure 7, the mortality rate in the COVID-19 cohort surpassed that of the control group. Individuals not hospitalized during the acute phase may progressively face increasing risks and limitations related to cardiovascular conditions such as ischemic heart disease, atrial fibrillation and flutter, tachycardia, myocardial infarction, pulmonary embolism, and thromboembolic disorders [85]. TriNetX Research Network has reported that COVID-19 survivors were found to have a higher probability of developing cardiovascular problems compared to the control group during a 12-month follow-up period (Wang W, Long-term cardiovascular outcomes in COVID-19 survivors among non-vaccinated population: A retrospective cohort study from the TriNetX US collaborative networks. , 2022 N.O.V.) as described below. Higher risks of cerebrovascular complications, such as stroke (H.R. = 1.52 [1.43-1.62]) and T.I.A. (H.R. = 1.503 [1.353-1.670]) were observed in the COVID-19 survivors [85]. Atrial fibrillation and flutter (H.R. = 2.407 [2.296-2.523]), tachycardia (H.R. = 1.682 [1.626-1.740]), bradycardia (H.R. = 1.599 [1.521-1.681]), and ventricular arrhythmias (H.R. = 1.600 [1.535-1.668]) were also associated with elevated risks. In particular, myocarditis (H.R. = 4.406 [2.890-6.716]) and pericarditis (H.R. = 1.621 [1.452-1.810]) were more common among COVID-19

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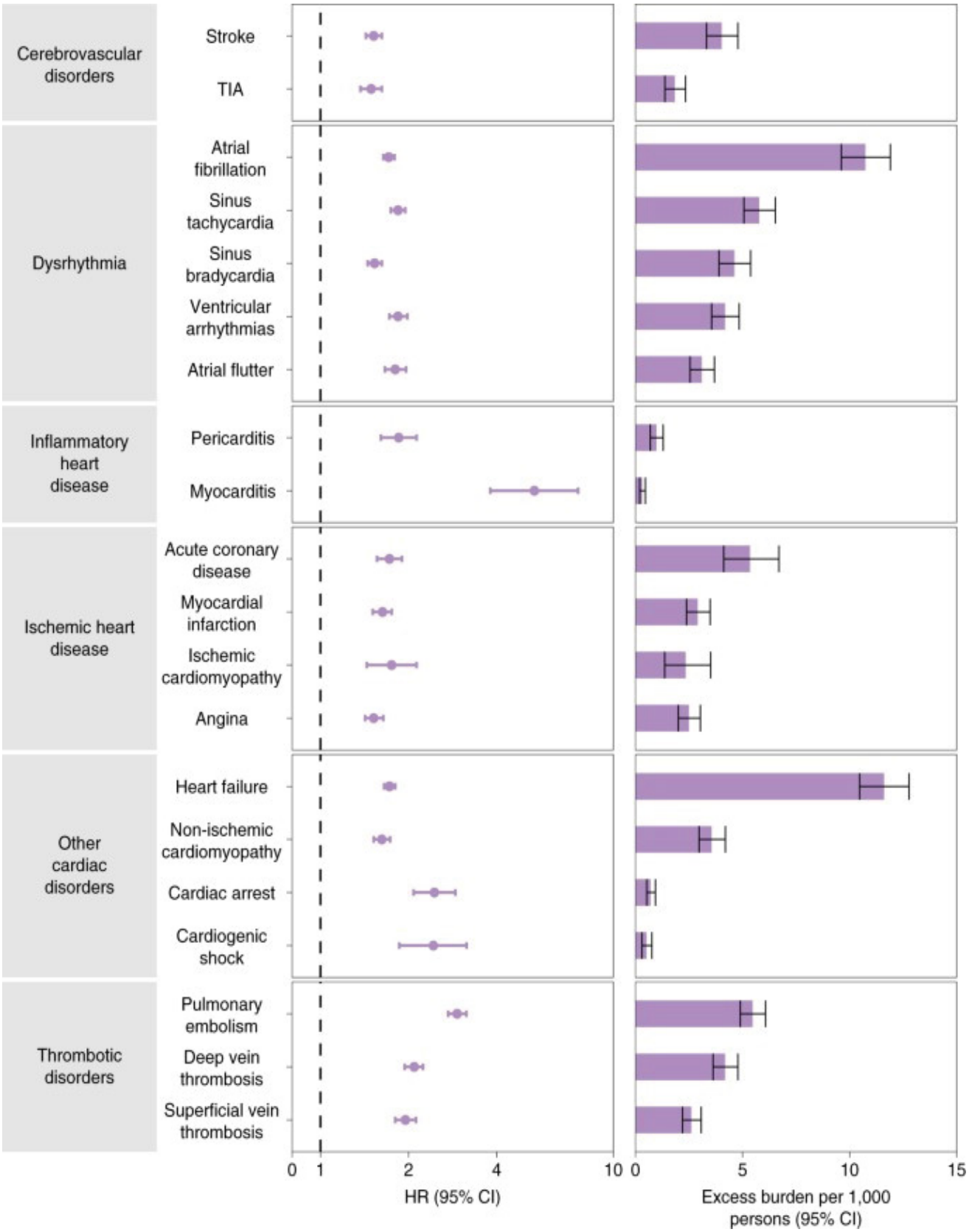

Figure 6: Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes compared with the contemporary control cohort [84].

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survivors. Ischemic heart disease (I.H.D.), including angina (H.R. = 1.707 [1.545-1.885]), acute coronary syndrome (H.R. = 2.048 [1.752-2.393]), myocardial infarction (H.R. = 1.979 [1.831-2.138]), and ischemic cardiomyopathy (H.R. = 2.811 [2.477-3.190]). The mortality rate in the COVID-19 group was higher than in the control group (H.R. = 1.604 [1.510–1.703]).

Long-Term Cardiovascular Results with Covid-19 Pearls

1. The management of post-COVID syndrome requires comprehensive methods instead of organ- or disease-specific treatments.
2. The elevated risk was particularly pronounced among those under the age of 70 and individuals belonging to ethnic minority groups.
3. Long-term recovery intervention primarily target those with significantly reduced pulmonary diffusion capabilities and aberrant chest imaging symptoms.
4. Many individuals reported experiencing joint pain, chest pain, fatigue, and dyspnoea.
5. Various cardiovascular diseases such as cerebrovascular disorders, dysrhythmias, pericardial or heart inflammation, ischemic heart disease, atrial fibrillation and flutter, tachycardia, myocardial infarction, pulmonary embolism, and thromboembolic diseases were documented.
6. Healthcare planning should account for the increased likelihood of post-event complications that may arise.
7. These results imply that cardiovascular health and illness should be part of care pathways, even for individuals who do not need to be hospitalized.
8. A concerted, long-term, worldwide response plan will be necessary to meet the difficulties of COVID-19.

Genetics of COVID19-induced heart complications

Molecular biology and genetics play a role in every physiological function or pathological condition. Many recent publications have focused on elucidating the molecular genetic underpinnings of cardiovascular complications in individuals affected by COVID-19. Besides its impact on the respiratory system, the COVID-19 pandemic also has detrimental effects on the cardiovascular system (86). Cardiovascular disorders can be caused by atypical gene expression in vascular endothelial cells and cardiomyocytes, which are crucial in regulating heart function. Numerous genes were found to be differentially expressed in cardiomyocytes and vascular endothelial cells of COVID-19-infected heart patients as reported by Xu et al, including MALAT1, CD36, LARGE1, RYR2, PLCG2 (in cardiomyocytes), MALAT1, ID1, ID3, MT-CO1 and EGFL7 (in vascular endothelial cells) [87]. These genes regulate many vital functions in these cardiomyocytes [88-96, 97-103].

The discovery of these novel contributors of COVID-19 mediated cardiac pathophysiology may help identify novel therapeutic targets. Luo et al. recalled HSP90AA1, HSPA9, and SRSF1 regulated by Mir-16-5p and KLF9 transcription factors as hub genes involved in the co- pathogenesis of

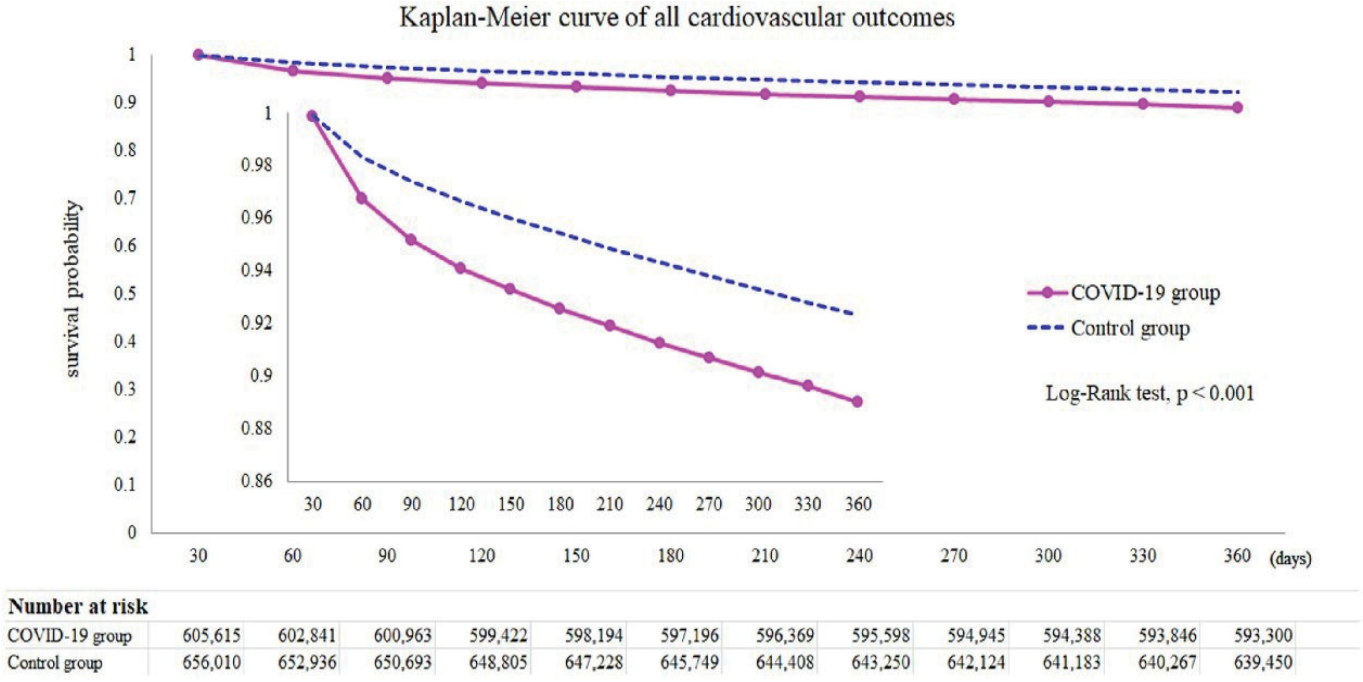

Figure 7: Cardiovascular outcomes survival probability in COVID-19 survivors among control group [85].

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ischemic cardiomyopathy (I.C.M.) and COVID-19, and they demonstrated that the co-pathogenesis of I.C.M. and COVID-19 may be associated to angiogenesis [104]. It was hypothesized that vindesine and ON-01910 may act as possible therapeutic agents. The results of their research will add to a more in-depth knowledge of the correlation between I.C.M. and COVID-19. In a similar study carried out by Qi et al, V.E.G.F.A, FOXO1, CXCR4, and SMAD4 were found to be upregulated hub genes in COVID19-induced cardiomyopathy, whereas downregulated hub genes included K.R.A.S. and T.X.N. [105]. Liu et al. have successfully identified some hub genes in ischemic stroke induced by COVID-19. The identified gene list included IL1R2 (interleukin 1 receptor type 2), NCR3 (natural cytotoxicity triggering receptor 3), OLR1 (oxidized low-density lipoprotein receptor 1), IL18R1 (interleukin 18 receptor 1), and JAK2 (Janus kinase 2). Among these genes, JAK2 is a potential biomarker and could be used to develop novel therapeutics. [106].

Recent reports have discussed the involvement of specific genes and micro-RNAs in COVID-19-inducing heart failure (H.F.). Gao and co-authors have demonstrated upregulation of OAS1, OAS2, OAS3, and O.A.S.L. genes in cardiomyocytes from heart failure patients infected with SARS-CoV-2[107]. These genes belong to the OAS-gene family, contributing to antiviral and innate immune responses [108]. The authors found differential expression of micro-RNAs associated with these genes, including hsa- miR-15a-3p, hsa-miR-23a-5p, hsa-miR-26b-5p, hsa-miR-186-3p, hsa-miR-4433a-3p, hsa-miR-548aq-5p, hsa-miR-548d-5p, hsa-miR-576-5p, hsa-miR-580-3p, and hsa-miR-6850-5p [107]. Furthermore, Estradiol was identified to be the common molecule that regulates the four O.A.S. genes. Estradiol's ability to treat severe heart failure is mediated by the classical estrogen receptor beta (E.R.) in the heart [109]. In pulmonary hypertension, estradiol protects right ventricular function via BMPR2 and apelin, according to Frump et al. [110].

These results demonstrate that Estradiol has a cardioprotective effect, even on the COVID-19 heart, and therefore can help treat patients infected with COVID-19 suffering from heart failure and other cardiac diseases COVID-19. New insights into the effect of the COVID-19 genes on cardiac stem cells have revealed some fascinating findings. Liu et al. have reported that COVID-19 genes (Nsp6, Nsp8, and M) severely damage human pluripotent stem cell-derived cardiomyocytes, emphasizing the importance of ATP homeostasis in cardiomyocyte mortality and functional abnormalities caused by these SARS-CoV-2 genes [111]. They found that hESC-CMs, overexpression of SARS-CoV-2 viral genes promoted cell death/apoptosis-associated gene expression and upregulated Nsp6, Nsp8, and M hESC-CM proteins caused cardiac fibrosis, arrhythmia, inflammation, and heart failure. These findings show that Nsp6, Nsp8, and M may reduce cellular ATP generation and trigger apoptosis in hPSC-CMs. They reported that FDA-approved antiparasitic and antiemetic drugs ivermectin and meclizine can alleviate this effect. Despite its main application in treating parasite diseases, ivermectin has been shown to preserve mitochondrial ATP in C.M.s by upregulating Cox6a2 transcription in HL-1 CMs [112].

However, meclizine promotes CM glycolysis [113], which increases ATP production, reduces ATP depletion, and protects mitochondrial function [114-115]. The abovementioned findings suggest that ivermectin and meclizine may boost ATP levels to reduce SARS-CoV-2-induced cell death in hPSC- CMs, revealing that ivermectin and meclizine can help treat cardiac patients infected with COVID-19. Similarly, Wu et al in very recent findings have elucidated the molecular biomarkers and genetic pathogenesis of COVID-19-induced ischemic heart failure [116]. Moreover, all these recent findings show how deep insights into COVID-19-induced cardiac diseases using state-of-the-art molecular and cell biological techniques, along with other multidisciplinary approaches, and their application in multi-system-based evaluations of COVID-19 patients, can help unravel associated pathogenesis and help find novel potential therapeutic agents for patient-tailored treatment of COVID-19-associated cardiovascular diseases that is a major focus of personalized medicine in 21st century [43, 86, 103, 116,117].

Conclusions

Ultimately, the relationship between COVID-19 and CV risk is complex and multifaceted. While COVID-19 primarily affects the respiratory system, it can also significantly affect CV health. Emerging evidence suggests that COVID-19 survivors may experience long-term CV effects. These include persistent myocardial inflammation, myocardial fibrosis, cardiac dysfunction, and an increased risk of future CV events. Moreover, recent reports show the involvement of a large number of genomic alterations, microRNAs, and novel viral as well as host proteins in different types of cardiocytes, which has helped identify some novel drug targets to treat COVID-19-related cardiovascular complications. Long-term follow-up studies are ongoing and demanded to understand these underlying effects better, to identify novel molecular biomarkers of different cardiovascular diseases, and to find novel therapeutic agents for personalized treatment of resulting clinical complications.

Competing Interest

The authors have declared that no competing interests exist.

Scope Statement

Letter to Reviewers Dear respected: COVID-19 interacts

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with and influences the cardiovascular system. COVID19-associated cardiovascular (CV) complications are common, resulting in high acute phase mortality and a large number of morbidities in the chronic phase, thus severely impacting patients' quality of life and health outcomes. Nevertheless, clinical, cellular and molecular biological factors underlying pathophysiology of cardiovascular complications associated with COVID-19 are poorly understood. This review investigates putative underlying clinical factors and cellular molecular biological mechanisms by which COVID-19 leads to acute CV complications, including state-of-the-art genomic sequencing-based findings, assessing Long-Term CV consequences of COVID-19, aiming to shed light on developing strategies for differential diagnosis, risk prognostic stratification, prevention and clinical management of CV sequel in COVID-19 patients. We found that the relationship between COVID-1.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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