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Review Article

LONG-TERM COVID-19 EFFECT TO ENDOTHELIAL DAMAGE TROUGH EXTRINSIC APOPTOSIS LED TO CARDIOVASCULAR DISEASE PROGRESSION: AN UPDATE REVIEW

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ABSTRACT

COVID-19 can involve persistence, sequelae, and other medical complications that last weeks to months after initial recovery; these prolonged symptoms called as long-term covid-19 effect. Symptoms, signs, or abnormal clinical parameters persisting two or more weeks after COVID-19 onset that do not return to a healthy baseline can potentially be long-term effects of the disease. SARS-CoV-2 affects the cardiovascular system and causes conditions such as myocarditis, arrhythmias, and myocardial injury. Vascular damage from COVID-19 has been affected directly by the SARS-CoV-2 virus infection and indirectly by systemic inflammatory cytokine storm. This damage can be long-lasting and lead to various cardiovascular complications. Fas ligand (FasL)-Fas complex is a death factor that induces cell apoptosis. Fas and FasL have been detected in the endothelial wall, and it has been proposed that Fas-mediated apoptosis has a role in physiological and pathological cell turnover in the endothelial wall. High concentrations of inflammatory cytokines, such as cytokines storm induced by SARS-CoV-2 infection, are thought to increase the expression of FasL, which leads to an increase in the regulation of extrinsic apoptosis in endothelial cells leading to endothelial damage. This article summarises the current understanding of the long-term covid-19 effect on endothelial damage through extrinsic apoptosis Fas-FasL complex.

Keywords: COVID-19, Long-term effect, Endothelial damage

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INTRODUCTION

The COVID-19 pandemic, caused by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing and globally occurring pandemic with unprecedented morbidity and mortality. After recovering from COVID-19, most patients' health will gradually improve within days or weeks and make a full recovery [1]. However, 40% of these patients still experience some unexpected side effects from COVID-19 remaining in their bodies even though they have recovered from COVID-19 for more than four weeks, this condition is referred to as post-COVID-19 condition, long-term effects of COVID-19, or chronic COVID-19 [2, 3]. Post-COVID-19 conditions are defined as any new, returning, or ongoing health problems that survivors may experience four weeks or more after being negative from the infection, these conditions are sometimes experienced by survivors who are at a mild level of Covid-19 severity [4]. Several factors determine the emergence of this post-Covid condition, such as the severity of COVID-19 infection and co-morbidities that increase the damage rate of COVID-19 infection. The COVID-19 disease, which initially only attacks the respiratory system, has now been recognized as a multi-organ disease [5]. Post-COVID-19 syndrome is found in various organ systems, including endothelial damage and damage to other organ systems such as lung organs, coagulation disorders in hematology, nerve, kidney, endocrine and gastrointestinal damage (fig. 1) [6].

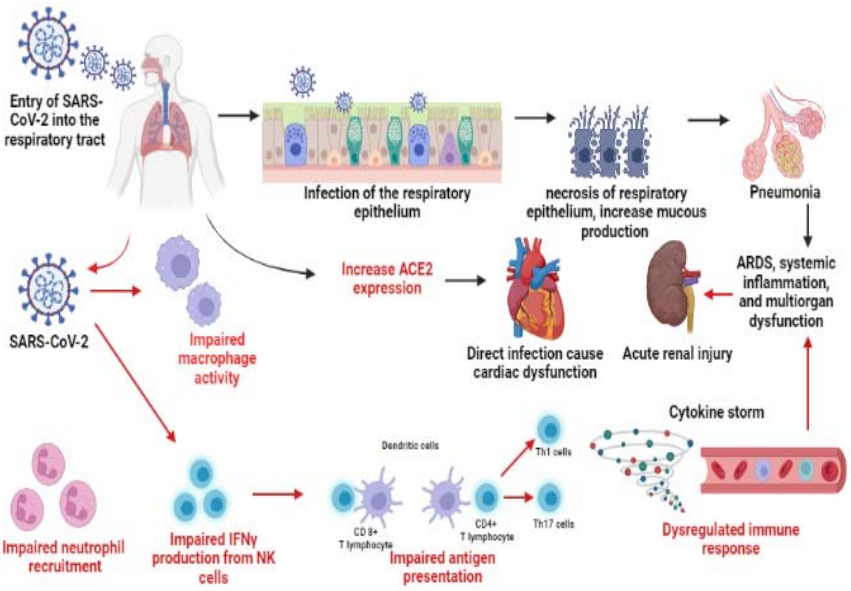

Fig. 1: Overview of SARS-CoV-2 pathogenesis mechanism (created with BioRender.com)

The main pathophysiological process in severe and prolonged COVID-19 involves endothelial dysfunction [7, 8]. Systemic inflammation caused by viral infection can induce apoptosis in endothelial cells, resulting in endothelial dysfunction [9–11]. According to a study published in the European Society of Cardiology (ESC), COVID-19 infection can cause endothelial damage by activating inflammatory factors, leukocyte infiltration, thrombosis, platelet aggregation, increased production of reactive oxygen species (ROS), and increased apoptosis [12, 13]. This oxidative stress can induce excessive Fas/Fas ligand expression, thereby increasing apoptosis in endothelial cells [14] A study proved that under oxidative stress conditions, increased concentrations of Fas/Fas ligand [15, 16]. In addition, a study by [17] showed that high Fas levels correlated with an increased risk of cardiovascular disease. Induction of apoptosis as a systemic inflammatory response plays a vital role in endothelial damage; therefore, knowing the correlation between biomarkers that induce apoptosis after systemic inflammation is important to determine the risk of future cardiovascular events [18, 19]. Until now, there has been much research on the relationship between COVID-19 infection and its long-term effects. However, research on the relationship between Fas/FasL markers in COVID-19 survivors remains very limited. Knowing the role of Fas/FasL relation with currently available markers of systemic inflammation can be helpful for COVID-19 survivors regarding the risk of endothelial damage, leading to an increased risk of cardiovascular disease.

MATERIALS AND METHODS

This article was compiled by conducting a literature search using the keywords “covid-19”, “long term effect”, and “endothelial damage”. The literature must fulfill the inclusion criteria, namely, the maximum literature publications from the last 10 y in English and discuss the long-term effect of COVID-19 specially the long-term effect of COVID-19 to endothelial cell damage. The search results were re-sorted according to the inclusion criteria. 10 publications met the inclusion criteria. The number of publications excluded was 30 publications because they did not meet the requirements.

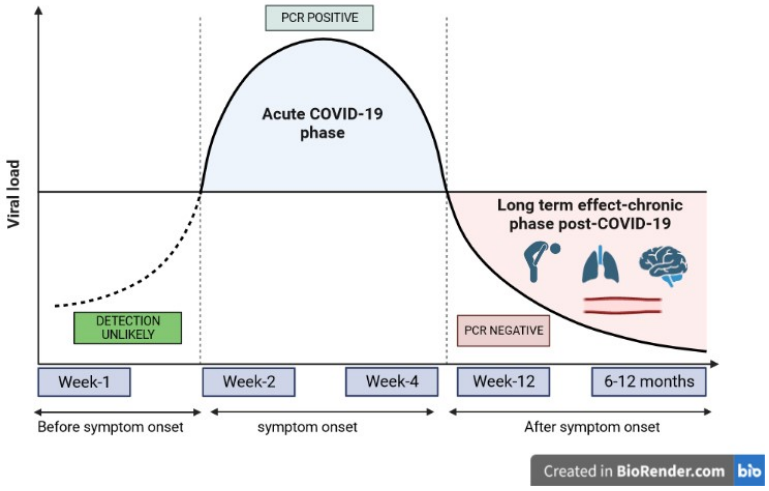

Fig. 2: Post-acute COVID-19 cycle affected several prominent organs in humans (created with BioRender.com)

RESULTS

Long-term effects of COVID-19

Mild or moderate COVID-19 illness lasts about two weeks in most people [20, 21]. However, some patients suffer persistent health problems even after recovering from the acute phase of their disease [22–24]. Under this circumstance, there is no viable coronavirus left, and when tested, the person reports a negative result for coronavirus. This condition is called post-COVID syndrome, post-acute COVID-19, or long-term COVID by the National Institutes of Health [25]. People who suffer from this are called "long haulers". According to the most recent research, the condition is further break down into two groups: (1) subacute or ongoing symptomatic COVID-19, which includes symptoms and abnormalities that appear 4 to 12 w after acute COVID-19, and (2) chronic or post-COVID-19 syndromes, which includes symptoms and abnormalities that last or appear longer than 12 w after acute COVID-19 and are not linked to an alternative diagnosis (fig. 2) [26–28]. According to the Centers for Disease Control and Prevention (CDC), the most prevalent long-term symptoms include exhaustion, shortness of breath, coughing, joint pain, and chest pain. Other issues include cognitive issues, difficulties concentrating, sadness, muscle aches, migraines, a quick heartbeat, and sporadic fever [2, 29, 30]. In addition, the long-term effects of COVID-19 infection are also felt by patients who have mild symptoms or even have no symptoms, the severity of the long-term effects of COVID-19 infection is also found to be higher in adult female patients [31, 32].

Manifestation of COVID-19 long-term effects can be varied, among survivors. A meta-analysis study stated that there are 50 manifestations of covid-19 infection long-term effects [33]. In a three-month follow-up study of COVID-19 survivors, pulmonary radiological abnormalities and functional impairments were detected in 71% and 25% of participants, although only less than 10% had severe pneumonia [34]. Another study has also observed reduced lung diffusion capacity that correlated with radiological abnormalities in 42% of COVID-19 survivors at three-month post-hospital discharges, regardless of initial disease severity [35]. Even six months after symptom onset, lung radiological abnormalities associated with persistent symptoms were still present in about half of COVID-19 survivors [36]. Many other studies have found radiological evidence of lung fibrosis lasting up to six months after hospital discharge among COVID-19 survivors, which correlates with initial disease severity. A separate study discovered that symptoms of long COVID persist even when pulmonary radiological and functional examinations improve [37].

Long COVID may involve other pathophysiology besides pulmonary lesions, such as lasting neurological complications [38, 39]. For instance, at three-month post-discharge, brain structural and metabolic abnormalities were reported among COVID-19 survivors, which correlated with persistent neurological symptoms such as memory loss, anosmia, and fatigue [40]. This finding is concerning because most participants had mild COVID-19 at baseline, implying that even mild COVID-19 can have long-term effects on the brain. Another study found 43 cases of severe brain diseases caused by COVID-19 (e. g., encephalopathies, delirium, hemorrhage, and stroke) [41]. There is also evidence of cardiac injury in long COVID [42]. A radiological study of 100 COVID-19 discharged patients discovered cardiac abnormalities and myocardial inflammation in 78% and 60% of participants, respectively, unrelated to initial COVID-19 severity [43]. In another study of 26 college athletes with asymptomatic SARS-CoV-2 infection, 46% of them also presented with myocardial

inflammation [44]. Even at three-month post-hospital discharge, radiological abnormalities of ventricular remodeling were still evident in 29% of 79 COVID-19 survivors [45]. Cardiac symptoms such as chest pain, heart palpitations, and tachycardia commonly persist among COVID-19 survivors for up to six months [46–49]. Finally, long COVID may be associated with long-term organ damage. According to one preprint report, young adults, who are mostly free of risk factors for severe COVID-19, frequently develop long COVID with multi-organ impairment after a four-month follow-up. In particular, 66% of survivors had at least one radiological abnormality in the lungs, heart, liver, pancreas, kidneys, or spleen [48]. Similarly, another study involving modern-ate-to-severe COVID-19 patients has shown radiological evidence of lung, heart, brain, liver, and kidney impairments persisting f discharged COVID-19 patients found increased risks of new events of respiratory, diabetes, and cardiovascular diseases occurring within the subsequent 140 d compared to controls [50]. Therefore, future research on long COVID should consider possible extrapulmonary or multi-organ involvement that may be less obvious. Or at least 2–3 mo after hospital discharge [51]. Furthermore, a study of over 40,000 discharged COVID-19 patients found increased risks of new events of respiratory, diabetes, and cardiovascular diseases occurring within the subsequent 140 d compared to controls [50].

Pathophysiology of COVID-19 infection

The inflammatory response mediated by COVID-19 infection is divided into primary and secondary responses [52, 53]. Like other CoVs, SARS-CoV-2 relies on the angiotensin-converting enzyme-2 (ACE-2) receptor to enter the target cells [54–56]. Studies showed that ACE-2 is mainly concentrated on the surface of endothelial cells (ECs) and mucosal epithelial cells, such as the nasal and oral cavities, vascular endothelial cells, the lungs, and the intestinal tract [57, 58]. The primary inflammatory response usually occurs following viral infection before the appearance of antibodies [59]. Therefore, the response is thought to be driven by active viral replication, which is accompanied by virus-mediated downregulation and shedding of ACE-2; once the virus enters the ECs, it begins to translate, replicate, and directly induce endothelial cell injury and apoptosis [60–62]. The secondary inflammatory response begins with adaptive immunity and antibody neutralization. Furthermore, it has been reported that after acute infection, myocardial damage is exacerbated in patients with increased inflammatory activity, platelet activation, increased thromboxane synthesis, and impaired fibrinolytic function [63–65]. Furthermore, in COVID-19 patients, there is a cellular inflammatory storm induced by an imbalance in T-helper (Th1) and Th2 responses, and levels of inflammatory mediators such as interleukin (IL)-4, IL-10, and IL-6 are elevated [66, 67]. Plasma levels of IL-6 and IL-10 were higher in COVID-19 patients than in controls in research involving 123 patients. Furthermore, CD4+and CD8+T lymphocytes were decreased in individuals with severe COVID-19 infection compared to patients with mild infection [68, 69]. In these patients, inflammatory factors and cellular inflammatory storms have been linked to the heart failure process. C-reactive protein (CRP) levels in COVID-19 patients are elevated, indicating inflammation. This data from COVID-19 participants demonstrates that cytokine storms are closely connected to illness severity and associated with inflammatory heart disorders. In patients with severe COVID-19 infection, there is an increase in plasma concentrations of pro-inflammatory factors, such as IL-1β, interferon-γ, monocyte chemotactic protein-1, interferon-inducible protein-10, and Th1 activation, tumor necrosis factor-α (TNF-α), and granulocyte colony-stimulating factor (G-CSF) [70–72]. About 12% of COVID-19 patients are found to have cardiac muscle injuries. Aside from infection with the SARS-CoV-2 virus, other comorbid diseases and risk factors such as increasing age, gender, obesity, and cancer can all increase the risk of cardiovascular disease. The SARS-CoV-2 virus can attach to the angiotensin-converting enzyme 2 (ACE2) receptor in heart tissue, causing inflammation of the heart's myocardial muscle [73, 74]. In COVID-19 patients, however, cardiovascular disorders are common indirectly due to the systemic inflammatory response and immune system dysfunction during disease development. COVID-19 manifestation can cause various complications related to cardiovascular disease, either directly or indirectly [75, 76].

COVID-19 infection induces extrinsic apoptosis leading to endothelial cell damage

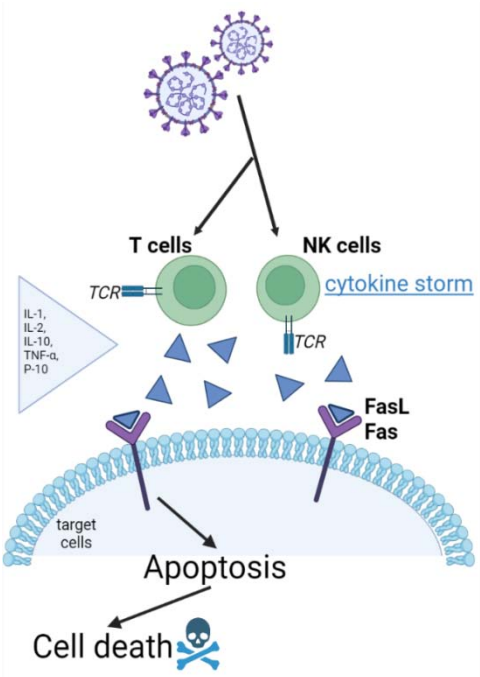

Fig. 3: SARS-CoV-2 induces Fas-FasL mediated cell apoptosis (created with BioRender.com)

Endothelial dysfunction is characterized by a decrease in vasodilation, a proinflammatory state, and a prothrombotic state. It has been linked to nearly every type of cardiovascular disease, including hypertension, coronary artery disease, chronic heart failure, peripheral vascular disease, diabetes, chronic renal failure, and severe viral infections. Free radicals can disrupt the NO balance, cause endothelial damage, and make the endothelium overly porous, allowing toxins to penetrate human tissues [77]. During the inflammatory process induced by different risk factors such as hypertension, oxidized LDL (oxLDL), and diabetes, there is an increase in the production of interleukin-1 (IL-1), interleukin-6 (IL-6), TNF-α and C-reactive protein (CRP) that generate the endothelial proinflammatory phenotype characterized by an increase in E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) expression [78, 79]. Some studies suggest that Long-COVID-19 symptoms may be due to persistent endothelial dysfunction [80]. In fact, the SARS-CoV-2 infection of endothelial cells at vascular smooth muscle cells (VSMC) is associated with changes in cell morphology and endothelial cell apoptosis that could persist several weeks after the acute infection [81]. Besides direct infection, the presence of inflammatory cytokines as an immune response to infection, such as IFNγ, IL-1β, or IFNα, can also increase cell death. *In vitro* studies showed that exposure to pro-inflammatory cytokines in VSMC cells significantly increased apoptosis and cell death [82] Cell apoptosis is induced by intrinsic and extrinsic factors; in this case, extrinsic factors play a significant role in cell death. Fas, one of the main death receptors of the apoptosis extrinsic pathway, activates apoptosis when binding with its ligand. Then, a death signal is generated that will activate caspase-8 and then will activate caspase-3 leading to cellular damage by extrinsic apoptosis (fig. 3) [83] Fas is ubiquitously expressed. In contrast, expression of Fas ligand (FasL), is usually restricted to inflammatory cells (T cells, B cells, and macrophages) and tissues that routinely encounter inflammatory cells. Another study from 43 Caucasian COVID-19 patients showed an increase of Fas in circulating CD4 and CD8 T cells [84]. Expression of Fas and FasL has been detected in normal and diseased vessel walls, and it has been proposed that Fas-mediated apoptosis in endothelial cells

contributes to atherogenesis, atherosclerotic plaque instability, arteriopathy, and the acute inflammatory response to cytokines. Several recent studies have examined the role of Fas-mediated cell death in blood vessels. A study has demonstrated the susceptibility of vascular cells to Fas-mediated cell death and the expression of Fas regulatory components by vascular smooth muscle cells and endothelial cells. For example, it has been shown that VSMC undergoes apoptosis both *in vitro* and *in vivo* after infection with adenovirus [85]. In addition, oxidative stress, and inflammation due to viral infection can also increase the expression of FasL in T cells, thereby increasing the extrinsic induction of cell apoptosis [84]. Inflammatory activation and dysfunction of the endothelium are vital events in the development and pathophysiology of atherosclerosis and are associated with an elevated risk of cardiovascular events. There is great interest in further understanding the pathophysiologic mechanisms underlying endothelial dysfunction and atherosclerosis progression, and to identifying novel biomarkers and therapeutic strategies to prevent endothelial dysfunction, atherosclerosis, and risk of developing cardiovascular disease (CVD) and its complications.

Manifestation of long-term effects of covid-19 on cardiovascular disease

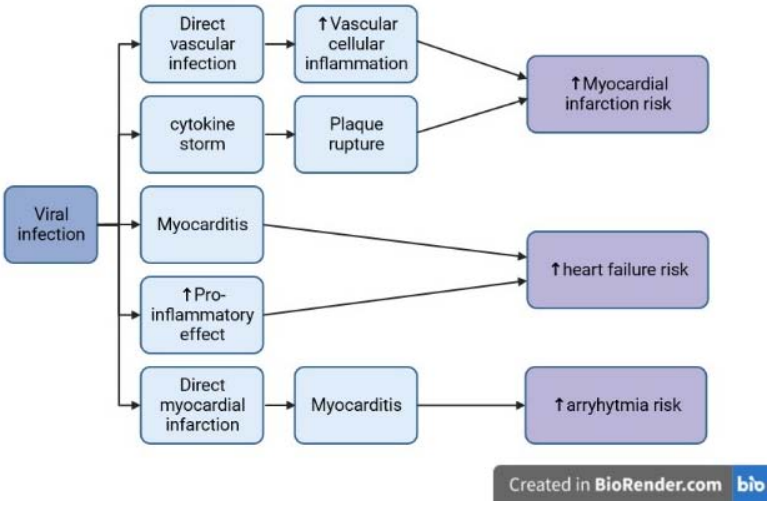

Fig. 4: Overview of COVID-19 effect on cardiovascular disease (created with BioRender.com)

Infection from Covid-19 can cause various disorders that lead to a decrease in the performance of the heart organ, coupled with risk factors such as age, hypertension, and diabetes (fig. 4). The effects of COVID-19 infection on the heart can be through various factors such as the presence of systemic inflammation which causes thromboembolism and acute coronary syndrome with a prevalence rate of 1% and a mortality rate of 23%, can be through direct infection which causes inflammation of the heart muscle with a prevalence reaching 36%. and mortality reaches 60% and is also due to side effects in the treatment of COVID-19 infection [75, 76]. This is also confirmed by a study conducted by [86] out of 650 post-covid patients admitted to the hospital around half of the total patients suffer from various symptoms of cardiovascular disease such as positive echo chest pain, shortness of breath, and angina.

Acute coronary syndrome

COVID-19 can affect the heart, causing damage to vital life-sustaining organs. Thus, cardiac damage is associated with morbidity and mortality. COVID-19 infection results in chronic damage/injury and acute cardiac injury to the cardiovascular system. Myocardial damage caused by COVID-19 infection increases the difficulty and complexity of treatment in this patient population. The risk of in-hospital death in patients with severe COVID-19 can be predicted by markers of myocardial injury, and is associated with older age, inflammatory response, and cardiovascular comorbidities. Information about the exact mechanism by which COVID-19 can cause myocardial injury is still unclear. However, the mechanism put forward by experts in the field regarding myocardial injury caused by direct infection with COVID-19 causes systemic inflammation, myocyte damage, myocardial interstitial fibrosis, coronary plaque destabilization, and hypoxia. In some patients suffering from COVID-19, it is known to increase cardiac troponin I (cTnI) levels [87]. It has been reported that 10 out of 138 (7.2%) patients with COVID-19 had acute myocardial injury during infection, and those admitted to the ICU tend to develop cardiac complications and show an increase in high-sensitivity troponin I level. cTnI was significantly increased in patients suffering from severe COVID-19 infection compared to individuals with moderate forms of the disease. The current study shows that 11.8% of deceased COVID-19 patients who initially did not have CVD subsequently developed appreciable cardiac damage, accompanied by elevated cTnI levels or cardiac arrest during their hospitalization. Further validating the above statistics, another study of 99 COVID-19 patients showed that 11% of patients who died had no previous chronic heart disease [88]. Worsening causes of death in COVID-19 patients with cardiovascular events (CVDs) have been suggested to be the sudden onset of inflammation, and the events and accumulation of lactic acid. In addition, patients who have been diagnosed with ACS and COVID-19 infection often display a poor prognosis. Nonetheless, these patients' lower cardiac function reserve may be due to myocardial necrosis or ischemia. In addition, patients with the pre-existing cardiovascular metabolic disease may be at increased risk for developing an acute state, along with accompanying comorbidities, and significantly affect the prognosis for COVID-19 patients. On the other hand, COVID-19 itself can exacerbate damage/injury to the heart. In fact, at least 8.0% of patients with COVID-19 suffer acute cardiac injury [89–91].

Cardiac arrhythmias

It is indicated that cardiac arrhythmias are associated with COVID-19 patients. Arrhythmias can be caused by electrolyte and hemodynamic disturbances due to high inflammatory stress in patients with COVID-19. Acute ventricular arrhythmias and myocarditis may appear as the first clinical manifestations. In addition, electrolyte imbalances caused by the interaction of COVID-19 with the Renin-angiotensin-aldosterone system (RAAS) can contribute to hypokalemia, resulting in an increased risk of arrhythmias [92]. One study demonstrated the presence of arrhythmias in 44 of 170 patients with cardiac injury in a retrospective cohort study involving 1284 patients with severe COVID-19 [93]. In addition, Guo *et al.* reported that malignant ventricular arrhythmias had a higher prevalence in the group with elevated troponin levels compared those with normal troponin levels [94].

Myocarditis

Myocarditis refers to heart muscle inflammation due to various communicable and non-communicable diseases. Viral etiology remains a significant cause of myocarditis in the United States and has been documented as a complication in patients infected with enteroviruses, including coxsackievirus, parvovirus B-19, H1N1 and members of the coronavirus group, including MERS. The precise pathophysiology of SARS-CoV-2-associated myocarditis is still elusive at this time; proposed mechanisms may include systemic immune system-mediated and direct viral infection-induced [95]. In immune-mediated myocarditis, the immune response is innate and may contribute to myocardial injury with sequelae of dilated cardiomyopathy. Autoimmune-mediated myocarditis may develop in response to the release of cryptic antigens from cardiac myocytes that are normally sequestered from the immune system after virus-mediated injury. There is also evidence to support the hypothesis that molecular mimicry involving epitopes shared among viral capsid proteins, cardiac myosin, and other unidentified proteins on the surface of cardiac myocytes stimulates autoimmune reactions. When viruses evade the innate immune system, they replicate and manufacture viral proteins that cause direct myocardial injury by promoting cellular apoptosis and necrosis ([96]. SARS-CoV-2 likely causes myocarditis in humans via a pathway like other viral pathogens; in the case of COVID-19, the SARS-CoV-2 virus uses spike protein to bind to ACE2, allowing cells to open and viral material to enter. Intracellular SARS-CoV-2 can interfere with the formation of granular stress so that the virus can replicate and damage cells. Then the antigen-presenting cell (APC) will carry antigen from the sars-cov-2 virus to T lymphocyte cells, which in turn CD8 T cells migrate to cardiomyocytes and cause myocardial inflammation through a cytokine storm. In a cytokine storm, proinflammatory cytokines are released into the circulation, T lymphocyte activation increases and releases more cytokines. This result introduces a positive feedback loop of immune activation and myocardial damage [97].

Potential biomarkers

Endothelial dysfunction and inflammation play a central role in long covid-19 and CVD progression. Several biological markers can be used to determine the long-term effects of COVID-19, especially on endothelial damage and the progression of cardiovascular disease. A systemic review Identified from 28 studies representing six biological classifications, 113 biomarkers were significantly associated with long COVID: (1) Cytokine/Chemokine (33.6%); (2) Biochemical markers (21.2%); (3) Vascular markers (17.7%); (4) Neurological markers (5.3%); (5) Acute phase protein (4.4%); and (6) Others (17.7%). Compared with healthy control or recovered patients without long COVID symptoms, 79 biomarkers were increased, 29 were decreased, and 5 required further determination in the long COVID patients. Up-regulated Interleukin-6, C-reactive protein, and tumor necrosis factor-alpha might be the potential diagnostic biomarkers for long COVID-19 [98].

High-sensitivity C-reactive protein (hs-CRP)

CRP is a systemic inflammatory mediator and a central acute phase reactant produced mainly by hepatocytes after cytokine stimulation, such as IL-1, IL-6, and TNF-α. CRP down-regulates synthase endothelial nitric oxide (eNOS) transcription in ECs, resulting in decreased NO release. Several clinical trials have consistently reported that CRP levels are associated with endothelial dysfunction. Higher hs-CRP plasma levels were associated with coronary endothelial dysfunction, suggesting it is an independent marker of abnormal coronary vasoreactivity in patients with non-obstructive coronary disease [99]. Recently, high hs-CRP levels correlate positively with IL-6 and LDL-cholesterol and increased risk of long COVID symptoms. A study of 120 adult post-COVID-19 patients showed that COVID-19 survivors have higher CRP and D-dimer levels [100]. Another study of 1207 patients showed that elevated CRP was associated with an increased mortality risk after recovery from COVID-19 [101].

Interleukin-6 (IL-6)

Interleukin-6 is an important cytokine involved in many different immunological processes, such as the major regulator of acute phase response proteins and plays a crucial role in COVID-19 symptoms progression [102]. A cohort study of 317 patients diagnosed with COVID-19 showed that subjects with long COVID symptoms have higher IL-6, IL-10, and IL-4 [103].

High-sensitivity troponin-I (hs-troponin I)

Troponin is a marker of myocardial injury, but it is also found to be raised in several conditions. Recent reports demonstrated high troponin levels in patients affected by COVID-19. A cohort of 416 positive patients reported that 86 patients had evidence of myocardial damage, as indicated by an increase in troponin levels [104]. Those patients with higher troponin levels had also increased in-hospital mortality. In the long-term effect of COVID-19, hs-troponin I can be used as a risk stratification for cardiovascular risk in the general population who have tested negative for COVID-19 infection [105]. WOSCOPS (West of Scotland Coronary Prevention Study) showed that an increase of hs-troponin I can predict cardiovascular risk at both 5-and 15-year follow up [106]. Also, another study showed that hs-troponin I provided 35% reclassification improvement for predicting future cardiovascular disease when added to the Framingham score [107]. ARIC study (Atherosclerosis Risk in Communities) suggests that hs-troponin I can be used as a CVD risk prediction and divided the concentration into three categories for men and women, low risk (<6/4 ng/l); moderate risk (6-12/4-10 ng/l); and high risk (>12/10 ng/l) [108].

Tumor necrosis factor-α (TNFα)

TNF, a prototype inflammatory cytokine, plays a crucial role in mammalian immunity and vascular inflammation. Decreased eNOS expression and NO bioavailability are mainly associated with TNF-α-induced endothelial dysfunction. The interaction between TNF-α and TNFR (TNF receptor) 1 induces the expression of EC adhesion molecules (ICAM-1, VCAM-1, and E-selectin), resulting in increased leukocyte adhesion to the endothelial surface and enhanced transendothelial migration. Besides, TNF-α affects EC anticoagulant properties through TF (tissue factor), which contributes to thrombin generation, fibrin clot formation, and intravascular fibrin deposition. Besides favoring coagulation, TNF-α impairs fibrinolysis through suppressed tissue-type plasminogen activator (tPA) expression via NF-κB and p38 MAPK signaling pathways. Furthermore, TNF-α increases the rate of EC apoptosis in a concentration-and time-dependent manner. Low concentrations of TNF-α contribute to ischemic preconditioning protection, while high concentrations of TNF-α aggravate myocardial dysfunction, MI, myocardial hypertrophy, fibrosis, and apoptosis. Given the crucial role of TNF-α, blocking TNF signaling by biologics (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol) that directly bind to either TNF or TNFR is an effective therapeutic approach for inflammatory diseases. However, their efficacy in treating CVD remains unknown [109, 110].

The pathogenesis of SARS-CoV-2 infection can be divided in 2 ways: direct damage to organs and indirect damage caused by cytokine storm. This infection can cause lasting effects even after the patient has tested negative, which is called as long-term effect of COVID-19. One of these long-term effects is endothelial damage caused by direct endothelial cell infection and increasing endothelial cell apoptosis infection due to a cytokine storm. Cytokine storm increases the expression of Fas and Fas ligand; these proteins play a role in the mechanism of extrinsic apoptosis. This causes damage to the endothelial cells, leading to cardiovascular disease. This endothelial damage can be identified by increasing several blood markers such as interleukin-6, high sensitivity C-reactive protein, hs-troponin I, and tumor necrosis factor-alpha (fig. 5).

This review presents the current understanding of long covid and its correlation with endothelial damage. Infection of long covid can induce an extrinsic apoptosis through the Fas-Fas ligand complex; this causes VSMC death and leads to CVD progression. The long covid symptoms, pathophysiology, extrinsic apoptosis pathway, and the after effect of COVID-19 infection to CVD have been discussed. However, much remains to be clarified about long COVID. Hence, future research might be interested in finding the clear pathway of long COVID to endothelial damage (fig. 6).

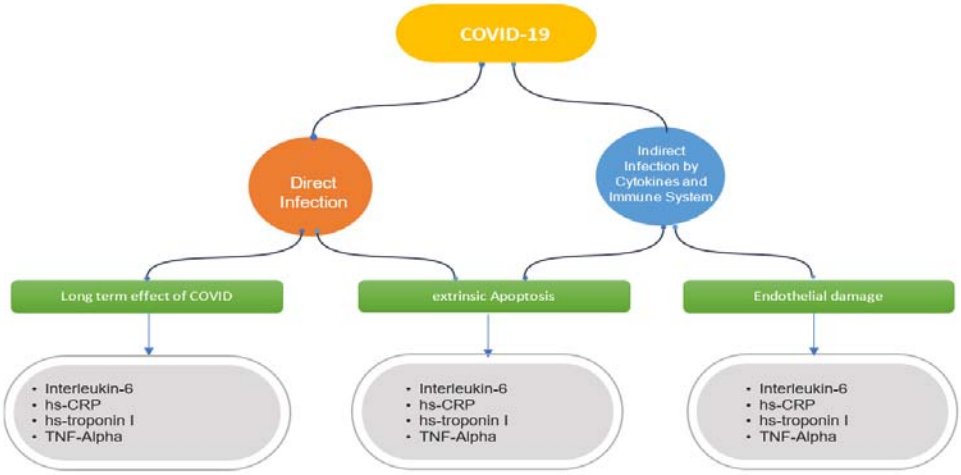

Fig. 5: General pathological and biomarker of the cardiovascular disease complication mediated by COVID-19 (created with biorender.com)

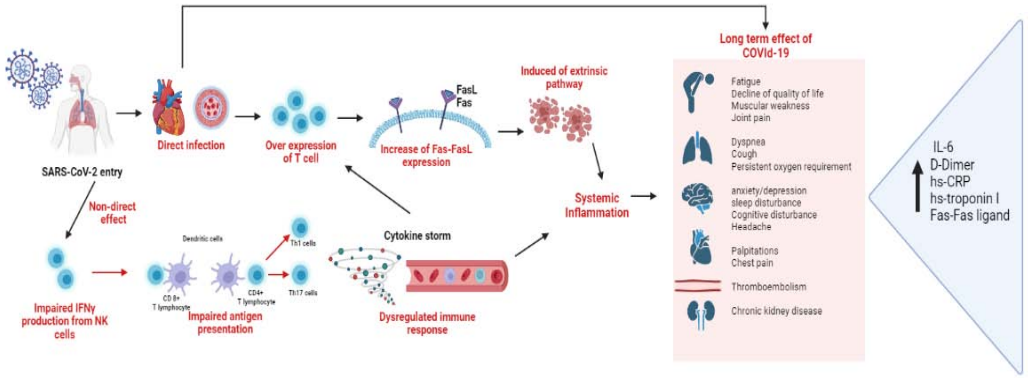

Fig. 6: The current mechanism and correlation of Covid infection and endothelial damage (created with BioRender.com)

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AUTHORS CONTRIBUTIONS

Conceptualization, G. F.; M. J.; T. Y methodology, G. F.; M. J.; T. Y.; data curation, G. F.; M. J.; T. Y.; formal analysis, M. J; writing—original draft preparation, M. J.; G. W.; writing—review and editing, M. J.; G. F.; T. Y.; visualization, M. J.; G. F; supervision, T. Y. and G. W.; funding acquisition, G. W. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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