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Article

COVID-19, Vaccination, and the Heart: Understanding Injury Pathways and Clinical Implications

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Abstract

Cardiovascular involvement in SARS-CoV-2 infection and following vaccination has emerged as a clinically relevant phenomenon with distinct yet overlapping mechanisms. Myocardial injury in COVID-19 results from a complex interplay between direct viral effects, immune-mediated inflammation, endothelial dysfunction, oxidative stress, and, in rare occasions, cytokine storm. The virus primarily binds to ACE2 receptors, which are highly expressed in endothelial cells and pericytes, leading to microvascular damage and a systemic prothrombotic state. Additional viral entry pathways, including CD147, Neuropilin-1, and CD26, further contribute to vascular and myocardial injury, which is a rather immune-driven process rather than a direct cytopathic one. Histopathological studies that reveal macrophage-rich infiltrates, microthrombosis, and patchy fibrosis support the immune-driven process theory. In contrast, vaccine-associated myocarditis – predominantly reported following mRNA vaccines – presents a self-limiting clinical course, with mechanisms probably involving molecular mimicry, aberrant immune activation, or hypersensitivity reactions. Despite an increased incidence in young males after the second dose, the overall risk remains low compared to infection-related myocarditis. Understanding the pathophysiological interplay between infection- and vaccine-related cardiac involvement is essential for accurate risk assessment, improved diagnostic strategies, and targeted therapeutic approaches. Future research should focus on elucidating immune pathways, refining biomarkers, and developing personalized management strategies in order to mitigate cardiovascular sequelae of both COVID-19 and vaccination.

Keywords: SARS-CoV-2; myocarditis; endothelial dysfunction; cardiovascular injury; COVID-19 vaccination; mRNA vaccines; immune-mediated inflammation; cytokine storm; oxidative stress; ACE2 receptor

1. Introduction

With the emergence of the COVID-19 pandemic, SARS-CoV-2 has demonstrated clear potential for cardiovascular involvement, with myocarditis increasingly being recognized as one of the most common inflammatory cardiac manifestations associated with both natural infection and, to a much lesser extent, vaccination against COVID-19 [1–3]. Clinical studies and post-authorization surveillance systems have documented an increased risk of myocardial injury following SARS-CoV-2 infection, reflecting mechanisms that include direct viral invasion, immune dysregulation, and microvascular and thrombotic imbalances [1,3–5]. The incidence of both SARS-CoV-2-related and vaccine-associated myocarditis is higher than that reported in pre-COVID-19 viral infections. Myocardial involvement in COVID-19 is often patchy, and unlike other viral myocarditis—where lymphocytic infiltration is common—in most cases of SARS-CoV-2 myocarditis, lymphocytic invasion is minimal or absent, making myocarditis an immune-mediated condition rather than a result of direct viral cell damage. [4,6]. The initial step involves the virus binding to the host cell membrane via the angiotensin-converting enzyme 2 (ACE2) receptor, followed by cellular entry. ACE2 is highly expressed in vascular endothelial cells and perivascular mural cells (pericytes), whereas its expression in cardiomyocytes is comparatively lower [7].

Acute SARS-CoV-2 infection has been linked not only to myocarditis but also to acute myocardial infarction caused by atherothrombotic plaque disruption, as well as to infarction resulting from an imbalance between myocardial oxygen supply and demand. It can also cause myocardial injury secondary to multisystem inflammatory syndrome, new-onset or decompensated heart failure in patients with preexisting cardiovascular disease, pulmonary embolism, and a wide range of arrhythmias. These findings highlight the complex cardiovascular burden of COVID-19, which goes beyond myocarditis and emphasizes the need for comprehensive cardiac evaluation and follow-up in affected patients. [8,9].

Meanwhile, global vaccination efforts using mRNA-based platforms have been linked to a small but measurable rise in myocarditis cases, usually occurring within the first week after vaccination, more often after the second dose, and mainly affecting young male recipients. [5]. The Israeli Ministry of Health reported notably lower rates of myocarditis after the third dose compared to the second dose, regardless of age or gender. [10]. Nevertheless, the absolute risk of myocarditis after vaccination remains low, compared to the much higher incidence of COVID-19-related cardiac involvement, which is estimated to be up to 100 times greater. [3].

This paper aims to synthesize the latest epidemiological and mechanistic evidence on the link between COVID-19, vaccination, and myocarditis; to explore their proposed pathogenic pathways and clinical implications; and to provide practical recommendations for evaluation, management, and monitoring. It emphasizes the importance of integrating both post-marketing safety data and comparative infection risk, especially in a specific demographic group—mainly adolescent and young adult males—where individualized risk assessment and counseling are recommended.

2. Methodology

To compile this review, our team conducted extensive literature research across major electronic databases such as PubMed, Google Scholar, and Embase. The search strategy used a combination of key terms like “viral myocarditis,” “endothelial dysfunction,” “cardiovascular injury,” “mRNA vaccines,” “immune-mediated inflammation,” “cytokine storm,” and “oxidative stress” alongside “COVID-19” and “SARS-CoV-2 vaccination” to identify relevant publications. Additionally, our team reviewed grey literature sources to ensure a broad and unbiased overview of the topic and to include studies that might not be indexed in major databases. We only considered articles published in English and available in full text.

3. Epidemiology of Myocardial Involvement in COVID-19

Myocarditis, defined as inflammation of the myocardium caused by infectious agents or non-infectious processes, has an estimated global prevalence of 10.2-105.6 cases per 100,000 people annually [11], with a higher prevalence in males [12]. Viral infections account for 69% of myocarditis cases [12], and 1-5% of patients with viral infections develop myocarditis [13].

The incidence of myocarditis before COVID-19 was lower than the incidence reported during COVID-19. The incidence of myocarditis pre-COVID was 1 to 10 cases per 100,000 individuals [14], whereas during SARS-CoV-2 infection, it ranges from 150 to 4000 cases per 100,000 individuals [14,15].

The incidence of myocarditis linked to COVID-19 is estimated to be about 450 cases per million young adults, although the true rate remains unknown [16]. It has been diagnosed in 2 to 4 patients per 1000 hospitalizations [17]. Myocardial injury, defined as an increase in troponin levels, is more common among patients with SARS-CoV-2 infection, with a prevalence of 22% among all hospitalized patients, rising to nearly 30% in elderly patients or those with severe disease [18]. The incidence of acute myocardial infarction (AMI) in patients with SARS-CoV-2 varies depending on the studied population. A systematic review and meta-analysis of over 1.2 million COVID-19 survivors found an incidence of 3.5 cases per 1000 people (0.35%), compared to 2.02 cases per 1000 patients (0.2%) in the control group [19]. The incidence of AMI in hospitalized patients ranges from 1.1% to 8.9% [20]. In a large US surveillance study, the incidence was 5.5% [21].

4. Histology of COVID-19 Myocarditis

Generally, the typical histological changes of viral myocarditis include infiltrates of lymphocytes, neutrophils, monocytes, histiocytes, eosinophils, or giant cells, along with vasculitis, necrosis, and myocardial fibrosis [12]. Fulminant myocarditis is characterized by multiple areas of active inflammation and myocyte necrosis [12].

Histopathological analyses of myocardial tissue from patients with confirmed SARS-CoV-2 infection have revealed a pattern that differs substantially from that of classical viral myocarditis. In contrast to enteroviral or adenoviral myocarditis, which are characterized by diffuse lymphocytic infiltration and direct myocyte necrosis are predominant, most COVID-19 autopsy studies demonstrate minimal or focal inflammatory infiltrates, often insufficient to fulfill Dallas criteria for active myocarditis [6,22]. Myocarditis, even when observed, tends to be patchy and usually occurs without the dense mononuclear infiltrates typically seen in conventional viral myocarditis, indicating that direct cytopathic injury is not the main mechanism. [23].

Autopsies of patients with severe COVID-19 revealed significant arterial vascular changes in various organs, such as hemorrhage and endothelitis [24–26], associated with thrombosis and inflammation [6,27]. Thrombotic microangiopathy, a result of endothelial dysfunction, underlies many ischemic events, as well as heart failure and renal dysfunction [28]. A consistent histological feature reported across multiple cohorts is extensive microvascular and endothelial involvement. SARS-CoV-2 demonstrates tropism for endothelial cells and pericytes due to high ACE2 expression, resulting in endothelial swelling, endothelitis, and microvascular rarefaction [4]. Numerous studies have described capillary congestion, endothelial activation, microthrombi, fibrin deposits, and complement-mediated lesions. All these findings support a model of microcirculatory dysfunction rather than primary myocyte invasion. These vascular abnormalities are thought to contribute to myocardial ischemia, regional injury, and the patchy necrotic lesions observed in most histological specimens [4,29].

The most common histologic pattern in COVID-19 myocarditis is described as a cellular infiltrate, mainly consisting of macrophages (CD68) and granulomas (giant cells and eosinophils) [27]. Unlike other viral myocarditis, where lymphocytic infiltration is prominent, most cases of SARS-CoV-2 myocarditis lack lymphocytic invasion; even near necrotic myocytes, typical lymphocytic infiltrates are not observed [29]. Some autopsy studies show limited infiltrates of T-cells (CD4)

without significant CD8+ cells or B-cells (CD20) infiltration [30]. Multiple studies have shown mild interstitial edema without clear myocyte destruction [6,31].

The myocardial fibrosis in COVID-19 is a controversial topic; some authors have reported only limited interstitial fibrosis [30].

One study [27] on individuals who died with COVID-19 showed viral replication within the heart, a direct correlation between the myocardial density of macrophages and lymphocytes, a direct relationship between the presence of SARS-CoV-2 infected myocytes and myocarditis, and a connection between apparent SARS-CoV-2 infected endothelial cells and thrombosis. Other autopsy reports indicated that the percentage of SARS-CoV-2 evidence in the hearts of deceased individuals was high (62%), without extensive cell infiltrates or necrosis within the myocardium (V. Coronaviridae Study Group of the International Committee on Taxonomy of the species Severe acute respiratory syndrome-related coronavirus). Most studies have found that detection of SARS-CoV-2 RNA or proteins within myocardial cells is variable and often low, further supporting the idea that immune-vascular mechanisms play a key role in COVID-19 myocardial pathology [22,31–33].

The inconsistency in lymphocytic infiltration, along with the prominence of macrophage infiltration and microvascular lesions, supports the idea that COVID-19-related myocardial damage results from systemic immune dysregulation, cytokine-driven injury, and endothelial dysfunction rather than direct viral cytotoxicity [34].

5. Myocarditis Pathophysiology

It is not yet clear whether direct viral intervention or autoimmunity is the main determinant of viral myocarditis. After entry into myocytes, the virus is eliminated through macrophage and lymphocyte intervention, or, if the viral genome persists, inflammation and the autoimmune response cause myocardial damage [35,36].

The pathogenesis of viral myocarditis is explained as a three-phase model. The acute phase, characterized by high virus levels, lasts 1-7 days and is represented by acute cardiac cell damage and cellular death, secondary to the innate immune response [37]. The presence of the virus in heart tissue triggers immune system activation, production of inflammatory mediators, and cardiac auto-antibodies [38], activation of macrophages, and accumulation of mast cells, natural killer T cells, and neutrophils in the myocardium [39,40].

The viruses multiply within the cardiomyocytes, causing cytoskeletal breakdown, which leads to myocardial damage [41], and also result in the release of myocyte antigens, IL-1 β , pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs) into the bloodstream [38]. IL-1 β , PAMPs, and DAMPs promote extramedullary hematopoiesis, including the release of pro-inflammatory Ly6Chigh monocytes [42], which are precursors to macrophages. The cardiomyocytes produce interferon gamma (IFN γ), stimulating fibroblasts to produce chemokines and chemoattractants for Ly6Chigh monocytes [43]. Monocyte recruitment is a double-edged sword—effective for removing the virus from the myocardium, but also a trigger for the loss of myocyte contractile units [43].

Mast cells and neutrophils (PMNs) migrate within the myocardium as early events in viral infections [12], leading to different outcomes. Mast cells produce cytokines with antiviral effects (such as TNF α , IL-1 β , and IL-4) [41], enzymes acting as fibroblast inductors, such as matrix metalloproteinases, fibrinogenic mediators like chymases and tryptases, which offer protective effects against myocardial fibrosis and necrosis [44]. PMNs are involved in both initiating and sustaining inflammation, forming extracellular neutrophil traps [45]. Their recruitment is followed by the release of pro-inflammatory mediators (myeloperoxidase, IL-6, IL-8, TNF α , alarmins) and adhesion to fibrinogen and fibronectin [41,46]. Furthermore, PMNs promote the migration of CD8+ T lymphocytes to the affected myocardium, contributing to myocarditis progression [47].

Besides mast cells, natural killer (NK) cells [12] also play protective roles. NKs are involved in clearing viral infections and limiting both viral replication and inflammatory responses [48]. NKs also suppress monocyte maturation [43]. Figure 1

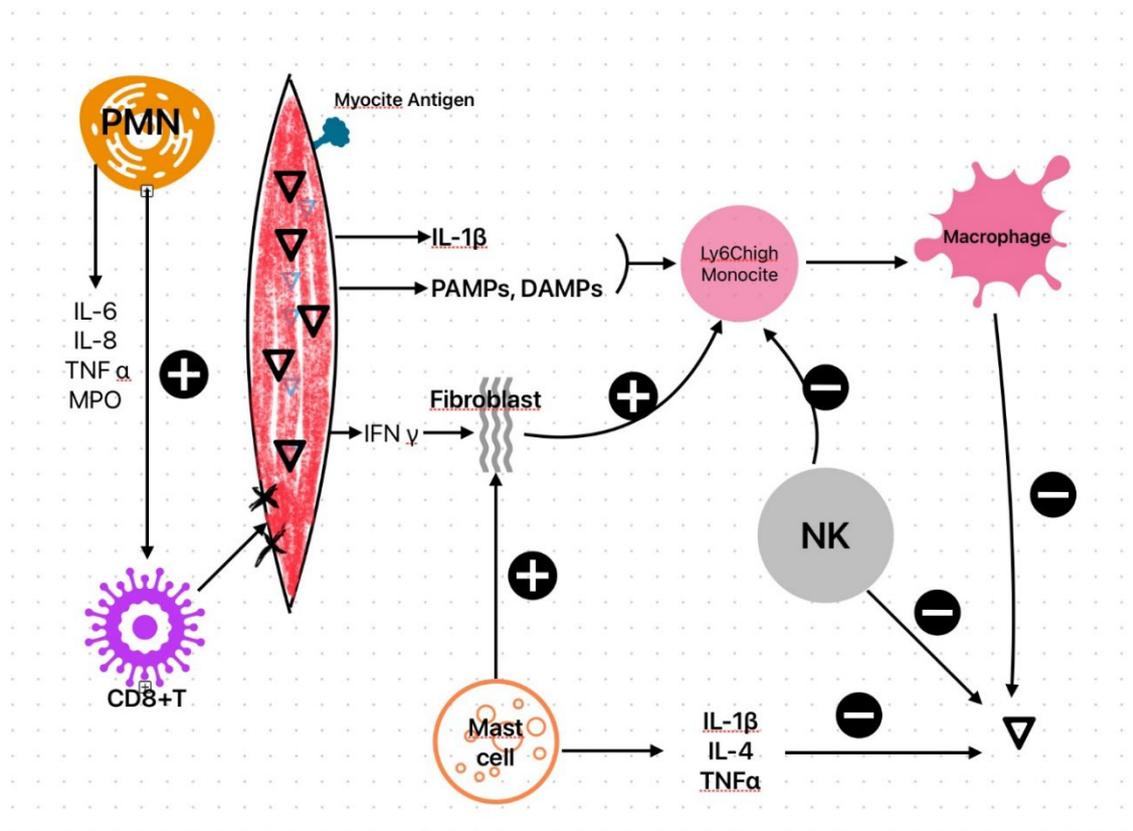


Figure 1. The acute phase of viral myocarditis. Mast cells and neutrophils (PMN) migration within the myocardium is observed earlier in viral infections, with different consequences on inflammation; the cytokines synthesized by mast cells have antiviral action, meanwhile, the cytokines secreted by PMNs have proinflammatory effects. The natural killer cells (NK) limit both viral replication and inflammatory responses. The virus multiplies within cardiomyocytes, leading to the release of Ly6Chigh, precursors of macrophages. PAMPs- pathogen-associated molecular patterns, DAMPs- damage-associated molecular patterns; TNF α - α tumor necrosis factor; IFN γ - γ interferon; virus.

The subacute immune phase lasts from 1 to 4 weeks, with CD4⁺ T cells playing a key role [37] in the adaptive immune response. During this phase, viral titres are lower than in the earlier phase [12]. Activated Th1 cells release various inflammatory markers, such as IL-1 α , IL-1 β , and TNF- α , which contribute to the destruction of contractile units and the interstitial matrix of infected myocytes [38,49]. Myocyte secretion of IL-1 and TNF α stimulates macrophages to produce IL-1 β , with harmful effects on cardiomyocytes [50].

Regulatory T-cells (Treg), through their secretion of inhibitory cytokines (TGF- β 1 and IL-10) or by expressing surface molecules such as the glucocorticoid-induced TNF receptor, lead to a decrease in inflammation and provide protective effects on cardiac myocytes [51]. Th17 levels correlate with inflammation and the likelihood of myocarditis, dilated cardiomyopathy, and heart failure [52]. Th2 cells produce IL-10 and IL-13, which have anti-inflammatory properties, inhibiting macrophage function and cytokine secretion [53,54]. Heart-specific antibodies, observed in over 60% of cases of viral cardiomyopathy [41], are involved in the progression of heart disease [55]. These antibodies target structural components (such as anti-membrane, anti-sarcolemma, and anti-cytoskeleton antibodies), myosin chains (anti-myosin alpha and beta heavy chains antibodies), troponin, certain receptors (anti-acetylcholine receptor antibodies and anti-beta-1 adrenergic antibodies), mitochondrial components (NAD, creatine kinase, and pyruvate kinase), and heat shock proteins [39,55]. Viruses that damage heart tissue expose intracellular cardiac antigens and may initiate the production of heart-specific autoantibodies. Such antibodies have been identified in both

experimental coxsackievirus B3 myocarditis and in patients with clinical and biopsy-confirmed myocarditis, supporting an autoimmune role in ongoing myocardial injury [52,56] (see figure 2).

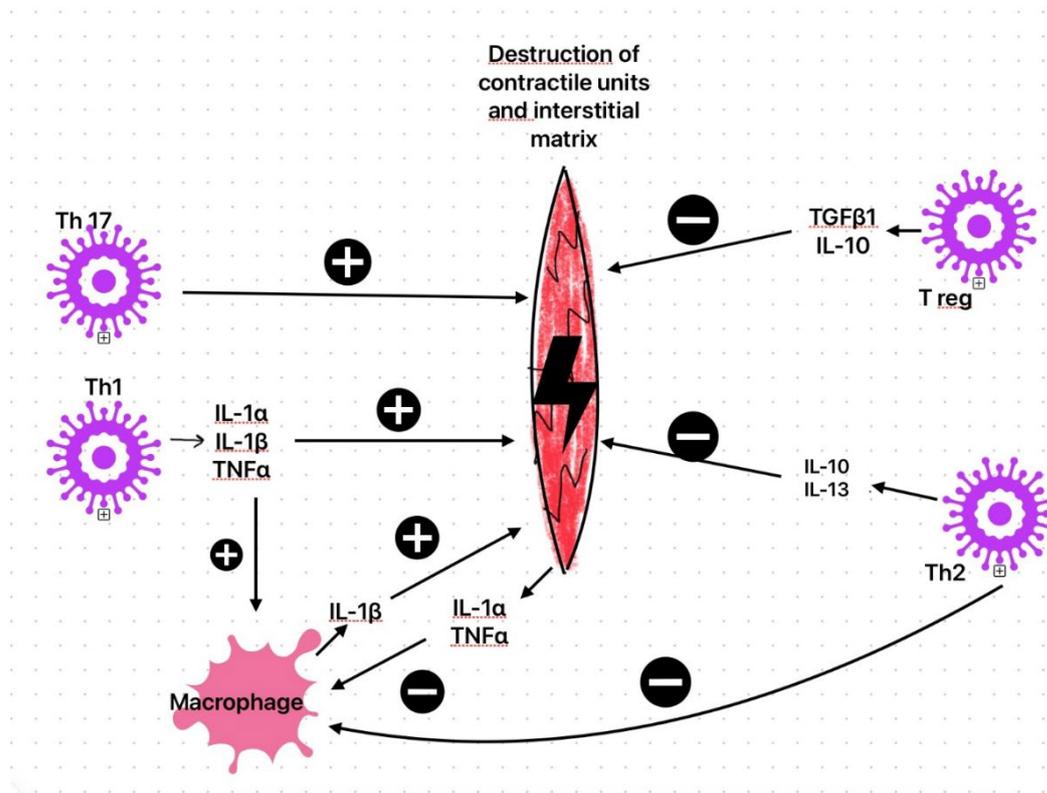


Figure 2. The subacute phase of viral myocarditis. The T cell populations have different effects on cardiomyocytes; Treg and Th2 prevent the destruction of contractile units and interstitial matrix, meanwhile Th17 and Th1 populations have deleterious effects on cardiomyocytes.

The recovery phase is the longest, lasting weeks or months [12]. This phase concludes with the restoration of cardiac function or progresses to chronic myocarditis and cardiac remodeling toward dilated cardiomyopathy [57]. The shift toward harmful remodeling is encouraged by the persistence of the virus within endothelial cells and myocytes, the inflammatory response, the balance between NK and Treg cells, and the involvement of autoimmune mechanisms [12]. Extracellular matrix remodeling is driven by pro-inflammatory cytokines such as TNF- α and IL-1 β [58], which activate matrix metalloproteinases (collagenase, elastase, and gelatinase) [12]. MicroRNAs like miR-21, miR-208b, and miR-499 may also play a role in the progression of viral myocarditis to dilated cardiomyopathy [59].

COVID-19 myocarditis results from both the harmful effects of the virus on cardiac myocytes and the activation of immune processes [60]. Most authors argue that COVID-19 myocarditis is more likely immune-mediated rather than caused directly by viral damage [61]. Therefore, in patients previously treated with glucocorticoids, the prevalence of myocarditis and myocardial inflammation was lower than in patients treated with IL-6 blockade [27]. In one autopsy series of 40 patients who died during the first pandemic wave in northern Italy, it was shown that neither the viral genome nor the Spike protein was detected in patients with lymphocytic myocarditis, but was detected in cardiomyocytes without signs of myocarditis [62].

Some studies on hearts from deceased individuals reported no specific viral lesions despite detecting viral RNA replication [63]. Other researchers found viral RNA but not viral particles within the hearts [64] or inside cardiomyocytes [65]. Additional studies indicated that in patients who died from SARS-CoV-2 infection, the presence of SARS-CoV in the heart was linked to increased macrophage infiltration, myocardial damage, and reduced myocardial ACE2 protein levels [66].

The first step in SARS-CoV-2 myocarditis involves the virus binding to the host cell membrane, followed by its entry into the cells via endocytosis. After entry, SARS-CoV-2 releases positive-strand RNA into the cytoplasm, where it is translated into polyproteins and structural proteins. This is followed by the assembly of the viral genome and envelope. The immature virion then moves to the endoplasmic reticulum, fuses with the cell membrane, and is subsequently released from the host cell [67,68].

The primary route for viral binding is through angiotensin-converting enzyme 2 (ACE2). Both the binding process and viral entry processes are facilitated by the viral envelope S-protein into S1 and S2 subunits. The S1 domain binds to ACE2, while the S2 domain facilitates the fusion of the virion envelope with the cell membrane [69]. There are two forms of ACE2: a membrane-bound form, which acts as a receptor for SARS-CoV-2, and a soluble form, which neutralizes free virions by shielding the viral spike protein (S) [70]. Angiotensin II receptor type 2 (AGTR2) has a higher affinity for the spike protein than ACE2 [71].

The tropism of SARS-CoV-2 for the heart (generally for SARS-CoV viruses—[72] is explained by the fact that cardiomyocytes, pericytes, and endothelial cells strongly express the ACE2 receptor [73]. In diabetic patients and in patients with heart diseases, especially those susceptible to SARS infections, ACE2 expression is increased [74,75].

ACE2 is highly expressed by the vascular endothelium [76] and by perivascular mural cells (pericytes). Pericytes express higher levels of ACE2 than cardiomyocytes [7]. Unlike smooth muscle cells, which are located in the coronary arteries or arterioles, pericytes extend outside the capillary and venules' endothelium, suggesting that pericytes are a target for SARS-CoV-2 [7] and may contribute to endothelial cell dysfunction and microcirculatory issues. Pericytes interact with endothelial cells and neuron-like cells, which is relevant for medications that improve microcirculation and could help reduce or alleviate heart injury [7].

Regarding the expression of ACE2 in the heart, opinions vary: some authors report low levels [7,77], while others argue that ACE2 is highly expressed [78]. In any case, ACE2 levels in the heart are lower than in the intestine and kidney, but higher than in the lung [7].

ACE converts angiotensin I to angiotensin II and inactivates bradykinin [72]. ACE2 does not affect angiotensin II production but converts angiotensin II (Ang II) to Ang 1-7 [79], which has protective roles for the heart, has been demonstrated in experimental models and humans. In ACE2 knockout mice, angiotensin II levels rise, and heart contractility decreases [80]. Down-regulation of ACE2 is linked to oxidative stress, leading to impaired degradation of angiotensin II [81]. Reduced ACE2 expression is associated with age-related cardiomyopathy [66,80,82]. ACE2 levels increase in pregnant women, helping to protect them from hypertension [83].

In murine models [66], it was shown that SARS-CoV-2 reduces myocardial ACE2 mRNA expression. ACE2 downregulation was seen not only with SARS-CoV-2 but also with other viruses, such as HIV and measles [84]. The mechanisms behind the complete loss of ACE2 protein in hearts infected with SARS-CoV may involve either activation of ADAM17 / TACE by the SARS spike protein, leading to cleavage and release of ACE2 [85], or SARS-CoV binding to ACE2 in endothelial cells, which causes endocytosis of the ligand/receptor complex [86,87], resulting in intracellular degradation of ACE2. SARS-CoV-2 infection causes the loss of ACE2, decreasing protective Ang 1-7 levels and increasing angiotensin II, which then leads to cardiomyocyte autophagy and apoptosis [88,89].

Besides ACE2, SARS-CoV-2 uses other pathways to enter cells, such as Zinc aminopeptidase N, CD147, and neuropilin-1. Zinc aminopeptidase N (APN) serves as a binding site for various coronaviruses [90].

CD147, a glycosylated transmembrane protein (also known as basigin or extracellular matrix metalloproteinase- Alipoor, 2022), is expressed in blood cells [91,92] and may function as a receptor for SARS-CoV, including SARS-CoV-2 [93,94]. The interaction between the viral spike protein and CD147 on red blood cells leads to hypoxemia and abnormal interactions with endothelial cells [95]. CD147 is highly expressed in the heart, kidney, lungs, and lymphocytes (where ACE2 expression is

very low) and plays a role in lymphocytic signaling [96]. CD147 may act as a T-cell receptor for SARS-CoV-2, facilitating viral entry into T-cells [97]. CD147 expression is higher in males and in persons with obesity or chronic obstructive pulmonary disease [91], conditions associated with a worse COVID-19 prognosis. CypA is the ligand for CD147 [97]. SARS-CoV-2 promotes dysregulation of the CD147-CypA signaling pathways, which may contribute to thrombotic events, cardiac hypertrophy, and even heart failure [95].

Neuropilin-1 (NRP1) is expressed by endothelial and epithelial cells in the respiratory and olfactory systems, as well as by vagal and sensory neurons—structures that show low levels of ACE2 [98–101]. NRP1 functions as a co-receptor for vascular endothelial growth factor (VEGF) [100], playing a role in vascular permeability and angiogenesis [94]. The spike protein of SARS-CoV-2 binds to NRP1 [102]. Notably, NRP1 is highly expressed on vascular endothelial cells, where it regulates endothelial cell adhesion and permeability [97].

CD26 (DPP4) is a peptidase widely expressed in leukocytes, lungs, and kidneys, and it plays important roles in T cell activation [103]. CD26 interacts with the S1 domain of SARS-CoV-2 [104]. These interactions are under analysis, especially in diabetic patients. CD26 dysregulation is observed in obesity and diabetes [105].

Integrins may be entry receptors for SARS-CoV-2 [97].

Some viral infections can lead to increased production of reactive oxygen species (ROS) and can disrupt the host's antioxidant response. This causes redox stress, heightened inflammation, cellular apoptosis, and tissue damage, which contribute to disease development and increased viral replication. The group of viruses that can induce higher ROS production includes SARS-CoV-2, influenza A virus, dengue virus, Zika virus, herpes simplex, hepatitis B and C viruses, human immunodeficiency virus-1, respiratory syncytial virus, and enteroviruses. [106]. For example, influenza A virus induces ROS production leading to induction of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) (NOX2 and NOX4 and suppression of the nuclear factor erythroid 2-related factor 2 (Nrf2), a protein with a complex role, a master regulator of proteostasis and metabolism of the cell, primarily involved in redox balance. This effect triggers apoptosis, inflammation, and lung injury, while enhancing viral replication and pathogenesis [106]. ROS production is common in some viral infections. Although the mechanism may vary and ROS can be either beneficial or harmful, excessive ROS generation almost always causes damage to the host. [106,107].

A cytokine storm, a severe, dysregulated hyperinflammatory response, can occur in the context of various viral infections, including influenza A (H5N1/H1N1), SARS-CoV-1 and 2, MERS, viral hemorrhagic fevers, and some chronic viral diseases. It is characterized by excessive activation of innate and adaptive immune cells, leading to systemic inflammation, endothelial activation, capillary leak, and a sepsis-like clinical picture, all associated with high mortality rates and significant morbidity [108–110].

The primary effects of virus presence within cells are the massive release of cytokines (known as the cytokine storm) and oxidative stress.

The cytokine storm and oxidative stress play a significant role in damage and loss of cardiomyocytes in SARS-CoV-2 infection [76]. The cytokine storm is directly linked to more severe disease and a worse prognosis [111]. This storm, typical of COVID-19, is marked by high levels of pro-inflammatory mediators such as IL-1 β , IL-6, IL-17, and GM-CSF, which are all involved in the differentiation of Th17 cells [112], a subgroup of CD4⁺ lymphocytes [113]. IL-17 promotes the secretion of IL-6 [114]. Notably, elevated IL-6 levels are significant because they promote the differentiation of Th17 cells [114].

Until now, the functional significance of impaired Th17 response in COVID-19 remains unclear. However, tissue-resident memory-like Th17 cells (Trm17 cells) appear to play an important role in the hyperinflammation seen in severe COVID-19 cases [115]. Th17 blockers therapy may be useful for improving T cell antiviral responses against SARS-CoV-2 [116,117].

Both inflammation and oxidative stress facilitate SARS-CoV-2 entry into myocytes, cause protein oxidation, and lead to myofilament contractile dysfunction [76]. The reactive oxygen species (ROS) induce mitochondrial hyperpermeability, triggering autophagy, apoptosis, and necrosis in cardiomyocytes [76].

The NLRP3 inflammasome contributes to SARS-CoV-2 myocarditis through IL-1b and IL-18 promotion of IL-6 release [118]. It is activated by various mechanisms, such as Ang II accumulation, ROS production, and complement cascade activation caused by SARS-CoV-2 infection, among others [115]. Suppressing the NLRP3 inflammasome may prevent cytokine storms [118], offering a potential therapeutic approach for COVID-19-related myocarditis. Examples include Anakinra—a recombinant form of the natural IL-1 receptor antagonist (IL-1Ra) that inhibits IL-1a and IL-1b activity; Canakinumab—an IL-1b-neutralizing antibody; MCC950—a specific NLRP3 inflammasome inhibitor; Colchicine—an NLRP3 inflammasome activation inhibitor; and IL-37—an inhibitor of NLRP3 inflammasome activity [119].

6. Vascular Involvement in COVID-19

SARS-CoV-2 causes widespread endothelitis, leading to endothelial dysfunction characterized by thrombosis, hemorrhages, and edema [63]. Evidence of endothelial injury is primarily seen in post-mortem studies of pulmonary arteries, as well as in the heart, lungs, liver, and kidneys [120–122]. Levels and activity of von Willebrand factor, markers of inflammation-activated endothelial dysfunction, are significantly increased [123]. Patients with severe disease exhibit a hypofibrinolytic state, indicated by elevated levels of plasminogen activator inhibitor [123].

The physiopathology of vascular involvement is multifactorial, primarily involving the direct effects of the virus on endothelial cells, the cytokine storm, oxidative stress, the renin–angiotensin–aldosterone system (RAAS), autoimmune responses, and ferroptosis—a type of cell death caused by excessive peroxidation of polyunsaturated fatty acids due to loss of glutathione peroxidase activity [28,124,125]. The viral nucleocapsid protein stimulates infected cells to produce new pro-coagulant factors [122,126]. Oxidative stress increases the production of proinflammatory cytokines (such as TNF α , IL-6, IL-1), which cause endothelial dysfunction by decreasing endothelial nitric oxide synthase (eNOS) activity and nitric oxide (NO) production [28]), while also oxidizing NO into peroxynitrite [127], reducing NO bioavailability. The reactive oxygen species (ROS) and decreased NO levels impair endothelial repair and promote endothelial cell senescence [128].

SARS-CoV-2 binding to ACE2 and CD147 destroys intercellular junctions [100], leading to exposure of subendothelial collagen and a prothrombotic state. Additionally, some ultrastructural studies have detected virus-like particles within endothelial cells [122,129], resulting in ultrastructural changes in the endothelium.

After virus entry into the endothelial cells, ACE2 is downregulated, while the ACE-Angiotensin II–AT1R pathway is amplified [72]. Angiotensin II promotes the production of pro-inflammatory cytokines (such as IL-6, TNF α , TGF β), decreases the release and production of vasodilators (NO and prostacyclin), and increases ROS generation [130], and activates macrophages, leading to the production of inflammatory cytokines [131].

Activated endothelial cells secrete monocyte chemoattractant protein 1 [28]. The activated monocytes, on one hand, induce high levels of tissue factor expression, and on the other hand, promote significant NO production (in an NOs-inducible manner), leading to thrombosis, opening of endothelial gaps, and loss of barrier function [132]. IL-6, secreted by the endothelial cells, stimulates cytokine release, complement activation, and the expression of adhesive molecules [133,134]. IL-8 and MCP-1 secreted by endothelial cells possess vasodilator properties, which facilitate gap junction opening [132]. Cytokines also contribute to platelet activation and leukocyte recruitment to the microcirculation [134].

7. Acute Myocarditis After Vaccination

With an unprecedented response, the medical world managed to produce and distribute several types of vaccines in a year since the start of the COVID pandemic. The global COVID-19 vaccination campaign has been instrumental in reducing both morbidity and mortality from SARS-CoV-2 infection. Over 10 billion doses of various COVID-19 vaccines have been administered worldwide, utilizing different platforms including mRNA technology, viral vectors, recombinant proteins, and inactivated virus preparations. However, the vaccination campaign was also associated with an increased number of reports regarding side effects. Amongst these, myocarditis and pericarditis, particularly following mRNA vaccines, have raised important clinical considerations [135,136].

Acute myocarditis is reported after vaccination against COVID-19, mainly with vaccines based on mRNA technology, probably because of the immune response related to mRNA [137]. mRNA has the functional quality of an antigen, so that it activates the inflammatory cascade, by cross-reactions between SARS-CoV-2 spike glycoproteins and myocardial proteins [37].

The temporal association between vaccination and cardiac symptoms, coupled with characteristic imaging findings, has established a causal relationship that requires careful clinical consideration and ongoing surveillance even after the WHO declared an end to the pandemic [138–144]. Anyway, the mortality rate in persons with myocarditis after mRNA vaccination is lower than in those with viral infection-related myocarditis.

The incidence of vaccine-associated myocarditis varies significantly across different populations and vaccine types. An umbrella review of all systematic reviews with meta-analyses published until 2024 showed that the overall incidence ranged from 0.89 to 2.36 cases of myocarditis per 100,000 doses of vaccine administered [145]. Other authors reported a higher incidence of vaccine-associated myocarditis, as high as 3–5 cases per 100,000 vaccinated people [146–148], occurring mainly in the first week after vaccination, and more frequent in male subjects [37].

The meta-analysis published by Bouchlarhem et al. in 2024 [149] concluded that the overall incidence is low and does not differ from that described in the general population before vaccination [145]. Another study has shown that the pooled incidence of myocarditis/pericarditis was 4.5 (95% 3.14–6.11) per 100,000 vaccinations across all doses [150]. All in all, COVID-19 vaccination was associated with an increased risk of myocarditis or pericarditis (RR=2.04, (5% CI=1.33–3.14) with a higher risk in people who received the second dose. This meta-analysis included 11 studies with 58,620,611 subjects [151].

The relatively low risk of myocarditis after vaccination is in contrast to the incidence of COVID-19-associated cardiac involvement, which is estimated to be 100 times higher (1000 to 1400 cases per 100,000 people with SARS-CoV-2 infection [152]. SARS-CoV-2 infection confers a consistently higher myocarditis risk across most ages/sexes. For example, in England, infection markedly increased myocarditis risk across age groups in the general population; while vaccine-associated risks were concentrated in young males, infection risk exceeded vaccine risk in the general population. The only exception was in men <40 years old, where a second-dose mRNA-1273 produced more excess events per million than a positive SARS-CoV-2 test (97 [95% CI, 91–99] versus 16 [95% CI, 12–18])[153]. Another cohort study of 23 million residents from 4 countries in the North of Europe showed that in high-risk young males, second-dose mRNA-1273 can yield on the order of tens per 100,000 excess events over 28 days; again, infection produces fewer excess events in that specific subgroup population but more in the general population. Among males aged 16 to 24 years, the adjusted incidence risk ratio was 12.50 for a second dose of BNT162b2 and 38.29 for a second dose of mRNA-1273[154]. In conclusion, most studies highlight a narrow populational group for which the risk assessment and counselling are necessary.

Another important aspect when comparing infection versus vaccination is the clinical severity of the cases. In contrast to the overall mild presentation and good outcome of vaccine-associated myocarditis, COVID-19 is associated with a major risk of cardiovascular complications[155,156]. For example, a study published by Aikawa et al. [157] found that among patients with COVID-19, 10% of outpatients and 40% of hospitalized patients had clinically significant myocardial injury, while

advanced age and comorbidities such as obesity, diabetes mellitus, hypertension, and renal dysfunction were the main predisposing factors[155]. Husby et al. showed that in patients aged between 12-39 y.o (who had the highest risk of developing myocarditis after vaccination), COVID-19 myocarditis was associated with an increased risk of heart failure or death within 90 days of admission (relative risk 5.78, 1.84 to 18.20) compared with myocarditis associated with vaccination[158].

Young males, especially adolescents and young adults, represent the clearest high-risk population for myocarditis following mRNA SARS-CoV-2 vaccination, as shown by multiple large population studies and active surveillance reports. The highest incidence is concentrated in males aged approximately 12-39 years, with risk peaking in the week after the second mRNA dose.

Product-specific analyses from large Nordic and national cohorts additionally showed a greater excess risk after mRNA-1273 (Moderna) than after BNT162b2 (Pfizer-BioNTech) in young males.

Another important aspect is the fact that shorter inter-dose intervals have been associated with increased myocarditis reporting.

Females of all ages had a significantly lower risk across all age groups [136,144,154]. Viral vector vaccines (ChAdOx1, Ad26.COV2.S) are associated with different risk profiles, with myocarditis being less commonly reported compared to mRNA platforms[159–161].

The pathophysiology of SARS-CoV-2 vaccine-associated myocarditis remains incompletely understood, and multiple mechanisms are being proposed based on current evidence. The leading mechanistic hypotheses include:

- An aberrant innate immune activation by the vaccine platform (mRNA and lipid nanoparticle components) that triggers myocardial inflammation in predisposed individuals. The higher prevalence of myocarditis in young males may be explained by higher levels of androgens, especially testosterone, which can enhance the pro-inflammatory response by Th1 lymphocytes and pro-inflammatory cytokine production [162,163]. The lipid nanoparticles may act as adjuvants, enhancing immune responses, but could potentially contribute to excessive inflammatory reactions in susceptible individuals[164].
- An adaptive immune response in which anti-spike antibodies or spike-directed T cells cross-react with cardiac antigens. This represents the molecular mimicry hypothesis and was described by Nunez et al. [165]. The molecular mimicry is associated with a cross-reaction of antibodies against the spike protein with self-antigens such as heavy chains of myosin or troponin C1.[166]
- A hyper-inflammatory recall response after repeat antigen exposure, consistent with a short latency and robust anamnestic immunity.

However, no single mechanism has been definitively proven. Most observational studies signal that risk is higher after products containing larger mRNA payloads and that risk is concentrated in young males. This supports a model in which antigen dose, immune priming/timing, and host susceptibility (including sex-hormone-modulated immune responses play crucial roles [138,165,167].

The management of vaccine-associated myocarditis follows established principles for acute myocarditis care, with modifications based on the typically mild and self-limiting nature of this condition [144,168,169]. Non-steroidal anti-inflammatory drugs represent the cornerstone of anti-inflammatory therapy, with patients showing clinical improvement within 24-72 hours on initiation, Ibuprofen or indomethacin being commonly used. Colchicine may be considered as an alternative or adjunctive therapy, particularly in cases with concomitant pericarditis. Corticosteroids are generally reserved for severe cases or those not responding to first-line anti-inflammatory therapy. The routine use of corticosteroids is limited by concerns regarding potential interference with immune responses and unclear benefit in this specific patient population [144,170–172].

For patients who develop myocarditis associated with SARS-CoV-2 vaccinations, decisions regarding future doses require careful individualized risk-benefit assessment. Currently, major

health organizations generally advise deferring additional doses until complete recovery, with preference for vaccines demonstrating lower myocarditis risk profiles when future vaccination is indicated. The main factors influencing future vaccination decisions include severity and duration of initial episode, complete recovery versus persistent cardiac abnormalities, individual COVID-19 risk factors and exposure risk, availability of alternative vaccine platforms, and evolving epidemiological data on breakthrough infections [144,172,173].

Future research priorities include elucidating the complete pathophysiological mechanisms, optimizing treatment protocols, establishing definitive long-term outcome data, and developing personalized risk assessment tools to guide individual vaccination decisions.

8. Clinical Manifestations of Cardiac Involvement

Although primarily a respiratory illness, COVID-19 is linked to various cardiac complications, both acute and long-term. The clinical presentation varies greatly depending on the extent and type of cardiac damage, preexisting risk factors and comorbidities, as well as the severity of the respiratory illness.

Acute SARS-CoV-2 infection has been linked to myocarditis, both type 1 and type 2 acute myocardial infarction, myocardial damage from multisystem inflammatory syndrome, as well as new-onset or decompensated heart failure in patients with a history of cardiovascular disease, pulmonary embolism, and arrhythmias [174,175].

In patients with COVID-19, the presence of symptoms such as disproportionate fatigue, dyspnea, palpitations, chest pain, or chest tightness during exertion should be a warning sign for systematic evaluation to exclude myocarditis. However, it should be noted that some patients experience no symptoms or deteriorate suddenly with the appearance of arrhythmias, acute heart failure, or even cardiogenic shock [1]. Most studies on COVID-19 report that myocarditis occurs more frequently in young men aged 16 to 30 years [176]. Therefore, in this patient group, specific tests are recommended in the clinical context described above.

A variety of cardiovascular symptoms, such as fatigue, shortness of breath, chest pain, and palpitations, have been reported in patients who have recovered from the acute phase of SARS-CoV-2 infection. According to the definition first established by the authors of the 2020 NICE guideline, long-term COVID refers to the persistence of symptoms more than 4 weeks after infection (NICE guideline [NG188]). This term includes two phases: the ongoing symptomatic phase (4-12 weeks) and the post-COVID-19 syndrome (>12 weeks). Pathophysiological mechanisms for long COVID are still poorly understood, but the underlying cardiovascular changes include chronic myocardial inflammation, myocardial infarction, right ventricular dysfunction, and arrhythmias [177].

Post-vaccination myocarditis is most often linked to mild symptoms that occur within the first few days after the initial or second dose of mRNA vaccine, with chest pain being the most common symptom (96% of patients) [178]. Fatigue, shortness of breath, or arrhythmias are less frequently seen in patients with vaccine-induced myocarditis. An increased risk of extrasystoles was observed, rising from 1.17 after the first dose (95% CI 1.06–1.28) to 1.22 after the second dose (1.10–1.36) [179].

9. Diagnosis of Cardiac Involvement

Early diagnosis and prompt treatment of cardiovascular complications related to COVID-19 are crucial for reducing morbidity and mortality caused by the disease. Therefore, in addition to a comprehensive medical history and thorough physical examination, electrocardiogram (ECG) and cardiac biomarkers (troponin I, troponin T, NT-proBNP, and BNP) serve as highly useful initial screening tools in hospitalized patients and/or those at high risk for cardiovascular events.

Studies conducted on hospitalized COVID-19 patients showed ECG changes in 53% to 85% of cases, depending on the severity of the disease [100]. The most common ECG findings were ST-T changes, followed by heart rate and rhythm abnormalities [100,180]. Besides ST-T changes, other potential ECG signs seen in patients with myocarditis include: new bundle branch block,

pseudoinfarction, new-onset atrial fibrillation, QT prolongation, ventricular arrhythmia, bradyarrhythmia, advanced atrioventricular block, or ST elevation and PR depression in patients with associated pericarditis. However, these findings are not sensitive, and their absence does not rule out myocarditis [1].

Elevated cardiac troponin, caused by ischemic or non-ischemic myocardial injury, is a common finding in patients with SARS-CoV-2 infection, with a prevalence of 7% to 44% among hospitalized patients [181]. In the study by Majure et al. [182], the patients with mild or severely elevated troponin had a two- to fourfold higher risk of death compared to those with normal troponin levels. The troponin level is an independent predictor of in-hospital mortality, regardless of previous cardiovascular disease, ECG changes suggestive of acute coronary syndrome, or the degree of elevation of inflammatory markers. Accordingly, the measurement of troponin level is mandatory for risk stratification and helps identify patients who may require additional imaging and closer monitoring. Notably, a normal cardiac troponin level does not rule out myocarditis, especially in cases of giant cell myocarditis or during the chronic phase of myocardial injury [181]. In one study, the sensitivity of elevated TnI for myocarditis was only 34% [183].

Natriuretic peptide (BNP and NT-proBNP) levels are elevated during COVID-19 infection as indicators of cardiac injury and dysfunction. Severe SARS-CoV-2 infection, mechanical ventilation, and hospitalization are associated with increased BNP or NT-proBNP levels, and assessing natriuretic peptide levels could help identify patients at high risk who need closer monitoring and additional cardiac imaging evaluations [184].

In patients with ECG and/or cardiac biomarker abnormalities, echocardiography is a very useful method for initial evaluation, establishing the subsequent diagnostic approach, and risk stratification. The main echocardiographic changes in patients with myocarditis may include reduced left ventricular (LV) ejection fraction, increased wall thickness due to edema, regional or diffuse wall motion abnormalities, diastolic dysfunction, right ventricular dysfunction, pericardial effusion, and reduced LV global longitudinal strain (GLS) [175]. A reduced LV ejection fraction is associated with increased inpatient mortality in patients with COVID-19 [185]. Of note, a normal LV ejection fraction does not exclude myocardial involvement. Studies have shown that cardiac involvement could be present in 52 to 70% of patients with SARS-COV-2 infection, but the most common findings were subclinical changes, such as reduced GLS or diastolic dysfunction.

The latest European Society of Cardiology guidelines for managing myocarditis and pericarditis have developed several diagnostic algorithms based on initial clinical presentation. [186]. We propose a diagnostic approach algorithm adapted for COVID-19 patients. (see figure 3).

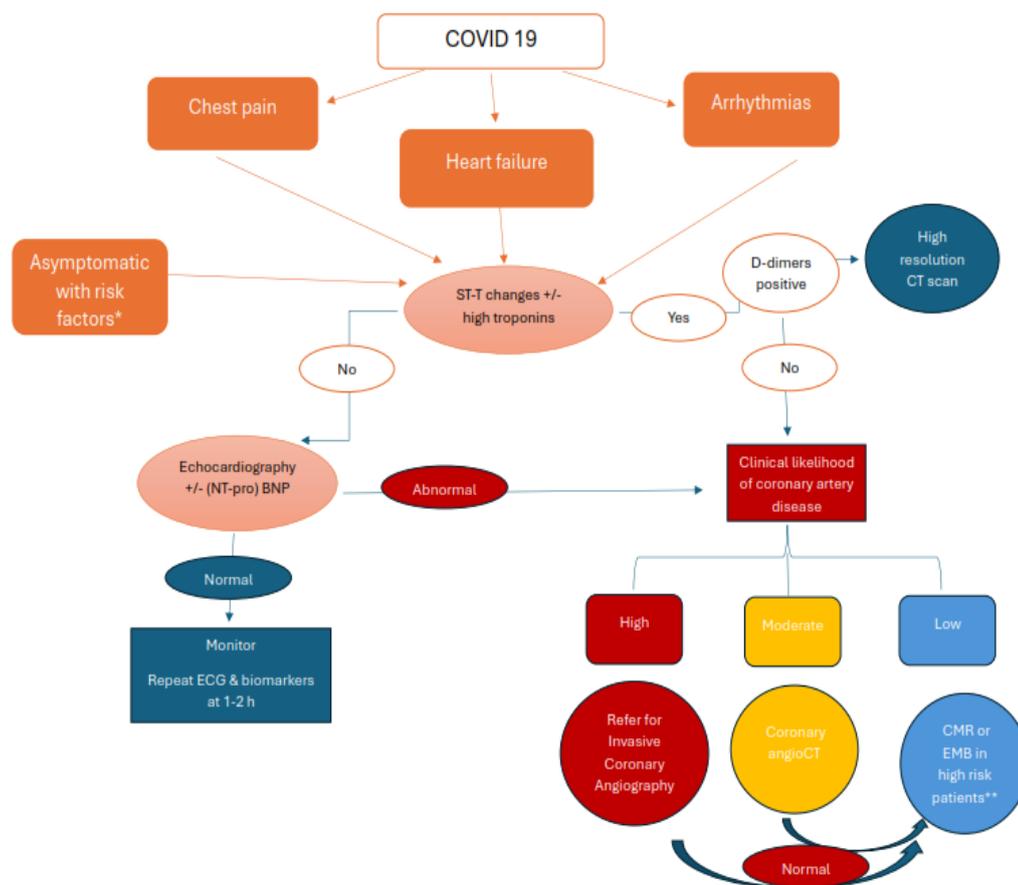


Figure 3. Diagnostic algorithm of cardiac involvement in COVID-19 patients based on initial clinical presentation. CT- computer tomography; CMR- Cardiac Magnetic Resonance; EMB-Endomyocardial biopsy.

The presence of acute chest pain lends itself to a differential diagnosis that should include acute coronary syndromes, myocarditis with or without associated pericarditis, or non-cardiac pain. The triad of chest pain, specific ST-T changes on ECG, and elevated troponin levels requires ruling out obstructive coronary artery disease, either through coronary angiography in patients with high clinical suspicion or by CT angiography in patients with moderate likelihood.

In patients with COVID-19 who develop new or worsening heart failure (HF), the diagnostic approach recommended by the ESC guidelines, summarized by the acronym CHAMPIT (acute Coronary syndrome, Hypertension, Mechanical causes, Arrhythmia, Pulmonary embolism, Infection, Tamponade), is very useful [186]. Acute or worsening dyspnea in patients with SARS-CoV-2 infection requires urgent computed tomography pulmonary angiography (CTPA) due to the high incidence of PE in this setting. A systematic literature review revealed an incidence of PE ranging from 0% to 1.1% in ambulatory patients, 0.9% to 8.2% in hospitalized patients, and 1.8% to 18.9% in ICU patients [187]. In patients in whom we have excluded the causes of HF have been ruled out, Cardiac Magnetic Resonance (CMR) imaging is recommended for the definitive diagnosis of infectious myocarditis. Endomyocardial biopsy (EMB) remains the gold standard for histological evaluation of suspected giant cell myocarditis in patients with rapidly progressive or refractory HF, cardiogenic shock, and/or malignant ventricular arrhythmias.

CMR is the best option for non-invasive evaluation of stable cases and provides valuable information by characterizing changes in the magnetic properties of tissues. CMR studies in patients with COVID-19 have shown a wide range of myocarditis prevalence, from 0 to 60%, depending on the diagnostic criteria used and patient selection [188]. There are no specific changes for SARS-CoV-2 myocarditis; the diagnosis is supported based on the updated Lake Louise criteria for myocarditis

[189]. Evidence of both myocardial edema (T2-based criteria: abnormal T2 mapping and T2-weighted imaging) and non-ischemic myocardial injury (T1-based criteria: abnormal native and post-contrast T1 mapping and late gadolinium enhancement) is required for the diagnosis of CMR-proven myocarditis. When only one of these two diagnostic criteria is met, the condition is classified as CMR-uncertain myocarditis, and additional signs such as pericardial involvement or global or regional left ventricular systolic dysfunction on cine imaging may help establish the diagnosis [186].

LGE burden has a poorer prognosis and predisposes to ventricular arrhythmias, heart failure, and death. Studies showed that myocarditis with septal LGE was associated with worse outcomes [190]. In one small study, LGE was located in the basal-to-mid inferior wall in COVID-19 patients. Li et al. demonstrated that patients with COVID-19 myocarditis linked to multisystem inflammatory syndrome (MIS) exhibited more widespread myocardial inflammation and edema, unlike patients without MIS, who only showed regional lesions [191]. Additionally, the distribution of LGE was at the level of the interventricular septum in patients with MIS, while in patients without MIS, LGE was evident at the inferior ventricular wall. Twenty-five percent of patients had persistent myocardial edema at a median follow-up of 102 days, but the LGE burden decreased over time in both groups. Figure 4 displays the CMR of a patient with persistent LGE after COVID-19 myocarditis.



Figure 4. CMR-LGE 4-chamber view showing mid and basal lateral wall subepicardial scar (red arrow) in a 58-year-old patient with ventricular arrhythmia and history of COVID-19 myocarditis.

The same standard diagnostic approach will be used for patients with suspected vaccine-associated myocarditis. COVID-19 vaccine-associated myocarditis has a predominantly mild clinical course, with low prevalence and limited cardiac dysfunction, but myocardial injury is common, especially in adolescent males presenting after the first or second dose of an mRNA vaccine, with 82% presenting with elevated troponin levels and late gadolinium enhancement (LGE). LGE was 2.74 times more common (95% CI: 1.28, 5.83, $p = 0.009$) in older adolescents (>15 years) compared to younger patients, 3.28 times more frequent (95% CI: 0.99, 10.6, $p = 0.052$) in males versus females, 7.18 times higher (95% CI: 1.05, 49.09, $p = 0.045$) after the first dose, and 4.5 times higher (95% CI: 1.23, 16.44, $p = 0.023$) after the second dose compared to the third dose of the mRNA vaccine. LGE was observed in 60% of patients at follow-up [178].

10. Future Directions

Future perspectives in managing myocardial and vascular injury in patients with COVID-19 concentrate on several key areas: improved risk assessment, targeted immunotherapy, advanced diagnostic tools, and long-term monitoring. Progress in biomarker discovery and imaging is expected to enhance early detection of cardiovascular complications and enable better risk assessment, allowing for more personalized management and improved selection of patients for vaccination, specific treatments, and close follow-up. Emerging evidence underscores the crucial role of immune dysregulation and endothelial dysfunction in COVID-19-related myocardial and vascular injury. Future treatment approaches are likely to focus on immune modulation, including agents that target specific cytokines and inflammatory pathways. [192]. Long-term follow-up and preventive strategies are increasingly recognized as essential, given the risk of severe illness in some categories of patients, the cardiovascular sequelae, and post-acute COVID-19 syndromes. Research is ongoing to define optimal surveillance protocols and preventive interventions for these patients.

Finally, future management will likely incorporate lessons from ongoing and completed randomized trials, focusing on evidence-based therapeutic algorithms and multidisciplinary care models to address the complex interactions of viral, immune, and vascular factors in COVID-19-related cardiac injury. [192,193].

Future efforts in managing COVID-19-related myocardial and vascular injury are also expected to benefit from advancements in multi-omics technologies, including transcriptomics, proteomics, and metabolomics. These new methods have started to identify molecular signatures linked to ongoing inflammation, endothelial dysfunction, and dysregulated immune pathways in both acute and post-acute COVID-19, providing new therapeutic targets. [194,195]. The integration of omics-based biomarkers into clinical approaches may enable more accurate differentiation between immune-mediated myocardial injury, microvascular involvement, and direct viral effect on the heart. In parallel, mechanistic studies have shown potential roles for complement inhibition, antithrombotic medication, mitochondrial stabilization, and targeted endothelial protection as emerging therapeutic strategies [195,196].

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