The Epidemiology of COVID-19 Vaccine-Induced Myocarditis

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1. Introduction

1.1. Classic Myocarditis

1.1.1. Classification and Aetiology. Myocarditis signifies inflammation within the myocardium, the heart's middle layer, leading to degeneration and eventual necrosis [1]. It can manifest as acute, subacute, chronic, or fulminant myocarditis. Acute myocarditis presents symptoms within a month, accompanied by elevated high-sensitivity troponin levels. According to the later-discussed Dallas criteria, it exhibits histological features of active myocarditis characterized by infiltrating mononucleated cells and monocyte necrosis [2]. Subacute myocarditis emerges when ongoing myocardial inflammation leads to sustained myocardial damage, with symptoms arising between one and three months. Chronic myocarditis denotes a persistent inflammatory process featuring fibrosis but no myocyte necrosis, often overlapping with subacute myocarditis [3]. Fulminant myocarditis, associated with severe acute myocarditis and hemodynamic compromise, frequently leads to cardiogenic shock. Endomyocardial biopsy (EMB) reveals diffuse inflammatory infiltrates, as elaborated later [2]. As far as the aetiology of myocarditis is concerned, the causes can
1.1.2. Epidemiology. The true incidence of myocarditis is challenging to quantify due to the variability in clinical presentation [5]. While endomyocardial biopsy (EMB) is the gold standard for definitive diagnosis, its invasive nature limits its use [6]. Electroanatomic mapping (EAM) has emerged as an alternative for diagnosing myocarditis, offering improved sensitivity and reduced false-negative rates compared with EMB [7].

Before the emergence of COVID-19, the Global Burden of Cardiovascular Disease reported an annual prevalence of 4.4 cases per 100,000 people aged 35–39 years in women and 6.1 cases in men, with corresponding mortality rates of 0.1 and 0.2 per 100,000 people, respectively [8]. However, during the first 8 months of the pandemic, the prevalence of excess cardiovascular deaths in England and Wales rose to 12 per 100,000 people, while, in England, there was a marked 8% increase in acute cardiovascular disease deaths [9]. Concurrently, in the United States, hypertensive and ischemic heart disease rose compared with the year before [10].

A study published in February 2020, examining sex differences in myocarditis clinical presentation, found that the majority of patients with myocarditis were male (82%) and young adults (average age: men: 40 ± 16; women: 40 ± 17) [11].

1.1.3. Pathophysiology. The academic community extensively investigates the molecular and cellular pathophysiology of postviral myocarditis in animal models [12]. A simplified three-stage process elucidates cellular and molecular pathogenesis.

(1) Immune Activation: in the initial stage, pathogens, typically viruses or toxins, injure cardiac myocytes, exposing intracellular antigens such as cardiac myosin and activating the innate immune system [13, 14]. This stage involves upregulating Toll-like receptor 4 (TLR4) on macrophages, maturing antigen-presenting cells (APCs), and releasing pro-inflammatory cytokines, including interleukin-1 (IL-1) [15].

(2) Inflammatory Response: in the second stage, CD4+ T-lymphocytes play a key role, producing cytokines that lead to a Th1/Th2/Th17/Th22 (T-helper)-biased immune response [16]. B-lymphocytes also contribute to inflammation by producing antibodies.

(3) Outcome Variation: in the third stage, most patients experience a reduced immune response, leading to viral clearance facilitated by cytotoxic CD8+ T-lymphocytes [17]. However, in some cases, viral clearance remains elusive, resulting in persistent myocyte injury [17].

The pathways implicated in the pathogenesis of vaccine-associated myocarditis closely resemble those observed in viral myocarditis discussed above, suggesting a shared pathophysiology. In this case, however, tumour necrosis factor-alpha (TNF-α), interferon gamma (IFN-γ), IL-6, and IL-1 are the inflammatory cytokines involved, with genetic predispositions to IL-6-induced inflammation thought to exacerbate vaccine reactions [18]. Furthermore, in contrast to classic myocarditis, the spike protein utilized in the vaccine could induce molecular mimicry with α-myosin, akin to phenomena observed in certain COVID-19 infections [19]. Additionally, there is a plausible autoimmune aspect through molecular mimicry [18].

1.1.4. Evaluation and Diagnosis. Due to the overlap in symptoms with other clinical presentations, the diagnosis of myocarditis is often challenging. It is, therefore, important to highlight that a preceding acute febrile illness, symptoms of connective tissue disease, and a viral infection should always lead to suspicion [20–22]. Figure 2 provides an overview of the investigations used in the diagnosis of myocarditis and respective findings [21, 23].

1.1.5. Treatment. Determining the aetiology in classic myocarditis cases using a multidisciplinary approach is crucial for effective management. For example, myocarditis caused by immune-mediated diseases requires immunosuppressants (e.g., corticosteroids), and viral-induced myocarditis necessitates anti-infective agents [24]. However, when the cause is unknown, treatment primarily focuses on supportive care, including managing complications such as heart failure or arrhythmias [25].

1.2. COVID-19 Pandemic and Vaccine Development

1.2.1. The Coronavirus Disease 2019 (COVID-19). As of January 2021, the COVID-19 pandemic had a significant global impact, with over 100 million infections and 2 million deaths, affecting the economy, psychology, and health [1, 26]. The FDA’s emergency use authorization in December 2020 for two mRNA vaccines, Pfizer-BioNTech and Moderna, was pivotal. These vaccines demonstrated high safety and effectiveness, with reported rates of 94-95% efficacy after two doses [27]. However, concerns about potential side effects due to the rapid vaccine development increased hesitancy toward mRNA vaccine acceptance [26, 28].

1.2.2. The mRNA Vaccine Platform. The discussed vaccines are lipid nanoparticle-encapsulated mRNA vaccines, encoding prefusion stabilized spike proteins [28, 29]. Nanoparticles are extensively studied in vaccine development and serve as common vectors for in vivo RNA delivery, preventing mRNA degradation and facilitating endocytosis [30]. Positively charged lipid nanoparticles aid mRNA delivery to the negatively charged cell membrane, enabling cytoplasmic endocytosis. Once inside, mRNA is released, leading to spike protein translation in ribosomes. The final steps involve spike protein secretion, internalization by
APCs, and incorporation into the major histocompatibility complex (MHC) class II antigen-presenting complex [31]. This process generates an adaptive immune response, fostering antibody and cell-mediated immunity against SARS-CoV-2 spike proteins [32,33]. Figure 3 illustrates the mRNA vaccine mechanism [34].

1.3. COVID-19 Vaccine-Induced Myocarditis. The extensive COVID-19 vaccination program, launched in December 2020, prompted the FDA and Centers for Disease Control and Prevention (CDC) to assess vaccine side effects through the Vaccine Adverse Event Reporting System (VAERS), which encourages voluntary reporting of postvaccine side effects [4, 35]. The CDC was the first to link the two mRNA COVID-19 vaccines with myocarditis, estimating an incidence of 0.48 per 100,000 in the general population and 1.2 per 100,000 in individuals aged 18 to 29 [35]. In April 2021, the CDC classified patients’ adverse vaccine reactions according to working case definitions for probable or confirmed myocarditis. Figure 4 illustrates the classification [36].

As of June 2021, in a cohort of 300 million mRNA-vaccinated patients, there were 1226 reports of probable myocarditis [37]. Notably, 79% of these cases occurred in males, with a median age of 24 years, and symptoms typically emerged about a week after the second vaccine dose. Common symptoms included chest pain and dyspnoea, with or without palpitations. Among male adolescents, 86% experienced chest pain, 64% had elevated cardiac enzymes, and 61% exhibited ECG changes [37]. Among 323 confirmed myocarditis cases, 310 patients were hospitalized and later discharged with symptom resolution [37]. However, the reasons for this male predominance remain unknown, despite recognition by the CDC.

Although the exact mechanisms behind mRNA COVID-19 vaccine-related myocarditis are unclear, several hypotheses have been proposed [38]. Some researchers suggest direct viral invasion as a potential mechanism, while others propose host cell inflammatory responses. Notably, cardiac histopathology studies have reported a lack of diffuse lymphocytic myocarditis, which is characteristic of the classic presentation [39, 40]. Research on inflammatory infiltrates suggests that an exaggerated innate immune system response, increased pro-inflammatory cytokines, and endothelial dysfunction may contribute to the pathophysiology of COVID-19 vaccine-related myocarditis [18]. Certain individuals with genetic predispositions may experience...
hyperimmune responses to mRNA, leading to both aberrant innate and adaptive immune responses [18]. TLR-expressing cells exposed to RNA may express activation markers and cytokines, with potential differences when exposed to modified RNA compared with unmodified RNA [41]. This may trigger the immune system to detect mRNA in the vaccine as an antigen, leading to immune activation and pro-inflammatory cascades [18]. Additionally, stress, ischemia, and hypoxia-induced myocardial injury are suggested as alternative mechanisms [42].

Figure 3: Visual representation of the mechanism of action of the mRNA vaccine: the lipid nanoparticle and mRNA vaccine complex enter the muscle cell or APC by endocytosis. Translocation and translation to spike proteins take place in the ribosomes. Secretion of the spike protein into the extracellular environment, internalization into APCs via endocytosis, and incorporation as part of MHC class II take place. Antibody and cell-mediated immunity against SARS-CoV-2 take place.

Figure 4: Illustration of the CDC definition of myocarditis. ECG: electrocardiogram; TTE: transthoracic echocardiogram; MRI: magnetic resonance imaging.
Long-term outcomes, cardiac function, and implications in affected patients are still unknown, necessitating ongoing follow-up [43–45]. Currently, there is no consensus on the management of COVID-19 vaccine-induced myocarditis, raising questions about whether the traditional myocarditis treatment plan should be followed in these cases [46, 47].

This paper aims to review existing literature and secondary data on mRNA COVID-19 vaccine-induced myocarditis, exploring its epidemiology, including age, ethnicity, and gender associations, with a focus on male predominance. The paper will also analyse the immunopathophysiologial mechanisms and outline the principles of diagnosis, clinical presentation, and management, emphasizing early identification and timely therapy.

2. Methodology

A literature review was undertaken to examine the association between mRNA vaccination against SARS-CoV-2 and myocarditis. The primary databases employed in the sourcing of material in this review were PubMed, Embase, and Queen Mary University of London Library Services. The articles were selected on the basis that they were peer-reviewed, reliable, and published between January 2000 and December 2023. The terms employed in the research include “myocarditis,” “coronavirus disease 2019,” “SARS-CoV-2,” “mRNA Covid-19 vaccines,” “Covid vaccine-associated myocarditis,” “epidemiology,” “potential mechanisms,” “myocarditis diagnosis,” and “myocarditis management.” The inclusion and exclusion criteria used in the database search are summarized in Table 1.

3. Results

During the literature search, we identified a total of 107 articles and evaluated them to determine their alignment with our inclusion and exclusion criteria. Among these, 8 of the 107 papers met our criteria and were subsequently subjected to a thorough review.

A search of electronic databases, including the World Health Organization’s (WHO) Global Literature on Coronavirus Disease, identified 22 eligible randomized controlled trials and observational studies reporting the risk of COVID-19 vaccines and myocarditis on a global scale [48]. Between December 2019 and May 2022, among 58 million people, 55.5 million received the COVID-19 vaccination. Only 12 studies received Moderna, Pfizer-BioNTech, or mixed mRNA vaccines. Among 37.6 million mRNA vaccine recipients, 588 developed myocarditis, with 66% being men and number of deaths totalling 3. The median follow-up from vaccination to myocarditis was 28 days. Table 2 shows the baseline study characteristics.

3.1. Risk of Myocarditis Associated with the COVID-19 Vaccination. Evaluating the risk of COVID-19 vaccine-induced myocarditis involves considering several factors. Firstly, there is the background risk of myocarditis in different geographic locations, and over time, it is influenced by the viral pandemic [43]. Current data primarily capture cases with more than minimal symptoms, leaving the full extent unknown [48].

The meta-analysis following the systematic review reported an increasing risk of myocarditis associated with younger age. Even though there was an increased association between the risk of myocarditis, mRNA vaccines, and male gender in the USA, the association was not statistically significant. In addition, the risk of hospitalization and death following COVID-19 vaccine-induced myocarditis was low, and it did not result in more serious outcomes compared with those unrelated to vaccination.

3.2. Age-Specific Risk of Myocarditis Associated with the COVID-19 Vaccination. The prevalence of COVID-19 vaccine-induced myocarditis risk, especially in young males, remains uncertain [46, 47]. Nevertheless, assessing population-based risk estimates for vaccine-related myocarditis across age, gender, and ethnicity is crucial, especially as vaccination efforts target young individuals and additional doses are administered.

Regarding age, similar results have also been reported by VAERS in the USA. Table 3 illustrates the number of observed myocarditis cases based on gender and age in a 7-day risk window following the second dose of mRNA vaccination through June 11, 2021 [60]. The observed cases of myocarditis demonstrate a higher incidence in males than females and higher at younger ages than older ones with the highlight being 18–24 years of age [60].

The crude reported cases of myocarditis including death reports per million mRNA COVID-19 vaccine doses are presented in Table 4. According to the results published by VAERS in the USA through June 11, 2021, male rates per million doses are higher than female rates [60].

Pharmacovigilance systems in France and other countries, including Israel, reported similar results [61–63]. Population-based cohort studies in European countries such as Denmark and the United Kingdom also showed a higher risk associated with the Moderna vaccine [56, 64].

This increased risk, particularly notable among individuals aged 12 to 39 in Denmark [65], remained low overall, even among young recipients. These findings highlight an elevated risk of COVID-19 vaccine-related myocarditis occurring within one week after mRNA vaccination, especially following the second dose of the Moderna vaccine [56].

Current studies suggest that while the risk of myocarditis is elevated when the mRNA vaccine is given as a booster dose, this is still lower than after the second dose [66, 67]. The notable difference in risk was evident, especially after the mRNA-1273 vaccine, when comparing the second dose to the booster dose. According to Milano et al., the mRNA content in mRNA-1273 during booster administration is 50 micrograms, which is half the dosage administered during the priming phase [68]. In contrast, the BNT162b2 vaccine utilizes 30 micrograms for both priming and boosting. Hence, the potential risk of myocarditis subsequent to mRNA vaccines might be influenced by the mRNA dosage, potentially attributable to the presence of double-stranded RNA capable of inducing dose-related innate immune
activation and found in low quantities in mRNA vaccines [68]. The rapid onset of symptoms postvaccination, even after the first dose, aligns with the plausibility of such a direct effect [68].

There is currently no statistical evidence as to whether a lower mRNA COVID-19 vaccine dose will reduce the risk of myocarditis. It is therefore evident that additional research is needed to assess the myocarditis risk related to the COVID-19 lower dose, considering an extended observation period.

3.3. Gender-Specific Risk of Myocarditis Associated with the COVID-19 Vaccination. COVID-19 vaccine-induced myocarditis exhibits a male predominance, with a male-to-female ratio of 1:7:1, although the underlying cause remains unknown [69, 70]. One possible explanation is related to sex hormones and their interaction with receptors in host cardiac and immune cells [71].

In particular, oestradiol provides a cardioprotective effect by triggering both IL-4-associated Th2-type and anti-inflammatory M2 macrophage responses while promoting mitochondrial fusion in the cardiomyocytes [72]. In contrast, testosterone promotes mitochondrial fission, resulting in an increased production of reactive oxygen species (ROS) and the release of mitochondrial damage-associated molecular patterns (DAMPs) [73]. The outcome involves the activation of the nucleotide-binding and oligomerization domain (NOD), leucine-rich repeat (LRR), and pyrin domain-containing protein 3 (NLRP3) inflammasome. This leads to a pro-inflammatory immune response characterized by the release of IL-1β and IL-18, as well as the activation of both M1 macrophages and the Th1 subset of CD4+ T cells [73, 74].

Studies in mouse models of coxsackievirus infection have shown that testosterone promotes TLR4 signalling in myocarditis, which might contribute to increased levels of IL-1β and IL-18, leading to cardiomyocyte apoptosis and contractile dysfunction [75, 76]. Indeed, IL-1β has demonstrated its role in determining cardiomyocyte apoptosis through the activation of caspase-dependent pathways (via the release of cytochrome C, subsequently activating caspase 3) and caspase-independent pathways (via the upregulation of endonuclease G). Additionally, IL-1β inhibits survivin, a member of the inhibitor of apoptosis protein family [77]. Simultaneously, IL-18, through its binding to Toll-like receptors (TLRs), instigates the MyD88 signalling axis. This, in turn, leads to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and an augmented production of inducible nitric oxide synthase (iNOS), resulting in diminished myocardial contractile function [78]. Hence, the observed sex differences in the modulation of mitochondrial dynamics and inflammatory responses may contribute to the pathogenesis of COVID-19 vaccine-induced myocarditis, elucidating the higher incidence of this complication in males.

The gender bias is also linked to differences in inflammatory and cardiac biomarkers between genders. A retrospective cohort study by Cheng et al. revealed an independent risk relationship between myocardial injury and inflammatory response in male patients, who are more susceptible to inflammatory stress [79]. The role of angiotensin-converting enzyme 2 (ACE2) in this context is important. ACE2’s binding with viral spike proteins not only facilitates SARS-CoV-2 entry into cells but also leads to ACE2 downregulation and uncontrolled activation of the renin-angiotensin-aldosterone system [80]. Notably, the ACE2 gene’s location on the X chromosome may contribute to the increased risk of myocardial injury in males due to differences in methylation and sex chromosome activation [81].

In contrast, females tend to have higher oestrogen levels than males, which enhances ACE2 activity and expression in a concentration-dependent manner [82]. This leads to upregulated angiotensin-(1–7) expression, encouraging vasodilation, nitrogen oxide release, and reduced smooth muscle cell proliferation [82, 83]. Oestrogen also plays a protective role against inflammatory injury to the vascular endothelium [84].

3.4. Diagnosis

3.4.1. Clinical Presentation. Clinical presentation varies among patients, with some experiencing mild, nonspecific symptoms such as dyspnoea, fatigue, chest pain, and exertional tightness, while others are asymptomatic, possibly due to limited pericardial involvement [43, 85, 86]. In contrast to viral-induced myocarditis, most patients with vaccine-associated myocarditis present with chest pain, but this might reflect a selection bias favoring the identification of symptomatic individuals [54, 87]. Cardiac troponin levels are typically elevated in most patients and peak between 48 and 72 hours after symptom onset [57, 88, 89]. Inflammatory markers, such as C-reactive protein, also show an increase. According to Haussner et al., electrocardiogram (ECG) changes in vaccine-associated myocarditis are subtle, nonspecific, and similar to those in classical myocarditis.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Publication year</th>
<th>Country</th>
<th>Type of study</th>
<th>Mean age (years)</th>
<th>Sample size</th>
<th>Follow-up (days)</th>
<th>Male (% total)</th>
<th>mRNA vaccine type</th>
<th>Number of myocarditis cases</th>
<th>Male (% myocarditis)</th>
<th>Myocarditis diagnostics</th>
<th>Number of hospitalizations</th>
<th>Number of deaths</th>
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<td>46</td>
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<td>Pfizer/Moderna</td>
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<td>Israel</td>
<td>Population study</td>
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<td>Population study</td>
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<td>Pfizer</td>
<td>21</td>
<td>91</td>
<td>Clinical</td>
<td>N/A</td>
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These may include nonspecific or mild diffuse ST-segment changes and PR-segment depressions. Some patients may present with sinus tachycardia, while ventricular and supraventricular arrhythmias occur rarely and typically in severe cases [90].

Overall, patients with COVID-19 vaccine-induced myocarditis usually develop a mild disease with favorable outcomes [91]. However, like in classic myocarditis, clinicians must remain vigilant for severe cases, as a limited number of cases have reported associations with fulminant myocarditis characterized by giant cells, eosinophilic myocarditis, and lymphocytic myocarditis [92]. These patients require early detection and vigorous intervention, as discussed in the management section.

Current research suggests that adverse outcomes are rare in patients with vaccine-induced myocarditis [93]. However, acute arrhythmias should be monitored for several days following patient admission. Discharge may occur if there is clinical improvement with no major arrhythmias or deterioration in cardiac function. Figure 5 illustrates the clinical characteristics of COVID-19 vaccine-induced myocarditis [85].

3.4.2. Endomyocardial Biopsy and Cardiac Magnetic Resonance Imaging. Diagnosing myocarditis can be challenging, with endomyocardial biopsy (EMB) traditionally considered the gold standard [94]. However, EMB is rarely performed in COVID-19 vaccine-associated myocarditis, as cases are often mild [95].

Cardiac magnetic resonance (CMR) offers a noninvasive and accurate method for diagnosing clinically suspected myocarditis. The European Society of Cardiology suggests that clinically suspected myocarditis can be diagnosed when clinical symptoms are present, along with at least one of four clinical criteria, including evidence of late gadolinium enhancement (LGE) on CMR [96]. Asymptomatic cases require at least two clinical criteria. Although CMR is highly accurate for diagnosing “infarct-like” myocarditis characterized by fever, chest pain, and elevated ST segments on the ECG, its accuracy is limited in primarily arrhythmic presentations [23]. The updated “Lake Louise Criteria” from 2018 by the International Consensus Group incorporates oedema, T1-mapping, LGE, extracellular volume, and T2-mapping techniques on CMR for myocarditis diagnosis [97]. Figure 6 illustrates the updated Lake Louise Criteria [23].

Cooper et al. emphasize the importance of standard endomyocardial biopsy (EMB) approaches, particularly the left ventricular approach, in diagnosing myocarditis [98]. Additionally, the morphomolecular characteristics of inflammatory myocardial lesions can provide insights into pathophysiology and the clinical course [99].

Regarding the diagnosis of COVID-19 vaccine-induced myocarditis, reports are limited due to the small number of clinical findings and different referral patterns, often lacking confirmation through CMR or EMB. The accurate number of asymptomatic myocarditis cases following COVID-19 vaccination based on CMR criteria remains unknown, as recent observational studies have not consistently included CMR [100]. Experts recommend that elevated laboratory values, such as troponin, and echocardiogram abnormalities should trigger CMR and, if indicated, EMB interventions [101, 102]. Figure 7 outlines a potential workflow for CMR use in patients with suspected COVID-19 vaccine-induced myocarditis [85].

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**Table 3:** Report of the observed number of myocarditis cases in a 7-day risk window after the second dose of mRNA COVID-19 vaccination according to USA VAERS through June 11, 2021.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Average doses administered</th>
<th>Observed cases</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
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<td>12–17</td>
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<td>50–64</td>
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</tr>
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<td>&gt;65</td>
<td>19875261</td>
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</table>

**Table 4:** Report of myocarditis crude rates and related deaths per million mRNA vaccine doses administered by age, sex, and dose number to VAERS following mRNA COVID-19 vaccination through June 11, 2021.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Female rates per million doses</th>
<th>Male rates per million doses</th>
<th>Death reports per million doses administered</th>
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<td></td>
<td>All doses</td>
<td>Dose 1</td>
<td>Dose 2</td>
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<td>4.2</td>
<td>1.1</td>
<td>9.1</td>
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<td>18–24</td>
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</tbody>
</table>
3.5. Pathology of COVID-19 Vaccine-Induced Myocarditis. Due to the low severity of COVID-19 vaccine-induced myocarditis, autopsy reports including histopathological analysis have been limited in number [103, 104]. The clinical community has documented that the majority of cases reflect a lymphocyte predominance, with some cases encompassing additional neutrophil cells [105].

3.6. Possible Mechanisms of COVID-19 Vaccine-Induced Myocarditis

3.6.1. Molecular Mimicry of Spike Proteins. One crucial immune mechanism involves molecular mimicry between SARS-CoV-2 spike proteins and self-antigens [105]. Moderna and Pfizer-BioNTech’s mRNA vaccines employ lipid
nanoparticles for in vitro transcribed (IVT) mRNA delivery encoding the viral spike protein and activating an adaptive immune response [106]. This leads to IgG antibody generation by B-lymphocytes targeting spike proteins, aiding viral neutralization by preventing attachment to ACE2 host cell surface proteins [107].

Some argue that heart-reactive antibodies do not cause myocarditis, but past research suggests they can affect cardiac cells, especially in genetically susceptible individuals [104, 108]. The cross-reactivity of antibodies against viral spike proteins with structurally similar human peptides, including alpha-myosin, raises concerns about vaccine-induced autoimmunity [109]. Research is needed to assess SARS-CoV-2 antigens’ potential to induce autoimmunity.

Consider autoantibody generation as a potential mechanism in postvaccination myocarditis for susceptible individuals. Case reports show a peak in IgM and IgG antibodies on day 2 alongside symptoms, without the expected decline as the clinical condition improves [110]. Some argue these autoantibodies may not be pathogenic but a result of myocardial inflammation. Additionally, in the same case reported by Muthukumar et al., there was a twofold increase in natural killer (NK) cell frequency, which remains unclear in its contribution to disease resolution or pathology [110].

### 3.6.2. Overactive Immune System Response

Research on mRNA vaccines highlights their potential to induce myocarditis through excessive immune responses [106]. Prior studies proposed that RNA components and lipid nanoparticles in COVID-19 vaccines can trigger an exaggerated innate immune response, potentially causing vaccine-associated myocarditis [111]. Despite being the first clinical use of IVT mRNA, mRNA vaccines faced early challenges due to mRNA molecule instability and inherent immunogenicity. Wolff et al. investigated endosomal Toll-like receptors in immune cells and cytosolic receptors such as TLR3, TLR7, TLR8, RIG-I, and MDA5’s potential to cross-react with IVT mRNA [112]. Activation of these receptors initiates an inflammatory cascade, leading to inflammasome assembly, type I interferon production, and NF-κB translocation [113].

Recent literature suggests lipid nanoparticles may trigger TLR-mediated pro-inflammatory cytokine release and complement activation-related hypersensitivity reactions [113]. These findings show that overly aggressive immune responses could contribute to COVID-19 vaccine-induced myocarditis.

### 3.7. Management of Vaccine-Related Myocarditis

Regarding management, most cases of COVID-19 vaccine-induced myocarditis are self-limiting [114]. However, clinicians must assess myocardial risk, especially in young males with postvaccination chest pain. Initial evaluation includes interpreting ECG, cardiac troponin, and inflammatory marker levels [115]. Individuals with suspected COVID-19 vaccine-induced myocarditis should consider consultation with a cardiologist and assessment using CMR and TTE [115]. Managing arrhythmias and heart failure associated with the COVID-19 vaccination should also be addressed [97].
For arrhythmias and heart failure, guideline-directed therapies recommend heart failure drugs such as angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), beta-blockers, sodium-glucose cotransporter 2 inhibitors, and mineralocorticoid receptor antagonists [116].

There is controversy regarding ACE-Is and ARBs due to early reports from China highlighting that patients with hypertension exhibited worse outcomes [117, 118]. However, analyses were crude and confounders, i.e., older age and cardiovascular disease, associated with hypertension were also present [119]. ACE-Is could theoretically increase SARS-CoV-2 infection risk due to ACE2’s role as a binding site [120]. Although these drugs do not directly affect ACE2 activity, animal studies suggest they may upregulate ACE2 in the heart, raising concerns about COVID-19 susceptibility [121]. However, no human study supports this hypothesis [120]. In turn, the European Society of Cardiology issued the position statement that ACE-Is/ARBs should not be discontinued, while current evidence suggests that there is no significant association between these agents with COVID-19 diagnosis or worse outcomes [122, 123].

In fulminant myocarditis cases, characterized by severe hemodynamic instability, the American Heart Association recommends EMB as a class 1 indication [124, 125]. Mechanical circulatory support can also benefit cases with left ventricular dysfunction. Table 5 summarizes the management of COVID-19 vaccine-induced myocarditis.

Some published case reports have used corticosteroids and colchicine to manage patients, including those with persistent mild symptoms. Hajjo et al. proposed an approach that carefully weighs the benefits and risks of immunosuppression in COVID-19 vaccine-induced myocarditis, suggesting the selective use of corticosteroids, particularly glucocorticoids, for a limited duration in patients with acutely impaired left ventricular function [126–128]. Additionally, aspirin, intravenous immunoglobulin, beta-blockers, and angiotensin-converting enzyme inhibitors may be considered for patients with left ventricular systolic dysfunction [129, 130].

3.8. Recovery and Surveillance. Regarding the recovery from COVID-19 vaccine-induced myocarditis, several dilemmas exist [129]. A study from the Multicenter Lombardy Registry in 2018, which examined 429 adult patients who survived acute myocarditis, found that only 4.5% of them had residual left ventricular dysfunction at the 3-year follow-up [130]. As myocarditis can have long-term consequences, postacute care involving laboratory tests, ECG, and TTE is essential [130]. Furthermore, there is limited evidence available on the effects of exercise restriction for 3–6 months postvaccine-induced myocarditis on recovery and the prevention of sudden cardiac death [131].

4. Discussion

Extensive research has established a clear association between the mRNA COVID-19 vaccination and myocarditis. Diaz et al. [53] reported a distinct myocarditis syndrome primarily occurring after the second vaccine dose, with an incidence of 1.0 per 100,000 individuals. Albert et al. [63] also supported this link, particularly among males aged 16 to 30. The literature review explained the male predominance by examining gender-based differences in inflammatory pathways, cardiac biomarkers, and sex hormones.

Additionally, the lack of a definite immunopathophysiologic mechanism underscores the need for further exploration to understand the reasons behind COVID-19 vaccine-induced myocarditis, differentiating it from infection-related myocarditis and assessing the impact of elevated cytokine levels on various organs, as observed in COVID-19 infection.

Furthermore, a detailed analysis of diagnostic and management strategies highlights the absence of guidelines for acute patient presentations. Challenges include determining the appropriate timeframe for guideline-driven therapy and managing cases with persistent symptoms but without significant cardiac abnormalities or troponin elevations. Questions also arise about administering the second vaccine dose to individuals with COVID-19 vaccine-induced myocarditis after the first dose and selecting the appropriate vaccine agent.

4.1. Limitations. Firstly, due to the emergence of COVID-19 vaccine-induced myocarditis in early 2021, there is a lack of prior research on this topic. Consequently, epidemiological data are limited, primarily sourced from a few countries such as the USA, France, Denmark, the UK, and Israel. Furthermore, studies reporting these data may exhibit selection bias, often relying on cohort and case-controlled studies for participant selection, overestimating the cases of myocarditis.

The proposed hypotheses may lack strong direct empirical evidence and often rely on limited data from case series. Additionally, the mild presentation of affected individuals has contributed to the scarcity of invasive investigations, such as endomyocardial biopsy (EMB).

4.2. Recommendations for Research. Based on the analysis and literature review of COVID-19 vaccine-associated myocarditis, the following recommendations are proposed:

(1) Immunopathological Mechanisms Research: future investigations should aim to confirm the immunopathophysiologic mechanisms of COVID-19 vaccine-induced myocarditis. This research should determine whether these mechanisms are unique to mRNA vaccination or associated with spike protein delivery via mRNA. Strategies for reducing inflammatory vaccine reactions could involve modifying IVT mRNA components, utilizing modified nucleosides to mitigate innate immune responses, and eliminating dsRNA by-products and abortive RNA transcripts. Although some experimental therapies have explored innate immune inhibitors with IVT mRNA, these approaches have not yet been applied to the two distinct mRNA COVID-19 vaccines. Redesigning lipid nanoparticles may also assist...
in reducing immunogenicity. It is essential to strike a balance between these efforts and the necessity of generating a robust immune response for effective vaccine protection.

(2) Role of Immune Cell Populations: research should prioritize elucidating the roles played by specific immune cell populations in post-COVID-19 vaccine immunization, infection, myocardial injury, and COVID-19 vaccine-associated myocarditis. A comprehensive understanding of how different immune cells contribute to these processes can provide valuable insights into vaccine safety and efficacy.

(3) Risk-Benefit Analysis for Different Demographics: subsequent studies should thoroughly investigate the potential risks and benefits of COVID-19 vaccination across various gender and age groups, with a specific focus on different vaccine doses. Prospective screening for myocarditis following the mRNA COVID-19 vaccination should target diverse population groups, paying particular attention to gender and age-related characteristics, notably among young males. Additionally, highly physically active individuals may benefit from cardiac screening, even in the absence of symptoms, to detect significant cardiac complications.

5. Conclusion
In summary, this literature review aimed to explore the link between myocarditis and mRNA COVID-19 vaccination. The research reviewed indicates that myocarditis is indeed a rare outcome of the mRNA COVID-19 vaccination. While the precise mechanistic explanations remain uncertain, the roles of spike proteins and inflammatory cytokines should not be disregarded pending further investigation. Additionally, the observed male predominance in COVID-19 vaccine-related myocarditis may have implications for assessing the risk-benefit ratio of subsequent mRNA COVID-19 vaccine doses. Future research efforts should prioritize investigating this association using a collaborative registry approach that collects comprehensive data on patient demographics, clinical presentation, laboratory biomarkers, imaging findings, and other relevant investigations. This will provide clearer guidance on managing myocardial injury associated with the mRNA COVID-19 vaccination.

**Acronyms**

- **ACE-Is**: Angiotensin-converting enzyme inhibitors
- **ACE2**: Angiotensin-converting enzyme 2
- **APCs**: Antigen-presenting cells
- **ARB**: Angiotensin receptor blocker
- **BNT162b2**: Pfizer-BioNTech vaccine
- **CDC**: US Centers for Disease Control and Prevention
- **CMR**: Cardiac magnetic resonance
- **COVID-19**: Coronavirus disease 2019
- **DAMPs**: Damage-associated molecular patterns
- **EAM**: Electroanatomic mapping
- **ECG**: Electrocardiogram
- **EMB**: Endomyocardial biopsy
- **FDA**: US Food and Drug Administration
- **IFN-γ**: Interferon gamma
- **IL**: Interleukin
- **iNOS**: Inducible nitric oxide synthase
- **IVT**: In vitro transcription
- **LGE**: Late gadolinium enhancement
- **LRR**: Leucine-rich repeat
- **MDA 5**: Melanoma differentiation-associated protein 5
- **MHC**: Major histocompatibility complex
- **mRNA-1273**: Moderna vaccine
- **mRNA**: Messenger RNA
- **NF-κB**: Nuclear factor kappa-light-chain-enhancer of activated B cells
- **NK**: Natural killer
- **NLRP3**: Pyrin domain-containing protein 3
- **NOD**: Oligomerization domain
- **RIG-I**: Retinoic acid-inducible gene I
- **ROS**: Reactive oxygen species
- **SARS-CoV-2**: Severe acute respiratory syndrome
- **Th**: T-helper cell

**Table 5: Summary of management of COVID-19 vaccine-induced myocarditis.**

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Chest pain</td>
<td>Initial evaluation using ECG, cardiac troponin, and inflammatory marker levels [114]</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Guideline-directed therapy based on arrhythmia type [115]</td>
</tr>
<tr>
<td>Heart failure with reduced ejection fraction</td>
<td>Angiotensin-converting enzyme inhibitors</td>
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<tr>
<td></td>
<td>Angiotensin receptor blockers</td>
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<tr>
<td></td>
<td>Beta-blockers</td>
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<td></td>
<td>Sodium-glucose cotransporter 2 inhibitors</td>
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<td></td>
<td>Mineralocorticoid receptor antagonists [115]</td>
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<tr>
<td>Fulminant myocarditis-cardiogenic shock</td>
<td>Short-term corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Mechanical circulatory support in left ventricular dysfunction [123, 124]</td>
</tr>
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The authors declare that they have no conflicts of interest.

Conflicts of Interest

The primary databases employed in the sourcing of material in this review were PubMed, Embase, and Queen Mary University of London Library Services.

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[118] M. Hoffmann, H. Kleine-Weber, S. Schroeder et al., “SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is


