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Post-Vaccine Myocarditis: Clinical Insights and Epidemiological Trends

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Abstract:- Myocarditis is a rare but key adverse event linked to mRNA COVID-19 vaccines, predominantly in young males. Epidemiological data indicate an incidence of approximately 12.6 cases per million doses administered to patients aged 12-39 years, mostly following the second dose of the vaccine. Most patients present with elevated levels of cardiac biomarkers, chest pain, and abnormal ECG findings within a few days of vaccination. Proposed mechanisms for the exact pathophysiology of this include molecular mimicry between the SARS-CoV-2 spike protein and cardiac antigens, activation of immune pathways, and dysregulated cytokine expression. Despite these findings, the overall benefit-risk balance for COVID-19 vaccination remains positive, as the majority of patients recover fully. In contrast, COVID-19-associated myocarditis is more common and more severe, with an estimated incidence of 1,000-1,400 cases per 100,000 infections. Clinical presentation of vaccine-associated myocarditis is usually mild and self-limiting, and most patients do recover without significant long-term effects. Treatment is usually supportive in nature and has an emphasis on ruling out acute coronary syndrome and symptomatic management for heart failure or arrhythmias if present. Given its low incidence and the generally good outcome, vaccination against COVID-19 is recommended from 12 years of age and above, with provision for ongoing surveillance for monitoring and management of rare adverse events like myocarditis.

Keywords:- *Myocarditis, COVID-19, Vaccination, mRNA Vaccine.*

I. INTRODUCTION

Myocarditis is a rare but serious complication associated with COVID-19 mRNA vaccines, primarily affecting young male adults and adolescents. According to the US Centers for Disease Control and Prevention, the incidence of myocarditis and pericarditis in individuals aged 12-39 is approximately 12.6 cases per million doses of the second mRNA vaccine dose [1,2]. In reported cases, patients commonly presented with elevated cardiac troponin levels and chest pain, with the majority of myocarditis cases diagnosed 2-3 days after the second dose of the mRNA vaccine. Cardiac MRI confirmed myocarditis in all evaluated patients, while the remainder showed abnormal ECGs with ST elevations. None of the cases were associated with acute COVID-19 or other viral infections. Notably, natural killer cells were elevated, autoantibodies to specific self-antigens were reduced, and one case tested positive on a heart disease gene panel [3].

Experimental hypotheses explaining vaccine-associated myocarditis include molecular mimicry between the SARS-CoV-2 spike protein and self-antigens, the triggering of immunologic pathways, immune responses to mRNA, and cytokine expression dysfunction. It remains unclear why males are more frequently affected than females, although several theories have been proposed. For instance, men may be more likely to be diagnosed with heart conditions than women, and differences in sex hormones may influence immune responses, potentially contributing to myocarditis. However, despite these occasional occurrences of myocarditis, most patients experienced improvement in imaging and diagnostic markers, as well as resolution of symptoms, with or without treatment. The benefit-risk analysis of COVID-19 vaccination demonstrates a favorable balance for all age and gender groups, even with the occasional occurrence of myocarditis. Therefore, we recommend vaccination for all individuals aged 12 years and older [4].

II. EPIDEMIOLOGY OF MYOCARDITIS AFTER COVID-19 VACCINATIONS

Before the emergence of COVID-19, the Global Burden of Cardiovascular Disease reported an annual prevalence of myocarditis cases at 6.1 per 100,000 persons aged 35-39 for men and 0.1 per 100,000 for women, with corresponding mortality rates of 0.2 and 0.1 per 100,000, respectively [5]. However, during the first eight months of the pandemic, the incidence of excess cardiovascular deaths in England and Wales rose to 12 per 100,000, accompanied by an 8% increase in acute cardiovascular disease mortality in England [6]. Simultaneously, the United States experienced a higher incidence of ischemic and hypertensive heart disease during the first 10 months of the COVID-19 pandemic compared to the previous year [7]. A study published in February 2020 examining sex differences in myocarditis presentation found that young individuals (average age: 40 ± 17 for women and 40 ± 16 for men) accounted for the majority of myocarditis cases (82%) [8].

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Myocarditis following COVID-19 vaccination appears to be rare, with case-series studies from the United States and Israel estimating an incidence of 0.3-5.0 cases per 100,000 vaccinated individuals. The highest prevalence occurred after the second vaccine dose, predominantly in young males (83 of 117 patients were aged ≤30 years, and only 15 were female) [9]. Most cases presented within the first week post-vaccination, typically 3-4 days after immunization. In cases of myocarditis unrelated to COVID-19 or its vaccines, over 80% of patients recover spontaneously. However, those hospitalized for myocarditis face a 4-5% risk of mortality or heart transplantation within the first year post-diagnosis. Conversely, up to 90% of individuals with COVID-19 mRNA vaccine-associated myocarditis may experience functional recovery, often after an initial episode of chest pain. To date, at least 13 deaths have been reported as potentially linked to vaccine-associated myocarditis, though establishing a causal relationship is challenging due to insufficient evidence [10].

In contrast, the incidence of COVID-19-associated myocarditis or cardiac injury is estimated to be 100 times greater (1,000-1,400 per 100,000 COVID-19 patients) than that of vaccine-related myocarditis. Additionally, COVID-19-related myocarditis generally presents with more severe symptoms and a worse prognosis compared to vaccine-induced myocarditis. Among COVID-19 patients, 10% of outpatients and 40% of hospitalized patients experience clinically significant myocardial injury, often in the absence of myocardial infarction [11].

The primary risk factors for cardiovascular complications in COVID-19 patients include advanced age and pre-existing comorbidities such as obesity, diabetes, hypertension, or renal impairment. Myocardial injury in these patients may result from sepsis and shock, hypoxia, and hemodynamic instability caused by severe COVID-19 pneumonia, as well as direct COVID-19-mediated microvascular injury and thrombosis. These factors can lead to elevated plasma troponin levels, ECG changes, heart failure, and arrhythmias [12]. Characteristics of Myocarditis associated with vaccine are listed out in table 1.

Table 1: Characteristics of Myocarditis Associated with COVID-19 and Post-COVID-19 mRNA Vaccination(13).

Type of Myocarditis	Rate of Occurrence	Survival Rate (%)	Possible Mechanisms
Viral myocarditis (common)	1 to 10 per 100,000 individuals annually	> 80	Genetic factors (e.g., variations in genes coding for sarcomeric, desmosomal, cytoskeletal, or HLA proteins), immune cross-reactivity, sex-related factors.
Myocarditis and cardiac damage associated with COVID-19	1,000 to 4,000 per 100,000 SARS-CoV-2 infections	30 to 80	Microthrombosis, endothelial damage, genetic factors (e.g., desmosomal, cytoskeletal, sarcomeric, or HLA protein coding genes), shock, and sepsis.
Myocarditis following COVID-19 mRNA vaccination	0.3 to 5.0 per 100,000 vaccinated individuals	> 99	Hypersensitivity reactions, genetic factors (e.g., variations in genes coding for sarcomeric, desmosomal, cytoskeletal, or HLA proteins), immune cross-reactivity, sex-related factors.

III. THE PATHOPHYSIOLOGY OF MYOCARDITIS IN RELATION TO THE COVID-19 VACCINE

The molecular and cellular pathogenesis of post-viral myocarditis, including that potentially triggered by the COVID-19 vaccine, has been extensively studied, particularly in animal models. The pathogenesis can be summarized in a three-step process:

A. Immune Initiation

When pathogens, typically viruses or toxins, damage cardiac tissue, the innate immune system is activated, exposing intracellular antigens such as cardiac myosin and myocytes [14, 15]. During this phase, pro-inflammatory cytokines like interleukin-1 (IL-1) are released, and antigen-presenting cells (APCs) mature. Additionally, Toll-like receptor 4 (TLR4) expression on macrophages is increased [16].

B. Inflammatory Response

The release of cytokines by CD4+ T-lymphocytes initiates an immunological response that is biased toward T1, T2, T17, and T22 helper cells. B-lymphocytes also play a role in this stage by producing antibodies that contribute to the inflammatory process [17].

C. Variation in Outcome

In most cases, the immune response diminishes in the third stage, allowing cytotoxic CD8+ T-lymphocytes to eliminate the virus. However, in some instances, the virus may persist, leading to ongoing damage to cardiac myocytes [18]. In the context of vaccine-associated myocarditis, the inflammatory cytokines involved include TNF-α, IFN-γ, IL-6, and IL-1. It is hypothesized that genetic predispositions to IL-6-induced inflammation could exacerbate vaccine responses [19]. Moreover, the spike protein in the vaccine may lead to molecular mimicry with α-myosin, a mechanism distinct from classic myocarditis but similar to some COVID-19 infections [20]. This molecular mimicry could also contribute to an autoimmune component [21].

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IV. MECHANISM

Myocarditis induced by viruses such as human herpesvirus or enterovirus is typically more severe in younger individuals and males. Genetic variants may increase the risk of acute myocarditis. COVID-19 mRNA vaccines could potentially trigger hyperimmunity through hormonal changes, mRNA immune reactivity, and autoantibodies. Factors like age, sex, and immunogenetic background can influence these processes. For instance, testosterone associated with the COVID-19 mRNA vaccination may affect the etiology of myocarditis [22].

V. VACCINE-RELATED MYOCARDITIS: CLINICAL PRESENTATION

Early diagnosis and appropriate care are crucial for preventing the progression of vaccine-related myocarditis into a more serious condition [23]. Symptoms generally appear within a few days after the administration of a COVID-19 vaccine, particularly in young males [24]. Most symptoms are mild and nonspecific, including subfebrile to febrile fever, shortness of breath, palpitations, lethargy, and chest discomfort or pressure, which may be dependent on respiration [25]. However, some individuals, particularly those with minimal pericardial involvement, may not respond well to treatment. Almost all patients seeking medical assistance for vaccine-related myocarditis report chest discomfort (95–100%), which is more frequent compared to myocarditis caused by autoimmune diseases or viruses. This observation might result from selection bias, where only symptomatic cases are identified [26]. Most patients present elevated troponin levels, peaking 48–72 hours after symptom onset. Inflammatory markers, such as C-reactive protein (CRP), may be elevated when concurrent pericarditis is present [27]. The signs and symptoms are listed below in the table 2.

Table 2: Signs and Symptoms of Myocarditis Associated with COVID-19 Vaccination.

Symptoms	Signs
Chest tightness or discomfort that may depend on breathing	Increased troponins (peak 48–72 hours after symptom onset)
Breathlessness	Elevated C-reactive protein (CRP)
Heart palpitations	Transthoracic echocardiography shows mild pericardial effusion
Malaise	Cardiac magnetic resonance imaging reveals inflammation in the heart
General weakness and fatigue	Changes in electrocardiography (usually mild and nonspecific): - Diffuse ST-segment modifications - PQ segment depressions - Nonspecific ST-segment modifications, sinus bradycardia - Ventricular or supraventricular arrhythmias (very rare)
Subfebrile or febrile temperatures	Severe arrhythmias and heart failure symptoms are quite rare

VI. EVALUATION AND DIAGNOSIS

Myocarditis is often challenging to diagnose due to overlapping symptoms with other clinical conditions [28]. It is crucial to maintain a high index of suspicion in cases with a history of viral infection, acute febrile illness, or connective tissue disease [29].

➢ *Laboratory Studies:*

- Full Blood Count: Eosinophilia and leukocytosis in cases of eosinophilic myocarditis.
- Inflammatory Markers: Elevations in Interleukins, CRP, and ESR.
- Cardiac Markers: Elevated Troponin-I or Troponin-T levels [30].

➢ *Imaging and Additional Studies:*

- ECG : Nonspecific ST segment changes.
- X-ray or Chest Radiograph: May show a pleural effusion, pulmonary edema, vascular congestion, or nonspecific heart enlargement.
- Cardiac Magnetic Resonance: Shows prolonged T1 and T2 relaxation times, which allows for presumptive diagnosis of myocardial inflammation.
- Coronary Angiography: Done to rule out coronary artery disease in a patient who has had sudden cardiac arrest.
- Endomyocardial Biopsy: It is considered the gold standard for the diagnosis of myocarditis, more so in making a definite diagnosis of myocardial inflammation [31].
- (Note: CRP stands for C-reactive protein; ESR stands for erythrocyte sedimentation rate)

VII. COMPARISON OF COVID-19 AND POST-VACCINATION MYOCARDITIS

The risk of myocarditis following COVID-19 infection needs to be compared with the incidence of myocarditis associated with mRNA vaccines. According to data from the Vaccine Adverse Event Reporting System (VAERS) and the Advisory Committee on Immunization Practices as of February 4, 2022, 164 million mRNA vaccine doses had been administered by January 13, 2022, with 359 cases of myocarditis identified within 0 to 7 days post-vaccination. The Centers for Disease Control and Prevention (CDC) reported 146 cases of myocarditis per 100,000 COVID-19 infections [32]. The risk was notably higher in males, individuals over 50, and children under 16. One study found that males aged 12 to 17 experienced myocarditis at a rate of approximately 450 cases per million infections [33]. This study involved healthcare providers serving a quarter of the U.S. population. Following the second dose of the mRNA

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vaccine, 67 cases of myocarditis per million boys in this age group were identified. The combined number of myocarditis cases after the first and second doses was 77 cases per million, nearly six times lower than the rate observed following COVID-19 infection. A different perspective comes from a recent study that compared vaccinated individuals with those who did not receive the BNT162b2 vaccine, finding that vaccination was highly effective in preventing severe COVID-19 requiring hospitalization [34]. The efficacy was reported at 98% against severe COVID-19 requiring life support and 98% against ICU admission. The study by Bettina Heidecker et al.[35] also highlighted avoided hospital stays and an excess number of myocarditis cases associated with COVID-19 vaccination, as detailed in Table 3.

Table 3: Avoided Hospital Stays and Excess Cases of Myocarditis Associated with COVID-19 Vaccination

Group (Age and Gender)	Inpatient Stays Avoided	Excess Vaccine-Associated Cases of Myocarditis
All adults (18 to 39 years)		
mRNA-1273 (Moderna®)	2982	33
BNT162b2 (Pfizer-BioNTech®)	2820	24
Males 18 to 39 years		
mRNA-1273 (Moderna®)	1903	68
BNT162b2 (Pfizer-BioNTech®)	1799	47

VIII. TREATMENT OF MYOCARDITIS CAUSED BY VACCINATIONS

In cases where patients present with chest pain, it is crucial to rule out acute coronary syndrome both clinically and angiographically, especially when the diagnosis is unclear. For those experiencing heart failure with a lower ejection fraction, treatment options include sodium-glucose cotransporter 2 inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and either angiotensin-converting enzyme inhibitors or angiotensin receptor-neprilysin inhibitors [36]. Arrhythmias should be treated according to guidelines specific to the type of arrhythmia. In the very rare instances of fulminant myocarditis or cardiogenic shock, temporary use of corticosteroids may be considered. Additionally, for patients with left ventricular failure, mechanical circulatory support and/or extracorporeal membrane oxygenation should be considered as temporary measures to aid in recovery.

Treatment recommendations for cardiac failure and arrhythmias resulting from a response to COVID-19 immunization should follow guidelines-directed therapy. Initial therapy for heart failure involves medications such as beta-blockers, angiotensin-converting enzyme inhibitors, sodium-glucose cotransporter 2 inhibitors, or angiotensin receptor-neprilysin inhibitors. Since most patients present with chest pain, acute coronary syndromes should be ruled out clinically and, if necessary, angiographically [37]. Most cases of myocarditis caused by mRNA vaccines have a normal or nearly normal left ventricular ejection fraction, and symptoms often resolve quickly. To relieve strain on the left ventricle and provide temporary support in cases of left ventricular failure, oxygenation (class IIA) should be considered [38]. The poorly characterized immunological mechanisms of cardiac damage following COVID-19 vaccination make the relative risks and benefits of anti-inflammatory medications unclear; however, case studies suggest activation of cellular immunity during the healing process. A strategy that balances the potential benefits and risks of short-term corticosteroid use is suggested for patients with severely affected left ventricular function. Hajjo et al. (2020)[39] identified glucocorticoids as a proposed therapy based on VAERS dataset information. Patients showing signs of cardiogenic shock fall into this category. Shared decision-making is crucial when discussing potential booster doses or additional vaccinations with patients. Moreover, individuals with "long COVID" syndrome (PASC) need ongoing monitoring. The link between PASC and vaccination remains poorly understood, and the epidemiology of this condition is still debated. Additionally, discussing the benefits and risks of receiving further vaccinations is important, especially with young men who experienced myocarditis after their initial or subsequent doses. Alternative vaccine platforms, such as the recombinant Spike (rS) protein nanoparticle vaccine NVX-CoV2373 (Novavax), have been given Emergency Use Authorization by the FDA for unvaccinated individuals aged 18 and older as of July 2022 [40].

IX. BENEFITS-RISKS ANALYSIS OF COVID-19 VACCINATION

A. Benefits

The benefits of COVID-19 vaccination are assessed based on the prevention of hospitalizations, ICU admissions, fatalities, and COVID-19 cases. These endpoints are significant public health outcomes that are trackable and quantifiable. To estimate the number of avoidable COVID-19 cases with a vaccine (CP) [41]. Factors such as vaccine efficiency, duration of protection, vaccination coverage, and incidence rates are considered. The formula used incorporates hospitalization rates (IH) and vaccine effectiveness against hospitalization (EH) to determine avoidable COVID-19 hospitalizations. Preventable ICU admissions and deaths are derived from hospitalization fractions (HP), focusing on individual, age, sex, and combined categories.

- *Duration of Vaccine Protection*

According to Pfizer's ongoing trial, the vaccine provides protection for six months. Sensitivity analyses consider a 12-month protection duration.

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➢ *Incidences of COVID-19 Cases*

The study estimates hospitalization rates proceeding to intensive care and the proportion of hospitalized patients who die, using CDC COVID Data Tracker for incidence rates from July 2021. Four-week averages are employed due to fluctuating rates [42].

➢ *Risks*

The risks associated with myocarditis and pericarditis following COVID-19 vaccination are significant and compared with benefit endpoints such as hospitalizations and deaths. Excess cases are estimated by subtracting 2019 rates from the study window [43].

➢ *Data and Assumptions*

The study uses data from the FDA's BEST system, including the Optum health claims database, covering hospital, physician, and prescription medication health insurance claims. The majority of myocarditis cases occur during the 7-day risk window following vaccination, highlighting the importance of rapid medical reporting [44].

X. FUTURE DIRECTIONS AND RESEARCH NEEDS

- Further research is needed to clarify the frequency and risk factors of myocarditis following COVID-19 immunization, including genetic susceptibility, prognosis, mechanisms, gender differences, clinical outcomes, treatment approaches, and long-term effects.
- Studies should investigate immune cell populations and their roles in COVID-19 development, immunity after vaccination, cardiomyopathy, and multisystem inflammatory syndrome in children related to COVID-19 and vaccinations.
- Research should focus on myocardium histology, immunohistochemistry, ultrastructural abnormalities, and their correlation with cardiac biomarkers and imaging results in the context of COVID-19-related myocardial damage.
- Prospective screening for potential heart injury and myocarditis following COVID-19 vaccinations should be conducted, with attention to age- and sex-related disparities.
- Investigate risk factors such as genetics, comorbidities, immunity, or autoimmune profiles related to vaccine-induced myocarditis or cardiac damage associated with COVID-19 [45].

Establishing a collaborative registry for myocarditis linked to COVID-19 immunization would be beneficial. This registry should include patient demographics, clinical presentation, biomarkers (e.g., cardiac troponin), diagnostic results from cardiac MRI, echocardiography, and ECG, along with a bio-repository of blood and heart tissue samples for rare post-vaccination health issues. Despite the low incidence of self-limited myocarditis, the benefit-risk assessment of COVID-19 vaccination shows a positive balance for all age and sex groups. Consequently, COVID-19 vaccination is recommended for all individuals aged 12 years and older.

XI. CONCLUSION

The development of myocarditis after receiving the COVID-19 mRNA vaccine, while rare, highlights the need for ongoing surveillance and monitoring of vaccine safety. Although myocarditis is more common in certain demographics, such as young males, the overall benefit-risk assessment of COVID-19 vaccination remains strongly positive across all age and gender groups. Understanding the pathophysiology, risk factors, and optimal management of vaccine-related myocarditis is crucial for ensuring the safety and efficacy of vaccination programs. Collaborative research and robust data collection will help refine vaccination strategies and bolster public confidence in COVID-19 immunization. Despite the rare instances of myocarditis, the broader benefits of vaccination in preventing severe COVID-19 illness, hospitalizations, and mortality far outweigh the potential risks associated with this adverse event. Continued vaccination efforts are essential in controlling the spread of COVID-19 and protecting global public health.

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