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# COVID-19 vaccines-associated Takotsubo cardiomyopathy: A narrative review

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## SUMMARY

Takotsubo cardiomyopathy (TTC) is a severe, acute, reversible, and self-limited cardiac dysfunction. It usually affects postmenopausal women and is mostly triggered by physical or emotional stressors. Following the COVID-19 pandemic, millions of doses of different types of COVID-19 vaccines are being administered globally. There have been reports of different cardiac complications after receiving COVID-19 vaccines. To our knowledge, there have been 16 reported cases of COVID-19 vaccination-associated TTC. In this study, we first provide a brief overview of TTC and then an overview of selected reported TTC cases following COVID-19 vaccinations. It is crucial to highlight that the occurrence of TTC after vaccination does not establish a direct cause-and-effect relationship between immunization and TTC. Further investigations are necessary to examine any potential association between COVID-19 vaccines and the incidence of TTC. Additionally, the benefits of receiving COVID-19 vaccines significantly outweigh the potential risks of developing adverse events.

*Keywords:* COVID-19 vaccine, Takotsubo cardiomyopathy, COVID-19 vaccine-associated Takotsubo cardiomyopathy, Takotsubo syndrome, stress cardiomyopathy.

## INTRODUCTION

Coronavirus disease (COVID-19), also known as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), mostly affects the lungs and usually causes respiratory symptoms and complications; however, it can also involve other organs such as the heart and cause cardiac symptoms and complications. Some of the cardiovascular complications following COVID-19 infection include myocardial injury, arrhythmias, myocarditis, thromboembolism, acute myocardial infarction (MI), heart failure (HF), and Takotsubo cardiomyopathy [1-5].

In the initial stages of the pandemic, the mortality rate was as high as 13.2% and mostly affecting older males [4]. Several factors reported as predictors of severe disease and future mortality including cardiac biomarkers and abnormal procalcitonin levels [6].

Takotsubo cardiomyopathy (TTC), also known as Takotsubo syndrome (TTS), is a severe, acute, reversible, and self-limited cardiac dysfunction. Data on the incidence of TTS is limited, but it is reported to affect between 1.5% to 1.8% of acute coronary syndrome cases [7]. Earlier investigations have indicated a rise in the frequency of this condition [8]. Notably, a study revealed a significant surge of 7.8% in TTS incidence during the COVID-19 pandemic [7]. A nationwide study from hos-

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pital records documented that 5.2 out of 100,000 females and 0.6 out of 100,000 males had TTS resulting in a prevalence of 0.02% among hospitalized individuals [9]. It usually affects postmenopausal women and is mostly caused by physical or emotional stressors. The clinical features of TTC may include symptoms that resemble acute coronary syndrome (ACS) such as chest pain, ischemic changes on electrocardiogram (ECG) (mostly in the anterior leads), and increased biomarkers such as troponin and N-terminal pro-brain-type natriuretic peptide (NT-proBNP) [3, 10-13].

The COVID-19 pandemic has caused physical and psychological stress for many individuals worldwide. There have been reports of TTC during the pandemic and following COVID-19 infection. The underlying triggers of COVID-19-associated TTC have been reported to be due to the emotional and physical stress caused by the pandemic or COVID-19 infection [3]. Furthermore, there have been two reports of TTC following the administration of influenza vaccines [14, 15]. Following the massive global administration of various types of COVID-19 vaccines, some side effects, and adverse events, such as TTC, are being reported [16-22]. In this study, we aim to give an overview of the selected reported TTC cases following different types of COVID-19 vaccinations and the suggested possible pathogenesis. First, we provide a brief overview of Takotsubo cardiomyopathy and then we discuss the cases.

*Clinical presentations of Takotsubo cardiomyopathy*

In the acute phase, patients with TTC usually present with symptoms, such as chest pain or discomfort, dyspnea, dizziness, and syncope that are similar to the symptoms of patients with ACS. Patients usually present with elevated troponin level, which is comparable to patients with ACS, although patients with ACS tend to experience a greater increase in the troponin levels. In addition, creatinine kinases elevation is not a prominent finding in individuals with TTC. Interestingly, patients with TTC were more inclined to have greater levels of brain natriuretic peptide which significantly surpassed levels in patients with ACS [11, 12].

*Causes of Takotsubo cardiomyopathy*

TTC, also known as stress cardiomyopathy or broken heart syndrome, is usually caused by emotional or physical triggers. However, it may also occur without any emotional or physical stressors in as many as 28.5 % of the cases. In addition, it has been reported that positive emotional stress may also cause TTC which is known as happy heart syndrome [3, 11, 23].

*Pathophysiology of Takotsubo cardiomyopathy*

The exact pathogenesis of TTC is still unclear. However, several mechanisms have been suggested to be the cause of developing TTC. The most common mechanism that has been suggested is the increase in catecholamine levels (epinephrine, norepinephrine, and dopamine) that lead to increased oxygen demand, stimulation of vasospasm, and direct myocardial injury [13, 23]. An increase in epinephrine results in apical ballooning through the stimulation of β2-androgen cardiac receptors leading to their conversion from Gs to Gi coupling [13]. In addition, it is suggested that stimulation of the autonomic sympathetic nervous system (ASNS) leads to norepinephrine-stimulated cardiac cells [24]. On the other hand, spasm of the coronary arteries a or coronary microvascular spasm has also been reported to be involved in the pathogenesis of TCC [24]. Furthermore, sympathetic hyperactivation of the heart, estrogen deficiency, and endothelial dysfunction have also been reported to be involved in the pathogenesis of TTC [3, 23, 24].

*Risk factors and comorbidities of Takotsubo cardiomyopathy*

The risk factors that have been associated with TTC include hypertension (HTN) (54%), diabetes mellitus (DM) (12.6% to 22.8%), hyperlipidemia (HLD) (43%), obesity (9.7%), chronic kidney disease (CKD) (6.7%), gender [female-to-male ratio of 9:1 (89.8%-91.7% female)], and age (in men it is 50-72 years and in females it is 70-76 years) [23]. Although female gender is associated with TTC more frequently, male gender is associated with higher mortality. Additionally, the possibility of developing TTC increases as women age older than 55 years old, however, the incidence of TTC in men is not affected by their age [25].

*Classification of Takotsubo cardiomyopathy*

Different types of TTC may be classified as apical, mid-ventricular, basal, focal, and biventricular depending on the area that has cardiac wall-motion abnormalities. The most common type is apical [3].

*Diagnostic workup and findings in Takotsubo cardiomyopathy*

In TTC patients, the levels of cardiac enzymes, creatine kinase (CK), CK-MB, and cardiac troponin, and NT-proBNP are increased [13, 26]. In addition, the levels of serum catecholamines, neuropeptide-Y, and serotonin are also increased [26]. ECG evaluation in these patients usually shows ST elevation or depression, inversion of the T-wave, and prolongation of the QT-interval [13, 26]. On echocardiography, which is the first-line imaging modality for TTC evaluation, LV dysfunction, ballooning (mostly apical), wall-motion abnormalities, and abnormalities of the valves are detected. In addition, to apical ballooning, other types of TTC involve the mid-ventricular, basal, and focal locations. Furthermore, the right ventricular (RV) or biventricular areas may also be involved [3, 26]. LV strain echocardiography is a type of echocardiography that may help to differentiate TTC from ACS [13]. Coronary angiography (CA) is usually performed to rule out coronary artery obstruction and ACS [13, 26]. Left ventriculography used to be also utilized to detect TTC, but currently, echocardiography is mostly used [3]. However, it may be used along with CA to confirm the diagnosis and type of TTC [26]. In addition, cardiac computed tomography angiography (CTA) may be performed to assess coronary artery stenosis and wall-motion abnormalities. Furthermore, cardiovascular magnetic resonance imaging (CMR) is the imaging diagnostic tool of choice to evaluate, confirm the diagnosis, and assess the prognosis of TTC. It also helps to rule out other disorders such as myocarditis, MI, pericarditis, hypertrophic cardiomyopathy (HCM), edema of the myocardium, and the absence of late gadolinium enhancement (LGE) [26]. The CMR findings of TTC include wall-motion and ventricular abnormalities, acute complications [such as ventricular thrombus, LV outflow obstruction (LVOTO), and mitral regurgitation (MR)], strain and motion assessment, myocardial edema (in TTC it has a diffuse and transmural distribution in the areas with wall-motion abnormalities; in ACS it is restricted to a coronary artery, and in myocarditis, there is a patchy distribution in the mid-myocardial or sub-epicardial areas), and myocardial inflammation (pericardial effusion). Additionally, early gadolinium enhanced (EGE) can evaluate myocardial inflammation, LV thrombus, and apical thrombus. LGE is usually absent in TTC, although it may also be present in some cases of TTC [26].

*Diagnostic criteria of Takotsubo cardiomyopathy*

The Mayo Clinic diagnostic criteria for TTC includes the presence of transient LV wall-motion abnormalities that may or may not have apical involvement, the extension of LV wall-motion abnormalities beyond the perfusion area of a single epicardial coronary artery, presence or absence of a stressful trigger, absence of obstructive CAD or presence of an acute plaque rupture on angiography, presence of new abnormalities on ECG or elevation in cardiac troponin levels, and the absence of myocarditis and pheochromocytoma [27]. Recently, the International Takotsubo Registry (InterTAK) has been introduced and used as a clinical diagnostic criterion that is used to evaluate the development of TTC. A score of 50 or more points viral is diagnostic for TTC in about 95% of the patients with TTC. The diagnostic criteria include female gender (25 points), emotional trigger (24 points), physical trigger (13 points), absence of ST depression (except in the aVR lead) (12 points), psychiatric disorders (11 points), neurologic disorders (9 points), and prolongation of QTc (6 points) [28]. Additionally, the 2019 Heart Failure Association suggested revised diagnostic criteria for TTS which no longer considers the presence of coronary artery disease as an exclusion criterion, acknowledging the coexistence of both conditions. This update also introduces a new criterion, endorsed by imaging studies, focusing on the improvement of ventricular systolic function within 3 to 6 months after diagnosis [29]. Three sets of diagnostic criteria for TTS are presented in Table 1.

*Prognosis and complications of Takotsubo cardiomyopathy*

TTC is usually considered a benign and self-limiting disorder. However, recent studies have reported that the acute phase of TTC has a wide spectrum (low to very high risk). The recovery of TTC depends on the risk level in the acute phase. The recurrence risk rate has been reported to be around 2% to 11%. In addition, there have been reports of a mortality rate of 3.5-10.6% and a risk rate of 1.7% per patient/year of developing cardio- and cerebrovascular complications [3, 11]. Some of the complications of TTC include left

**Table 1** - Definition of TTS across various diagnostic criteria.

| *Criteria* | *Characteristics Findings* | | *Supportive Clinical Features* | | *Factors to consider/ Exclude* |
|---|---|---|---|---|---|
| Mayo Clinic Criteria [48] | Clinical Findings | WMA extending beyond coronary artery distribution | Postmenopausal women | Presence of preceding triggers | Absence of coronary artery disease explaining the WMA |
| | ECG findings | ST elevation or T wave inversion | | | |
| | Biomarkers | Modest elevation of cardiac enzymes | | | Absence of Myocarditis |
| | Imaging Studies | Not required | | | Pheochromocytoma |
| International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria) [49] | Clinical Findings | Presence of left ventricular dysfunction in the territory or beyond territory of a coronary artery | Postmenopausal women | CMR to confirm TTS diagnosis | Evidence of myocarditis Should be excluded via imaging |
| | ECG Findings | New ECG findings can be present, but not obligatory | Presence of preceding triggers including neurologic disorders (SAH, CVA, seizure, TIA) and pheochromocytoma | Presence of WMA for a prolonged period is possible | Presence of obstructive CAD is not contraindicated |
| | Biomarkers | Elevation of cardiac enzymes including significant elevation of BNP | | | |
| | Imaging Studies | MRI findings suggestive of TTS and excluding myocarditis | | | |
| 2019 Heart Failure Association Criteria [29] | Clinical Findings | Presence of WMA usually extends beyond territory of a single coronary artery | Presence of preceding trigger | Recovery of LV dysfunction within 3-6 months approved by imaging | Absence of CAD explaining the territory of LV dysfunction |
| | ECG Findings | New ECG changes, but not obligatory | | | Absence of myocarditis |
| | Biomarkers | Elevation of cardiac enzymes including significant elevation of BNP | | | |
| | Imaging Studies | Recovery of LV dysfunction approved by imaging | | | |

*Abbreviations:* CAD, coronary artery disease. CMR, cardiac magnetic resonance. CVA, cerebral vascular attack. LV left ventricle. TIA, transient ischemic attack. WMA, wall motion abnormality.

ventricular outflow tract obstruction (LVOTO), mitral regurgitation (MR), pulmonary edema, congestive heart failure, wall rupture of the left ventricle, tachycardia, arrhythmias, thrombus, syncope, and cardiogenic shock. Furthermore, involvement of the RV is correlated with poor prognosis [3, 17, 26]. It has also been reported that a history of HTN is associated with recurrent TTC and a history of obesity or CKD is associated with a poor prognosis. Although there have been reports that the history of HLD is inversely associated with complications, this association still requires further investigation. In addition, the association of the history of DM with TTC is still unknown. Male gender and younger age are associated with poor prognosis [23].

*Treatment and follow-up of Takotsubo cardiomyopathy*

There is no definitive guideline or protocol to treat TTC. Medications that are used to treat HF are usually prescribed. Treatment with ACE inhibitors or angiotensin receptors (ARBs) has been reported to improve the survival of the patients and decrease TTC recurrence. There is controversy over the uses of beta-blockers, especially their effects on survival improvement. However, they may be used to prevent recurrences and decrease the impact of stress hormones. In addition, psy-

chiatric evaluation, or psychotherapy (for preceding emotional stress) should also be considered. Management of comorbidities, especially those that may be associated with a risk of TTC recurrence is important [3, 12, 24]. An echocardiogram is usually used to determine the recovery of LV function in follow-up assessments and visits [26].

*Takotsubo cardiomyopathy associated with infections and sepsis*

TTC has been mostly reported in bacterial infections and sepsis [30, 31]. The most common bacterial sepsis associated with TTC is caused by *Escherichia coli*, *Klebsiella pneumonia*, and *Staphylococcus aureus*. Viral sepsis by cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), influenza A, influenza A (H1N1), and influenza B have also been reported in patients with TTC [31-33]. In addition, parasitic infection such as babesiosis has also been associated with TTC [31]. Several mechanisms have been suggested to be involved as the underlying pathogenesis in sepsis induced TTC. For example, a myocardial impairment may be caused by the systemic inflammation that is induced by sepsis which leads to the production of inflammatory mediators and microbial products that damage the myocardium. Other involved factors are increased catecholamines or administration of exogenous catecholamines in patients that develop septic shock. In addition, sepsis causes insufficient coronary blood flow that may lead to myocardial ischemia [31].

*Takotsubo Cardiomyopathy associated with COVID-19 infection*

The COVID-19 virus has a spike protein that has two main subunits. The S1 subunit binds to the receptor of the host cells and the S2 subunit incorporates the membranes of the viruses and host cells. On the other hand, the angiotensin-converting enzyme 2 (ACE2) which is mainly present in the lung, is also found in other organs such as the heart (expressed in myocytes and the vascular endothelium). The receptor-binding domain (RBD) of the spike S1 protein recognizes ACE2 as a receptor for the COVID-19 virus. Consequently, these mechanisms facilitate the entry of the COVID-19 virus into the host cell. Therefore, ACE2 may be the underlying cause of direct myocardial injury in COVID-19 infection [1, 12, 34].

There have been reports of the development of COVID-19-associated TTC. The emotional and physical stress caused by the pandemic, quarantine, and self-isolation or the COVID-19 infection itself have been reported as the underlying triggers of COVID-19-associated TTC [3].

The pathogenesis of TTC is not clearly understood. However, several factors have been suggested to be associated with TTC-associated COVID-19 infection. The COVID-19-stimulation of sympathetic nervous system activity increases catecholamines which, in turn, lead to myocardial injury and TTC. In addition, the HPA (hypothalamic-pituitary-adrenal) axis is also activated during severe COVID-19 infection resulting in impairment in the cortisol metabolism. This leads to increased levels of cortisol and, in turn, suppression of corticotropin. On the other hand, the HPA axis induces catecholamines secretion leading to TTC development [35]. In heart failure, the neurohormones are also activated. For example, the increased ventricular wall stress leads to the release of NT-proBNP. Moreover, the increased level of NT-proBNP is associated with the severity of LV dysfunction [36]. Another involved factor in the development of COVID-19-induced TTC is microvascular and coronary microvascular dysfunction. This may be due to the systemic inflammatory response caused by COVID-19 infection itself or due to the microthrombi that are produced in hypercoagulable conditions [37]. Furthermore, COVID-19 infection causes a cytokine storm with increased pro-inflammatory cytokines, such as TNF-α (tumor necrosis factor-α), interleukin-6 (IL-6), and IL-1β, which may cause cardiac dysfunction and lead to TTC development [3, 12, 13]. All these factors cause increased oxygen demand, induce vasospasm and epicardial coronary spasm, direct myocardial injury, and microvascular dysfunction and can be implicated in the pathophysiology of COVID-19 induced TTS.

*Takotsubo Cardiomyopathy associated with COVID-19 Vaccines*

Different types of COVID-19 vaccines have been developed and administered massively worldwide. The main types of COVID-19 vaccines that are being administered include mRNA-based (such as Pfizer/BioNTech and Moderna), adenovirus vector vaccines (such as AstraZeneca and Janssen), and inactivated vaccines (such as Sinovac and Sinopharm) [38]. The RNA vaccines (such

as Pfizer/BioNTech and Moderna) are lipid nanoparticles of the SARS-CoV-2-nucleoside-modified mRNA that encode the SARS-CoV-2 spike protein without replicating. Adenovirus vector vaccines (such as AstraZeneca and Janssen) use recombinant DNA technology and encode the SARS-CoV-2 spike protein without replicating. The vectors used in these vaccines include a human adenovirus vector, Ad26, in the Janssen vaccine, and a chimpanzee adenovirus vector, ChAdY25, in the AstraZeneca vaccine [34, 38]. These non-replicating vaccines, mRNA, and adenovirus vectors, effectively stimulate the immune system (humoral and cellular) by expressing the SARS-CoV-2 spike protein. As a result, the antigens are sufficiently presented to CD4+ T-cells and CD8+ T-cells in major histocompatibility complex (MHC) II and I, respectively [34].

There have been sixteen reports of TTC following the administration of COVID-19 vaccines [16-20,39] which include eight cases following Pfizer-BioNTech, six cases following Moderna (mRNA mRNA-1273), and two cases following AstraZeneca (ChAdOx1 nCoV-19). Of these reported cases, seven cases occurred after the second dose of the vaccine and one case was after the third COVID-19 vaccine [40-44]. The exact pathogenesis of TTC following COVID-19 vaccination is unknown. Crane et al. suggested that the myocardial dysfunction in TTC may have resulted from an extreme systemic inflammation that was stimulated by the vaccine leading to excessive catecholamine release [19]. On the other hand, Fearon et al. suggested a combination of significant risk factors as the cause of developing TTC in their case. These risk factors included the patient's gender (female), age (menopause), anxiety (due to vaccine administration), history of MI with no obstructive coronary atherosclerosis, and the adverse events caused by the vaccine itself [17]. Additionally, in the case reported by Sakamoto et al., the stress and concern about COVID-19 vaccine adverse events were reported to be the cause of TTC [20]. It is worth mentioning that whether the observed association of TTC with COVID-19 vaccines is incidental or not, the prognosis of the patients has been excellent and in the previous reported cases, 87.5% of patients discharged from the hospital with recovery which speaks for transient nature of this association. Surprisingly, patients who passed away following COVID-19 vaccination were teenager with no heart related complaints at the time of presentations or previous personal history of heart disease, however, the autopsy findings of their cardiac sections were suggestive of TTC [45]. It is therefore premature to assume that TTC following COVID-19 vaccine is the cause of death. However, it is still recommended that physicians be mindful of such associations and co-incidents. Interestingly, a recent population-based study investigating the association between COVID-19 infection and its vaccine and TTC incidence did not show any statistically significant relationship. According to this study, the incidence of TTS decreased in the first year of pandemic and then increased to the previous year. Also, this study revealed that neither COVID-19 infection, nor vaccination against this agent are associated with TTS development [46].

*Characteristics of patients developing COVID-19 or vaccines-associated Takotsubo cardiomyopathy*

A summary of selected cases following COVID-19 vaccines with clinical presentation, lab, and imaging findings as well as outcome shown in table 2. Briefly, we included 8 of the 16 reported cases.

**Table 2** - Select cases of COVID-19 vaccine-associated Takotsubo cardiomyopathy (TTC).

| *Cases* | *Sex* | *Age* | *PMH* | *H/O physical stress* | *H/O emotional stress* | *Type of COVID-19 vaccine* | *Symptoms* | *Timeline of symptoms after vaccination* | *Workup findings of TTC* | | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Case 1 [16] | F | 63 | No significant PMH | No | | Moderna, first dose (mRNA-1273) | Dyspnea, fever | 1 day after first dose | Lab | Normal CK and CKMB, High troponin-T, NT-pro-BNP, CRP | |

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| *Cases* | *Sex* | *Age* | *PMH* | *H/O physical stress* | *H/O emotional stress* | *Type of COVID-19 vaccine* | *Symptoms* | *Timeline of symptoms after vaccination* | *Workup findings of TTC* | | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | ECG | Negative T-waves (Inferior and anterior leads) | |
| | | | | | | | | | CA | No CAD | |
| | | | | | | | | | Imaging | LVEF: 40%, Mid-ventricular to apical ballooning, Preserved basal contraction, Negative LGE | |
| Case 2 [17] | F | 73 | MINOCA, HTN, CKD, RA, asthma, GERD, HCC resection (2017), possible viral pericarditis (2018) | No | Yes (anxiety before vaccination) | Moderna, First dose (mRNA) | Chest pain radiating to the back, shortness of breath, exertional dyspnea, orthopnea, nausea, vomiting, fatigue | < 1 day | Lab | High troponin, Pro-BNP, Pro-calcitonin | Recovered |
| | | | | | | | | | ECG | Poor progression of anterior R-wave, ST-wave (infero-lateral ischemia) | |
| | | | | | | | | | CA | No CAD (two months ago) | |
| | | | | | | | | | Imaging | LVEF: 20%, Mid-ventricular ballooning, Mild hypokinesis of LV, Negative LGE | |
| Case 3 [18] | F | 65 | Asthma, glaucoma, hyperlipidemia, nephrectomy due to RCC (2000) | No | No | Moderna, first dose (mRNA-1273) | Nausea, fatigue, myalgia, headache, chest pressure, shortness of breath, lighth-eadedness | 1 to 3 days | Lab | Troponin: high | Recovered |
| | | | | | | | | | ECG | ST-T changes (inferolateral ischemia) | |
| | | | | | | | | | CA | Mild CAD | |
| | | | | | | | | | Imaging | LVEF: 35%, Apical ballooning | |

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| *Cases* | *Sex* | *Age* | *PMH* | *H/O physical stress* | *H/O emotional stress* | *Type of COVID-19 vaccine* | *Symptoms* | *Timeline of symptoms after vaccination* | *Workup findings of TTC* | | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Case 4 [19] | M | 72 | Asymptomatic IHD, CABG, HTN, DM (type 2), UC, hypercholesterolemia | No | No | AstraZeneca (ChAdOx1 nCov-19) | Fatigue, lethargy, fever, myalgia, arthralgia, retrosternal chest pain, dyspnea | 4 to 9 days (symptoms presented 4 days after vaccination and pt recovered after 9 days) | Lab | Troponin I: high | Recovered |
| | | | | | | | | | ECG | Sinus tachycardia, First degree and RBBB block, No ischemic changes | |
| | | | | | | | | | CA | Evidence of grafts, no new CAD | |
| | | | | | | | | | Imaging | LVEF: 37%-39%, Apical ballooning, Hyperdynamic base, Akinesia in the mid to distal LV segments, Severe hypokinesis of the apical cap, Negative LGE | |
| Case 5 [20] | F | 64 | No significant PMH | No | Yes (anxiety about vaccination side effects) | Unknown | Severe chest pain | 10 days after second dose | Lab | Troponin-I: positive | Recovered |
| | | | | | | | | | ECG | Negative T-waves | |
| | | | | | | | | | CA | No significant stenosis | |
| | | | | | | | | | Imaging | Apical ballooning, LV apical akinesia, Basal hyperkinesia | |
| Case 6 [45] | M | teenager | History of attention deficit hyperactivity syndrome | Not mentioned | Not mentioned | Pfizer-BioNTech (2nd dose) | Headache and gastric upset | 3 days | Lab | Coagulative band necrosis in biopsy | Died |
| | | | | | | | | | ECG | Not mentioned | |
| | | | | | | | | | CA | Not mentioned | |
| | | | | | | | | | Imaging | Not mentioned | |

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| *Cases* | *Sex* | *Age* | *PMH* | *H/O physical stress* | *H/O emotional stress* | *Type of COVID-19 vaccine* | *Symptoms* | *Timeline of symptoms after vaccination* | *Workup findings of TTC* | | *Outcome* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Case 7 [45] | M | teenager | Obesity | Not mentioned | Not mentioned | Pfizer-BioNTech (2nd dose) | No complaints | 4 days | Lab | Hyper eosinophilic myocytes, contraction band necrosis | Died |
| | | | | | | | | | ECG | Not mentioned | |
| | | | | | | | | | CA | Not mentioned | |
| | | | | | | | | | Imaging | Not mentioned | |
| Cases 8 [40] | F | 59 | Hypercholesterolemia, hypothyroidism, celiac disease | No | No | Moderna (3rd dose) | Sudden onset dyspnea, intermittent chest pain | 3 days | Lab | Troponin-I: positive, elevated CKMB, elevated CRP | Recovered |
| | | | | | | | | | ECG | ST elevation in leads V2-V5 | |
| | | | | | | | | | CA | Normal coronary arteries | |
| | | | | | | | | | Imaging | LVEF: 30%, moderate hypokinesia of apex and anterolateral wall, Apical ballooning | |

Abbreviations: Past medical history (PMH), History of (H/O), Takotsubo cardiomyopathy (TTC), Late Gadolinium enhancement (LGE), Coronary angiography (CA), Left ventricular LV), Left ventricular ejection fraction (LVEF), Creatine kinase (CK), B-type natriuretic peptide (BNP), N-terminal-pro BNP (NT-proBNP), C-reactive protein (CRP), Myocardial infarction with no obstructive coronary atherosclerosis (MINOCA), Hypertension (HTN), Chronic kidney disease (CKD), Coronary artery disease (CAD), Rheumatoid arthritis (RA), Hepatocellular carcinoma (HCC), Gastroesophageal reflux disease (GERD), Renal cell carcinoma (RCC), Right bundle branch block (RBBB), Ischemic heart disease (IHD), Coronary artery bypass graft (CABG), Diabetes mellitus (DM), and Ulcerative colitis (UC).

Their ages ranged from teenager to 73 years old. Five of the cases were female. Patients' comorbidities are mentioned in the table in detail. Four of the cases did not have any medical history. There were no specific physical or emotional triggers to explain the development of TTS in any of the cases except for the stress of receiving immunization which was reported in one of the cases. Patients' manifestations mostly include sudden onset chest pain and shortness of breath, but also included non-specific symptoms like headache and fatigue. Symptoms were mostly presented within one to three days post-vaccination. However, in one of the cases symptoms developed 10 days after the immunization. Patients had various ECG changes including ST segment changes and elevated cardiac enzymes.

## CONCLUSIONS

TTC has been reported after sepsis, COVID-19 infection, COVID-19 vaccines, and COVID-19 boosters. Reviewing previous reports indicate that TTC occurred following various types of vaccines and even after various booster times. The timeline of clinical presentations differs case by case and

ranges from 15 minutes to 14 days. Of the presented cases in the current literature, only 6 cases presented after administration of same vaccines. Similarly, a systematic review of TTC cases during COVID-19 era reported 66.7% of patients had simultaneous COVID-19 infection [47].

There have been two reports of influenza-vaccine-associated TTC. Several mechanisms have been suggested to be involved as the underlying pathogenesis in influenza-vaccine-induced TTC. These include increased catecholamines, cardiac hyper-sensitization to catecholamines, induction of a systemic inflammation that may lead to hyperactivity of the cardiac sympathetic system, and induction of a sympatho-vagal imbalance (with more adrenergic dominance). Influenza vaccine associated with the development of TTS was (Fluad® Novartis, a single dose of 0.50 ml i.m.; containing an A/California/7/2009 (H1N1)pdm09-like virus 15 µg (HA), an A/Victoria/ 361/2011 (H3N2)-like virus 15 µg (HA), a B/Wisconsin/1/ 2010-like virus 15 µg (HA)) [14,15]. This evidence is in favor of possible coincidence between TTC and COVID-19 infection or immunization. Further investigations are necessary to examine any potential association between COVID-19 infection or vaccines and the incidence of TTC. With the worldwide administration of various types of COVID-19 vaccines and flu vaccines there is a possibility that more cases will be reported. However, the benefits of receiving immunization outweigh its risk of developing rare adverse events such as TTC. Also, it is important to emphasize that such observations do not establish causal relationship.

**Conflict of interest**

Authors have no conflict of interest to disclose.

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