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Citation

A review of the presentation and outcome of takotsubo cardiomyopathy in COVID-19

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Authors' contributions
KJJ and AKM contributed to the conceptual design of the study. KJJ and AKM independently screened the articles and extracted the data. KJJ, AKM and AL contributed to write-up and submission of the study. AKM and AL reviewed the final manuscript. All authors reviewed and agreed with the final content of the article.

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Consent for publication: Not applicable
Abstract

Although the most frequent presentation of the novel Coronavirus disease-2019 (COVID-19) is a respiratory syndrome, cardiac involvement is being increasingly recognized. One such entity is takotsubo cardiomyopathy. We sought to review the various cases of takotsubo cardiomyopathy reported during the COVID-19 pandemic and consolidate the information available on its clinical features, evaluation and treatment. We performed a PubMed search using the MeSH terms “Takotsubo Cardiomyopathy” or “Stress Cardiomyopathy” and “COVID-19”, and identified 16 case reports, two case series, and one retrospective cohort study. There was a total of 24 reported patients with COVID-19 infection, who developed takotsubo cardiomyopathy, and two patients without COVID-19 who developed takotsubo cardiomyopathy due to the emotional stress associated with the global pandemic. The mean age of the patients was 67.19 years (SD 15.83) and 16(59.3%) were women. Chest pain was reported in only ten patients (38.46 %) and ST-elevation was seen in 11 patients (42.3%). While most patients had typical takotsubo cardiomyopathy, four patients had inverted(reverse) takotsubo cardiomyopathy, two had bi-ventricular involvement, one had median takotsubo and another had global takotsubo with apical sparing variant. Most patients had a positive outcome with complete or near-complete reversal of cardiac dysfunction at the time of discharge. Five deaths (19.23%) were reported. Takotsubo cardiomyopathy is a rare, but increasingly reported reversible cardiomyopathy that can be seen in patients with COVID-19 infection and the diagnosis must be actively sought for in these patients.

Introduction

Coronavirus disease 2019 (COVID-19) emerged from China in December of 2019 and continues to be a public health emergency of international concern. As of November 10, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected 50.8 million individuals worldwide and has caused more than 1.26 million deaths. COVID-19 can be asymptomatic or symptomatic. The incubation period is generally within 14 days following exposure, and most symptomatic infections occur approximately four to five days after exposure [1,2]. The most common symptoms in decreasing order of occurrence are cough, fever, myalgia, headache, dyspnea, sore throat, diarrhea, nausea or vomiting, loss of smell, abdominal pain and rhinorrea
As our understanding of this novel pathogen improves and more cases are reported, unusual and rare presentations associated with COVID-19 are being recognized.

Takotsubo cardiomyopathy (also known as transient apical ballooning, stress cardiomyopathy and ‘broken heart syndrome) is a unique reversible form of cardiomyopathy which presents with symptoms and signs mimicking acute myocardial infarction, without actual coronary artery stenosis, thrombosis or spasm [4,5]. The name is derived from the shape the heart takes, which resembles a Japanese octopus fishing pot called a ‘takotsubo’. Takotsubo cardiomyopathy occurs predominantly in postmenopausal women in the setting of extreme physical or emotional stress. There have been reports of increased incidence of takotsubo cardiomyopathy after natural calamities, such as what was observed during the Niigata earthquake when the incidence of takotsubo cardiomyopathy was 24-fold higher near the epicenter, one month after the earthquake [6]. It has been estimated that 1-2% of all patients presenting with an initial diagnosis of acute coronary syndrome have takotsubo cardiomyopathy [5].

Although a respiratory syndrome is the predominant clinical presentation of COVID-19, cardiac involvement is being increasingly recognized. One such cardiac complication is takotsubo cardiomyopathy. In this article, we review the various cases of takotsubo cardiomyopathy reported during the COVID-19 pandemic and attempt to consolidate the available information on its clinical features, evaluation and treatment.

Methods

In this review, we included articles on COVID-19 and takotsubo cardiomyopathy published in PubMed. We used the search terms “COVID-19” and “Takotsubo Cardiomyopathy” or “Stress Cardiomyopathy” under the Mesh database in PubMed. Case reports, case series, retrospective, and prospective observational studies on adult patients with COVID-19 were eligible to be included. We excluded opinions, recommendations and reviews which did not include clinical details of patients. Two independent clinicians were involved in the screening of the articles.

Results

We identified 22 articles on “Takotsubo Cardiomyopathy” or “Stress Cardiomyopathy” and “COVID-19” published in PubMed till 10th November 2020. One article was a review of the
cardiovascular manifestations of COVID-19, and was excluded as there were no patient details in the study. Two papers which were commentaries were also excluded. Sixteen case reports, two case series, and one retrospective cohort study that investigated the incidence of takotsubo cardiomyopathy during the SARS-CoV-2 pandemic were included in the review. A case report which was in Italian was translated using Google translator.

Among the 16 case reports and 2 case series, there were a total of 24 patients with COVID-19 infection, who developed takotsubo cardiomyopathy [7–22]. Twenty-three of these patients had COVID-19 infection confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR) test and one patient had serological evidence of acute infection. Also, there were two patients who had features of takotsubo cardiomyopathy, without evidence of COVID-19 infection [7,8]. Both of them had reported emotional stress as a result of the COVID-19 pandemic and social isolation, which presumably lead to the development of takotsubo cardiomyopathy. All 26 patients were included in the final analysis.

**Clinical presentation**

The mean age of the patients was 67.19 years (SD 15.83) and 16 (59.3%) were women (Table 1). Chest pain was reported in only ten patients (38.46%) (Figure 1). The other presenting symptoms were fever, shortness of breath, cough, fainting and diarrhea. Two patients presented with cardiac symptoms alone, and the diagnosis of COVID-19 was made after a screening test was sent [9,10]. Another patient was initially diagnosed with pericardial effusion in tamponade, and developed features of takotsubo cardiomyopathy after admission to the hospital [11]. Two others were diagnosed with takotsubo cardiomyopathy when they were evaluated for chest pain after admission to the hospital for treatment of COVID-19 infection; one on day 3 and the other on day 7 [12,13].

**Electrocardiography (ECG)**

ST-elevation was seen in 11 patients (42.3%). Other electrocardiography (ECG) patterns seen were sinus tachycardia, atrial flutter, atrial ectopics, atrial fibrillation, sinus tachycardia, QT-prolongation, T-wave inversion and non-specific ST-segment and T-wave changes. Cardiac troponins were elevated in 22 patients (84.61%).

**Echocardiogram**
Echocardiography was a crucial diagnostic tool in all cases. Although most patients had typical takotsubo cardiomyopathy, four patients had inverted (reverse) takotsubo cardiomyopathy (15.38%)\cite{14-16}. Two others (7.69%) had bi-ventricular involvement, one (3.8%) had median takotsubo and another (3.8%) had global takotsubo with apical sparing variant \cite{9,16,17}. Ejection fraction was below 50% in all but one of the reported cases.

**Angiogram and ventriculography**

Conventional coronary angiography was done in nine patients (34.61%). Eight of these patients did not have significant obstructive coronary lesions. One patient had significant lesions on the proximal left anterior descending (LAD) artery and first diagonal artery, and two drug-eluting stents were placed. However, since there were regional wall motion abnormalities in a different vascular territory than the ones supplied by obstructed arteries, the authors made a diagnosis of median takotsubo syndrome \cite{9}. Another patient underwent Computed Tomography (CT) angiogram which showed absence of obstruction \cite{18}. There was one patient who did not undergo coronary angiogram, but was found to have normal coronaries during autopsy \cite{19}. The other patients did not undergo coronary angiography, either because they were too unstable to be shifted for the procedure, or because the treating team had already made a diagnosis and the angiogram would not have given any additional information. This would also avoid unnecessary viral exposure to the healthcare team and supporting staff. When ventriculography was done, it showed features similar to that seen on echocardiography.

**Other imaging modalities**

Cardiac Magnetic Resonance Imaging (CMR) was done for one patient on day 7 of admission. It showed an improvement of systolic function from that at admission, with the persistence of mild hypokinesia at basal and mid-left ventricular segments \cite{18}.

**Management**

Management of most patients was done following local protocols for management of COVID-19 pneumonia and acute coronary syndrome or heart failure. Five patients received antiviral therapy consisting of a combination of lopinavir-ritonavir or darunavir-cobicistat \cite{15,18,19}. One of them also received therapeutic plasma exchange \cite{18}. Interleukin-6 antagonists were received by two
patients – one received tocilizumab while the other received sarilumab [12,13]. With such a small sample size, it is difficult to comment on the efficacy of any of these therapies in reversing takotsubo cardiomyopathy.

**Outcome**

Most patients had a positive outcome with complete or near-complete reversal of cardiac dysfunction at the time of discharge. Five deaths (19.23%) were reported [13,16,19]. One of them had recovered cardiac function and died due to other factors. One patient was admitted at 38-weeks of gestation, and had an uneventful caesarean section delivery and was discharged on day 16[10].

**Takotsubo cardiomyopathy in patients who tested COVID-19 negative**

There are two case reports of elderly women, who presented with chest pain, ST-elevation on ECG and elevated cardiac troponins, but were not found to have any obstructive coronary lesions on angiography [7,8]. Both ladies reported emotional stress related to the ongoing pandemic and social isolation, which was probably the trigger for takotsubo cardiomyopathy. A retrospective cohort study at cardiac catheterization laboratories in Ohio compared the incidence of Takotsubo cardiomyopathy in the pre-COVID and post-COVID era [11]. The incidence, which was 1.5-1.7% of all patients presenting with acute coronary syndrome in the pre-COVID era, had increased to 7.8% in the post-COVID era. All the patients in the study had a negative RT-PCR test for COVID-19, suggesting that the increase in incidence was due to factors other than infection itself. This study did not find a change in mortality rate or 30-day rehospitalization between the two time periods.

**Discussion**

At the end of 2019, the novel coronavirus was identified as the cause of a cluster of cases presenting with pneumonia in the city of Wuhan in the Hubei province of China. It rapidly spread throughout China and later, the world. On 30th January, 2020 the World Health Organization (WHO) declared this disease, a Public Health Emergency of International Concern (PHEIC) and on Feb 2020, it officially named this coronavirus disease as COVID-19. COVID-19 infection can be asymptomatic or symptomatic, and the severity of symptomatic infection can be mild to severe. Pneumonia is the most frequent serious manifestation of symptomatic infection and is
characterized by fever, cough and dyspnea [20]. Several complications of COVID-19 have been described, such as, acute respiratory distress syndrome, cardiac arrhythmias, acute cardiac injury, pulmonary embolism, stroke, Guillain-Barre syndrome and secondary infections. Cardiovascular complications include thromboembolic events (22%), heart failure (12-23%), rhythm abnormalities (7-16%), myocarditis (8-12%), cardiogenic shock(7%), pericarditis or effusions (1-4%) and acute coronary syndromes(<1%) [21]. A rare complication of COVID-19 is takotsubo cardiomyopathy, also known as stress cardiomyopathy, apical ballooning syndrome and ‘broken heart syndrome’. The typical clinical presentation of takotsubo cardiomyopathy is indistinguishable from an acute coronary syndrome [5]. However, the disease is conspicuous for its absence of significant coronary lesions. Another remarkable feature of takotsubo cardiomyopathy is its association with emotional and physical stressful triggers. Although the exact mechanism of takotsubo cardiomyopathy is unclear, the catecholamine surge associated with these triggers almost certainly has a role in its pathogenesis.

Our review of the literature revealed two patterns of takotsubo cardiomyopathy associated with the COVID-19 pandemic. Some patients with COVID-19 infection had features of takotsubo cardiomyopathy. The stress response to the infection and hyper-adrenergic state may be responsible for this association, although viral myocarditis cannot be ruled out. The other group of patients presented with takotsubo cardiomyopathy as a result of the intense emotional stress caused by the global pandemic. Governments around the world have undertaken public health interventions to reduce the rate of transmission of COVID-19. One such measure is social distancing. Although effective in reducing the spread of infection and ‘flattening the curve’, it may be the cause of intense emotional distress, especially in the elderly who may find it difficult to use technology to stay in contact with their loved ones. This may act as a trigger for takotsubo cardiomyopathy in these individuals.

While the exact mechanism of takotsubo cardiomyopathy is unclear, there have been various postulates. Various theories such as multi-vessel coronary artery vasospasm, microvascular coronary impairments, catecholamine-induced myocyte injury and neurogenic myocardial stunning exist, but none have been proven conclusively [22]. Primary takotsubo cardiomyopathy is triggered by acute emotional and physical stress, while secondary takotsubo cardiomyopathy develops in patients hospitalized for other reasons (Figure 2). COVID-19 is a unique disease in
that it can trigger takotsubo cardiomyopathy by both these mechanisms. The current pandemic, resultant social and economic instabilities, public health measures adopted by most governments including social distancing, inability to interact with loved ones and the anxiety of getting infected may all contribute to primary takotsubo cardiomyopathy. On the other hand, patients admitted for treatment of COVID-19 infection, particularly those requiring intensive care, seem to be more prone to develop secondary takotsubo cardiomyopathy.

At the time of writing this review, there is one study that shows an increase in the incidence of takotsubo cardiomyopathy during the COVID-19 pandemic [11]. However, considering that in the past, the incidence of takotsubo cardiomyopathy has increased after natural calamities such as earthquakes, it is likely that the results of this study are valid and can be generalized [6]. As mentioned before, the exact mechanism of cardiac injury in takotsubo cardiomyopathy is unclear. SARS-CoV2 enters human cells by binding its spike protein to the membrane protein angiotensin-converting enzyme [23]. Viral RNA of Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV, have been isolated from heart tissues of infected animals indicating cardiotropism [24]. However, the mechanism of takotsubo cardiomyopathy is most likely neurohormonal, rather than direct viral injury. Endomyocardial biopsy was performed in one patient with takotsubo cardiomyopathy and COVID-19 infection [18]. It showed diffuse T-lymphocytic inflammatory infiltrates with huge interstitial oedema and limited foci of necrosis, with no evidence of SARS-CoV-2 genome within the myocardium. Other mechanisms may also include procoagulant state, immune-mediated damage, endothelial injury and microvascular dysfunction. Viral RNA of Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV, have been isolated from heart tissues of infected animals indicating cardio-tropism.

The evidence concerning optimal management of patients with takotsubo cardiomyopathy is unclear and most patients are managed with supportive care along the lines of management of heart failure. Also, it has to be noted that adrenergic stimulation is high in these patients, and therefore, exogenous catecholamine-inotropes such as dopamine, dobutamine, and norepinephrine can exacerbate neurocardiogenic injury and calcium overload in an already stressed myocardium. Therefore, the use of non-catecholamine inotropes such as milrinone and levosimendan may prove beneficial [25,26]. Patients with COVID-19 admitted in critical care may require hemodynamic support. Indeed, these catecholamine-inotropes may contribute to secondary takotsubo
cardiomyopathy. Therefore, the treating team may consider levosimendan or milrinone as an alternative inotrope in situations where takotsubo cardiomyopathy is suspected. Beta-blockers may be beneficial in some cases of takotsubo cardiomyopathy, however, their use without invasive cardiac pressure gradient monitoring is controversial [27,28]. Therapeutic plasma exchange was employed for one patient as rescue therapy, however, it cannot be concluded whether it was that intervention which rescued the patient [18]. Plasma exchange is proposed to work by removing inflammatory cytokines such as interleukin-6 and may be especially beneficial at the onset of the cytokine-release syndrome. Using IL-6 antagonists such as sarilumab and tocilizumab are also proposed to work by the same mechanism. However, there are several unknowns at this point – the optimal dose and duration of therapeutic plasma exchange, as well as IL-6 antagonists, are yet to be determined. It is also unclear how reducing inflammatory mediators improves takotsubo cardiomyopathy - it may have a direct effect by reducing cardiac inflammation or may work indirectly by improving oxygenation and left ventricle filling pressures.

Takotsubo cardiomyopathy is considered to be a reversible form of cardiomyopathy with complete recovery of left ventricular function within weeks of presentation. This is reflected in the cases reviewed in this paper, with most patients having documented reversal of cardiac function at the time of discharge. Of the five patients who died, one had recovered cardiac function and succumbed due to other factors. It is difficult to say whether the other four patients died of cardiac or other causes.

Most likely, cases of takotsubo cardiomyopathy in COVID-19 are under-reported; either the diagnosis being missed completely, or being misdiagnosed as viral myocarditis. It is important to actively seek this diagnosis for two reasons. Firstly, once a diagnosis is made, invasive investigations such as angiography can be avoided, since they add minimal additional information and the management of takotsubo cardiomyopathy is largely supportive. This can also protect healthcare workers from unnecessary viral exposure during transportation and the procedure itself. Secondly, a diagnosis of takotsubo cardiomyopathy may urge the treating team to modify their management of critical ill COVID-19 patients, especially with regards to limiting exposure to catecholamine-inotropes and considering the use of non-catecholamine inotropes. Because of these reasons, we recommend modification of protocols for evaluation of acute chest pain to include an echocardiography prior to coronary angiography in order diagnose takotsubo cardiomyopathy.
Reassuringly, takotsubo cardiomyopathy in itself seems to have a good prognosis in patients with COVID-19 infection. As more cases are reported, we may gain more insights into the optimal evaluation and management of this complication.

**Limitation**

There are several limitations to this review. The sample size is rather small and this affects the generalizability of these observations. It is possible that there are many unreported cases of takotsubo cardiomyopathy and if they were to be included, our observations may have been different. There is a chance for publication bias, as more challenging cases and those with a positive outcome are likely to be reported. Also, we do not have complete details on inotrope requirement, ventilation, hospital stay and drug interactions-factors that may have affected the outcome[29,30]. Furthermore, there were no children included in the review. Lastly, The non-uniform drug therapies for COVID-19 due to changing recommendations make it difficult to comment on the efficacy of therapeutic interventions for takotsubo cardiomyopathy.

**Conclusion**

Takotsubo cardiomyopathy is a rare cardiovascular complication associated with the COVID-19 pandemic. With increasing cases of COVID-19, more cases of takotsubo cardiomyopathy are being reported. Takotsubo cardiomyopathy in COVID-19 can be primary takotsubo cardiomyopathy due to the emotional stress associated with the global pandemic, or secondary takotsubo cardiomyopathy due to COVID-19 infection. Less than half of the patients presented with chest pain. Although ECG abnormalities were commonly seen, ST-segment elevation was present in only 42.3% of the patients. Echocardiogram was the most important diagnostic tool and showed the classical findings of takotsubo cardiomyopathy or its variants. Management was mostly supportive and mortality was reported in 19.2% of patients.

**References**


Figure 1. Presentation and diagnosis of takotsubo cardiomyopathy in patients with COVID-19
Figure 2. Association between takotsubo cardiomyopathy and COVID-19.
Table 1. Case reports of takotsubo cardiomyopathy during the COVID-19 pandemic.

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Reference</th>
<th>Age in years</th>
<th>Sex</th>
<th>Presenting complaint</th>
<th>COVID-19 test</th>
<th>ECG</th>
<th>Cardiac troponins</th>
<th>Echo-cardiogram</th>
<th>Takotsubo variant</th>
<th>Angiogram</th>
<th>Management</th>
<th>Remarks</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(7)</td>
<td>85</td>
<td>F</td>
<td>Sudden onset substernal chest pain</td>
<td>Negative</td>
<td>Septal q-ST pattern in leads V1-V3</td>
<td>Elevated</td>
<td>Basal hyperkinesis and apical ballooning, ejection fraction 35%</td>
<td>Typical</td>
<td>Non-significant coronary artery disease, left ventriculogram revealed basal hyperkinesis and apical ballooning</td>
<td>Supportive care</td>
<td>Takotsubo cardiomyopathy related to stress of COVID-19 pandemic</td>
<td>Discharged, repeat echocardiogram after 5 days showed complete recovery of LV systolic function</td>
</tr>
<tr>
<td>2</td>
<td>(31)</td>
<td>87</td>
<td>F</td>
<td>fever, fatigue and shortness of breath x 2 weeks</td>
<td>Confirmed by RT-PCR</td>
<td>Negative T waves and repolarization phase alterations</td>
<td>Elevated</td>
<td>Apical akinetic expansion (apical ballooning) and hypokinesia of the mid-ventricular segments with slightly reduced systolic function, ejection fraction 48%</td>
<td>Typical</td>
<td>Not done</td>
<td>Supplemental oxygen, azithromycin, methylprednisolone, bisoprolol and fondaparinux.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>(18)</td>
<td>43</td>
<td>F</td>
<td>Chest pain and dyspnea for 3 days</td>
<td>Confirmed by RT-PCR</td>
<td>low atrial ectopic rhythm, mild ST-segment elevation in leads V1–V2 and aVR, reciprocal ST depression in V4–V6, and QTc 452 ms with diffuse U-waves.</td>
<td>Elevated</td>
<td>mild left ventricular systolic dysfunction (LVEF 43%) with inferolateral wall hypokinesis</td>
<td>Typical</td>
<td>CT angiogram (CTA) done was normal</td>
<td>Continuous positive airway pressure for hypoxia. Empirical treatment with lopinavir/ritonavir 500 mg b.i.d. and hydroxy-chloroquine 200 mg b.i.d.</td>
<td>CMR (day 7) showed a recovery of systolic function (from 52% by CTA to 64% by CMR), although with persistence of a mild hypokinesia at basal and mid left ventricular segments; at the same sites, diffuse myocardial oedema, determining wall pseudo-hypertrophy, was observed on short T1 inversion recovery (STIR) sequences and confirmed by T1 and T2 mapping (average native T1 = 1188 ms, normal value &lt;1045; average T2 = 61 ms, normal value &lt;50); reserved systolic function (LVEF 65%) was maintained, ECG normalized, and both troponin T and C-reactive protein showed progressive improvement. The patient was discharged with no symptoms (day 13).</td>
<td>-</td>
</tr>
<tr>
<td>Sl. No</td>
<td>Reference</td>
<td>Age in years</td>
<td>Sex</td>
<td>Presenting complaint</td>
<td>COVID-19 test</td>
<td>ECG</td>
<td>Cardiac troponins</td>
<td>Echo-cardiogram</td>
<td>Takotsubo variant</td>
<td>Angiogram</td>
<td>Management</td>
<td>Remarks</td>
<td>Outcome</td>
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<tr>
<td>4</td>
<td>(14)</td>
<td>50</td>
<td>M</td>
<td>Cough, dyspnea, fever x 8days. Chest pain x 1 day</td>
<td>Confirmed by RT-PCR</td>
<td>2mm ST elevation in inferior and lateral leads</td>
<td>Elevated Akinesia of all basal segments.</td>
<td>Inverted(basal)</td>
<td>Normal coronaries, Left ventricular angiography: basal segment akinesis and hypercontractility of the mid-apical segments with elevated diastolic pressure</td>
<td>Supportive care Inverted(basal) Takotsubo cardiomyopathy</td>
<td>Discharged. Before discharge, echocardiogram showed absence of left ventricular contractility.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(9)</td>
<td>71</td>
<td>F</td>
<td>Fainting</td>
<td>Confirmed by RT-PCR</td>
<td>Sinus rhythm with prolonged QT interval</td>
<td>Median significant lesions on the proximal left anterior descending (LAD) artery and the first diagonal arteries. Ventriculogram showed regional</td>
<td>Two drug-eluting stents were placed. Patient received mechanical ventilation.</td>
<td>Median takotsubo syndrome</td>
<td>No data</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sl. No</td>
<td>Reference</td>
<td>Age in years</td>
<td>Sex</td>
<td>Presenting complaint</td>
<td>COVID-19 test</td>
<td>ECG</td>
<td>Cardiac troponins</td>
<td>Echo-cardiogram</td>
<td>Takotsubo variant</td>
<td>Angiogram</td>
<td>Management</td>
<td>Remarks</td>
<td>Outcome</td>
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<tr>
<td>6</td>
<td>(32)</td>
<td>83</td>
<td>F</td>
<td>Medio sternal non-radiating chest discomfort associated with mild breathlessness and dry cough x 3 days</td>
<td>Nasopharyngeal swab was negative for SARS-CoV-2, but the initial positive immunoglobulin A and negative immunoglobulin G serology pattern proved acute infection.</td>
<td>Elevated</td>
<td>Typical left ventricular apical ballooning with hyperkinetic basal segments</td>
<td>Typical</td>
<td>Non-significant coronary lesions, typical takotsubo syndrome image on ventriculography</td>
<td>Heart failure medication</td>
<td>Echocardiography showed only mild residual apical hypokinesis on the day of discharge (day 10).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(19)</td>
<td>84</td>
<td>M</td>
<td>fever, cough with dyspnea, atypical chest pain after admission</td>
<td>Confirmed by RT-PCR</td>
<td>Elevated</td>
<td>Dyskinesia of the left ventricle apex (apical ballooning) and basal wall hypercontractility with systolic dysfunction</td>
<td>Typical</td>
<td>Not done</td>
<td>High-flow nasal cannula, antiviral, hydroxychloroquine.</td>
<td>Discharged home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(19)</td>
<td>85</td>
<td>F</td>
<td>fever, cough with dyspnea and atypical chest pain</td>
<td>Confirmed by RT-PCR</td>
<td>Elevated</td>
<td>Ejection fraction 30%, typical takotsubo syndrome</td>
<td>Typical</td>
<td>Not done</td>
<td>Mechanical ventilation, antiviral, hydroxychloroquine.</td>
<td>Death. Autopsy showed normal coronaries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(19)</td>
<td>81</td>
<td>M</td>
<td>fever, cough with dyspnea and atypical chest pain</td>
<td>Confirmed by RT-PCR</td>
<td>Elevated</td>
<td>Ejection fraction 42%, typical takotsubo syndrome</td>
<td>Not done</td>
<td>High-flow nasal cannula, antiviral, hydroxychloroquine</td>
<td>Discharged home</td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>(33)</td>
<td>52</td>
<td>M</td>
<td>Dyspnea</td>
<td>Confirmed by RT-PCR</td>
<td>ST segment elevations in</td>
<td>Typical</td>
<td>Non-obstructive coronary arteries.</td>
<td>Intubated and ventilated, colchicine</td>
<td>Hospital day 6, he was</td>
<td></td>
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<tr>
<td>Sl. No</td>
<td>Reference</td>
<td>Age in years</td>
<td>Sex</td>
<td>Presenting complaint</td>
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<td>Outcome</td>
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<td>11</td>
<td>34</td>
<td>59</td>
<td>F</td>
<td>Fever and dyspnea</td>
<td>Confirmed by RT-PCR</td>
<td>sinus tachycardia, right axial deviation (left posterior hemiblock type), intraventricular conduction delay and widespread alterations in repolarization with negative T waves in III and aVF, Elevation of ST-T wave changes</td>
<td>Elevated Apex akinesia with apical ballooning as per typical takotsubo syndrome and moderate reduction in systolic function (-40-45%).</td>
<td>Typical</td>
<td>Coronary arteries free from significant lesions.</td>
<td>Hydroxychloroquine, darunavir-cobicistat 800 mg / 150 mg was set, azithromycin 500 mg and low molecular weight heparin 8000 IU.</td>
<td>The patient subsequently remained asymptomatic and in good hemodynamic compensation for the next 10 days of hospitalization, with gradual improvement in respiratory failure and subsequent home discharge in trust quarantine.</td>
<td>Discharge</td>
<td></td>
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<tr>
<td>12</td>
<td>17</td>
<td>58</td>
<td>F</td>
<td>Cough, fatigue, fever, and diarrhea x 5 days</td>
<td>Confirmed by RT-PCR</td>
<td>Sinus tachycardia and 1-mm upsloping ST-segment elevations in leads I and aVL, mild diffuse PR interval depressions, and diffuse ST-T wave changes</td>
<td>Elevated akinetic middle to distal anterior, anteroseptal, anterolateral, and apical segments, moderately hypokinetic middle and distal inferolateral segments, and hyperdynamic basal segments. Apical ballooning was also noted. Left ventricular ejection fraction was 20%. The distal third or apical right</td>
<td>Typical</td>
<td>Not done</td>
<td>Dual antiplatelet, heparin, hydroxychloroquine</td>
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<td>Sl. No</td>
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<td>Echo-cardiogram</td>
<td>Takotsubo variant</td>
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<tr>
<td>13</td>
<td>(12)</td>
<td>59</td>
<td>F</td>
<td>Fever, chills, fatigue, myalgia, cough</td>
<td>Confirmed by RT-PCR</td>
<td>Slight ST-segment elevations diffusely with nonspecific T-wave inversion</td>
<td>Elevated on day 3</td>
<td>Severe hypokinesis of the mid-left ventricular cavity, with normal-to-hyperdynamic contractility of basal and apical left ventricular segments and a moderately reduced biplane ejection fraction of 36%</td>
<td>Typical</td>
<td>Not done</td>
<td>Mechanical ventilation, supportive care and sarilumab</td>
<td>Profound hypoxemic respiratory failure and vasodilatory shock, multiple episodes of monomorphic ventricular tachycardia responding to lidocaine.</td>
<td>Repeat transthoracic echocardiogram the same day, 10 days after the initial transthoracic echocardiogram, revealed resolution of the stress cardiomyopathy, with normal biventricular systolic function. She was ultimately discharged to a rehabilitation facility.</td>
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<tr>
<td>14</td>
<td>(35)</td>
<td>67</td>
<td>F</td>
<td>Cough, mild shortness of breath, and left shoulder pain</td>
<td>Confirmed by RT-PCR</td>
<td>T-wave inversions in precordial leads (V2 to V6)</td>
<td>Elevated in hospital</td>
<td>Hypokinesis of the apical and pericardial walls</td>
<td>Patient was admitted with pericardial effusion in tamponade</td>
<td>Hydroxychloroquine and low-dose glucocorticoids, colchicine</td>
<td>Repeat TTE prior to discharge demonstrated stable ejection fraction and resolution of pericardial effusion.</td>
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<td>15</td>
<td>(36)</td>
<td>40</td>
<td>M</td>
<td>Cough, chest pain, myalgia x 4 days</td>
<td>Confirmed by RT PCR</td>
<td>Non-specific ST segment and T wave changes</td>
<td>Elevated</td>
<td>left ventricular (LV) basal and midventricular akinesia with apex sparing (ejection fraction: 30%) and depressed cardiac output (2.8 L/min)</td>
<td>Reverse</td>
<td>Not done</td>
<td>Mechanical ventilation and vasopressors, plus antivirals (lopinavir/ritonavir), and prophylactic anticoagulation, Therapeutic plasma exchange</td>
<td>Reversed Takotsubo cardiomyopathy; CT and CAG not done as patient was too unstable to be shifted</td>
<td>Discharged, alive at 2 months follow up</td>
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<td>Remarks</td>
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<tr>
<td>16</td>
<td>(8)</td>
<td>71</td>
<td>F</td>
<td>Chest pain</td>
<td>Negative</td>
<td>Elevated</td>
<td>Dilated left ventricle with an akinetic apex and preserved contraction of the basal segments suggestive of takotsubo cardiomyopathy</td>
<td>Typical</td>
<td>No obstructive coronary lesions</td>
<td>Supportive care in intensive care unit.</td>
<td>Reported significant anxiety about not being able to visit family due to social distancing, and was particularly saddened by being unable to see her grandchildren.</td>
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<tr>
<td>17</td>
<td>(13)</td>
<td>59</td>
<td>W</td>
<td>Dyspnea, cough, wheezing, fever, chills, myalgia, poor oral intake, and diarrheax5 days</td>
<td>Confirmed by RT-PCR</td>
<td>Elevated on day 7</td>
<td>Normal right ventricular function, left ventricular ejection fraction 26% with preserved basal function, and apical ballooning consistent with takotsubo cardiomyopathy</td>
<td>Typical</td>
<td>Not done</td>
<td>Hydroxychloroquine, methylprednisolone, albuterol/ipratropium inhaler, ceftriaxone, and doxycycline, was transferred to the intensive care unit, and given 1 dose of tocilizumab. Intubation, vasopressors and Continuous Renal Replacement Therapy.</td>
<td>Death</td>
<td></td>
<td></td>
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<tr>
<td>18</td>
<td>(10)</td>
<td>32</td>
<td>F</td>
<td>Palpitations x 3 days</td>
<td>Confirmed by RT-PCR</td>
<td>Elevated</td>
<td>Hypokinetic mid and akinetic apical left ventricular (LV) segments and hypercontractile basal segments with prominent apical ballooning typical of takotsubo cardiomyopathy, EF of 38%</td>
<td>Typical</td>
<td>Not done initially. Subsequent angiogram on day 14 revealed non-obstructive coronary artery disease involving the left anterior descending artery</td>
<td>Bisoprolol and enoxaparin</td>
<td>38-week gestation</td>
<td>Underwent an uneventful caesarean section delivery under spinal anesthesia for fetal distress and associated cephalopelvic disproportion. Repeat TTE on day 13 on transfer to the cardiology ward showed the normalization of the left ventricle. Discharged on day 16</td>
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<tr>
<td>19</td>
<td>(37)</td>
<td>82</td>
<td>M</td>
<td>Chest pain</td>
<td>Confirmed by RT-PCR</td>
<td>1 mm ST segment elevation in leads V2-V3 and DI-AVL</td>
<td>Same findings as ventriculography</td>
<td>Typical</td>
<td>Coronary angiography showed coronary arteries free of lesions. Cardiac ventriculography showed a very reduced left ventricular ejection fraction with extensive apical akinesia</td>
<td>Was treated according to the acute myocardial infarction protocol</td>
<td></td>
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<td>He did not have lung involvement secondary to the COVID-19 disease. Ten days after admission, he was discharged with only ongoing neurohormonal treatment.</td>
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<tr>
<td>20</td>
<td>(16)</td>
<td>71</td>
<td>F</td>
<td>Cough, myalgia, lethargy</td>
<td>Confirmed by RT PCR</td>
<td>Atrial flutter RVR with diffuse ST elevations</td>
<td>Elevated Ejection fraction 15%. Typical takotsubo cardiomyopathy</td>
<td>Typical</td>
<td>Intubation</td>
<td>Acute kidney injury, shock liver.</td>
<td>Death</td>
<td></td>
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<tr>
<td>21</td>
<td>(16)</td>
<td>78</td>
<td>M</td>
<td>AMS, fever, urinary incontinence</td>
<td>Confirmed by RT PCR</td>
<td>AF with RVR, diffuse deep T-wave inversions</td>
<td>Elevated EF=53%, Biventricular takotsubo cardiomyopathy</td>
<td>Biventricular</td>
<td>Intubation</td>
<td>Acute kidney injury-recovered</td>
<td>Discharged to skilled nursing facility</td>
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<tr>
<td>22</td>
<td>(16)</td>
<td>70</td>
<td>F</td>
<td>Dyspnea</td>
<td>Confirmed by RT PCR</td>
<td>Sinus rhythm with diffuse ST-T changes</td>
<td>Elevated EF=45%, Reverse takotsubo cardiomyopathy</td>
<td>Reverse</td>
<td>Intubation, hydroxychloroquine and azithromycin</td>
<td>Acute respiratory distress syndrome, chronic respiratory failure</td>
<td>Discharged to long-term acute care</td>
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<tr>
<td>23</td>
<td>(16)</td>
<td>78</td>
<td>F</td>
<td>Fever, cough, Dyspnea</td>
<td>Confirmed by RT-PCR</td>
<td>Sinus rhythm with deep T-wave inversions</td>
<td>Elevated Ejection fraction 20%. Typical takotsubo cardiomyopathy</td>
<td>Typical</td>
<td>Hydroxychloroquine and azithromycin</td>
<td>Acute respiratory distress syndrome, shock</td>
<td>Death</td>
<td></td>
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<tr>
<td>24</td>
<td>(16)</td>
<td>88</td>
<td>M</td>
<td>Dyspnea, lethargy, worsening hypoxia</td>
<td>Confirmed by RT-PCR</td>
<td>Atrial fibrillation, with diffuse ST-T changes</td>
<td>Elevated Ejection fraction 30%, Global with apical cap sparing takotsubo cardiomyopathy</td>
<td>Global with apical cap sparing takotsubo cardiomyopathy</td>
<td>Intubation</td>
<td>Bilateral pleural effusion s/p thoracentesis, acute kidney injury, non-sustained ventricular tachycardia</td>
<td>Recovered cardiac function but died secondary to other complications of COVID-19</td>
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<tr>
<td>25</td>
<td>(16)</td>
<td>58</td>
<td>M</td>
<td>Dyspnea</td>
<td>Confirmed by RT-PCR</td>
<td>Sinus tachycardia with premature atrial complexes and T-wave inversions</td>
<td>Elevated Ejection fraction 40%, Reverse takotsubo cardiomyopathy</td>
<td>Reverse</td>
<td>Intubation, hydroxychloroquine and azithromycin</td>
<td>Bilateral pneumothorax s/p chest tube placement, transient transaminitis</td>
<td>Recovered cardiac function, long-term acute care</td>
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<tr>
<td>26</td>
<td>(16)</td>
<td>56</td>
<td>M</td>
<td>Dyspnea and fever</td>
<td>Confirmed by RT-PCR</td>
<td>Sinus tachycardia with diffuse ST-T changes</td>
<td>Elevated</td>
<td>Ejection fraction 45%. Typical takotsubo cardiomyopathy</td>
<td>Typical</td>
<td></td>
<td>Intubation</td>
<td>Acute kidney injury, metabolic encephalopathy</td>
<td>Recovered cardiac function. But died.</td>
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</table>