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Takotsubo Syndrome and COVID-19: Associations and Implications

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Abstract: Incidence of cardiovascular complications has increased during the COVID-19 (Coronavirus disease 2019) pandemic, both population-wide and in patients diagnosed with the disease. This increase has presented complications in patient care, leading to increased hospitalizations, adverse outcomes, and medical costs. A condition of interest is takotsubo syndrome, which may be associated with the novel coronavirus. To understand this connection, a narrative review was performed by analyzing primary studies and case reports available. The findings showed increased incidence of takotsubo cardiomyopathy in both the general population and COVID-19 patients. Proposed mechanisms for the linkage include generalized increases in psychological distress, the cytokine storm, increased sympathetic responses in COVID-19 patients, and microvascular dysfunction. Moreover, natural disasters are noted as likely being associated with increases of takotsubo syndrome. As the pandemic continues, treating COVID-19 as a systemic condition is imperative, with the increase in takotsubo syndrome marking a significant impact of the novel coronavirus. (Curr Probl Cardiol 2021;46:100763.)
COVID-19: A Systemic Condition

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated COVID-19 infection has rapidly spread across the globe. The transmission of the virus is suspected to have begun through a zoonotic source, yet its quick and wide diffusion is attributed to human-to-human contact. The infection is most commonly identified within adult male populations, with an increased mortality rate in patients with concomitant health conditions. The identification of these developed comorbidities, such as acute cardiac injury and arrhythmia makes it increasingly clear that the virus is systemic and not solely isolated to the respiratory system.

Cardiovascular complications in patients with COVID-19 require particular attention. Conditions such as hypertension and coronary artery disease have been linked to increased mortality. Conversely, the novel coronavirus increases risk of developing cardiovascular pathologies, including acute coronary syndrome, myocarditis, cardiomyopathy with ventricular dysfunction, thromboembolism, and various arrhythmias. In certain cases, the virus can cause myocardial infarction, which confers the greatest mortality in COVID-19 patients. Medications used to treat COVID-19 can also cause cardiac complications, with hydroxychloroquine and azithromycin leading to QT-prolongation and various arrhythmias.

Takotsubo Syndrome: Introduction, Diagnostic Criteria, Treatments

Takotsubo syndrome (TTS) is a cardiovascular condition that has shown a drastic increase in the general population during the time of COVID-19. This condition, also referred to as stress-induced cardiomyopathy, is distinguished by acute segmental ventricular dysfunction in a noncoronary distribution. It commonly occurs in reaction to severe emotional or physical stress and can cause significant clinical problems. Patients have presentations mimicking acute coronary syndrome, with symptoms such as shortness of breath, hypotension, and chest pain. To diagnose stress-induced cardiomyopathy, physicians use tools like echocardiography and coronary angiography. As TTS is a diagnosis of exclusion, angiograms do not reveal significant coronary blockages, while echocardiograms demonstrate segmental left ventricular dysfunction.

There remain questions about the proper treatment of TTS. Physicians typically utilize ACE inhibitors, beta blockers, and diuretics for treatment of heart failure. Long-term solutions are unknown, but indefinite use of
beta blockers has been shown to prevent recurrence and decrease the impact of stress hormones.\textsuperscript{11} Patients may also go through psychotherapy to promote rehabilitation from emotional stress, a common precipitant for TTS.\textsuperscript{12} Left ventricular dysfunction from TTS typically resolves in weeks, with most patients fully recovering within 2 months.\textsuperscript{13}

As this review will highlight, TTS appears to be more prominent in the era of COVID-19, whether due to cardiovascular complications caused directly or indirectly by the virus or because of the psychosocial toll of the pandemic. The impact of the novel coronavirus on the cardiovascular system is important for providers to understand to provide optimal care for patients and to prevent adverse outcomes during the developing global crisis.

**Methods**

This narrative review is intended to analyze the existing literature on the potential associations between the COVID-19 pandemic and the development of stress-induced cardiomyopathy. Several case reports and larger studies were identified using PubMed searches with the key terms “COVID-19 and Takotsubo Cardiomyopathy,” “COVID-19 and Stress-Induced Cardiomyopathy,” “COVID-19 and Takotsubo Syndrome,” and “Coronavirus and Cardiomyopathy.” Articles that were included met the criteria of (1) discussing the comorbidity of COVID-19 and takotsubo syndrome, or (2) analyzing incidences of takotsubo syndrome during the timeframe of the COVID-19 pandemic. The literature search was performed periodically from August 1 to August 21, 2020. The articles chosen for inclusion were reviewed by all authors to determine relevance. Ultimately, thirteen case reports for fifteen patients and 3 larger studies were identified through this search process. The results of the literature search are described in Table 1.

**Increases in Takotsubo Syndrome Incidence During the COVID-19 Pandemic**

The increased incidence of TTS within the general population was noted by a large cohort study performed at the Cleveland Clinic, which analyzed 1914 patients presenting with acute coronary syndrome, a diagnosis that must be excluded prior to diagnosing stress-induced cardiomyopathy. The research found that 7.75% of patients presenting with acute coronary syndrome were diagnosed with stress-induced cardiomyopathy during the COVID-19 pandemic. Before the pandemic, however, only between 1.5% and 1.8% of patients in this population were diagnosed...
with TTS. The study demonstrated a large increase in TTS incidence during the pandemic within this population, which suggests a connection between the 2 conditions. To date, the Cleveland Clinic study is the only large cohort study performed, underscoring the need for further research.

Alongside this increase in TTS cases within the uninfected population, case reports and larger studies have suggested there is a greater rate of TTS diagnoses within COVID-19 positive patients. A study examining this link was performed by the European Association of Cardiovascular Imaging, analyzing 1216 COVID-19 positive patients with echocardiography to determine potential cardiovascular implications of the virus. The study concluded that 2% of patients had concomitant diagnoses of stress-induced cardiomyopathy, significantly higher than in the general population. In a separate study performed at Mount Sinai Hospital, 118 patients confirmed to have COVID-19 underwent clinically indicated transthoracic echocardiograms (TTE). In this study, 4.2% of patients were determined to have features consistent with stress-induced cardiomyopathy. Several case reports indexed in Table 1 have also described patients with the diagnosis.

Table 1. Literature search results

| Author & Year | Article type | Description of sample and size |
|---------------|--------------|-------------------------------|
| Minhas A, 2020 | Case Report  | 58-year-old female patient    |
| Jabri A, 2020  | Retrospective Cohort Study | Cardiac patients presenting with acute coronary syndrome N = 1914 |
| Dweck M, 2020  | Prospective International Survey | Patients with presumed or confirmed COVID-19 between April 3 and 20, 2020 N = 1216 |
| Giustino G, 2020 | Retrospective Observational Study | Laboratory-confirmed COVID-19 patients who underwent clinically indicated transthoracic echocardiograms N = 118 |
| Dabbagh M, 2020 | Case Report  | 67-year-old female patient    |
| Kariyanna P, 2020 | Case Report  | 72-year-old woman             |
| Taza F, 2020   | Case Report  | 52-year-old male resident of a nursing home |
| Chadha S, 2020 | Case Report  | 85-year-old woman             |
| Meyer P, 2020  | Case Report  | 83-year-old woman             |
| Moderato L, 2020 | Case Report | 59-year-old female patient |
| Nguyen D, 2020 | Case Report  | 71-year-old woman             |
| Pasqualetto M, 2020 | Case Report | Two male patients aged 81 and 84 and an 85-year-old female patient |
| Roca E, 2020   | Case Report  | 87-year-old woman             |
| Sattar Y, 2020 | Case Report  | 67-year-old female patient    |
| Solano-López J, 2020 | Case Report | 50-year-old man |
| Tsao C, 2020   | Case Report  | 59-year-old woman             |
Narrative Themes

From our literature search, 4 key themes were identified for discussion: (1) clinical factors associated with COVID-19 and takotsubo syndrome, (2) psychosocial drivers behind the increase in takotsubo syndrome incidences, (3) pathophysiological connections between the 2 conditions, and (4) the potential for observing surges in TTS incidence in other disasters.

Medical History Associated With COVID-19 and Takotsubo Syndrome

In the case reports we analyzed, several clinical factors were associated with the development of COVID-19 and takotsubo syndrome: hypertension, history of diabetes mellitus, gender, and age. The information from these case reports is referenced in Table 2.

Of the 15 patients in the case reports, 10 patients (66%) had hypertension listed as a comorbidity. Hypertension has been associated with increased hospitalizations in COVID-19 patients, with several retrospective studies determining it to be a commonly found comorbidity associated with worse outcomes and more severe COVID-19 disease. In COVID-19 patients presenting with TTS, hypertension also appears to be the most common concomitant condition. However, hypertension has not been established as a risk factor for TTS, as typical cardiac risk factors have not been found to be strong predictors for the condition. Therefore, though hypertension appears to be associated with COVID-19-linked TTS, it is unclear whether it can be used to predict risk.

A history of diabetes mellitus was another common finding in the case reports, observed in 7 patients (47%). Like hypertension, diabetes is associated with COVID-19 respiratory failure and poor prognosis. Prior research has suggested that it is not uncommon for patients with takotsubo cardiomyopathy to have concomitant diabetes and that it may be an independent predictor of adverse outcomes in these patients.

Eleven patients (73% of the analyzed population) with COVID-19 and TTS were women. That a majority of patients would be women would be expected, as women are at the greatest risk for developing takotsubo syndrome, accounting for 90% of TTS cases. The sex of a patient can be an important predictor of this diagnosis, which is particularly significant when clusters of TTS, a typically rare condition, appear.

TTS diagnoses are predominantly made in elderly patients, and as expected, all patients diagnosed with TTS in the case studies were ≥ 50 years old. It is noteworthy that COVID-19 mortality rates are highest in
| Author & Year | Sex  | Age | Medical history                                                                 | LVEF                  | Diagnoses                                                                                      |
|--------------|------|-----|----------------------------------------------------------------------------------|-----------------------|------------------------------------------------------------------------------------------------|
| Minhas A, 2020 | Female | 58  | Hypertension, type II diabetes, dyslipidemia                                     | 20% initial, 55% recovered | COVID-19, takotsubo syndrome, mixed shock                                                        |
| Dabbagh M, 2020 | Female | 67  | Nonischemic cardiomyopathy with LVEF of 15% in 2018                             | 40%                  | COVID-19, takotsubo syndrome, large symptomatic hemorrhagic pericardial effusion causing cardiac tamponade |
| Kariyanna P, 2020 | Female | 72  | Hypertension, diabetes, obesity, hyperlipidemia, penicillin allergy              | N/A                  | COVID-19, apical takotsubo syndrome, ischemic stroke, cardiogenic shock                          |
| Taza F, 2020    | Male  | 52  | Hypertension, schizophrenia, diabetes mellitus                                  | 45%                  | COVID-19, takotsubo syndrome                                                                     |
| Chadha S, 2020  | Female | 85  | None                                                                            | 35%                  | COVID-19, takotsubo syndrome                                                                     |
| Meyer P, 2020   | Female | 83  | Chronic hypertension                                                            | N/A                  | COVID-19, takotsubo syndrome                                                                     |
| Modarato L, 2020 | Female | 59  | Diabetes, hypertension obesity, anxiety disorders                               | 50% initial, 40-45% after 12 hours | COVID-19, takotsubo syndrome                                                                     |
| Nguyen D, 2020  | Female | 71  | Hypertension, normotensive hydrocephalus treated by ventriculoperitoneal shunt, hypercholesterolemia, taking amlodipine and rosuvastatin | N/A                  | COVID-19, median takotsubo syndrome                                                               |
| Pasqualetto M, 2020 | Male  | 81  | Diabetes, arterial hypertension                                                  | 42%                  | COVID-19, takotsubo syndrome                                                                     |
| Pasqualetto M, 2020 | Male  | 84  | Diabetes, arterial hypertension                                                  | 53%                  | COVID-19, takotsubo syndrome                                                                     |
| Pasqualetto M, 2020 | Female | 85  | Arterial hypertension                                                          | 30%                  | COVID-19, takotsubo syndrome, septic shock, pseudomonas aeruginosa infection, multisystem organ failure |
| Roca E, 2020    | Female | 87  | Breast cancer                                                                   | 48%                  | COVID-19, takotsubo syndrome                                                                     |
| Sattar Y, 2020  | Female | 67  | Hypertension, type II diabetes, taking aspirin and a statin for coronary artery disease prevention | 30%                  | COVID-19, takotsubo syndrome, new-onset atrial fibrillation                                       |
| Solano-López J, 2020 | Male  | 50  | Benign mediastinal tumour developed in childhood                               | N/A                  | COVID-19, reverse takotsubo syndrome                                                              |
| Tsao C, 2020    | Female | 59  | Obesity                                                                         | 36%                  | COVID-19, takotsubo syndrome                                                                     |

iv, intravenous; LVEF, left ventricular ejection fraction; N/A, was not discussed in report; sc, subcutaneous.
older patients. Perhaps 1 mechanism might be the development of TTS card-
diomyopathy. Our sample of case studies is small, however, so further investi-
gation could be useful in determining predictors of TTS in COVID-19
patients.

Psychosocial Impacts of the Global Pandemic

The etiology of TTS cardiomyopathy has been attributed to severe
emotional or physical stress, which can lead to rapid cardiac dysfunction.
Such triggers include intense emotions such as fear, anger, grief, and anx-
xiety. During the COVID-19 global pandemic, there has been a well-
documented increase in psychosocial and economic distress, as studies
have found worsened anxiety, panic, and depression levels in the pub-
lic. The adverse effects on mental health may be consequences of social
distancing, economic worry, and fear of contracting the virus, among
other concerns. These effects may be responsible for an increase in the
incidence of stress-induced cardiomyopathy in the general population.

Notably, the study performed at the Cleveland Clinic on patients pre-
senting with acute coronary syndrome found that none had concurrent
TTS and COVID-19. This finding suggests that the generalized increase
in incidence of TTS within the overall population is not due to coexisting
COVID-19 but may be because of the mental health crisis instead.

The case reports suggest that anxiety associated with the pandemic has
increased the incidence of TTS. As Table 3 shows, of the thirteen case reports
analyzed, 8 discussed psychosocial factors contributing to the diagnosis of
TTS. In certain cases, the author noted that stress brought by patients’
COVID-19 diagnosis and treatment was the most probable cause of TTS.
One example may be found in a July 2020 case study in which the author
writes that a patient developed troponin elevation and apical hypokinesis
postintubation and pericardiocentesis, with stress from those procedures as a
possible etiology for the stress-induced cardiomyopathy that developed
shortly afterward. As the case illustrates, along with the generalized psycho-
logical impacts within the population, the distress associated with a COVID-
19 diagnosis may itself lead to the development of takotsubo syndrome.

Pathophysiological Connections Between COVID-19 and
Stress-Induced Cardiomyopathy

As the studies we reference demonstrate, there has been an increased
incidence of TTS in COVID-19 patients. This association may be
explained by potential pathophysiological links between the 2 conditions.
Though these direct connections are not fully understood, they may be attributable to 3 factors: overactive immune response from cytokine
storm, sympathetic nervous system surge, and the development of microvascular dysfunction.

In the context of COVID-19, a cytokine storm is defined by a heightened release into the bloodstream of pro-inflammatory cytokines and chemokines, namely tumor necrosis factor-α, IL-6, and IL-1β. The release of these agents has been speculated to be triggered by both vascular leakage and epithelial/endothelial cell apoptosis, which occur due to replication in the early phase of the virus. When these proinflammatory agents are released, cardiac function can be affected, often causing myocardial injury that may lead to takotsubo syndrome. A case report in June 2020 discussing a 52-year-old male patient with a history of schizophrenia, diabetes, and hypertension is instructive. The patient was first diagnosed with COVID-19 before being diagnosed with stress-induced cardiomyopathy in the setting of hemodynamic instability and ST segment elevations on ECG. The criteria for TTS was met through a nonobstructive coronary angiogram, along with ventricular dysfunction and apical ballooning on ventriculography. Of note, a hyperinflammatory state was identified, suggesting evidence for cytokine storm. To inhibit the cytokine IL-6, the patient was given tocilizumab. Hemodynamic improvement after the introduction of the treatment was noted, suggesting a potential association between the cytokine response and TTS.

Another theory is that along with the cytokine storm comes an increase in sympathetic nervous system activity, causing catecholamine-induced myocardial stunning, thus leading to the development of stress-induced cardiomyopathy. In a case report the inflammatory state of a patient due to both acute COVID-19 and an ischemic stroke was thought to have contributed to a catecholamine surge, leading to the development of TTS.

Microvascular dysfunction is another noted pathology in COVID-19 that has been associated with stress-induced cardiomyopathy. This noted association with coronary microvascular dysfunction makes it speculated to be a physiological mechanism responsible for TTS. However, it is still unclear whether this involvement is the primary cause of the condition or a secondary occurrence. In COVID-19 patients, microvascular dysfunction can stem from a systemic inflammatory response, as well as from the formation of microthrombi during a state of hypercoagulability. Therefore, whether as a primary or secondary factor, microvascular dysfunction may directly connect TTS, and COVID-19.
Previous Disasters and Takotsubo Syndrome

As we have discussed, the major contributor to the increased incidence of TTS in the COVID-19 pandemic may be population-wide increases in psychological distress. In fact, data show that there have been previous spikes in TTS incidences in past crises. In 2004, a major earthquake was recorded with a magnitude of 6.8 on the Richter scale in Niigata Prefecture in Japan. Within a month after the earthquake, 16 patients had presented with TTS, of which 11 (68.75%) were diagnosed on the day that the disaster hit. Furthermore, 13 of the patients lived in locations that recorded the greatest seismic intensities, often being near the epicenter of the earthquake.33 A similarly large earthquake was recorded in 2011, devastating Christchurch, New Zealand, and accounting for 185 fatalities. Within 4 days of the earthquake, 21 women had been diagnosed with TTS in response to the distress brought by the crisis, a dramatic increase from the typical levels of TTS incidences.34

In 2011, a nationwide study was performed in the United States, comparing the rates of TTS incidence within each state. After controlling for population sizes, Vermont had the largest ratio of cases (380 per 1,000,000), followed by Missouri (169 per 1,000,000). Of note, Vermont was hit by Tropical Storm Irene that year, while Missouri was struck by the Joplin Tornado, one of the deadliest tornadoes in U.S. history. Because of their devastation and the ensuing psychological toll, these natural disasters were thought to have caused the large clusters of TTS seen after their occurrence.35 Studies analyzing TTS in other types of population-wide crises, such as economic disasters or past pandemics, are largely unavailable.

Implications and Gaps

There appears to be an association between stress-induced cardiomyopathy and COVID-19 in both the general population reeling from the adverse psychosocial effects of the pandemic and in COVID-19 patients. To better quantify the general increase in cases of stress-induced cardiomyopathy, further studies should be performed with larger cohort sizes. Research should also be done to gain insights into potential causes, such as adverse changes in population-scale mental health. Such research may document a need for interventions to protect the emotional health of communities during widespread disasters.

The association between stress-induced cardiomyopathy and COVID-19 underscores the importance of establishing a protocol for improved treatments. By studying the physiological connections between the 2 conditions, optimal therapies can be determined, such as anticoagulation for
microvascular dysfunction or immunosuppressive therapy for cytokine storm. Since a large driver behind the greater incidence of TTS may be widespread increases in population stress, future disasters, such as earthquakes, will likely have similar implications. In the short-term, with the pandemic permeating everyday life, it is important to treat COVID-19 as a systemic condition rather than just a respiratory one. Stress-induced cardiomyopathy is ultimately one of many consequences of the virus that warrants further research into how best to approach patient care. Moving beyond the pandemic, it is important to learn from this disaster to improve the response to future clusters of takotsubo syndrome that may appear.

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**Summary**

The manuscript intends to review available literature and discuss associations between COVID-19 and takotsubo syndrome in the general population and COVID-19 patients.

**Contributors Statement**

All authors reviewed the manuscript, approved the final manuscript, and agree to be held responsible for all aspects of the work.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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