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.)

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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.[1] The infection is most commonly identified within adult male populations, with an increased mortality rate in patients with concomitant health conditions.[2] The identification of these developed comorbidities, such as acute cardiac injury and arrythmia makes it increasingly clear that the virus is systemic and not solely isolated to the respiratory system.[3]

Cardiovascular complications in patients with COVID-19 require particular attention.[4] Conditions such as hypertension and coronary artery disease have been linked to increased mortality.[5] 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.[4] Medications used to treat COVID-19 can also cause cardiac complications, with hydroxychloroquine and azithromycin leading to QT-prolongation and various arrhythmias.[6]

Takotsubo Syndrome: Introduction, Diagnostic Criteria, Treatments

Takotsubo syndrome (TTS) is 1 cardiovascular condition that has shown a drastic increase in the general population during the time of COVID-19.[6] 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.[7] 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[8] and coronary angiography. As TTS is a diagnosis of exclusion, angiograms do not reveal significant coronary blockages,[9] while echocardiograms demonstrate segmental left ventricular dysfunction.[10]

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.[11] Patients may also go through psychotherapy to promote rehabilitation from emotional stress, a common precipitant for TTS.[12] Left ventricular dysfunction from TTS typically resolves in weeks, with most patients fully recovering within 2 months.[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

Table 1. Literature search results

Author & Year	Article type	Description of sample and size
Minhas A, 2020[13]	Case Report	58-year-old female patient
Jabri A, 2020[14]	Retrospective Cohort Study	Cardiac patients presenting with acute coronary syndrome N = 1914
Dweck M, 2020[15]	Prospective International Survey	Patients with presumed or confirmed COVID-19 between April 3 and 20, 2020 N = 1216
Giustino G, 2020[16]	Retrospective Observational Study	Laboratory-confirmed COVID-19 patients who underwent clinically indicated transthoracic echocardiograms N = 118
Dabbagh M, 2020[26]	Case Report	67-year-old female patient
Kariyanna P, 2020[27]	Case Report	72-year-old woman
Taza F, 2020[29]	Case Report	52-year-old male resident of a nursing home
Chadha S, 2020[30]	Case Report	85-year-old woman
Meyer P, 2020[36]	Case Report	83-year-old woman
Moderato L, 2020[37]	Case Report	59-year-old female patient
Nguyen D, 2020[38]	Case Report	71-year-old woman
Pasqualetto M, 2020[39]	Case Report	Two male patients aged 81 and 84 and an 85-year-old female patient
Roca E, 2020[40]	Case Report	87-year-old woman
Sattar Y, 2020[41]	Case Report	67-year-old female patient
Solano-López J, 2020[42]	Case Report	50-year-old man
Tsao C, 2020[43]	Case Report	59-year-old woman

with TTS.[14]. 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.[15] In a separate study performed at Mount Sinai Hospital, 118 patients confirmed to have COVID-19 underwent clinically indicated transthoracic echocardiography (TTE). In this study, 4.2% of patients were determined to have features consistent with stress-induced cardiomyopathy.[16] Several case reports indexed in Table 1 have also described patients with the diagnosis.

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[17] associated with worse outcomes and more severe COVID-19 disease.[18] In COVID-19 patients presenting with TTS, hypertension also appears to be the most common concomitant condition.[19] 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.[20] 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.[21] 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.[22]

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.[13]

TTS diagnoses are predominantly made in elderly patients, and as expected, all patients diagnosed with TTS in the case studies were $\geq$ 50 years old. It is noteworthy that COVID-19 mortality rates are highest in

Table 2. Case reports & clinical factors associated with COVID-19 and Takotsubo Syndrome

Author & Year	Sex	Age	Medical history	LVEF	Diagnoses
Minhas A, 2020[13]	Female	58	Hypertension, type II diabetes, dyslipidemia	20% initial, 55% recovered	COVID-19, takotsubo syndrome, mixed shock
Dabbagh M, 2020[26]	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[27]	Female	72	Hypertension, diabetes, obesity, hyperlipidemia, penicillin allergy	N/A	COVID-19, apical takotsubo syndrome, ischemic stroke, cardiogenic shock
Taza F, 2020[29]	Male	52	Hypertension, schizophrenia, diabetes mellitus	45%	COVID-19, takotsubo syndrome
Chadha S, 2020[30]	Female	85	None	35%	COVID-19, takotsubo syndrome
Meyer P, 2020[36]	Female	83	Chronic hypertension	N/A	COVID-19, takotsubo syndrome
Moderato L, 2020[37]	Female	59	Diabetes, hypertension obesity, anxiety disorders	50% initial, 40-45% after 12 hours	COVID-19, takotsubo syndrome
Nguyen D, 2020[38]	Female	71	Hypertension, normotensive hydrocephalus treated by ventriculoperitoneal shunt, hypercholesterolemia, taking amlodipine and rosuvastatin	N/A	COVID-19, median takotsubo syndrome
Pasqualetto M, 2020[39]	Male	81	Diabetes, arterial hypertension	42%	COVID-19, takotsubo syndrome
Pasqualetto M, 2020[39]	Male	84	Diabetes, arterial hypertension	53%	COVID-19, takotsubo syndrome
Pasqualetto M, 2020[39]	Female	85	Arterial hypertension	30%	COVID-19, takotsubo syndrome, septic shock, pseudomonas aeruginosa infection, multisystem organ failure
Roca E, 2020[40]	Female	87	Breast cancer	48%	COVID-19, takotsubo syndrome
Sattar Y, 2020[41]	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[42]	Male	50	Benign mediastinal tumour developed in childhood	N/A	COVID-19, reverse takotsubo syndrome
Tsao C, 2020[43]	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.[23] Perhaps 1 mechanism might be the development of TTS cardiomyopathy. Our sample of case studies is small, however, so further investigation 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 anxiety.[24] 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 public.[25] 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 presenting 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.[14]

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.[26] As the case illustrates, along with the generalized psychological 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.

Table 3. Notes discussing psychosocial impact in case reports

Author & Year	Notes discussing psychosocial impact in case report
Minhas A, 2020[13]	N/A
Dabbagh M, 2020[26]	"In our case, troponin elevation and apical hypokinesis occurred only after intubation and pericardiocentesis; therefore, stress from these procedures is also a possible etiology"
Kariyanna P, 2020[27]	"She was found at her home with altered mental status" "The developed stress cardiomyopathy/takotsubo cardiomyopathy is likely a result of stress, catecholamines and sympathetic overdrive from the ischemic stroke and ongoing COVID-19 infection" "Takotsubo Cardiomyopathy, is known to be caused by physical stressors like stroke, sepsis, infections"
Taza F, 2020[29]	"The patient is a nursing home resident with history of schizophrenia" "In the emergency room, he underwent endotracheal intubation due to acute hypoxic respiratory failure and altered mental status"
Chadha S, 2020[30]	"Patient mentioned being extremely stressed due to current COVID-19 pandemic" "A history of either an acute medical illness or intense emotional or physical stress can often be elicited in these patients, which acts as a trigger for development of TCM. No such underlying cause was identified in our patient and anxiety related to ongoing COVID-19 pandemic was most likely the inciting event, as she was extremely concerned for her health"
Meyer P, 2020[36]	"The huge emotional stress at the population level and respiratory infections caused by COVID-19 may represent potential triggers in this context"
Moderato L, 2020[37]	"However, since all patients with SARS-CoV-2 present with hypoxemia and systemic inflammation, an emotional contributing cause in a predisposed subject cannot be excluded. In particular, in the case presented, the association between anxious syndrome (a known condition predisposing TTS) and a recent bereavement (husband) following SARS-CoV-2 pneumonia. The spread of SARS-CoV-2 pneumonia in family clusters can represent a further factor capable of significantly increasing the levels of emotional stress (also in light of the inability to communicate or have contact with hospitalized family members), thus favoring a state of central adrenergic hyperactivation in the determinism of TTS"
Nguyen D, 2020[38]	N/A
Pasqualetto M, 2020[39]	"This pandemic disease may induce stress manifesting as an increase in cases of stress cardiomyopathy"
Roca E, 2020[40]	N/A
Sattar Y, 2020[41]	"Physical examination revealed an anxious woman"
Solano-López J, 2020[42]	N/A
Tsao C, 2020[43]	N/A

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.[5] 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.[27] When these proinflammatory agents are released, cardiac function can be affected, often causing myocardial injury that may lead to takotsubo syndrome.[28] 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.[29]

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.[30] 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.[27]

Microvascular dysfunction is another noted pathology in COVID-19 that has been associated with stress-induced cardiomyopathy.[9] This noted association with coronary microvascular dysfunction makes it speculated to be a physiological mechanism responsible for TTS.[31] 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.[32] 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.

REFERENCES

1. Khan T, Agnihotri K, Tripathi A, et al. (2020, May 15). *COVID-19: A Worldwide, Zoonotic, Pandemic Outbreak*. Alternative therapies in health and medicine. https://pubmed.ncbi.nlm.nih.gov/32412918/.
2. Harapan H, Yufika Itoh, N, et al. Coronavirus disease 2019 (COVID-19): A literature review. *J Infect Public Health.* 2020;13(5):667–73 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7142680/.
3. Yi Y, Lagniton P, Ye S, et al. COVID-19: what has been learned and to be learned about the novel coronavirus disease. *Int J Biol Sci* 2020;16:1753–66. https://doi.org/10.7150/ijbs.45134.
4. Kwenandar F, Japar KV, Damay, et al. Coronavirus disease 2019 and cardiovascular system: A narrative review. *Int J Cardiol Heart Vasc.* 2020;29:100557 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7266760/.
5. Nishiga M, Wang DW, Han Y, et al. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol.* 2020;17(9):543–58 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7370876/.
6. Lang JP, Wang X, Moura F, et al. (2020). *A current review of COVID-19 for the cardiovascular specialist*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7252118/pdf/main.pdf.
7. Zvonarev V. Takotsubo cardiomyopathy: medical and psychiatric aspects. role of psychotropic medications in the treatment of adults with "broken heart" syndrome.. *Cureus* 2019;11:e5177. https://doi.org/10.7759/cureus.5177.
8. Zorzi A, Baritussio A, El Maghawry M, et al. Differential diagnosis at admission between Takotsubo cardiomyopathy and acute apical-anterior myocardial infarction in postmenopausal women. *Eur Heart J Acute Cardiovasc Care* 2016;5:298–307. https://doi.org/10.1177/2048872615585515.

9. Virani SS, Khan AN, Mendoza CE, et al. Takotsubo cardiomyopathy, or broken-heart syndrome. *Tex Heart Inst J* 2007;34(1):76–9 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1847940/.
10. Izumo M, Akashi YJ. Role of echocardiography for takotsubo cardiomyopathy: clinical and prognostic implications. *Cardiovasc Diagn Ther.* 2018;8(1):90–100. https://doi.org/10.21037/cdt.2017.07.03.
11. Sattar Y, Siew K, Connerney M, et al. Management of Takotsubo Syndrome: a comprehensive review. *Cureus* 2020;12:e6556. https://doi.org/10.7759/cureus.6556.
12. Zuin M, Dal Santo P, Picariello C, et al. Takotsubo cardiomyopathy in an elderly. Woman with Alzheimer's Disease: a rare association. Case report and mini-review of the literature. *J Am Geriatr Soc* 2016;64:916–7. https://doi.org/10.1111/jgs.14071.
13. Minhas AS, Scheel P, Garibaldi B, et al. Takotsubo syndrome in the setting of COVID-19 infection. *JACC. Case reports.* 2020;2(9):1321–5 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7194596/.
14. Jabri A, Kalra A, Kumar A, et al. Incidence of stress cardiomyopathy during the Coronavirus Disease 2019 Pandemic. *JAMA network open* 2020;3(7):e2014780 https://pubmed.ncbi.nlm.nih.gov/32644140/.
15. Dweck MR, Bularga A, Hahn RT, et al. Global evaluation of echocardiography in patients with COVID-19. *Eur Heart J Cardiovasc Imaging.* 2020;21(9):949–58 https://pubmed.ncbi.nlm.nih.gov/32556199/.
16. Giustino G, Croft LB, Oates CP, et al. Takotsubo Cardiomyopathy in COVID-19. *J Am Coll Cardiol* 2020;76:628–9. https://doi.org/10.1016/j.jacc.2020.05.068.
17. Kulkarni S, Jenner BL, Wilkinson I. COVID-19 and hypertension. *J Renin Angiotensin Aldosterone Syst.* 2020;21. https://doi.org/10.1177/1470320320927851.
18. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection. *Lancet Respir Med.* 2020;8. e21. 10.1016/S2213-2600(20)30116-8.
19. Castillo Rivera AM, Ruiz-Bailén M, Rucabado Aguilar L. Takotsubo cardiomyopathy−a clinical review. *Med Sci Monit* 2011;17:RA135–47. https://doi.org/10.12659/msm.881800.
20. Sharkey SW, Lesser JR, Maron BJ. Cardiology Patient Page. Takotsubo (stress) cardiomyopathy. *Circulation.* 2011;124:e460–2. https://doi.org/10.1161/CIRCULATIONAHA.111.052662.
21. Dhama K, Khan S, Tiwari R, et al. Coronavirus Disease 2019-COVID-19. *Clin Microbiol Rev* 2020;33. e00028-20. 10.1128/CMR.00028-20.
22. Stiermaier T, Santoro F, El-Battrawy I, et al. Prevalence and prognostic impact of diabetes in takotsubo syndrome: insights from the International, Multicenter GEIST Registry. *Diabetes Care* 2018;41:1084–8. https://doi.org/10.2337/dc17-2609.
23. Liu Y, Mao B, Liang S, et al. Shanghai Clinical Treatment Experts Group for COVID-19 (2020). Association between age and clinical characteristics and outcomes of COVID-19. *Eur Respir J* 2020;55:2001112. https://doi.org/10.1183/13993003.01112-2020.
24. Ramaraj R. Stress cardiomyopathy: aetiology and management. *Postgrad Med J* 2007;83(982):543–6 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2600114/.

25. Vindegaard N, Benros ME. COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. *Brain Behav Immun* 2020:531−542 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7260522/.
26. Dabbagh MF, D'Souza Aurora, L, et al. Cardiac Tamponade Secondary to COVID-19. *JACC. Case reports* 2020:1326−1330 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7177077/.
27. Kariyanna PT, Chandrakumar HP, Jayarangaiah A, et al. (2020). Apical Takotsubo Cardiomyopathy in a COVID-19 Patient Presenting with Stroke: A Case Report and Pathophysiologic Insights. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7377629/.
28. Albuquerque JA, Marcondes-Braga FG, Moura LZ, et al. (2020). Coronavirus Disease 2019 and the Myocardium. *Arq. Bras. Cardiol.* https://pubmed.ncbi.nlm.nih.gov/32638896/.
29. Taza F, Zulty M, Kanwal A, Grove D. Takotsubo cardiomyopathy triggered by SARS-CoV-2 infection in a critically ill patient. *BMJ case reports* 2020. e236561 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7298682/.
30. Chadha, S. (2020). *'COVID-19 Pandemic' Anxiety induced Tako-tsubo Cardiomyopathy*. Central Florida Cardiovascular consultants. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7188117/pdf/hcaa135.pdf.
31. Vitale C, Kaski JC, Rosano GMC. Role of coronary microvascular dysfunction in Takotsubo Cardiomyopathy. *Circ J.* 2016 https://pubmed.ncbi.nlm.nih.gov/26763468/.
32. Montone RA, Iannaccone G, Meucci MC, et al. Myocardial and microvascular injury due to Coronavirus Disease 2019. *European cardiology* 2020 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7325215/.
33. Sato M, Saito Fujita, S, et al. Increased incidence of transient left ventricular apical ballooning (so-called 'Takotsubo' cardiomyopathy) after the mid-Niigata Prefecture earthquake. *Circ J.* 2006;70:947–53. https://doi.org/10.1253/circj.70.947.
34. Chan C, Troughton R, Elliott J, Zarifeh J, Bridgman P. One-year follow-up of the 2011 Christchurch Earthquake stress cardiomyopathy cases. *N Z Med J* 2014;127: 15–22.
35. Pant Sadip, Deshmukh Abhishek, Mehta Kathan, et al. Clustering Of Takotsubo Cardiomyopathy Cases in United States in 2011. *J Am Coll Cardiol* 2014;Volume 63 (Issue 12). https://doi.org/10.1016/S0735-1097(14)60828-7. SupplementPage A828, ISSN 0735-1097.
36. Meyer P, Degrauwe S, Van Delden C, et al. Typical takotsubo syndrome triggered by SARS-CoV-2 infection. *Eur Heart J* 2020;41(19):1860 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7184501/.
37. Moderato L, Monello A, Lazzeroni D, et al. Takotsubo syndrome during SARS-CoV-2 pneumonia: a possible cardiovascular complication. *G Ital Cardiol* 2020;21 (6):417–20 https://www.giornaledicardiologia.it/articoli.php?archivio=yes.
38. Nguyen D, Nguyen T, De Bels D, et al. A case of Takotsubo cardiomyopathy with COVID 19. *Eur Heart J Cardiovasc Imaging* 2020;21(9):1052 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7239208/.

39. Pasqualetto MC, Secco E, Nizzetto M, et al. Stress Cardiomyopathy in COVID-19 Disease. *Eur J Case Rep Intern Med* 2020;7(6):001718 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7279910/.
40. Roca E, Lombardi C, Campana M, et al. Takotsubo Syndrome Associated with COVID-19. *Eur J Case Rep Intern Med* 2020;7(5):001665 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7213829/.
41. Sattar Y, Connerney M, Ullah W, et al. (2020). *COVID-19 Presenting as Takotsubo Cardiomyopathy complicated with atrial fibrillation*. cardiology heart and vasculature. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7348613/.
42. Solano-López J, Sánchez-Recalde A, Zamorano JL. SARS-CoV-2, a novel virus with an unusual cardiac feature: inverted takotsubo syndrome. *Eur Heart J* 2020;41(32):3106 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7239192/.
43. Tsao CW, Strom JB, Chang JD, et al. (2020). *COVID-19−associated stress (Takotsubo) cardiomyopathy*. circulation: cardiovascular Imaging. https://www.ahajournals.org/doi/10.1161/CIRCIMAGING.120.011222?url_ver=Z39.88-2003.