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CASE REPORT

Takotsubo Cardiomyopathy and COVID-19: A Case Report and Literature Review

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Abstract: ***Background*:** Takotsubo cardiomyopathy is characterized by transient regional ventricular abnormalities in the absence of coronary artery disease and is reported as a complication of COVID-19.

***Case Presentation*:** It can have a diverse clinical presentation, occasionally resembling an acute coronary syndrome, and progress to acute heart failure and cardiogenic shock, adversely affecting patients' prognosis. A high index of suspicion and a thorough diagnostic approach supported by ancillary studies like echocardiography and coronary angiography is key for an accurate diagnosis and correct medical treatment. Herein, we report a patient with severe COVID-19 who developed Takotsubo cardiomyopathy.

***Conclusion*:** We also present a detailed literature review regarding the relationship between COVID-19 and Takotsubo cardiomyopathy.

Keywords: Takotsubo cardiomyopathy, stress cardiomyopathy, apical ballooning syndrome, COVID-19, SARS-CoV-2 infection, cardiogenic shock, heart failure.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, can present a wide spectrum of clinical manifestations and severity [1]. Although atypical pneumonia is the hallmark of COVID-19 infection, cardiovascular complications are frequent extrapulmonary manifestations [2, 3]. Takotsubo cardiomyopathy, also known as stress cardiomyopathy or apical ballooning syndrome, has been seldomly reported as a cardiovascular complication of COVID-19, and the relationship between these two entities remains inconclusive [4]. We report the case of a patient with severe COVID-19 pneumonia who developed Takotsubo cardiomyopathy and cardiogenic shock. We also present a complete review of the available literature.

2. CASE REPORT

A 62-year-old woman with type-2 diabetes mellitus and high blood pressure came to the emergency department with nine days of malaise, high-grade fever, cough, and progressive dyspnea, which led to acute respiratory failure that required invasive mechanical ventilation. A polymerase chain reaction for the SARS-CoV-2 virus was positive. Chest radiography showed bilateral ground-glass opacities and alveolar infiltrates. Biochemical analyses showed leukocytosis (13 000 cells/mm3) with neutrophilia (11 900 cells/mm^3), lymphopenia (510 cells/mm^3), and an elevated hs-C reactive protein (5 mg/dl), with preserved renal and liver function. She was started on IV dexamethasone and transferred to the intensive care unit.

On the third day, the patient had a sudden hemodynamic collapse with hypotension, tachycardia, and increased blood lactate levels, requiring vasopressor support. An electrocardiogram showed ST-segment elevation in the precordial leads with diffuse T-wave inversion (Fig. **1**). Transthoracic echocardiography showed severe left ventricular (LV) systolic dysfunction, with regional wall motion abnormalities characterized by extensive mid and apical dyskinesia with preserved mobility in the basal segments (Fig. **2**) (Supplementary Video). Hs-Troponin I was measured and found to be 8000 ng/L (reference value: 14 ng/L). An emergency coronary angiography was performed to rule out an acute ST-elevation myocardial infarction. We documented normal flow in all coronary arteries and no relevant obstructions.

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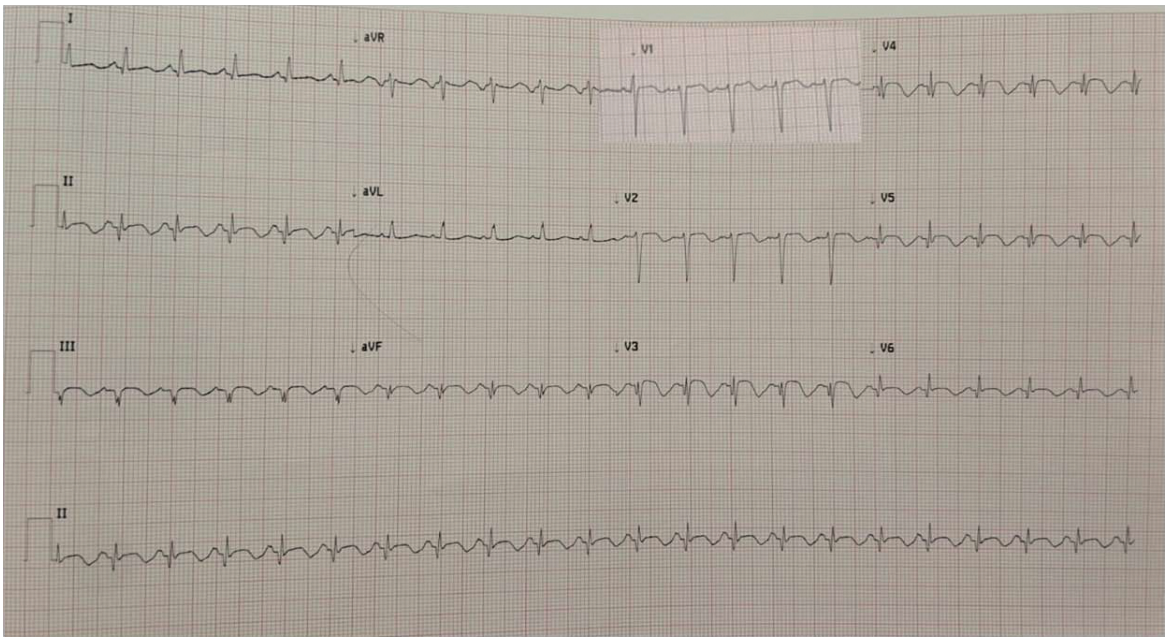

Fig. (1). Electrocardiogram showing ST-segment elevation in leads V1-V6, DII, DIII, and aVF with diffuse T-wave inversion. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

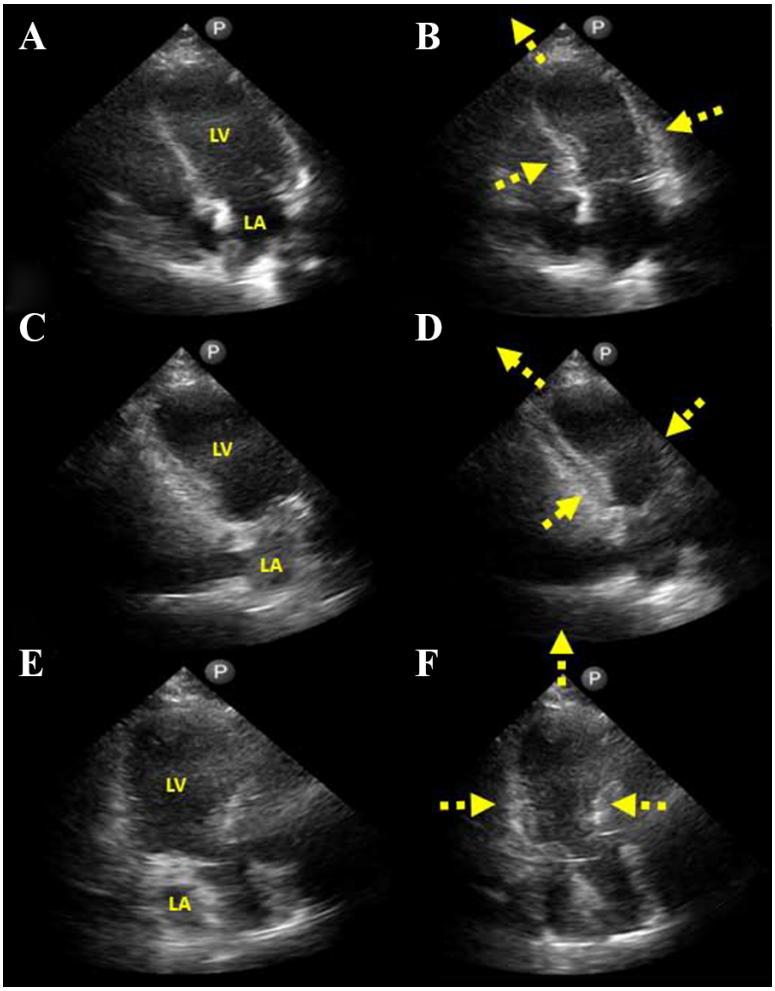

Fig. (2). Echocardiogram showing apical 4-chamber (**A, B**), 2-Chamber (**C, D**), and 3-Chamber (**E, F**) views that demonstrate dyskinesia of apical segments and preserved contractility of basal segments with an apical ballooning configuration (arrows). LV: Left ventricle. LA: Left atrium. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

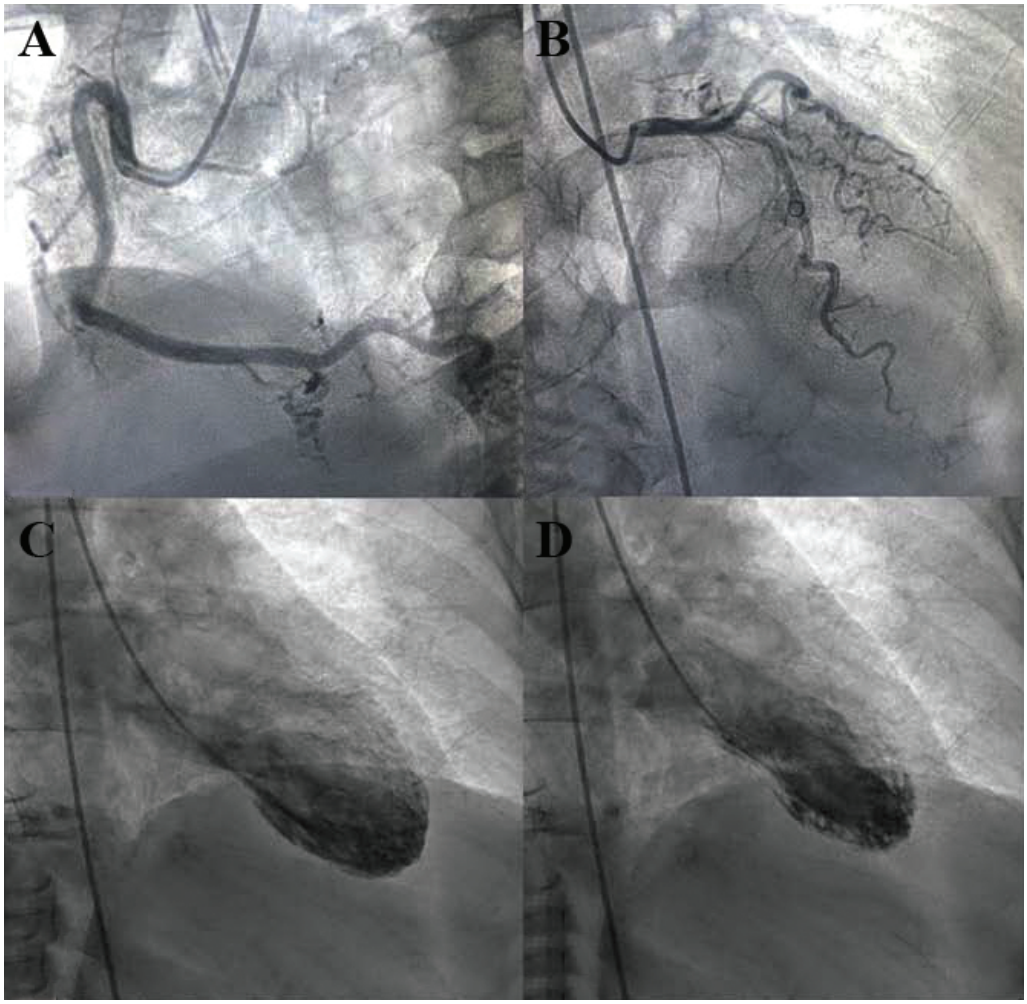

Fig. (3). (**A, B**) Coronary angiography showing normal coronary arteries. (**C, D**) Left ventriculography showing apical dyskinesia with preserved basal segment contractility with the typical "apical ballooning" image. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Left ventriculography showed diffuse apical dyskinesia with basal segment hyperkinesia and apical ballooning, consistent with an apical variant of Takotsubo syndrome (TTS) (Fig. **3**) (Supplementary Video).

She was started on levosimendan and her hemodynamic parameters and clinical status improved, which allowed us to withdraw vasopressors. We continued the management of severe COVID-19 pneumonia with respiratory support. Echocardiography showed normal wall motion in all territories and recovery of LV function on day seven (Supplementary Video). The patient had a good clinical evolution, was weaned from respiratory support, and was discharged with complete recovery after one month of hospitalization.

3. RESULTS AND DISCUSSION

Cardiovascular complications of COVID-19 have been reported [5-7]. Previous studies document a prevalence between 2.5% and 15% in hospitalized patients with a higher fatality rate (10.2% *vs*. 2.2%) [8-16]. Takotsubo cardiomyopathy is a complex cardiovascular syndrome characterized by transient regional ventricular abnormalities without significant coronary artery disease, typically presenting with apical akinesia and apical ballooning. Detailed reviews regarding this topic have been published [17, 18]. An increased incidence of Takotsubo syndrome was noted during the COVID-19 pandemic [19]. However, evidence of a direct relationship between these two entities comes mainly from case reports and small case series. We extensively reviewed the literature regarding Takotsubo cardiomyopathy and COVID-19 and found 71 subjects in 35 published reports (Table **1**) [20-52]. A descriptive analysis showed these subjects had a median age of 67 years (58-75), 26 (36.6%) were male, 26 (36.6%) female, and 19 (26.8%), gender was not specified. Regarding the prevalence of cardiovascular risk factors and cardiovascular disease, 38% had high blood pressure, 26.8% had diabetes, 25.4% had dyslipidemia, 7% had obesity, and 2.8% had coronary artery disease. Other comorbidities were reported, such as COPD, previous heart failure, and some neoplastic diseases. Also, one case was reported in a pregnant subject [50]. This data is limited by high heterogeneity in the reported cases and the details available in many.

Takotsubo syndrome is typically preceded by a physical or emotional event that acts as a trigger [18]. Although the particular physiopathology of TTS in COVID-19 is not completely understood, some mechanisms of TTS from other causes are shared, such as myocardial toxicity due to high

Table 1. Clinical characteristics of patients with Takotsubo syndrome and COVID-19 reported in the medical literature.

Author, Year	N	Age (Years)	Sex	Comorbidities	TTS Presentation	Time from COVID-19	Cardiovascular Complications	Electrocardiogram	Troponin	LVEF (%)	Variant	Coronary Angiography	Outcome
Meyer P, 2020 [20]	1	83	M	Hypertension	Chest pain, dyspnea, cough	NA	Heart failure	ST segment elevation and T-wave inversions in precordial leads	Elevated	NA	Apical	Normal coronary arteries	Discharge
Dabbag M, 2020 [21]	1	67	F	Non-ischemic cardiomyopathy	Dyspnea, cough	7 days	Heart failure, Tamponade	T-wave inversions in V2-V6	Elevated	40	Apical	NA	Discharge
Minhas A, 2020 [22]	1	58	M	Hypertension, diabetes, dyslipidemia	Respiratory failure	5 days	Heart failure, cardiogenic shock	Sinus Tachycardia, ST segment elevation DI, AvL, diffuse ST-T wave changes	Elevated	20	Apical	NA	DIscharge
Nguyen D, 2020 [23]	1	71	M	Hypertension, coronary artery disease, dyslipidemia, normotensive hydrocephalus	Dyspnea	NA	NA	Prolonged QT interval	Elevated	NA	Median	LAD significant lesion	Discharge
Moderato L, 2020 [24]	1	59	F	Hypertension, diabetes, dyslipidemia, obesity	Dyspnea	7 days	Heart failure	Diffuse ST-T wave changes	Elevated	50	Apical	NA	Discharge
Roca E, 2020 [25]	1	87	F	None	Dyspnea	0	0	T-wave inversions	Elevated	NA	Apical	NA	Discharge
Giustino G, 2020 [26]	5	66 (57-68)	M (5)	None	Dyspnea (4), Chest pain (1)	Mean 6.5 days	NA	Diffuse ST-segment elevations (2), atrial fibrillation (1), diffuse T-wave inversions (1), sinus tachycardia (1)	Elevated	36 (35-37)	Apical (4), Basal (1)	NA	Death (2), Discharge (3)
Taza, 2020 [27]	1	52	M	Hypertension, diabetes, schizophrenia	Dyspnea	0	Heart failure, cardiogenic shock	ST-segment elevation DII, DIII, AvF	Normal	45	Apical	Normal coronary arteries	Discharge
Kariyanna, 2020 [28]	1	72	F	Hypertension, diabetes, dyslipidemia, obesity	Altered mental status	4 days	Heart failure, stroke	ST segment elevation V3,V4,V5; T-wave inversion in V6, Q waves in V1-V2	Elevated	NA	Apical	NA	Death
Solano, 2020 [29]	1	50	M	None	Dyspnea, cough	8 days	Cardiogenic shock	ST-segment elevation in inferior and lateral leads	Elevated	NA	Basal	NA	Discharge
Sattar, 2020 [30]	1	67	F	Hypertension, diabetes	Chest pain	14 days	Heart failure, atrial fibrillation	Atrial fibrillation	Elevated	30	Apical	NA	Discharge
Tsao, 2020 [31]	1	59	F	Obesity	Dyspnea, cough	0	Heart failure	Diffuse ST-segment elevation and non-specific T-wave inversion	Elevated	36	Median	NA	Discharge
Dweck, 2020 [32]	19	NA	NA	NA	Chest pain (4)	NA	Heart failure (5)	ST-segment elevation (4)	Elevated (11)	NA	NA	NA	NA
Pasqualeto, 2020 [33]	3	81, 84, 85	M (2), F(1)	Hypertension (3), Diabetes (2),	Dyspnea (1), Chest pain (1), Critical condition (1)	NA	Heart failure (1)	Diffuse T-wave inversion, QT interval prolongation	Elevated	30, 42, 53	Apical (1)	Normal coronary arteries (1)	Discharge (1), Death (1)

(Table 1) Contd…

Author, Year	N	Age (Years)	Sex	Comorbidities	TTS Presentation	Time from COVID-19	Cardiovascular Complications	Electrocardiogram	Troponin	LVEF (%)	Variant	Coronary Angiography	Outcome
Sala, 2020 [34]	1	43	F	None	Dyspnea, chest pain	NA	0	Low atrial rhytm, ST-segment elevation in V1-V2, ST depression in V4-V6, QT interval prolongation	Elevated	43	Basal	NA (Normal Angiocoronary CT)	Discharge
Faqihi, 2020 [35]	1	40	M	None	Chest pain, cough	4 days	Heart failure, cardiogenic shock	Non specific ST-segment and T wave changes	Elevated	30	Basal	NA	Discharge
Titi, 2020 [36]	1	83	M	Hypertension, Diabetes, Dyslipidemia, COPD	Dyspnea	7 days	Heart failure, cardiogenic shock	Diffuse ST segment elevation	Elevated	NA	Apical	Normal coronary arteries	Death
Van Osch, 2020 [37]	1	72	F	Atrial fibrillation	Dyspnea	7 days	None	Diffuse negative T-waves, prolonged QT interval	Elevated	30	Apical	NA (Normal Angiocoronary CT)	Discharge
Hedge, 2020 [38]	7	71, 78, 70, 78, 88, 58, 56	F (3), M (4)	Diabetes (5), Hypertension (6), Dyslipidemia (7), Cerebrovascular disease (4), atrial fibrillation (4), Heart failure (1), Schizophrenia (1), chronic kidney disease (1)	Cough (2), Altered mental status (3), dyspnea (6)	NA	Heart failure (6), cardiogenic shock (6), atrial flutter(1)	Diffuse ST segment changes (4), Diffuse T-wave inversions (3), atrial flutter (1), atrial fibrillation (2)	Elevated (6)	15, 53, 45, 20, 30, 40, 45	Apical (3), basal (2), biventricular (1), global (1)	NA	Death (3), discharge (4)
Bottiroli, 2020 [39]	1	76	F	None	Dyspnea	25 days	Heart failure, cardiogenic shock	ST-segmento elevation in V2-V4	Elevated	25	Apical	NA	Discharge
Gomez, 2020 [40]	1	57	F	Crohn disease	Dyspnea	9 days	Heart failure, cardiogenic shock	Sinus tachycardia	Elevated	25	Apical	NA	Discharge
Bernardi, 2020 [41]	1	74	M	Hypertension, Diabetes, Dyslipidemia,	Dyspnea, chest pain	7 days	Heart failure	ST segment elevation in anterolateral leads	Elevated	30	Apical	NA	Discharge
Panchal, 2020 [42]	1	65	M	Hypertension, Diabetes, atrial fibrillation	Dyspnea, cough	24 days	Heart failure, cardiogenic shock	Non specific ST-T wave abnormalities	Elevated	NA	Basal	NA	Death
Fujisaki, 2020 [43]	1	60	M	Hypertension, diabetes, dyslipidemia	Dyspnea	14 days	Heart failure, cardiogenic shock, atrial fibrillation	T-wave inversion in DI, AvL, V2-V6	Elevated	15	Biventricular	NA	Discharge
Kong, 2021 [44]	2	88, 79	M (1), F (1)	Prostate cancer (1), dementia (1), multiple sclerosis (1)	Dyspnea (2)	NA	Heart failure, cardiogenic shock	ST segment elevation anteroseptal (1) and anterolateral (1)	Elevated	NA	Apical (2)	Non-obstructive coronary artery disease (2)	Death (1), discharge (1)
Sanchez-Recalde, 2020 [45]	4	42, 50, 75, 37	M (2), F (2)	Mediastinal tumor (1), copper metabolism disorder (1), history of thromboembolism (1)	Dyspnea (4), Chest pain (1)	12, 8, 2, 10 days	Heart failure (4), cardiogenic shock (4), atrioventricular block (1)	Left bundle branch block (1), ST-segment elevation lateral (1), complete atrioventricular block (1), ST-segment elevation inferior (1), Inconclusive anterior ST segment elevation (1)	Elevated	NA	Global (1), Basal (2), NA	Normal coronary arteries (2), occlusion o right coronary artery (1)	Death (3), discharge (1)

(Table 1) Contd…

Author, Year	N	Age (Years)	Sex	Comorbidities	TTS Presentation	Time from COVID-19	Cardiovascular Complications	Electrocardiogram	Troponin	LVEF (%)	Variant	Coronary Angiography	Outcome
Chitturi, 2020 [46]	1	65	F	Hypertension, diabetes, dyslipidemia, obesity, Transient ischemic attack, breast cancer	Dyspnea, Cough	7 days	Heart failure, cardiogenic shock	T-wave inversions in V1-V2, QT interval prolongation	Elevated	25	Biventricular	NA	Discharge
Bapat, 2020 [47]	1	67	F	Hypertension, diabetes, asthma	Dyspnea	8 days	None	T wave inversions, QT interval prolongation	Elevated	61	Apical	NA	Discharge
Mishra, 2020 [48]	1	70	M	Hypertension, Diabetes, Dyslipidemia, COPD, atrial fibrillation	Dyspnea	7 days	Heart failure	T-wave inversions V1-V6	NA	NA	Basal	NA	NA
Bhattacharyya, 2020 [50]	1	32	F	Pregnancy	Dyspnea	0	Heart failure	ST-segment elevation in inferolateral leads	Elevated	38	Apical	NA	Discharge
Torabi, 2021 [49]	1	42	F	Crohn disease, Guillain-Barre Syndrome	Altered mental status	7 days	Heart failure, cardiogenic shock, cardiac tamponade	Low voltage	Elevated	45	Apical	NA	Death
Namburu, 2021 [51]	1	69	M	Hypertension	Dyspnea, chest pain	10 days	Heart failure	ST elevation in V1-V3	Elevated	45	Apical	Non-obstructive coronary artery disease	Discharge
Hoepler, 2021 [52]	3	67, 60, 73	F (3)	Hypertension (2), Dyslipidemia (1), chronic kidney disease (1), COPD (1), depression (1); Cauda equina syndrome (1)	Chest pain (1), dyspnea (2)	NA (2), 3 days (1)	Heart failure (3), cardiogenic shock (1)	T-wave inversions DI, AvL, V1-V3 (1), ST-segment elevation (V4-V5) and T-wave inversion DII, DIII, AvF, and V2-V6 (1), T-wave inversion in V3-V6	Elevated	65 (1), NA (2)	Apical (2), Medium (1)	Normal coronary arteries (1), non-obstructive coronary artery disease (1), 3-vessel coronary artery disease with percutaneous intervention (1)	Discharge (3)

levels of catecholamines and cytokines, sustained inflammation, and microvascular dysfunction, all of which are predominant in subjects with severe COVID-19 [4, 53-55]. A study from the Cleveland Clinic found an increased incidence of TTS during the pandemic with a rate ratio of 4.58. Interestingly, none of these subjects had COVID-19. Cases could have been linked to the sanitary contingency and isolation psychological stress [19]. All these factors could have a role in developing TTS in COVID-19.

TTS many times is at first clinically indistinguishable from the acute coronary syndrome. Subjects commonly present chest pain, dyspnea, and sometimes complications such as heart failure, cardiogenic shock, or ventricular arrhythmias [56, 57]. COVID-19-associated TTS is not usually considered in the initial differential diagnosis of cardiovascular collapse due to its rarity and complex diagnostic approach. Our literature review found that the median time of presentation of TTS after COVID-19 diagnosis was five days. The most frequent symptoms at presentation were dyspnea (43%), chest pain (11.3%), a combination of both (7%), and an altered mental status (5.6%). Thirty-three of the available cases does not have information regarding the clinical presentation. Importantly, a high proportion of patients developed heart failure (59.2%) and some cardiogenic shock (33.8%), which played a key role in the hemodynamic deterioration and critical condition of these subjects [44, 45]. Rhythm disorders were also reported, and atrial fibrillation (7%) was the most common.

We found that the main electrocardiographic manifestation of TTS in COVID-19 was ST-elevation (33.8%), followed by T-wave inversions (21.1%). Elevated cardiac biomarkers (troponin) were reported in 81.7% of patients. This finding has been related to an adverse prognosis in subjects with COVID-19 [5, 6]. An analysis of transthoracic echocardiograms from 118 patients with COVID-19 showed five (4.2%) features of Takotsubo cardiomyopathy. These subjects had a more pronounced systolic dysfunction, higher cardiac Troponin I values, higher inflammatory and prothrombotic biomarkers, and higher mortality than subjects with other cardiac injuries and those without myocardial involvement [26]. Several patterns of TTS are recognized. An earlier review by Singh et al. that included seven patients with COVID-19 and Takotsubo cardiomyopathy showed most presented the classical apical phenotype, and 91% had a good clinical outcome [58]. In our review, the most frequent type was apical in 43.7%, followed by basal in 14.1%, and biventricular in 4.2%. In 31% of cases, the pattern of affection was not specified. LV ejection fraction was not

reported in over half of the available subjects. In the remaining group, 65.7% had a depressed LVEF (<40%).

A diagnosis of TTS is currently established using the Mayo Clinic score or International Takotsubo (InterTAKS) diagnostic criteria [17, 59]. It requires the exclusion of significant obstructive coronary artery disease as a cause of wall motion abnormalities. During the COVID-19 pandemic, this represented a complex situation. We found that coronary angiography was performed in just 22.5% of cases reported in the literature, making it impossible to rule out significant atherosclerotic disease. This finding represents a considerable limitation in the available information, given that differential diagnoses (*e.g.*, myocardial infarction, myocarditis) could not be ruled out, and key life-saving therapeutic options like revascularization could have been foregone. In the context of COVID-19, significant issues arose at cath labs regarding safety protocols for patients and operators, with some literature recommending the return of fibrinolytic for managing STEMIs during the pandemic. This topic would later be settled, making it feasible to perform an invasive coronary angiography according to current guidelines, just as in the general population [60].

Treatment of TTS is guided by clinical presentation, including heart failure therapy, hemodynamic support for cardiogenic shock, prevention of complications and treatment of the underlying disorder [59]. We found high heterogeneity in our review regarding treatment provided to subjects with TTS and COVID-19. This was mainly because some cases occurred in the early stages of the pandemic, where treatments that would later prove to be without clinical benefit were broadly used, the variable presentation of TTS and its severity, the presence of comorbidities, and the development of cardiac and non-cardiac complications of COVID-19.

Prognosis in this population depends on the severity of each of the two components. We found that 52% of patients were successfully discharged, 18.3% died, and in 29.6%, clinical outcome was not reported. It is worth mentioning that most cases occurred at the beginning of the pandemic when vaccination was not available. It is known that vaccination greatly reduces the severity of COVID-19 and the probability of hospitalization. The impact this protection could have in reducing cases of TTS related to COVID-19 remains to be studied [61]. In addition, cases of TTS associated with COVID-19 vaccination have been reported, all with a favorable outcome [62, 63].

CONCLUSION

Takotsubo cardiomyopathy should be considered in differential diagnoses of patients with COVID-19 that develop heart failure or cardiogenic shock with compatible clinical and echocardiographic features. A pragmatic approach to an accurate diagnosis must exclude other urgent entities and establish adequate monitoring and management.

LIST OF ABBREVIATIONS

COVID-19	=	Coronavirus 2019
TTS	=	Takotsubo syndrome

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

The patient provided informed consent for the publication of this report.

STANDARDS OF REPORTING

CARE guidelines were followed.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material and the published article are available on the publisher's website.

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