Tako-Tsubo syndrome in patients with COVID-19: a single-center retrospective case series

Alessandro Alonzo,[1] Stefania Angela Di Fusco,[1] Lorenzo Castello,[1] Andrea Matteucci,[1] Antonella Spinelli,[1] Gaetano Marino,[1] Stefano Aquilani,[1] Giuseppe Imperoli,[2] Furio Colivicchi[1]

[1]Clinical and Rehabilitation Cardiology Division, San Filippo Neri Hospital, Rome; [2]Medicine Unit, Emergency Department, San Filippo Neri Hospital, Rome, Italy

Abstract

Growing evidence shows that COVID-19 is associated with an increase in Tako-Tsubo syndrome (TTS) incidence. We collected data from patients hospitalized in our multidisciplinary COVID-19 department who had a diagnosis of TTS during the second and third waves of the pandemic in Italy. We reported four cases of TTS associated with COVID-19. Except for COVID-19, no patient had any classical TTS triggers. The mean age was 72 years (67-81) and all patients had COVID-19-related interstitial pneumonia confirmed by computed tomography. Typical apical ballooning and transitory reduction in left ventricle (LV) systolic function with a complete recovery before discharge were observed in all patients. The mean LV ejection fraction at TTS onset was 42% (40-48%). The electrocardiogram showed ST-segment elevation in two cases, while an evolution with negative T waves and corrected QT prolongation was observed in all patients. Three patients underwent coronary angiography. Two patients had Alzheimer's disease. The time interval from hospital admission to TTS onset was 4 (2-6) days, and the time interval from COVID-19 symptom onset to TTS diagnosis was 10 (8-12) days. COVID-19 may be a trigger for TTS, though TTS pathophysiology in COVID-19 patients remains unclear, likely due to its multifactorial nature.

Correspondence: Alessandro Alonzo, Clinical and Rehabilitation Cardiology Division, San Filippo Neri Hospital, ASL Roma 1, Via Giovanni Martinotti 20, 00135 Rome, Italy.
E-mail: alessandro.alonzo@aslroma1.it

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Introduction

The COVID-19 pandemic is still spreading worldwide. Since the first isolation of the novel coronavirus in Wuhan in December 2019, more than 631 million confirmed cases have been reported globally, causing approximately 6.5 million deaths [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is characterized by a wide range of symptoms, from mild flu-like symptoms to severe acute respiratory distress. In addition, a direct correlation between SARS-CoV-2 infection and an increased risk of developing cardiovascular complications, including acute cardiac injury, myocarditis, acute coronary syndrome (ACS), arrhythmia, heart failure, and thromboembolic events, has emerged [2,3]. Among these complications, Tako-Tsubo syndrome (TTS) has also been reported [4,5]. TTS is a well-known stress-induced cardiomyopathy characterized by transient left ventricle (LV) dysfunction with temporary wall motion abnormalities (hypokinesia, akinesia, and/or dyskinesia), often involving the LV apex and identified as apical ballooning. Clinical presentation may be indistinguishable from ACS, with angina and/or dyspnea, electrocardiogram (ECG) abnormalities, including ST-segment elevation or depression, T wave inversion, and corrected QT (QTc) prolongation, and elevated cardiac troponin serum levels [6,7]. Other clinical manifestations may be due to more severe LV dysfunction. These may include pulmonary edema, cardiogenic shock [8], and cardiac arrest [9]. Independent of clinical manifestations, TTS may be elicited by emotional or physical distress. The pathophys-

iology of TTS is unclear. Sympathetic nervous system activation with elevated catecholamine-circulating levels plays a pivotal role in TTS development. However, several other mechanisms are also reported to contribute to its pathophysiology, such as inflammation, abnormal myocardial metabolism, microvascular dysfunction, and vasospasm [6]. Since 2003, when Abe *et al*. reported the first criteria to recognize TTS [10], different diagnostic criteria have been proposed, though with a lack of worldwide consensus [11]. Currently, the most used criteria are those developed by the International Expert Consensus Document on TakoTsubo Syndrome, known as the InterTAK Diagnostic Criteria [7]. In the recent fourth universal definition of myocardial infarction, TTS is classified as a myocardial injury [12]. Growing evidence suggests that COVID-19 is related to an increase in TTS incidence, possibly due to psychological, social, and economic stress. In this context, a recent retrospective analysis conducted in the Veneto region of Italy showed a significant increase in the number of TTS cases during the first and second waves of the COVID-19 pandemic (+15.6%, p=0.03, and +12.5%, p=0.04, compared to 2018 and 2019, respectively) [13]. In addition, Jabri *et al.* reported a 7.8% incidence of stress-induced cardiomyopathy among patients presenting with ACS, which was significantly higher than that reported before the pandemic [14]. In the same period, another multicenter Italian study found a high TTS incidence rate of 9.8% in COVID-19 patients presenting with ACS (3 of 31 patients) [15]. Moreover, during the first wave of the pandemic, a global survey including more than 1216 patients evaluated the echocardiography features of hospitalized patients with confirmed or likely COVID-19 and reported that approximately 2% of these patients had concomitant stress-induced cardiomyopathy, a rate significantly higher than that reported in the general population [16]. Finally, another study performed in 2020 at Mount Sinai Hospital demonstrated that 4.2% of 118 COVID-19 hospitalized patients had echocardiographic findings compatible with TTS [17]. In this article, we report a case series of patients hospitalized for COVID-19 who were diagnosed with TTS during the hospitalization.

Materials and Methods

We retrospectively studied all adult patients (>18 years) hospitalized in our multidisciplinary COVID-19 department who had a diagnosis of TTS. A confirmed case of COVID-19 was defined as the concomitant presence of a positive nasopharyngeal swab for SARS-CoV-2 analyzed by reverse transcriptase polymerase chain reaction assay and SARS-CoV-2-related interstitial pneumonia. Lung involvement was assessed by computed tomography (CT) imaging. The criteria to hospitalize patients were: i) the presence of symptoms and signs of mild-moderate COVID-19 pulmonary involvement, and ii) the ratio of partial pressure of oxygen and the fraction of inspired oxygen (P/F ratio) >200. It is important to note that on this basis, all patients hospitalized in our COVID-19 department had a concomitant, albeit clinically mild, SARS-CoV-2-related pneumonia. TTS was diagnosed according to the InterTAK diagnostic criteria (Table 1) [7]. The study comprised the second and third waves of the pandemic in Italy, more precisely from November 1, 2020, to May 31, 2021.

Results

Over the study period, 635 patients were admitted to our COVID-19 department. Among these, we report four cases, two males and two females, with TTS associated with COVID-19. The mean age was 72 years (67-81). One patient was a current smoker (25%), two (50%) had arterial hypertension, and among these, one also had a previous diagnosis of diabetes mellitus type 2 and dyslipidemia (25%). One patient had permanent atrial fibrillation (25%). For three patients (75%), the clinical presentation upon hospital admission was fever and dyspnea, and for one, fatigue and mental confusion. Two patients (50%) had Alzheimer's disease. The exact duration of the disease was unknown, though patient 1 had an early-onset form. No patient had any established trigger for TTS except for COVID-19. Three patients were admitted to our department from the emergency room of our hospital, and one patient was transferred from an intensive care unit (ICU) of another center after the stabilization of a critical respiratory distress syndrome that required oro-tracheal intubation. Three patients (75%) had bilateral interstitial pneumonia documented on a CT scan, and one had monolateral involvement of the lung parenchyma. ECG findings in the acute phase were characterized in two cases by anterior ST-segment elevation and in the other two cases by T wave inversion. All patients showed QTc prolongation on ECG in the sub-acute phase and at discharge (Figure 1). Moreover, typical

Table 1. InterTAK diagnostic criteria. Reproduced from: Ghadri *et al.* (2018).

International Tako-Tsubo diagnostic criteria
1. Patients show transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, kinetic abnormalities may transition from one region to another.
2. An emotional and/or physical trigger can precede the Tako-Tsubo syndrome event, but this is not obligatory.
3. Neurologic events (*e.g.*, subarachnoid hemorrhage, stroke/transient ischaemic attack, or seizures) as well as pheochromocytoma may serve as triggers for Tako-Tsubo syndrome.
4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.
6. Significant coronary artery disease is not a contradiction in Tako-Tsubo syndrome.
7. Patients have no evidence of infectious myocarditis.
8. Postmenopausal women are predominantly affected.

ECG, electrocardiogram; QTc, corrected QT.

apical ballooning/akinesia and a transient reduction in LV systolic function were present in all four patients. The mean LV ejection fraction (LVEF) at TTS onset was 42% (40-48%) with a complete recovery before discharge. In the acute phase, all patients were transferred to the ICU, which was part of our department, with a median stay of 9 days. The long ICU stay duration was due primarily to intercurrent superinfections. The mean value of the high-sensitivity cardiac troponin T (hs-cTnT) peak was 748 ng/L. All patients had the typical mild increase in TnT(hs) levels in the acute phase of TTS, with a subsequent progressive reduction (the TnT peak is reported in Table 2). During the hospital stay, no significant changes were found for D-dimer, while C-reactive protein (CRP) levels initially increased to progressively decrease before discharge. The mean value of CRP was 5.3 mg/dL at admission and <0.6 mg/dL at discharge. No significant changes were observed for hemoglobin, white blood cell count, platelets, creatinine, or D-dimer values between admission and discharge. Cathecolamine levels were not checked. At TTS onset, all patients were in a COVID-19 status requiring oxygen, but always with a P/F ratio >200. No one needed mechanical ventilation. Three patients underwent coronary angiography, with no evidence of significant abnormalities of the epicardial coronary arteries in two cases. One patient had an intramyocardial bridge, a subcritical lesion (40%) on the left anterior descending artery, and a left coronary fistula to the pulmonary artery. None of the patients who underwent coronary angiography performed left ventriculography. One patient did not undergo coronary angiography because of an intercurrent episode of hemorrhagic shock due to a spontaneous psoas muscle hematoma. We based our diagnosis on clinical presentation, ECG abnormalities, hs-TnT serum levels, and echocardiographic findings. In the acute phase, one patient needed vasopressors, and another experienced an episode of atrial fibrillation. In one patient,

Table 2. Laboratory findings.

	Hemoglobin (g/dL)		WBC (×10^3/uL)		PLTs (×10^3/uL)		Creatinine (mg/dL)		hs-CRP (mg/dL)			D-Dimer (ug/mL)		Peak hs-cTnT (ng/L)
	Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Discharge	Admission	Peak	Discharge	Admission	Discharge	
Patient 1	15.3	13.9	6800	16830	271	387	1.06	0.92	4.18	5.92	<0.6	0.95	0.45	1277
Patient 2	12.8	11.3	7590	6890	287	290	1.01	0.75	4.23	7.43	<0.6	1.78	1.66	1076
Patient 3	11.9	9.1	4270	2590	161	201	1.03	0.83	1.48	14.86	<0.6	0.27	0.39	429
Patient 4	11	11.7	6480	8330	300	302	1.17	1.28	11.31	30.78	<0.6	0.71	0.48	212

WBC, white blood cells; PLTs, platelets; hsCRP, high sensitivity C reactive protein; hs-cTnT, high sensitivity-cardiac troponin T.

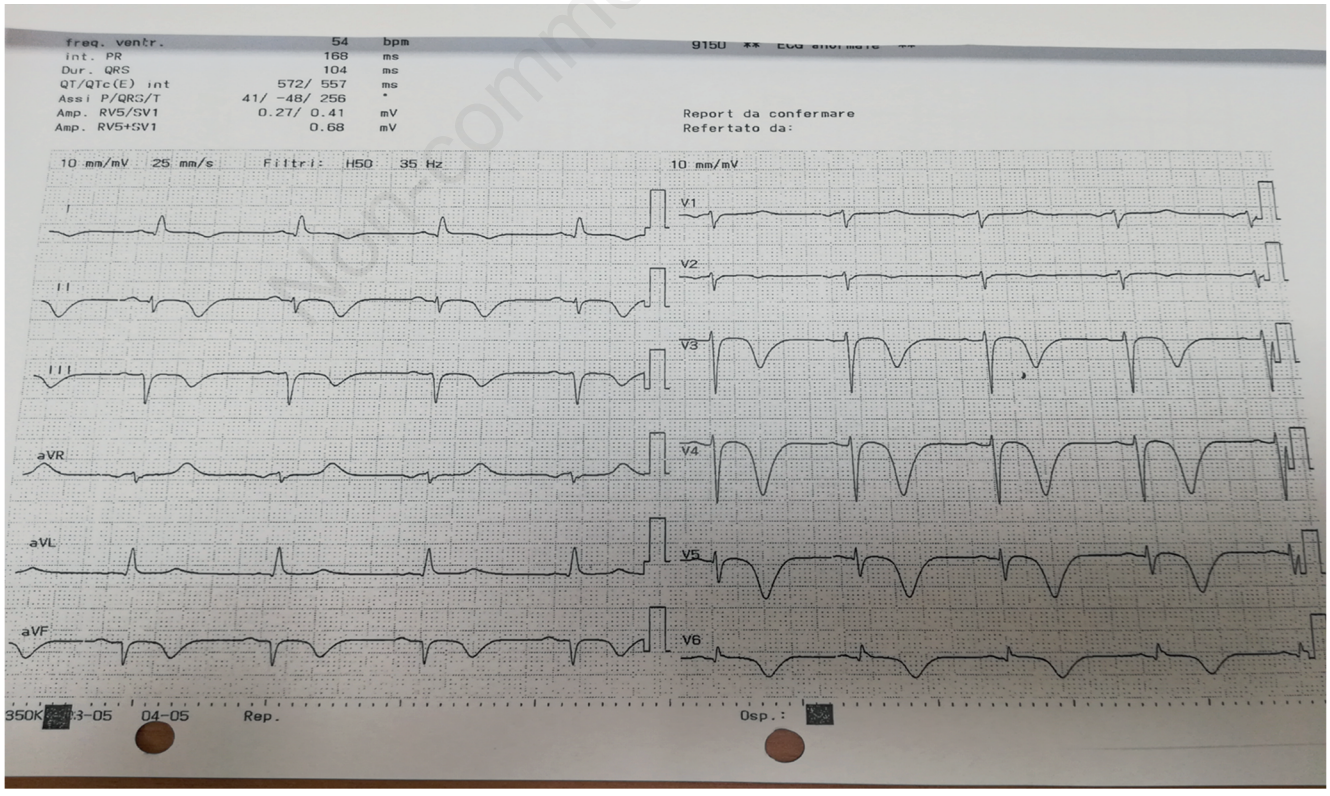

Figure 1. Electrocardiogram showing diffuse negative T waves with corrected QT prolongation (549 msec).

a differential diagnosis between TTS and myocardial infarction with non-obstructive coronary artery was discussed, but we leaned towards TTS mostly due to the echocardiographic features. Apical ballooning and its restoration were decisive for our conclusion. One patient had a dubious echocardiographic image of apical thrombosis in the acute phase, a very rare complication of TTS. However, it was no longer visible in subsequent exams, and it did not influence the following therapeutic strategy. In our case series, no fatal events were observed during hospitalization. The time interval from hospital admission to TTS onset was 4 (2-6) days, while the time interval from COVID-19 symptom presentation to TTS diagnosis was 10 (8-12) days. The mean hospital stay was 32 days (26-37). The clinical features of our patients are presented in Table 3.

Discussion

In our case series, we retrospectively evaluated data from four patients primarily hospitalized for COVID-19 who developed TTS during their hospital stay. To our knowledge, this case series is one of the largest reported by a single center [18]. All TTS diagnoses were based on clinical presentation, ECG abnormalities, hs-TnT serum levels, and echocardiographic findings. Coronary angiography was performed on three patients (one urgent and two deferred). Conversely, the fourth patient did not perform cardiac catheterization due to an intercurrent hemorrhagic complication. Consistent with other literature data [19], all patients in our population developed the typical apical ballooning and akinesia with a subsequent transient reduction of LVEF, and all patients recovered systolic function without sequelae. Although literature data report a greater TTS prevalence in females, in our small case series collected during the pandemic, males comprised half of the cases. Another interesting finding in our study was the prevalence (50%) of cognitive impairment. However, the association between TTS and dementia was previously reported in the scientific literature, albeit rarely, and dementia can contribute to TTS development [20,21]. Our percentage may be vitiated by the multidisciplinary nature of our COVID-19 department, in which we admitted patients with multiple comorbidities. Another interesting finding of our case series was the time interval between COVID-19 symptom onset and TTS development, which was approximately 10 days, an interval consistent with what was observed in a systematic review of published cases [4]. This time interval seems to coincide with the peak of the phenomenon known as "cytokine storm" [22], suggesting a possible pathophysiological role of cytokine release in triggering a catecholaminergic surge [23] and the subsequent myocardial stunning typical of TTS [6]. However, TTS pathophysiology in COVID-19 patients remains unclear, likely due to its multifactorial nature. Overall, the main potential mechanisms underlying TTS in patients with COVID-19 include i) the direct action of SARS-CoV-2, which can produce myocardial injury with different mechanisms, such as direct cardiomyocyte damage, or by inducing myocardial interstitial fibrosis, hypoxia, coronary plaque destabilization, and dysregulation of immune response [24]; ii) the psychological distress of being in a pandemic state. In this context, literature shows that TTS incidence increases in the days immedi-

Table 3. Patient demographic and clinical characteristics, electrocardiogram and imaging findings, and clinical course.

Patient	Age (years)	Sex	CVD risk factors	Past medical history	Presenting symptoms	Chest imaging	ECG findings at TTS onset	ECG findings at discharge	Cardiac imaging	Coronary angiography	Complications	Time from COVID-19 to TTS diagnosis
1	69	M	None	Alzheimer's disease	Fever, fatigue, dyspnea	Bilateral interstitial pneumonia	ST-segment elevation in V3-V6	Negative T waves with Qtc prolongation	Apical akinesia with LVEF 40%	Non-significant lesions	None	16
2	81	F	Arterial hypertension	Permanent atrial fibrillation; Alzheimer's disease	Fatigue; mental confusion	Bilateral parenchymal consolidations, ground glass and crazy paving areas	ST-segment elevation in V2-V3	Negative T waves with Qtc prolongation	Apical akinesia with LVEF 42% and dubious image of apical thrombosis	Not performed	Hemorrhagic shock due to spontaneous psoas muscle hematoma	10
3	67	F	Arterial hypertension; diabetes mellitus; dyslipidemia	Colon cancer surgically treated	Fever; dyspnea	Monolateral ground glass areas	Negative T waves and repolarization phase alterations	Negative T waves with Qtc prolongation	Apical akinesia with LVEF 48%	Tortuosity; non-significant lesions	None	9
4	72	M	Smoking history	None	Fever; dyspnea	Bilateral interstitial pneumonia	Negative T waves from V1-V6, infero-lateral diphasic T waves and QTc prolongation	Negative T waves with Qtc prolongation	Apical ballooning with LVEF 40%	Intramyocardial bridge and subcritical lesion (40%) on LAD artery; Left coronary fistula to the pulmonary artery	Atrial fibrillation; critical respiratory distress syndrome requiring intubation	9

M, male; F, female; CVD, cardiovascular disease; LVEF, left ventricle ejection fraction; TTS, Tako-Tsubo syndrome; ECG, electrocardiogram; Qtc, corrected QT; LAD, left anterior descending.

ately following disasters [25], such as after the earthquake recorded in Niigata Prefecture in Japan in 2004 [26]; iii) the emotional stress associated with COVID-19 diagnosis, the physical stress of the infection itself, and respiratory conditions, such as hypoxia and oro-tracheal intubation [27]. Furthermore, quarantine and self-isolation can also trigger TTS due to the depression, stress, insomnia, anxiety, and frustration experienced by isolated patients [28,29]; iv) the direct effect of the "cytokine storm", which determines the intense release of pro-inflammatory cytokines and chemokines [*e.g.*, tumor necrosis factor-α, interleukin (IL)-6, and IL-1β] that can lead to organ damage and catecholaminergic surge [3,30]; and v) microvascular dysfunction, which may also represent a common pathophysiologic mechanism of COVID-19 [31,32], and TTS [6] (Figure 2).

The major limitations of our study are the small number of cases and the retrospective data collection. Other important limitations are the lack of magnetic resonance imaging data, the lack of a clear definition of the coronary tree in one patient due to a hemorrhagic complication, and the missed dosage of the available circulating factors, which could help us better understand the pathophysiological mechanism of the development of TTS in COVID-19 patients (*e.g.*, cathecolamines or IL-1 and IL-6 levels). However, these limitations should be interpreted in light of the pandemic context in which all diagnostic processes and hospital pathways were reorganized, and most resources were directed to cope with the acute and critical phases.

Conclusions

Despite efforts to investigate a possible relationship between COVID-19 and TTS, the real incidence of TTS and its pathophysiology remain unknown, though our observations may add useful information to understand the role of COVID-19 in the pathogenesis of TTS. More data and larger, prospective, and multicentric studies are required to clarify the exact mechanism through which SARS-CoV-2 may lead to TTS.

Figure 2. Multifactorial potential pathophysiologic mechanisms triggering Tako-Tsubo syndrome in COVID-19 patients.

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