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Takotsubo syndrome a rare entity in patients with COVID-19: An updated review of case-reports and case-series

Since December-2019 coronavirus disease 2019 (COVID-19) has swept the world. As of 19th July, it has affected 14,043,176 people and 5,97,583 death with CFR of 4.25 globally as per WHO Situation Report. COVID-19 infection has myriad cardiac manifestation with preceding coronavirus outbreaks such as SARS and MERS [1]. Various Cardiovascular complication have been reported in previous published studies and can manifest as ACS, stress cardiomyopathy, myocarditis, myopericarditis, heart failure, arrhythmias, pericardial effusion, cardiac tamponade, thromboembolic complications, and cardiogenic shock amongst COVID-19 patients. [2]. It is hypothesized that virus causes cardiac injury via direct cytotoxic effects or via immune-mediated mechanisms. Current evidence suggests that Sars-Cov-2 binds to ACE-2 receptor present on various tissues like lung, kidney, heart, vascular endothelium and downregulates expression of this enzymes, producing enhanced vasoconstriction and deleterious effects of unopposed reticuloendothelial system [1]. Takotsubo syndrome (TTS) is a rare cardiac complication which might be misdiagnosed in high risk cardiac patients of COVID-19. However, there is limited data available on TTS in COVID-19. We aimed to perform a review of the published case reports and series and pertinent outcomes of TTS in COVID-19.

Online databases including PubMed, Embase, Scopus were retrospectively searched. The search strategy followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" guidelines by using MeSH and keywords like "Takotsubo cardiomyopathy syndrome", "COVID-19", "SARS-COV-2". We exclusively selected case reports and/or case series. Irrelevant articles were excluded. Five articles were from USA [3–7] and four articles were from Italy [8–11] and one was from Switzerland [12].

The search yielded a total of 16 patients with TTS in COVID-19 of which 11/16 patient's individual data were available, amongst whom 8/16 (50%) were male. Giustino G and colleagues reported 5 male patients of TTS with COVID-19 positive. Reported median age was 57 years (IQR: 39–65). The study reported that median time from symptoms onset to TTS diagnosis was 6.5 days (IQR: 1.0–8.0), troponin-1.4 ng/ml (IQR: 0.55–12.55), CK-MB-26.9 ng/ml, BNP-153 pg/ml, CRP-207 mg/dl, IL-6–56 pg/ml, Ejection fraction of 36% (IQR: 35%–37%). Four out 5(80%) patients suffered from acute kidney injury during hospitalization (Table 2).

For other 11 individual patient's data, calculated median age was 67 years (IQR: 58–84). There were broad range of comorbidities reported amongst these patients, including hypertension (72.7%), Diabetes (45.5%), psychiatric illness (18.2%), malignancy (9.1%), dyslipidemia (9.1%) and one patient also had ischemic cardiomyopathy (9.1%). Four out of 11 (36.4%) patients had cardiac complications such as atrial fibrillation, pericardial effusion, cardiogenic shock, heart failure. Ten out of 11 (90.1%) patients reported an elevated troponin T/I, reduced left ventricular ejection fraction with a median of 41% (IQR: 30%–45.75%). One patient had both right and left ventricular wall motion abnormalities. All patient had specific abnormalities on ECG and cardiac imaging suggestive of TTS. Ten out of 11(9.1%) had improvement either clinically or on repeat echocardiography (Table 1).

Amongst the cohort, 12 patients were discharged, and one was hospitalized due to Acute-Respiratory-Distress-Syndrome and on Extracorporeal-membrane-oxygenation and there were 3 deaths amongst the cohort.

COVID-19 can cause variety of cardiomyopathies, one of that is Takotsubo syndrome, characterized by transient regional left ventricular dysfunction in the absence of significant coronary artery disease. It is hypothesized that emotional stress, high catecholamines, exaggerated inflammatory response, and direct viral cytotoxicity may be the mechanisms of development of TTS in COVID-19 [3–5,10]. Myocardial injury in patients with COVID-19 could also be due to plaque rupture, coronary spasm, microthrombi or direct endothelial or vascular injury besides other mechanism [1]. Previous studies reported that female sex, postmenopausal women, schizophrenia, anxiety/depression, asthma/Chronic-obstructive-pulmonary-diseases, diabetes, chronic medications, substance abuse disorders were common risk factors associated with development of TTS [13]. Interestingly, our findings are consistent with the study done by Templin and colleagues that male patients are more often affected from a physical stressful event in the setting of COVID-19, while in three out of eight female, combination of emotional and physical stressful events were observed, among two of them had psychiatric illness and one was anxious during hospital admission [4,7,11,13], which are the known condition predisposing the TTS. One case report of cardiac tamponade in the setting of COVID-19 with TTS reported that elevation of troponin and apical hypokinesis ensued only after intubation and pericardiocentesis. However, the case was successfully managed with pericardiocentesis, colchicine, corticosteroids, and hydroxychloroquine [3]. Pericardial effusion could also have been due to systemic inflammation, and hemodynamics instead of direct viral infection. The spread of SARS-CoV-2 pneumonia in family clusters can represent an additional factor capable of significantly increasing the levels of emotional stress (in terms of having contact with hospitalized family members), thus leading to a state of central sympathetic hyper-activation in the determinism of TTS [14]. The cardiomyopathy that developed in each patient had all the features of TTS, including reversibility, troponin elevation, nonspecific electrocardiographic abnormalities, reduced ejection fraction and few had negative work-up for ischemia. Previous published autopsy series of patients with COVID-19, have demonstrated that there was no lymphocytic myocarditis found on heart tissue but in contrast, study done by Sala S. et al found lymphocytic myocarditis in

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Table 1
Outcomes, Clinical and laboratory characteristics in COVID-19 with TTS of individual patient data.

Author	Country/ Study Design	Age/ Sex	Comorbidities/ PMH	Clinical Features and Medical Illness during Hospitalization	Ejection Fraction LV (%)	ECG findings	Cardiac Imaging	Troponin-I/T (ng/L)	Improvement/Outcome	Medical Management
Moderato L.	Italy/CR	59/F	HTN, DM, obesity and anxiety disorders	Dyspnea and tachypneic, Chest pain	40–45	Lateral elevation of the ST tract with lateral giant symmetric negative T waves in the front and elongated QTc (511 ms)	Apical akinesia with ‘‘apical ballooning” as per TTE	1137 (cTnI)	Discharged after 10 days from respiratory improvement with resolution of symptoms and good haemodynamic compensation	IV betablocker, diuretic, nitrate, HCQ, darunavir cobicistat, azithromycin, LMWH
Dabbagh M	USA/CR	67/F	Non-ischemic cardiomyopathy with LVEF 15% managed with improvement of 40%	Dyspnea, Orthopnea and Pericardial effusion	40	Deep T-wave inversions in precordial leads (V2 to V6)	Hypokinesis of the apical and periapical walls	2410 (cTnI)	Improvement of dyspnea & discharged from the hospital	Pericardiocentesis, elective intubation, HCQ, colchicine, low dose glucocorticoids
Taza F	USA/CR	52/ M	schizophrenia, DM, HTN	Dyspnea, Tachypneic, Hemodynamically unstable, ARDS	45	ST segment elevations in the inferior leads (II, III, Avf)	Apical ballooning on ventriculogram	<15 (cTnI)	Clinically improved and discharged	Colchicine and methylprednisolone, IV heparin, Tocilizumab
Minhas A	USA/CR	58/F	DM Type-2, HTN, and Dyslipidemia	Cough, Fever. Diarrhea, ARDS and Cardiogenic or Septic shock during hospitalization.	20	Sinus Tachycardia and 1-mm upsloping ST-segment elevations in leads I and aVL, mild diffuse PR interval depressions, and diffuse ST-T wave changes, no Q wave MI	Akinetic middle to distal anterior, anteroseptal, anterolateral, and apical segments, moderately hypokinetic middle and distal inferolateral segments, and hyperdynamic basal segments. Apical ballooning and distal third or apical right ventricular (RV) free wall was akinetic, with hyperdynamic RV basal wall motion	11,020 (cTnI)	Rapid improvement in function on repeat Echocardiography and Hospitalized due to ARDS and on ECMO	Antiplatelet therapy and anticoagulation with continuous intravenous heparin and discontinued HCQ, dobutamine
Roca E	Italy/CR	87/F	Breast Cancer	Fever, Fatigue, Tachycardia, Tachypnea	48	Negative T waves and Repolarization phase alteration	Alterations in the left ventricle: apical akinetic expansion (apical ballooning) and hypokinesia of the mid-ventricular segments	5318 (cTnI)	Discharged with good clinical condition	Azithromycin, Ceftriaxone, methylprednisolone, bisoprolol and fondaparinux
Sattar Y	USA/CR	67/F	HTN, Type-2 DM	Fever, Chill, Cough, malaise, and myalgias, Anxious on Physical examination, Atrial fibrillation	30	T inversion in V1, V3; RBBB; Atrial fibrillation at rapid ventricular response	Diffuse anterior wall, apical akinesia, and apical ballooning.	423 (cTnT)	On Clinical symptom and oxygen requirement improved and discharged.	HCQ, Azithromycin, aspirin, clopidogrel, high dose statin, amiodarone, rivaroxaban
Pasqualetto M	Italy/CS	84/ M	HTN, DM	Fever, Dyspnea, Cough, Chest pain, Hypertensive crisis	53	NR	Apical ballooning with basal wall hypercontractility and systolic dysfunction	70,000 (Hs cTnT)	Discharged	Antiviral, HCQ, Fondaparinux, Aspirin, Nitroglycerine, Metoprolol
Pasqualetto M	Italy/CS	85/F	HTN	Fever, Dyspnea, Cough, Chest pain, Septic Shock, Respiratory Failure	30	NR	Apical ballooning with basal wall hypercontractility and systolic dysfunction	647,000 (Hs cTnT)	Died	Antiviral, HCQ, Fondaparinux, Aspirin, Inotropic support
Pasqualetto M	Italy/CS	81/ M	HTN, DM	Fever, Dyspnea, Cough, Chest pain	42	NR	Apical ballooning with basal wall hypercontractility and systolic dysfunction	596,000 (Hs cTnT)	Discharged	Antiviral, HCQ, Fondaparinux, Aspirin, Metoprolol
Sala S	Italy/CR	43/F	None	Chest Pain, Dyspnea	43	Mild ST elevation in V1-V2 and aVR, Reciprocal ST depression in V4-V6, QT prolongation	Hypokinesia LV mid and basal segment normal apical contraction S/O reverse TTS	135,000 (Hs cTnT)	Discharged	HCQ, Lopinavir/ ritonavir
Mayer P.	Switzerland/ CR	83/F	HTN	Acute chest pain, cough, SOB, HF	NR	ST Elevation in precordial leads with T wave inversion	Apical ballooning with hyperkinetic basal segment	1142 (cTnT)	Discharged	Conventional Heart Failure medication.

Abbreviations: M: Male, F: Female, PMH: past medical history, HTN: hypertension, DM: diabetes mellitus, LVEF: left ventricular ejection fraction, cTnT: cardiac troponin T,cTnI: cardiac troponin I, Hs cTnT: High sensitivity cardiac troponin T, ARDS: : acute respiratory distress syndrome, MI: myocardial infarction, HF: Heart Failure, SOB: Shortness of Breath, RBBB: right bundle branch block, Afib: atrial fibrillation, RV: right ventricle, TTS: takotsubo syndrome, HCQ: hydroxychloroquine, LMWH: low molecular weight heparin, IV: Intravenous, NR: Not reported, CS: Case-series, CR: Case –report.

Table 2
Observational case series involving Clinical and laboratory characteristics, Outcomes in TTS with covid-19 patients.

Author	Country and Sample (N)	Age (N) Median (IQR)	Comorbidities	Clinical Features and Medical Illness during Hospitalization	Ejection Fraction % median (IQR)	ECG changes	Cardiac Imaging	Troponin I ng/L median (IQR)	Improvement or Outcome	Management
Giustino G	USA N:5	57 (39–65)/M	Not Reported	4: Dyspnea 1: Chest pain (Acute Ischemic Stroke) 4: ARDS 4: AKI	36 (35–37)	2: ST Segment Elevation 1: Afib. with Rapid Ventricular response 1: Diffuse T wave Inversion 1: Sinus Tachycardia	4: Regional wall abnormalities typical of TTC including circumferential hypokinesis or akinesis of the apical and mid wall segments 1: patient had circumferential hypokinesis of the basal walls (consistent with reversed TTS).	11,400 (550–12,550)	2: Resolution of motion wall abnormalities on repeat TTE & discharged 1: Clinically improved & discharged 1: died on Mechanical Ventilation 1: died on VV ECMO	Not Reported

Abbreviations: IQR Interquartile range, VV ECMO veno-venous extracorporeal membrane oxygenation, TTE: Trans-thoracic echocardiography, ARDS: Acute respiratory distress syndrome, AKI: Acute kidney injury, Afib: Atrial fibrillation, TTS: Takotsubo Syndrome, M: Male.

endomyocardial biopsy in COVID-19 with TTS. Although, none of the studies reported direct viral insult on heart tissue [9,15]. Studies have reported that TTS is often complicated by atrial fibrillation, cardiogenic shock, and pericardial effusion, hypertensive crisis [3,5,7,8]. A markedly reduced left ventricular EF was reported in the early phase of disease in majority of patients of TTS and the prognosis depends on triggers. Overall, the prognosis of TTS is favorable, with 5–6% death rate and most of the patients have full recovery of left ventricular function eventually [14]. We observed that most of the cases (75%) recovered and were discharged successfully. However, few limitations warrant attention while analyzing the data due to low quality of data (small sample size, missing data, publication bias, demographics).

Clinicians should be aware of the diversity of cardiovascular complications and focused cardiac ultrasound study and echocardiography performed at bedside are effective options to screen for cardiovascular complications of COVID-19 infection. A brief medical history during admission of prior psychiatric illness, and other associated risk factors for the development of takotsubo syndrome may help in screening in high risk COVID-19 patients. Furthermore, diagnosis should be kept in mind, and optimal medical treatment should be started.

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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