Review

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Takotsubo cardiomyopathy after solid organ transplantation: a scoping review

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Abstract

Takotsubo syndrome (TTS) is a stress-induced cardiomyopathy that causes temporary left ventricular wall motion abnormalities and abrupt reversible heart failure. The incidence of perioperative TTS is proportional to the severity of surgical trauma, the duration of the procedure, and the degree of apparent sympathetic activity. A growing number of articles have discussed TTS after a solid organ transplant (SOT), which is one of the circumstances in which physical and emotional stress are at their highest levels. The majority of published cases involved patients who had received an orthotopic liver transplant (OLT). TTS occurred in 0.3–1.7% of liver transplant recipients, but a limited number of cases of TTS in patients who had received kidney, heart, or lung transplants have also been documented. In this study, we analyzed the TTS instances that developed after SOT, highlighting the symptoms and causes as well as the various treatment approaches that were applied. Most TTS cases following OLT and kidney transplant cases occurred in the first week of the surgery. However, the majority of cases occurred years after heart transplantation. Dizziness, dyspnoea, and chest discomfort are the most typical symptoms. Patients may also experience syncope and generalized weakness. In spite of this, the symptoms differ depending on the transplanted organ. Dyspnoea is a common symptom after lung transplants, whereas chest discomfort and dizziness are a common symptom after liver and kidney transplants. Yet, chest pain is not a typical symptom after a heart transplant.

Keywords: heart transplantation, kidney transplantation, liver transplantation, lung transplantation, postoperative complications, Takotsubo cardiomyopathy

Introduction

Takotsubo syndrome (TTS) is an acute reversible heart failure syndrome; it is a form of stress-induced cardiomyopathy characterized by transitory left ventricular wall motion abnormalities[1,2]. Several pathophysiologic mechanisms have been proposed, such as the contributions of the autonomic sympathetic nervous system, circulating catecholamines, or endothelial dysfunction; however, the exact pathophysiology remains unknown[1]. The majority of patients diagnosed with TTS are initially believed to be experiencing acute coronary syndrome (ACS). Approximately 2% of individuals initially thought to have ACS are eventually diagnosed with Takotsubo cardiomyopathy. The similarities in presenting symptoms, ECG changes, and lab results between ACS and TTS can make it challenging to differentiate between the two conditions at first[1]. However, TTS possesses several unique features. These include non-obstructed coronary arteries, a distinctive antero-septal-apical dyskinetic "ballooning" pattern in the left ventricle, and hyperkinetic basal segments[1,3]. (Fig. 1).

A substantial portion of the perioperative cardiac complications can be attributed to TTS, which is commonly triggered by surgery[4,5]. According to studies, the incidence of perioperative TTS will increase in proportion to the severity of the surgical trauma, the duration of the operation, and the degree of apparent sympathetic activation. Perioperative TTS exhibited a poorer left ventricular ejection fraction (LVEF), was more likely to be fatal, and looked to be caused or prompted by surgical operations in 3-23% of cases in a number of TTS case series[4,6].

Solid organ transplant (SOT) is at the top of the conditions in which physical and emotional stress is at the highest level, and an increasing number of articles have reported on TTC occurring post-SOT[5,7]. Most publications concern orthotopic liver transplant (OLT) patients[5,8,9], although kidney, heart and lung transplant patients are also being discussed[7,8,10]. The higher occurrence of TTS following liver transplants might be attributed to the immense stress on the cardiovascular system from the surgery itself and the impaired stress response in liver transplant candidates due to the inflammation associated with hepatic cirrhosis[9]. Due to the rarity of this condition and reported cases, no data are available on the prevalence. However, TTS studies

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showed that TTS occurred in 0.3–1.7% in liver transplant recipient[5]. For the cases following OLTs, most cases occurred early post-surgery[11], the same is for the kidney transplant cases[3,8,12–14]. However, the majority of cases that occurred after heart transplantation were observed years following the transplant and were predominantly induced either by dobutamine injection during a stress test or after catheterization[15]. TTS post-lung transplantation is mostly linked to respiratory diseases, with acute respiratory failure leading to stress cardiomyopathy and occurring after months of transplantation[10].

The presentation of TTS in patients who have undergone a SOT is relatively comparable to that of any other TTS occurrence and is similar to ACS. The most prevalent signs are chest discomfort, dyspnoea, and dizziness. Patients may also have generalized weakness and, rarely, syncope[7,16]. Yet, depending on the transplanted organ, the symptoms vary. For instance, dyspnoea is a typical symptom following lung transplants in TTS patients, whereas chest discomfort is a typical complaint following liver and kidney transplants. Chest pain was not a typical presentation following a heart transplant, likely due to the denervated state of the transplanted heart, which suggests limited sensory afferent reinnervation[17].

Up until now, no clinical trials have been conducted to evaluate treatment alternatives or medical interventions for TTS, contributing to the enigmatic nature of the syndrome[1]. TTS following SOT necessitates hospitalization and cardiology services; the treatment is primarily supportive and persists until the left ventricular function spontaneously recovers, typically occurring within 21 days from the syndrome's onset[16]. The intensity of TTS varies greatly. Patients with mild manifestations may not require any intervention, while those with severe cases might need assertive medical treatment and, if unresponsive, mechanical support for the left ventricle[16,18].

In-hospital mortality from Takotsubo is ~4%[1]. On the other hand, it was reported that the index/in-hospital mortality among TTS following OLT reached as high as 7%[5]. Moreover, there were rare reports of a small number of TTS deaths following lung and OLT[19,20]. Furthermore, mortality during readmissions within the calendar year was higher in OLTs with TTS in comparison to non-TTS recipients in one study (5.4% vs. 1.7%, $P = 0.02$)[5]. Patients who survive the acute episode typically recover their LV systolic function within 1–4 weeks. Short-term outcomes are excellent, with complete resolution reported in the majority of SOT cases[16].

In this study, we review cases of TTS following SOT, aiming to elucidate the common symptoms and precipitating factors associated with these cases and evaluate the various treatment modalities employed to gain a better understanding of this rare condition in the context of SOT. Recognizing the risk factors, presentation, and management of TTS after SOT is essential for ensuring optimal patient outcomes. This study emphasizes the importance of identifying the signs and symptoms of TTS in transplant recipients and implementing appropriate treatment strategies. Further research is needed to better comprehend the mechanisms underlying the development of TTS in this population and to discover preventative measures that may reduce its incidence.

HIGHLIGHTS

- This is the first comprehensive study to assess Takotsubo syndrome (TTS) across different types of solid organ transplants, providing novel insights into its occurrence, characteristics, and management in this unique patient group.
- TTS primarily occurs after solid organ transplants, with a notable prevalence in orthotopic liver transplant (OLT) recipients. Incidence rates vary from 0.3 to 1.7% in liver transplant cases, with fewer cases documented in kidney, heart, and lung transplant recipients.
- Symptoms of TTS, including dizziness, dyspnoea, and chest discomfort, typically manifest within the first week post-transplant for liver and kidney recipients but can occur years later in heart transplant patients. Symptom presentation varies based on the type of transplanted organ.
- Treatment for TTS post-transplant is mainly supportive, focusing on managing symptoms until spontaneous recovery, usually within 21 days. Severity varies, with some patients requiring aggressive medical intervention or mechanical support.
- The prognosis of TTS after transplant varies. In-hospital mortality rates are around 4% generally but can be higher in specific transplant groups like OLT recipients. Most patients recover left ventricular function within 1–4 weeks. TTS post-transplant appears to have a slight female predominance in liver, heart, and kidney transplant cases. Age distribution and presentation also vary across different types of organ transplants. Despite increasing case reports, the rarity of TTS post-transplant necessitates further research for better understanding, especially regarding its pathogenesis, preventive strategies, and treatment modalities in transplant recipients.

Methods

Database search: We searched electronic databases for relevant articles published up to February 2023. The databases used included PubMed, Scopus, and Web of Science.

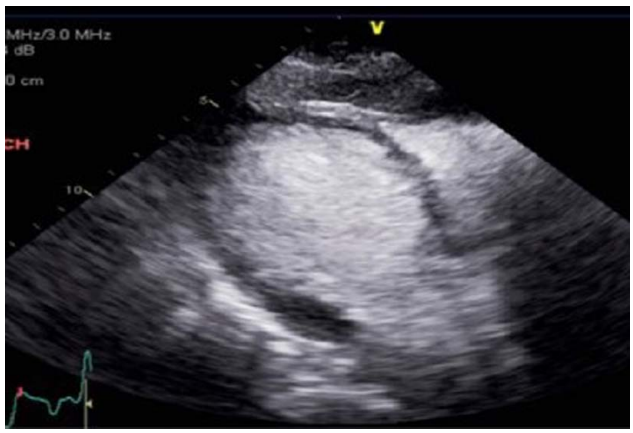

Figure 1. Echocardiography shows typical picture of Takotsubo cardiomyopathy on echocardiography. antero-septal-apical dyskinetic "ballooning" of the left ventricle and hyperkinetic basal segments.

Search strategy: To identify eligible studies, we used the following search terms and their combinations: "Takotsubo syndrome," "Takotsubo cardiomyopathy," "stress-induced cardiomyopathy," "broken heart syndrome," "solid organ transplant," "organ transplantation," "liver transplant," "kidney transplant," "heart transplant," and "lung transplant." The search was limited to articles published in English.

Study selection: After removing duplicates, two independent reviewers screened the titles and abstracts of the identified articles for relevance. Studies were considered eligible for inclusion if they were case reports, case series, or original research articles that reported on TTS in SOT recipients. Review articles, editorials, and letters to the editor were excluded, as were studies not published in English. Any disagreements between the reviewers were resolved through discussion and consensus.

Data extraction: For each included study, the following data were extracted: author(s), year of publication, study design, sample size, type of organ transplant, patient demographics (age and sex), time from transplantation to TTS diagnosis, TTS triggers and risk factors, presenting symptoms, diagnostic criteria, treatment modalities, and patient outcomes. A third reviewer verified the accuracy of the extracted data.

Data synthesis: Due to the heterogeneity of the included studies and the predominance of case reports and case series in the literature, we conducted a narrative synthesis of the findings. We organized the results by the type of organ transplant and discussed the incidence, risk factors, presentation, and management of TTS in each transplant population. Additionally, we compared the similarities and differences between TTS cases following different SOTs and highlighted areas for future research.

TTS after liver transplantation

Liver transplantation surgery itself provokes a huge amount of stress on the cardiovascular system due to hemodynamic instability, massive blood transfusions to compensate the intraoperative blood loss, major vascular manipulations such as vessel clamping, and the long procedure time. In addition to the stress imposed by the perioperative period, liver transplant candidates are particularly vulnerable to developing TTS due to the impaired stress response in the inflammatory milieu of hepatic cirrhosis[9].

TTS was first reported in OLT patients in 2007[21]. Since then, more than 300 post-OLT TTS cases have been reported (Table 1)[5,8,9,11,18,20,24,25]. Compared to non-OLT surgery, OLT patients appear to be at a higher risk for the development of TTS[5,9,25,26]. Furthermore, compared to other SOT patients, OLT patients appear to be at a higher risk for the development of TTS. The prevalence of TTS among those who underwent OLT is estimated to be 0.3%[9], 0.5%[5], 1.4%[18], 1.5%[23] and 1.7%[11]. One study showed that the rates of TTS cardiomyopathy among OLT patients increased from 0.27% in 2015 to 1.54% in 2020[9]. This higher event rate may be attributed to the increasing numbers of patients undergoing OLT and, perhaps more importantly, to better recognition and improved diagnosis of the syndrome. Additionally, data from observational studies reported that the COVID-19 pandemic, which started in early 2020, may have contributed to the higher incidence of TTS[27]. A literature review performed by Milana *et al*. showed that the main indication for OLT cases that had TTS was alcohol-related liver disease (25%), followed by hepatitis C virus cirrhosis (17.86%), hepatocellular carcinoma (10.71%), non–alcohol-related steatohepatitis (8.9%), Budd-Chiari syndrome (3.57%), and hepatitis B virus cirrhosis (3.57%)[25].

OLT recipients who developed TTS, compared to those who did not, were more likely to be older females[5,9]. However, Aniskevich found an equal distribution of TTS in men and women[18], while Yang and colleagues showed that the majority of their TTS cases were males (> 60%). There were almost general findings that the majority of TTS cases occurred in the first 5 days after OLT, if not intraoperatively[11,16]. In a recent literature review, Most cases were found to be occurred postoperatively in (82.14%), and 16.08% of cases occurred intraoperatively, with 1 case occurring preoperatively[25].

Patients with a diagnosis of TTS were more likely to have other medical diseases, including hypertension, hyperlipidemia, atherosclerosis, coronary artery disease, chronic kidney disease, sepsis, anxiety, and mood disorders[9]. Furthermore, TTS patients after OLT were found to have other complications post-incident, including cerebrovascular accidents, liver failure, gastrointestinal bleeding, and an increased requirement for invasive mechanical ventilation and renal replacement therapy[5,9]. Hepatic artery thrombosis as a potential consequence of TTS after OLT has also been reported[28]. After OLT, TTS patients required higher resource utilization in the form of mechanical ventilation, haemodialysis, vasopressors, and intra-aortic balloon pumps (IABP). TTS patients not only experienced a longer length of stay but also incurred a higher cost on index hospital admission[5]. Cardiogenic shock, which affected 32.14% of patients, was found to be the most frequent TTS complication in a recent literature review. Acute renal injury occurred in 12.50% of cases, arrhythmia in 8.93%, cardiac arrest in 5.36%, stroke, hepatic artery thrombosis, Clostridium difficile infection, and pulmonary embolism each occurred in 3.57% of cases[25].

Predictors of TTS development after OLT included decompensated cirrhosis, the presence of ascites, hepatic encephalopathy, and portal hypertension[5,11]. In a large retrospective study of 2,181 adult patients, Yang *et al*.[11] found that alcoholic cirrhosis and a high MELD-Na score were independent preoperative risk factors for TTS. Furthermore, they found that higher doses of epinephrine and lower doses of fentanyl intraoperatively were associated with the development of TTS[11]. In contrast, Aniskevich's control study found no statistically significant differences between patients with TTS following liver transplant and those without TTS in terms of intraoperative drugs and intraoperative hemodynamic measurements, MELD score, age, sex and transplantation indication[18]. This study found that dopamine, continuous veno-venous haemodialysis, and DCD donations did not play a role in the pathogenesis of TTS[18].

Yang and colleagues found that of the 38 TTS post-OLT patients, the majority were treated medically; however, seven patients required invasive interventions (five intra-aortic balloon pumps and two veno-arterial extracorporeal membrane oxygenation). All TTS patients had a full recovery of cardiac function as measured by postoperative echocardiography. He also found that the multivariable logistic regression revealed two preoperative risk factors (alcoholic cirrhosis and a model for end-stage liver disease—sodium scores) for TTS. Post-propensity match analyses showed that TTS patients had significantly higher doses of epinephrine and lower doses of fentanyl during LT compared with non-TTS patients[11]. In a recent literature review, Milanda and

Table 1

Takotsubo cases after liver transplantation. We included case series of two cases and more, case reports were not included

Author (year)	Country	No. cases	Age (in years)/sex	Triggers/risk factors	Clinical presentation	Timing	Management	Outcome
Saner *et al.*[19] (2009)	Germany	2	Case 1: 60/ male Case 2: 62/ female	Case 1: catecholamine infusion Case 2: NA	Case 1: Chest pain and dyspnoea Case 2: Cardiogenic shock	Case 1: POD18 Case 2: POD0	Medical treatment	Case 1: Recovered on POD20. Case 2: Died on POD1.
Pires *et al.*[2] (2012)	Brazil	2	Case 1: 33/ female Case 2: 36/ male	Intraoperative post-reperfusion syndrome	Cardiogenic shock	Case 1: POD5 Case 2: POD4	Medical treatment	Ventricular function completely recovered in both cases. Case 2 died on POD27 from bacterial endocarditis.
Tandon *et al.*[22] (2017)	India	6	26–55/ 4 males, 2 females	NA	2 Hypotension 2 Cardiogenic shock 1 Ventricular tachycardia 1 Respiratory distress	4 cases within 24 h of transplant. 1 case POD2 1 case POD3	Medical treatment	2 cases survived. 4 cases died.
Galván *et al.*[8](2018)	USA	6	34–66/ 5 males, 1 female	NA	Cardiogenic shock	3 cases within 48 h of transplant. 2 cases POD3 1 case POD7	4 cases: IABP 2 cases: pVAD	5 cases survived. 1 case died from GI bleeding attributed to a heparin infusion for the IABP on POD2.
Maestas *et al.*[23] (2019)	USA	7	47–68/ 4 females, 3 males	NA	Cardiogenic shock	4 cases within 24 h of transplant. 3 cases within 1 week.	6 cases: Medical treatment 1 case: ECMO with IABP	6 cases survived. 1 case died.
Patel *et al.*[5] (2020)	USA	141	57.5 (±1.3)/ 53.3% females	Multifactorial	NA	82% ($n=115$) developed early TTS on the index admission for LT	95% medical treatment. 5% IABP	Overall mortality: 5.4%
Shamaa *et al.*[20] (2021)	USA	2	Case 1: 65/ Female Case 2: 60/ female	Case 1: NA Case 2: Recent stress-induced events	Case 1: Shock Case 2: Elevated troponins and low cardiac output	Case 1: 6 months Case 2: 10 days	Medical treatment	Case 1: Died Case 2: Survived
Yang *et al.*[11] (2021)	USA	38	54.4 (±10.7)/ 60.1% males	Multifactorial	NA	71% within 5 days	5 cases: IABP 2 cases: VA-ECMO.	Overall mortality: 0%
Zmaili M *et al.*[9] (2022)	USA	110	38.2%: > 65, 61%: 18–65/ 72.7% females	NA	Cardiogenic shock	16 weeks (cumulative percentage plateau)	NA	NA

IABP, intra-aortic balloon pumps; NA, not applicable; POD, postoperative day.

colleagues found that the survival rate was (69.64%) survived, while 30.36% died. Four patients (14.81%) had a recurrence of TTS[25]. However in a Patel *et al.*[5] case series they found that the mortality rate was 5.4.

Yang *et al.*[11] also found that patients with and without TTS had comparable 1-year survival. However, Patel and colleagues found that 5.2 percent of TTS patients who underwent OLT also required the use of an intra-aortic balloon pump. There was not a statistically significant difference in the mortality rate of TTS in the OLT group when compared to the control group (7.0% vs. 4.0%, $P = 0.20$). Nonetheless, mortality rates during readmissions within the same calendar year were significantly higher in the TTS after OLT group (5.4% vs. 1.7%, $P = 0.02$)[5].

TTS after cardiac transplantation

Given the total denervation that occurs after transplantation, the presence of TTS cardiomyopathy in heart transplant recipients is fairly unexpected (Table 2)[17]. Heart transplantation causes extrinsic cardiac denervation by surgically interrupting the sympathetic and parasympathetic nerve fibres in the heart. Nonetheless, it should be emphasized that cardiac reinnervation has been shown to occur; however, it is dependent on time after transplantation and does not occur in all recipients[17]. Using metaiodobenzylguanidine scintigraphy, Buendia-Fuentes *et al.*[37] were able to demonstrate that sympathetic reinnervation occurs and is present in up to 40% of recipients at 1 year after heart transplantation. Therefore, it is conceivable that sympathetic reinnervation had already occurred in previously reported cases of TTS after heart transplantation[7,17,32]. However, TTS can occur in heart transplant recipients with poor sympathetic reinnervation, suggesting that complete cardiac nerve regeneration to connect between the cardiac afferent and efferent fibres is not a prerequisite in the pathophysiology of TTS as suggested in one case report[17], and the description of TTS on the first day after heart transplant, and another case report off TTS that occurred 5 months after heart transplantation supports this statement, the authors hypothesized that the heart tissues remain a target for catecholamine-induced cardiac failure due to the support supplied by inotropic medications[15,33]. In the absence of globally regenerated nerves after heart transplantation, the development of TTS is hypothesized to be due to an increase in adrenergic receptors on the transplanted heart, which could modulate inotropic responses and enhance susceptibility to TTS. Moreover, the absence of parasympathetic reinnervation may cause an excessive reaction to the circulating catecholamines[17].

In addition to direct neural sympathetic stimulation, several pathophysiological factors contribute to the development of TTS. Among these potential mechanisms are the impact of circulating factors, such as epinephrine, on the transplanted heart and generalized microvascular dysfunction. The authors also hypothesized a link between immunosuppressive therapy and the development of TTS. Calcineurin inhibitors may exacerbate epicardial endothelial dysfunction and cause direct myocardial injury. In turn, this may increase the tendency of heart transplant recipients to develop TTS[33].

Eleven case reports of TTS after heart transplantation have been published, with the bulk of those instances occurring at least 6 years after a cardiac transplant. Less than a year after a heart transplant, there were two incidents; intriguingly, one occurred just one day after the transplant[15,17,27,29–36].

Table 2
Takotsubo cases after heart transplantation

Author (year)	Country	Age (in years)/sex	Triggers/risk factors	Clinical presentation	Timing	Management	Outcome
Gastwirth *et al.*[29] (2009)	USA	55/ female	Dobutamine stress echocardiography	Asymptomatic. Echocardiogram showed EF 30%.	POD 1	N/A	Full recovery after 5 days.
Behnes *et al.*[30] (2015)	Germany	64/ male	NA	Sudden onset of dyspnoea	9 years	Medical treatment	Full recovery after 5 days.
Redfors *et al.*[31] (2015)	Sweden	34/ male	NA	NA	NA	Medical treatment	Full recovery after 1 month.
Chinali *et al.*[32] (2018)	Italy	21/ female	Angry debate	Reduced tolerance to activity and fatigue	10 year	Medical treatment	Full recovery after 20 days.
Al Humaid *et al.*[15] (2019)	Saudi Arabia	39/ female	Inotropic drug administration	T wave changes	POD 1	NA	Survived
Zadok *et al.*[33] (2019)	Israel	44/ female	Emotional stressful event	Asymptomatic. Abnormal findings on routine echocardiogram.	5 months	Medical treatment	Full recovery after 5 days.
Miyake *et al.*[17](2020)	Japan	67/ male	Emotional and strenuous physical stress.	Dyspnoea	10 years	Medical treatment	Full recovery after 4 weeks.
Tsuji *et al.*[34] (2020)	Japan	40/ female	Epileptic seizure	NA	15 months	Medical treatment	Full recovery after 18 days.
Berg *et al.*[27] (2021)	USA	66/ male	SARS-CoV-2 infection	Fatigue, dyspnoea, and nausea.	7 years	Medical treatment	Full recovery after 3 days.
Sagray *et al.*[35] (2022)	USA	14/ male	Dobutamine stress echocardiography	NA	NA	NA	NA
Damera *et al.*[36] (2022)	USA	56/ male	Status epilepticus	Cardiogenic shock	1 year	IABP	Full recovery after 1 week.

IABP, intra-aortic balloon pumps; NA, not applicable; POD, postoperative day.

Emotionally stressful circumstances, status epilepticus, COVID-19, and dobutamine induced during stress echocardiography were the triggers in these cases.

Importantly, these patients only reported heart failure-related symptoms, such as acute dyspnoea and desaturation, and not chest pain, which is a common TTS symptom, suggesting the limited sensory afferent reinnervation of their hearts[23,24]. No mortalities were reported, and all patients made a full recovery[30,37].

Even though these cases are rare, they demonstrate that TTS needs to be considered in the differential diagnosis of heart transplant recipients who suddenly develop graft dysfunction that seems to be acute graft rejection or acute coronary syndrome.

TTS after renal transplantation

TTS has very rarely been described after kidney transplants. The fact that kidney transplants are seen as less stressful than liver transplants may be responsible for these results. The bulk of TTS instances that were recorded in the literature as occurring after kidney transplants exhibited symptoms ranging from anxiety, chest pain, and tachycardia to cardiac arrest[3]. On their electrocardiograms, the majority of patients had a left bundle branch block and also elevated troponin[3].

Only five case reports of TTC in the population of renal transplant recipients have been published thus far (Table 3). Most of the patients described had TTS manifest within 48 h of the perioperative period[3,8,12–14]. Surgery for a renal transplant is thought to be the primary initial cause of TTS. Yet, in the documented renal transplant cases, there have been other factors that have been connected to TTS. The calcineurin inhibitor (CNI) toxicity had a potential influence on the patient's TTS and delayed graft function, according to a case study that was published in the literature. There was an immediate clinical improvement with the resolution of LBBB and complete recovery of all biochemical parameters after lowering the tacrolimus trough level.[14]. Another case of TTS after renal transplant suggested that the initiation of norepinephrine along with their immediate resolution after the discontinuation of the drug might suggest a causal relationship[12].

All of these cases had cardiogenic shock with biventricular failure and significant decreases in ejection fraction and cardiac function. Four patients were treated with medical management; however, one patient required mechanical cardiac support. This case involved a 60-year-old woman who reported an arrhythmia, a need for intracardiac device insertion, and a double chamber pacemaker requirement for arrhythmia as a side effect of TTC[3].

TTS after lung transplantation

Due to improvements in survival rates in lung transplantation procedures, a growing number of patients now benefit from this last-hope technique[38]. The majority of lung transplanted patients are between 50 and 64 years old at the time of transplantation[38,39], and they frequently display comorbidities, especially cardiovascular conditions, with the risk of organ failure and complications either during or after transplantation. On the other hand, hypoxia and hypercarbia that are associated with end-stage lung diseases may play an important role in the pathophysiology of TTS[40]. The bulk of TTS instances that were

Table 3

Takotsubo cases after kidney transplantation

Author (year)	Country	Age (in years)/ gender	Donor characteristics/cause of death[a]	Triggers/ risk factors	Clinical presentation	Timing	Management	Outcome
Chrapko *et al.*[13] (2012)	Poland	46/ female	NA	NA	Tachycardia, anxiety, and feeling hot.	POD 1	Medical treatment	Discharged on POD30 with a normal graft function on follow up visits.
Gołębiewska *et al.*[14] (2014)	Poland	68/ female	45 male/ SAH	Tacrolimus toxicity	Chest pain	POD 1	Medical treatment	Discharged on POD 22 with a normal graft function.
Vailas *et al.*[12] (2016)	Greece	51/ male	41 Male/ SAH	NA	Chest pain	POD 2	Medical treatment	Discharged on POD 7.
Galván *et al.*[8] (2018)	USA	45/ female	Living donor	NA	Cardiac arrest after ventricular tachycardia	POD 2	Medical treatment	Discharged on POD 9 with normal graft function.
Pearson *et al.*[3] (2022)	USA	60/ female	NA	Acute respiratory failure	Hypotension and bradycardia	POD 1	Permanent dual chamber pacemaker	Discharged on POD 14 with improvements in graft function.

NA, not applicable; POD, postoperative day.
[a]Cause of death for deceased donors.

Table 4
Takotsubo cases after lung transplantation.

Author (year)	Country	Age (in years)/ sex	Cause of lung failure	Triggers/risk factors	Clinical presentation	Timing	Management	Outcome
Michel-Cherqui *et al.*[41] (2010)	France	55/ female	Lung fibrosis	Acute respiratory failure	Hemodynamic instability	Preoperative	Medical treatment and ventilator support	Repeat echocardiographic evaluations showed rapid improvement of cardiac function. The patient had an urgent lung transplantation 24 h later.
Ghadri *et al.*[42] (2014)	Switzerland	51/ female	Systemic sclerosis	Acute respiratory distress	Hemodynamic instability	7 years post-transplant	Medical treatment and ventilator support	Survived
Bharat *et al.*[43] (2016)	USA	Mid 60s/ female	Systemic sclerosis	Seizures and intracerebral haemorrhage	Hypoxaemia and hypotension	POD 10	VV-ECMO and medical treatment	Survived
Duclos *et al.*[44] (2017)	France	50/ male	COPD	NA	Cardiogenic shock	Intraoperative	Medical treatment	Survived
Omosule *et al.*[10] (2018)	USA	63/ female	Sarcoidosis	Acute respiratory failure	Hemodynamic instability	POD 4	ECMO	Died
Yazıcıoğlu *et al.*[40] (2018)	Turkey	61/ male	COPD	NA	ST elevation in the inferior and lateral leads	POD 1	VA-ECMO	Survived
Kassegne *et al.*[38] (2019)	France	58/ female	COPD	Lung transplant offer phone call	Dyspnoea, chest pain, and anxiety.	NA	Non-invasive ventilation and medical treatment	Survived

NA, not applicable; POD, postoperative day.

recorded in the literature as occurring after lung transplants exhibited symptoms ranging from acute hypoxic respiratory failure with pulmonary oedema to cardiogenic shock (Table 4).

Five cases of TTS were reported in the perioperative period[10,41–44], two after the 3rd and 4th days of lung transplant, one upon induction, one after one month of the transplant and the other one 7 years after lung transplant. Among the cases reported, 3 of them needed ECMO to reverse the hypoxia, after which one patient's hemodynamics rapidly improved after VA-ECMO initiation, the LV function normalized rapidly, and gradually the patient was weaned off ECMO days later[40]. One needed mechanical ventilation for LV support with an LVAD and RV support combined with VV-ECMO[43]. However, the other case died after several months of the lung transplant[10].

Postoperative acute respiratory failure and hypoxia were identified as potential triggering factors in TTS cases following lung transplantation. The suggested mechanism for hypoxia may be through peripheral and central chemoreceptors. Peripheral receptors are located in the carotid body and exhibit a sensitive response to hypoxia[45]. Contrary to peripheral chemoreceptors, central chemoreceptors respond to blood gas pH and hypercarbia. Both systems are related to sympathetic drive, and arterial blood gas alteration stimulates receptors, and this stimulation is connected to the sympathetic system, which produces catecholamine[45]. Therefore, catecholamine secretion, independent from emotional or physical stress, including hypoxia, hypercarbia, and pH alterations, is thought to play a major role in those cases of TTS after lung transplantation[46].

Interestingly, there were two reported cases of TTS in patients who were awaiting a lung transplant. The first case was reported for a 55-year-old woman presenting with end-stage lung fibrosis who was referred for lung transplantation and developed rapidly progressive respiratory failure. In this case, rapid improvement of hypoxaemia using ventilation allowed successful lung transplantation without the need for an associated heart transplant[41]. The second case was for a 58-year-old patient who experienced severe respiratory failure caused by TTS, triggered by a call for lung transplantation, with subsequent recovery. After the call and during her transfer by ambulance, she began to experience shortness of breath, chest pain, and anxiety. She was discharged 13 days after her admission and 37 days after the stressful episode, and a pulmonary graft was once again proposed to the patient 1 month later. The lung transplantation was successfully carried out under beta-blocker therapy[38].

Summary and conclusions

TTS post-SOT is rare, yet its incidence has risen over the past 5 years. Despite extensive medical literature on the subject, there is still much to learn about TTS. Expanding our understanding of TTS by identifying its precise pathogenesis and exploring additional therapeutic targets will improve patient care. Age-related cardiovascular comorbidities and cardiac comorbidities in SOT candidates and recipients make them more vulnerable to post-operative complications when exposed to the hemodynamic stress that follows the early post-transplant period.

Our review of published case reports analyzed patients who developed TTS following liver, heart, lung, and kidney transplantation. The mean ages for each transplant group were 50.0 years for liver, 45.5 years for heart, 54.0 years for kidney,

and 56.6 years for lung transplant recipients. The age range of patients varied across different organs: 26–68 years for liver, 14–67 years for heart, 46–68 years for kidney, and 50–63 years for lung transplant recipients. It is important to note that these findings are based on published case reports and may not be representative of the entire population of organ transplant recipients who develop TTS. Further research, including larger-scale studies, is needed to better understand the factors contributing to TTS development in organ transplant recipients and to optimize patient care.

We also observed that there is a slight predominance of female patients in liver, heart, and kidney transplant cases, while lung transplant cases have a more balanced gender distribution. This suggests that gender may play a role in the development of TTS following organ transplantation, with females potentially being at a higher risk.

Compared to the International Takotsubo Registry, the proportion of female patients and the average age of all SOT patients were both lower. This difference is likely due to the diverse primary diseases leading to end-stage organ failure, which have distinct epidemiological characteristics. Moreover, the number of cases reported after SOT is low.

It is clear that liver transplant candidates are a group with a significant risk of cardiovascular comorbidities. Patients who underwent OLT had a higher likelihood of developing TTS compared to other SOT patients. Cirrhosis-related cardiovascular complications, along with increased age, elevate the risk of developing postoperative cardiac issues. TTS during perioperative SOT requires inpatient treatment and consultations with cardiologists. Treatment primarily focuses on providing support and continues until the spontaneous recovery of left ventricular function, which typically occurs within 21 days from the onset of the syndrome. This review has several limitations that should be acknowledged. The generalizability of our review's findings may be limited by patient population heterogeneity, various SOT types, and diverse clinical settings. Prospective, multicenter studies are needed to improve our understanding of TTS in SOT recipients. The literature reviewed lacked information on psychiatric history and stress for patients developing TTS post-transplantation. Future research should consider these factors for a more comprehensive understanding of TTS development, risk stratification, and targeted interventions in transplant recipients.

Ethics statement

Our research does not include studies on human subjects, human data or tissue, or animals.

Consent

It's a review article, no consent required.

Source of funding

No financial support was received for this project.

Author contribution

All authors have made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be submitted.

Conflicts of interest disclosure

The author declares no conflicts of interest.

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Data availability statement

Data are available upon request.

Provenance and peer review

Not applicable.

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