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SYSTEMATIC REVIEW AND META-ANALYSIS

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# A New Insight Into Sudden Cardiac Death in Young People

## *A Systematic Review of Cases of Takotsubo Cardiomyopathy*

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**Abstract:** Takotsubo cardiomyopathy (TTC) causes sudden cardiac death and has garnered increased attention worldwide in recent years. However, few studies have clearly classified the risk factors for this disease, including gender, race and morbidity, as well as the physical and mental stressors that can exacerbate the disease, particularly in young patients. To better analyze the characteristics of young TTC patients, we performed a systematic review of reported cases involving young patients.

A computer-assisted search was performed using prominent electronic medical information sources to identify literature published between January 1965 and December 2013. Relevant studies containing clinical data of young TTC patients were included.

Ninety-six records that included information about 104 cases were ultimately selected for our review. Several of the following results were noted: First, physical stress was more likely to exacerbate TTC than was mental stress in young patients. Second, more female than male TTC patients were noted among both young patients and the general population. Third, ethnicity appears to play no role in the disease, as no significant differences were noted among individuals of different races with respect to clinical characteristics, morbidity or stressors. Fourth, the clinical manifestations of TTC were similar to those of other cardiac diseases, including coronary heart disease. However, TTC may be detected using the combination of echocardiography and ventriculography.

Clinicians should consider TTC if young patients present with symptoms similar to those of coronary heart disease so that harmful treatments such as coronary artery stent placement may be avoided. Moreover, the answers to questions regarding the clinical diagnostic criteria, etiology, pathophysiology, and the management of this syndrome in youth remain unclear; therefore, further research is needed.

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**Abbreviations**: ACEI = angiotensin-converting enzyme inhibitors, ACS = acute coronary syndrome, AMI = acute myocardial infarction, DIC = disseminated intravascular coagulation, HPA = hypothalamic–pituitary–adrenocortical, IABP = intraaortic ballon pump, MODS = multiple organ dysfunction syndrome, PCAS = post-cardiac arrest syndrome, SCD = sudden cardiac death, TTC = Takotsubo cardiomyopathy.

## INTRODUCTION

Among the 12 million people who die from cardiovascular disease worldwide each year, half die of sudden cardiac death (SCD). Thus, SCD is one of the primary emergent events that leads to cardiovascular death. Acute coronary syndrome (ACS) is one of the primary causes of SCD.[1] Meta analyses indicate that among the 1% to 2% of all admissions that occur due to ACS, left ventricular dysfunction, electrocardiographic changes, and myocardial enzyme elevations suggestive of an acute myocardial infarction (AMI), a reversible trend was noted, and subsequent coronary angiography was normal.[2] For these patients, the use of ventriculography revealed an apical ballooning appearance and a hypercontractile base of the heart. This disease is called Takotsubo cardiomyopathy (TTC). However, due to the limited knowledge regarding this disease and the inability of clinicians to identify it, many cases of TTC are misdiagnosed; therefore, its true prevalence is underestimated.[3,4]

TTC, also known as stress-induced cardiomyopathy, left ventricular apical ballooning syndrome, transient ventricular ballooning syndrome, ampulla cardiomyopathy, and broken heart syndrome, is characterized by transient left ventricular systolic dysfunction and apical ballooning that resembles the shape of a traditional Japanese octopus trap, the rationale for the name ''Takotsubo.''[5] Following its inclusion among the cardiomyopathies by the International Society of Cardiology, TTC has gradually gained more recognition in recent years. The clinical manifestations of TTC and AMI are so similar that TTC may be easily misdiagnosed as an AMI. However, TTC differs significantly from AMI with respect to treatment and prognosis. More than 95% of patients with TTC have favorable prognoses that entail the full recovery of left ventricle (LV) function; however, serious complications such as heart failure, malignant arrhythmia, and death have also been reported.[6,7] As catecholamine-mediated cardiotoxicity is widely accepted as the primary pathophysiological mechanism of TTC,[2,8–10] beta receptor blockers and angiotensin-converting enzyme inhibitors (ACEI) are commonly chosen to treat the disease rather than thrombolytic agents, coronary artery stents, coronary bypass, or long-term antiplatelet or lipid-lowering drugs.[11]

Physical and mental stressors are recognized as the leading causes of TTC.[9,10] With the increasing pressure of work and life in modern society, the morbidity of TTC in large cities is gradually increasing. TTC has drawn increased attention as a new mechanism of SCD. Under these circumstances, an early diagnosis and the administration of appropriate and timely treatment may avoid unnecessary coronary angiography, avert fatal complications, and improve the survival rates of SCD patients.[1] Although many countries have reported cases of TTC in last 10 years,[3,5,12] including Japan, Korea, America, and Australia, only a limited number of studies has focused on young patients, who make up the largest proportion of the metropolitan population. No randomized controlled studies have been performed in this cohort either in China or aboard. Therefore, to better understand the prevalence, risk factors, clinical characteristics, and prognosis of TTC in young patients, we performed a systematic review of the existing literature on this topic.

## METHODS

A computer-assisted search was performed using the CBMDISC, PUBMED, EMBASE, SCI, and Cochrane Library databases to identify relevant literature published between January 1965 and December 2013. We used the search terms ''stress cardiomyopathy,'' ''Takotsubo,'' ''Tako-tsubo,'' ''apical ballooning,'' ''ampulla cardiomyopathy,'' ''amphora cardiomyopathy,'' and ''broken heart syndrome,'' paired with the terms ''adult,'' ''infant,'' or ''child.'' The criteria for the inclusion of publications in this study were as follows: reports describing original data that contained complete individual patient information; patient age $\leq$40 years old; transient dyskinesis or akinesis of the left ventricular apex, midventricular wall-motion abnormalities, basal ballooning, and a pattern of regional wall-motion abnormalities beyond the range of a single epicardial coronary arterial distribution, as noted via echocardiography or left ventriculography; and coronary angiography demonstrating the absence of acute plaque ruptures or signs of obstructive coronary disease (normal coronary arteries or luminal stenosis $<$50%). The generated list of articles obtained via the literature search was checked manually by 2 investigators, and the study eligibility was confirmed by all authors. Publications were selected for further detailed review when the titles or abstracts indicated that they were likely to meet the inclusion criteria. Furthermore, we analyzed the references of these papers to identify additional relevant articles. We chose the latest publication when several publications were found that described the same case series, although we included data from earlier publications if necessary. For each selected study, 2 reviewers independently extracted data, including data regarding the demographic characteristics, risk factors, clinical presentation, complications, treatment and prognosis of TTC. Differences were resolved by consultation or by a third independent reviewer. Due to the heterogeneity of the collected data, we conducted a narrative synthesis of the reported cases and case series instead of a formal meta-analysis. The purpose of our study was to identify the baseline characteristics, risk factors, treatment and prognosis of young patients with TTC. Cases with patients who died were analyzed based on their clinical data.

Stata 7.0 (StataCorp, College Station, TX) was used to perform all statistical evaluations. Quantitative variables are presented as means $\pm$ standard deviations, and categorical data are presented as absolute values and percentages. Continuous variables were compared using Student *t* test and the Chi-square test. Fisher exact test was used to compare categorical data. Any $P \leq 0.05$ was considered statistically significant.

## RESULTS

### Search Results

Using the retrieval strategy described above, a total of 858 articles were identified. Articles were screening by reading the titles and abstracts to exclude any articles that did not meet our inclusion criteria as well as to exclude reviews and repeat articles; 397 articles were ultimately selected. Based on our exclusion criteria, we removed 277 papers that included patients older than 40 years of age. Nineteen articles with incomplete clinical data were also excluded, as were 5 additional articles without any data regarding coronary angiography. Ninety-six records, including 104 cases, were selected for our research (Figure 1).[13–108]

### Baseline Characteristics

We undertook a systematic review of the reported cases that included information regarding the clinical characteristics of TTC in the young patients. A total of 104 cases were selected for our study. The basic characteristics of these patients are described in detail in Table 1. The average age of the patients was $28.53 \pm 8.92$ years old. Among these patients, the majority were 31 to 40 years old (48.08%) and were female (74.04%), similar to the general population.[5,109] Caucasians represented a significant percentage of the patients (75.00%), followed by people of Asian origin (22.12), whereas Hispanic individuals accounted for only 2.88% of patients. The most common presenting symptoms were chest pain and chest congestion (38.46%). Dyspnea (31.73%) and cardiac arrhythmia (25.96%) were the second and third most common clinical manifestations. More than 10% of patients experienced an episode of syncope during the progression of their illnesses, and other patients experienced cardiac arrest, seizures, or gastrointestinal symptoms. Most interestingly, physical stress accounted for 88.46% of cases of TTC among young patients. Among these patients, drugs, anesthesia (34.62%), trauma, surgery (25.96%), and pheochromocytoma (10.58%) were the most common physical stressors. Chronic pain, subarachnoid hemorrhage, smoking, high blood pressure, allergic reactions, asthma and the other physical stressors that induced TTC were less common among young individuals. Mental stress (20.19%) also played a role in the etiology of TTC among young patients. Emotional stress represented the majority (13.46%) of mental stress that caused TTC; depression and mental illness ranked second and third, respectively. The most common complications associated with TTC were as follows: pulmonary edema (16.35%), malignant arrhythmia (9.62%), and shock (8.65%). Current treatments for TTC among youth primarily included β-blockers (42.31%), ACEI (30.77%), vasoactive agents (36.54%), diuretics (22.12%), aspirin (12.50%), nitroglycerin (7.69%), intraaortic balloon pumps (7.69%), and symptomatic and supportive treatments for patients with concurrent pericardial effusions, mural thrombi and additional ailments. As in the general patient population TTC has an excellent prognosis among young people. Among the 104 cases studied, 93 had a favorable prognosis, and patients experienced full recovery of their cardiac function. Two (1.92%) cases recurred,[34,110] and 2 (1.92%) cases had a poor prognosis.[83,105] Unfortunately, there were 7 cases (6.73%) in which patients died from TTC, and no clear explanation for their deaths was found[24,27,37,52,98,106,111]; further

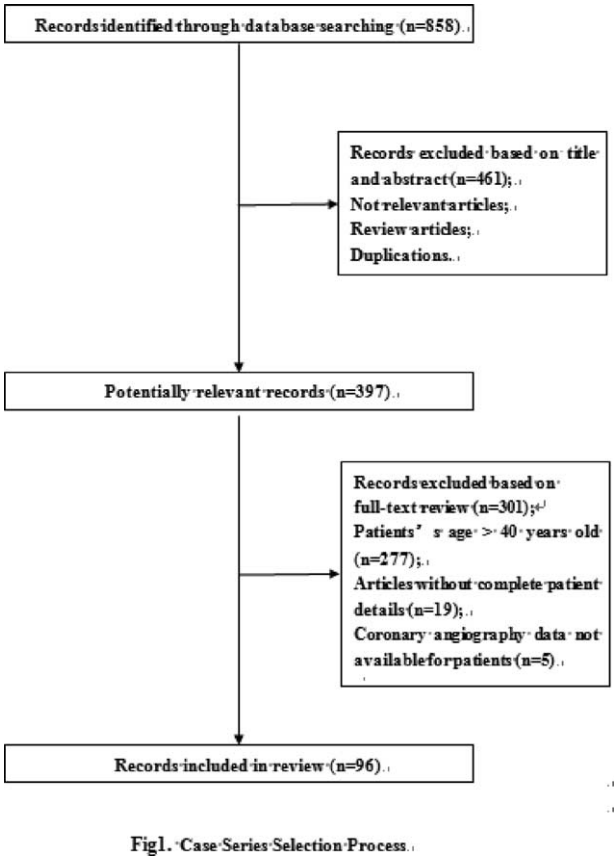


Fig1. Case Series Selection Process.

**FIGURE 1.** Case series selection process.

research and analyses are needed to elucidate the mechanisms underlying this phenomenon.

## Stress

As stated previously, most cases of apical ballooning are preceded by stressful events, either mental or physical in origin. This relationship holds true in young patients. In our study, we compared the clinical characteristics of young patients exposed to different stressors (Table 2). Physical stress was more likely to exacerbate TTC than was mental stress (88.46% vs. 20.19%, $P < 0.0001$) among young patients, a finding that differed from the findings of previous reports involving the general population.[5,109] Patients who suffered from physical stress were much younger than those who suffered from mental stress ($27.916 \pm 9.130$ vs. $33.571 \pm 4.739$, $P < 0.05$). The results pertaining to both morbidity (19.05% vs. 27.17%, $P = 0.4417$) and mortality (4.76% vs. 6.52%, $P > 0.9999$) did not differ significantly with respect to exposure to different stressors, results similar to those pertaining to the rates of complications (38.10% vs. 40.22%, $P = 0.8577$). Meanwhile, the gender ratio was the same with respect to the numbers of men and women who experienced both mental and physical stress.

## Race

We compared the clinical characteristics of Caucasian TTC patients with Asian and Hispanic TTC patients (Table 3) and observed no significant differences with respect to race for the following characteristics: age ($30.348 \pm 8.505$ vs. $28.016 \pm 9.024$, $P = 0.2708$), gender (female: 86.96% vs. 70.37%, $P = 0.1829$), mortality (0% vs. 8.64%, $P = 0.3230$), stress (mental stress: 26.09% vs. 18.52%, $P = 0.6145$; physical stress: 78.26% vs. 91.36%, $P = 0.1722$), or complications (43.38% vs. 38.27%, $P = 0.8094$).

## Prognosis

As they represent the main body of social productivity, young patients' prognoses are particularly noteworthy. With respect to the 7 cases of death included in our study, we performed a detailed analysis of the baseline characteristics of the affected individuals (Table 4) as well as a series of statistical calculations (Table 5).[24,27,37,52,98,106,111] The results indicated that the mortality rate of the male patients was significantly higher (71.43% vs. 28.57%, $P < 0.05$) among young patients. The majority of the patients who died were Caucasian (85.71%).[24,27,37,52,98,106,111] The average age of the patients who died did not differ significantly from that of the patients who survived ($29.286 \pm 8.240$ vs. $28.477 \pm 9.009$, $P = 0.8105$). Common clinical presentations of the patients who died included syncope (57.14%),[24,98,106,111] cardiac arrest (28.57%),[37,52] and seizure (14.29%).[27] Systematic complications included shock (28.57%),[27,52] multiple organ dysfunction syndrome (MODS) (14.29%),[27] and disseminated intravascular coagulation (DIC) (14.29%).[27] Vasoactive agents were used to treat 3 of the patients in question (42.86%),[52,98,111] and a similar proportion of surviving patients were also treated with vasoactive agents (36.08%). With respect to predisposing factors, no significant difference were noted regarding the incidences of mental stress (14.29% vs. 20.62%, $P = 0.8197$) or physical stress (85.71% vs. 88.66%, $P = 0.5876$) between the decreased patients and the surviving patients. The most prominent form of mental stress was emotional stress (14.29%); the most prominent physical stressors included subarachnoid hemorrhage (57.14%),[37,98,106,111] drugs and anesthesia (28.57%).[27,111] The most interesting result observed in our study was that the majority of the youth who suffered a subarachnoid hemorrhage later died (1.03% vs. 57.14%, $P < 0.0001$).

# DISCUSSION

TTC is a newly recognized disease that was first described in 1991 by Dote et al in Japan.[3,5,12] Following the original description, several case series involving other ethnic groups, including studies featuring Caucasian and Hispanic patients, have been published, suggesting that this syndrome is a worldwide problem and represents a new phenotype of SCD. Most of the studies involving patients with TTC have been conducted in the general population or with postmenopausal women,[4,5] whereas the clinical characteristics, risk factors, morbidity and mortality of young patients with TTC has been relatively unexplored. However, young people are always under either physical stress or mental stress, often as a result of an unhealthy lifestyle, particularly in larger cities. Therefore, this particular cohort warrants attention. To shed light on the complexity of this entity, a comprehensive analysis of the clinical characteristics, particularly stressors triggering exacerbations, and the underlying risk factors for death in young patients suffering from TTC was performed.

## Stress

Either mental or physical stress was noted to be a trigger in the majority of young patients, as previously described in a general cohort.[9,112] However, this finding prompts questions

**TABLE 1.** Demographic and Clinical Characteristics of TTC Patients

| | |
|---|---|
| Patients, n | 104 |
| Clinical data, n (%) | |
| Gender | |
| Male | 27 (25.96) |
| Female | 77 (74.04) |
| Age, y | |
| Mean ± SD | 28.53 ± 8.92 (range 1.30–40.00) |
| 0–10 | 4 (3.85) |
| 11–20 | 12 (11.54) |
| 21–30 | 38 (36.54) |
| 31–40 | 50 (48.08) |
| Race | |
| Caucasians | 78 (75.00) |
| Mongoloid | 23 (22.12) |
| Hispanic | 3 (2.88) |
| Clinical presentation, n (%) | |
| Chest pain/congestion | 40 (38.46) |
| Dyspnea | 33 (31.73) |
| Arrhythmia | 27 (25.96) |
| Dysaemia | 19 (18.27) |
| Syncope | 17 (16.35) |
| Palpitation | 12 (11.54) |
| Hypertension | 9 (8.65) |
| Cardiac arrest | 6 (5.77) |
| Seizures | 5 (4.81) |
| Abdominal pain | 3 (2.88) |
| Vomiting | 2 (1.92) |
| Risk factors, n (%) | |
| Mental stress | 21 (20.19) |
| Emotion stress | 14 (13.46) |
| Depression | 5 (4.81) |
| Mental illness | 2 (1.92) |
| Physical stress | 92 (88.46) |
| Drug and anesthesia | 36 (34.62) |
| Trauma and surgery | 27 (25.96) |
| Pheochromocytoma | 11 (10.58) |
| Stimulation and chronic pain | 6 (5.77) |
| Subarachnoid hemorrhage | 5 (4.81) |
| Smoking | 5 (4.81) |
| Hypertension | 4 (3.85) |
| Allergy | 2 (1.92) |
| PCAS | 2 (1.92) |
| Asthma | 2 (1.92) |
| Bleeding | 2 (1.92) |
| Diabetes | 2 (1.92) |
| Else* | 13 (12.50) |
| Complication, n (%) | |
| Pulmonary edema | 17 (16.35) |
| Malignant arrhythmia | 10 (9.62) |
| Shock | 9 (8.65) |
| Heart failure | 8 (7.69) |
| Pulmonary congestion | 5 (4.81) |
| Respiratory failure | 3 (2.88) |
| MODS | 3 (2.88) |
| Pleural effusion | 2 (1.92) |
| Mural thrombus | 2 (1.92) |
| DIC | 1 (0.96) |
| Treatment, n (%) | |
| β-blockers | 44 (42.31) |
| ACEI | 32 (30.77) |
| Vasoactive agents | 38 (36.54) |
| Diuretics | 23 (22.12) |
| Aspirin | 13 (12.50) |
| IABP | 8 (7.69) |
| Nitroglycertin | 8 (7.69) |
| Outcomes, n (%) | |
| Fully recovery | 93 (86.42) |
| Recurrence | 2 (1.92) |
| Poor prognosis | 2 (1.92) |
| Death | 7 (6.73) |

ACEI = angiotensin-converting enzyme inhibitors, DIC = disseminated intravascular coagulation, IABP = intraaortic ballon pump, MODS = multiple organ dysfunction syndrome, PCAS = post-cardiac arrest syndrome.

* n = 1, including: bilateral vertebral artery dissection, radiating, postpartum, anorexia nervosa, congenital long QT syndrome, Addison disease, chronic obstructive pulmonary disease, Graves' disease, alcohol abuse, acute disseminated encephalomyelitis, severe diarrhea, severe vomiting.

concerning the unique clinical characteristics and underlying pathophysiology of the disease. It is unclear why only certain individuals exposed to stressors suffer from TTC. What type of stress is the primary culprit? What type of stress plays a more important role? What amount of a particular type of stress results in disease?

One interesting result noted by our study was that compared with the general population, young patients appeared to suffer from TTC as a result of physical stress rather than mental stress. In our cohort, the number of patients who suffered from physical stress was much higher than the number of patients who suffered from mental stress (88.46% vs. 20.19%, $P < 0.0001$). Drugs, trauma, anesthesia, surgery, chronic pain, subarachnoid hemorrhage, smoking, allergic reactions, high blood pressure, asthma, and other physical stressors were common triggers of TTC. Compared with mental triggers, physical stressors have been speculated to be associated with more acute catecholamine surges that cause more significant cardiac stress and may explain why physical stressors are more often noted among youth with TTC.[113] Chronic mental stress has also been associated with increased odds of developing TTC among young patients; TTC has been shown to cause structural changes in the cerebrum, alterations of the hypothalamic–pituitary–adrenal axis, and chronic and repetitive catecholamine release.[113,114] The factor that predisposes patients suffering from chronic mental stress to TTC is believed to be a large emotional burden, such as that incurred via the death of a loved one, sudden bankruptcy, or unexpected unemployment. Either physical or mental stress, as well as either endogenous or exogenous catecholamine surges, may precipitate an exacerbation of TTC, which appears to be a response to whole-body stress that affects the cardiocirculatory syndrome and other organ systems. Therefore, stress avoidance is the key to reducing the morbidity of TTC among young patients.

## Gender

Male patients accounted for a small minority (26%) of patients with TTC in our cohort, a finding that is consistent with studies involving the general population. The precise reason for the predominance of female patients is unclear. Previous studies have suggested that estrogen exerts a desensitizing effect on the myocardial response to catecholamines; therefore, elderly women lacking the protection of estrogen may be vulnerable

**TABLE 2.** Number and Percentages of Patients in Which TTC, Complications, and Outcome Were Associated With Patient Mental and Physical Stress

| | Total (n = 104), n (%) | Gender: Male, n (%) | Age, Mean ± SD | Complications,* n (%) | Outcome: Dead, n (%) |
|---|---|---|---|---|---|
| Mental stress | 21 (20.19) | 4 (19.05) | 33.571 ± 4.739 | 8 (38.10) | 1 (4.76) |
| Emotional stress | 14 (13.46) | 3 (21.43) | 32.286 ± 5.105 | 5 (35.71) | 1 (7.14) |
| Physical stress | 92 (88.46) | 25 (27.17) | 27.916 ± 9.130 | 37 (40.22) | 6 (6.52) |
| Drug and anesthesia | 36 (34.62) | 8 (22.22) | 26.694 ± 8.287 | 16 (44.44) | 2 (5.56) |
| Trauma and surgery | 27 (25.96) | 5 (18.52) | 27.259 ± 10.132 | 11 (40.74) | 1 (3.70) |
| | **<0.0001 (M-P)** | 0.4417 (M-P) | **0.0070 (M-P)** | 0.8577 (M-P) | >0.9999 (M-P) |
| *P*-value | **0.0004 (E-D)** | >0.9999 (E-D) | **0.0230 (E-D)** | 0.5744 (E-D) | 1.0000 (E-D) |
| | **0.0365 (E-T)** | 0.8473 (E-T) | 0.0901 (E-T) | 1.0000 (E-T) | 1.0000 (E-T) |

SD = standard deviation.

The significance of bold used in the table is $p < 0.05$ which means a statistically significant difference.

* The complications included all of complications listed in Table 1: pulmonary edema, malignant arrhythmia, shock, heart failure, pulmonary congestion, respiratory failure, MODS, pleural effusion, mural thrombus, DIC.

to a rebound cardiac reaction to stress-reduced catecholamine release.[3,115–117] However, this mechanism does not explain the large numbers of young female patients with TTC. In our study, the proportion of young female patients was significantly higher than the proportion of males. Previous research has suggested that estrogen replacement may not mitigate the risk of developing TTC.[5,116] These findings suggest that other mechanisms in addition to estrogen deficiency may lead to TTC. Compared with male patients, the smaller left ventricular outflow tracts and reduced left ventricular volumes observed in female patients may explain the above-noted predominance.[3,5] Therefore, a smaller left ventricular volume and a lower density of adrenergic receptors in the cardiomyocyte membrane may predispose individuals to developing an outflow tract obstruction, as these individuals possess less protection against a severe catecholamine storm because the saturation of a smaller number of adrenoreceptors takes less time.

Disease is characterized by an unbalanced state of biology–society–psychology. With respect to biology, gender affects cardiomyocyte contractility.[118–120] Cardiomyocyte contractility studies have demonstrated that estrogen and testosterone exhibit contrasting inotropic actions and modulate $Ca^{2+}$ handling differently.[118] Golden et al reported that the androgen receptor protein is present in cardiac myocytes and exerts a positive inotropic effect in response to testosterone in cardiac myocytes.[119] Mellor et al demonstrated that myocytes from female patients with elevated AngII levels appeared to be more susceptible to contractility deficits, which may explain the female predominance among TTC patients.[120] Both social and psychological factors may play a role in the development of TTC. As a result of biological evolution, males and females exist in different physiological and social states; therefore, different psychological and physiological reactions to the same stress event occur as a result of natural selection and are affected synthetically by sex hormones and gender selection.[114,121,122] In most societies, men have been trained to withstand greater pressures than women. Long-term evolution has resulted in a higher threshold for stress in males than in females. Therefore, compared with females, males demonstrate stronger adaptability and tolerance to stress.[121,123] Due to their fragility and sensitive character traits, women possess a lesser capacity for mental adaptation; therefore, they respond with greater sensitivity to stressful events.[123] Research with animal models has demonstrated that compared with male monkeys, female monkeys' emotional states are more susceptible to environmental changes, similar to what has been observed in both rats and humans.[124] Kelly et al[121] demonstrated that males successfully withstood negative subjective experiences during a psychological test under stressful conditions, whereas females faired significantly worse; women were more irritable, timid, and

**TABLE 3.** Clinical Characteristics of Patients by Ethnicity

| | Caucasians | Mongoloid | Hispanic | *P*-Value |
|---|---|---|---|---|
| Total (n = 104), n (%) | 78 (75.00) | 23 (22.12) | 3 (2.88) | |
| Gender: female, n (%) | 55 (70.51) | 20 (86.96) | 2 (66.67) | 0.2744 |
| Age, mean ± SD | 27.760 ± 9.086 | 30.348 ± 8.505 | 34.667 ± 3.215 | 0.1897 |
| Stress, n (%) | | | | |
| Mental stress | 14 (17.95) | 6 (26.09) | 1 (33.33) | 0.5883 |
| Emotional stress | 9 (11.54) | 4 (17.39) | 1 (33.33) | 0.4562 |
| Physical stress | 71 (91.03) | 18 (78.26) | 3 (100.00) | 0.1981 |
| Drug and anesthesia | 30 (38.46) | 6 (26.09) | 0 (0.00) | 0.2421 |
| Trauma and surgery | 20 (25.64) | 6 (26.09) | 1 (33.33) | 0.9564 |
| Complication, n (%) | 29 (37.18) | 10 (43.48) | 2 (66.67) | 0.5339 |
| Outcomes: dead, n (%) | 6 (7.69) | 0 (0.00) | 1 (33.33) | 0.0759 |

SD = standard deviation.

**TABLE 4.** Characteristics of Patients Who Died

| | |
|---|---|
| Patients, n | 7 |
| Clinical data, n (%) | |
| Gender | |
| Male | 5 (71.43) |
| Female | 2 (28.57) |
| Age, y | |
| Mean ± SD | 29.286 ± 8.240 |
| 0–10 | 0 (0.00) |
| 11–20 | 1 (14.29) |
| 21–30 | 4 (57.14) |
| 31–40 | 2 (28.57) |
| Race | |
| Caucasians | 6 (85.71) |
| Mongoloid | 0 (0.00) |
| Hispanic | 1 (14.29) |
| Clinical presentation, n (%) | |
| Syncope | 4 (57.14) |
| Cardiac arrest | 2 (28.57) |
| Seizures | 1 (14.29) |
| Stress, n (%) | |
| Mental stress | 1 (14.29) |
| Emotion stress | 1 (14.29) |
| Physical stress | 6 (85.71) |
| Drug and anesthesia | 2 (28.57) |
| Trauma and surgery | 1 (14.29) |
| Subarachnoid hemorrhage | 4 (57.14) |
| Complication, n (%) | |
| Shock | 2 (28.57) |
| MODS | 1 (14.29) |
| DIC | 1 (14.29) |
| Treatment, n (%) | |
| Vasoactive agents | 3 (42.86) |

DIS = disseminated intravascular coagulation, MODS = multiple organ dysfunction syndrome, SD = standard deviation.

confused, indicating that gender affects stress responses. This response differential may represent an important theoretical basis that explains why females have previously demonstrated increased susceptibility to psychosomatic diseases. Several studies on animals have verified this hypothesis. Faverjon et al reported that under chronic stress, increased levels of acetylcholine are released in female rats.[125] Female animals are proposed to be characterized by sensitization to chronic stress, whereas male animals exhibit habituation.[114] Additionally, studies have demonstrated that physical stress improves the sensitivity of the hypothalamic–pituitary–adrenocortical (HPA) axis in females, which may be another reason for the high morbidity of TTC in females. These findings are consistent with those of our research, as we found that young patients with TTC suffered from physical stress more frequently than mental stress.[123]

## Race

We noted a much higher percentage of Caucasians among the young patients included in our study compared with other races (Table 1). The precise reason for this difference has not been well explained and may be related to economic conditions, living environments, lifestyle, dietary habits, and hereditary factors. A previous study reported that the incidence of hyperlipidemia and diabetes, both risk factors for cardiovascular disease, is much higher in Caucasians, which may explain the increased morbidity of TTC in this population.[126] Williams and Lawler[127] analyzed the stress–illness relationship of low-income women in a biracial group (African Americans and Caucasian Americans) and reported that race may affect stress; under high stress conditions, Caucasian women were more likely to suffer from illnesses.

We compared clinical characteristics among Caucasians, Asians, and Hispanics with respect to age, gender, stress, complications, and mortality; there were no significant differences in these parameters among Caucasians, Asians, and Hispanics in young patients with TTC. Whether the high incidence of TTC in Caucasians is due to their greater vulnerability to stress and whether the similarities in the demographic characteristics noted among different races depend on their genetic backgrounds remain to be determined. Thus, further investigation is warranted.

## Clinical Characteristics

The overall clinical symptoms and outcomes among young patients with TTC noted by our study were similar to the clinical symptoms and outcomes noted in the general population.[5] Chest pain, chest congestion, and dyspnea were the most common presenting clinical symptoms; additionally, cardiac arrhythmia, syncope, cardiac arrest, seizures, and gastrointestinal symptoms were reported. Severe complications, including pulmonary edema, malignant arrhythmia, and shock, were also noted in young patients at frequencies comparable with those of the general population.[12]

## Diagnosis and Treatment

TTC is often misdiagnosed as other cardiovascular diseases, particularly in young patients. Differentiating transient LV apical ballooning syndrome from ACS or other cardiovascular diseases is difficult but necessary. Misdiagnosis results in treatment with thrombolytic agents and may place patients at unnecessary risk of bleeding. Cardiac echocardiography and ventriculography may be used to confirm the diagnosis.[128] Early diagnosis and timely and appropriate treatment may not only avoid the need for coronary angiography but may also avert fatal complications and improve the survival rates of young patients with TTC. Significant debate surrounds the treatment for TTC, as several treatments, including the manipulation of intravenous fluids and the use of β-blockers, ACEI, aspirin, diuretics, vasoactive agents, nitroglycerin, or intraarterial balloon pumps, have been suggested.[129,130] It may be wise for doctors to adhere to the ''primum non nocere'' principle while awaiting information regarding evidence-based therapeutic methods for treating TTC. Most importantly, the treatment of this syndrome should be performed based on the unique characteristics of each patient.

## Prognosis

Most TTC patients, including young patients, recover following transient cardiac dysfunction. Although the abnormal kinetics of TTC typically reverse or improve within 4 to 5 weeks in young patients, and although the prognosis is favorable in this population, some patients develop complications such as pulmonary edema, malignant arrhythmia, shock, or death.[3,5,6] The overall in-hospital mortality rate was 6.73% among the young patients included in our study, a finding consistent with the mortality rates ranged from 0% to 8% in previous studies on the general population.[7,109,131] It is intriguing that the mortality rate noted in male patients was significantly higher (71.43% vs.

**TABLE 5.** Comparison of Characteristics of Patients Who Died and Those Who Survived

| | Cohort | | |
|---|---|---|---|
| **Variable** | **Dead** | **Survived** | ***P*-Value** |
| Patients, n (%) | 7 (6.73) | 97 (93.27) | |
| Gender, n (%) | | | |
| Male | 5 (71.43) | 22 (22.68) | 0.0166 |
| Female | 2 (28.57) | 75 (77.32) | |
| Age, mean ± SD | 29.286 ± 8.240 | 28.477 ± 9.009 | 0.8105 |
| Race, n (%) | | | |
| Caucasians | 6 (85.71) | 72 (74.23%) | 0.6770 |
| Stress, n (%) | | | |
| Mental stress | 1 (14.29) | 20 (20.62) | 0.8197 |
| Physical stress | 6 (85.71) | 86 (88.66) | 0.5876 |
| Drug and anesthesia | 2 (28.57) | 34 (35.05) | 0.9937 |
| Trauma and surgery | 1 (14.29) | 26 (26.80) | 0.7770 |
| Subarachnoid hemorrhage | 4 (57.14) | 1 (1.03) | <0.0001 |
| Treatment, n (%) | | | |
| Vasoactive agents | 3 (42.86) | 35 (36.08) | 0.9626 |

SD = standard deviation.

28.57%, $P < 0.05$) among young patients compared with the general population. Gender appears to play a role in disease prognosis.

A high risk of in-hospital mortality was noted in patients with an underlying critical illness, a finding corroborated by a study published by Song et al[132] and illustrated by our study, as the majority of the youth who died suffered a previous subarachnoid hemorrhage (57.14% vs. 1.03%, $P < 0.0001$). A significantly higher prevalence of all types of critical illnesses was noted in males compared with females and may have contributed to the higher mortality rate.[133] The precise mechanism underlying the higher mortality rate noted among young males remains unclear. Further study is necessary to determine the demographic and clinical predictors of mortality in the setting of TTC. Interestingly, the self-healing mechanisms that characterize TTC have provided us with new insight into cardiovascular disease as a whole.

## Pathophysiology

The mechanism of TTC has not been clearly elucidated. Adrenergic overstimulation, β-adrenoceptor (β-AR) stimulus trafficking, epinephrine-specific β2AR-Gi signaling, catecholamine-induced myocardial toxicity, coronary artery spasm, microvascular dysfunction, outflow tract obstruction, and the direct toxic effects of catecholamines on the myocardium have been reported as possible mechanisms that underlie the development of TTC.[5,9,117,134,135] The numbers of evidence-based studies and animal experiments are limited. Additional studies must be undertaken to elucidate the underlying mechanisms of TTC. We need more basic and clinical research to determine if takotsubo patients share any causal disease factors (eg, inherited genetic predisposition), and if clear diagnostic criteria can be identified that define this disease, and distinguish it from other similar disorders of cardiac ventricular function.

## LIMITATIONS

There were several limitations to our study. First, the absence of comparison groups limited the accuracy of our evidence and data interpretation; our paper was based on retrospective observational studies and included only case reports and case-series reports describing young patients with TTC. Second, not all data were included in the study; we removed those case series lacking comprehensive demographic and clinical data. Third, not all cases of TTC were included due to both investigator and publication bias in spite of careful electronic and manual searches.

## CONCLUSION

In conclusion, we conducted a systematic review of the reported cases of TTC in young patients in an attempt to better characterize the clinical and demographic characteristics of TTC patients in this cohort. TTC is a reversible phenomenon that has been associated with catecholamine surges and acute norepinephrine toxicity subsequent to stressful events. The findings of our study are as follows: First, physical stress is more likely to exacerbate TTC compared with mental stress among young patients. Second, females are more predominantly affected than males, both among young people and in the general population. Other parameters, including smaller left ventricular outflow tracts, reduced left ventricular volumes, and female psychological traits may play a pivotal role in the pathogenesis of TTC in young patients. Third, different human ethnic origins may not affect disease severity; therefore, individuals of different races do not experience significantly different disease characteristics, morbidity, or stressors. Fourth, TTC is not characterized by typical clinical symptoms; therefore, clinical characteristics alone are insufficient to make a diagnosis, and both echocardiography and ventriculography are important methods of disease detection. Thus, clinicians should be alert when evaluating young patients who present with symptoms similar to those of acute cardiomyopathy so that harmful treatments, including the use of thrombolytic drugs, coronary artery stents, bypass operations, long-term antiplatelet, and lipid-lowering drugs, may be avoided.

Additionally, the answers to questions regarding the clinical diagnostic criteria, etiology, pathophysiology, and

management of this syndrome remain unclear; further research is necessary to answer these questions.

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