

REVIEW ARTICLE

Prognostic factors of Takotsubo syndrome: A review

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Abstract

Takotsubo syndrome (TTS), also known as the “broken heart syndrome” or “stress cardiomyopathy,” is characterized by transient left ventricular systolic dysfunction, usually in the absence of significant obstructive coronary artery disease. The pathophysiology of TTS remains incompletely understood, though commonly proposed mechanisms include catecholamine surge, estrogen deficiency, and coronary circulation dysfunction. TTS was initially regarded as benign and reversible; however, studies indicate that it may have severe short- and long-term complications. There are several prognostic factors associated with TTS that may influence patient outcomes. In this review, we aim to explore these prognostic factors in relation to various clinical variables, including age, gender, trigger type, atrial arrhythmias, rate-corrected QT interval, baseline left ventricular systolic function, and comorbidities. While many factors are thought to influence TTS, current research findings remain inconsistent. To improve prognosis, there is an urgent need to develop better risk-assessment tools. This can be achieved through large-scale, multicenter studies and analysis of existing research. By understanding these prognostic factors, better prevention and intervention strategies can be developed for TTS, reinforcing its recognition as a serious cardiovascular condition.

Keywords: Takotsubo syndrome; Stress cardiomyopathy; Broken heart syndrome; Prognosis; Pathophysiology

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1. Introduction

The term Takotsubo syndrome (TTS) was first reported in 1990 and describes an acute cardiomyopathy that may mimic acute coronary syndrome with left ventricular

systolic dysfunction (LVSD), lacking significant coronary artery stenosis.^{1,2} Takotsubo, which means “octopus trap” in Japanese, is used to describe the classic morphology of the left ventricle in systole as seen on echocardiograms.³ Different terms have been used for this condition, including stress-related cardiomyopathy, transient left ventricular (LV) apical ballooning syndrome, broken heart (heartbreak) syndrome, and ampulla cardiomyopathy. In 2006, the American Heart Association incorporated this condition under the class of acquired cardiomyopathies.⁴ TTS is often characterized by an acute LV systolic dysfunction, transient apical ballooning, compensatory hypercontractility of the remaining myocardium,⁵ elevated cardiac enzymes, and ischemic changes on the electrocardiogram (ECG).²

Several demographic and clinical features have shown prognostic significance in TSS. For example, increased age, gender, physical and emotional triggers (ET), reduced baseline LV ejection fraction (LVEF), and presence of comorbidities have been consistently identified as predictors of short-term morbidity and mortality.⁶⁻⁸ In this narrative review, we aim to assess the association of different prognostic factors with TTS outcomes.

2. Methodology

This narrative review synthesized current evidence on the prognostic factors associated with TTS. Relevant literature was identified through an extensive search of databases, including PubMed and Google Scholar, using keywords such as TTS, stress cardiomyopathy, prognosis, outcomes, and prognostic factors like atrial fibrillation (AF) and LV function. Peer-reviewed articles published up to 2025 were included. Additional references were identified from the bibliographies of selected articles. Priority was given to large cohort studies, registry data, and meta-analyses. No formal quality assessment or risk of bias evaluation was performed, as it is not common for narrative reviews. The focus was to summarize and critically appraise the existing literature to highlight relevant clinical predictors of outcomes in TTS.

3. Pathophysiology

The pathophysiology⁹ of TTS is multifactorial, including catecholamine surge, estrogen deficiency, coronary microvascular dysfunction, and cardiac fatty acid metabolism abnormalities.⁹

3.1. Catecholamine surge

Catecholamines play a central role in TTS, as the acute presentation is often preceded by emotional or physical stress. The key to understanding the physiology of

this hypothesis is to know how the brain center and hypothalamic-pituitary-adrenal (HPA) axis secrete catecholamine in response to a given event and the response of the cardiovascular system⁹ (Figure 1).⁹ The primary area that secretes catecholamines is in the pons, known as the locus coeruleus. This area regulates the hemostasis response to a stressful trigger, activating the HPA axis, which stimulates the adrenal medulla. Catecholamines act at the adrenoreceptors, which are concentrated at the apex of the heart, causing LV dysfunction and, therefore, apical ballooning.¹⁰ In addition, studies have shown that the level of catecholamine increases 2 – 3 times in TTS than in myocardial infarction (MI). Therefore, conditions with excess secretion of catecholamines, such as pheochromocytoma, subarachnoid hemorrhage, seizure, ischemic stroke, and iatrogenic use of catecholamine, have been shown to cause an episode of TTS.

In addition, the use of combined alpha and beta-blockers on animals could normalize the ECG changes that occur as a response to catecholamine surge during stressful events, which does not occur when using potent coronary artery vasodilators, such as calcium channel blockers or nitroglycerin.¹¹ Furthermore, sympathetic overactivation in the myocardium causes interstitial mononuclear inflammation and contracted band fibrosis with or without myocardial necrosis, the hallmark of cardiotoxicity due to catecholamine observed in TTS, and is distinguished from the coagulative necrosis that occurs in MI. Thus, there is enough evidence to conclude that catecholamines play an important role in the pathogenesis of TTS.

3.2. Estrogen deficiency

The majority of Takotsubo cases occur in post-menopausal women, with a 5 times higher risk in women older than 55, suggesting that the level of estrogen may have a role in TTS. Estrogen has a known protective effect on the cardiovascular system, such as vasodilation and a decreased risk of endothelial dysfunction and atherosclerosis. In addition, it affects the vascular tone by increasing endothelial nitric oxide synthase and reducing the adrenergic receptors in myocardial cells.¹² This explains why pre-menopausal women can attenuate the effect of catecholamine surge during stress, while post-menopausal women cannot, and the latter can have LVSD in response to a subarachnoid hemorrhage. A study on ovariectomized rats showed that the drop in LV function was higher in rats without estrogen. In addition, estrogen increases cardioprotective factors such as heat shock protein and atrial natriuretic peptide, which protect the heart from the toxic effects of catecholamines and decrease oxidative stress.¹³ To that end, it can be fairly concluded that estrogen has a protective role, and a reduction in its levels can contribute to TTS.

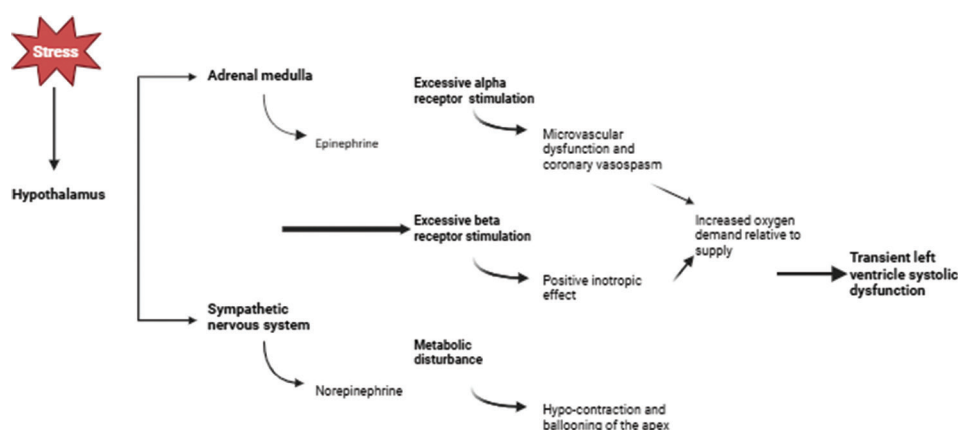


Figure 1. Pathophysiologic mechanisms in Takotsubo syndrome. Image created by the authors.

3.3. Coronary circulation dysfunction

The first study that described the case of TTS in 1990 suggests that coronary circulation dysfunction may be an underlying cause of TTS. The coronary system autoregulation provides a balance between the requirement and perfusion, and a reduction in perfusion is expected during an acute attack of TTS due to an enhanced systolic time and a reduced diastolic time. This coronary dysfunction may result from mediators such as endothelin, catecholamine, and reactive oxygen species.¹⁴ However, some studies have revealed evidence against the microcirculation hypothesis, as the positron emission tomography perfusion scans used in these studies showed hyperperfusion in the basal segment and normal perfusion in the apical segment. Thus, the coronary circulation dysfunction hypothesis has contradictory evidence, and more research is needed to understand it further.

3.4. Abnormal metabolism

An abnormal myocardial metabolism during an acute episode of TTS was documented at the apical segment using fluorodeoxyglucose-positron emission tomography, where the consumption of free fatty acids and glucose transporters was significantly reduced. The resulting lipid droplet accumulation in the cytoplasm of the myocardial cells led to further metabolic stunning. These droplets have been observed in the myocardial cells of humans and mice with TTS, but are not present during the recovery phase.^{15,16} The abnormal metabolism during acute TTS may be connected to its pathophysiology.

4. Types of TTS and clinical presentation

The two main types of TTS are based on the initial presentation: Primary and secondary. Primary TTS occurs without a clear cause or is triggered by emotions, while secondary TTS is caused by physical conditions

or comorbidities. Primary TTS mainly occurs in postmenopausal women and is mostly due to stress. These patients have non-obstructive coronary arteries with moderate LV dysfunction, which is believed to be caused by microvascular changes and has a good prognosis. In comparison, secondary TTS affects both genders and is usually due to coronary artery disease, resulting in severe LV dysfunction and delayed recovery.¹⁷

The different types of triggers associated with TTS were investigated systematically in the InterTAK Registry.¹⁸ Physical triggers (PT) such as surgery, acute asthma, stroke, and head injury were reported in 36% of the cases, while ET was reported in 27.7%. The most common presenting symptom in TTS is chest pain, followed by dyspnea. Severe cases may present with cardiogenic shock or thromboembolic events. However, some patients are completely asymptomatic, with ECG or biomarker abnormalities detected incidentally in the setting of an acute underlying illness such as sepsis.

5. Diagnostic criteria

The diagnostic criteria of TTS or cardiomyopathy have evolved, and currently, the modified Mayo Clinic diagnostic criteria are widely used.¹⁹ The distinct defining diagnostic points include the following: (i) Wall motion abnormality in the left ventricle not restricted to single coronary artery distribution, (ii) the absence of obstructive coronary artery disease, new ECG changes, or increased troponins, and (iii) the absence of myocarditis.

The Hopkins, Japanese, and Taskforce of the European Society of Cardiology criteria also include the absence of obstructive coronary artery disease for the diagnosis of TTS.²⁰ In contrast, the InterTAK Diagnostic Criteria states that significant coronary artery disease should not be considered as an exclusion (Table 1).

Table 1. InterTak diagnostic criteria and score

Criterion	Points
Female gender	25
Emotional stress	24
Physical stress	13
Absence of ST-segment depression	12
Psychiatric disorders	11
Neurologic disorders	9
Rate-corrected QT prolongation	6
Total score	100

Note: Score >70 indicates a high probability of Takotsubo syndrome, and a score of ≤70 indicates a low/intermediate probability of Takotsubo syndrome.

6. Prognostic factors

6.1. Gender

Takotsubo predominantly affects women in the post-menopausal state, with the risk increasing fivefold after the age of 55. The occurrence might be related to the influence of sex hormones on the sympathetic neurohormonal axis and on coronary vasoreactivity, whereby declining estrogen levels after menopause increase the susceptibility to TTS in women. In a retrospective cohort study by Arcari *et al.*²¹ comparing the gender differences in 2492 Takotsubo patients from the international multicenter German Italian Spanish Takotsubo (GEIST) registry, men comprised 11% of the total TTS population. They had a mean age of 69, significantly younger than the female cohort at presentation, which was 71. They were also more likely to have TTS caused by PT, as opposed to ET in females. In a study by Templin *et al.*¹⁸ on the outcomes of TTS, the total mortality was significantly higher in males, averaging 12.9% per year, compared to 5% in females. The 10-year mortality and incidence of clinical events were also significantly higher in males.¹⁸

6.2. Rate-corrected QT interval

A prolonged QT interval is defined by the American Heart Association/American College of Cardiology as a rate-corrected QT (QTc) interval greater than the 99th percentile for females and males, which is 480 ms and 470 ms, respectively.²² The prevalence of long QTc intervals in TTS is high, occurring in up to 86% of patients in the acute phase.²³ The pathophysiology by which QTc prolongation occurs is not completely understood, but it seems to involve an acute decrease in cardiomyocyte repolarization reserve due to autonomic dysfunction seen in TTS.²³

6.3. AF

AF is the most common pathological cardiac arrhythmia, with a higher prevalence in males. Its presence is associated

with an increased risk of stroke and mortality. In the context of TTS, the prevalence of AF has been reported to be between 5% and 25% and shown to be associated with worse short- and long-term mortality in patients with TTS.²⁴ In a meta-analysis by Prasitlumkum *et al.*²⁵ in 2018, five studies on 2321 patients with TTS found that AF was associated with increased all-cause mortality, especially in the long term. In a retrospective cohort study by El-Battrawy *et al.*²⁶ in 2021, 1584 patients with TTS were enrolled from the International Takotsubo Registry, in which 7.1% of patients had AF at admission. Those with AF proved to have a more complicated in-hospital course with lower LVEF, higher incidence of cardiogenic shock, and a higher in-hospital mortality compared to the non-AF group. Notably, those with AF tended to be older, were more frequently males, had PT of TTS, and higher brain natriuretic peptide, C-reactive protein, and whole blood count on admission, with more comorbidities such as hypertension²⁷ and diabetes, possibly distorting the effect of AF on the seemingly worse short-term prognosis.^{27,28} In the long term, AF was shown to be independently associated with a higher 5-year mortality rate, and patients with AF were at a higher risk of major adverse cardiac and cerebrovascular events. A recent retrospective study by Dai *et al.*²⁹ on 4733 patients with TTS from the National Inpatient Sample database showed that patients with AF had a higher rate of in-hospital complications (e.g., cardiogenic shock, ventricular arrhythmias, and respiratory failure) compared to the non-AF group. In summary, AF is a poor prognostic indicator for the short- and long-term aspects in patients with TTS. However, due to its association with other known prognostic factors on admission, its effect as an independent risk factor for in-hospital and short-term mortality needs to be further investigated.

6.4. Left ventricular systolic function

Takotsubo cardiomyopathy is characterized by transient LVSD that extends beyond the territory supplied by a single coronary vessel. LVEF is usually reduced in the acute phase and is associated with increased in-hospital and long-term mortality.^{30,31} A study by Alashi *et al.*³⁰ on 650 patients showed that 94% of the patients presented with a LVEF of <52%, and lower baseline LVEF was significantly associated with long-term mortality. A meta-analysis including 18 studies ($n = 5168$) concluded that reduced LVEF is associated with a threefold increase in mortality in TTS patients.³¹

6.5. Trigger types

TTS can result from PT or ET, although in some cases, no specific trigger can be identified. Examples of physical stress can include infections, trauma, and surgical

procedures. ETs are usually negative but can also be positive or “happy.” According to a recent GEIST registry study on 2482 patients, ET was the most common trigger, detected in 36.7% of patients, while PT was detected in 34.4%. No trigger was found in the remaining 28.9%. Adverse hospital events and long-term mortality were both significantly higher in patients with PT (27.1% and 21.6%, respectively) than in the ET and no trigger groups.³² The association between PT and worse outcomes has been seen in multiple studies, both for short- and long-term.³³

6.6. Diabetes

The presence of diabetes among TTS patients has been reported to be between 1.6% and 25.5%.³⁴ The catecholamine hypothesis is perhaps the most widely accepted pathophysiologic mechanism in TTS. Since diabetic autonomic neuropathy can mitigate catecholamine-mediated effects on the heart, it was proposed that concomitant diabetes might also lower the incidence and severity of TTS.³⁴ Several studies, on the other hand, refute the theory of “diabetes paradox,” particularly regarding the long-term outcome and mortality in TTS.^{35,36} In a multicenter GEIST registry performed on 826 patients with TTS, 21.1% had diabetes, and long-term follow-up (after a median of 2.5 years) showed that mortality was significantly higher in patients with diabetes compared with patients without diabetes. It is of note, however, that patients in the study with diabetes were older, had a higher prevalence of hypertension, lower LVEF, and were more frequently male, suggesting that these factors could have possibly contributed to the worse prognosis in these patients. While the data on diabetes in TTS is conflicting, it may be concluded that patients with diabetes and TTS have an in-hospital mortality that is comparable to or less than those without diabetes.³⁷ However, individuals with diabetes are likely to have a worse prognosis in the long term.

6.7. Age

TTS predominantly affects older post-menopausal women, and the risk of developing the syndrome increases 5 times in women after the age of 55. The increased risk with age can be attributed to a rise in sympathetic nervous activity and augmented cardiac sympathetic stimulation in older individuals.³⁸ In females, hormonal factors also play an important role, whereby declining sex hormone levels after menopause lead to an abnormal vasomotor function and loss of protective effects of estrogen that normally attenuate the sympathetic response.³⁹ The effect of age on mortality and in-hospital complications in patients with TTS is controversial. Most studies report an increased risk of in-hospital and long-term mortality in older individuals

with TTS.^{40,41} Several other studies report no difference,⁴²⁻⁴⁴ and many studies show a higher rate of in-hospital complications in younger patients.⁴⁵ A retrospective study of 10,861 patients with TTS from the Italian National Healthcare System Databank also found that increasing age was an independent predictor of in-hospital mortality in women, but not in men.⁴⁰

While older age is an independent risk factor for mortality, death in these patients is also driven by comorbidities, which are usually more prevalent compared to younger age groups. As for younger patients having a more complicated in-hospital course, a plausible explanation could involve the higher incidence of acute neurologic and psychiatric triggers that ultimately result in significant sympathetic stimulation and a more severe clinical course. More studies are still needed to establish a clearer understanding of age cutoffs for defining young and old patients in the context of TTS prognosis (Table 2).

7. Management

There is no definitive treatment for TTS, and the primary goal is to decrease complications, with management depending on the case severity. In mild cases, it varies from observation to a short course of pharmacological treatment, while in severely complicated cases, mechanical circulatory support may be considered. The most crucial step in acute presentation is to rule out and treat other causes, such as acute coronary syndrome.

7.1. Treatment of acute TTS

The treatment of TTS depends on the patient's presentation, and the mainstay of the treatment is supportive management until recovery takes place. However, in cases of complications such as heart failure and shock, intensive treatment is required according to guidelines. Furthermore, the most crucial treatment is to assess whether the patient has LV outflow tract obstruction (LVOTO) using a transthoracic echocardiogram or invasive angiography, as the treatment may change if the patient has LVOTO.^{46,47} After assessment, if patients are asymptomatic and hemodynamically stable with no sign of complications such as heart failure or arrhythmia, they should be admitted to the ward for further monitoring and treatment. Pharmacological treatment in such cases could be used according to the patient's tolerance, as they could lead to complications, and the recovery can take place without any intervention. If the patient has pulmonary congestion without hypotension, medications are used to reduce the venous return. If the patient is hypertensive, an arterial vasodilator can be used with caution, as those agents can worsen the LVOTO. Beta-blockers are employed as an added therapy for stable patients with hypertension, as this

is very helpful in LVOTO, decreasing basal contractility and reducing obstruction. Cardiogenic shock is a common complication that occurs in about 10% of cases, increasing mortality by up to 5 times. The treatment of cardiogenic shock depends on the presence of LVOTO. In the absence of obstruction, an inotropic agent can be considered, as it can increase the cardiac output. Still, short-term follow-up is needed, as those agents can cause obstruction even in patients with normal baselines. In a refractory case, a vasopressor agent can be considered, but in the lowest possible dose as a temporary treatment until further mechanical support is used as a bridge to recovery. In the

presence of LVOTO, the treatment is very challenging, as the use of an inotropic agent or any agent reducing the intravascular volume (such as diuretic or nitroglycerin) should be avoided because it can worsen the obstruction; hence maintaining the intravascular volume by intravenous fluid is the most critical step in management as it reduces obstruction. Beta-blockers can be considered for those with severe LVOTO, given their ability to improve cardiac output by decreasing obstruction. In addition, vasopressors can be used to increase blood pressure without worsening the obstruction. Finally, if all those steps fail, mechanical support may be required.

Table 2. Prognostic factors in Takotsubo syndrome

Prognostic factor	Key findings	Study/registry (year)
Gender	Males had higher in-hospital and long-term mortality compared to females	Templin <i>et al.</i> (2015) ¹⁸ ; Arcari <i>et al.</i> (2022) ²¹
Rate-corrected QT interval	QT prolongation occurred in about 86% during the acute phase, associated with arrhythmogenic risk	Behr and Mahida (2009) ²³
Atrial fibrillation	Atrial fibrillation is associated with worse in-hospital and long-term outcomes, as well as a higher risk of mortality and complications	Prasitlumkum <i>et al.</i> (2018) ²⁵ ; El-Battrawy <i>et al.</i> (2021) ²⁶ ; Dai <i>et al.</i> (2023) ²⁹
Left ventricular systolic function	Reduced left ventricular ejection fraction (<52%) is linked to increased long-term mortality and a 3 times higher mortality risk	Alashi <i>et al.</i> (2020) ³⁰ ; Chiang <i>et al.</i> (2021) ³¹
Trigger type	Physical triggers are associated with higher hospital events and long-term mortality than emotional or no triggers	Patz <i>et al.</i> (2023) ³² ; Uribarri <i>et al.</i> (2019) ³³
Diabetes	Conflicting evidence shows that the mitigation of acute stress is associated with higher long-term mortality in Takotsubo syndrome	Madias (2016) ³⁴ ; Stiermaier, Moeller <i>et al.</i> (2016) ³⁶
Age	Older age is associated with increased long-term mortality and worse outcomes, especially in women	Malanchini <i>et al.</i> (2020) ⁴⁰ ; Cammann <i>et al.</i> (2020) ⁴³

Table 3. Strengths and limitations of key studies on Takotsubo syndrome

Study	Strengths	Limitations
Templin <i>et al.</i> ¹⁸	Large sample size (1750 patients); multicenter international registry; robust analysis of clinical outcomes by gender	Observational design limits causal inference; potential for selection bias in registry data
Mahida ²² & Behr ²³	Explores the electrophysiological basis of rate-corrected QT prolongation in TTS; an early investigation into repolarization reserve	Focused more on mechanistic hypotheses than broad clinical applicability
Prasitlumkum <i>et al.</i> ²⁵	Meta-analysis pooling data from five studies; evaluated atrial fibrillation as a prognostic factor	Heterogeneity in included studies; potential publication bias
El-Battrawy <i>et al.</i> ²⁶	Data from the International Takotsubo Registry; analyzed outcomes of patients with AF in TTS	Retrospective design; AF cohort had more baseline comorbidities, possibly confounding outcomes
Alashi <i>et al.</i> ³⁰	Study of 650 patients assessing LVEF and mortality; demonstrated prognostic relevance of reduced baseline LV function	Single-center study; limited diversity in patient population
Patz <i>et al.</i> ³²	Multicenter GEIST registry data; large patient population; detailed classification of triggers	Observational nature; trigger classification may be subjective
Stiermaier <i>et al.</i> ³⁶	Long-term follow-up; analyzed prognostic role of diabetes; part of an international registry	Confounding from comorbidities; no randomization or matching
Cammann <i>et al.</i> ⁴³	Analyzed age-related differences in clinical features and outcomes; a large dataset	Lacked standardized age cutoffs; some subgroup sizes were small for analysis

Abbreviations: AF: Atrial fibrillation; GEIST: German Italian Spanish Takotsubo; LV: Left ventricular; LVEF: Left ventricular ejection fraction; TTS: Takotsubo syndrome.

7.2. Long-term management of TTS

TTS is a reversible cardiomyopathy with an annual recurrence rate of 2 – 4%. The recurrence may occur within 4 days or up to 10 years after the initial attack, affecting different areas of the heart. There is no current evidence-based long-term management for TTS, but experts recommend the use of beta-blockers, especially in patients who have high sympathetic tone, persistent anxiety, and ongoing cardiac symptoms. A retrospective analysis of a large international registry showed that the use of angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers reveals an improvement in survival after 1 year.⁴⁷ As TTS is a transient heart failure, the use of heart failure medications such as angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, and diuretics is recommended for at least 3 months or until complete recovery.

8. Conclusion

This review examines the factors that influence the outcome for patients with TTS. While most primary TTS cases have a positive prognosis, recognizing secondary forms and their associated risk factors is crucial for clinicians. Early intervention appears to improve outcomes in patients with TTS, and the mainstay therapy is supportive as patients' LV function begins to restore over several days and typically recovers fully within 3 – 4 weeks. A comparative synthesis of key studies highlights the strengths and limitations of current evidence (Table 3), underscoring the heterogeneity in study designs, populations, and prognostic markers. Future large-scale controlled studies are needed to address inconsistencies in known risk factors, as this would empower medical professionals to provide more accurate prognoses and better manage TTS in their patients.

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Conflict of interest

The authors declare that they have no competing interest.

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