ORIGINAL RESEARCH

Short- and Long-Term Prognosis of Patients With Takotsubo Syndrome Based on Different Triggers: Importance of the Physical Nature

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***Background*—**Takotsubo syndrome (TTS) is an acute reversible heart condition initially believed to represent a benign pathology attributable to its self-limiting clinical course; however, little is known about its prognosis based on different triggers. This study compared short- and long-term outcomes between TTS based on different triggers, focusing on various physical triggering events.

***Methods and Results*—**We analyzed patients with a definitive TTS diagnosis recruited for the Spanish National Registry on TTS (RETAKO [Registry on Takotsubo Syndrome]). Short- and long-term outcomes were compared between different groups according to triggering factors. A total of 939 patients were included. An emotional trigger was detected in 340 patients (36.2%), a physical trigger in 293 patients (31.2%), and none could be identified in 306 patients (32.6%). The main physical triggers observed were infections (30.7%), followed by surgical procedures (22.5%), physical activities (18.4%), episodes of severe hypoxia (18.4%), and neurological events (9.9%). TTS triggered by physical factors showed higher mortality in the short and long term, and within this group, patients whose physical trigger was hypoxia were those who had a worse prognosis, in addition to being triggered by physical factors, including age >70 years, diabetes mellitus, left ventricular eyection fraction <30% and shock on admission, and increased long-term mortality risk.

***Conclusions*—**TTS triggered by physical factors could present a worse prognosis in terms of mortality. Under the TTS label, there could be as yet undiscovered very different clinical profiles, whose differentiation could lead to individual better management, and therefore the perception of TTS as having a benign prognosis should be generally ruled out. **(*J Am Heart Assoc*. 2019;8:e013701. DOI: 10.1161/JAHA.119.013701.)**

Key Words: broken heart syndrome • classification • outcome • stress • stress-induced cardiomyopathy • Takotsubo cardiomyopathy

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Clinical Perspective

What Is New?

- Our data confirm that the prognosis of patients with Takotsubo syndrome is clearly influenced by the type of trigger.
- Patients with an emotional trigger have a better prognosis, whereas those with physical stress have the worst.
- Not all physical triggers influence the prognosis of patients in the same way, with triggering by hypoxia presenting a worse evolution in the short and long term.

What Are the Clinical Implications?

- Patients with Takotsubo syndrome related to physical stress could present a worse short- and long-term prognosis in terms of mortality.
- Therefore, these patients might be considered for surveillance and additional management not only during hospitalization, but also during follow-up.

Since its first description in Japan in 1990,[1] Takotsubo syndrome (TTS), also known as stress cardiomyopathy, has emerged as an important form of transient ventricular systolic dysfunction that mimics an acute myocardial infarction, without evidence of complicated coronary artery disease.[2] Although the global pathophysiology of this syndrome is still unclear, it seems that the sympathetic neurohormonal axis plays a key role, and several pathogenic theories have been suggested.[3] Some of the most globally postulated include coronary vasospasm, endothelial dysfunction, catecholamine-mediated toxicity, and alterations at the level of the hypothalamic-pituitary-adrenal axis.[4–9]

In several cases, emotional stress can be evidenced as a trigger that has led to the popular term "broken heart syndrome."[10] Some researchers propose a classification of patients according to the nature of the trigger, and as such, this emotionally triggered TTS should be considered TTS, whereas other cases with similar clinical conditions, but triggered by physical factors (surgery, hemorrhages, infections, etc), should be considered "Takotsubo-like syndrome" instead.[11] However, the Mayo Clinic criteria, modified in 2008, include all patients in the spectrum of global TTS, regardless of the nature of the triggering factor.[10] Our group has proposed a TTS classification based on the triggers, differentiating between primary (triggered by psychological stress or without an identifiable trigger) and secondary forms (precipitated by physical factors).[12] This is of the utmost importance, because secondary TTS could present a worse short- and long-term prognosis in terms of mortality, recurrences, and readmissions.[12] Recently, a classification for TTS has been proposed based on its possible prognostic implications, extracted from the InterTAK (International Takotsubo) registry.[13] However, the prognostic impact of this classification has not been confirmed in external cohorts that allow its usefulness to be validated. On the basis of this, we propose this study, which infers the idea of the prognostic importance of triggers in TTS.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients and Inclusion Criteria

The National Multicenter RETAKO (Registry on Takotsubo Syndrome) trial, supported by the Ischemic Heart Disease and Acute Cardiovascular Care Section of the Spanish Society of Cardiology, is a partially retrospective and prospective (from January 1, 2012 onward) voluntary observational registry that enrolled TTS patients from 38 centers in Spain. Its rationale and design have been previously described.[14] Main inclusion criteria required a definitive TTS diagnosis (at hospital discharge or within the first 6 months of follow-up) based on the modified Mayo Clinic criteria.[10]

The present study included data from subjects with a definitive TTS diagnosis between January 1, 2003 and July 31, 2018. Final date of follow-up was July 31, 2018. Baseline patient characteristics, triggering factors, in-hospital course, pharmacological treatment dispensed at the discretion of the attending physician, and short- and long-term outcomes were captured through a dedicated electronic case report form. The study complied with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Hospital Clinico San Carlos. All patients provided written informed consent.

Types of Triggers

All the possible triggers in each patient were collected and detailed and subsequently grouped into emotional, physical, or unknown stress. These are predefined variables in the registry that were included by the associated researchers of each of the participating centers according to the patient's medical history. Two researchers independently checked these data. Those patients presenting with physical stress were further stratified in 5 cohorts: infectious, neurological disorders, surgical/intervention, extreme physical activity/trauma, or hypoxia.

ECG and Echocardiographic Alterations

ECG variables are included in the registry database and include the following: rhythm on admission, affected wall,

initial ST-segment elevation, initial ST-segment depression, initial negative T-wave, ST-segment elevation during hospital stay, ST-segment depression during hospital stay, negative T-wave during hospital stay, and maximum QTc interval during hospital stay.

The pattern of LV dysfunction, based on angiography or echocardiographic evaluation, was classified as follows:

1. Apical type: This type is characterized by hypo-, a-, or dyskinesia of midventricular and apical parts of the anterior, septal, inferior, and lateral walls of the left ventricle, associated with hyperkinesia of basal segments.
2. Midventricular type: This type comprises hypo-, a-, or dyskinesia of midventricular segments, most often like a cuff, with normo- or hyperkinesia of basal and apical segments.
3. Basal type: This type involves hypo-, a-, or dyskinesia of basal segments and normo- or hyperkinesia of midventricular and anterior as well as anteroseptal and/or anteroapikal segments of the left ventricle. This basal type shows wall-motion abnormalities complementary to the apical type, and as such, the basal type is also referred to as the "inverse" form of takotsubo cardiomyopathy.
4. Focal type: This type is characterized by focal hypo-, a-, or dyskinesia of any segment of the left ventricle. In most cases, an anterolateral segment is involved.

Outcomes

We analyzed the occurrence of the following complications during hospitalization:

1. Severe heart failure, defined as acute pulmonary edema or cardiogenic shock.
2. Moderate or severe acute functional mitral regurgitation.
3. Dynamic left ventricular outflow tract obstruction. Obstructions were determined echocardiographically or from catheter pressure recordings; peak gradients >25 mm Hg were considered significant.
4. Others: intraventricular thrombus formation, systemic embolism and stroke, pulmonary thromboembolism, acute renal failure, catheterization complications, and in-hospital death.

Cardiovascular death was defined as death resulting from myocardial infarction, sudden cardiac death, heart failure, or other cardiovascular causes (peripheral arterial disease, cerebrovascular or aortic disease, pulmonary embolism, or cardiovascular bleeding). Any death not covered by this definition was classified as noncardiovascular. Follow-up after hospital discharge was conducted either by outpatient clinical visits or structured telephone interviews with patients or relatives. Follow-up outcomes were prespecified and defined as the occurrence of all-cause death (including cardiovascular or noncardiovascular mortality). If a prespecified outcome was observed, review of electronic medical records and consensus of 2 experienced local investigators was mandatory for event adjudication. Patients who did not experience the outcome of interest and those lost to follow-up were censored at the time of the last contact.

Statistical Analysis

Statistical analysis was performed with the IBM SPSS software package (version 20.0; IBM Corpp., Armonk, NY). Continuous variables are expressed as mean and SD, and differences were analyzed by the Student *t* test or the Wilcoxon rank-sum test for non-normal distribution. Categorical variables are expressed as frequency and percentage and were compared by the chi-square test. Outcome analysis was performed using Kaplan–Meier estimates and log-rank test, as well as a landmark analysis set at 90 days. Cox regression analysis was conducted to determine the hazard ratio and 95% CIs for long-term outcomes according to triggering factors using emotional stressor as a reference. To account for differences in baseline clinical characteristics and comorbidities between different TTS groups, a multivariable adjustment analysis, including covariates with a univariate $P<0.1$ or were likely to have a relationship to long-term mortality, was performed in a Cox regression model. Differences were considered significant at a 2-tailed $P<0.05$.

Results

A definite emotional stressor was detected in 340 patients (36.2%). A trigger factor could not be identified in 306 patients (32.6%), whereas 293 patients had a physical factor as a trigger (31.2%). Within the last group, the causes that triggered the syndrome were infection in 90 patients (30.7%), surgery in 66 patients (22.5%), trauma or extreme physical activity in 54 patients (18.4%), hypoxic conditions in 54 patients (18.4%), and neurological disorder in 29 patients (9.9%). Median follow-up of the cohort was 2.2 years (interquartile range, 3.6).

Main patient characteristics of all different groups are summarized in Tables 1 and 2. The prevalence of females was significantly higher in TTS related to emotional stress (93.5%) compared with the other groups. In the TTS group related to physical stress, we found a higher frequency of comorbidities such as lung disease, diabetes mellitus, and renal failure. Within this group, we observed a greater mean age in patients whose trigger was an infection (75±11 years) compared with the other groups. As expected, we observed a greater percentage of chronic lung disease in the hypoxia group.

Table 1. Clinical Characteristics of Different Triggering Groups

	No Stress Factor (N=306)	Emotional Stress (N=340)	Physical Stress (N=293)	*P* Value
Female (%)	267 (87.3%)	318 (93.5%)	233 (79.5%)	<0.001
Age, y	72±12	70±11	71±13	0.067
Hypertension	188 (61.4%)	226 (66.5%)	190 (64.8%)	0.401
Dyslipidaemia	167 (54.6%)	158 (46.5%)	141 (48.1%)	0.099
Diabetes mellitus	94 (30.7%)	59 (17.4%)	67 (22.9%)	<0.001
Smoker	103 (33.7%)	80 (23.5%)	101 (34.5%)	0.003
Lung disease	94 (30.7%)	58 (17.1%)	93 (31.7%)	<0.001
Renal insufficiency	58 (19.0%)	13 (3.8%)	26 (8.9%)	<0.001
TTS pattern				0.033
Apical	226 (86.6%)	278 (85.8%)	222 (77.6%)	
Midventricular	16 (6.1%)	17 (5.2%)	35 (12.2%)	
Basal	4 (1.5%)	4 (1.2%)	11 (3.8%)	
Focal	15 (5.7%)	25 (7.7%)	18 (6.3%)	
Clinical presentation				
Chest pain	231 (75.5%)	305 (89.7%)	157 (53.6%)	<0.001
Typical	193 (63.1%)	268 (78.8%)	118 (40.3%)	
Atypical	38 (12.4%)	37 (10.9%)	39 (13.3%)	
Vegetative symptoms	147 (48.0%)	170 (50.0%)	96 (32.8%)	<0.001
Dyspnea	112 (36.6%)	128 (37.6%)	129 (44.0%)	0.131
Syncope	17 (5.6%)	26 (7.6%)	34 (11.6%)	0.024
Shock on admission	20 (6.5%)	14 (4.1%)	44 (15.0%)	<0.001
ECG on admission				
Sinus rhythm	231 (87.2%)	295 (89.7%)	236 (83.4%)	0.251
ST-segment elevation	103 (39.2%)	128 (39.1%)	132 (47.8%)	0.055
ST-segment depression	41 (15.6%)	46 (14.2%)	48 (17.6%)	0.524
T-wave inversion	100 (30.3%)	106 (32.7%)	117 (42.5%)	0.045
QTc, ms*	504±71	497±69	510±65	0.211
LVEF, %	43±13	43±12	39±12	<0.001
In-hospital complications				
Max. Killip degree				<0.001
I	220 (71.9%)	245 (72.1%)	153 (52.2%)	
II	39 (12.7%)	47 (13.8%)	55 (18.8%)	
III	24 (7.8%)	27 (7.9%)	32 (10.9%)	
IV	23 (7.5%)	21 (6.2%)	53 (18.1%)	
Death during admission	9 (2.9%)	5 (1.6%)	12 (4.1%)	0.211
Mitral regurgitation	21 (6.9%)	23 (6.8%)	19 (6.5%)	0.376
LVOT gradient†	16 (5.2%)	12 (3.5%)	3 (1.0%)	0.015
Systemic embolism	9 (2.9%)	6 (1.8%)	6 (2.0%)	0.051
Ventricular arrhythmias‡	8 (2.6%)	8 (2.4%)	17 (5.8%)	0.004
Hospital stay, d	8±6	8±8	13±16	<0.001

LVEF indicates, left ventricular ejection fraction; LVOT, left ventricular outflow tract; Max., maximum; N, number; TTS, Takotsubo syndrome.
*QTc maximum during admission.
†Defined as a peak gradient >25 mm Hg without inotropics.
‡Ventricular arrhythmias that need treatment.

Table 2. Clinical Characteristics of Different Physical Triggering Groups

	Sepsis (N=90)	Neurological Disorders (N=29)	Surgery (N=66)	Extreme Physical Activity/Trauma (N=54)	Hypoxia (N=54)	*P* Value
Female (%)	74 (82.2%)	22 (75.9%)	51 (77.3%)	48 (88.9%)	38 (70.4%)	0.163
Age, y	75±11	70±12	67±14	73±12	68±15	0.001
Hypertension	65 (72.2%)	18 (62.1%)	37 (56.1%)	36 (66.7%)	34 (63.0%)	0.326
Dyslipidemia	42 (46.7%)	17 (58.6%)	28 (42.4%)	28 (51.9%)	26 (48.1%)	0.642
Diabetes mellitus	23 (25.6%)	6 (20.7%)	11 (16.7%)	14 (25.9%)	13 (24.1%)	0.696
Smoker	31 (34.4%)	8 (27.6%)	24 (36.4%)	11 (20.4%)	27 (50.0%)	0.024
Lung disease	38 (42.4%)	3 (10.3%)	19 (28.8%)	9 (16.7%)	24 (44.4%)	<0.001
Renal insufficiency	9 (10.0%)	1 (3.4%)	4 (6.1%)	5 (9.3%)	7 (13.0%)	0.563
TTS pattern						0.015
Apical	75 (83.3%)	21 (72.4%)	43 (67.2%)	42 (80.8%)	41 (80.4%)	
Midventricular	8 (8.9%)	2 (6.9%)	16 (25.0%)	5 (9.6%)	4 (7.8%)	
Basal	3 (3.3%)	4 (13.8%)	1 (1.6%)	0 (0.0%)	3 (5.9%)	
Focal	4 (4.4)	2 (6.9%)	4 (6.2%)	5 (9.6%)	3 (5.9%)	
Clinical presentation						
Chest pain	49 (54.5%)	11 (37.9%)	27 (40.9%)	38 (70.4%)	32 (59.3%)	0.035
Typical	34 (37.8%)	7 (24.1%)	21 (31.8%)	30 (55.6%)	26 (48.1%)	
Atypical	15 (16.7%)	4 (13.8%)	6 (9.1%)	8 (14.8%)	6 (11.1%)	
Vegetative symptoms	30 (33.3%)	6 (20.7%)	21 (31.8%)	25 (46.3%)	14 (25.9%)	0.108
Dyspnea	61 (67.8%)	6 (20.7%)	26 (39.4%)	13 (24.1%)	23 (42.6%)	<0.001
Syncope	5 (5.6%)	7 (24.1%)	10 (15.2%)	5 (9.3%)	7 (13.0%)	0.065
Shock on admission	16 (17.8%)	1 (3.4%)	9 (13.6%)	6 (11.1%)	12 (22.2%)	0.164
ECG on admission						
Sinus rhythm	70 (83.3%)	23 (79.3%)	51 (78.5%)	47 (90.4%)	45 (84.9%)	0.491
ST-segment elevation	48 (59.3%)	14 (51.9%)	31 (48.4%)	28 (54.9%)	23 (43.4%)	0.437
ST-segment depression	9 (11.2%)	6 (22.2%)	12 (19.4%)	8 (16.0%)	13 (24.5%)	0.332
T-wave inversion	39 (48.8%)	13 (46.4%)	28 (44.4%)	20 (39.2%)	17 (32.1%)	0.338
QTc, ms*	521±65	489±46	507±61	492±68	522±73	0.171
LVEF, %	37±11	42±12	38±12	42±11	40±11	0.054
In-hospital complications						
Max. Killip degree						0.071
I	38 (42.4%)	20 (69.0%)	31 (47.0%)	34 (63.0%)	30 (55.6%)	
II	23 (25.6%)	3 (10.3%)	10 (15.2%)	10 (18.5%)	9 (16.7%)	
III	12 (13.3%)	5 (17.2%)	9 (13.6%)	3 (5.6%)	3 (5.6%)	
IV	17 (18.9%)	1 (3.4%)	16 (24.2%)	7 (13.0%)	12 (22.2%)	
Death during admission	2 (2.2%)	2 (6.9%)	2 (3.0%)	1 (1.9%)	5 (9.3%)	0.204
Mitral regurgitation	5 (5.6%)	1 (3.4%)	4 (6.1%)	7 (13.0%)	2 (3.7%)	0.286
LVOT gradient†	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.7%)	1 (1.9%)	0.191
Systemic embolism	1 (1.1%)	3 (10.3%)	1 (1.5%)	0 (0.0%)	1 (1.9%)	0.021
Ventricular arrhythmias‡	4 (4.4%)	2 (6.9%)	8 (12.1%)	1 (1.9%)	2 (3.7%)	0.014
Hospital stay, d	13±12	14±16	14±18	11±11	15±22	0.722

LVEF indicates left ventricular ejection fraction; LVOT, left ventricular outflow tract; Max., maximum; N, number; TTS, Takotsubo syndrome.
*QTc maximum during admission.
†Defined as a peak gradient >25 mm Hg without inotropics.
‡Ventricular arrhythmias that need treatment.

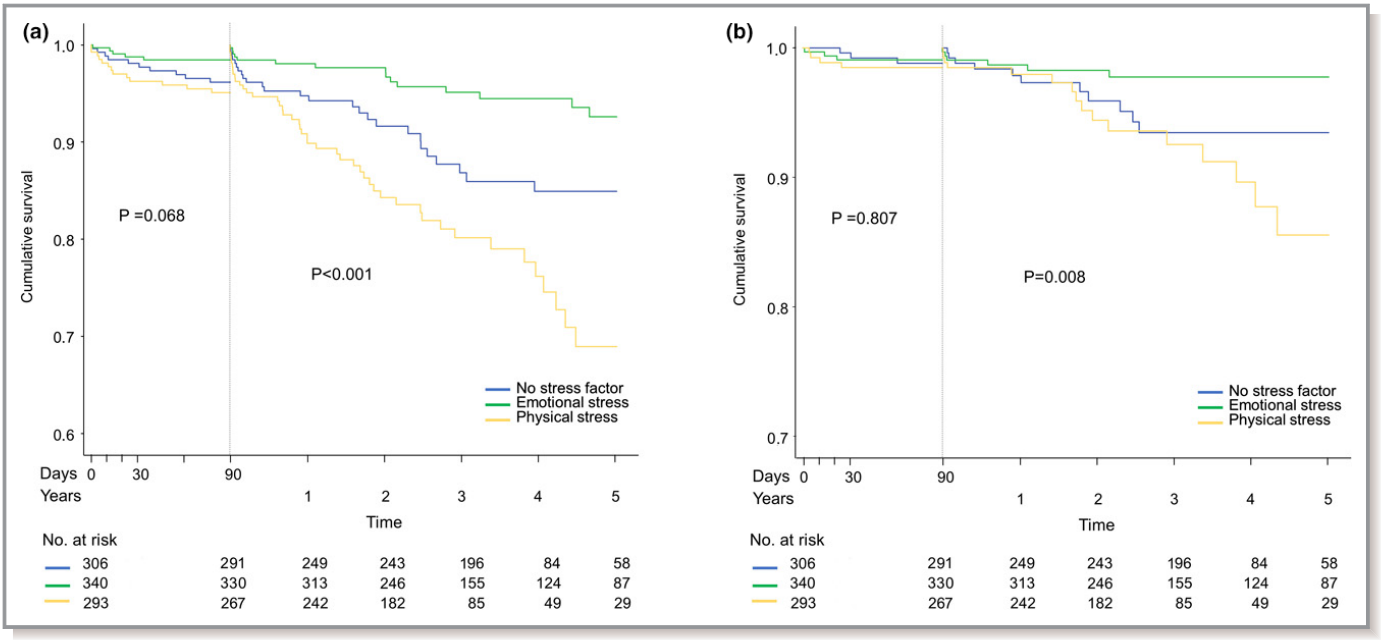

Figure 1. Kaplan–Meir survival landmark analysis by triggering events. **A**, All-cause death. **B**, Cardiovascular death.

Regarding debut symptoms, typical chest pain and vegetative symptoms were more prevalent in the TTS related to emotional stress group, whereas syncope and dyspnea were more common in the TTS related to physical stress group. In the latter group, we found a higher percentage of typical chest pain in patients whose physical trigger was exercise or trauma, whereas a greater percentage of syncope was evident in TTS triggered by neurological disorders.

We found a higher percentage of apical morphology in the TTS related to emotional stress and TTS without any identifiable trigger groups (primary forms). Midventricular and basal types was more frequent in patients with physical stress, and rate of focal pattern was similar in all 3 groups. In the TTS related to physical stress group (or secondary forms), apical forms were more frequently observed in the infection and physical activity/trauma groups, whereas midventricular morphology was

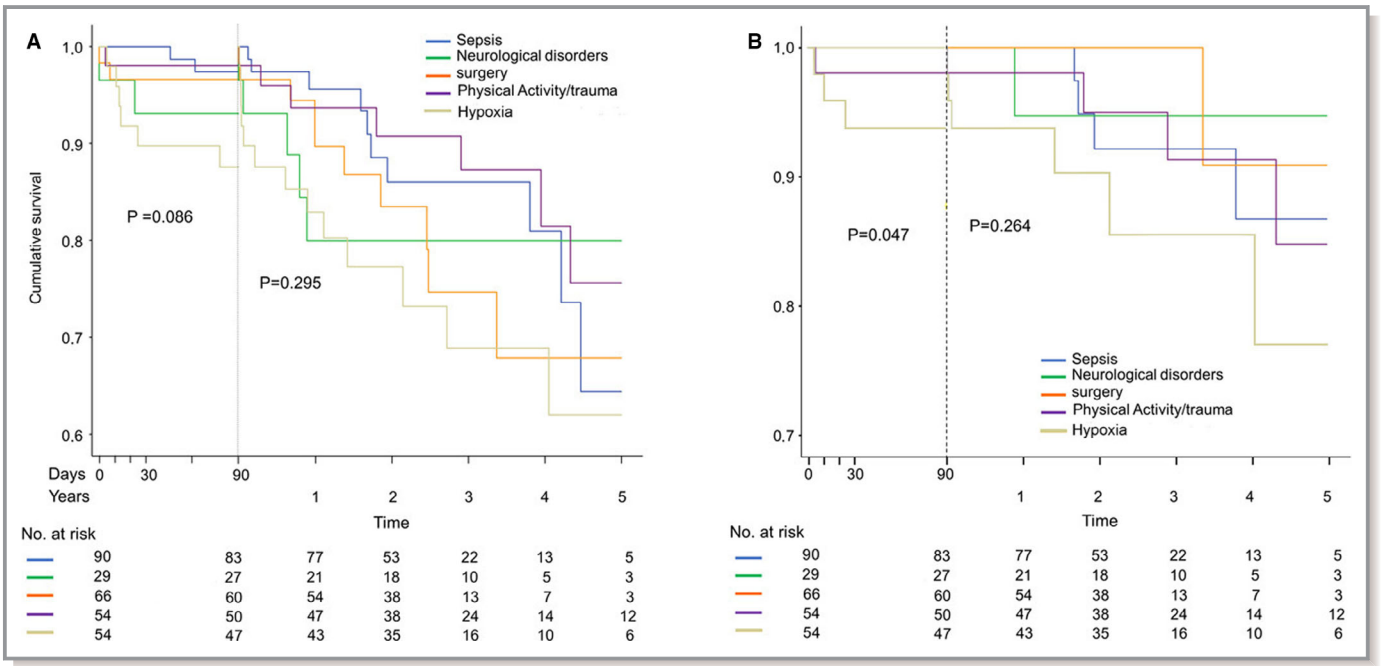

Figure 2. Kaplan–Meir survival landmark analysis by physical triggering events. **A**, All cause of mortality. **B**, Cardiovascular mortality. No. indicates number.

Table 3. Multiple Cox Regression for Long-Term Mortality (5 Years)

	HR (95% CI)	*P* Value
Physical trigger*	3.073 (1.758–4.302)	<0.001
No identifiable trigger*	1.913 (1.003–3.649)	0.049
Sex (male)	1.779 (0.925–3.419)	0.076
Age >70 y	2.894 (1.657–5.054)	<0.001
Left ventricular ejection fraction <30%	1.815 (1.132–2.910)	0.013
Significant mitral regurgitation	1.482 (0.732–3.001)	0.274
Shock on admission	2.048 (1.122–3.739)	0.020
Diabetes mellitus	2.750 (1.758–4.302)	<0.001
Atypical type†	0.962 (0473–1.955)	0.915

HR indicates hazard ratio.
*No identifiable trigger and physical trigger were identified as independent risk factors for 5-year mortality using preceding emotional stressors as the reference group.
†Based on transthoracic echocardiography. Atypical=midventricular type, basal type, or focal type.

predominant in TTS triggered by surgery procedures and the basal or inverse pattern predominated in TTS patients with neurological disorders. Finally, the focal pattern was more frequent in the physical activity or trauma group.

Patients with TTS related to physical stress had a longer hospital stay than patients with primary forms. In these patients, a greater number of in-hospital complications occurred, mainly a higher incidence and severity of heart failure and a higher incidence of ventricular arrhythmias. We did not observe differences in the incidence of thromboembolic complications or presence of significant mitral regurgitation. Furthermore, TTS related to physical stress patients had a worse ventricular function ("physical stress" left ventricular ejection fraction 39±12% versus "no stress" 43±13% versus "emotional stress" 43±12%; *P*=0.001).

Within the TTS group related to physical stress, we found a higher incidence and severity of heart failure in the surgical group, in addition to a higher incidence of ventricular arrhythmias.

Comparison of global and cardiovascular mortality at 90 days and 5 years among the different groups are shown in Figures 1 and 2. An increased early mortality was observed in the group with physical stress, whereas patients with emotional stress-related TTS showed the most favorable outcome. Interestingly, these findings persisted when analyzing cardiovascular mortality. In the physical trigger subgroups, the highest mortality was recorded in the hypoxia triggering group, whereas the best prognosis was recorded in the "extreme physical activity/trauma" and "sepsis" groups. In the long-term follow-up, the slight trend toward a worse short-term survival rate observed in physical TTS was statistically consolidated (log-rank test, *P*<0.001). Within this group, the worst survival rate was recorded in the hypoxia group.

The factors related to worse long-term prognosis are presented in Table 3. No identifiable trigger and physical triggers were noted as independent risk factors for 5-year mortality using preceding emotional stressors as the reference group (adjusted hazard ratio=1.9; 95% CI, 1.0–3.6; *P*=0.049 and hazard ratio=3.1; 95% CI, 1.8–4.3; *P*<0.001, respectively). Sex (male), age >70 years, left ventricular ejection fraction <30%, shock on admission, and diabetes mellitus were also independent predictors of long-term mortality.

The long-term main causes of death were the following: cardiovascular (33.0% of total deaths), infectious (21.2% of total deaths), and neurological (15.1% of total deaths). We did not observe relevant differences regarding cause of death among the type of stress groups.

Discussion

The main findings of the present study can be summarized as follows: (1) Short- and long-term prognosis depends on the trigger of TTS; (2) patients with an emotional trigger have a better prognosis, whereas those with physical stress have the worst; (3) not all physical triggers influence the prognosis of patients in the same way, with those triggered by hypoxia presenting a worse evolution in the short and long term; (4) incidence of physical, emotional, and unidentifiable triggers are similar; and (5) age >70 years, shock on admission, left ventricular ejection fraction <30%, and diabetes mellitus were also independent predictors of mortality during the follow-up.

Initial studies had suggested that TTS is predominantly preceded by emotional triggers.[15,16] Subsequent studies have proven that this syndrome may also be triggered by physical factors or even without any evident preceding trigger.[17–19] Some previous studies have shown that TTS related to physical stress could have a worse prognosis.[13,19,20] Recently, a classification for TTS has been proposed based on its possible prognostic implications.[13] The reason for this differentiation was to facilitate the identification and monitoring of phenotypes that could be related to a worse short- and long-term prognosis. Our current data confirm this point, showing a higher mortality in the group of TTS related to physical stress and a better survival rate in the group with emotional stress. In addition, our data add more information regarding the different types of physical triggers that exist showing a different prognosis. However, the reason for the difference in mortality still remains unclear. Although several hypotheses have been proposed to explain the mechanism of TTS, catecholamine release by the central nervous system is considered to have a central role in the pathophysiology of TTS.[2,21–23] Some researchers advocate for a differentiation in the pathophysiological mechanism that triggers TTS. On the one hand, emotional triggers may have a phasic nature, and

wax and wane with the emotional state, whereas physical triggers may chronically produce a catecholamine drive that cannot be reduced without recovery from the underlying disease. In fact, norepinephrine levels were higher in the nonphysical trigger group.[20]

Many of the conditions that are related to the physical triggers of TTS present variable prognoses that influence the overall survival of patients. The case of a previously healthy patient presenting TTS after a family discussion is completely different from the patient who is admitted because of a septic shock that develops TTS.

It is also important to identify comorbidities related to some diseases that may influence the prognosis. In addition to mortality attributable to these comorbidities, we might consider as well the mortality related to TTS itself (that, in these cases, may be higher because of the patient's general condition and which, ultimately, worsens the overall prognosis). Previous studies had shown a worse survival rate in patients with TTS secondary to neurological disorders.[23] This is not surprising, given that the prognosis of these patients is likely to be affected by the underlying disease. In other words, the increased mortality in patients with neurological triggers may result from the combined risk of TTS plus the intrinsic risk of any precipitating comorbidity, such as cerebrovascular hemorrhage. Unlike the previously published data, the worst prognosis in our cohort was observed when the trigger was hypoxia. When analyzing the baseline characteristics of these patients, it is important to mention that they had a higher prevalence of chronic lung disease, which could affect their overall long-term survival. However, when we analyzed cardiovascular mortality in this group, it was similar to that recorded in the other subgroups where the trigger was physical stress.

Our data show that the physical trigger also has an important influence in the long-term prognosis. In addition, other comorbidities, such as diabetes mellitus, age, and ventricular function, were also shown as powerful predictors. Recently, a meta-analysis was published in which these same characteristics were identified as predictors of mortality in TTS patients.[24]

Probably, differences in the short- and long-term prognosis of TTS patients are the result of adding pathophysiological differences that may exist among each of the triggers, as well as the individual prognosis of each of the comorbidities. Our data provide additional evidence to support the idea that under the TTS label, there could be as yet undiscovered very different clinical profiles, and therefore the perception of TTS as having a benign prognosis should be questioned in general. Moreover, in those TTS patients without a clear trigger, this condition could indicate some form of increased cardiovascular lability regarding the general population, explaining their worse prognosis compared with emotional TTS forms.

Our study has some limitations. Because of its observational nature, unmeasured confounders could constrain causal inference. However, prospective follow-up may permit the application of the causal inference methods. By dividing the group of physical stress into 5 different categories, the number of cases within each variable was significantly reduced, which could affect the statistical power of the subgroup analysis. Although a 5-year follow-up analysis was performed, there are a number of censored non-negligible cases, as reflected by the median follow-up and subjects at risk of survival analysis, so this should be taken into account when analyzing the results. In order to be able to include in the mutivariate analysis the largest number of patients, although there were differences in some clinical variables between groups (eg, type of chest pain, vegetative symptoms, etc), some of these variables were not included in the multivariate analysis because they were not considered potential confounders, and there are no previous studies that have associated them with the prognosis of these patients.

Conclusions

Patients with TTS related to physical stress could present a worse short- and long-term prognosis in terms of mortality. Therefore, these patients should be subject to thorough surveillance and aggressive management not only during the in-hospital stay, but also during outpatient follow-up as well, given that this subtype is not so benign. It is important to emphasize that not all physical triggers influence the prognosis of patients in the same way, being that those whose trigger is hypoxia are the ones presenting a worse evolution in the short and long term.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

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