Takotsubo Syndrome, Stressful Triggers, and Risk of Recurrence

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The risk of recurrence in takotsubo syndrome (TTS) appears to be low, although previous studies have shown conflicting results and factors associated with recurrences are unclear. The aim of this study is to evaluate the incidence and predictors of TTS recurrences. Adult patients included in the Spanish Multicenter REgistry of TAKOtsubo syndrome (RETAKO) between January 2003 and September 2019 were identified. Patients were categorized based on recurrences during follow-up and a multivariate logistic regression model was used to identify factors associated with recurrences. A total of 1097 patients (mean age 71.0±11.9 years, 87% females) were included, repeated TTS events were documented in 44 patients (4.0%), including 13 patients with prior TTS and 31 patients with recurrent TTS during a median follow-up of 279 days. Two patients (0.02%) had two episodes of recurrence. Compared to patients who had no recurrence of TTS, those with recurrent TTS more frequently had no identifiable stressful trigger in the index admission (20 [64.5%] vs 352 [33.0%], p <0.001). Primary TTS, defined as TTS without physical trigger, was also more common in the recurrence group (93.5% vs 68.3%, p <0.001). The only factor independently associated with recurrences was the absence of an identifiable trigger (odds ratio 3.7 [95% confidence interval 1.8-7.8], p=0.001). In conclusion, our data indicate that for patients presenting with TTS, the rate of early recurrent TTS is approximately 4% per year. Among TTS patients, those who have no identifiable trigger events appear to have a higher rate of recurrence. **© 2023 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2023;205:58−62)**

Keywords: takotsubo syndrome, recurrences, stressful triggers

Takotsubo syndrome (TTS) is a form of transient myocardial dysfunction frequently precipitated by a stressful event. After acute phase, normalization of left ventricular ejection fraction and regional wall motion abnormalities is the rule.[1,2] The pathophysiology of this unique condition is still not well known, but catecholamine-mediated cardiac stunning has a relevant role.[1,2] TTS might produce acute complications including arrhythmias, heart failure, and cardiogenic shock, along with an increased risk of mortality in the short- and long-term.[3−5] Left ventricular systolic dysfunction, physical stressful trigger, male gender, left ventricular outflow tract obstruction, and some electrocardiographic features (maximum corrected QT, atrial fibrillation, and advanced interatrial block) have been associated with poor outcomes.[5−9] TTS is also associated with a risk of recurrence, although recurrence rate has been variable among studies.[2,10−13] A different ballooning pattern can occur during recurrence in a significant number of patients.[12,13] It is not well understood why some patients experience recurrence whereas others do not. Studies

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This project was partially funded by a grant from the Fundación Mutua Madrileña Automovilista (Madrid, Spain). The electronic case report form and the REgistry of TAKOtsubo website were funded by AstraZaneca (Cambriodge, United Kingdom) until 2020; they are currently funded by Fundación Investigacion Cardiovascular (Madrid, Spain).

See page 61 for Declaration of Competing Interest.

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https://doi.org/10.1016/j.amjcard.2023.07.155

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investigating factors associated with recurrence have reported conflicting results,[11−13] and an effective treatment to avoid it is not well established.[13] The aim of this study is to evaluate the incidence and predictors of TTS recurrence.

Methods

Our data come from the Spanish Multicenter REgistry of TAKOtsubo syndrome (RETAKO), endorsed by the Ischemic Heart Disease and Acute Cardiovascular Care Section of the Spanish Society of Cardiology. RETAKO is a partially retrospective and prospective (from January 1, 2012 onward) voluntary observational study that enrolls patients with TTS from 38 centers. Its rationale and design have been previously described.[3] Main inclusion criteria require a definitive TTS diagnosis based on the modified Mayo Clinic criteria.[14]

The present study included subjects diagnosed between January 1, 2003 and September 2019. The index hospitalization for TTS at each institution was considered as the baseline assessment, and clinical data obtained during this hospitalization were defined as baseline characteristics. The registry specifically required information regarding trigger presence (physical, emotional, mixed, none), and this information was collected and included in the database at inclusion. There was also a free field regarding trigger type. Final date of follow-up was September 2019. Follow-up was performed by outpatient clinical visits, telephone contact with patients or relatives, or review of medical records. Recurrence was defined as a new nonfatal episode of TTS that occurred during follow-up after complete recovery from the previous TTS episode. Index TTS episodes occurring before registry inclusion that met the criteria according to clinical records were also documented. Recurrence was adjudicated after review of electronic medical records and consensus of 2 experienced investigators. Patients were categorized into 2 groups on the basis of the presence or absence of recurrence.

The study protocol complied with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Hospital Clinico San Carlos, Madrid, Spain. All patients provided written informed consent.

Statistical analyses were performed using SPSS version 24.0 (IBM SPSS, Armonk, New York). Continuous variables are reported as mean ± SD or median (interquartile range) and were compared by the Student's *t* test or the Mann−Whitney *U* test. Categorical variables were expressed as number (percentage) and compared by the chi-square test or Fisher's exact test. Multivariate logistic regression was used to identify clinical factors associated with TTS recurrences. Kaplan−Meier survival curves regarding recurrence and recurrence/death were used to compare patients with and without an identifiable trigger.

Results

A total of 1,097 patients were included (mean age 71.0 ± 11.9 years, 957 [87.2%] women). Repeated TTS events were documented in 44 patients (4.0%), including 2 patients (0.02%) with 2 episodes of recurrence. Of those, 13 patients had a TTS episode before their inclusion in our registry. The remaining 31 patients were included in the registry during their first TTS episode, and they presented with a prospective recurrence during follow-up. Median follow-up was 0.76 years (interquartile range 0.15 to 2.93 years), with a recurrence rate of 3.8%/year. For the rest of the analysis, we only included patients with prospective recurrences. Baseline characteristics in index admission of patients with and without recurrences are listed in Table 1. There were no relevant differences regarding demographic characteristics, cardiovascular risk factors, and major co-morbidities. However, patients without recurrences had a greater prevalence of immunosuppression and migraine than did those with recurrences.

Table 2 presents the clinical course during the index TTS episode of patients with and without recurrences. Absence of a stressful trigger was more common in the recurrence group (64.5% vs 33.0%). Primary TTS, defined as TTS without physical trigger, was also more common in the recurrence group (93.5% vs 68.3%). Syncope was an unusual symptom, more frequently found in the nonrecurrence group.

Variables with p <0.10 in the univariable analysis were included in the multivariable analysis. The only clinical factor independently associated with recurrence was absence of a stressful trigger (Table 3). Patients without a stressful trigger and patients with primary TTS had a lower recurrence rate during follow-up (Figure 1). There were no differences in mortality rate during follow-up in patients with or without trigger; however, those with secondary TTS had

Table 1
Baseline characteristics according to the presence of recurrences during follow-up

	Recurrence (N = 31)	No recurrence (N = 1066)	p
Age (years, mean ± standard deviation)	71.1±11.6	71.0±11.9	0.96
N (%)			
Female	28 (90.3%)	929 (87.1%)	0.60
Hypertension	22 (71.0%)	694 (65.1%)	0.49
Dyslipidemia	16 (51.7%)	486 (44.6%)	0.95
Diabetes	6 (19.4%)	196 (18.4%)	0.89
Smoking	3 (9.7%)	140 (13.1%)	0.57
Family history of takotsubo syndrome	2 (6.5%)	77 (7.2%)	0.45
Immunosuppression	0	35 (3.3%)	<0.01
Renal disease	3 (9.7%)	59 (5.6%)	0.39
Pulmonary history:			0.56
- No	26 (83.9%)	845 (79.3%)	
- Chronic obstructive pulmonary disease	4 (13.0%)	157 (14.8%)	
- Others	1 (3.1%)	17 (1.6%)	
Anemia	5 (16.1%)	78 (7.3%)	0.20
Migraine	0	32 (3%)	<0.01
Malignancy	2 (6.4%)	106 (9.9%)	0.48
Functional class			0.11
- I	27 (87.1%)	852 (79.9%)	
- II	4 (12.9%)	179 (16.8%)	
- III	0	35 (3.3%)	

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Table 2
Index admission clinical course according to the presence of recurrences during follow-up

	Recurrence (N = 31)	No recurrence (N = 1066)	p
N (%)			
Takotsubo syndrome type:			<0.001
- Primary	29 (93.5%)	728 (68.3%)	
- Secondary	2 (6.5%)	338 (31.7%)	
Stressful trigger:			<0.001
- None	20 (64.5%)	352 (33%)	
- Any:	11 (35.5%)	714 (67.0%)	
— Emotional	9 (29%)	376 (35.3%)	
— Physical	2 (6.5%)	276 (25.9%)	
— Mixed	0	62 (5.8%)	
Symptoms:			
- Chest pain	29 (93.5%)	789 (74%)	0.06
- Shortness of breath	13 (41.9%)	419 (39.3%)	0.77
- Palpitations	3 (9.7%)	89 (8.3%)	0.79
- Syncope	0	84 (7.9%)	<0.001
Acute renal injury	3 (9.7%)	116 (10.9%)	0.83
Infection	6 (19.3%)	280 (26.3%)	0.07
Cardiogenic shock	2 (6.5%)	87 (8.2%)	0.73
Death during follow-up	4 (12.9%)	112 (10.5%)	0.67

Table 3
Variables independently associated with recurrence

	OR (95% CI)	p
Age (years)	1.00 (0.97−1.03)	0.87
Female sex	1.4 (0.4−4.8)	0.58
Absence of a stressful trigger	3.7 (1.8−7.8)	0.001

Variables with p value < 0.10 in univariable analysis were included in multivariable analysis.

CI = confidence interval; OR = odds ratio.

significantly greater mortality than did those with primary TTS (Figure 2).

A stressful trigger was present in 725 patients (66.1%). Trigger was emotional in 385 (35.1%), physical in 278 (25.3%), and mixed in 62 (5.7%). Detailed information about trigger was available in 844 patients. The most common physical and emotional triggers are listed in Table 4. The recurrence rate and mortality rate per year according to different triggers are listed in Table 5.

Discussion

In this large multicenter registry, repeated TTS were documented in 4.0% during a median follow-up of 0.76 years, with a recurrence rate of 3.8%/year, and absence of a stressful trigger during the index event was independently associated with TTS recurrence during follow-up.

Patients with TTS experience full normalization of left ventricular ejection fraction and regional wall abnormalities. However, TTS is associated with a significant and increasingly recognized risk of recurrence. Previously reported recurrence rate has been variable (0% to 22%),[2] but most data came from small unicentric studies. A large retrospective study reported a rate of 1.8% per patient-year,[10] and a recent retrospective cohort reported a rate of 7.5% during a median follow-up of 5.2 years.[11] A meta-analysis that included >4,500 patients with TTS found an adjusted annual incidence of recurrence of 1.0% (95% confidence interval 0.7% to 1.3%).[15] Recurrence rate was 4.7% at a median follow-up of 2.5 years in the International Takotsubo Registry,[12] and 4% at a median follow-up of 2.2 years in the GErman Italian STress Cardiomyopathy (GEIST) Registry.[13] Our data are consistent with the

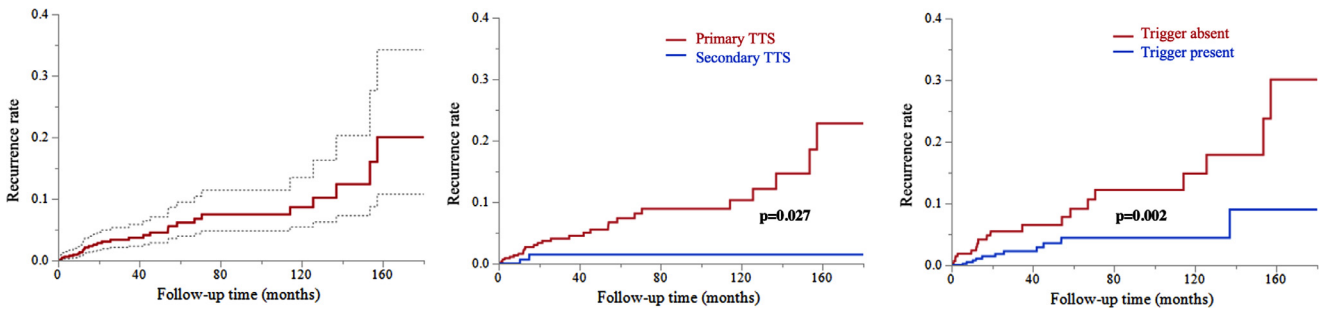

Figure 1. Curve showing recurrence rate in survivors during follow-up, in the whole sample, according to the type of TTS (p log−rank = 0.027), and according to the absence or presence of a stressful trigger (p log−rank = 0.002).

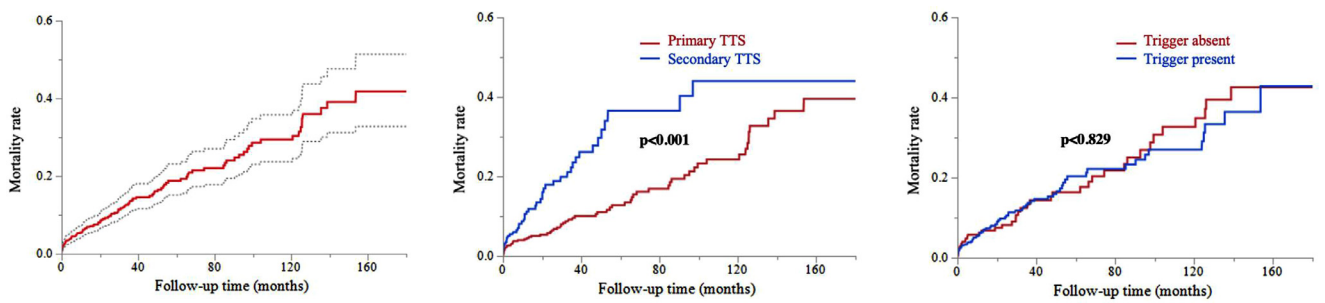

Figure 2. Curve showing mortality rate during follow-up, in the whole sample, according to the type of TTS (p log−rank <0.001) and according to the absence or presence of a stressful trigger (p log−rank = 0.829). **Color in print not needed for figures.

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Table 4
Most common physical and emotional triggers

Physical triggers (N = 340)*	Invasive procedures: 52 (15.3%)
	-Major surgery, general anesthesia: 37
	- Minor surgery, endoscopic or percutaneous procedure: 15
	Flu-like syndrome, upper respiratory tract infection: 41 (12.1%)
	Severe infection requiring hospital admission, sepsis: 35 (10.3%)
	Physical trauma and accident: 32 (9.4%)
	Pain and intense physical exercise: 26 (7.6%)
	Respiratory failure: 26 (7.6%)
	Stroke and acute neurological conditions: 21 (6.2%)
	Acute abdominal conditions: 17 (5.0%)
	Cardiovascular (heart block, pacemaker implantation, hypertensive crisis): 16 (4.7%)
	Renal colic and non-complicated urinary tract infection: 8 (2.4%)
	Catecholamine administration: 7 (2.1%)
	Cocaine use: 3 (0.9%)
	Hyponatremia: 3 (0.9%)
	Other / non-specified: 53 (15.5%)
Emotional triggers (N = 447)†	Bad news or acute emotional stress: 116 (26.0%)
	Severe argument: 73 (16.3%)
	Death of family member or friend: 68 (15.2%)
	Subacute/chronic stress: 42 (9.4%)
	Dangerous situation (robbery, assault, house fire, natural disaster): 19 (4.3%)
	Good news: 7 (1.6%)
	Suicide attempt: 5 (1.1%)
	Acute decompensation of psychiatric illness: 4 (0.9%)
	Other / non-specified: 113 (25.2%)

* Including patients with physical and mixed trigger.
† Including patients with emotional and mixed trigger.

Table 5
Recurrence and mortality rates per year according to trigger type

	Recurrence rate per year	Mortality rate per year
No trigger	7.3%	15.7%
Emotional trigger	2.3%	6.5%
Physical trigger	0.9%	17.3%
Mixed trigger	0%	36.5%

findings of these large multicentric registries. Recurrent cases have been reported to occur as early as 8 days and as late as 13 years after the initial event,[13,16] but early recurrences seem to be more common. A retrospective study in 100 patients from the Mayo Clinic described that recurrence rate was highest at 2.9%/year within the first 4 years, decreasing to 1.3%/year subsequently.[17]

In our cohort, absence of a stressful trigger was the only factor associated with TTS recurrence, an interesting finding that, to the best of our knowledge, has not been previously reported. A possible explanation is that patients who develop TTS without needing a stressful trigger could have greater susceptibility to this condition. TTS genetic predisposition is still under investigation, although a preliminary genome-wide association study did not identify any loci with a robust TTS association.[18] Catecholamine-mediated cardiac stunning has a central role in the pathophysiology of TTS syndrome.[2] Lower stress tolerance and increased release of epinephrine and norepinephrine with minimal insults, not even identified as triggers, could also play a role in patients with TTS recurrence. A previous study found opposing results, with physical trigger being associated with the risk of recurrence.[19] However, this study included only 8 patients with TTS recurrence, and its results have not been confirmed in larger cohorts. A previous study suggested an association between male gender and recurrence,[11] but the small number of men with TTS makes the confirmation of this hypothesis difficult. Regarding age, previous studies have found conflicting results.[2,11] Acquired factors as hypertension, diabetes mellitus, low body mass index, neurologic and psychiatric disorders, pulmonary disease, or chronic kidney disease have also been found to be associated with recurrences in some studies.[11–13,19–22]

In our cohort, clinical course during the index event did not differ between patients with and without recurrences. This has also been the case in most previous studies,[5,10–12,16,19] although the GEIST registry documented a higher rate of pulmonary edema in the recurrence group,[13] and the BOREAS registry found a higher rate of midventricular obstruction.[22] Given TTS implies a complete recovery, recurrence seems to be a new event not influenced by the previous episode. In fact, recurrence can even present with a different ballooning pattern in 20% to 79% of patients.[12,13,16]

The previously mentioned meta-analysis[15] found that a physical stressor was associated with death during follow-up but not with recurrences. A previous report from our group[6] also found that patients with a physical trigger had greater short- and long-term mortality. In most studies, mortality after TTS is mainly due to noncardiac causes.[15,16] It seems logical that patients with a physical trigger have greater mortality during follow-up because the prognosis of the precipitating event (commonly invasive procedures, severe infections, respiratory failure, or neurological events) adds to that of the co-morbidity predisposing to the event and to that of TTS itself. In contrast, our results suggest that patients without trigger show a higher rate of recurrence, given they might have another TTS episode without the need of a trigger.

This study has the inherent limitations of an observational, nonrandomized design. The relatively small number of patients with recurrent TTS reduces the statistical power of the study. Finally, we had no data regarding TTS pattern or pharmacologic treatment during index episode and recurrence.

In conclusion, approximately 4% of patients with TTS will present a recurrence during a median follow-up of 279 days. The risk of recurrence is greater in TTS episodes not associated with stressful triggers. We hypothesize that this could be explained by stronger susceptibility to the disease in these patients.

Declaration of Competing Interest

The authors have no competing interests to declare.

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