ORIGINAL RESEARCH

Incidence and Clinical Impact of Recurrent Takotsubo Syndrome: Results From the GEIST Registry

Ibrahim El-Battrawy, MD; Francesco Santoro, MD; Thomas Stiermaier, MD; Christian Möller, MD; Francesca Guastafierro, MD; Giuseppina Novo, MD, PhD; Salvatore Novo, MD; Enrica Mariano, MD, PhD; Francesco Romeo, MD; Fabiana Romeo, MD; Holger Thiele, MD; Federico Guerra, MD; Alessandro Capucci, MD; Irene Giannini, MD; Natale Daniele Brunetti, MD, PhD; Ingo Eitel, MD; Ibrahim Akin, MD

***Background*—**Current literature only reports variable information from single-center studies on the recurrence rate, the complications, and the outcome of patients with Takotsubo syndrome (TTS) experiencing recurrent TTS. Therefore, a detailed description of clinical characteristics, predictors, and the prognostic impact of patients with TTS and recurrences in a multicenter registry is needed.

***Methods and Results*—**We analyzed 749 patients with TTS from 9 European centers being part of the international, multicenter GEIST (German Italian Stress Cardiomyopathy) Registry. Patients were divided into the recurrence group and the nonrecurrence group. The recurrence rate at a median follow-up of 830 days (interquartile range, 118–1701 days) was 4%. Most recurrences were documented in the first 5 years after the index TTS episode. Up to 2 TTS recurrences were documented in 2 of 30 patients (6%). A variable ballooning pattern (n=6, 0.8%) with, in particular, involvement of the right ventricular occurred in 3 cases (0.4%) at the recurrence event. Except for the higher presence of arterial hypertension (86.7% versus 68.3%; P=0.03) in the recurrence group, no other baseline characteristics were different between groups. Observation of TTS complications during follow-up, including stroke, thromboembolic events, in-hospital death, and cardiogenic shock, revealed no significant differences between groups (P>0.05), except the higher presence of pulmonary edema in the recurrence group versus the nonrecurrence group (13.3% versus 4.9%; P=0.04).

***Conclusions*—**The incidence of TTS recurrence is estimated to be 4% in this multicenter TTS registry. A variable TTS pattern at recurrence is common in up to 20% of recurrence cases. **(*J Am Heart Assoc*. 2019;8:e010753. DOI: 10.1161/JAHA.118.010753.)**

Key Words: heart failure • Takotsubo cardiomyopathy • recurrence

Takotsubo syndrome (TTS) is characterized by a transient ventricular dysfunction. Patients have symptoms mimicking an acute coronary syndrome.[1,2] Despite the transient character of TTS, a significant number of adverse events has been reported.[3] Mainly in the short-term phase of TTS, patients are experiencing arrhythmias, including sudden cardiac death,[4–6] cardiogenic shock,[7] and thromboembolic events, including stroke.[8,9] First, it has been thought that TTS may affect only the left ventricle (LV), whereas some years later right ventricular or biventricular involvement has been also reported.[10,11] The recovery of these wall motion abnormalities is observed within days to weeks. The following 4 different TTS forms have been reported to date: apical form, midventricular form, basal form, and rare focal form.[12,13] In

From the First Department of Medicine, Faculty of Medicine, University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany (I.E.-B., I.A.); German Center for Cardiovascular Research (DZHK), Partner Site Heidelberg-Mannheim, Mannheim, Germany (I.E.-B., I.A.); Department of Medical and Surgery Sciences, University of Foggia, Foggia, Italy (F.S., F. Guastafierro, N.D.B.); Medical Clinic II (Cardiology/Angiology/Intensive Care Medicine) and German Center for Cardiovascular Research, Partner Site Hamburg/Kiel/Lübeck, University Heart Center Lübeck, Lübeck, Germany (T.S., C.M., I.E.); Cardiology Unit, Biomedical Department of Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy (G.N., S.N.); Division of Cardiology, University of Rome Tor Vergata, Rome, Italy (E.M., Francesco Romeo, Fabiana Romeo); Department of Internal Medicine/Cardiology, Heart Center Leipzig–University Hospital, Leipzig, Germany (H.T.); and Cardiology and Arrhythmology Clinic, Marche Polytechnic University, University Hospital "Umberto I–Lancisi–Salesi," Ancona, Italy (F. Guerra, A.C., I.G.).

Correspondence to: Ibrahim El-Battrawy, MD, First Department of Medicine, University Medical Centre Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. E-mail: ibrahim.el-battrawy@medma.uni-heidelberg.de

Received August 24, 2018; accepted March 8, 2019.

Clinical Perspective

What Is New?

- Takotsubo syndrome (TTS) is associated with a recurrence rate of 4%.
- A variable TTS pattern at recurrence is common in up to 20% of recurrence cases.

What Are the Clinical Implications?

- Patients with TTS are at risk of TTS recurrence.
- In patients with a history of TTS and new symptoms mimicking acute coronary syndrome, physicians should consider the possibility of recurrent TTS.

the past decade, different studies have shown that TTS is not associated with a favorable prognosis, with a mortality rate comparable to that of acute coronary syndrome.[3,14]

Current literature reports a recurrence rate of 1% to 6%.[15–17] However, these data are inconsistent and frequently limited by its single-center character. Moreover, it is not known which patients are at risk for recurrence and if the presence of TTS recurrences is associated with future cardiovascular events or mortality. In view of these limitations, we sought to comprehensively describe the incidence, clinical characteristics, predictors, and impact of recurrence in TTS in a large multicenter European registry.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure; they will be provided on request to the corresponding author. This multicenter GEIST (German Italian Stress Cardiomyopathy) Registry included 906 consecutive patients with TTS, enrolled from 9 centers: University Heart Center Lübeck (Lübeck, Germany); Heart Center Leipzig–University Hospital (Leipzig, Germany); University Medical Center Mannheim (Mannheim, Germany); University Hospital of Foggia (Foggia, Italy); Casa Sollievo della Sofferenza Hospital (San Giovanni Rotondo, Italy); San Paolo Hospital (Bari, Italy); University Hospital of Palermo (Palermo, Italy); University Hospital of Rome "Tor Vergata," (Rome, Italy); and University Hospital "Umberto I–Lancisi–Salesi" (Ancona, Italy). Patients were prospectively included in accordance with diagnostic criteria for TTS.[1] These criteria essentially highlight transient wall motion abnormality in the LV or right ventricle; and also describe an event that occurs frequently, but not always, in the wake of a stressful trigger. Other salient points mandate the absence of obstructive coronary disease related to wall motion abnormalities; focus on the appearance of new electrocardiographic pathological features, which mimic acute coronary syndrome or modest elevations in cardiac troponin levels; and underline the absence of pheochromocytoma or myocarditis in the patient. A ballooning pattern was defined, according to defined criteria, as being a transient systolic dysfunction with marked LV contraction abnormality attributable to akinesia or dyskinesia of the LV apical and/or midventricular or basal segments, extending beyond a single coronary perfusion bed.[12,18]

Recurrence of TTS was defined as new wall motion abnormalities in the absence of obstructive coronary disease after recovery of the index TTS events. The recurrence of TTS was assessed by medical record review and/or telephonic review. If medical records, treating physicians, patients, or relatives were able to provide further information about the circumstances of recurrence, the angiograms, echocardiograms, and ECGs were independently reviewed by 2 experienced cardiologists (I.E.-B., I.A., F.S., F. Gustafierro, N.D.B., T.S., C.M., I.E., G.N., S.N., E.M., Francesco Romeo, H.T., F. Guerra, A.C., I.G.) to evaluate the diagnosis of TTS. The study protocol was approved by the local Ethics Committee. All methods were performed in accordance with the relevant guidelines and regulations. The study was conducted in compliance with the Declaration of Helsinki on investigations in human subjects. Informed consent was waived by the Ethics Committee.

Statistical Analysis

Data are presented as means±SD for continuous variables with a normal distribution, median (interquartile range) for continuous variables with a nonnormal distribution, and frequency (percentage) for categorical variables. The Kolmogorov-Smirnov test was used to assess normal distribution. The Student *t* test and the Mann-Whitney *U*-test were used to compare continuous variables with normal and nonnormal distributions, respectively. The χ^2 test or Fisher's exact test was used to compare categorical variables. The log-rank test was used to compare Kaplan-Meier survival curves between the cardiopulmonary failure group and the noncardiopulmonary failure group. Factors with $P<0.10$ on univariate analysis were entered into the Cox multivariate regression to define independent risk factors for the end point. Statistical analysis was performed with SPSS 23.0 in all analyses; $P\leq0.05$ (2 tailed) indicated statistical significance.

Results

Of the 906 consecutive patients included in the GEIST Registry, follow-up was documented in 749. Baseline characteristics are illustrated in Table 1. Most patients were postmenopausal women (90.2%). A stressful event was documented in 70% of cases, with a predominance of a physical stress trigger (38.7%). The moderate reduced LV ejection fraction at the index event (median, 40% [interquartile range, 15%–71%]) was almost

Table 1. Baseline Clinical Characteristics

Variable	All Patients (n=749)	Patients With No Recurrence (n=719)	Patients With Recurrence (n=30)	*P* Value
Age, y	70±10	70±11	68±13	0.30
Women	676 (90.2)	651 (90.5)	25 (83.3)	0.19
Hypertension	596 (70.1)	491 (68.3)	25 (86.7)	0.03
Current smoking	187 (22.7)	159 (22.1)	10 (33.3)	0.15
Malignancy	123 (13.9)	95 (13.2)	3 (10.0)	0.61
Stressful event	526 (70.2)	505 (70.2)	21 (70.0)	0.98
Emotional	290 (38.7)	281 (39.1)	9 (30.0)	0.31
Physical	238 (31.8)	224 (31.1)	12 (40.0)	0.10
Ballooning pattern				
Apical	616 (82.2)	590 (82.4)	26 (86.7)	0.54
Midventricular	134 (17.8)	129 (17.9)	5 (16.7)	0.86
Basal	17 (2.3)	17 (2.4)	0 (0.0)	1.00
Focal	1 (0.1)	1 (0.2)	0 (0.0)	1.00
LVEF, %	40 (15–71)	40 (15–71)	40 (25–59)	0.87
Time of hospitalization, d	8 (1–96)	8 (1–96)	6 (2–16)	0.29
Follow-up LVEF, %	53 (20–77)	53 (20–77)	54 (40–72)	0.58

Data are presented as number (percentage) of patients, mean±SD for normal distribution, and median (interquartile range) for nonnormal distribution. *P* values were calculated for the comparison between patients with Takotsubo syndrome and recurrence. LVEF indicates left ventricular ejection fraction.

normalized through follow-up (median, 53% [interquartile range, 20%–77%]). Overall, TTS recurrence was documented in 30 patients (4%) at a median follow-up of 830 days (interquartile range, 118–1701 days; 95% CI, 981–1128 days).

Clinical Characteristics of the Patients With TTS Recurrence

Patients with TTS who experienced recurrence events tended to be younger (mean±SD, 68±13 versus 70±11 years; *P*=0.3). Cardiovascular risk factors, such as arterial hypertension (86.7% versus 68.3%; *P*=0.03), were significantly higher in the recurrence group. Observing the different TTS forms/ballooning patterns and the LV ejection fraction at index event and/or follow-up, there was no difference between both groups. Even more, further baseline characteristics, including malignancy and current smoking, were not different between both groups. At the recurrence episode, most patients (n=21) presented with the apical form, whereas the midventricular form was evident in 7 patients. In our cohort, 20% of patients presented with variable ballooning at the recurrence episode: 3 patients with an apical pattern at the index event and a midventricular pattern at the recurrence event and a further 3 patients with right ventricular involvement at the recurrence event. Detailed information of

Table 2. In-Hospital Events of Patients With TTS

Variable	All Patients (n=749)	Patients With No Recurrence (n=719)	Patients With Recurrence (n=30)	*P* Value
Cardiac electronic device implantation	9 (1.2)	9 (1.3)	0 (0.0)	1.00
In-hospital death	19 (2.5)	18 (2.5)	1 (3.3)	0.55
Thromboembolic events	21 (2.8)	20 (2.8)	1 (3.3)	0.58
Stroke	10 (1.3)	9 (1.3)	1 (3.3)	0.34
Cardiogenic shock	59 (7.8)	59 (8.2)	0 (0.0)	0.16
Pulmonary edema	39 (5.2)	35 (4.9)	4 (13.3)	0.04

Data are given as number (percentage) of patients. TTS indicates Takotsubo syndrome.

Table 3. Trigger Factors of Recurrence Episode of 30 TTS Cases

Case No.	No. of Recurrences	Physical Stressor	Emotional Stressor
1	1	–	–
2	1	–	+
3	1	Not documented	Not documented
4	1	–	–
5	1	+	–
6	1	–	+
7	1	–	+
8	1	–	+
9	1	–	–
10	1	–	+
11	2	–	–
12	1	–	+
13	1	+	–
14	1	–	–
15	1	+	–
16	1	–	+
17	1	+	–
18	2	+	+
19	1	+	–
20	2	+	–
21	1	+	–
22	1	Not documented	Not documented
23	1	+	–
24	1	Not documented	Not documented
25	1	Not documented	Not documented
26	1	–	–
27	1	–	+
28	1	–	+
29	1	–	+
30	1	–	–

+ Indicates yes; –, no; TTS, Takotsubo syndrome.

triggers of TTS recurrence is illustrated in Table 2. Interestingly, in 14 patients (46%), TTS has been triggered by a new stressor compared with the first TTS event (9 patients experienced an emotional trigger, and 5 patients experienced a physical trigger).

Predictors of Recurrence in TTS and Triggers of Recurrence

Using univariate Cox regression, no factors were identified as predictive for TTS recurrence (Table 3).

Table 4. Predictors of Recurrence in TTS

	Univariate	
Variable	Hazard Ratio (95% CI)	*P* Value
Diabetes mellitus	0.52 (0.15–1.73)	0.289
Age, y	0.99 (0.96–1.02)	0.700
Men	2.44 (0.93–6.38)	0.069
Current smoking	1.51 (0.71–3.19)	0.276
Hypertension	2.37 (0.82–6.79)	0.109
Malignancy	0.83 (0.25–2.74)	0.760
Physical trigger	0.72 (0.33–1.60)	0.431
Emotional trigger	1.20 (0.57–2.50)	0.622
Apical ballooning	2.10 (0.73–6.05)	0.165
Initial LVEF, %	0.98 (0.95–1.02)	0.467
Cardiogenic shock	0.55 (0.07–4.09)	0.564

LVEF indicates left ventricular ejection fraction; TTS, Takotsubo syndrome.

In-Hospital Events of the Recurrences of Patients With TTS

Different in-hospital events, including thromboembolic events (2.8% versus 3.3%), stroke (1.3% versus 3.3%), cardiogenic shock (8.2% versus 0%), and the use of cardiac electronic device implantation (1.3% versus 0%), were evaluated (Table 4). No significant difference was documented between both groups. Although pulmonary edema was more often documented in the recurrence group than in the nonrecurrence group (13.3% versus 4.9%; P=0.04) at the index event, the in-hospital mortality and the duration of hospital stay did not differ between both groups. Of 30 patients, 2 (6%) developed an in-hospital TTS recurrence.

Follow-Up Data Treatment and Clinical Outcome

The earliest time of recurrence was 8 days, and the latest time of recurrence was 2555 days. The Figure presents the recurrence-free survival of patients with TTS. Except for 2 patients with 2 recurrences, only 1 recurrence event was documented in all other patients.

Information about drugs at admission and discharge was documented in 22 patients experiencing a recurrence. At admission, these drugs included a β blocker (54%, n=12), an angiotensin-converting enzyme (ACE) inhibitor or AT (angiotensin-converting-enzyme)-II antagonist (36.6%, n=11), and a combination of a β blocker and an ACE inhibitor or AT-II antagonist (20%, n=6); and at discharge, these drugs included a β blocker (50%, n=15), an ACE inhibitor or AT-II antagonist (54%, n=12), and a combination of a β blocker and an ACE inhibitor or AT-II antagonist (33.3%, n=10).

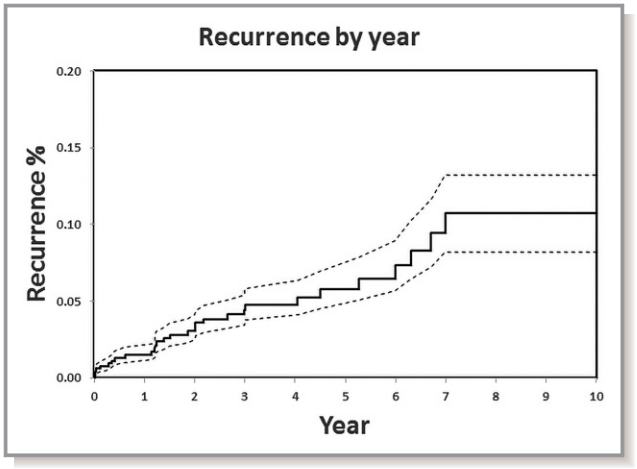

Figure. Recurrence-free survival presents that most recurrences are common the first years after a Takotsubo syndrome event.

Discussion

The present European multicenter TTS registry is one of the largest TTS cohorts reported yet. The main results of this study focusing on TTS recurrences are as follows: (1) the recurrence rate of TTS is 4%, with a predominance of a single recurrence event; (2) a variable TTS pattern at recurrence is common in up to 20% of recurrence cases; and (3) most clinical baseline characteristics and in-hospital complications are comparable between the recurrence and nonrecurrence group.

Incidence of TTS Recurrence

In the present large multicenter study, we describe a recurrence rate of 4.0% during a median follow-up of 830 days (interquartile range, 118–1701 days). The recurrence rate of TTS has been estimated to be between 1% and 11.4% in single-center studies and meta-analyses.[11,15–17,19–22] Although, previous studies have commented on the recurrence rate of TTS, these studies have had a single-center character with a low number of patients and variable information. Our study investigates in depth the characteristics of patients with TTS experiencing recurrence. Overall, it shows that most baseline characteristics, except arterial hypertension, and in-hospital events might be similar in the recurrence and nonrecurrence groups of patients with TTS. The mechanism of recurrence in TTS remains unclear. A genetic predisposition is still debated.[23]

Interestingly, our data, for the first time, demonstrate that in up to 20% of recurrence cases, a variable TTS pattern is presented. In addition, 46% of patients have had a new stress trigger at TTS recurrence. This observation has been reported elsewhere in small case series of TTS.[19] In our study, 3 patients with TTS (10%) showed a right ventricular involvement at the recurrence event and 3 patients (10%) with the apical form at initial TTS presented a midventricular TTS form at the recurrence event. This could not be explained by the proposed theory of TTS association with the gradient of β receptors. Although myocardial responsiveness to adrenergic stimulation is increased in the apical region, norepinephrine content is lower in the apex than in the base.[24] Another proposed hypothesis is that a previous episode of TTS form may protect this region of TTS involved in the TTS recurrence, with a higher vulnerability of other regions. However, we demonstrate, consistent with other reports, that there are recurrent cases of TTS with the same ballooning pattern, similar to the index event.[12]

Drug Therapy and Recurrence

Another interesting data point is that 2 patients (0.26%) experienced 2 recurrence episodes, and the highest number of recurrences was observed at an early time (up to 5 years) after the initial TTS event. It could be speculated that the myocardium remains vulnerable at this first stage after the first TTS event. Another possible explanation could be that the prescription of drugs, including β blockers, could be abandoned by patients and physicians after the first TTS event. In our study, >50% of patients were admitted with a β blocker, an ACE inhibitor, or an AT-II antagonist. Although TTS is associated with hyperadrenergic stimulation, the ACE inhibitor or AT-II antagonist was more able to reduce the recurrence rate than β blockers[15,25–27] in nonrandomized trials. Moreover, a combined treatment might be more effective than stand-alone treatment.[27] A combination of a β blocker and ACE inhibitor or AT-II antagonist was documented in 28% of recurrence cases. This might increase the speculation that a combined treatment is more effective. A possible explanation is that a reduction in sympathetic activity through interaction with the renin-angiotensin system or suppression inflammatory reactions on the myocardium is more effective on the combined treatment than on stand-alone treatment.

Finally, because our data are presenting that >50% of patients with TTS at the recurrence event are admitted with a β blocker, an ACE inhibitor or AT-II antagonist, or a combination of a β blocker and an ACE inhibitor or AT-II antagonist, this might raise the question of what is the optimal treatment strategy to avoid recurrences in TTS. This issue should be evaluated in future well-designed prospective randomized trials.

Limitations

Despite the multicenter character of the current study and high number of patients, the analysis has some limitations. First, it is a registry-based design with differences on the recorded parameters between centers. Some data are missing, such as

the compliance of patients regarding drug treatment after the index event. In addition, the duration of medical treatment could not be evaluated because of the small number of recurrences. However, the current report is the largest report of patients with TTS recurrence. Mortality analysis is not meaningful because of the low number of observations.

Conclusions

The recurrence rate of TTS is 4% in this multicenter registry. Up to 2 recurrences could be documented in patients with TTS and variable patterns. A variable TTS pattern at recurrence is documented in up to 20% of recurrence cases. In the present study, no predictors could be identified for recurrence of TTS.

Author Contributions

Akin and Eitel designed the study. Stiermaier, Santoro, Novo, Francesco Romeo, Giannini, El-Battrawy, Brunetti, and Eitel contributed to the design of the study. All authors collected the data. Akin and Eitel analyzed the data and wrote the manuscript. All authors discussed the results and implications and commented on the manuscript at all stages. Akin and Eitel are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None.

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