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ORIGINAL RESEARCH

Trigger-Associated Clinical Implications and Outcomes in Takotsubo Syndrome: Results From the Multicenter GEIST Registry

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BACKGROUND: Takotsubo syndrome is usually triggered by a stressful event. The type of trigger seems to influence the outcome and should therefore be considered separately.

METHODS AND RESULTS: Patients included in the GEIST (German-Italian-Spanish Takotsubo) registry were categorized according to physical trigger (PT), emotional trigger (ET), and no trigger (NT) of Takotsubo syndrome. Clinical characteristics as well as outcome predictors were analyzed. Overall, 2482 patients were included. ET was detected in 910 patients (36.7%), PT in 885 patients (34.4%), and NT was observed in 717 patients (28.9%). Compared with patients with PT or NT, patients with ET were younger, less frequently men, and had a lower prevalence of comorbidities. Adverse in-hospital events (NT: 18.8% versus PT: 27.1% versus ET: 12.1%, $P<0.001$) and long-term mortality rates (NT: 14.4% versus PT: 21.6% versus ET: 8.5%, $P<0.001$) were significantly lower in patients with ET. Increasing age ($P<0.001$), male sex ($P=0.007$), diabetes ($P<0.001$), malignancy ($P=0.002$), and a neurological disorder ($P<0.001$) were associated with a higher risk of long-term mortality, while chest pain ($P=0.035$) and treatment with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker ($P=0.027$) were confirmed as independent predictors for a lower risk of long-term mortality.

CONCLUSIONS: Patients with ET have better clinical conditions and a lower mortality rate. Increasing age, male sex, malignancy, a neurological disorder, chest pain, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and diabetes were confirmed as predictors of long-term mortality.

Key Words: broken heart syndrome ■ outcome ■ stress-induced cardiomyopathy ■ takotsubo syndrome

Takotsubo syndrome (TTS) was first described in 1990[1] and is generally considered to be acute heart failure with impaired regional left ventricular contractility in the absence of a corresponding coronary stenosis or plaque rupture. In the past, TTS was regarded as a benign disease with an overall good prognosis.[2] However, recent studies have shown that in-hospital mortality is comparable with acute myocardial infarction.[3] Moreover, evidence suggests that TTS is associated with higher mortality rates than those found in a matched population with ST-segment elevation myocardial infarction.[4] Therefore, it is necessary to identify clinical parameters

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CLINICAL PERSPECTIVE

What Is New?

- Patients with an emotional trigger of Takotsubo syndrome have lower rates of in-hospital complications and lower long-term mortality rates compared with patients with physical or no trigger.
- Takotsubo syndrome recurrence was 3.7% at a median follow-up of 824 days.
- Increasing age, male sex, malignancy, a neurological disorder, chest pain, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and diabetes were confirmed as predictors of long-term mortality.

What Are the Clinical Implications?

- Patients with a physical trigger or no triggers of Takotsubo syndrome may require a higher level of awareness during the hospitalization and in outpatient aftercare.

Nonstandard Abbreviations and Acronyms

AT-R	angiotensin receptor
ET	emotional trigger
NT	no trigger
PT	physical trigger
TTS	Takotsubo syndrome

for estimating short-term and long-term outcomes in TTS.

Extensive investigations have been conducted on the pathogenesis of the disease,[5–10] but the exact pathogenesis remains still unclear. Overall, study results show a high association with a physical trigger (PT) or emotional trigger (ET) event.[11] It is remarkable that both somatic diseases and emotional events could be triggers for TTS.[11] This is particularly relevant since the triggering mechanism appears to affect the outcome in patients suffering from TTS. Recent study results indicate that in-hospital outcomes of patients with TTS, especially with an ET, are better than those of patients with a PT or without an identified trigger.[12] This association also seems to be confirmed in the long-term prognosis.[13] However, evidence in trigger-associated clinical presentation and outcome is still limited. Therefore, the aim of this study was to examine clinical characteristics and outcomes sorted by a trigger mechanism in the large, international GEIST (German-Italian-Spanish Takotsubo) registry. Moreover, we try to identify independent predictors of short-term and long-term outcomes.

METHODS

Data Availability

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

Study Population

This is a multicenter, population-based observational trial of the GEIST registry including 2492 patients suffering from TTS. Major findings and key structures of this registry as well as the definition of TTS and the inclusion criteria had been published elsewhere.[14] Briefly, data were collected partially retrospectively and partially prospectively from 2017 onwards in 49 participating study centers in Germany (3 sites, n=488), Italy (9 sites, n=971), and Spain (38 sites, n=1033 with patients included in the Spanish National Takotsubo Registry [RETAKO; Registro Nacional Sobre Syndrome Takotsubo]). All patients underwent coronary angiography to exclude a coronary artery disease (defined as stenosis >50%) before inclusion.[15] Several demographic data, cardiovascular risk factors, comorbidities, clinical presentation, electrocardiographic findings, echocardiographic parameters, and medications were analyzed by trigger mechanism including patients with ET, PT, and no identifiable trigger (NT). Specific description of all ETs and outcome variable had been published before.[14] Follow-up echocardiography was done before discharge and 3 to 6 months after discharge. Participants with potential combination of PT and ET, which could not be clearly separated, and patients with missing data related to the trigger mechanism were excluded from the analysis (n=10). The study was conducted according to Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before inclusion in the registry, which meets the requirements of the respective local ethics committees. Afterwards, all data were anonymously transferred into the registry.

Outcome Variables

For the current analysis, the study group was divided into 3 subgroups, including patients with NT, PT, and ET. Baseline characteristics and in-hospital complication were analyzed separately according to these subgroups. In-hospital complications were defined as death, cardiogenic shock, pulmonary edema, or stroke and evaluated separately and as a combined end point. The detailed definitions of the specific in-hospital complications have already been published.[14]

In addition, all-cause mortality was assessed during long-term follow-up with a median follow-up time of 487 days (interquartile range [IQR], 86–1551 days). These data were collected through regular outpatient visits, medical records, and telephone interviews with patients, family members, and treating physicians.

Statistical Analysis

The statistical analysis was performed with IBM SPSS Statistics 27.0. Categorical variables were examined using Chi-squared test or Fisher exact test and are expressed as numbers and percentages. Continuous variables were analyzed using Kruskal–Wallis tests and are expressed as median with IQR. Differences in mortality rates between the 3 trigger groups were tested by means of the log-rank test. Kaplan–Meier curves illustrate the mortality rate graphically. Influencing factors on in-hospital complications were analyzed using binary and multivariable stepwise forward logistic regression. Only significant variables from the univariate analysis were included in the multivariable tests. The results of these logistic regressions are presented as odds ratios (ORs) and 95% CI. Similarly, univariate and stepwise multivariable Cox regression models of all significant variables in the univariate analysis were performed to determine independent predictors of long-term mortality, which are presented as hazard ratios (HRs) with 95% CI. A 2-sided *P* value <0.05 was classified as statistically significant.

RESULTS

Trigger-Specific Comparison of Baseline Characteristics

A total of 2482 patients were included in this study, consisting of 910 patients (36.7%) with an ET, 855 patients (34.4%) with a PT, and 717 patients (28.9%) with NT. Patients with an ET were significantly younger (NT: 74 years [IQR, 64–80 versus PT: 74 years [IQR, 66–81] versus ET: 70 years [IQR, 61–77], *P*<0.001) and less frequently men (NT: 10.6% versus PT: 18.5% versus ET: 5.9%; *P*<0.001). Diabetes (NT: 18.1% versus PT: 23.4% versus ET: 16.5%; *P*=0.001), obesity (NT: 18.4% versus PT: 18.3% versus 13.1%; *P*=0.008), atrial fibrillation (NT: 16.9% versus PT: 18.3% versus ET: 11.6%; *P*=0.001), malignancy (NT: 13.4% versus PT:19.6% versus ET: 10.6%; *P*<0.001), pulmonary disease (NT: 12.0% versus PT: 23.7% versus ET: 10.6%; *P*<0.001), and neurologic disorders (NT: 17.7% versus PT: 23.3% versus ET: 13.1%; *P*<0.001) could be observed significantly less frequently in patients with an ET, whereas coronary artery disease (NT: 8.2% versus PT: 8.3% versus ET: 11.7%; *P*=0.033) was more often seen in these patients.

Furthermore, several significant differences in the clinical presentation could be observed (Table 1). Patients with ET reported more often chest pain (NT: 63.4% versus PT: 38.4% versus ET: 77.0%; *P*<0.001), but, in contrast, had the lowest proportion of patients with dyspnea (NT: 37.4% versus PT: 43.3% versus ET: 27.2%; *P*<0.001). In addition, the proportion of patients with low Killip class on admission was also highest in the ET group (NT: 74.1% versus PT: 66.3% versus ET: 81.4%; *P*<0.001).

When considering the left ventricular ejection fraction (LVEF), only the initial assessment showed significantly lower values in patients with PT (NT: 40% [IQR, 35–50], PT: 38% [IQR, 30–45] versus ET: 40% [IQR, 35–45]; *P*<0.001). This difference was no longer apparent at follow-up (*P*=0.325).

Moreover, significant differences in medication at discharge were identified. Aspirin (NT: 59.2% versus PT: 52.1% versus ET: 61.3%; *P*=0.001), beta-blocker (NT: 72.3% versus PT: 65.2% versus ET: 77.6%; *P*<0.001), angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor (AT-R) blocker (NT: 70.7% versus PT: 63.3% versus ET: 73.6%; *P*<0.001), and statins (NT: 54.6% versus PT: 45.5% versus ET: 57.2%; *P*<0.001) were most frequently taken by patients with ET and least frequently by patients with PT. In contrast, patients with PT took diuretics significantly more often compared with the other groups (NT: 32.8% versus PT: 39.2% versus ET: 29.5%; *P*=0.003). Oral anticoagulation was prescribed most frequently in patients with PT (NT: 20.3% versus PT: 18.2% versus ET: 14.4%; *P*=0.036).

In-Hospital Complications and Long-Term Outcomes

In-hospital course and long-term outcome were also analyzed separately by trigger mechanism. Significant differences were found in almost all variables (Table 2). The combined end point for in-hospital complication (*P*<0.001) as well as all individual complications (death [*P*<0.001], cardiogenic shock [*P*<0.001], pulmonary edema [*P*=0.013], stroke [*P*<0.001]) could be seen less frequently in patients with an ET and, in contrast, were mostly seen in the group of patients with PT (Table 2). Patients with ET also had the shortest length of stay in hospital (NT: 7 days [5, 10], PT: 8 days [5, 13], ET: 6 days [4, 8], *P*<0.001). Only mechanical circulatory support showed no statistically significant difference. The association between trigger mechanism and prognosis was also confirmed in the 5-year survival analysis (Figure, *P*<0.001). Long-term mortality analysis revealed better outcomes for patients with an ET compared with those with a PT or NT. A follow-up with respect to the recurrence rate was available in 844 patients. Overall, TTS recurrence was documented in 31 patients (3.7%) at a

Table 1. Baseline Clinical Characteristics

Variable	All patients (n=2482)	No trigger (n=717)	Physical trigger (n=855)	Emotional trigger (n=910)	*P* value
Age, y	72 (63–79)	74 (64–80)	74 (66–81)	70 (61–77)	<0.001‡
Male sex	285/2482 (11.5)	76/717 (10.6)	158/855 (18.5)	51/910 (5.9)	<0.001‡
Cardiovascular risk factors					
Hypertension	1684/2473 (68.1)	511/717 (71.3)	574/850 (67.5)	599/906 (66.1)	0.079
Diabetes	478/2473 (19.3)	130/717 (18.1)	199/851 (23.4)	149/905 (16.5)	0.001‡
Hypercholesterolemia	984/2333 (42.2)	290/682 (42.5)	314/791 (39.7)	380/860 (44.2)	0.178
Current smoking	439/2473 (17.8)	133/717 (18.5)	159/851 (18.7)	147/905 (16.2)	0.327
Obesity*	351/2137 (16.4)	114/620 (18.4)	134/733 (18.3)	103/784 (13.1)	0.008‡
Comorbidity					
Coronary artery disease	204/2148 (9.5)	52/635 (8.2)	59/715 (8.3)	93/798 (11.7)	0.033‡
Atrial fibrillation	344/2227 (15.4)	110/650 (16.9)	140/766 (18.3)	94/811 (11.6)	0.001‡
Malignancy	310/2132 (14.5)	80/599 (13.4)	146/744 (19.6)	84/789 (10.6)	<0.001‡
Pulmonary disease	340/2182 (15.6)	73/609 (12.0)	181/765 (23.7)	86/808 (10.6)	<0.001‡
Neurologic disorder	358/1985 (18.0)	99/560 (17.7)	165/708 (23.3)	94/717 (13.1)	<0.001‡
Psychiatric disorder	261/1958 (13.3)	73/541 (13.5)	77/673 (11.4)	111/744 (14.9)	0.157
Clinical presentation					
Chest pain	1326/2213 (59.9)	407/642 (63.4)	289/753 (38.4)	630/818 (77.0)	<0.001‡
Dyspnea	791/2212 (35.8)	240/641 (37.4)	326/753 (43.3)	225/818 (27.2)	<0.001‡
Killip class at admission					<0.001‡
1	1839/2482 (74.1)	531/717 (74.1)	567/855 (66.3)	741/910 (81.4)	
2	233/2482 (9.4)	75/717 (10.5)	90/855 (10.5)	68/910 (7.5)	
3	182/2482 (7.3)	53/717 (7.4)	77/855 (9.0)	52/910 (5.7)	
4	228/2482 (9.2)	58/717 (8.1)	121/855 (14.2)	49/910 (5.4)	
ST-segment change	1757/2146 (81.9)	509/617 (82.5)	590/724 (81.5)	658/805 (81.7)	0.886
Ballooning pattern†					0.331
Apical	2129/2481 (85.8)	625/717 (87.2)	714/855 (83.5)	790/909 (86.9)	
Midventricular	296/2481 (11.9)	78/717 (10.9)	119/855 (13.9)	99/909 (10.9)	
Basal	48/2481 (1.9)	12/717 (1.7)	20/855 (2.3)	16/909 (1.8)	
Focal	8/2481 (0.3)	2/717 (0.3)	2/855 (0.2)	4/909 (0.4)	
Initial LVEF (%)	40 (33–45)	40 (35–50)	38 (30–45)	40 (35–45)	<0.001‡
Follow-up LVEF (%)	60 (55–65)	60 (55–64)	60 (55–64)	60 (55–65)	0.325
Discharge medication					
Aspirin	1264/2196 (57.6)	393/664 (59.2)	386/741 (52.1)	485/791 (61.3)	0.001‡
Dual antiplatelet therapy	169/1630 (10.4)	54/524 (10.3)	62/555 (11.2)	53/551 (9.6)	0.698
Oral anticoagulation	356/2011 (17.7)	125/617 (20.3)	127/696 (18.2)	104/698 (14.4)	0.036‡
Beta-blocker	1503/2092 (71.8)	456/631 (72.3)	458/702 (65.2)	589/759 (77.6)	<0.001‡
ACE inhibitor/AT-R blocker	1532/2213 (69.2)	472/668 (70.7)	470/743 (63.3)	590/802 (73.6)	<0.001‡
Aldosterone antagonist	127/1631 (7.8)	46/524 (8.8)	46/555 (8.3)	35/552 (6.3)	0.284
Diuretic	538/1591 (33.8)	171/522 (32.8)	209/533 (39.2)	158/536 (29.5)	0.003‡
Statin	1147/2187 (52.4)	359/658 (54.6)	336/739 (45.5)	452/790 (57.2)	<0.001‡

Data are presented as number (percentage) of patients and median (interquartile range). ACE indicates angiotensin-converting enzyme; AT-R, angiotensin receptor; and LVEF, left ventricular ejection fraction.

*Defined as body mass index ≥30 kg/m^2.

†One patient exhibited isolated right ventricular ballooning.

‡Numbers indicate a significant difference.

median follow-up of 824 days (IQR, 118–1672 days). A total of 83.9% (26 of 31 patients) of these patients were women. In the initial event, stressful triggers could be documented in 21 patients (67.7%), whereas NT could be identified in 7 patients (22.6%). Trigger documentation was missing in 3 patients.

Table 2. In-Hospital Course and Long-Term Outcome

Variable	All patients (n=2482)	No Trigger (n=717)	Physical Trigger (n=855)	Emotional Trigger (n=910)	*P* value
In-hospital complication*	477/2482 (19.2)	135/717 (18.8)	232/855 (27.1)	110/910 (12.1)	<0.001†
In-hospital death	77/2482 (3.1)	24/717 (3.3)	42/885 (4.9)	11/910 (1.2)	<0.001†
Pulmonary edema	198/2482 (8.0)	59/717 (8.2)	84/855 (9.8)	55/910 (6.0)	0.013†
Cardiogenic shock	229/2482 (9.2)	59/717 (8.2)	121/855 (14.2)	49/910 (5.4)	<0.001†
Catecholamine therapy	216/2255 (9.6)	59/671 (8.8)	114/784 (14.5)	43/800 (5.4)	<0.001†
Mechanical circulatory support	41/2364 (1.7)	11/701 (1.6)	16/805 (2.0)	14/858 (1.6)	0.791
Stroke	48/2173 (2.2)	11/619 (1.8)	30/760 (3.9)	7/794 (0.9)	<0.001†
Length of stay in hospital, d	7 (5–10)	7 (5–10)	8 (5–13)	6 (4–8)	<0.001†
Long-term mortality	335/2274 (14.7)	94/651 (14.4)	170/788 (21.6)	71/835 (8.5)	<0.001†

Data are presented as number (percentage) of patients and median (interquartile range).
P values were calculated for the comparison between all types of trigger mechanism.
*Death, cardiogenic shock, pulmonary edema, or stroke.
†Numbers indicate a significant difference.

Predictors for In-Hospital Complications and Long-Term Mortality

Table 3 shows the results of the binary and multivariable logistic regression analyses for in-hospital complications. In univariate regression analysis, increasing age (*P*<0.001), male sex (*P*<0.001), diabetes (*P*<0.001), atrial fibrillation (*P*<0.001), malignancy (*P*=0.039), pulmonary disease (*P*<0.001), neurologic disease (*P*<0.001), chest pain (*P*<0.001), dyspnea (*P*<0.001), Killip class at admission (*P*<0.001), apical ballooning (*P*=0.015), initial LVEF (*P*<0.001), and a PT of TTS (*P*<0.001) showed a significant influence on in-hospital complications. All significant variables were analyzed in a multiple stepwise binary regression model. In this multivariable analysis, a neurologic disorder (*P*=0.002), Killip class at admission (*P*<0.001), initial LVEF (*P*=0.002) and a PT (*P*=0.016) proved to be independent predictors of in-hospital complications.

We also performed this analysis for predictors of long-term mortality (Table 4). In univariate Cox regression analysis increasing age (*P*<0.001), male sex (*P*<0.001), hypertension (*P*=0.017), diabetes (*P*<0.001), atrial fibrillation (*P*<0.001), malignancy (*P*<0.001), pulmonary disease (*P*<0.001), neurologic disease (*P*<0.001), chest pain (*P*<0.001), dyspnea (*P*<0.001), Killip class at admission (*P*<0.001), apical ballooning (*P*=0.004), initial LVEF (*P*<0.001), follow-up LVEF (*P*<0.001), aspirin (*P*<0.001), a PT for TTS (*P*<0.001), beta-blocker (*P*<0.001), ACE inhibitor/AT-R blocker (*P*<0.001) and a diuretic medication (*P*=0.002) had a significant impact on long-term survival. Again, all of these significant variables were analyzed in a stepwise multivariable model. In this model, increasing age (*P*<0.001), male sex (*P*=0.007), diabetes (<0.001), malignancy (*P*=0.002), chest pain (*P*=0.035), a neurological disorder (*P*<0.001) and a treatment with ACE inhibitor/AT-R blocker (*P*=0.027) were confirmed as independent predictors of long-term mortality.

DISCUSSION

This international, large, registry cohort study shows that patients with an ET of TTS have better clinical baseline conditions and a lower rate of in-hospital complications compared with patients with PT or NT. The lower prevalence of in-hospital complications was confirmed when considered as a combined end point as well as in the analysis of all individual variables. In addition, patients with ET also had lower long-term mortality rates compared with patients with PT or NT. We were also able to demonstrate that a neurologic disorder, Killip class at admission, a lower initial LVEF and a PT proved to be independent predictors of a higher risk for in-hospital complications. Moreover, increasing age, male sex, diabetes, malignancy, and a neurological disorder were associated with an increased risk of long-term mortality, whereas chest pain and a treatment with ACE inhibitors/AT-R blocker were identified as independent predictors for a lower risk of long-term mortality.

Emotional events seem to play an important role in the pathogenesis of TTS. While former studies were mainly based on the idea of a "broken heart syndrome" caused by a negative emotional event, recent trials also implement the importance of positive emotional events as triggers of TTS[14] as well as physical events and patients without any identifiable trigger.[12,16] In this context, patients with ET seem to have a better prognosis compared with patients with other causes for the occurrence of TTS. Nevertheless, the reason for the difference in mortality remains unclear. The increased mortality rate in patients with PT may be attributable to the underlying disease itself and may have a negative

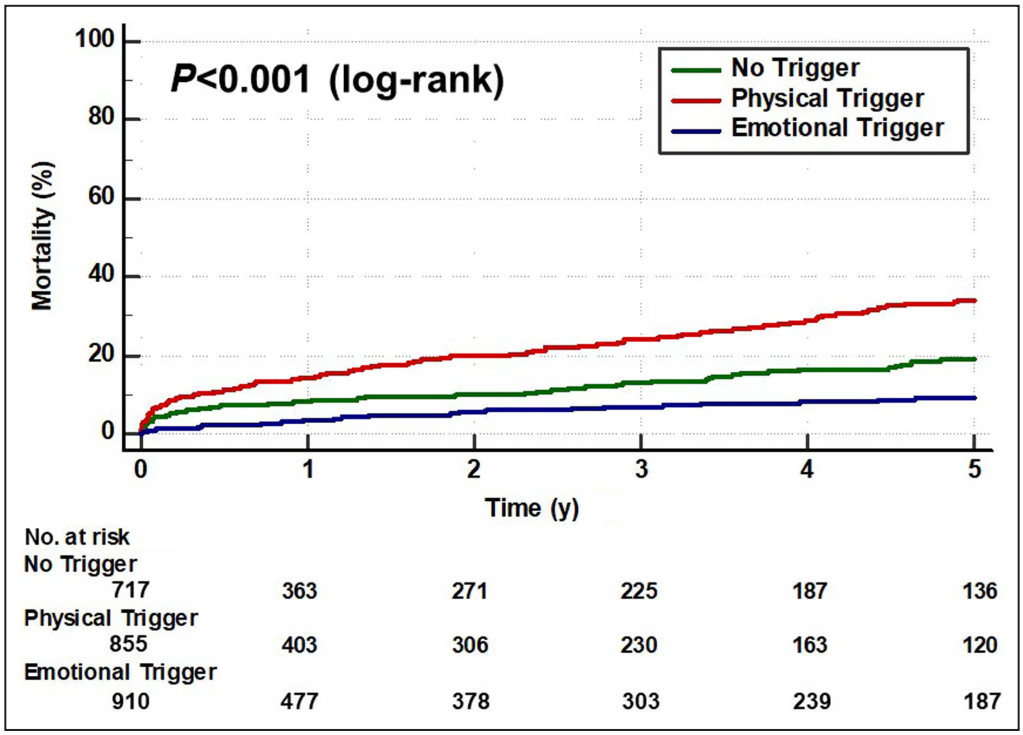

Figure. Study flow diagram.

effect on prognosis. Nevertheless, the release of catecholamines seems to play also an important role in the pathophysiology of TTS.[17,18] Thus, it remains conceivable that in the context of an emotional event, a sudden catecholamine surge has a different effect than the chronic catecholamine release in the context of a PT.[17] Study data also suggest that a failure of transmitter inactivation at postfunctional receptors with aging would increase neural signaling and could trigger adverse stress-induced cardiovascular events in the presence of myocardial disease.[19] Therefore, considering the significantly higher age in patients with PT and NT, age-related changes in neuronal catecholamine uptake must also be considered. Further studies should address this issue. Overall, our data confirm other study results demonstrating a better outcome in patients with ET compared with patients with a PT or NT of TTS.[12,16] Despite the fact of a known association between trigger mechanism and outcome, the reason for the difference in mortality rates still remains unclear. However, with respect to the baseline characteristics, significant differences between trigger groups could be observed. Overall, the majority of patients in the study were women with a mean age of 72 years. This is consistent with former study results showing a predominance of the female sex and similar mean age of diagnosis.[20–22] On the other hand, there was a significant difference in the proportion of sexes when considering separate trigger factors. Thus, patients with ET were significantly more likely to be women than patients with PT or no identifiable trigger. This result is in line with other study data choosing an equal categorization of trigger factors[12] or at least similar criteria.[16,23] On the other hand, sex could not be confirmed as an independent predictor. Previous analyses of this registry demonstrated that male sex remained independently associated with both in-hospital and long-term mortality.[24] However, the poor long-term prognosis for these patients could not be confirmed after propensity matching.[24] This might suggest that sex influence the type of triggering factor, but in contrast, it does not directly predict the long-term prognosis. Overall, baseline characteristics of our study population were similar to other study results in terms of mean age and predominance of female sex.

In addition, more favorable clinical conditions were seen in the patients with ET compared with patients with PT or NT. In our trial, patients with ET were significantly younger and important comorbidities such as diabetes, obesity, atrial fibrillation, malignancy, pulmonary disease, and neurologic disorders were observed less frequently in these patients. Study data indicate that these comorbidities influence the outcome of patients suffering from TTS.[13] This aspect was also reflected in our survival analysis. Patients with PT or NT of TTS faced a higher mortality rate compared with patients with an ET (Figure). Therefore, these patients should receive particular consideration in clinical

Table 3. Predictors for In-Hospital Complications

Variable	Univariate		Multivariable	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age, y	1.02 (1.01–1.03)*	<0.001*	…	…
Male sex	2.36 (1.80–3.09)*	<0.001*	…	…
Hypertension	1.01 (0.81–1.25)	0.965		
Diabetes	1.74 (1.38–2.20)*	<0.001*	…	…
Hypercholesterolemia	0.93 (0.75–1.15)	0.495		
Current smoking	1.00 (0.77–1.30)	0.982		
Obesity	1.09 (0.82–1.45)	0.539		
Coronary artery disease	1.09 (0.76–1.57)	0.634		
Atrial fibrillation	2.64 (2.05–3.41)*	<0.001*	…	…
Malignancy	1.36 (1.02–1.81)*	0.039*	…	…
Pulmonary disease	1.62 (1.23–2.12)*	<0.001*	…	…
Neurologic disease	2.02 (1.56–2.63)*	<0.001*	2.78 (1.44–5.39)*	0.002*
Psychiatric disorder	1.21 (0.88–1.67)	0.232		
Chest pain	0.33 (0.26–0.41)*	<0.001*	…	…
Dyspnea	4.06 (3.25–5.07)*	<0.001*	…	…
Killip class at admission	19.64 (15.19–25.39)*	<0.001*	18.10 (12.57–26.06)*	<0.001*
ST-segment change	1.30 (0.97–1.76)	0.081		
Apical ballooning	1.48 (1.08–2.02)*	0.015*	…	…
Initial LVEF	0.92 (0.91–0.93)*	<0.001*	0.96 (0.93–0.98)*	0.002*
Physical trigger	2.11 (1.73–2.59)*	<0.001*	2.03 (1.14–3.59)*	0.016*

Predictors for in-hospital complications in logistic regression analysis. LVEF indicates left ventricular ejection fraction.
*Significant predictors. The multivariable model included only significant predictors in univariable analysis.

follow-up evaluation. The fact that in-hospital complications were also higher in patients without an ET (Table 2) emphasizes the awareness of this subset of patients with TTS. In addition, despite the limited number of hospital beds in times of the SARS-CoV-2 pandemic, consideration should be given to monitoring these patients with PT as inpatients for longer periods of time.

Although patients with a PT of TTS had significantly lower LVEF on admission, it is noticeable that a corresponding heart failure therapy with beta-blockers and ACE inhibitors /AT-R receptor blockers was administered significantly less frequently at discharge. The reasons for this remain speculative. It is possible that relevant comorbidities limited the use of the medication. On the other hand, diuretics were significantly more frequently prescribed in patients with PT at discharge, which might have been a consequence of the higher Killip class at admission and the subsequent necessity for diuretic therapy. In summary, however, despite the medication differences, there was no significant difference in follow-up LVEF and, therefore, the difference in medication had no effect on LVEF over time.

In-hospital mortality in our study cohort was 3.1%, which is in line with other study results showing similar in hospital mortality rates.[22,25] Nevertheless, data regarding in-hospital mortality vary significantly between 0% and 12.2%.[17,20,26–28] In this context, a direct comparison between the different study results is limited because of different baseline characteristics with, for example, a greater amount of patients with a PT.[17] Overall, however, this highlights the fact that TTS is not a purely benign illness, but a disease with a possible fatal outcome. In addition, the general complication rate in our study cohort was also significantly high at 19.2%, with a cardiogenic shock rate of almost 10% in all patients with TTS. These complications occurred especially in patients with PT and highlight the potential critical clinical course within this subgroup.

Overall, the majority of patients with TTS seem to have a quite favorable outcome, however, study results like our data consistently show a proportion of patients with critical course of the disease. Therefore, short- and long-term prediction of complications or adverse events can be useful to assess risk profiles.[29] We evaluated in-hospital complications as well as short-term and long-term mortality in patients suffering from TTS. In our cohort, a neurological disease, a higher Killip class at admission, a lower LVEF on admission and a PT proved to be independent predictors of in-hospital clinical complications. This is in line with other study results showing similar predictors of in-hospital complications.[22] For example, study results of 1750

Table 4. Predictors for Long-Term Mortality

	Univariate		Multivariable	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age, y	1.07 (1.05–1.08)*	<0.001*	1.08 (1.05–1.11)*	<0.001*
Male sex	2.24 (1.69–2.95)*	<0.001*	2.26 (1.25–4.10)*	0.007*
Hypertension	1.36 (1.06–1.74)*	0.017*	…	…
Diabetes	2.26 (1.78–2.84)*	<0.001*	2.51 (1.54–4.08)*	<0.001*
Hypercholesterolemia	1.02 (0.80–1.28)	0.892		
Current smoking	0.77 (0.58–1.03)	0.081		
Obesity	0.81 (0.59–1.12)	0.199		
Coronary artery disease	1.55 (1.08–2.23)*	0.019*	…	…
Atrial fibrillation	2.39 (1.85–3.08)*	<0.001*	…	…
Malignancy	2.46 (1.89–3.20)*	<0.001*	2.37 (1.37–4.11)*	0.002*
Pulmonary disease	2.17 (1.66–2.84)*	<0.001*	…	…
Neurologic disease	2.29 (1.78–2.93)*	<0.001*	2.38 (1.50–3.80)*	<0.001*
Psychiatric disorder	1.05 (0.73–1.49)	0.809		
Chest pain	0.39 (0.31–0.50)*	<0.001*	0.61 (0.38–0.96)*	0.035*
Dyspnea	2.04 (1.60–2.61)*	<0.001*	…	…
Killip class at admission	1.70 (1.56–1.84)*	<0.001*	…	…
ST-segment change	1.29 (0.90–1.84)	0.161		
Apical ballooning	1.66 (1.18–2.34)*	0.004*	…	…
Initial LVEF	0.95 (0.94–0.96)*	<0.001*	…	…
Follow-up LVEF	0.95 (0.94–0.97)*	<0.001*	…	…
Aspirin	0.64 (0.51–0.82)*	<0.001*	…	…
Dual antiplatelet therapy	1.11 (0.76–1.62)	0.578		
Oral anticoagulation	1.32 (0.97–1.79)	0.079		
Beta-blocker	0.63 (0.50–0.81)*	<0.001*	…	…
ACE inhibitor/AT-R blocker	0.53 (0.42–0.67)*	<0.001*	0.58 (0.36–0.94)*	0.027*
Aldosterone antagonist	0.93 (0.54–1.61)	0.795		
Diuretic	1.61 (1.20–2.16)*	0.002*	…	…
Statin	0.87 (0.69–1.10)	0.255		
Physical trigger	2.40 (1.93–2.97)*	<0.001*	…	…

Univariable and multivariable Cox regression analysis of predictors for long-term mortality. LVEF indicates left ventricular ejection fraction.
*Significant predictors. The multivariable model included only significant predictors in univariable analysis.

patients with TTS show that the LVEF on admission, physical stress, as well as neurological or psychiatric disease were independent predictors for in-hospital complications. However, in contrast to our study, the Killip classification at admission was not considered in this trial. Overall, the association between Killip class on admission and outcome in patients with TTS is not surprising, since this aspect has been described in several studies in the past.[30–32] However, to our best knowledge, this is the first trial demonstrating such a high association between in-hospital complications and Killip classification on admission. This might be attributable to the fact that previous studies tended to focus on long-term prognosis or had a smaller study sample size.[30–32]

When considering variables for long-term outcome, we were able to identify age, male sex, diabetes, malignant disease, neurological disease, chest pain, and treatment with ACE inhibitors/AT-R blockers as independent predictors for long-term mortality in line with former study results.[22,33–36] It is noteworthy that initial chest pain is the only clinical predictor that appears positive. This association was also shown when considering predictors of in-hospital complications, whereby a statistically significant level could only be reached in the univariate analysis. The exact reason for the positive effect remains speculative. It is possible that chest pain leads to earlier cardiac catheterization, resulting in earlier correct diagnosis and also earlier initiation of heart failure therapy. However, since the time from clinical presentation to cardiac catheterization was not captured in the current study, further analyses are needed. In the current publication, we were also able to extend the evidence on the topic of recurrence rates in patients with TTS by including a larger patient collective, thus also confirming the results of previous

publications.[37] Because of the overall limited data, a large statistical variance between 1% and 11.4% in single-center studies and meta-analyses had been estimated.[2,3,38–41] Despite the fact that previous studies have examined the recurrence rate of TTS, these studies were limited by a single-center character and a low number of patients and variable information. In contrast, our study investigates the aspect of TTS recurrence in the context of an international, multicenter trial. On the other hand, our results are limited because of the missing data in a significant number of patients with TTS and, therefore, should be confirmed in further studies.

Limitations

Our results are limited by the nature of a nonrandomized observational registry, but, in contrast, this is one of the largest cohorts in the field. Some static aspects also have to be considered in the interpretation of the study results. For example, we cannot exclude the possibility that country or center-specific factors had an impact on the study results. On the other hand, TTS therapy is a standard therapy for heart failure with currently established medications. In addition, no center had a specific therapy option available, which was not available to the other sites. Furthermore, no sensitivity analysis of the regression analysis was performed. Such an analysis would have emphasized the robustness of the statistical analysis. On the other hand, the primary analysis is based on one of the largest data sets of patients with TTS. Therefore, the validity of the primary conclusion should not be generally questioned. Hemodynamic and laboratory parameters, such as catecholamines, also seem to have an impact on outcome in patients with TTS. These were not assessed in the current study and should be considered in further research. On the other hand, the Killip classification on admission is presented in the current study, which gives indirect information about the hemodynamic situation. In addition, the length of clinical follow-up varied significantly among patients and participating sites. Although our study reveals some interesting aspects in patients with TTS with different trigger mechanisms, it cannot provide insights into the exact pathophysiological mechanisms. These aspects need to be investigated in future experimental studies. In addition, the exact cause of death was not documented. It remains to be assumed that cardiac causes are leading in the short-term outcome, whereas noncardiac diseases become more relevant for long-term outcome.

CONCLUSIONS

In this large international, multicenter registry trial, patients with an ET of TTS had better clinical baseline conditions and a lower rate of in-hospital complications compared with patients with PT or NT. In addition, patients with ET also had lower long-term mortality rates compared with patients with PT or NT. Therefore, these patients should be closely monitored in the clinical follow-up. Neurological disorder, Killip class at admission, initial LVEF, and a PT proved to be independent predictors of in-hospital complications, whereas increasing age, male sex, diabetes, malignancy, a neurological disorder, chest pain, and a treatment with ACE inhibitor/AT-R blocker were identified as independent predictors of long-term mortality.

ARTICLE INFORMATION

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