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Assessment of the German and Italian Stress Cardiomyopathy Score for Risk Stratification for In-hospital Complications in Patients With Takotsubo Syndrome

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IMPORTANCE Takotsubo syndrome (TTS) is an acute, reversible heart failure syndrome featured by significant rates of in-hospital complications. There is a lack of data for risk stratification during hospitalization.

OBJECTIVE To derive a simple clinical score for risk prediction of in-hospital complications among patients with TTS.

DESIGN, SETTING, AND PARTICIPANTS In this prognostic study, 1007 consecutive patients were enrolled in the German and Italian Stress Cardiomyopathy (GEIST) registry from July 1, 2007, through December 31, 2017, and identified as the derivation cohort; 946 patients were enrolled in the Spanish Registry for Takotsubo Cardiomyopathy (RETAKO) as the external score validation. An admission risk score was developed using a stepwise multivariable regression analysis from 2 registries. Data analysis was performed from March 1, 2018, through July 31, 2018.

MAIN OUTCOMES AND MEASURES In-hospital complications were defined as death, pulmonary edema, need for invasive ventilation, and cardiogenic shock. Four variables were identified as independent predictors of in-hospital complications and were used for the score: male sex, history of neurologic disorder, right ventricular involvement, and left ventricular ejection fraction (LVEF).

RESULTS Of the 1007 patients enrolled in the GEIST registry, 107 (10.6%) were male, with mean (SD) age of 69.8 (11.4) years. Overall rate of in-hospital complications was 23.3% (235 of 1007) (death, 4.0%; pulmonary edema, 5.8%; invasive ventilation, 6.4%; and cardiogenic shock, 9.1%). The GEIST prognosis score was derived by providing 20 points each for male sex and history of neurologic disorders and 30 points for right ventricular involvement and then subtracting the value in percent of LVEF (decimal values between 0.15 and 0.70). Score accuracy on area under the receiver operating characteristic curve analysis was 0.71, with a negative predictive power of 87% with scores less than 20. External validation in the RETAKO population (124 [13.1%] male; mean [SD] age, 69.5 [14.9] years) revealed an area under the curve of 0.73 (P = .46 vs GEIST xderivation cohort). Stratification into 3 risk groups (<20, 20-40, and >40 points) classified 316 patients (40.9%) as having low risk; 342 (44.3%) as having intermediate risk, and 114 (14.8%) as having high risk of complications. The observed in-hospital complication rates were 12.7% for low-risk patients, 23.4% for intermediate-risk patients, and 58.8% for high-risk patients (P< .001 for trend). After 2.6 years of follow-up, patients with in-hospital complications had significantly higher rates of mortality than those without complications (40% vs 10%, P = .01).

CONCLUSIONS AND RELEVANCE The GEIST prognostic score may be useful in early risk stratification for TTS. High-risk patients with TTS may require an intensive care unit stay, and low-risk patients with TTS could be discharged within a few days. In-hospital complications in patients with TTS may be associated with increased risk of long-term mortality.

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Supplemental content

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Takotsubo syndrome (TTS) is an acute heart failure syndrome featured by transient and reversible left ventricular (LV) dysfunction.[1] The mechanism leading to the transient LV systolic dysfunction characteristic of TTS is still unclear; however, increased serum levels of catecholamines may be one of the main causes.[2]

Although considered for a long time to be a relatively benign condition, data[3] have shown high rates of in-hospital and adverse events at long-term follow-up among individuals with TTS. During hospitalization, approximately 25% of patients experience in-hospital complications, whereas the rate of subsequent major adverse cardiac and cerebrovascular events has been estimated to be 9.9% per year.[3] In a comparison of patients diagnosed with ST-segment elevation myocardial infarction, the mortality rate at 3-year follow-up was higher among patients with TTS (24.7% vs 15.1%).[4]

In-hospital complications during hospitalization for TTS are mainly represented by cardiovascular adverse events. The most common in-hospital complication is acute heart failure including pulmonary edema and cardiogenic shock[5,6]; however, in-hospital death and stroke are not rare, with a prevalence of about 5%. Moreover, life-threatening arrhythmias[7] and rare cases of ventricular septal rupture have also been described.[8]

Reported factors associated with in-hospital complications in previous TTS cohorts are right ventricular (RV) involvement, male sex, physical stressor, and diabetes.[3,9,10] However, data on in-hospital risk stratification are poor and mainly come from small, single-center study cohorts.

The aim of this study was to assess potential predictors of in-hospital complications in a large, international multicenter registry and to develop a simple clinical prognostic score to stratify the risk of in-hospital complications among patients with TTS at admission.

Key Points

Question Which patients with takotsubo syndrome should be considered at high risk for in-hospital complications?

Findings In this multicenter prognostic study of 1007 patients from the German and Italian Stress Cardiomyopathy (GEIST) registry and 946 patients from the Spanish Registry for Takotsubo Cardiomyopathy (for external validation), male sex, history of neurologic disorder, right ventricular involvement, and left ventricular ejection fraction were identified as predictors of in-hospital complications using the GEIST score, a score for prediction of in-hospital complications.

Meaning The findings suggest that evaluation of 4 clinical and echocardiographic variables may identify patients with takotsubo syndrome who have a high risk for in-hospital complications.

Methods

Study Population

This prognostic study included 1007 consecutive patients with TTS who were enrolled in a multicenter international registry (German and Italian Stress Cardiomyopathy [GEIST] registry) from July 1, 2007, through December 31, 2017. The study took place at 12 institutions in Italy and Germany (University Heart Center Lübeck, Germany; Heart Center Leipzig-University Hospital, Germany; University Medical Center Mannheim, Germany; Department of Cardiology, Asklepios Klinik-St Georg, Hamburg, Germany; Ospedali Riuniti, University Hospital of Foggia, Italy; Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy; San Paolo Hospital, Bari, Italy; Lorenzo Bonomo Hospital, Andria, Italy; University Hospital of Palermo, Italy; University Hospital of Rome Tor Vergata, Italy; University Hospital Umberto I-Lancisi-Salesi, Ancona, Italy; and San Giovanni di Dio Hospital, University of Cagliari, Cagliari, Sardinia, Italy). All patients gave written informed consent for participation in the GEIST registry. The current study received approval by the institutional review board of each participating institution. Data analysis was performed from March 1, 2018, through July 31, 2018.

Inclusion Criteria

All patients with suspected TTS underwent coronary and LV angiography. The diagnosis of TTS was based on the revised Mayo Clinic criteria: (1) transient hypokinesis, akinesis, or dyskinesis of the LV mid-segments, with or without apical involvement (the regional wall-motion abnormalities extend beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present); (2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and (4) absence of pheochromocytoma and myocarditis.[11]

Clinical and Echocardiographic Examination

All patients underwent clinical examination, and baseline characteristics, including age, sex, medical history, and type of triggering events or stressors, were recorded. Medical history, including history of neurologic disorders (cerebrovascular accidents, neurodegenerative disorders, and epilepsy), was also recorded. A 2-dimensional Doppler echocardiographic examination was performed at admission and then serially according to clinical condition. The LV ejection fraction (LVEF) was calculated using the Simpson biplane method from the apical 4-chamber and 2-chamber views.[12] The pattern of LV dysfunction was classified as follows: apical ballooning type (akinesia or dyskinesia of the LV apex), mid-ventricular ballooning type (akinesia or dyskinesia of the mid-ventricular LV segments), and basal type (akinesia or dyskinesia of the LV basal segments).[13] At 2 institutions, cardiac magnetic resonance imaging was also performed in patients without contraindications during hospitalization to confirm the diagnosis of TTS.[14]

Definition of Outcome

The primary clinical end point was in-hospital major cardiac adverse events, including death, pulmonary edema, need for invasive mechanical ventilation, and cardiogenic shock. Pulmonary edema was considered to be present in cases of respiratory distress and pulmonary rales due to pulmonary congestion, as confirmed by chest radiography, a respiratory rate of more than 20 breaths per minute, and an arterial hydrogen ion concentration greater than 45 nmol/L (pH, <7.35).[15]

Cardiogenic shock was considered to be present if a patient had a systolic blood pressure lower than 90 mm Hg for more than 30 minutes and clinical signs of pulmonary congestion and impaired organ perfusion, defined as at least 1 of the following: (1) altered mental status; (2) cold, clammy skin and extremities; (3) oliguria (urine output ≤30 mL per hour); or (4) arterial lactate level of 2 mmol/L or more (to convert to mg/dL, divide by 0.111).[16]

Statistical Analysis

Continuous variables were expressed as mean (SD) and compared with a *t* test or Mann-Whitney test as required. Categorical variables were presented as percentages and compared with a χ^2 or Fisher test as required. The Kolmogorov-Smirnov test was used to identify variables with normal distribution. Linear regression was assessed with a Pearson test. Logistic regression analysis was used to estimate the risk of in-hospital complications associated with clinical variables; odds ratio (ORs) and 95% CIs were also calculated.

First, variables significantly associated with in-hospital complications in univariable testing ($P < .10$) were further examined in multivariable analysis. Four variables remained statistically significantly associated with in-hospital complications. These variables constitute the score measures. Only patients with complete data sets for these 4 score candidate variables were considered for further testing. Regression coefficients were used to estimate the association of each variable with in-hospital complications and to derive a clinical score for the prediction of in-hospital complications. Three categories of risk (low, intermediate, and high) were identified and compared with logistic regression and ORs. The accuracy of the score was assessed with receiver operating characteristic curves analysis and validated in an adjunctive population of 946 patients from the Spanish Registry for Takotsubo Cardiomyopathy (RETAKO).[17] The final model was tested for goodness of fit using the Hosmer-Lemeshow statistic. $P < .05$ (2-tailed) was considered as statistically significant.

Results

Of the 1007 patients enrolled in the GEIST registry (107 [10.6%] male; mean (SD) age, 69.8 [11.4] years), 235 patients (23.3%) were excluded because of incomplete or insufficient data mainly owing to missing data concerning RV involvement and/or history of neurologic disorders. Of the 946 patients in the RETAKO registry (124 [13.1%] male; mean [SD] age, 69.5 [14.9] years), 117 (12.4%) were not included in the validation cohort for the same reasons. Consequently, the final derivation cohort consisted of 772 patients, and the validation cohort included 829 patients with complete clinical data (eFigure 1 in the Supplement). Baseline population features are summarized in **Table 1**. The in-hospital complication rate was 23.3% (235 of 1007 patients) in the GEIST cohort. Complications included death (4.0% [40]), pulmonary edema (5.8% [58]), invasive mechanical ventilation (6.4% [64]), and cardiogenic shock (9.1% [92]). Similarly, the in-hospital complication rate was 20.4% (193 of 946) in the RETAKO population, with death in 1.9% (18), pulmonary edema in 8.6% (81), invasive mechanical ventilation in 6.4% (61), and cardiogenic shock in 10.0% (95) (Table 1).

Table 1. Baseline Features and In-hospital Complications Among Patients Admitted for Takotsubo Syndrome in the GEIST and RETAKO Cohorts[a]

Characteristic	GEIST Derivation Cohort (n = 772)	RETAKO Validation Cohort (n = 829)
Age, mean (SD), y	69.9 (11.4)	69.9 (15.0)
Male sex	85 (11.0)	108 (13.0)
Cardiovascular risk factors		
Hypertension	540 (69.9)	531 (64.1)
Dyslipidemia	309 (40.0)	290 (35.0)
Diabetes	162 (21.0)	158 (19.1)
Smoking	170 (22.0)	216 (26.1)
Comorbidities		
Previous or chronic neurologic disorder	116 (15.0)	116 (14.0)
Cerebrovascular accidents	371 (48.1)	464 (56.0)
Neurodegenerative disease	270 (35.0)	265 (32.0)
Epilepsy	131 (17.0)	99 (11.9)
History of cancer	108 (14.0)	108 (13.0)
Clinical presentation		
Angina	417 (54.0)	531 (64.1)
Atypical chest pain	93 (12.0)	91 (11.0)
No chest pain	262 (33.9)	199 (24.0)
Dyspnea	247 (32.0)	348 (42.0)
Stressors		
Emotional	340 (44.0)	340 (41.0)
Physical	239 (31.0)	240 (29.0)
None	185 (24.0)	282 (34.0)
Echocardiographic features at admission		
LVEF, mean (SD), %	39.6 (9.9)	42.6 (11.9)
Ballooning type		
Apical	625 (81.0)	713 (86.0)
Mid-ventricular	131 (17.0)	91 (11.0)
Basal	15 (1.9)	25 (3.0)
Electrocardiogram features at admission		
ST-segment elevation	455 (59.0)	481 (58.0)
Negative T waves	401 (51.9)	307 (37.0)
Atrial fibrillation	116 (15.0)	66 (8.0)
In-hospital complications		
Total	178 (23.1)	166 (20.0)
Pulmonary edema	46 (6.0)	75 (9.0)
Invasive ventilation	46 (6.0)	53 (6.4)
Cardiogenic shock	69 (9.0)	83 (10.0)
Death	31 (4.0)	17 (20.5)

Abbreviations: GEIST, German and Italian Stress Cardiomyopathy; LVEF, left ventricular ejection fraction; RETAKO, Spanish Registry for Takotsubo Cardiomyopathy.

[a] Data are presented as number (percentage) of individuals unless otherwise indicated.

Table 2. Predictors of In-hospital Complications

	Univariable Analysis		Multivariable Analysis	
Variable	Odds Ratio (95% CI)	*P* Value	β (95% CI)	*P* Value
Left ventricular ejection fraction	0.93 (0.92 to 0.95)	<.001	−0.0088 (−0.0136 to −0.0039)	<.01
Right ventricular involvement	2.66 (1.70 to 4.18)	<.001	0.2850 (0.0788 to 0.4911)	<.01
History of neurologic disorders	2.44 (1.61 to 3.68)	<.001	0.1992 (0.0817 to 0.3167)	<.01
Dyspnea	2.41 (1.72 to 3.37)	<.001	NA	NA
Male	2.46 (1.61 to 3.75)	<.001	0.1807 (0.0307 to 0.3307)	.01
Chest pain	0.50 (0.35 to 0.70)	<.001	NA	NA
Atrial fibrillation	2.35 (1.57 to 3.50)	<.001	NA	NA
Lung disease	1.85 (1.25 to 2.74)	<.01	NA	NA

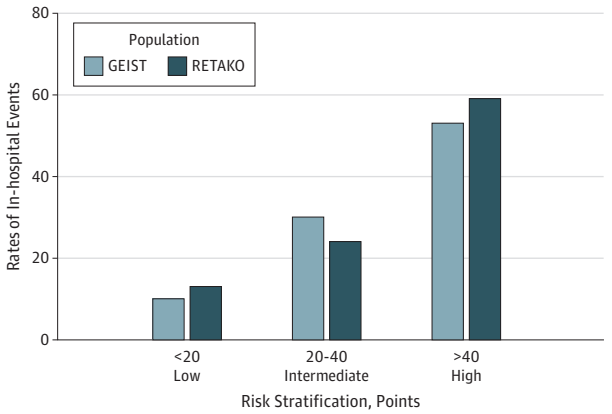
Abbreviation: NA, not applicable.

Table 3. Clinical Predictors for In-hospital Complications Included in the GEIST Score and Their Weighted Contribution

Variables in the GEIST Score	Points
Male sex	+20
History of neurologic disorders	+20
Right ventricular involvement	+30
LVEF (%)	−1 × LVEF (%)

Abbreviations: GEIST, German and Italian Stress Cardiomyopathy; LVEF, left ventricular ejection fraction (decimal values between 0.15-0.70).

Figure 1. Observed In-hospital Complications According to Risk Stratification in the German and Italian Stress Cardiomyopathy (GEIST) Registry and Spanish Registry for Takotsubo Cardiomyopathy (RETAKO) Validation Population



Derivation of the GEIST Prognosis Score

Variables included in the model were LVEF at admission; age; sex; dyspnea; chest pain; atrial fibrillation; RV involvement; apical, mid-, or basal ballooning; physical or emotional stressor; diabetes; neurologic disease; hypertension; ST-segment elevation at admission; and history of cancer.

In addition to several predictors (LVEF, RV involvement, history of neurologic disorders, dyspnea, male sex, chest pain, atrial fibrillation, and lung disease) of in-hospital complications in univariate logistic regression analysis (**Table 2**), the following variables were identified as independent predictors of in-hospital complications: LVEF (OR, 0.93; 95% CI, 0.92-0.95; *P* < .001), RV involvement (OR, 2.66; 95% CI, 1.70-4.18; *P* < .001), history of neurologic disorders (OR, 2.44; 95% CI, 1.61-3.68; *P* < .001), and male sex (OR, 2.46; 95% CI, 1.61-3.75; *P* < .001). According to the coefficients in multivariable regression analysis, the GEIST prognosis score was derived by attributing 20 each points for male sex and history of neurologic disorders and 30 points for RV involvement and then subtracting the value in percent of LVEF (expressed as a decimal) (**Table 3**). The score equation was the following for the probability of in-hospital complications: +20 points for male, +20 points for neurologic disorder, +30 points for RV involvement, and -0.15 to 0.70 for LVEF values.

Stratification into 3 risk groups (<20, 20-40, and >40 points) classified 316 of 772 patients (40.9%) as having low risk, 342 (44.3%) as having intermediate risk, and 114 (14.8%) as having high risk of complications. The observed complication rates were 12.7% (40 of 316) for low-risk patients, 23.4% (80 of 342) for intermediate-risk patients, and 58.8% (67 of 114) for high-risk patients (*P* < .001 for trend) (**Figure 1** and eTable in the Supplement). Patients in the intermediate group had an increased risk of in-hospital complications (OR, 2.11; 95% CI, 1.39-3.19; *P* < .001) compared with the low-risk group; the OR for in-hospital complications for the high-risk group vs low-risk group was 9.84 (95% CI, 5.97-16.20; *P* < .001).

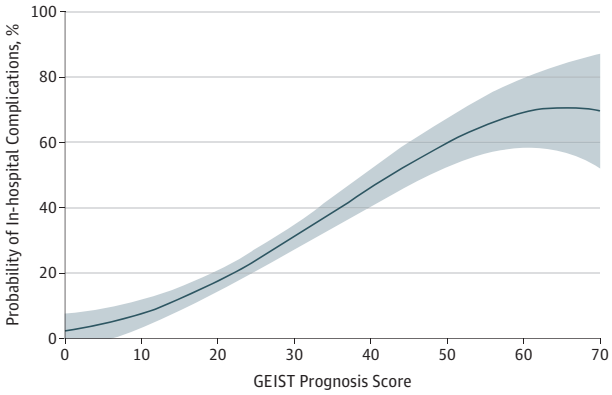
The GEIST prognosis score showed a good prediction of in-hospital complications (**Figure 2**) with an area under the curve (AUC) of 0.71 (95% CI, 0.68-0.75; *P* < .001) (eFigures 2-4 in the Supplement). In the receiver operating characteristic curve analysis, negative predictive power was 87% with score values less than 20. The AUC was 0.73 (95% CI, 0.61-0.82) for male patients and 0.70 (95% CI, 0.68-0.73) for female patients (eFigure 5 in the Supplement). Distribution of GEIST score values by sex is given in eFigure 6 in the Supplement.

The *P* value for GEIST score goodness of fit tested by use of the Hosmer-Lemeshow statistic was not significant (eFigure 7 in the Supplement). Calibration of the GEIST score in quintiles associated with in-hospital complications is provided in eFigure 8 in the Supplement).

Validation of the GEIST Score

Of the 829 patients with complete data in the validation cohort, 51.5% (427 of 829) were in the low-risk group, 39.1% (324 of 829) in the intermediate-risk group, and 9.4% (78 of 829)

Figure 2. Predicted Probability of In-hospital Complications During Admission for Takotsubo Syndrome According to German and Italian Stress Cardiomyopathy (GEIST) Prognosis Score



The curve shows the predicted probabilities for a given score. Line indicates predicted events, and shading indicates 95% CI.

in the high-risk group. In-hospital complication rates were 9.6% (41 of 427) in the low-risk group, 29.6% (96 of 324) in the intermediate-risk group, and 52.6 (41 of 78) in the high-risk group ($P < .001$) (Figure 1). The C statistic revealed a good discrimination of the GEIST score even in the validation cohort, with an AUC of 0.74 (95% CI, 0.70-0.77; $P < .001$) ($P = .46$ vs GEIST population) (eFigure 2 in the Supplement).

Long-term Follow-up

Sixty-two patients (6.3%) were lost to long-term follow-up. After a mean (SD) of 2.6 (2.0) years of follow-up, patients with in-hospital complications had statistically higher rates of mortality than patients without complications (40.1% [93 of 232 patients] vs 10.0% [65 of 647 patients]; $P = .01$).

Discussion

This was the first study, to our knowledge, to propose a simple clinical score for the prediction of in-hospital complications based on 4 clinical variables from a large multicenter international registry of patients with TTS. In this study, male sex, history of neurologic disorder, RV involvement, and LVEF were independent predictors of in-hospital complications and could be combined into a novel risk score. Furthermore, the newly developed GEIST prognosis score accurately stratified the risk of in-hospital complications among patients with TTS, and its performance was validated in an external cohort with good predictive value. Also, patients with TTS and in-hospital complications had high mortality rates at long-term follow-up.

Takotsubo syndrome is featured by a transient LV dysfunction and, during hospitalization, is associated with several complications. However, there is a paucity of data regarding in-hospital complications and how to promptly recognize and manage them. Several studies showed that TTS may have severe prognostic implications at long-term follow-up; 88% of patients with TTS had persisting heart failure symptoms and cardiac limitation on exercise testing in one study.[18] Despite recovery of LVEF, patients with previous TTS may present with an impaired cardiac energetic status.[18] A recent study[19] showed that chronic inflammation could also be present in patients with TTS; during the acute and subacute phase of TTS, higher serum levels of anti-inflammatory interleukins are present in TTS than in acute myocardial infarction.

Secondary forms of TTS, with a stressor represented by exacerbation of a comorbidity-like chronic obstructive pulmonary disease or kidney insufficiency, have been associated with a worse outcome at short- and long-term follow-up in other TTS cohorts.[20] However, in the present study, secondary forms of TTS were not associated with a higher risk of in-hospital complications.

In-hospital Complications in TTS

In-hospital complications among patients with TTS mainly consisted of acute heart failure, including cardiogenic shock and pulmonary edema, with an incidence ranging from 12% to 45%.[3,9,10] Cardiogenic shock is associated with an increased 28-day mortality (28.6% vs 4.1%)[21] and a need for prompt treatment (pharmacologic with levosimendan,[22] esmolol,[23] and catecholamines[24]) or early mechanical circulatory support. Left ventricular ejection fraction in one study[21] was the only significant predictor of cardiogenic shock. Age of more than 70 years, presence of a physical stressor, and LVEF less than 40% were found as predictors of acute heart failure in patients with TTS in the Mayo Clinic score.[5] The presence of 1 variable was associated with 28% risk of acute heart failure, 2 variables with 58% risk, and 3 variables with 85% risk.[5] Our proposed risk score is, to our knowledge, the first that targets not only heart failure but also other important in-hospital complications reflecting severe morbidity and mortality in TTS.

The in-hospital mortality rate for TTS was approximately 4.2%, with a higher rate among male patients (8.4% vs 3.6%; $P < .01$) and among patients with secondary TTS in another study.[25] A total of 81.4% of patients with in-hospital mortality had underlying critical illnesses in that study. In the present study, male patients had higher in-hospital mortality rates (9.3% vs 3.3%; $P = <.01$). However, differences between secondary TTS and primary or emotional TTS were not statistically significant (3.6% vs 2.7%; $P = .51$). Patients with TTS without a clear stressor had higher in-hospital mortality rates (6%).

Risk Stratification During TTS Hospitalization

A European consensus paper[1] defined high-risk patients with TTS as those 75 years or older with systolic blood pressure lower than 110 mm Hg, presence of pulmonary edema, LVEF less than 35%, LV outflow tract gradient more than 40 mm Hg, mitral regurgitation, and LV thrombi, whereas minor risk factors were biventricular involvement, persistent ST-segment elevation, or Q-wave at admission and physical stressors.

Several variables associated with in-hospital complications have also been previously reported. Templin et al[3] found that physical triggers, acute neurologic or psychiatric diseases, high troponin levels, and low LVEF at admission were independently associated with in-hospital complications. Murakami et al[26] found that, in a Japanese multicenter TTS reg-

istry, blood cell count and brain natriuretic peptide were independently associated with in-hospital complications.[26] In another registry, lower systolic blood pressure at admission, diabetes mellitus, and β-blocker use before admission were independently associated with in-hospital complications.[10]

In a German registry (n = 209),[27] patients with TTS who had complications were older (70 years vs 67 years), had faster heart rates (91 vs 83 bpm), had Q-waves on their admission electrocardiogram (36% vs 21%), and had a lower LVEF (47% vs 54%). On multivariate regression analysis, Q-waves at admission and LVEF of 30% or lower were independently associated with in-hospital complications.[27]

Echocardiography performed at admission could also stratify risk of complications among patients with TTS. Citro et al[6] found in a cohort of 227 patients that 3 echocardiographic measures (LVEF, E:e′ ratio, and reversible moderate to severe mitral regurgitation) were associated with major adverse cardiac events.

Our study is in line with previous reports and shows the importance of echocardiographic measures for risk stratification. Two of 4 measures included in the prognosis score were echocardiographic variables: LVEF and RV involvement. Our study further supports the concept that echocardiographic evaluation of both the LV and RV at hospital admission is crucial in patients with TTS. Right ventricular involvement in TTS has been proved in several studies to be associated with poor outcome at short- and long-term follow-up[28,29] and, in the present study, was associated with the highest risk scores (30 points vs 20 points for the other variables). Moreover, RV involvement was shown to be associated with a more severe impairment in LV systolic function.[30] Prognostic relevance of LVEF at admission instead plays a less marked role compared with RV involvement, and modulating the effects of other predictors included in the score may be useful in refining the risk stratification in addition to other GEIST score items.

Male sex was also associated with a poorer outcome in the GEIST registry. Male patients with TTS were younger than females, and physical stressors were more common among men than were emotional triggers. During hospitalization, male patients had a higher incidence of severe heart pump failure (defined as Killip Class>III) and need for cardiopulmonary supportive therapies.[31] Hormones, especially estrogens, may have a protective role, especially in female patients with TTS.[32]

History of neurologic disease was also associated with in-hospital complications. Neurologic diseases included cerebrovascular accidents, neurodegenerative disorders, and epilepsy. Acute neurologic disease, such as acute stroke or head trauma, were recorded as physical triggers for TTS and were not included in the proposed GEIST score.

These data further support the heart-brain connection as 1 potential pathophysiologic mechanism of TTS.[33] The potential associations between TTS and such conditions were heterogenous and were mainly associated with sympathetic upregulation or central autonomic dysfunction and increased circulating catecholamine levels.[27]

A recent brain imaging study showed substantial anatomic differences (reduced connectivity) between patients with TTS and healthy controls in the limbic network comprising the left amygdala, both hippocampi, left parahippocampal gyrus, left superior temporal pole, and right putamen, all of which were involved in the control of emotional processing, cognition, and the autonomic nervous system.[34]

In-hospital Complications and Long-term Follow-up

In-hospital complications may be associated with a worse outcome at long-term follow-up. In our study, patients with TTS who had in-hospital complications had higher mortality rates at 2.6 (±2) years follow-up (40% vs 10%; $P = .01$). In line with this high mortality rate, Stiermaier et al[4] reported a 24.7% mortality rate at 3-year follow-up.[4] Patients with in-hospital complications may have more comorbidities, such as neurologic disease and higher prevalence of biventricular involvement during hospitalization. This finding suggests that patients with TTS who had in-hospital complications may require a strict follow-up and that TTS is not a benign disease, as it has often been considered.

Clinical Implications of the GEIST Score

Categorization of patients with TTS according to the proposed GEIST score may serve as a tool for early clinical risk stratification that can be performed within the first days after hospital admission. All variables can easily be assessed and are readily available. We believe that it might also be helpful for clinical decision-making with respect to the selection of management strategies (eg, length of stay in the intensive care unit and hospital or supporting early discharge among low-risk patients).

Limitations

The GEIST score was derived from a multicenter observational registry in which data were collected from several different institutions. The accuracy of the score is appreciable and comparable with other clinical scores but does not exceed 70%, and some high-risk patients may be missed. However, the specificity of the score is appreciable and might help to facilitate clinical decisions in TTS.

Another limitation is that a certain number of patients were excluded from the analyses because of missing data regarding the score variables (23.3%), mainly owing to the lack of data concerning RV involvement and/or history of neurologic disorders. However, the GEIST and RETAKO registries are some of the largest existing TTS registries to date. Cardiac magnetic resonance imaging may represent the benchmark method to evaluate the presence of RV involvement in TTS; however, it was performed routinely only in 2 of 12 centers (288 of 1007 [28.6%] patients received cardiac magnetic resonance imaging).

Conclusions

The GEIST prognostic score, a simple score based on 4 clinical and echocardiographic variables, may be useful in early risk stratification of TTS. In-hospital complications among patients with TTS may be associated with increased risk of mortality during long-term follow-up.

ARTICLE INFORMATION

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