Journal of the American Heart Association

ORIGINAL RESEARCH

Age-Related Differences in Takotsubo Syndrome: Results From the Multicenter GEIST Registry

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BACKGROUND: The role of age in the short- and long-term prognosis of takotsubo syndrome (TTS) is controversial. The aim of the present study was to evaluate age-related differences and prognostic implications among patients with TTS.

METHODS AND RESULTS: In total, 2492 consecutive patients with TTS enrolled in an international registry were stratified into 4 groups (<45, 45–64, 65–74, and ≥75 years). The median long-term follow-up was 480 days (interquartile range, 83–1510 days). The primary outcome was all-cause mortality (in-hospital and out-of-hospital mortality). The secondary end point was TTS-related in-hospital complications. Among the 2479 patients, 58 (2.3%) were aged <45 years, 625 (25.1%) were aged 45 to 64 years, 733 (29.4%) were aged 65 to 74 years, and 1063 (42.6%) were aged ≥75 years. Young patients (<45 years) had a higher prevalence of men (from youngest to oldest, 24.1% versus 12.6% versus 9.7% versus 11.4%; $P<0.01$), physical triggers (46.6% versus 27.5%, 33.9%, and 38.4%; $P<0.01$), and non-apical forms of TTS (25.9% versus 23.7%, 12.7%, and 9%; $P<0.01$) than those aged 45 to 64, 65 to 74, and ≥75 years. During hospitalization, young patients experienced a higher rate of in-hospital complications (32.8% versus 23.4%, 27.4%, and 31.9%; $P=0.01$), but in-hospital mortality was higher in the older group (0%, 1.6%, 2.9%, and 5%; $P=0.001$). Long-term all-cause mortality was significantly higher in the older cohort (5.6%, 6.4%, 11.3%, and 22.3%; log-rank $P<0.001$), as was long-term cardiovascular mortality (0%, 0.9%, 1.9%, and 3.2%; log-rank $P=0.01$).

CONCLUSIONS: Young patients with TTS have a typical phenotype characterized by a higher prevalence of male sex, non-apical ballooning patterns, and in-hospital complications. However, in-hospital and long-term mortality are significantly lower in young patients with TTS.

REGISTRATION: URL: https://classic.clinicaltrials.gov/ct2/show/NCT04361994. Unique identifier: NCT04361994.

Key Words: age variation ■ short- and long-term outcome ■ takotsubo syndrome

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This article was sent to Tochukwu M. Okwuosa, DO, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.030623

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Takotsubo syndrome is uncommon in young patients.
- Young patients with Takotsubo have the highest prevalence of male sex, non-apical-ballooning patterns.

What Are the Clinical Implications?

- Young patients have a higher rate of in-hospital complications.
- Young patients with Takotsubo have lower in-hospital and long-term mortality rates than older patients.

Nonstandard Abbreviation and Acronym

TTS	takotsubo syndrome

Since the description of takotsubo syndrome (TTS) in 1990, many reports have been published.[1] Initially, TTS was described as acute reversible left ventricular (LV) heart failure and included several ballooning patterns, most often the apical TTS form.[2] Recent reports have shown that TTS may also affect the right ventricle (RV).[3–5]

Several complications of TTS have been reported (eg, cardiogenic shock, LV outflow tract obstruction, need for inotropes, stroke, malignant arrhythmias, and atrial fibrillation).[6–9] In addition, recurrence of TTS has been reported in up to 4% of patients.[10]

Age is one of the most important risk factors for worse cardiovascular and oncological outcomes.[11–13] Whether this is also true for TTS is controversial. In support of age as a predictor of adverse outcomes in patients with TTS, 2 registries reported that older patients with TTS experienced more adverse in-hospital events than younger patients.[14,15]

In contrast, recently published data from 2092 patients with TTS in the InterTAK (International Takotsubo Registry) revealed that younger patients had more in-hospital complications, such as cardiogenic shock, invasive and noninvasive ventilation, catecholamine use, cardiopulmonary resuscitation, and numerically higher in-hospital mortality.[16] Moreover, data from the National Inpatient Sample USA database of TTS between 2009 and 2015 showed that younger patients may experience more in-hospital complications.[17]

Therefore, the current evidence about age in TTS remains controversial. This study aimed to evaluate the effect of age on in-hospital and long-term outcomes in a comprehensive manner using data from the large multicenter GEIST (German Italian Spanish Takotsubo) Registry.

METHODS

The data of this study are available from the corresponding author upon reasonable request. We analyzed data from a prospective registry that enrolled 2492 consecutive patients with TTS from 2002 to 2018.[18] Patients were included according to the Heart Failure Association of the European Society of Cardiology TTS diagnostic criteria. These criteria included transient regional wall motion abnormalities of the ventricle frequently triggered by stress, absence of a culprit coronary artery disease, new and reversible electrocardiography and echocardiographic abnormalities with normalization at follow-up, and elevated cardiac troponin and serum natriuretic peptide levels.

Before inclusion, all patients underwent coronary angiography to exclude coronary artery disease (defined as stenosis >50%)[19] or a culprit lesion that would explain the wall motion abnormalities.

Several demographic data and baseline characteristics were extracted. Stressful triggers for TTS were divided into 3 forms (emotional, physical, and "happy heart" triggers).[18,20] Ballooning patterns were categorized as apical, midventricular, basal, or focal. Ballooning patterns, including midventricular, basal, and focal TTS, were combined for statistical reasons and were named the atypical or apical-sparing forms. In addition, RV TTS was defined as wall motion abnormalities (akinesis or dyskinesis) of the RV free wall, with or without apical involvement, as determined by echocardiography or cardiac magnetic resonance imaging (in 230 patients). Further criteria for RV involvement were considered to confirm RV involvement.[3–5] Follow-up echocardiography was performed before discharge and 3 to 6 months after discharge. Resolution of RV and LV wall motion abnormalities at the time of follow-up was viewed as confirmation of transient RV/LV TTS. A stressful trigger was defined as a physical or emotional trigger. The reference category was patients without stressful triggers (see the values below).

In-hospital complications, including LV thrombus, LV outflow tract obstruction, pulmonary edema, cardiogenic shock, cardiac arrest, extracorporeal membrane oxygenation, mechanical ventilation, stroke, and arrhythmias, were recorded.[21] The long-term outcome and recurrence of TTS were verified by outpatient visits, medical records, or telephone interviews.[10] Patients were divided into different age groups: <45 years (n=58), 45 to 64 years (n=625), 65 to 74 years (n=733), and ≥75 years (n=1063). The baseline characteristics,

in-hospital complications, and outcomes of these groups were compared. The median follow-up time was 480 days (interquartile range, 83–1510 days).

The study protocol was approved by the local ethics committees of the participating centers, and the study was conducted in compliance with the Declaration of Helsinki. Clinical trial registration number was NCT04361994. The study was approved by an institutional review committee, and the subjects provided informed consent.

Statistical Analysis

Continuous variables with a nonnormal distribution are presented as median (interquartile range), as mean±SD for normally distributed variables, and as frequency (percentage) for categorical variables. Their normality was assessed using the Kolmogorov-Smirnov test. Categorical variables were compared with the Pearson χ^2 test, and continuous variables were analyzed with 1-way ANOVA and the Kruskal-Wallis test. A log-rank test was used to compare the Kaplan-Meier survival curves of patients with TTS of different age groups. The number of patients lost to follow-up is provided in Table S1. Factors with $P \leq 0.05$ in univariate analysis were entered into a Cox multivariable regression analysis to identify independent risk factors for in-hospital mortality. To determine conformity with the assumption of proportional hazards, we looked at the graphs of log(–log[St]) versus time. As the graphs of the 2 corresponding groups seemed to be approximately parallel, we assumed that the precondition of proportional hazards was fulfilled.

The statistical analysis was performed using SPSS 24.0. A 2-tailed $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

The baseline clinical features are reported in Table 1. In comparison to other age groups, there were more men in the younger age group ($P=0.006$). Among the comorbidities, older patients had significantly more cardiovascular comorbidities, and the number of patients with neurologic diseases was significantly greater ($P<0.001$). Psychiatric diseases were significantly more prevalent at younger ages ($P=0.04$).

At admission and follow-up, the LV ejection fraction was significantly lower in the older age groups. Consistent with these data, older groups more often received angiotensin-converting enzyme inhibitors or angiotensin-receptor antagonists ($P<0.001$), aldosterone antagonists ($P<0.001$), and diuretics ($P<0.001$) at discharge (Table 2). Beta blockers were similarly prescribed in all age cohorts at discharge.

The apical TTS form was more often diagnosed among older patients ($P<0.001$), and the apical-sparing TTS (including midventricular, basal, and focal forms) was more common in younger patients ($P<0.001$).

A stressful trigger was more often observed in younger age groups ($P=0.008$). Although physical stress triggers were significantly more prevalent in those aged <45 years ($P<0.001$), emotional triggers were most common in the 45- to 64-year age group ($P<0.001$). Notably, positive emotional triggers (happy heart) were significantly more common in younger patients ($P=0.03$).

Short- and Long-Term Outcomes

A greater incidence of cardiogenic shock was found in the younger age group ($P=0.01$) (Table 3). Other complications (eg, LV outflow tract obstruction, vasoactive treatment, cardiac arrest, and the use of extracorporeal membrane oxygenation) were similar in all age groups. Pulmonary edema and mortality were significantly higher in the older age group (pulmonary edema; $P=0.001$). Notably, a composite of all components of in-hospital complications was highest among the youngest and oldest age groups ($P=0.002$). The same result was observed when in-hospital complications were compared, excluding in-hospital death ($P=0.013$).

The mean±SD follow-up time of the entire cohort was 955.4±1130.8 days. The mean±SD follow-up times of the different groups were as follows: <45 years, 1256.9±1488.7 days; 45 to 64 years, 1094.9±1189.7 days; 65 to 74 years, 1012.3±1183.6 days; and ≥75 years, 814.5±1011.4 days. Long-term mortality was significantly higher in the older cohort than in the other cohorts (from youngest to oldest, 5.6%, 6.4%, 11.3%, and 22.3%; log-rank $P<0.001$) (Figure [A]). Moreover, cardiovascular long-term mortality was significantly higher in the older cohort than in the other cohorts (0%, 0.9%, 1.9%, and 3.2%; log-rank $P=0.01$) (Figure [B]).

Predictors of In-Hospital Mortality

According to univariate analyses, age ≥75 years, sex, ejection fraction ≤35%, and atrial fibrillation were significant contributors to in-hospital mortality, but multivariate analysis revealed that only age ≥75 years and ejection fraction ≤35% were significant ($P=0.03$). In addition, in the multivariable analysis of in-hospital mortality in all age groups, age significantly increased mortality (hazard ratio [HR], 1.04 [95% CI, 1.01–1.07]; $P=0.009$) (Table S2). When we tested the interaction between age and other factors, a significant interaction was found between coronary artery disease and age ($P=0.010$). Thus, multiple analyses were performed separately for the subgroups with and without coronary artery disease. For patients with coronary artery disease, no multivariable statistical model could be constructed. For patients without coronary artery disease, the following

Table 1. Patient Characteristics According to Age

Variables	All patients (n=2479)	Patients aged <45 y (n=58)	Patients aged 45–64 y (n=625)	Patients aged 65–74 y (n=733)	Patients aged ≥75 y (n=1063)	*P* value
Male sex, n/total (%)	285/2479 (11.5)	14/58 (24.1)	79/625 (12.6)	71/733 (9.7)	121/1063 (11.4)	0.006
BMI, median (IQR), kg/m^2	24.8 (21.4–28.3)	22.6 (20.5–31.0)	24.0 (21.0–28.0)	25.0 (21.8–29.0)	25.0 (22.0–28.4)	0.366
Obesity, n/total (%)	351/2134 (16.4)	4/54 (7.4)	106/554 (19.1)	99/619 (16)	142/907 (15.7)	0.085
Duration of hospitalization, mean±SD, d	9.0±9.5	9.7±14.7	8.1±10.1	9.3±9.5	9.3±8.7	<0.001
Medical history, n/total (%)						
Arterial hypertension	1685/2469 (68.2)	13/58 (22.4)	334/623 (53.6)	506/729 (69.4)	832/1059 (78.6)	<0.001
Dyslipidemia	982/2329 (42.2)	8/54 (14.8)	237/567 (41.8)	310/689 (45.0)	427/1019 (41.9)	0.003
Diabetes	476/2468 (19.3)	4/58 (6.9)	73/622 (11.7)	158/729 (21.7)	241/1059 (22.8)	<0.001
Current smoking	439/2469 (17.8)	21/58 (36.2)	215/624 (34.5)	125/729 (17.1)	78/1058 (7.4)	<0.001
Coronary artery disease	205/2145 (9.6)	4/55 (7.3)	40/549 (7.3)	53/643 (8.2)	108/898 (12.0)	0.011
Atrial fibrillation	344/2222 (15.5)	0/51 (0)	36/551 (6.5)	96/663 (14.5)	212/957 (22.2)	<0.001
Pacemaker	43/370 (11.6)	0/4 (0)	3/75 (4.0)	12/111 (10.8)	28/180 (15.6)	0.052
Pulmonary disease	342/2178 (15.7)	3/50 (6)	63/548 (11.5)	107/648 (16.5)	169/932 (18.1)	0.002
Malignancy	308/2128 (14.5)	2/49 (4.1)	47/534 (8.8)	103/644 (16.0)	156/901 (17.3)	<0.001
Neurologic disease	356/1984 (17.9)	6/47 (12.8)	66/509 (13.0)	79/581 (13.6)	205/847 (24.2)	<0.001
Psychiatric disease	262/1956 (13.4)	9/46 (19.6)	83/504 (16.5)	76/590 (12.9)	94/816 (11.5)	0.042
Symptoms, n/total (%)						
Angina pectoris	1320/2206 (59.8)	30/52 (57.7)	370/533 (69.4)	399/657 (60.7)	521/964 (54.0)	<0.001
Dyspnea	789/2204 (35.8)	15/51 (29.4)	158/533 (29.6)	231/655 (35.3)	385/965 (39.9)	0.001
ECG, n/total (%)						
ST-segment elevation	1754/2142 (81.9)	44/52 (84.6)	421/531 (79.3)	524/630 (83.2)	765/929 (82.3)	0.310
Killip classification, n/total (%)						
I	1835/2479 (74.0)	40/58 (69.0)	517/625 (82.7)	557/733 (76.0)	721/1063 (67.8)	<0.001
II	233/2479 (9.4)	6/58 (10.3)	33/625 (5.3)	56/733 (7.6)	138/1063 (13.0)	
III	183/2479 (7.4)	4/58 (6.9)	25/625 (4.0)	51/733 (7.0)	103/733 (9.7)	
IV	228/2479 (9.2)	8/58 (13.8)	50/625 (8.0)	69/733 (9.4)	101/1063 (9.5)	
Trigger, n/total (%)						
Stressful trigger	1754/2471 (71)	51/58 (87.9)	448/622 (72.0)	538/732 (73.5)	717/1059 (67.7)	0.008
Physical	853/2471 (34.5)	27/58 (46.6)	171/622 (27.5)	248/732 (33.9)	407/1059 (38.4)	<0.001
Emotional	906/2471 (36.7)	23/58 (39.7)	279/622 (44.9)	292/732 (39.9)	312/1059 (29.5)	<0.001
Happy heart	37/2449 (1.5)	3/57 (5.3)	6/618 (1.0)	15/725 (2.1)	13/1049 (1.2)	0.034
No. of triggers, n/total (%)						
0	716/2471 (29)	7/58 (12.1)	174/622 (28)	193/732 (26.4)	342/1059 (32.3)	<0.001
2	851/2471 (34.4)	27/58 (46.6)	171/622 (27.5)	246/732 (33.6)	407/1059 (38.4)	<0.001
3	867/2471 (35.1)	21/58 (36.2)	271/622 (43.6)	278/732 (38)	297/1059 (28)	<0.001
4	37/2471 (1.5)	3/58 (5.2)	6/622 (1)	15/732 (2)	13/1059 (1.2)	<0.001
Pathognomonic wall motion abnormalities, n/total (%)						
LV ballooning						
Apical	2126/2478 (85.8)	43/58 (74.1)	476/624 (76.3)	640/733 (87.3)	967/1063 (91)	<0.001
Atypical	352/2478 (14.2)	15/58 (25.9)	148/624 (23.7)	93/733 (12.7)	96/1063 (9)	
RV ballooning	61/1816 (3.4)	3/48 (6.3)	12/454 (2.6)	14/537 (2.6)	32/777 (4.1)	0.234
EF, mean±SD, %						
EF at admission	40.6±10.6	41.6±14.4	42.1±10.4	41.1±10.8	39.1±10.1	<0.001
EF at follow-up	58.7±8.4	59.5±6.1	58.9±8.4	59.4±7.7	58.0±9.0	0.008

For qualitative factors, absolute and relative frequencies are given. Quantitative variables are presented by their median values and quartiles. BMI indicates body mass index; EF, ejection fraction; IQR, interquartile range; LV, left ventricular; and RV, right ventricular.

Table 2. Medication at Discharge

Medication	All patients (n=2479)	Patients aged <45 y (n=58)	Patients aged 45–64 y (n=625)	Patients aged 65–74 y (n=733)	Patients aged ≥75 y (n=1063)	*P* value
Aspirin	1262/2192 (57.6)	25/54 (46.3)	304/550 (55.3)	393/645 (60.9)	540/943 (57.3)	0.071
DAPT	168/1625 (10.3)	1/41 (2.4)	41/410 (10.0)	51/479 (10.6)	75/695 (10.8)	0.390
Oral anticoagulant	354/2008 (17.6)	6/54 (11.1)	45/511 (8.8)	102/580 (17.6)	201/863 (23.3)	<0.001
ACEI or ARB	1534/2211 (69.4)	25/54 (46.3)	370/557 (66.4)	470/651 (72.2)	669/949 (70.5)	<0.001
Beta blocker	1500/2088 (71.8)	35/51 (68.6)	371/518 (71.6)	449/616 (72.9)	645/903 (71.4)	0.877
Statin	1142/2182 (52.3)	11/54 (20.4)	257/547 (47)	345/643 (53.7)	529/938 (56.4)	<0.001
Diuretic	537/1586 (33.9)	4/41 (9.8)	66/385 (17.1)	146/463 (31.5)	321/697 (46.1)	<0.001
Aldosterone antagonist	127/1626 (7.8)	1/41 (2.4)	13/411 (3.2)	34/478 (7.1)	79/696 (11.4)	<0.001

Data are given as number/total (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and DAPT, dual-antiplatelet therapy.

parameters were significant predictors of in-hospital death: ejection fraction ≤35% at admission (*P*=0.021; HR=2.26), atrial fibrillation (*P*=0.045; HR=1.94), and age (*P*=0.006; HR=1.05 per year). This finding indicates that age is most important to the survival of patients without coronary artery disease.

DISCUSSION

To the best of our knowledge, our comprehensive multicenter analysis is one of the largest studies to date assessing the clinical and prognostic impact of age in patients with TTS. Our findings can be summarized as follows:

1. A total of 2.3% of patients with TTS were aged <45 years; young patients with TTS had the highest prevalence of male sex, non-apical ballooning patterns, and in-hospital complications.
2. Patients aged ≥75 years more frequently experienced cardiovascular and noncardiovascular comorbidities and had a higher rate of in-hospital and long-term mortality or long-term cardiovascular mortality than the other groups.
3. Older age (≥75 years) and ejection fraction ≤35% are independent predictors of in-hospital mortality.

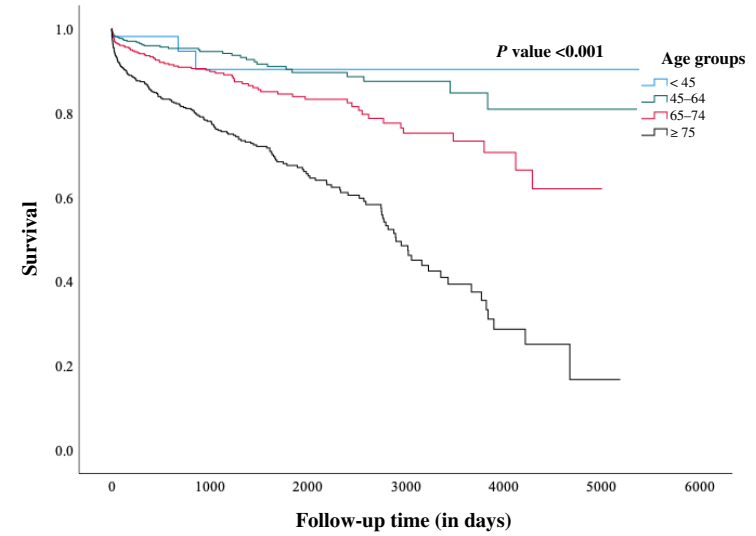
Few studies have explored age-associated differences in TTS, including clinical characteristics and outcome data. The present study evaluated several clinical features of age-related differences in TTS.

Interestingly, in the present study, the prevalence of male patients grew higher with decreasing age, peaking at 24% in patients aged <45 years. These findings are in line with data from the InterTAK, which evaluated a cohort of 2098 patients with TTS and reported an incidence of 15% male sex among young patients.[16] However, we

Table 3. In-Hospital Complications According to Age

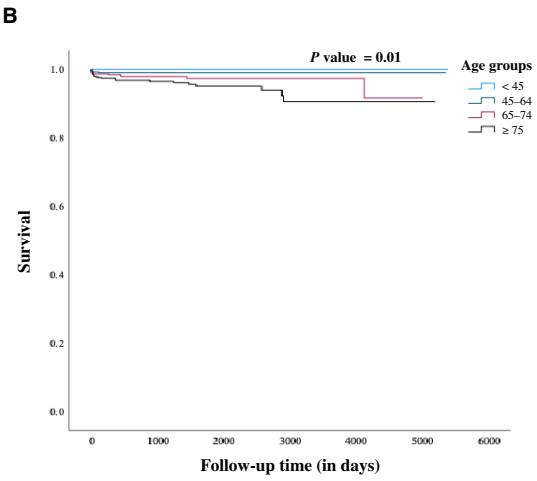
Complication	All patients (n=2479)	Patients aged <45 y (n=58)	Patients aged 45–64 y (n=625)	Patients aged 65–74 y (n=733)	Patients aged ≥75 y (n=1063)	*P* value
LV thrombus	60/2033 (3)	4/54 (7.4)	14/526 (2.7)	22/599 (3.7)	20/854 (2.3)	0.107
LVOT obstruction	58/980 (5.9)	1/23 (4.3)	9/241 (3.7)	19/292 (6.5)	29/424 (6.8)	0.392
Pulmonary edema	199/2479 (8.0)	5/58 (8.6)	30/625 (4.8)	54/733 (7.4)	110/1063 (10.3)	0.001
Cardiogenic shock	229/2479 (9.2)	8/58 (13.8)	51/625 (8.2)	69/733 (9.4)	101/1063 (9.5)	0.491
Cardiac arrest	53/397 (13.4)	1/7 (14.3)	13/111 (11.7)	21/123 (17.1)	18/156 (11.5)	0.536
ECMO	41/2362 (1.7)	0/56 (0)	9/595 (1.5)	14/698 (2)	18/1013 (1.8)	0.689
Mechanical ventilation	173/2331 (7.4)	6/54 (11.1)	43/569 (7.6)	45/690 (6.5)	79/1018 (7.8)	0.558
Stroke	48/2170 (2.2)	1/53 (1.9)	9/563 (1.6)	15/643 (2.3)	23/911 (2.5)	0.691
Arrhythmias	162/1297 (12.5)	6/30 (20.0)	33/317 (10.4)	47/382 (12.3)	76/568 (13.4)	0.358
In-hospital death	77/2272 (3.4)	0/54 (0)	9/574 (1.6)	20/682 (2.9)	48/962 (5.0)	0.001
Composite end point[†]	689/2479 (27.8)	18/58 (31)	138/625 (22.1)	198/733 (27)	335/1063 (31.5)	<0.001
Composite end point after exclusion of in-hospital death	684/2479 (27.6)	19/58 (32.8)	146/625 (23.4)	196/733 (26.7)	323/1063 (30.4)	0.013

ECMO indicates extracorporeal membrane oxygenation; LV, left ventricular; and LVOT, LV outflow tract.
[†]A composite end point is a combination of all clinical outcomes (in-hospital complications).



Number at risk for all patients:

Time in days	1000	2000	3000	4000	5000
Number (n)					
All patients	791	383	169	52	6
<45	19	14	8	5	2
45–64	234	114	55	16	2
65–74	245	126	61	20	1
≥75	293	129	45	11	1



Cardiovascular mortality by different age groups

Number at risk for all patients, cardiovascular mortality.

Time in days	1000	2000	3000	4000	5000
Number (n)					
All patients	789	379	167	49	4
<45	19	13	8	5	1
45–64	233	113	54	15	2
65–74	244	125	61	19	0
≥75	293	128	44	10	1

Figure 1. A, Kaplan-Meier curves of all-cause mortality in patients with TTS of different age groups (<45 vs 45–64 vs ≥65–74 vs ≥75 years).
B, Kaplan-Meier curve analysis of cardiovascular mortality in patients with TTS of different age groups (<45 vs 45–64 vs ≥65–74 vs ≥75 years). Central illustration: flowchart presenting a composite of in-hospital complication and long-term mortality rates in different age groups (<45 vs 45–64 vs ≥65–74 vs ≥75 years). TTS indicates takotsubo syndrome.

defined young patients as those aged <45 years, whereas the InterTAK defined the youngest group as those aged ≤50 years. Moreover, in the present study, young patients had a greater incidence of psychiatric disease.

Triggering events for TTS varied between younger and older patients. At the youngest age (<45 years), a stressful trigger was more prevalent than it was in other age groups, and the prevalence of physical stressful triggers was significantly greater than that in the other age groups. Notably, concerning emotional triggers at age <45 years, a happy heart trigger was found in up to 5% of these patients, which was significantly more common than in the other groups.

Data from previous studies showed that the prevalence of cardiogenic shock, need for intensive cardiac care treatment, including noninvasive and invasive ventilation, and in-hospital mortality were significantly higher in younger patients with TTS than in older patients.[15,16] The present data are not completely in line with these data. Indeed, we found a higher rate of cardiogenic shock, but not an of in-hospital mortality, in these patients than in individuals in other age groups. Nevertheless, a composite of all in-hospital complications showed similar event rates in the youngest and oldest age groups, whereas patients in the middle age groups exhibited lower event rates.

In-hospital mortality was higher in the older age groups than in the young age group. Mortality in patients with TTS is mainly driven by comorbidities, which are more prevalent among older patients. Moreover, a greater percentage of young patients than older patients had apical-sparing TTS. Notably, patients with the apical TTS form had a significantly greater mortality rate than did those with the atypical/apical-sparing TTS form.[22,23] All these factors may explain the lower in-hospital mortality of young patients than of old patients, as described before. Irrespective of these contributing factors, age was also an independent predictor of in-hospital mortality. According to our multivariate Cox regression analysis, only age ≥75 years and ejection fraction ≤35% were significant independent predictors of in-hospital mortality.

The present study showed that at all ages, there was a predominance of female patients (85%–90%). It is well known that TTS affects predominantly female patients.[24] This finding could be because a low estradiol level may increase the susceptibility of myocytes to catecholamine excess.[25] Interactions between age, sex, and triggers certainly play important roles in the short- and long-term prognosis of patients with TTS. Additional studies are warranted to better evaluate these interactions.

Limitations

Several limitations color the results of this study. First, although the GEIST Registry is a prospective registry, this analysis was in part a retrospective study, so bias cannot be excluded. Second, the prevalence of TTS might be higher, but many cases may be missed. Third, there was no review of the quality of the imaging interpretations from the multiple sites. However, at each center, 2 independent physicians evaluated the medical records and images. Fourth, the enrolling centers used different assays to measure the serum levels of cardiac biomarkers, so no data on these were provided in the article.

CONCLUSIONS

Patients aged <45 years represented 2.3% of the cases of TTS. These patients had a typical phenotype characterized by a higher prevalence of male sex, non-apical ballooning patterns, and stressful triggers. Young patients have a higher rate of in-hospital complications. However, in-hospital and long-term mortality are significantly lower in these patients than in older patients. Age ≥75 years and ejection fraction ≤35% are independent predictors of in-hospital mortality.

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Received June 21, 2023; accepted January 9, 2024.

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Acknowledgments

The authors are responsible for all content of the article.

Sources of Funding

None.

Disclosures

None.

Supplemental Material

Data S1

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