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ORIGINAL INVESTIGATIONS

Age-Related Variations in Takotsubo Syndrome

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ABSTRACT

BACKGROUND Takotsubo syndrome (TTS) occurs predominantly in post-menopausal women but is also found in younger patients.

OBJECTIVES This study aimed to investigate age-related differences in TTS.

METHODS Patients diagnosed with TTS and enrolled in the International Takotsubo Registry between January 2011 and February 2017 were included in this analysis and were stratified by age (younger: ≤50 years, middle-age: 51 to 74 years, elderly: ≥75 years). Baseline characteristics, hospital course, as well as short- and long-term mortality were compared among groups.

RESULTS Of 2,098 TTS patients, 242 (11.5%) patients were ≤50 years of age, 1,194 (56.9%) were 51 to 74 years of age, and 662 (31.6%) were ≥75 years of age. Younger patients were more often men (12.4% vs. 10.9% vs. 6.3%; $p = 0.002$) and had an increased prevalence of acute neurological (16.3% vs. 8.4% vs. 8.8%; $p = 0.001$) or psychiatric disorders (14.1% vs. 10.3% vs. 5.6%; $p < 0.001$) compared with middle-aged and elderly TTS patients. Furthermore, younger patients had more often cardiogenic shock (15.3% vs. 9.1% vs. 8.1%; $p = 0.004$) and had a numerically higher in-hospital mortality (6.6% vs. 3.6% vs. 5.1%; $p = 0.07$). At multivariable analysis, younger (odds ratio: 1.60; 95% confidence interval: 0.86 to 3.01; $p = 0.14$) and older age (odds ratio: 1.09; 95% confidence interval: 0.66 to 1.80; $p = 0.75$) were not independently associated with in-hospital mortality using the middle-aged group as a reference. There were no differences in 60-day mortality rates among groups.

CONCLUSIONS A substantial proportion of TTS patients are younger than 50 years of age. TTS is associated with severe complications requiring intensive care, particularly in younger patients. (J Am Coll Cardiol 2020;75:1869–77)

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Takotsubo syndrome (TTS) is an important differential diagnosis in patients presenting with acute chest pain and/or acute heart failure (1,2). TTS is characterized by typical left ventricular (LV) wall motion abnormalities and elevated cardiac biomarkers, and it affects predominantly post-menopausal women (3). However, given the growing awareness of the disease entity, TTS is increasingly recognized also in younger and male patients (3–5).

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In general, age is regarded as one of the most important cardiovascular risk factors associated with worse outcomes in patients with acute myocardial infarction, atrial fibrillation, and heart failure among others conditions (6–8). Age-related differences in the clinical profile of TTS patients have been suggested in smaller studies (9,10), but data remain conflicting. Whether younger TTS patients exhibit a different disease phenotype has not yet been fully investigated, and age-related differences in the presentation and outcomes of TTS remain uncertain.

The present study therefore aimed to examine age-related clinical features and outcomes of TTS patients enrolled in the International Takotsubo Registry (InterTAK Registry).

METHODS

STUDY DESIGN. The design and rationale of the InterTAK Registry have previously been described (11). For the present study, data were collected from 2011 to 2017 from patients who were diagnosed with TTS at 36 participating sites in 11 countries (Australia, Austria, Czech Republic, Finland, France, Germany, Italy, Poland, Switzerland, United Kingdom, and United States) between 1998 and 2017. Diagnosis of TTS was based on modified Mayo Clinic Diagnostic Criteria (12): 1) transient LV wall motion abnormalities beyond a single epicardial coronary artery distribution territory; 2) absence of obstructive coronary artery disease or acute plaque rupture; 3) evidence of new electrocardiographic abnormalities and/or elevation in cardiac troponin levels; and 4) absence of myocarditis. Exceptions to these criteria were (3): patients who matched all other criteria but had wall motion abnormalities corresponding to the territory of a single coronary artery, patients who had coronary artery disease that could not explain the wall motion abnormality, as well as those who died during the acute phase prior to complete LV wall motion recovery. Data on demographics, triggering factors, laboratory profile, imaging studies, acute cardiac care treatment, and in-hospital complications were collected. Follow-up information was gathered through personal telephone interviews, clinical visits, or medical records. Follow-up time was defined as the time from date of TTS diagnosis to the date of death or last contact. If the last contact was on the discharge date, it was assumed that these patients survived until 60 days. This is assumable as patients were only discharged if they had recovered from the acute TTS episode.

All patients were stratified according to age at index event and categorized into 3 age groups (younger: ≤50 years, middle-age: 51 to 74 years, and older: ≥75 years). Clinical characteristics, hospital course, as well as short- and long-term mortality were compared between groups and factors associated with in-hospital mortality were assessed.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
LV = left ventricular/ventricle
OR = odds ratio
TTS = Takotsubo syndrome
ULN = upper limit of the normal range

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STATISTICAL ANALYSIS. Categorical variables are presented as numbers and percentages, and continuous variables as mean ± SD or median (interquartile range). Comparisons of categorical variables were conducted with the Pearson chi-square test and continuous variables were analyzed with 1-way analysis of variance and Kruskal-Wallis test. Baseline variables with significant differences between groups and that were likely to have an impact on in-hospital mortality were included in the multivariable logistic regression model to assess the adjusted risk of younger and older age using the middle-aged group as a reference. Prior to multivariable analysis, multiple imputation for missing data was performed. Odds ratios (ORs) are presented with the respective 95% confidence intervals (CIs). Kaplan-Meier estimates were used to analyze all-cause mortality, and the log-rank test was executed for group comparisons. Furthermore, a landmark analysis with a landmark set at 60 days was conducted to investigate long-term mortality beyond the acute phase. To assess age-related parameters affecting in-hospital mortality decision tree algorithms with Classification And Regression Trees and exhausted Chi-squared Automatic Interaction Detector were used. All tests were 2-sided and a p value <0.05 was considered statistically significant. R version 3.5 (R Foundation, Vienna, Austria) and SPSS version 26.0 (IBM Corp., Armonk, New York) were used for statistical analyses, and Prism 8 (GraphPad, La Jolla, California) for figure preparation.

RESULTS

CLINICAL CHARACTERISTICS. Of the 2,098 TTS patients included, 242 (11.5%) patients were ≤50 years of age, 1,194 (56.9%) were 51 to 74 years of age, and 662 (31.6%) were ≥75 years of age. Mean age of the patients was 66.9 ± 12.8 years (90.4% women), and there was no statistical difference in age ($p = 0.53$) and sex ($p = 0.66$) distribution when analyzing each year of TTS diagnosis. The prevalence of men was highest among younger TTS patients (age ≤50 years: 12.4%, 51 to 74 years: 10.9%, and ≥75 years: 6.3%; $p = 0.002$). Baseline comparisons between age groups are detailed in Table 1.

Older TTS patients had no evident triggering event more often (21.9% vs. 26.7% vs. 29.9%; $p = 0.049$), whereas middle-aged patients presented with an emotional trigger more frequently (28.9% vs. 32.0% vs. 25.7%; $p = 0.017$). The prevalence of physical triggers did not differ among groups (40.9% vs. 34.8% vs. 36.7%; $p = 0.19$). Younger TTS patients displayed acute neurological disorders more often, including seizures, intracranial hemorrhages, and migraine attacks or headache disorders (16.3%, vs. 8.4% vs. 8.8%; $p = 0.001$). The prevalence of psychiatric disorders, particularly affective and adjustment disorders, was higher in younger patients compared with middle-aged and elderly TTS patients (14.1% vs. 10.3% vs. 5.6%; $p < 0.001$).

Younger patients had higher troponin levels at admission (as expressed as x-fold increase above the upper limit of normal [ULN]) than middle-aged or elderly TTS patients (9.50 [interquartile range (IQR): 2.38 to 30.83] vs. 7.50 [IQR: 2.50 to 19.29] vs. 9.23 [IQR: 3.00 to 26.80]; $p = 0.017$). Similarly, creatine kinase values at admission were increased in younger TTS patients (1.03 [IQR: 0.54 to 2.19] vs. 0.87 [IQR: 0.56 to 1.41] vs. 0.86 [IQR: 0.51 to 1.44]; $p = 0.049$). There were no significant differences in brain natriuretic peptide values among groups. C-reactive protein levels at admission were higher in elderly TTS patients compared with younger and middle-aged TTS patients (3.85 [IQR: 1.00 to 11.38] vs. 3.75 [IQR: 1.38 to 11.05] vs. 5.00 [IQR: 2.00 to 17.20]; $p = 0.006$).

Elderly TTS patients more often presented with atrial fibrillation compared with younger or middle-aged TTS patients (2.4% vs. 4.5% vs. 11.4%; $p < 0.001$) and more frequently presented with ST-segment elevation (37.3% vs. 40.1% vs. 50.3%; $p < 0.001$). The prevalence of ST-segment depression, T-wave inversion, and QTc prolongation did not differ among groups.

Younger TTS patients had a higher heart rate (91.5 ± 24.9 beats/min vs. 87.8 ± 21.6 beats/min vs. 85.9 ± 19.8 beats/min; $p = 0.009$) and a lower systolic blood pressure (125.1 ± 28.9 mm Hg vs. 131.2 ± 28.8 mm Hg vs. 132.0 ± 29.0 mm Hg, $p = 0.012$) at presentation as compared to middle-aged and elderly TTS patients. No significant difference in LV ejection fraction was observed among groups (40.2 ± 12.4% vs. 41.0 ± 11.7% vs. 40.5 ± 11.2%; $p = 0.59$). The typical form of TTS was less often observed in younger and middle-aged TTS patients (66.5% vs. 67.9% vs. 79.3%; $p < 0.001$) compared with older TTS patients.

Younger TTS patients more frequently needed acute cardiac care measures including catecholamines (23.7% vs. 11.4% vs. 9.6%; $p < 0.001$), noninvasive and invasive ventilation (28.6% vs. 16.6% vs. 12.5%; $p < 0.001$), and/or cardiopulmonary resuscitation (11.6% vs. 5.9% vs. 3.9%; $p < 0.001$). The prevalence of cardiogenic shock was higher in younger TTS patients (15.3%, vs. 9.1% vs. 8.1%; $p = 0.004$), with numerically higher rates of in-hospital mortality observed in younger and older patients (6.6% vs. 3.6% vs. 5.1%; $p = 0.07$) (Central Illustration).

TABLE 1 Characteristics of Takotsubo Patients According to Age Groups

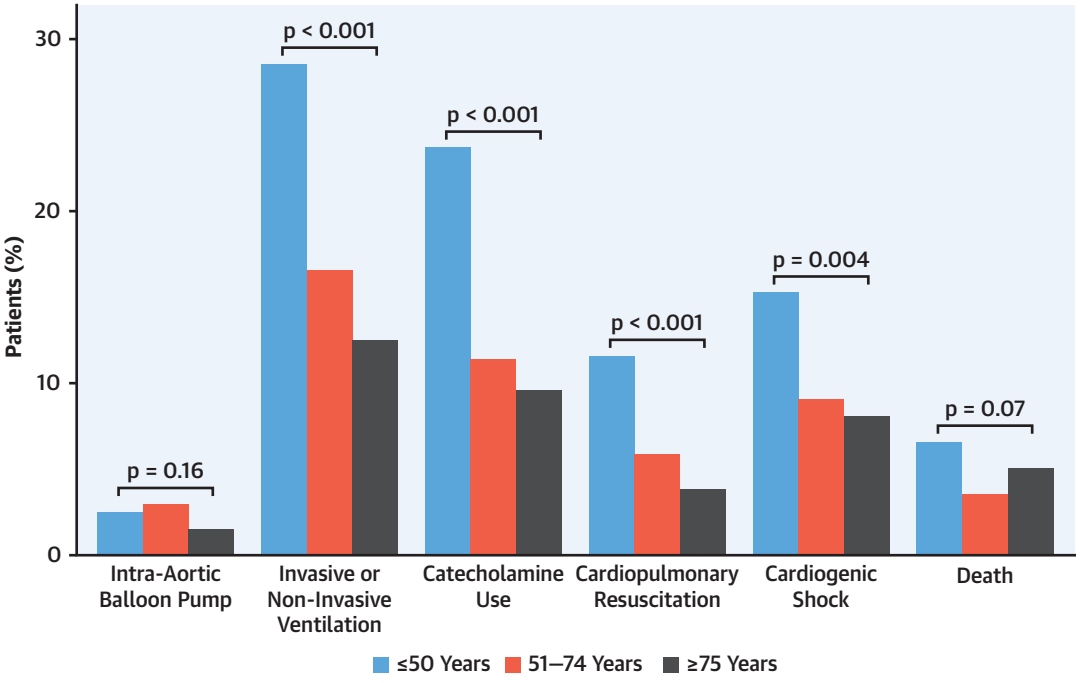
	Age			
	≤50 Years n = 242 (11.5%)	51–74 Years n = 1,194 (56.9%)	≥75 Years n = 662 (31.6%)	p Value
Demographics				
Male	30/242 (12.4)	130/1,194 (10.9)	42/662 (6.3)	0.002
Triggers				
Physical	99/242 (40.9)	416/1,194 (34.8)	243/662 (36.7)	0.19
Emotional	70/242 (28.9)	382/1,194 (32.0)	170/662 (25.7)	0.017
No evident trigger	53/242 (21.9)	319/1,194 (26.7)	198/662 (29.9)	0.049
Acute neurological disorders	36/221 (16.3)	90/1,067 (8.4)	52/593 (8.8)	0.001
Seizure	14/221 (6.3)	38/1,067 (3.6)	8/593 (1.3)	0.001
Intracranial bleeding	15/221 (6.8)	17/1,067 (1.6)	12/593 (2.0)	<0.001
Stroke or TIA	2/221 (0.9)	22/1,067 (2.1)	20/593 (3.4)	0.08
Migraine or headache disorder	12/221 (5.4)	12/1,067 (1.1)	9/593 (1.5)	<0.001
Others	6/221 (2.7)	14/1,067 (1.3)	6/593 (1.0)	0.17
Acute psychiatric disorders	31/220 (14.1)	110/1,066 (10.3)	33/592 (5.6)	<0.001
Affective disorder	10/220 (4.5)	37/1,066 (3.5)	9/592 (1.5)	0.029
Anxiety disorder	6/220 (2.7)	18/1,066 (1.7)	5/592 (0.8)	0.13
Reaction to severe stress or adjustment disorder	10/220 (4.5)	38/1,066 (3.6)	6/592 (1.0)	0.003
Others	8/220 (3.6)	38/1,066 (3.6)	14/592 (2.4)	0.38
Laboratory profile on admission				
Troponin, factor increase in ULN*	9.50 (2.38–30.83) (175)	7.50 (2.50–19.29) (923)	9.23 (3.00–26.80) (501)	0.017
Creatine kinase, factor increase in ULN	1.03 (0.54–2.19) (157)	0.87 (0.56–1.41) (787)	0.86 (0.51–1.44) (450)	0.049
BNP, factor increase in ULN†	4.95 (1.07–18.52) (56)	6.22 (2.08–17.50) (322)	6.50 (2.74–16.22) (171)	0.29
CRP, mg/l	3.85 (1.00–11.38) (134)	3.75 (1.38–11.05) (738)	5.00 (2.00–17.20) (426)	0.006
ECG on admission				
Atrial fibrillation	5/209 (2.4)	47/1,047 (4.5)	67/589 (11.4)	<0.001
ST-segment elevation	78/209 (37.3)	420/1,047 (40.1)	296/589 (50.3)	<0.001
T-wave inversion	75/209 (35.9)	442/1,047 (42.2)	248/589 (42.1)	0.22
QTc, ms	457.4 ± 45.5 (161)	458.1 ± 47.0 (833)	461.3 ± 50.3 (432)	0.48
TTS type and hemodynamic findings				
Apical	161/242 (66.5)	811/1,194 (67.9)	525/662 (79.3)	<0.001
Heart rate, beats/min	91.5 ± 24.9 (191)	87.8 ± 21.6 (914)	85.9 ± 19.8 (513)	0.009
Systolic blood pressure, mm Hg	125.1 ± 28.9 (197)	131.2 ± 28.8 (936)	132.0 ± 29.0 (517)	0.012
Left ventricular ejection fraction, %‡	40.2 ± 12.4 (212)	41.0 ± 11.7 (1,057)	40.5 ± 11.2 (582)	0.59
Cardiovascular risk factors				
Hypertension	87/231 (37.7)	738/1,166 (63.3)	515/645 (79.8)	<0.001
Diabetes mellitus	19/231 (8.2)	185/1,169 (15.8)	108/639 (16.9)	0.005
Current smoking	79/225 (35.1)	262/1,121 (23.4)	52/617 (8.4)	<0.001
Hypercholesterolemia	40/227 (17.6)	408/1,148 (35.5)	210/634 (33.1)	<0.001
Comorbidities				
COPD or asthma	24/229 (10.5)	217/1,149 (18.9)	98/634 (15.5)	0.004
Cancer	19/211 (9.0)	175/1,102 (15.9)	112/582 (19.2)	0.002
Hyperthyroidism	9/227 (4.0)	58/1,161 (5.0)	40/636 (6.3)	0.32
Hypothyroidism	22/227 (9.7)	151/1,161 (13.0)	83/636 (13.1)	0.36

Values are n/N (%), median (interquartile range) (n), or mean ± SD (n). *Including upper limits of the normal range for troponin T, high-sensitivity troponin T, and troponin I. †Including upper limits of the normal range for brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide. ‡Data obtained during catheterization or echocardiography; if both results were available, data from catheterization were used.

BNP = brain natriuretic peptide; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ECG = electrocardiogram; QTc = QT interval corrected for heart rate; TIA = transient ischemic attack; TTS = Takotsubo syndrome; ULN = upper limit of the normal.

At multivariable logistic regression analysis, younger (OR: 1.60; 95% CI: 0.86 to 3.01; p = 0.14) and older age (OR: 1.09; 95% CI: 0.66 to 1.80; p = 0.75) were not independently associated with in-hospital mortality using the middle-aged group as a reference; while male sex (OR: 2.18; 95% CI: 1.26 to 3.77; p = 0.005), atrial fibrillation (OR: 5.33; 95% CI: 3.00 to 9.48; p < 0.001), first troponin >10× ULN (OR: 1.62; 95% CI: 1.01 to 2.61; p = 0.047), and acute neurological disorders (OR: 3.03; 95% CI: 1.79 to 5.16;

CENTRAL ILLUSTRATION **Acute Cardiac Care Measures and Complications According to Age Groups**



Cammann, V.L. et al. J Am Coll Cardiol. 2020;75(16):1869-77.

Bar charts are showing that younger Takotsubo syndrome (TTS) patients more often needed acute cardiac care measures, including catecholamines, noninvasive and invasive ventilation, and cardiopulmonary resuscitation compared with middle-aged and elderly TTS patients. In addition, rates of cardiogenic shock and death were higher in younger TTS patients compared with middle-aged and elderly TTS patients.

$p < 0.001$) were factors associated with in-hospital mortality (Figure 1).

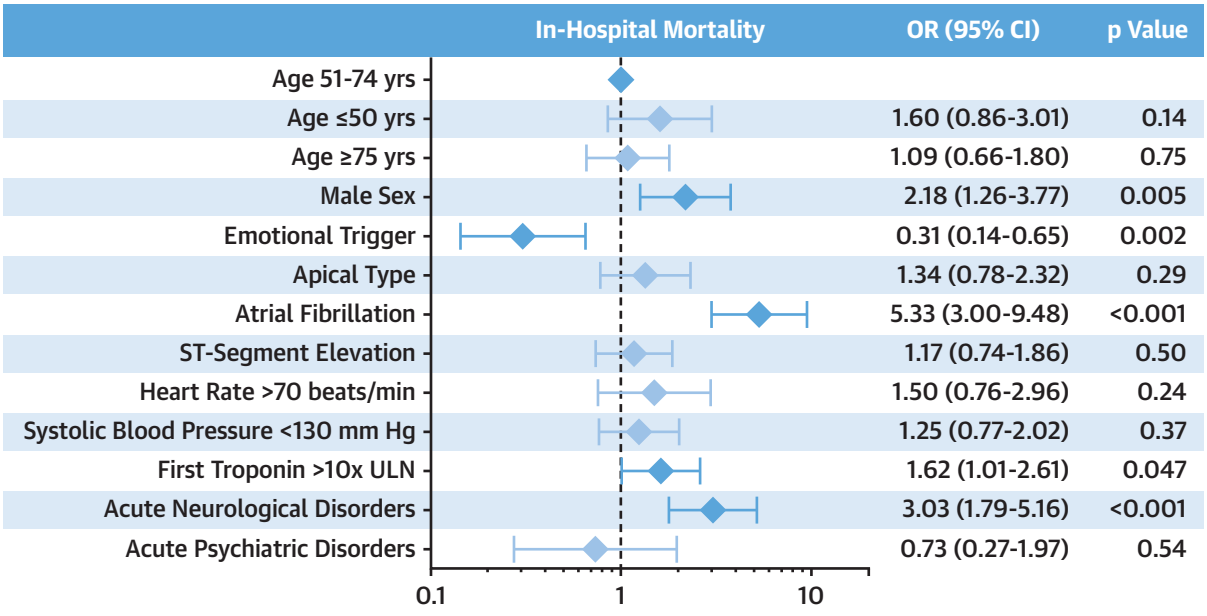
Decision tree analysis demonstrated that physical stress is the most important parameter for in-hospital death in younger and middle-aged TTS patients, while atrial fibrillation emerged as the most important prognostic factor for elderly TTS patients (Supplemental Figure 1). Kaplan-Meier survival analysis revealed no statistically significant differences between the different age groups within the first 60 days after TTS (Figure 2). After 60 days, elderly TTS patients had a significantly higher mortality compared with younger and middle-aged TTS patients ($p < 0.001$) (Supplemental Figure 2).

DISCUSSION

This study based on the InterTAK Registry provides comprehensive data on age-related characteristics and outcomes of patients diagnosed with TTS. The main findings of the study are: 1) patients ≤50 years of age accounted for about 10% of TTS patients and presented with atypical TTS forms more often; 2) younger TTS patients had an increased prevalence of coexisting acute neurological and/or psychiatric disorders; 3) younger TTS patients presented with cardiogenic shock and had an increased need for acute cardiac care treatment more often; and 4) younger and older age were not independently associated with in-hospital mortality.

Although TTS is known to characteristically affect post-menopausal women, a substantial proportion of patients experiencing TTS are below 50 years of age. Giving the increased awareness of the disease, it could be hypothesized that younger and male patients were diagnosed more frequently in more recent years. However, when analyzing age and sex distribution over the entire study period, we could not confirm this assumption. Interestingly, the prevalence of male patients increased with decreasing age and was highest in younger patients. These findings are in line with a prior study that suggested males are younger at the time of index event (13). The pathophysiological mechanisms underlying this observation are

FIGURE 1 **Multivariable Logistic Regression Analysis for In-Hospital Mortality**



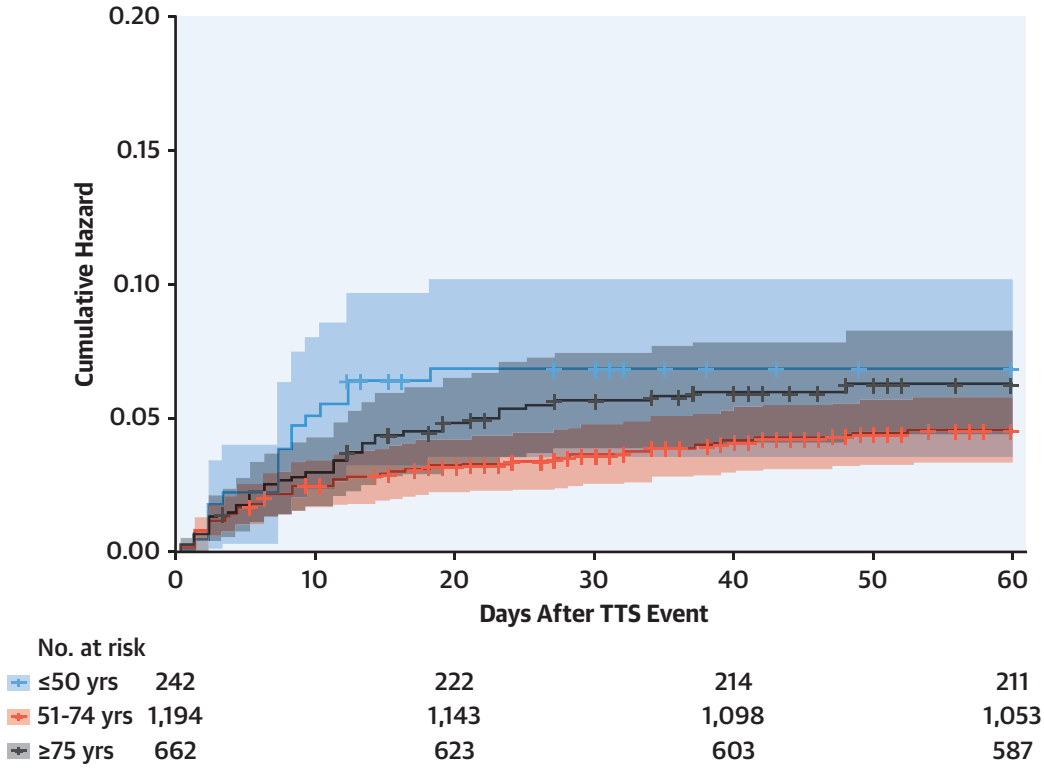
Male sex, atrial fibrillation, first troponin >10× ULN, and acute neurological disorders emerged as factors associated with in-hospital mortality, whereas younger and older age was not associated with in-hospital mortality when using the middle-aged group as a reference. **Error bars** indicate 95% confidence intervals. **Blue** indicates statistically significant variables, while **light blue** is not significant. CI = confidence interval; OR = odds ratio; ULN = upper limit of the normal range.

unknown. Sympathetic stimulation and alterations in the autonomic nervous system are considered to be involved in the pathogenesis of TTS (14-16), and age-related changes in sympathetic stimulation or myocardial susceptibility to catecholamine excess may exist. Indeed, younger patients had higher heart rates, reflecting more extensive sympathetic activation. Given that estrogen exerts a sympatholytic effect by altering β-adrenergic receptor signaling (17), it has been suggested that estrogen depletion following menopause may play a causative role in the pathology of TTS, putting post-menopausal women at particularly high risk (18-20). However, data on the role of estrogen in TTS remain conflicting (21), and cardioprotective endogenous estrogen effects seem to not be sufficient to prevent TTS in a substantial number of younger pre-menopausal women as indicated by the increased heart rate. Particularly in younger patients, the type and severity of the triggering event may predominantly be involved in the development of TTS, as the prevalence of triggering events was higher in younger as compared to middle-aged and elderly patients. Which pathophysiological pathways are predominantly involved in men and women of different age groups remains to be clarified, along with the role of genetic susceptibility in TTS (22).

Most interestingly, the prevalence of atypical TTS was higher in younger patients. It may therefore be speculated that myocardial susceptibility to triggering factors as well as protective defense mechanisms may vary according to age, and these alterations in turn may result in distinct and age-related variants of wall motion abnormalities and disease severity in TTS patients. Alternatively, the activation of midbrain structures and in turn the topical activation of specific nerve fibers may differ with age. Whether and to what extent age- and sex-related changes in sympathetic activity of the left ventricular apex determine the course of the disease remains to be elucidated (23).

Both neurological and psychiatric disorders are known predisposing factors for TTS (3,24,25). Interestingly, the prevalence of acute neurological disorders was significantly higher in younger patients compared with middle-aged and elderly TTS patients. Rates were mainly driven by an increased prevalence of seizures, intracranial bleedings, and migraine attacks or headache disorders. Considering the prevalence of migraine attacks is highest in middle-aged persons in the general population and that intracranial bleedings mainly occur with advanced age (26,27), this observation is of particular importance.

FIGURE 2 Kaplan-Meier Estimates With 95% Confidence Intervals of All-Cause Mortality Stratified by Age Groups



Kaplan-Meier analysis revealed no statistically significant differences in 60-day mortality among younger, middle-aged, and elderly Takotsubo syndrome (TTS) patients ($p = 0.16$).

Similarly, acute psychiatric disorders, particularly affective and adjustment disorders, were more prevalent among younger TTS patients. Whether age-related nervous system or myocardial alterations affect the patient's susceptibility to distinct triggering factors is unknown.

The prevalence of cardiogenic shock and the need for intensive cardiac care treatment including catecholamine use and noninvasive and invasive ventilation was particularly high in younger TTS patients. These findings are supported by data obtained from a cohort of 114 TTS patients showing trends toward increased rates of mechanical ventilation and catecholamine use in patients ≤65 years of age (10). Although patients ≤50 years of age had numerically higher rates of in-hospital mortality compared with middle-aged and elderly patients, this difference did not reach statistical significance and younger age was not independently associated with in-hospital death. Given that male sex and acute neurological disorders emerged as independent predictors of mortality whereas age did not, similar to prior registry data (13,28,29), it is conceivable that differences in baseline characteristics may at least partially account for the worse in-hospital outcomes in patients ≤50 years of age.

Long-term outcome analysis revealed that elderly TTS patients had the highest mortality rate compared with younger and middle-aged TTS patients. This finding might be explained by the fact that advanced age itself is a negative prognostic factor and that elderly TTS patients had a higher prevalence of comorbidities and cardiovascular risk factors.

STUDY LIMITATIONS. First, this was an in-part retrospective study and therefore, suffers from inherent limitations. Second, the prevalence might be higher, especially in elderly and in males, due to a probability of undiagnosed cases.

CONCLUSIONS

About 10% of patients experiencing TTS are below 50 years of age and exhibit a distinct clinical profile.

Male sex, atypical type, and acute neurological and/or psychiatric disorders are more common among younger TTS patients. Given the substantially worse in-hospital course, younger TTS patients present as a particularly vulnerable patient subset in need for close monitoring and intensive care.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Approximately 10% of patients with TTS are age <50 years, and there is a higher proportion of men in the younger group than in older patients with TTS. Cardiogenic shock, respiratory failure, catecholamine requirement, and resuscitation were also more frequent in younger than in older patients with TTS.

TRANSLATIONAL OUTLOOK: Additional studies are needed to identify characteristics other than age that distinguish various subtypes of TTS that may have bearing upon management and prognosis.

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KEY WORDS age, broken heart syndrome, outcome, Takotsubo syndrome

APPENDIX For supplemental figures, please see the online version of this paper.