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Long-term Risk of Death and Hospitalization in Patients With Heart Failure and Takotsubo Syndrome: Insights From a Nationwide Cohort

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ABSTRACT

Background: Data concerning the long-term risk of heart failure (HF) in patients with takotsubo syndrome (TTS) are sparse. We compared the rates of death and hospitalization due to HF with matched individuals from the background population and patients with ST-segment elevation myocardial infarction (STEMI).

Methods: In this nationwide observational cohort study, all patients with first-time TTS (2011−2018) who were alive at discharge were identified by using data from Danish nationwide registries. These were matched for age and sex with individuals from the background population (1:4 matching) and with patients with STEMI who were alive at discharge (1:3 matching).

Results: A total of 881 patients with TTS who were alive at discharge were identified (median age 70 years; 89.4% men). During a mean follow-up of 2.9 years, the incidence rates of death, HF hospitalization, and TTS recurrence in survivors of TTS were 6.9, 0.9 and 1.1 events per 100 person-years. The corresponding absolute 3-year risks were 9.3%, 1.8% and 2.5%, respectively. Survivors of TTS had higher associated rates of death compared with the background population (hazard ratio [HR] 2.05 [95% CI, 1.62−2.60]) and survivors of STEMI (HR 1.69 [1.34−2.13]). Similarly, survivors of TTS had higher associated rates of hospitalization due to HF compared with the background population (HR 4.24 [1.88−9.53]), but lower rates compared with survivors of STEMI (HR 0.34 [0.20−0.56]). Propensity-score matched analyses yielded similar results.

Conclusions: Survivors of TTS had significantly higher associated mortality rates than the background population and survivors of STEMI. Survivors of TTS had lower HF hospitalization rates than survivors of STEMI, but the rates were higher than those of the background population. (*J Cardiac Fail 2022;28:1534−1544*)

Key Words: Takotsubo syndrome, heart failure, myocardial infarction, outcomes, epidemiology.

Takotsubo syndrome (TTS), also known as broken-heart syndrome, stress cardiomyopathy and apical ballooning syndrome, is a reversible form of acute heart failure (HF) that is commonly triggered by physical or psychological stress and is characterized by a distinctive pattern of wall-motion abnormalities and dysfunction of mainly the left ventricle.[1,2] Despite the absence of significant obstructive coronary artery disease, TTS shares common features with acute coronary syndrome, including symptoms at onset (eg, acute chest pain and dyspnea), signs of myocardial ischemia on electrocardiograms and elevation of cardiac biomarkers.[1−4] Although TTS is a reversible condition, the initial presentation may be

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accompanied by fatal complications, including cardiogenic shock, conduction disturbances and lethal arrhythmias, and the in-hospital mortality rate is similar to that of acute coronary syndrome.[3,5–16]

During the past decade, the traditional notion of TTS as a transient and benign condition has been challenged. Accumulating data suggest that TTS may portend worse long-term prognoses than those for an age- and sex-matched population without TTS and even those with acute myocardial infarction.[8,10,17,18] It has also been suggested that TTS, despite initial recovery, may cause long-term structural and metabolic alterations in the myocardium and may progress to a persistent HF phenotype.[19] However, data concerning the long-term prognoses of patients with this condition are limited by the selected or small numbers of patients,[3,8,10–15,17,18] and the long-term risk of clinical HF has not been investigated. Thus, there is a need to better characterize long-term outcomes, including death and the development of clinical HF, in a large, unselected cohort of patients with TTS. Characterizing the long-term prognosis in this population may have important implications in the counseling and follow-up of these patients.

Consequently, we investigated the long-term incidence of death, hospitalization due to HF and recurrence of TTS in a Danish nationwide, all-comers cohort of patients with TTS who were alive at discharge. In addition, we compared the long-term rate of death and hospitalization due HF in patients with TTS with (1) matched individuals from the background population and (2) a matched cohort of patients with ST-segment elevation myocardial infarction (STEMI) who were alive at discharge.

Methods

Data Sources

All citizens in Denmark are assigned a unique personal identification number at birth or upon immigration, which enables accurate linkage of nationwide administrative registries at an individual level. For the purpose of this study, data from the following nationwide administrative registries were obtained: (1) The Danish National Patient Registry, which contains data on all hospital admissions and outpatient contacts according to the International Classification of Diseases (8th Revision [ICD-8] until 1993 and 10th Revision [ICD-10] thereafter) as well as surgical procedures, coded according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures[20]; (2) The Danish National Prescription Registry, which comprises detailed information on dispensing date, strength and quantity of all claimed drug prescriptions in Denmark[21]; (3) The Danish Civil Registration System, which holds information on birth date, sex and vital status (ie, whether a person is alive and resident in Denmark, disappeared, emigrated, or dead, along with the dates of these events)[22]; and (4) the Danish Registry of Causes of Death, which holds information about the date, place, and manner of death (natural, accident, violence, suicide, uncertain) as well as the underlying cause (the disease or condition that started the process that led to death), coded according to the ICD-10, based on death certificates.[23] The Danish registries are validated, are of high quality and have been described in detail previously.[20–23]

Study Population. All Danish residents who were admitted with TTS (any in-hospital diagnosis) between January 1, 2011, and October 31, 2018, were eligible for inclusion. Patients were excluded if they (1) had an in- or outpatient diagnosis code of TTS prior to the index admission (to include patients with first-time TTS diagnoses [the code for TTS was introduced in 2008 in Denmark]); (2) had undergone percutaneous coronary intervention or coronary artery bypass graft surgery during admission (to exclude patients with myocardial infarction misclassified as having TTS); or (3) died during admission (to avoid introducing immortal time bias, given that TTS is not diagnosed at the date of admission]). The TTS diagnosis in the Danish National Patient Registry has previously been validated as having a positive predictive value of 100%.[24]

To compare outcomes between patients with TTS and the background population, a nationwide background population was identified. For patients with TTS, the index date was defined as the date of discharge; individuals from the background population were randomly assigned the same index date as a case from the population with TTS. Each patient with TTS was matched with 4 individuals from the background population by age (up to a 1-year difference), sex and year of index date.

Similarly, a nationwide cohort of patients admitted with STEMI was identified in order to compare outcomes between patients with TTS and patients with STEMI. For patients with both TTS and STEMI, the index date was defined as the date of discharge. Thus, as with the TTS cohort, patients with STEMI had to be alive at discharge. Each patient with TTS was matched with 3 patients with STEMI by age (up to a 1-year difference), sex and year of index date.

Comorbidities and Pharmacotherapy

Comorbidities prior to admission and at the time of discharge were defined by primary or secondary in- or outpatient diagnosis codes given at any time prior to the admission or discharge date, respectively (eTable 1 for diagnosis codes). For the background population, comorbidities were defined as diagnosis codes given at any time prior to the index date. Diabetes and hypertension were identified by

using both diagnosis codes and claimed drug prescriptions, as described previously.[25,26] Pharmacotherapy was defined by claimed prescriptions within 6 months prior to the admission date (or the index date for the background population) (eTable 2 for Anatomical Therapeutic Chemical Classification System codes).

Outcomes. The primary outcome was death from any cause. Secondary outcomes were hospitalization due to HF (overnight hospital stay with HF as the primary diagnosis code) and recurrent TTS (hospital admission with TTS as the primary diagnosis code). The diagnosis codes for hospitalization due to HF have been validated with high positive predictive values in the Danish National Patient Registry.[24,27] For the all-cause mortality and HF hospitalization outcomes, patients were followed from the date of discharge until the outcome of interest, death, emigration, or the end of the study (December 31, 2018), whichever came first. To be included in the recurrent TTS analysis, patients were required to be alive 90 days after discharge, and patients were, therefore, followed from 90 days after the date of discharge until recurrent TTS, death, emigration, or end of study, whichever came first. This was done to ensure that admissions with TTS within the first 90 days (which most likely are related to the index event, given that the ejection fraction in most patients recovers within this timeframe) were not counted as recurrent TTS. No patients were lost to follow-up.

We also examined causes of death. Cause of death was categorized as cardiovascular (ICD-10 category code I as the underlying cause of death obtained from death certificates) or noncardiovascular death. Data on causes of death were available only until December 31, 2017. Therefore, patients who died in 2018 were not included in this analysis.

Statistics

Baseline characteristics were reported as frequencies, with proportions and medians in the 25th−75th percentiles for categorical and continuous variables, respectively, and differences were examined using the ^{2} or Fisher exact test for categorical variables and the Wilcoxon test for continuous variables. Absolute risks of hospitalization due to HF and recurrent TTS were estimated using the Aalen-Johansen estimator, taking the competing risk of death into account, and differences between groups were assessed using the Gray test. Absolute risks of death of any cause were estimated using the Kaplan-Meier estimator, and differences between groups were assessed using the log-rank test. Incidence rates per 100 person-years with 95% confidence intervals (CIs) were calculated for all outcomes. Cox proportional-hazards regression models conditional on the matching (comparing cases with their matched controls) were used to compare the rates of outcomes between groups. Reported were hazard ratios (HRs) with 95% CI, adjusted for comorbidities at the time of discharge (ie, atrial fibrillation, ischemic stroke, hypertension, peripheral artery disease, diabetes, thyroid disease, malignancy, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, and epilepsy) and histories of HF prior to admission. The proportional hazards assumption was fulfilled, and there was no interaction with sex, age or calendar year for any of the outcomes. For the outcome of HF hospitalization, a Fine-Gray competing risk analysis was also performed, with death of any cause considered a competing risk.

The level of statistical significance was set at 5%. Data management and statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Sensitivity Analyses

A number of sensitivity analyses were performed to test the robustness of our findings. (1) For the HF hospitalization outcome, we restricted the TTS population, background population and STEMI population to individuals who did not have histories of HF. (2) A substantial proportion of patients admitted with STEMI develop HF during admission or shortly thereafter.[28] To examine whether a possible difference in the risk of HF hospitalization between the STEMI and TTS cohort was driven by a high incidence of HF hospitalization early after discharge in patients admitted with STEMI, we performed a landmark analysis at 90 days and followed patients from 90 days until HF hospitalization, death, emigration, or end of the study. Patients with TTS were compared with age- and sex-matched patients with STEMI, and only patients who had no HF hospitalization until day 91 and were alive at this time point entered the analysis. (3) To account for differences in baseline characteristics, we also performed propensity score matching. The propensity scores were calculated using multivariable logistic regression and were generated from baseline characteristics including history of HF, atrial fibrillation, stroke, hypertension, peripheral artery disease, diabetes, malignancy, chronic kidney disease, chronic obstructive lung disease, and liver disease. Thus, each patient with TTS was matched with 4 individuals from the background population by age, sex, year of index date, and propensity score (no difference). Similarly, each patient with was matched with 3 patients with STEMI by age, sex, year of index date, and propensity score (up to a 0.005 difference). (4)

Given that the diagnosis of TTS is confirmed with recovery of left ventricular wall motion abnormalities during follow-up with, for example, echocardiography, we restricted the TTS cohort to patients who had also had an outpatient visit due to TTS within 90 days after discharge and were alive at this time point. Patients with TTS were compared with age- and sex-matched individuals from the background population and age- and sex-matched patients with STEMI who were also alive 90 days after discharge and followed from 90 days until death, emigration or end of the study. (5) We performed a landmark analysis from 90 days after discharge and compared the sensitivity TTS cohort (ie, patients with TTS with an outpatient visit within 90 days after discharge) with the full TTS cohort (ie, patients with TTS with or without an outpatient visit within 90 days after discharge). (6) Among patients with TTS, we compared outcomes in patients treated with either an antidepressant or an antipsychotic drug prior to admission with outcomes in patients not treated with these drugs.

Ethics

This study was approved by Capital Region of Denmark (approval #P-2019-348) in accordance with the General Data Protection Regulation. In Denmark, there is no requirement for ethics committee approval in registry-based studies in which individuals cannot be identified.

Results

From January 1, 2011, to October 31, 2018, 935 patients without histories of TTS were admitted with TTS in Denmark. During admission, 32 (3.4%) died, and 22 (2.4%) underwent percutaneous coronary intervention or coronary artery bypass graft surgery. After excluding these patients, 881 patients were included in the study. The median age was 70 years (25th–75th percentile 61–77 years), and 89.4% were women. The median length of stay was 5 days (25th–75th percentile, 4–9 days).

All 881 survivors of TTS were matched with 4 individuals from the background population (n = 3524). Baseline characteristics for the groups are shown in Table 1. Compared with the background population, survivors of TTS were more likely to have cardiovascular comorbidities, including histories of ischemic heart disease and HF, atrial fibrillation, hypertension, peripheral artery disease, and diabetes. They were also more likely to have chronic obstructive pulmonary disease, chronic kidney disease and histories of malignancy. Treatment with antidepressants (13.1% vs 20.4%), antipsychotics (3.1% vs 4.5%), and benzodiazepines (4.7% vs 7.6%) was also more common in survivors of TTS compared with the background population.

Table 1. Baseline characteristics of patients with takotsubo syndrome matched 1:4 for age, sex and year of diagnosis with individuals from the background population

	Background n = 3,524	TTS n = 881	*P* value
Demographics			
Age, median (25th–75th percentile)	70 (61-77)	70 (61-77)	N/A
Male, n (%)	372 (10.6)	93 (10.6)	N/A
Comorbidities, n (%)			
Ischemic heart disease*	371 (10.5)	160 (18.2)	<0.001
Myocardial infarction*	134 (3.8)	66 (7.5)	<0.001
Heart failure*	105 (3.0)	51 (5.8)	<0.001
Atrial fibrillation	243 (6.9)	114 (12.9)	<0.001
Ischemic stroke	150 (4.3)	72 (8.2)	<0.001
Cerebrovascular disease	221 (6.3)	104 (11.8)	<0.001
Hypertension	1,331 (37.8)	458 (52.0)	<0.001
Peripheral artery disease	75 (2.1)	36 (4.1)	<0.001
Diabetes	310 (8.8)	99 (11.2)	0.03
Thyroid disease	507 (14.4)	136 (15.4)	0.43
Malignancy	427 (12.1)	156 (17.7)	<0.001
Chronic kidney disease	89 (2.5)	42 (4.8)	<0.001
Chronic obstructive pulmonary disease	213 (6.0)	224 (25.4)	<0.001
Liver disease	71 (2.0)	35 (4.0)	<0.001
Epilepsy	56 (1.6)	37 (4.2)	<0.001
Concomitant medical treatment, N (%)*			
Beta-blockers	558 (15.8)	163 (18.5)	0.06
Calcium-blockers	625 (17.7)	127 (14.4)	0.02
ACEi or ARB	1,024 (29.1)	326 (37.0)	<0.001
Loop diuretics	256 (7.3)	112 (12.7)	<0.001
Lipid-lowering medication	899 (25.5)	271 (30.8)	0.002
Antiplatelets	612 (17.4)	221 (25.1)	<0.001
Oral anticoagulants	211 (6.0)	75 (8.5)	0.007
Antidepressants	463 (13.1)	180 (20.4)	<0.001
Antipsychotics	109 (3.1)	40 (4.5)	0.03
Benzodiazepines	165 (4.7)	67 (7.6)	<0.001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; TTS, takotsubo syndrome.

N/A, not applicable (as the groups were matched upon these variables).

*Prior to admission/index.

Baseline characteristics for the TTS and the unmatched STEMI cohorts are displayed in eTable 3. In total, 807 (91.6%) survivors of TTS were matched with 3 survivors of STEMI (n = 2421). Baseline characteristics for the matched groups are shown in Table 2. Survivors of TTS were more likely to have cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, and a history of malignancy but were less likely to have diabetes compared with matched survivors of STEMI. Survivors of TTS were also more often treated with antidepressants (13.4% vs 20.6%) and antipsychotics (2.2% vs 4.3%) than survivors of STEMI.

All-cause Mortality

During a mean follow-up of 2.9 years, 165 (18.7%) and 265 (7.5%) patients died in the TTS and

Table 2. Baseline characteristics of patients with takotsubo syndrome matched 1:3 for age, sex and year of diagnosis with patients with ST-segment elevation myocardial infarction

	STEMI n = 2,421	TTS n = 807	*P* value
Demographics			
Age, median (25th–75th percentile)	70 (61–77)	70 (61–77)	N/A
Male, n (%)	276 (11.4)	92 (11.4)	N/A
Comorbidities, n (%)			
Ischemic heart disease*	419 (17.3)	144 (17.8)	0.73
Myocardial infarction*	206 (8.5)	61 (7.6)	0.40
Heart failure*	121 (5.0)	47 (5.8)	0.36
Atrial fibrillation	274 (11.3)	100 (12.4)	0.41
Ischemic stroke	147 (6.1)	66 (8.2)	0.04
Cerebrovascular disease	209 (8.6)	98 (12.1)	0.003
Hypertension	1,213 (50.1)	415 (51.4)	0.52
Peripheral artery disease	127 (5.3)	33 (4.1)	0.19
Diabetes	332 (13.7)	88 (10.9)	0.04
Thyroid disease	331 (13.7)	126 (15.6)	0.17
Malignancy	284 (11.7)	144 (17.8)	<0.001
Chronic kidney disease	157 (6.5)	40 (7.0)	0.12
Chronic obstructive pulmonary disease	266 (11.0)	205 (25.4)	<0.001
Liver disease	58 (2.4)	31 (3.8)	0.03
Epilepsy	41 (1.7)	35 (4.3)	<0.001
Concomitant medical treatment, n (%)*			
Beta-blockers	517 (21.4)	146 (18.1)	0.047
Calcium-blockers	486 (20.1)	120 (14.9)	0.001
ACEi or ARB	782 (32.3)	298 (36.9)	0.02
Loop diuretics	244 (10.1)	101 (12.5)	0.05
Lipid-lowering medication	628 (25.9)	244 (30.2)	0.02
Antiplatelets	508 (21.0)	202 (25.0)	0.02
Oral anticoagulants	106 (4.4)	62 (7.7)	<0.001
Antidepressants	325 (13.4)	166 (20.6)	<0.001
Antipsychotics	54 (2.2)	35 (4.3)	0.002
Benzodiazepines	144 (5.9)	62 (7.7)	0.08

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; STEMI, ST-segment elevation myocardial infarction; TTS, takotsubo syndrome.

N/A, not applicable (as the groups were matched upon these variables).

*Prior to admission/index.

background population, respectively. The absolute 3-year risk of death was 19.3% (95%CI, 16.3%–22.6%) and 7.2% (6.2%–8.3%) in the TTS and the background population, respectively (Fig. 1A). The corresponding 6-year risks were 29.0% (95%CI, 24.5%–33.6%) and 15.3% (13.3%–17.5%), respectively. Compared with matched individuals from the background population, survivors of TTS had a higher associated rate of death (adjusted HR 2.05 [95%CI, 1.62–2.60]) (Table 3).

In total, 161 (20.0%) and 311 (12.8%) patients died in the TTS and STEMI populations, respectively, during follow-up. The absolute 3-year risks of death were 19.7% (16.6%–23.0%) in survivors of TTS and 11.3% (9.9%–12.8%) in survivors of STEMI (Fig. 2A). The corresponding 6-year risks were 29.4% (24.8%–34.1%) and 21.8% (19.2%–24.6%), respectively. Survivors of TTS had a higher associated rate of death compared with matched survivors of STEMI (adjusted HR 1.69 [1.34–2.13]) (Table 3).

During follow-up, the majority of patients with TTS died from noncardiovascular causes (82.9%). The most common causes of death were cancer (31.5%) and chronic obstructive pulmonary disease (21.6%). Among deceased individuals in the matched background population, the proportion of noncardiovascular causes of death was 81.5%. The proportion of patients who died from noncardiovascular causes in the matched STEMI population was 62.4%.

Hospitalization due to Heart Failure

The median time to HF hospitalization was 0.8 years (25th–75th percentile, 0.2–3.3 years) in the TTS population. Baseline characteristics of patients with TTS who were later admitted for HF vs those who were not are shown in eTable 4. Patients with HF hospitalizations during follow-up, compared to those without, were more likely to have histories of myocardial infarction, HF and. chronic obstructive pulmonary disease and were more commonly treated with beta-blockers, loop diuretics and antiplatelets.

The absolute 3-year risks of HF hospitalization were 1.8% (1.0%–3.0%) and 0.9% (0.6%–1.4%) in the TTS and the background population, respectively (Fig. 1B). The corresponding 6-year risks were 3.3% (2.0%–5.3%) and 1.6% (1.1%–2.4%), respectively. Compared with the background population, survivors of TTS had a higher associated rate of HF hospitalization (adjusted HR 4.24 [1.88–9.53]; adjusted subdistribution HR 2.65 [1.45–4.86]) (Table 3).

The absolute 3-year risks of HF hospitalization were 1.8% (1.0%–3.0%) and 6.9% (5.8%–8.0%) in the TTS and the STEMI population, respectively (Fig. 2B). The corresponding 6-year risks were 3.3% (2.0%–5.3%) and 9.1% (7.6%–10.8%), respectively. TTS was associated with lower postdischarge rate of HF hospitalization compared with STEMI (adjusted HR 0.34 [0.20–0.56]; adjusted subdistribution HR 0.32 [0.20–0.51]) (Table 3).

Recurrence of Takotsubo

Among the 825 patients with TTS who were alive 90 days after discharge, 22 (2.7%) had recurrent TTS. The rate of recurrent TTS was 1.0 events per 100 person-years, with an absolute 3- and 6-year risk of 2.5% and 4.7%, respectively. The median time to recurrent TTS was 1.9 years (25th–75th percentile, 0.9–3.5 years). Compared with patients without recurrence, those with recurrent TTS were younger, more likely to have histories of myocardial infarction and HF and more often treated with lipid-lowering medication (eTable 5). They were also more often

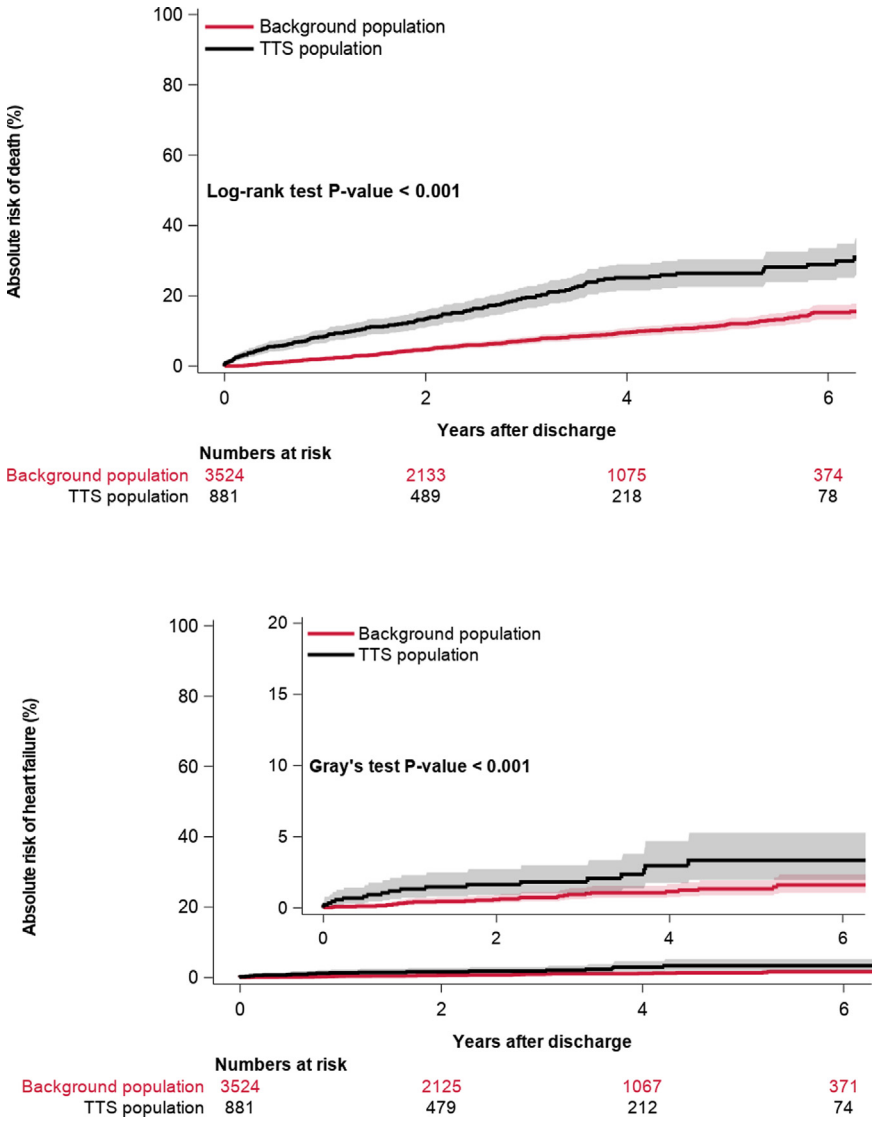

Fig. 1. Absolute risk of outcomes after discharge in patients with TTS and in individuals from the background population. A, All-cause mortality. B, Hospitalization due to heart failure. Patients with TTS were matched with 4 individuals from the background population by age (up to a 1-year difference), sex and year of index date. TTS, takotsubo syndrome.

treated with calcium-channel blockers, antiplatelets and antidepressants. There was no difference between groups with respect to treatment with beta-blockers or angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.

Sensitivity Analyses

A number of sensitivity analyses were performed to test the robustness of our findings.

1. Among individuals without histories of HF, TTS was associated with higher postdischarge rates of hospitalization due to HF than those of the background population (adjusted HR 5.10 [95%CI, 2.03−12.82]), but lower than the STEMI population (adjusted HR 0.31 [0.18−0.54]; adjusted subdistribution HR 0.30 [0.18−0.50]).
2. In the 90-day landmark analysis, TTS was not significantly associated with lower postdischarge rates of HF hospitalization than STEMI, although there was a trend toward a lower rate (adjusted HR 0.51 [0.26−1.01]; adjusted subdistribution HR 0.53 [0.28−1.00]).
3. Baseline characteristics of the propensity-score matched cohorts are shown in eTable 6 (background population vs TTS) and eTable 7 (STEMI vs TTS). In the propensity score matching analysis, survivors of TTS had significantly higher rates of death compared with matched individuals from the background population (adjusted HR 2.17 [1.75−2.69]) and survivors of STEMI (adjusted HR 1.79 [1.31−2.45]). Similarly, and in accordance

Table 3. Outcomes in patients with takotsubo syndrome compared with matched individuals from the background population and matched patients with ST-segment elevation myocardial infarction

	Comparison with Background Population*		Comparison with STEMI Population**	
	Background n = 3524	TTS n = 881	STEMI n = 2421	TTSn = 807
All-cause mortality				
n (%)	265 (7.5)	165 (18.7)	311 (12.8)	161 (20.0)
Incidence rate per 100 person-years (95% CI)	2.0 (2.2−2.8)	6.9 (5.9−8.1)	4.3 (3.8−4.8)	7.0 (6.0−8.2)
Hazard ratio (95% CI)***	2.05 (1.62−2.60)		1.69 (1.34−2.13)	
HF hospitalization				
N (%)	31 (0.9)	20 (2.3)	162 (6.7)	19 (2.4)
Incidence rate per 100 person-years (95% CI)	0.3 (0.2−0.4)	0.9 (0.6−1.3)	2.3 (2.0-2.7)	0.8 (0.5−1.3)
Hazard ratio (95% CI)***	4.24 (1.88−9.53)		0.34 (0.20−0.56)	
Subdistribution hazard ratio (95% CI)***	2.65 (1.45−4.86)		0.32 (0.20−0.51)	
TTS recurrence				
N (%)	N/A	22 (2.7)****	N/A	22 (2.7)****
Incidence rate per 100 person-years (95% CI)	N/A	1.0 (0.7-1.6)	N/A	1.0 (0.7-1.6)
Hazard ratio (95% CI)***	N/A		N/A	

N/A, not applicable; STEMI, ST-segment elevation myocardial infarction; TTS, takotsubo syndrome.

*Patients with TTS were matched with 4 individuals from the background population by age (up to a 1-year difference), sex and year of index date.

**Patients with TTS were matched with 3 patients with STEMI by age (up to a 1-year difference), sex and year of index date.

***Hazard ratios were stratified according to the matching (ie, comparing cases with their matched controls) and adjusted for atrial fibrillation, ischemic stroke, hypertension, peripheral artery disease, diabetes, malignancy, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, epilepsy, and heart failure. All covariates were defined at the time of discharge, except heart failure (defined before admission).

****The denominator is 825; recurrent TTS was defined as a hospitalization with TTS as primary diagnosis from 90 after discharge of the primary event, and patients were therefore required to be alive at 90 days after discharge.

with the main findings, TTS was associated with a higher postdischarge rate of HF hospitalization compared with a matched background population (adjusted HR 2.93 [1.51−5.68) but a lower rate compared with a matched STEMI population (adjusted HR 0.29 [0.14−0.63]; adjusted subdistribution HR 0.26 [0.11−0.59]).

4. In total, 393 (44.6%) patients with TTS had outpatient visits due to TTS within 90 days after discharge and were alive at this time point. These patients (ie, the sensitivity cohort) did not have a significantly different rate of death than matched individuals from the background population (although there was a trend toward a higher rate; adjusted HR 1.52 [0.98−2.38]) and patients with STEMI who were alive 90 days after discharge (adjusted HR 1.17 [0.78−1.76]) (eFigure 1).
5. In a landmark analysis from 90 days after discharge, the sensitivity cohort (ie, patients with TTS with an outpatient visit within 90 days after discharge) did not appear to have a different risk of death compared with the full cohort (ie, patients with TTS with or without an outpatient visit within 90 days after discharge) (eFigure 2).
6. Among the 881 patients with TTS, 195 (22.1%) were treated with either an antidepressant or an antipsychotic prior to admission. In adjusted analyses, use of either an antidepressant or an antipsychotic prior to admission was not significantly associated with a higher risk of death (1.32 [95% CI, 0.92−1.88]) or HF hospitalization (adjusted HR 1.15 [95% CI, 0.39−3.38]; adjusted subdistribution HR 1.13 [95% CI, 0.39−3.32]).

Discussion

In this Danish nationwide cohort study, we investigated the long-term rate of death, hospitalization due to HF and recurrence of TTS in an all-comers cohort of patients with TTS who were alive at discharge. The study yielded the following major findings. First, the rate of death by any cause among survivors of TTS was significantly higher than that of age- and sex-matched individuals from the background population and survivors of STEMI. Second, the rate of hospitalization due to HF among survivors of TTS was higher than that of the background population but lower than that of survivors of STEMI. Third, the rate of recurrent TTS was 1.8 events per 100 person-years.

Mortality

The short-term prognoses for patients with TTS have been well described,[3,5,14−16,6−13] but data concerning the long-term prognoses are sparse, and most studies are limited by selected or small numbers of patients.[8,10−15,17,18] However, in a large study from the International Takotsubo Registry, comprising data from 26 cardiovascular centers across 9 countries, the mortality rate was 5.6% per patient-year among 1750 patients with TTS

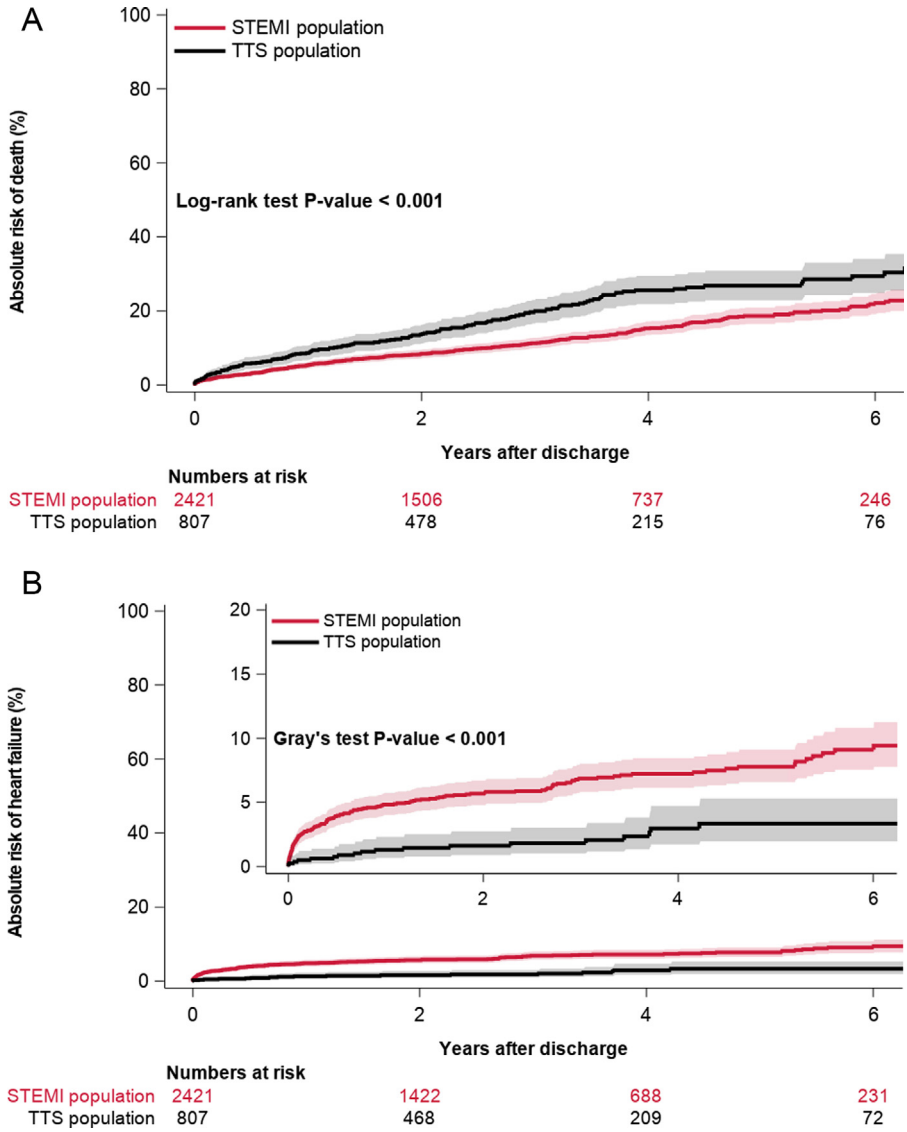

Fig. 2. Absolute risk of outcomes after discharge in patients with TTS and ST-segment elevation myocardial infarction. A, All-cause mortality. B, Hospitalization due to heart failure. Patients with TTS were matched with 3 patients with STEMI by age (up to a 1-year difference), sex and year of index date. STEMI, ST-segment elevation myocardial infarction; TTS, takotsubo syndrome.

diagnosed between 1998 and 2014.[3] In our nationwide unselected cohort of survivors of TTS, we found a slightly higher mortality rate of 6.9% per patient-year, which may, in part, be explained by the greater age in our TTS cohort (70 vs 66 years). To put these numbers into perspective, it is important to compare the mortality risk with that of the background population. In a small observational study including 136 patients with TTS and 136 age- and sex-matched individuals, patients with stress cardiomyopathy had a significantly higher mortality rate than matched individuals during a mean follow-up of 2.3 years, particularly within the first year after diagnosis.[10] In contrast, another small observational study did not find any significant difference in mortality between 100 patients with TTS and age- and sex-matched matched individuals during a mean follow-up of 4.4. years.[11] In a larger and unselected cohort, we found that survivors of TTS had a substantially higher associated rate of death of any cause compared with age- and sex-matched individuals from the background population, even after rigorous adjustment for several comorbidities and propensity score matching.

It is also of interest to compare the long-term prognoses of patients with TTS with those of patients with myocardial infarction, given that these patients share common features and that historically, TTS has been regarded as STEMI. In a Swedish registry-based case-control study including 505 patients with TTS and 1010 age- and sex-matched patients with STEMI or unstable coronary artery

disease, the 3-year cumulative of death of any cause was 10% in both groups.[17] Similarly, in another, smaller retrospective study from Sweden, there was no significant difference in mortality rates between 302 patients with TTS and 6595 STEMI and 8207 non-STEMI patients in propensity-score adjusted analyses during a median follow-up of 25 months.[13] Both of these studies followed patients from admission, and patients with coronary artery disease and myocardial infarction had substantially higher mortality rates during hospitalization compared with patients with TTS.[13,17] In contrast, Stiermaier et al. found a significantly higher mortality rate in 286 patients with TTS who were recruited from 2 tertiary care centers in Germany, compared with 286 age- and sex-matched patients with STEMI during a mean follow-up of 3.8 years.[8] Likewise, a study from the International Takotsubo Registry demonstrated that TTS secondary to neurological diseases had a significantly higher mortality rate than sex- and age-matched patients with acute coronary syndrome.[18] In accordance with these studies, we found that survivors of TTS overall had a higher mortality rate than matched survivors of STEMI.

Our findings substantially expand knowledge regarding the long-term prognosis in TTS, but possible explanations for the observed excess mortality rates are not clear. Patients with TTS were more comorbid than both the background and the STEMI population, and the causes of death were predominantly noncardiovascular (in particular, cancer and chronic obstructive pulmonary disease). It is, therefore, not unlikely that the excess mortality rates, despite thorough adjustment for potential confounders and propensity score matching, may simply reflect the underlying comorbidity burden rather than the condition itself. Whatever the reason, our data further support that TTS is not a transient and benign condition, and further studies are, therefore, needed to better understand the observed excess mortality in TTS.

Heart Failure

Although TTS is characterized by a distinctive pattern of wall-motion abnormalities and dysfunction of the left ventricle in the acute phase, this condition is reversible, including a complete recovery of the left ventricular dysfunction in the weeks after onset.[1–4] The apparently reversible nature of TTS has led to the commonly accepted belief that TTS is a transient and benign condition. However, in a small observational case-control study, 37 patients with prior TTS had reduced exercise capacity, impaired left ventricular strain patterns and reduced cardiac energetic status compared with 37 age-, sex-, and comorbidity-matched controls.[19] That study also demonstrated that the majority of patients with TTS had persisting symptoms compatible with HF, including fatigue and dyspnea, even though they were included in the study more than 12 months after the index event and had a complete remission of the left ventricular ejection fraction.[19] Although that study suggests that TTS is associated with long-term structural and metabolic alterations in the myocardium and may progress to a persistent HF phenotype, the long-term risk of developing more severe HF (ie, hospitalization due to HF) after TTS has not been investigated. To our knowledge, our study is the first to examine the long-term incidence of HF hospitalization in a large, unselected cohort of patients with TTS and to compare the rate of HF hospitalization with that of individuals from the background population and patients with STEMI. The absolute 6-year risk of HF hospitalization in survivors of TTS was approximately 3%, which was lower than that of survivors of STEMI. Although this difference was particularly pronounced within the first months after discharge, HF hospitalizations were also less common in patients with TTS in a landmark analysis in which HF events during the first 3 months were not included. This finding is not surprising, given that left ventricular systolic dysfunction (which increases the risk of developing clinical HF) is not uncommon after STEMI.[29,30] More surprising is the finding that survivors of TTS had a substantially higher rate of HF hospitalization than age- and sex-matched individuals from the background population, even after rigorous adjustment for several comorbidities and propensity score matching. This novel finding further supports the understanding that TTS is not a transient and benign condition, but additional studies are needed to establish whether TTS confers a greater risk of developing clinical HF compared with the background population, and a better understanding of the mechanisms is warranted to improve the outcome of these patients.

Recurrent Takotsubo Syndrome

Data concerning the long-term risk of recurrent TTS are inconsistent and are limited by data from single centers and low numbers of patients.[9–12,14] In our nationwide cohort study, we found that the rate of recurrent TTS was 1.1 events per 100 person-years, which is slightly lower than that in the International Takotsubo Registry[3,31] but is similar to the rate found in other studies. We did not have granular data on the recurrent event (eg, triggers, echocardiographic findings, in-hospital complications, and subsequent prognosis), but our data nevertheless support previous findings in that the risk of recurrent TTS is not negligible. Thus, there is a need to better characterize recurrent TTS events in order to prevent them.

Strengths and Limitations

The main strength of this study is the completeness of data in a large nationwide, unselected cohort of patients with TTS followed in a real-world setting and with long-term follow-up. The Danish health care system, funded by taxes, provides equal access to health care services for all residents, regardless of socioeconomic or insurance status.

The findings of this study should be viewed in the context of a number of limitations. Patients with TTS were identified through the Danish National Patient Registry, which is based on ICD codes, though the diagnosis of TTS has previously been validated with a high positive predictive value.[24] In order to ensure the diagnosis and to avoid immortal time bias, patients with TTS were followed from the date of discharge, and patients who died during admission were, therefore, excluded. In addition, and reassuringly, a landmark analysis demonstrated a similar risk of death in the sensitivity cohort (ie, patients with TTS and with an outpatient visit within 90 days after discharge) and the full cohort (ie, patients with TTS with or without an outpatient visit within 90 days after discharge). Although the sensitivity cohort comprised only half of the full cohort, there might be several plausible explanations, including that patients had to be alive until day 90 to be included, might still have TTS despite not being coded as such during an outpatient visit or, for some reason, did not have an outpatient visit. However, the TTS diagnosis in the Danish National Patient Registry has previously been validated as having a high positive predictive value. In the analysis of recurrent TTS, in which patients were required to be alive 90 days after discharge and followed from 90 days after the date of discharge, we were not able to account for left truncation of censoring. The observational nature of this study precludes the assessment of cause-effect relationships, and the possibility of residual confounding cannot be excluded despite rigorous adjustment for potential confounders and propensity score matching. In addition, data on clinical characteristics, including symptoms at admission and presumed triggers, severity of comorbidities (for example, hypertension), cardiac biomarkers, in-hospital complications, and echocardiographic findings were not available. The last is particularly important because it would be interesting to characterize patients developing HF in greater detail, for example, whether they developed HF with reduced or preserved ejection fraction. Moreover, it is likely that some patients in the TTS cohort may have had a TTS event before inclusion, given that the diagnosis code for TTS was introduced in 2008. Finally, despite a high positive predictive value, the sensitivity of the TTS diagnosis code may have been lower in the years following the introduction of this code into the ICD-10. However, we tried to address this issue by starting the inclusion in 2011.

Conclusions

In this nationwide cohort study, survivors of TTS had a significantly higher associated mortality rate compared with matched individuals from the background population and matched survivors of STEMI. Survivors of TTS had a lower associated HF hospitalization rate compared with matched survivors of STEMI, but the rate was higher than that of a matched background population. These findings further support that TTS is not a transient and benign condition.

Lay Summary

We compared the risk of death and admission due to heart failure in 881 patients with takotsubo syndrome, also known as broken heart syndrome or stress cardiomyopathy, with age- and sex-matched individuals from the background population and patients with heart attack. Patients with takotsubo syndrome have a higher risk of mortality than individuals from the background population and patients with heart attack. Although patients with takotsubo syndrome have a lower risk of being admitted with heart failure compared with patients with heart attack, they have a higher risk of being admitted with heart failure compared with individuals from the background population.

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Conflicts of Interest

All authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2022.02.002.

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