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ORIGINAL RESEARCH

Sex differences of in-hospital outcome and long-term mortality in patients with Takotsubo cardiomyopathy

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Background: Previous studies revealed that patients with Takotsubo cardiomyopathy (TTC) have a higher mortality rate than the general population. It is still unclear whether sex differences may influence long-term prognosis of TTC patients. The purpose of this study was to determine whether sex differences do influence the short- and long-term outcomes of TTC.

Methods and results: A total of 114 patients with TTC were admitted to the University Medical Centre Mannheim from January 2003 to September 2015 and entered into the TTC database of the University Medical Centre Mannheim, and retrospectively analyzed. Patients were diagnosed by the Mayo Clinic criteria. All-cause mortality over mean follow-up of 1,529±1,121 days was revealed. Significantly more male patients died within long-term follow-up compared to female TTC patients (log-rank test; P=0.01). Most males died of noncardiac causes. In multivariate Cox regression analysis, the male sex (P=0.02, hazard ratio [HR] 2.8, 95% CI 1.1–7.2), the ejection fraction ≤35% (P=0.01, HR 3.3, 95% CI 1.2–9.2) and glomerular filtration rate <60 mL/min (P<0.01, HR 3.1, 95% CI 1.4–7.0) figured out as independent predictors of the adverse outcome.

Conclusion: This study shows that males suffering from TTC reveal a higher long-term all-cause mortality rate than females over a 5 year follow-up period.

Keywords: Takotsubo cardiomyopathy, sex differences, outcome, mortality

Introduction

Takotsubo cardiomyopathy (TTC) is a reversible clinical condition mimicking an acute myocardial infarction (AMI).[1] It consists of a transient left ventricular (LV) dysfunction being characterized by defined wall motion abnormalities in the absence of significant coronary artery stenosis.[2] Even if there is no coronary artery stenosis, TTC may be associated with critical complications such as life-threatening arrhythmias, thromboembolic events, cardiac rupture and cardiogenic shock.[2–6]

The classification system of TTC is based on the ballooning pattern of ventricular walls, diagnosed by transthoracic echocardiography and laevocardiography.[1] There are four different ballooning patterns: the apical form is the most common (81.75%), followed by the mid-ventricular form (14.6%) and the rare forms, such as the basal (2.2%) and focal (1.5%) patterns. In daily routine, TTC is a rarely diagnosed disease and its causes are still not understood completely.[1,7–10] One of the most described reasons for the development of TTC may consist of emotional stress. Therefore, a link was attributed pathologically to the so-called brain–heart axis.[11,12]

As it is widely known, defined cardiovascular risk factors, such as patients' age and sex, do exist influencing the occurrence and severity of many diseases.[13]

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Specifically for the development of TTC, it was shown that most patients were postmenopausal women.[14] Accordingly, most studies evaluating TTC patients focused on older female study populations. However, only a few scientific evidence is available about the differences in both sex distributions, ie, males and females, in patients with TTC.[15] Murakami et al[16] obtained clinical information of a multi-center database (Tokyo CCU Network). They observed 368 patients suffering from TTC during a follow-up of 3 years. They have shown that males seem to have more cardiac complications during hospitalization than females.[16] Schneider et al[15] reported about sex differences in the manifestation of TTC. A total of 296 female patients and 28 male patients were included. They presented a female predominance for developing a TTC but not a significant difference in the mortality between male and female patients.[15–17] Brinjikji et al[17] found that mortality was significantly higher in male patients with TTC during a follow-up of 1 year.[16]

In comparison to Murakami et al, Schneider et al and Brinjikji et al, we analyzed a database of 114 patients with a follow-up of 5 years to report about the all-cause mortality during this time in relation to sex.

Additionally, it is still unclear, whether sex differences may influence long-term prognosis of TTC patients with regard to all-cause mortality.

The purpose of this study was to investigate sex differences in prevalence and outcome of patients with TTC.

Methods

A total of 114 patients with TTC were admitted from January 2003 to September 2015 in the TTC database of our institution. Patients were diagnosed by the following Mayo Clinic criteria:[18]

1. transient hypokinesis, akinesis or dyskinesis of the LV midsegment with or without apical involvement; the regional wall motion abnormalities extending beyond a single epicardial vascular distribution; a stressful trigger often but not always present;
2. absence of obstructive coronary disease or angiographic evidence of acute plaque rupture;
3. new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and
4. absence of pheochromocytoma or myocarditis.

The angiograms, echocardiograms and electrocardiograms (ECGs) were reviewed by two experienced independent cardiologists to evaluate the diagnosis of TTC. This retrospective study was conducted in compliance with the Declaration of Helsinki with regard to investigations in human subjects, and the study protocol was approved by the ethics committee of University Medical Centre Mannheim. A patient consent to review the medical records was not required.

In-hospital events, arrhythmias, cardiac rupture, thromboembolic events, pulmonary congestion with the use of non-invasive positive-pressure ventilation (NPPV), intubation, use of a temporary pacemaker, use of inotropic agents and in-hospital death were assessed based on chart review. All-cause mortality was revealed over a mean follow-up of 1,529±1,121 days as assessed by chart review and/or telephone review. If medical records, treating physicians or relatives were unable to provide further information concerning the circumstances of death, it was defined as death due to unknown case.

Blood sample collection

The peripheral venous or central venous blood of the probands was taken in sterile monovettes using the aspiration system.[19,20] The monovettes contained EDTA, heparin and in the serum monovette a clot activating gel. All samples were analyzed immediately in the laboratory of the University Medical Centre Mannheim.

Statistics

Data are presented as mean ± standard deviation (SD) for continuous variables with a normal distribution, median (interquartile range) for continuous variables with a non-normal distribution or as frequency (%) for categorical variables. The Kolmogorov–Smirnov test was used to assess normal distribution. The Student's *t*-test and the Mann–Whitney *U* test were used to compare continuous variables with normal and non-normal distributions, respectively. The chi-squared test or Fisher's exact test was used to compare categorical variables. The log-rank test was used to compare the survival curves between female and male patients. Factors with $P<0.10$ on univariate analysis were entered into the Cox multivariate regression to define independent risk factors for the outcome. Statistical analysis was performed with IBM SPSS software in all analyses; $P\leq0.05$ (two tailed) was considered to indicate statistical significance.

Results

Study population

Most patients were females (82%, n=93). A total of 114 patients being admitted to our hospital due to acute TTC

were included in the present study. In all, 18 patients with uncertain TTC due to absence of coronary angiogram and/or follow-up echocardiogram were excluded. The baseline characteristics are shown in Table 1. The median age of all patients was 68 years (range 41–91 years). The mean duration of intermediate care unit (ICU) treatment was 4.43 days. All patients underwent coronary angiography and transthoracic echocardiography at the time of TTC development.

Differences in patient characteristics related to female and male sex

Comparing the age in the female and male groups, no statistically significant difference was shown (Table 1). Vital signs such as blood pressure and heart rate were also similar in both groups. Regarding patient's history, the ratio of female patients suffering from angina was not different from the ratio of men (54% versus 37%, $P>0.05$). Female patients did not complain more often about emotional stress than male patients (30% versus 11%, $P=0.15$). Males also did not more likely suffer from physical stress than female patients (63% versus 55%, $P=0.49$).

The prevalence of malignancy was higher in male patients compared to females, but this was not statistically significant.

ECG recordings revealed a higher incidence of ST segment elevations and QT prolongation in females compared to males (33% versus 16%). However, no difference in T-wave inversions was observed. Transthoracic echocardiography show an increased incidence of right ventricular (RV) involvement in male patients compared to females (32% versus 21%). The apical type of TCC was most common (70% in females and 79% in males), followed by midventricular type occurring in 27% of females and 21% of males.

Regarding baseline laboratory values, no differences were observed for troponin I, C-reactive protein (CRP) or creatinine. Compared to females, males revealed significantly higher levels of creatinine kinase (CK).

No statistically significant differences were observed with respect to medical treatment at the time of TTC development between males and females.

The in-hospital events are shown in Table 2. Although males did have a higher incidence of life-threatening arrhythmias, in-hospital death and resuscitation than females, this difference was not significant. A difference was shown in the mechanical respiratory support ($P=0.06$). Males had a higher incidence of NPPV and intubation than females. No difference was shown in the length of stay at ICU. Noteworthy, the incidence for thromboembolic events was higher in females than in males.

Table 1 Baseline characteristics of patients with TTC according to sex difference

Variables	Female (n=95)	Male (n=19)	*P*-value*
Demographics			
Age, mean ± SD	67.72±11.33	64.37±10.60	0.23
Symptoms, n (%)			
Dyspnea	36 (37.89)	7 (36.84)	0.93
Chest pain	51 (53.68)	7 (36.84)	0.18
Clinic parameter, mean ± SD			
Systolic BP, mmHg	131.96±29.78	128.68±42.19	0.69
Diastolic BP, mmHg	76.81±14.46	76.00±27.42	0.87
Heart rate, bpm	98.55±25.87	109.89±31.35	0.10
ECG data, n (%)			
ST-segment elevation	31 (32.63)	3 (15.78)	0.17
Inversed T-waves	84 (88.42)	18 (94.73)	0.55
PQ interval	158.56±27.71	169.22±34.26	0.16
QTc (ms), mean ± SD	483.24±53.45	459.42±42.30	0.07
Stress factor, n (%)			
Emotional stress	28 (29.47)	2 (10.52)	0.15
Physical stress	52 (54.73)	12 (63.15)	0.49
None	20 (21.05)	5 (26.31)	0.56
Laboratory values, mean ± SD			
Troponin I (U/L)	3.38±4.90	5.54±7.17	0.12
Creatine phosphokinase (U/L)	350.77±756.58	2,173.94±6,201.52	<0.01
CKMB	30.42.±32.94	58.91±116.16	0.14
CRP (mg/L)	47.47±78.78	58.97±85.30	0.57
Hemoglobin	12.19±1.75	11.87±2.96	0.52
Creatinine (mg/dL)	1.11±0.72	1.35±0.67	0.18
Echocardiography data, n (%)			
LV EF%	38.67±9.28	36.95±10.51	0.47
RV involvement	20 (21)	6 (31.5)	0.37
Apical ballooning	67 (70.52)	15 (78.94)	0.77
Mitral regurgitation	51 (53.68)	9 (47.36)	0.61
Tricuspid regurgitation	41 (43.15)	8 (42.10)	0.93
Medical history, n (%)			
Smoking	26 (27.36)	10 (52.63)	0.03
Diabetes mellitus	22 (23.15)	4 (21.05)	1.00
Obesity (BMI >25 kg/m^2)	25 (26.31)	6 (31.57)	0.47
Hypertension	55 (57.89)	11 (57.89)	1.00
COPD	16 (16.84)	6 (31.57)	0.13
Atrial fibrillation	18 (18.94)	3 (15.78)	1.00
Coronary artery disease	17 (17.89)	5 (26.31)	0.52
History of malignancy	11 (11.57)	5 (26.31)	0.14
Drugs on admission, n (%)			
Beta blocker	30 (31.57)	5 (26.31)	0.43
ACE inhibitor	28 (29.47)	7 (36.84)	0.88
Acetylsalicylic acid	24 (25.26)	5 (26.31)	1.00
Anticoagulation	7 (7.36)	0 (0)	0.34

Note: *P-values for the comparison between female and male groups.

Abbreviations: TTC, Takotsubo cardiomyopathy; SD, standard deviation; BP, blood pressure; ECG, electrocardiogram; CKMB, creatine kinase myocardial band; CRP, C-reactive protein; LV, left ventricular; EF, ejection fraction; RV, right ventricular; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme.

Table 2 In-hospital events and treatment strategy of TTC patients according to sex difference

Variables	Female (n=95)	Male (n=19)	*P*-value*
Life-threatening arrhythmia, n (%)	10 (10.52)	3 (15.78)	0.45
Mechanical respiratory support (NPPV and intubation), n (%)	29 (30.52)	10 (52.63)	0.06
Inotropic agents, n (%)	15 (15.78)	6 (31.57)	0.10
Resuscitation, n (%)	6 (6.31)	3 (15.78)	0.17
Defibrillator implantation, n (%)	1 (1.05)	0 (0)	1.00
VA-ECMO, n (%)	0 (0)	1 (5.2)	1.00
Admission to ICU, length of stay, mean ± SD	4.14±6.39	5.94±5.73	0.26
In-hospital death	6 (6.31)	3 (15.78)	0.17
Thromboembolic events	13 (13.68)	1 (5.26)	0.45
Acquired long QTs	61 (64.21)	12 (63.15)	0.50
Cardiogenic shock	17 (17.89)	5 (26.31)	0.54

Note: *P-values for the comparison between female and male groups.
Abbreviations: TTC, Takotsubo cardiomyopathy; NPPV, non-invasive positive-pressure ventilation; VA-ECMO, venoarterial extracorporeal membrane oxygenation; ICU, intermediate care unit; SD, standard deviation.

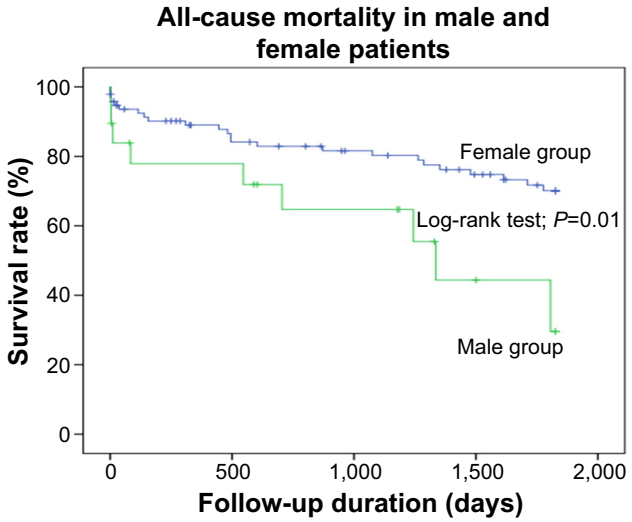

Figure 1 Survival analysis (Kaplan–Meier analysis): survival time of all patients with TTC – a comparison between female and male patients.
Abbreviation: TTC, Takotsubo cardiomyopathy.

Long-term all-cause mortality in TTC patients related to sex

As men showed higher mortality by tendency than women during 4 and 5 years (P=0.085 and P=0.093, respectively, significant by tendency), we included as further information the exact time of death in the continuous calculation and performed a Kaplan–Meier analysis. Analyzing the survival curves, within 5 years, the risk for death (all-cause mortality) of male patients revealed to be 2.6 times higher than that for female patients (hazard ratio [HR] 2.6, 95% CI 1.2–5.7, P=0.01; Figure 1). Most males died of noncardiac causes such as progressive cancer disease and sepsis. The mortality regarding cardiac death was equal in females and males. In Cox univariate analysis, male sex (P=0.01), CRP (P<0.01), glomerular filtration rate (GFR) <60 mL/min (P=0.01), ejection fraction (EF) ≤35% (P<0.01), shock (P<0.01) and the use if inotropic drugs (P<0.01) were associated with all-cause mortality. In multivariate Cox regression analysis, male sex (P=0.02, HR 2.8, 95% CI 1.1–7.2), EF ≤35% (P=0.01, HR 3.3, 95% CI 1.2–9.2) and GFR <60 mL/min (P<0.01, HR 3.1, 95% CI 1.4–7.0) figured out as independent predictors of all-cause mortality even after adjusting for all other variables being significant in univariate analysis (Table 3).

Discussion

The present monocentric retrospective study investigated sex differences of baseline characteristics and 5 years all-cause mortality in patients suffering from TTC. First, this study confirmed that sex differences were found for patients' symptoms at baseline clinical presentation. For instance, a higher rate of angina and emotional stress was found in females, whereas a higher rate of physical stress, smoking status and malignancies was found in males. Second, the present study demonstrated a higher rate of all-cause mortality after 5 years in male TTC patients compared to females, triggered by death due to cancer.

Previous studies have shown that sex differences might influence the development of TTC. Most TTC patients are older and females, whereas the incidence of TTC in males has been described to be even rare.[15] Our study showed in

Table 3 Univariate and multivariate Cox regression analyses of TTC patients show that male sex is an independent predictor of adverse outcome, all-cause mortality after 5 years

Variable	Univariate analysis			Multivariate analysis[a]		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Male	2.6	1.2–5.7	0.01	2.8	1.1–7.2	0.02
CRP	1.0	1.0–1.0	<0.01	1.0	0.9–1.0	0.36
GFR ≤60 mL/min	2.5	1.2–5.1	0.01	3.1	1.4–7.0	<0.01
Cardiogenic shock	4.1	2.0–8.4	<0.01	3.8	0.6–23.4	0.13
EF ≤35%	4.8	2.2–104	<0.01	3.3	1.2–9.2	0.01
Emotional stress	0.4	0.1–1.1	0.10			
Inotropic drugs	3.9	1.9–7.9	<0.01	0.4	0.0–2.8	0.40
Diabetes mellitus Type II	1.0	0.7–1.4	0.81			
Hypertension	0.9	0.7–1.2	0.64			
Apical ballooning	1.1	0.8–1.4	0.39			
History of cancer	1.7	0.7–4.2	0.21			
Smoking	0.7	0.3–1.6	0.49			

Note: [a]Only the following variables with significant effects in univariate analysis were analyzed by multivariate Cox regression: male, CRP, GFR ≤60 mL/min, cardiogenic shock, EF ≤35% and inotropic drugs.
Abbreviations: TTC, Takotsubo cardiomyopathy; HR, hazard ratio; CRP, C-reactive protein; GFR, glomerular filtration rate; EF, ejection fraction.

accordance to further studies a lower incidence of male sex (16%) in TTC and younger age of these patients compared with female patients. These findings have been reported by Templin et al[2] in 1,750 TTC patients. The predominance of females suffering from TTC is in clear contrast to patients with an AMI – representing the most important differential diagnosis of TTC – of which presumably males are more commonly diseased.[14–16,18]

This study confirms a higher rate of emotional stress in females compared to male TTC patients, whereas the sex groups were of similar age (mean: male, 64 years; female, 68 years). As it is widely known, emotional stress playing a major causative role for the development of TTC was therefore called "the broken heart syndrome". Accordingly, a link was attributed pathologically to the so-called brain–heart axis.[11,12,21] The so-called biopsychosocial disease model was described first in 1977 by Engel.[22] This model expresses that the human body can manage diseases autoregulatively. This system is controlled by a circuit of several neurotransmitters, catecholamines and hormones implementing different axes to end organs such as the heart or the gastrointestinal tract. Within this model, disease development represents a dynamic process, in which the clinical manifestation follows a loss of function or overload of this controlling circuit.[1,23] Beside the concept of the brain–heart axis, physical stress increases the synthesis of potentially cardiotoxic catecholamines such as epinephrine and metanephrine.[23] In this context, recently published data of Templin et al presented a higher rate of physical triggers compared to emotional triggers in patients suffering from TTC.[2]

The etiology of TTC is understood poorly, whereas the role of impaired estrogen release is considered as a main pathomechanism,[15,16] since most TTC patients are postmenopausal women.[1,2] Estrogen reveals several cardioprotective effects, such as antioxidant effects, inhibition of the renin–angiotensin system and modulation of atrial natriuretic peptide.[16] In human beings, the secretion of estrogen is lower in postmenopausal compared to premenopausal women and estrogen levels in postmenopausal women appear to be lower than in men at the same age.[24] Therefore, the present study complements the evidence of former studies, widening the characterization of TTC patients in males and females.

As it was shown recently, emotional stress may also encourage the development of depressive disorders.[25,26] Depressive symptoms were not documented in the present study cohort; however, the implication of standardized questionnaires, such as the Hospital Anxiety and Depression Scale, may become helpful to picture the intangible effects of depression and anxiety in patients with TTC.[25,26] Interestingly, a prolongation of the QT interval on ECG recordings was shown to be associated with depressive symptoms in patients after suffering from an acute coronary syndrome.[27] Accordingly, the present study shows that the incidence of QT-interval prolongation is very high. In addition, the data set of Templin et al[2] represents a significant prolongation in the QT interval in male and female patients suffering from TTC. Schneider et al[15] was able to identify a significant difference in ST-segment elevation, being less frequently in male TTC patients.[18] However, no further ECG differences were found in the present study.

This study demonstrates that the 5-year all-cause mortality rate following TTC is higher in men compared to women. In patients suffering from an AMI, large-scale studies found conflicting results about sex-adjusted differences of long-term mortality.[25,28] Some studies favor a higher mortality rate in women, whereas others demonstrate increasing mortality rates in males.[29–31] The large International Takotsubo Registry also reported about higher long-term mortality rate in male patients compared with female patients. During long-term follow-up, cardiovascular and cerebrovascular events were more observed among male patients. In our study, the mortality rate of male patients (n=9, 47.3%) was higher than that of female patients (n=24, 25.2%), but nevertheless cardiac cause of death and cardiovascular events were similar in male and female patients. Most males died of noncardiac causes such as progressive cancer disease and sepsis.

Even if TTC is defined as a benign disease, it is associated with several complications such as peripheral or central thromboembolism.[4,6] Elevated CRP levels, elevated D-dimers and severely impaired LV function seem to be a risk factor of developing thromboemboli. In our TTC cohort, the incidence of thromboembolic events is high and females are more affected than males. Templin et al[2] also showed a high risk for thromboembolic events such as stroke in patients suffering from TTC. In comparison to our results, they could not show a significant sex difference.

Within a large-scale registry of TTC patients, Murakami et al[16] found that male sex represents a general independent risk factor for the development of adverse cardiac events, including cardiovascular death. However, a clear follow-up in this observational analysis was not defined clearly. In addition, Brinjikji et al[17] analyzed a large national database of TTC patients and found that mortality was significant higher in male patients with TTC during a follow-up of 1 year.[15,16] The studies did not report about a 5-year outcome in male patients with TTC.

It might be speculated whether the female predominance of TTC is overestimated due to the fact that male patients

were shown to die at earlier stages of TTC development even before definite diagnostic assessment.[18] Schneider et al showed that males were more often admitted to hospital after successful or fatal cardiopulmonary resuscitation (CPR) than females, implying an impaired prognosis in males even after successful CPR.[15] This might indicate a higher electrical vulnerability within the early phase of the TTC development.[32] Accordingly, the rates of sudden cardiac deaths and CPR are more frequent in males than in females suffering from AMI.[18] On the other hand, male patients revealed a higher rate of physical stress, smoking status and malignancies in the present study cohort. However, these risk factors were not shown to influence long-term all-cause mortality in male patients in the present study.

Conclusion

This study shows that males suffering from TTC reveal a higher risk for all-cause mortality than females over a 5 year follow-up period. A vital component of the diagnostic and disease management chain is the physicians' experience treating patients with TTC, the involvement of an interdisciplinary team and the streamlined treatment of such complications on a patient-individualized basis. Currently, the underlying pathomechanism for sex differences in TTC is not clarified yet. Whether emotional stress, depressive symptoms and estrogen decrease may explain the differences in long-term prognosis need to be investigated in upcoming prospective randomized studies.

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Disclosure

The authors report no conflicts of interest in this work.

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