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Natural history and predictors of mortality of patients with Takotsubo syndrome☆

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ABSTRACT

Background: Takotsubo syndrome is a unique transient cardiomyopathy. The pathogenesis, management, and long-term prognosis of Takotsubo syndrome are incompletely understood. The study was designed to evaluate the natural history and determinants of outcomes in patients with Takotsubo syndrome patients.
Methods: We analyzed 265 patients in the Mayo Clinic Takotsubo syndrome registry for clinical presentation, treatment, and long-term outcomes with a focus on identifying prognostic factors for mortality and recurrence.
Results: 95% of patients were women with a mean age of 70 ± 11.8 years. Among 257 patients discharged alive, there were 89 (34.6%) deaths, 18 (6.8%) non-fatal myocardial infarction, 12 (4.7%) cerebrovascular accidents and 23 (8.9%) re-hospitalization for heart failure over a mean follow-up of 5.8 ± 3.6 years. Only 4 (5%) patients died from cardiac causes. Cancer was the single leading cause of death. Overall 1-year survival rate was 94.2%. Independent prognostic predictors of mortality were a history of cancer (HR 2.004, 1.334–3.012, $p = 0.004$), physical stress as precipitating factors (HR 1.882, 1.256–2.822, $p = 0.012$), history of depression (HR 1.622, 1.085–2.425, $p = 0.009$) and increased age (HR 1.059, 1.037–1.081, $p < 0.001$) after multivariate analysis. Beta-blockers and ACE inhibitors at discharge were not significant predictors. There were 24 (9.1%) recurrences during follow-up, but there were no significant differences in medical therapy compared to patients without recurrence.
Conclusion: The high mortality rate is related to non-cardiac co-morbidities such as cancer. Additional determinants include physical stressors, increased age, and history of depression. Use of beta-blockers and ACE inhibitors did not affect development, prognosis or recurrence.

1. Introduction

Takotsubo syndrome, also known as stress cardiomyopathy, or apical ballooning syndrome was first reported in Japan in 1990 by Sato et al. [1]. Many reports have described clinical features and potential mechanisms, but the precise pathogenesis remains undefined. This is further complicated by the multiple clinical settings and triggers associated with Takotsubo syndrome. Major acute neurological injury such as cerebral hemorrhage, ischemic stroke has long been known to cause neurogenic myocardial stunning [2,3]. The entity of Takotsubo syndrome has extended this to include the syndrome precipitated by extreme emotional and non-neurological physical stressors in postmenopausal women [4,5]. The presence of a precipitating stressor suggests a significant role for the sympathetic nervous system. However, Takotsubo syndrome occurs in the absence of a stressor in as many as one-third cases. The heterogeneity in clinical presentation and incomplete understanding of the pathophysiology has resulted in the absence of the evidence base for guiding management strategy, and current practice is largely based on expert consensus. This includes the use of beta-blockers due to the hypothetical benefit as sympatholytic agents.

Early studies indicated that overall prognosis of Takotsubo syndrome patients was favorable with the long-term prognosis being similar to age, and sex-matched cohorts [6,7]. Recent reports describe less favorable prognosis, with similar survival to acute coronary syndrome [8–10]. Determining the prognosis in individual Takotsubo syndrome patient is uncertain due to limited data on predictive factors. Potential prognostic factors include presenting clinical features, co-morbidities,

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biomarker values, the severity of left ventricular dysfunction, and use of pharmacological interventions such as beta-blockers and those directed at treating any traditional cardiovascular risk factors.

The aim of this study was to determine the long-term mortality following Takotsubo syndrome and identify independent predictive risk factors associated with mortality and recurrence of Takotsubo syndrome.

2. Methods

2.1. Study population

We enrolled patients in the Mayo Clinic Apical Ballooning Syndrome prospective observational registry database from January 2002 through December 2016. This study was approved by the Mayo Foundation Institutional Review Board and informed consent was obtained from each patient. The diagnosis was made according to the Mayo Clinic diagnostic criteria for Takotsubo syndrome [11]. A total 265 patients who met the criteria were enrolled from our hospital registry. Coronary angiography was performed in 262 patients to identify epicardial coronary artery obstruction. Three patients who were not eligible for the invasive angiogram were confirmed by coronary CT angiography. During coronary angiography, left ventricular angiogram was performed and patterns of wall motion abnormalities were assessed to confirm that wall motion abnormalities were not compatible with single coronary artery territory and to discriminate typical apical hypokinesia from variants. Wall motion abnormalities, ejection fraction of the left ventricle and baseline echocardiographic parameters were examined by transthoracic echocardiography. At initial presentation, serial ECGs were analyzed for ST-segment elevation or depression, T wave inversion, QTc intervals, and the presence of atrial fibrillation. Laboratory tests included CK-MB, troponins, and BNP. Serum catecholamines were obtained to rule out pheochromocytoma and primary hyperaldosteronism if clinically indicated.

2.2. Personal and medication history

Electronic medical records were extensively reviewed to extract patient history. Patient's cardiovascular risk factors including hypertension, diabetes mellitus, dyslipidemia and smoking and significant co-morbidities such as chronic obstructive pulmonary disease, depression, and the presence of malignancies diagnosed before the index episode or during a 1-year follow-up were recorded. Family history included premature cardiovascular death, premature cardiovascular disease, and psychiatric disease. Initial presentation symptoms and precipitating cause of Takotsubo syndrome were identified. Precipitating causes were categorized into three groups; intense emotional event, physical stress such as severe medical illness, or no definitive triggering event. Patient medication use was recorded at the date of admission, discharge, outpatient follow-ups and at a second admission in case of a recurrent Takotsubo syndrome with special attention to beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, statins and antiplatelet agents. In addition, beta-blockers use was evaluated on the post-discharge follow-up at 1 month and 1 year.

2.2.1. Follow-up

Transthoracic echocardiography was performed to evaluate changes in left ventricular wall motion abnormalities and ejection fraction 4–6 weeks following discharge. Patients were questioned about the current symptoms such as chest pain or dyspnea. Follow-up analysis documented the cause of death, diagnosis of congestive heart failure, stroke, coronary artery disease, hypertension, recurrence of Takotsubo syndrome, limitation by any disease, employment. If hospitalization occurred, date, and reason for hospitalization, cardiac procedure, and clinical outcomes were recorded. Major adverse cardiac and cerebrovascular events (MACCE) included all-cause mortality, non-fatal myocardial infarction, stroke, hospitalization for heart failure and the need for revascularization. All follow-up data were collected from review of electric medical records or telephone interview.

2.3. Statistical analysis

Descriptive data are expressed as numbers (percentage) or mean ± SD in the case of normally distributed continuous variables. Categorical variables were compared using chi-square test or Fisher's exact test. Continuous variables were compared using Mann-Whitney test. Kaplan-Meier survival analysis with log-rank test was used for 1-year and long-term survival. The observed risk in the Takotsubo syndrome patient cohort was matched and compared to the expected risk of mortality in the Minnesota population based on age, gender, and birth year. Population rates were not available after the year 2004, so rate was carried forward from there [12,13]. Predicted risk of mortality was analyzed using Cox proportional hazard models. We analyzed all possible factors could affect mortality using separate univariate analysis. Multivariate analysis was used with significant predictors. We defined time from index event to death or to December 31, 2016. A p-value < 0.05 was considered statistically significant. All data analysis was done using SPSS 23 (IBM, Armonk, New York), JMP 10.0 (SAS Institute, Cary NC).

3. Results

3.1. Baseline clinical characteristics

Clinical characteristics of the 265 patients are described in Table 1. Mean age was 69.9 ± 11.8 years old. Among them, 252 (95%) were women and 77.7% were older than 60 years and 252 (95%) were living in Minnesota. A physical stressor led to the development of Takotsubo syndrome in 116 (45%) patients, more than those triggered by an emotional stressor (59, 23%). A trigger was not identified in 81 (32%) patients. At coronary angiography, 21% patients had one or more significant coronary stenosis (>50% diameter stenosis). Those did not correlate with the extensive wall motion abnormalities. Frequent co-morbidities included chronic obstructive airway disease, history of depression, and cancer. Among 70 patients in whom the diagnosis was established prior to the index admission, breast cancer was the most frequent followed by gastrointestinal and gynecological malignancies. Baseline characteristics between patients with cancer and without cancer were described in Supplement Table 1 and detailed types of cancers were in Supplement Table 2. There was no significant difference between patients with cancer and without cancer except age.

3.2. Presentation and hospital course

The most common presenting symptom was chest pain (Table 1) followed by dyspnea, syncope, weakness, and nausea. 116 (45%) patients had ST-segment elevation on the ECG at presentation. ST depression was evident in 18 (7%) patients and deep T-wave inversions were seen in 108 (42%). Mean QTc interval was 499.79 ± 52.60. Most patients were in sinus rhythm and atrial fibrillation was present in 38 (14%) patients. Left ventricular ejection fraction at presentation was 38 ± 11%, which improved to 61 ± 8% on the follow-up transthoracic echocardiography (Supplement Table 3). 161(63%) patients showed typical apical ballooning on wall motion. There were 8 (3%) in-hospital deaths on index admission. Among them, 4 patients died due to the cardiac cause; ventricular fibrillation ($n = 2$), cardiogenic shock (n = 2), and the remaining 4 patients died from the non-cardiac cause, such as pneumonia, sepsis, and cancer. Beta-blockers (89%) and ACE inhibitors or angiotensin

Table 1
Baseline characteristics.

	N
Total population	265
Age ± SD, yrs	69.9 ± 11.8
Female (%)	252 (95)
Hypertension (%)	186 (70)
Diabetes mellitus (%)	37 (14)
Dyslipidemia (%)	114 (43)
Smoking (%)	104 (39)
Comorbidity (%)	
COPD	71 (27)
Depression	83 (31)
Cancer	70 (26)
Presenting symptom (%)	
Chest pain	172 (65)
Dyspnea	125 (47)
Others	77 (29)
Family history (%)	
Premature CVD	42(16)
Premature CV death	24 (9)
Psychological history	37 (14)
Precipitating factors (%)	
Emotional	62 (23)
Physical	119 (45)
None	84 (32)

SD, standard deviation; yrs., years; COPD, chronic obstructive airway disease; CVD, cardiovascular disease; CV, cardiovascular.