



Clinical characteristics and outcomes of South-East Asian patients with Takotsubo (stress-induced) cardiomyopathy

Kristopher Kow¹, Timothy James Watson¹, David Foo¹, Hee Hwa Ho^{*,1}

Department of Cardiology, Tan Tock Seng Hospital, Singapore

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ABSTRACT

Background: There is limited data on the natural history of Takotsubo (stress-induced) cardiomyopathy in South-East Asian patients. We aim to evaluate the clinical characteristics, predisposing factors and outcomes of patients diagnosed with Takotsubo cardiomyopathy in our region.

Methods: From January 2010 to March 2017, 98 patients were diagnosed with Takotsubo cardiomyopathy in our institution. Data were collected retrospectively on baseline clinical characteristics, presenting symptoms, precipitating factors, clinical investigations and in-hospital clinical outcomes.

Results: 82% of the patients were female. An antecedent physical stressor was more common than emotional trigger with 35% of patients having no identifiable stressor. The most common presenting symptoms were chest pain (53.1%), dyspnea (45%) and diaphoresis (18.5%).

The apical variant (89%) was the most common form of Takotsubo cardiomyopathy followed by the mid-ventricular type (5.1%). The mean left ventricular ejection fraction was $35 \pm 11\%$.

In-hospital mortality due to cardiovascular causes was 4.1%. 38% of patients developed in-hospital complications. By multi-variable analysis, lower left ventricular function was an independent predictor of in-hospital complication.

Conclusion: South-East Asian patients with Takotsubo cardiomyopathy are characterised by female predominance, higher incidence of physical triggers and low cardiovascular mortality. Lower left ventricular function was an independent predictor of adverse outcomes.

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1. Introduction

Takotsubo cardiomyopathy (TC), also known as stress-induced cardiomyopathy, was first described in Japan in 1990 [1]. Since then it has been described in non-Asian populations, specifically the United States and Europe [2]. It classically affects postmenopausal women and is characterised by transient regional systolic dysfunction of the left ventricle, presenting similar to acute myocardial infarction (AMI) but with no evidence of obstructive coronary artery disease (CAD) [3,4].

Prior studies on TC were conducted in East Asian countries mainly Japan and Korea [5–8] but there is limited data on the natural history of TC in South-East Asian patients. We therefore sought to evaluate the clinical characteristics, predisposing factors and outcomes of TC in the South-East Asian region.

2. Methods

From January 2010 to March 2017, 98 patients were diagnosed with TC in our institution. Data were collected retrospectively on baseline clinical characteristics, presenting symptoms, precipitating factors, clinical investigations and in-hospital clinical outcomes.

We adopted the Mayo Clinic diagnostic criteria [9] with four features required to make the diagnosis of TC: (1) transient abnormality in left ventricular wall motion that extend beyond a single epicardial coronary artery perfusion territory (2) absence of obstructive CAD or angiographic evidence of acute plaque rupture; (3) presence of new electrographic (ECG) abnormalities or elevation in cardiac troponin levels (4) absence of pheochromocytoma and myocarditis. Exception to these criteria was the presence of coexisting CAD.

TC was classified as apical, mid-ventricular, basal or focal subtypes according to the findings on left ventricular angiography and/or transthoracic echocardiography.

The major end points of this study include in-hospital cardiovascular (CVS) mortality and in-hospital complication. In-hospital CVS mortality was defined as death due to AMI, arrhythmia or any death in which a

* Corresponding author at: Department of Cardiology, Tan Tock Seng Hospital, 11, Jalan Tan Tock Seng, 308433, Singapore.

E-mail address: hee_hwa_ho@ttsh.com.sg (H.H. Ho).

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CVS cause could not be ruled out. In-hospital complication was a composite end-point that included cardiogenic shock, use of catecholamine, use of invasive and/or non-invasive ventilation, cardiopulmonary resuscitation and all-cause mortality. Subgroup analysis were made between those who develop in-hospital complication and those who did not, to identify predictors of in-hospital complication.

Continuous variables were expressed as mean \pm standard deviation. Dichotomous variables were expressed as counts and percentages. Statistical comparisons were performed using the Student *t*-test or chi square test as appropriate. Calculations were performed using SPSS software (version 16.0; SPSS, Inc., Chicago, Illinois). Two sided significance level of 0.05 was chosen for all the tests. All investigations were carried out in accordance with the Declaration of Helsinki and the study was approved by the local ethics committee.

3. Results

Table 1 summarizes the baseline clinical characteristics and predisposing factors of the study population.

The mean age at presentation was 69.3 ± 12.6 years. The majority of patients were female (82%) and 95% of the females were older than 50 years of age.

The most common symptom at presentation was chest pain (53.1%) followed by dyspnea (45%) and diaphoresis (18.5%). The main findings on ECG were ST-segment elevation (66.3%), T wave inversion (18.4%) and ST-segment depression (6.1%). Emotional triggers were less common than physical triggers (16.3% vs 46.9%) with 35% having no identifiable triggers. Women had a higher rate of emotional triggers (18% vs 11%) while men had a higher rate of physical triggers (56% vs 46%).

75.5% of patients had an elevated troponin I value with a median value of 4.6 (1–90) $\mu\text{g/L}$. Brain natriuretic peptide (BNP) was measured in 17.3% of patients and the median value was 571 (102–3531) pg/mL. 91% of patients had a reduced left ventricular ejection fraction (LVEF) at presentation with a mean value of $35 \pm 11\%$.

All patients underwent coronary angiography in our study and 17.3% were found to have obstructive CAD. About 10.1% of our patients had a normal coronary angiography. 24 patients (24.5%) had past history of neurological disorder whereas 4.1% patients had history of psychiatric disorder.

Table 2 shows the subtypes of TC and in-hospital clinical outcomes.

Table 1
Baseline clinical characteristics of patients with Takotsubo cardiomyopathy.

	N = 98
Female sex, n, %	80 (82)
Age, years	69.3 ± 12.6
Antecedent trigger, n, %	
Physical	46 (47)
Emotional	16 (16.3)
No evident trigger	34 (35)
Chest pain, n, %	52 (53.1)
Dyspnea, n, %	44 (45)
Diaphoresis, n, %	18 (18.5)
Body mass index, kg/m ²	23.9 ± 5.5
Systolic blood pressure, mmHg	125.5 ± 34.2
Median troponin I, $\mu\text{g/L}$, (range)	4.6 (1–90)
Median brain natriuretic peptide, pg/mL, (range)	571 (102–3531)
ST segment changes, n, %	
Elevation	65 (66.3)
Depression	6 (6.1)
T wave inversion	18 (18.4)
LVEF at presentation - %	35 ± 11
Underlying medical condition, n, %	
Coronary artery disease (obstructive)	17 (17.3)
Neurologic disorder	24 (24.5)
Psychiatric disorder	4 (4.1)

LVEF: left ventricular ejection fraction.

Table 2
Types of Takotsubo Cardiomyopathy and In-hospital Outcomes.

	N = 98
Takotsubo cardiomyopathy subtypes, n, %	
Apical	87 (89)
Basal (inverted Takotsubo)	3 (3.1)
Midventricular	5 (5.1)
Focal	2 (2.0)
Others (undefined)	1 (1.0)
Treatment, n, %	
Catecholamine	28 (28.6)
Invasive or noninvasive ventilation	30 (30.6)
Cardiopulmonary resuscitation	8 (8.2)
In-hospital outcomes, n, %	
Cardiogenic shock	10 (10.2)
Death due to any cause	11 (11.2)
Death due to cardiovascular cause	4 (4.1)
In-hospital Complications, n, %	37 (38)
Median length of hospital stay, days, (range)	6 (1–88)
Type of medications, n, %	
Beta-blockers	58 (59.2)
Angiotensin-converting enzymes inhibitors/Angiotensin-receptor blockers	45 (46)
Anti-platelet therapy	61/(62)

89% of patients were found to have the apical form of TC. 5.1% of patients had the mid-ventricular form while the basal and focal forms occurred in 3.1% and 2.0% of patients respectively.

28.6% of patients required catecholamine support and 30.6% of patients required invasive and/or non-invasive ventilation. 10.2% of our patients developed cardiogenic shock and 8.2% of patients required cardiopulmonary resuscitation during hospitalisation. All-cause mortality was at 11.2% whereas death due to CVS cause was at 4.1%.

38% of patients developed in-hospital complications. Factors associated with in-hospital complications by uni-variate analysis were male gender, physical stressor, emotional stressor, history of smoking and lower left ventricular function (defined as EF <35%) (Table 3). By multi-variable analysis, lower left ventricular function was an independent predictor of in-hospital complication (hazard ratio 5.35, 95% confidence interval: 1.95–14.6, $p = 0.001$).

4. Discussion

To the best of our knowledge, this is the largest observational study evaluating the clinical features and outcomes of South-East Asian patients with TC.

Our study showed that female was more commonly affected (82%) and the mean age at presentation was 69.3 ± 12.6 years. These findings are consistent with the results of prior studies [2,3,10] in the Western populations which showed female predominance with mean age of 62–75 years. However, the female to male ratio in our study seemed relatively lower than the ratio of 9:1 that is reported in the Western literature. In Japan, men are also reported to be prone to TC [11]. The reason why Asian men are affected relatively more than Western men is currently unknown and warrant further investigation.

In prior studies [3,10], TC has been reported to be more commonly associated with emotional triggers. However our study showed that physical triggers were more common than emotional triggers (46.8%

Table 3
Predictors of in-hospital complications.

Factor(s)	Hazard ratio	p value
Male gender	2.2	0.25
Physical stressor	2.1	0.16
Emotional stressor	0.2	0.1
Smoking history	3.1	0.09
Lower LVEF (<35%)	5.35	0.001*

* p value <0.05.

versus 16.3%) and some patients (35%) had no preceding triggers at all. Our findings are consistent with recent studies [2] involving Western populations which showed higher prevalence of physical triggers and absence of triggers do not preclude the diagnosis of this condition.

We also observed that women had a higher rate of emotional triggers while men had a higher rate of physical triggers in our study. 53% of our patients with emotional triggers had “non-specific” stress i.e. no specific emotional triggers such as grief/loss, anger/frustration or interpersonal conflict. In addition, only 4.1% of our patients was diagnosed to have a psychiatric illness, compared to 42% in a large study [2] conducted on Western populations. This could be due to underdiagnosis as Asian patients tend to suppress their emotions and fear stigmatization from the diagnosis of psychiatric illness [12]. A nationwide epidemiology study [13] on common mental illnesses in the adult Singapore population revealed that the majority of people with mental illness were not actively seeking help.

The acute presentation of TC mimics an AMI. In our study, 53% of patients presented with chest pain, 66.3% was found to have ST-elevation on ECG and 75.5% had elevated cardiac troponins. Early coronary angiography was necessary to rule out acute coronary syndrome and was performed for all patients. Although the Mayo Clinic diagnostic criteria for Takotsubo CMP rely on the “absence of significant obstructive CAD or angiographic evidence of plaque rupture”, several studies [2,14] have reported incidence of bystander CAD in 10–15% of cases. It is now increasingly accepted that the 2 conditions are not mutually exclusive, but can exist coincidentally. Since Takotsubo CMP is often observed in older patients, bystander CAD can be present. It is important to evaluate whether the coexisting CAD is sufficient to cause the degree or pattern of left ventricular dysfunction. In our study, 17.3% of our patients had obstructive CAD which is similar to the 15.3% reported in Western population [2]. In our study, the most common form of TC was the apical variant (89%) followed by mid-ventricular type (5.1%). These observations are consistent with the findings of prior studies [2,14].

In-hospital CVS mortality in our patients was 4.1%. This is consistent with the reported rate of 1–4.5% in the literature [2,10,14] as this disorder is generally regarded as relatively benign with rapid recovery of left ventricular function.

However, a variety of in-hospital complications can still occur and this was observed in 38% of our patients. The rate of in-hospital complications ranged from 22 to 50% in the literature [2,6,14,15] and many of these patients require intensive care. Factors associated with in-hospital complications in our study (by univariate analysis) were male gender, physical stressor, emotional stressor, history of smoking and lower left ventricular function. By multi-variable analysis, lower left ventricular function was an independent predictor of in-hospital complication.

Our findings are consistent with prior studies [2] which showed that male patients were more prone to in-hospital complications including in-hospital mortality. Patients who had emotional triggers were less prone to adverse outcomes and this phenomenon was observed in our study. Other independent predictors of in-hospital complications reported in the literature [2,15] were presence of physical triggers, lower left ventricular function, markedly elevated troponin level and acute neurologic/psychiatric illness. The first two predictors were also observed in our study.

Our study had several limitations. Firstly, our sample size was relatively small when compared to other studies. Secondly, patients in this retrospective study came from only center. Hence, our findings could be affected by selection bias.

In conclusion, South-East Asian patients with TC are characterised by female predominance, higher incidence of physical triggers and low CVS mortality. The rate of in-hospital complications was relatively high and lower left ventricular function was an independent predictor of adverse outcome.

Further studies involving a larger group of patients are needed to confirm our preliminary findings and to gain a better understanding on the natural history of TC in this region.

Declaration of interest

The authors report no conflicts of interest.

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