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ORIGINAL ARTICLE

Predictors of in-hospital cardiac complications in patients with Takotsubo syndrome

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Abstract

Takotsubo syndrome (TTS) has been recognized as a benign condition mainly due to its reversibility. However, recent researches have demonstrated that serious cardiac complications could occur during hospitalization. Thus, the aim of this study is to detect factors associated with in-hospital cardiac complications in patients with TTS. A total of 154 consecutive patients with TTS were enrolled retrospectively. In-hospital cardiac complications were observed in 61 patients (40%), including 44 patients with pulmonary edema (29%) and 25 patients with cardiogenic shock (16%). Multivariate logistic regression analysis identified lower systolic blood pressure on admission (OR 0.97, 95% CI 0.96–0.99, $p=0.001$), history of diabetes mellitus (OR 2.92, 95% CI 1.01–8.41, $p=0.04$), and β-blocker use before admission (OR 16.9, 95% CI 1.57–181.7, $p=0.006$) as independent predictors of in-hospital cardiac complications, while chest pain at onset was identified as a negative predictor of cardiac complications during hospitalization (OR 0.20, 95% CI 0.07–0.55, $p=0.001$). Patients with cardiac complications more often needed hemodynamic support and longer hospital stay than those without (21.2 ± 19.4 vs. 11.8 ± 16.8 days, $p=0.002$). TTS should be no longer recognized as a benign disease, but requiring careful management. We should obtain vital signs and patient's medical history carefully as soon as possible after admission to predict in-hospital cardiac complications.

Keywords Takotsubo syndrome · Takotsubo cardiomyopathy · Cardiac complications · Pulmonary edema · Cardiogenic shock

Introduction

Takotsubo syndrome (TTS) is characterized by non-ischemic transient cardiac dysfunction and has been recognized as a relatively benign condition since its first report in 1990 [1]. However, recent reports have demonstrated that serious cardiac complications that might be a cause of cardiac death including acute heart failure, cardiogenic shock, and arrhythmias could occur during hospitalization [2–9]. In addition, it has been reported that thromboembolism due to left ventricular thrombus could be developed in patients with apical ballooning [10–12]. Although more careful management should be needed in patients with such life-threatening complications, there is limited information about predictors of worse clinical course during hospitalization. Thus, the aim of the present study was to evaluate the prevalence of cardiac complications during hospitalization and to detect factors associated with worse in-hospital outcome in patients with TTS.

Methods

We enrolled consecutive patients with TTS who were admitted to Chiba University Hospital, Chiba Emergency Medical Center, and Kimitsu Chuo Hospital from June 2007 to May 2015 retrospectively based on catheterization databases. TTS was diagnosed based on the following criteria [6, 13]: (1) transient hypokinesis, akinesis, or dyskinesis of the left ventricle; regional wall motion abnormalities

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extending beyond a single epicardial vascular distribution; (2) absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture which can explain the left ventricular contraction abnormality; (3) new electrocardiographic abnormalities or modest elevation in cardiac troponin; and (4) absence of pheochromocytoma or myocarditis. There were exceptions to these criteria: (1) the presence of a wall motion abnormality that was identical to a single coronary artery distribution coincidentally in a patient matching all other criteria; (2) death during the acute phase before complete recovery of wall motion in a patient matching all other criteria. Cardiac catheterization including coronary angiography and left ventriculography were performed in all patients in the acute phase. Clinical information was collected from hospital charts by independent research personnel who were unaware of the objectives of the study. In-hospital cardiac complications consisted of pulmonary edema, cardiogenic shock, sustained ventricular tachycardia or ventricular fibrillation, complete atrioventricular block, thromboembolism, cardiac rupture, and cardiac death. Pulmonary edema was defined as radiologic signs of pulmonary congestion with dyspnea requiring oxygen therapy. Cardiogenic shock was defined as systolic blood pressure < 90 mmHg requiring inotropic agents or fluid therapy. The ethical committee of Chiba University approved this study.

Continuous variables are presented as mean ± SD and were compared with Student's *t* test. Categorical variables are presented as counts and percentages and were compared with Chi square test or Fisher's exact test, when appropriate. An association between clinical variables and in-hospital cardiac complications was examined by multiple logistic regression analysis. Explanatory variables were selected from clinical variables that had a p value < 0.05 in univariate analysis. Statistical analysis was performed using JMP Pro 13 (SAS Institute, Cary, NC, USA). A p value of < 0.05 was considered to be statistically significant.

Results

The study population included 154 patients with TTS; the baseline characteristics are summarized in Table 1. Of these patients, in-hospital cardiac complications were observed in 61 patients (40%), as summarized in Fig. 1. In patients with cardiac complications, 44 patients (29%) showed pulmonary edema secondary to TTS, and 25 patients (16%) had cardiogenic shock (16%). Sustained ventricular tachycardia or ventricular fibrillation, complete atrioventricular block, and thromboembolism were noted in 10 (7%), 4 (3%) and 4 patients (3%), respectively. Four patients died of cardiac causes (3%) including 1 case of cardiac rupture, while non-cardiac death during hospitalization was observed in 11 patients (7%).

We categorized all patients into 2 groups according to those with or without in-hospital cardiac complications. Table 1 shows the baseline characteristics including daily medications before admission. There was no difference in age and sex between the 2 groups. The prevalence of diabetes mellitus was significantly higher in patients with cardiac complications. No significant differences were observed in the past history of cardiovascular disease, cerebrovascular disease, or psychiatric disorder. Physical triggers were identified more frequently in patients with cardiac complications, while emotional triggers were more common in those without. There was no difference in electrocardiographic findings on admission between the 2 groups. Chest pain was found to be more common in patients without cardiac complications. β-Blockers were prescribed more frequently in patients with cardiac complications, while no significant difference was observed in other medications. Vital signs and the results of cardiac catheterization are summarized in Table 2. Patients with cardiac complications had significantly higher heart rate, lower systolic blood pressure, and lower LV ejection fraction on admission. On the other hand, there was no difference in left ventricular outflow tract obstruction, significant mitral regurgitation, types of ballooning, or coincidental coronary artery stenosis. Multiple logistic regression analysis demonstrated that history of diabetes mellitus, β-blocker use before admission, and lower systolic blood pressure were independent predictors of in-hospital cardiac complications, while chest pain at onset was identified as a negative predictor of in-hospital cardiac complications (Table 3).

In patients with cardiac complications, 20 patients (33%) needed catecholamine to maintain their hemodynamic status, and intra-aortic balloon pumping was also used in 9 patients (15%), while no patients without cardiac complications needed catecholamine or intra-aortic balloon pumping. Hospital stay was significantly longer in patients with cardiac complications than in those without (21.2 ± 19.4 vs. 11.8 ± 16.8 days, $p = 0.002$).

Discussion

The principal findings of this study were: (1) in-hospital cardiac complications were observed in 40% of patients with TTS; (2) history of diabetes mellitus, β-blocker use before admission, and lower systolic blood pressure were identified as independent predictors of in-hospital cardiac complications; (3) chest pain at onset was a negative predictor of in-hospital cardiac complications; (4) patients with cardiac complications more often needed hemodynamic support and longer hospital stay than those without.

Table 1 Baseline clinical characteristics

	Overall ($n=154$)	Complications (+) ($n=61$)	Complications (−) ($n=93$)	p value
Age (years)	70 ± 12	71 ± 12	70 ± 11	0.57
Female	130 (84%)	48 (79%)	82 (88%)	0.11
BMI (kg/m^2)	21.5 ± 3.6	21.8 ± 3.8	21.3 ± 3.5	0.42
Cardiovascular risk factors				
Hypertension	82 (53%)	36 (59%)	46 (49%)	0.25
Dyslipidemia	57 (37%)	16 (26%)	41 (44%)	0.02
Diabetes mellitus	32 (21%)	19 (31%)	13 (14%)	0.01
Smoking	22 (14%)	12 (20%)	10 (11%)	0.12
Past history				
Cardiovascular disease	15 (10%)	9 (15%)	6 (6%)	0.09
Cerebrovascular disease	8 (5%)	2 (3%)	6 (6%)	0.48
Psychiatric disorder	22 (14%)	10 (16%)	12 (13%)	0.54
Triggers				
Emotional stress	25 (16%)	4 (7%)	21 (23%)	0.008
Physical stress	76 (49%)	39 (64%)	37 (40%)	0.003
No apparent trigger	54 (35%)	18 (30%)	36 (39%)	0.21
Symptoms at onset				
Chest pain	76 (49%)	17 (28%)	59 (63%)	< 0.001
Dyspnea	34 (22%)	19 (31%)	15 (16%)	0.03
ECG findings				
ST elevation	106 (69%)	45 (73%)	61 (66%)	0.28
T wave inversion	99 (65%)	36 (60%)	63 (68%)	0.33
QTc (ms)	486 ± 60	492 ± 71	482 ± 51	0.31
Medications before admission				
ACEI/ARB	42 (28%)	18 (30%)	24 (26%)	0.63
Ca channel blocker	40 (26%)	19 (32%)	21 (23%)	0.24
β-Blocker	7 (5%)	6 (10%)	1 (1%)	0.01
Statin	20 (13%)	5 (8%)	15 (16%)	0.22
Antiplatelet drug	21 (14%)	9 (15%)	12 (13%)	0.71

ACEI angiotensin-converting-enzyme inhibitor, *ARB* angiotensin-receptor blocker, *BMI* body mass index, *ECG* electrocardiography

Although TTS has been thought to be a benign disease since its first description in 1990 from Japan, recent reports demonstrated that substantial number of TTS patients experienced cardiac complications during hospitalization. Murakami et al. revealed from the Tokyo CCU Network database in Japan that in-hospital cardiac complications including cardiac death, cardiac rupture, thromboembolism, pump failure, sustained ventricular tachycardia or ventricular fibrillation, and advanced atrioventricular block were observed in 38% of TTS patients, which is comparable to the present study [3]. They also demonstrated that white blood cell count and brain natriuretic peptide were independent predictors of in-hospital cardiac complications. There have been some reports regarding in-hospital cardiac complications in TTS patients from Europe and the USA. Citro et al. reported from the Tako-Tsubo Italian Network database focusing on echocardiography that major adverse events consisted of acute heart failure, cardiogenic shock, and cardiac death in 26% of TTS patients; LV ejection fraction, *E*/*e′* ratio, moderate to severe mitral regurgitation, and age ≥75 years were independent correlates of major adverse events [4]. A report from the National Inpatient Sample in the USA demonstrated that acute complications, which included cardiogenic shock, ventricular fibrillation or cardiac arrest, and acute heart failure, were shown in 34.5% of TTS patients during hospitalization [5]. The International Takotsubo Registry, which is one of the largest worldwide registries of TTS, revealed that in-hospital complications including cardiogenic shock, catecholamine use, invasive or noninvasive ventilation, cardiopulmonary resuscitation, and all-cause death were observed in 21.8% of TTS patients, which was equal to age- and gender-matched patients with acute coronary syndrome [6]. In comparison between the present study and a large registry of patients with acute

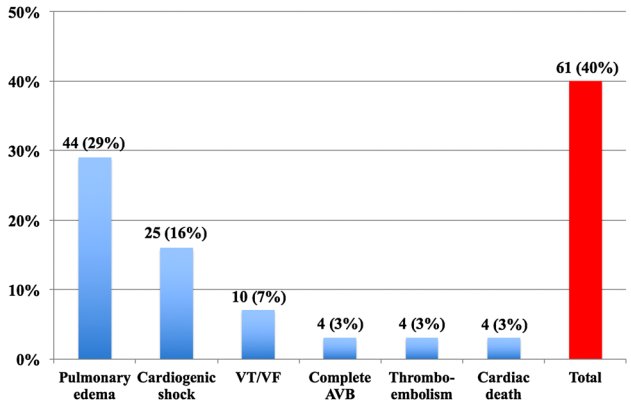

Fig. 1 In-hospital cardiac complications. During hospitalization, pulmonary edema and cardiogenic shock were observed in 44 patients (29%) and 25 patients (16%), respectively. Sustained ventricular tachycardia or ventricular fibrillation was noted in 10 (7%) patients. Four patients (3%) had thromboembolism. Four cardiac deaths (3%) occurred. In total, in-hospital cardiac complications were observed in 40% of patients with Takotsubo syndrome. *AVB* atrioventricular block, *VF* ventricular fibrillation, *VT* ventricular tachycardia

coronary syndrome (GRACE study), the incidence of congestive heart failure and cardiogenic shock in TTS was higher than that in patients with ST elevation myocardial infarction (TTS vs. STEMI, 29 vs. 18%, 16 vs. 7%, respectively) [14]. On the other hand, the prevalence of ventricular arrhythmia and complete atrioventricular block was lower compared to STEMI (TTS vs. STEMI, 7 vs. 10%, 3 vs. 5%, respectively), but higher than non-ST elevation myocardial infarction (TTS vs. NSTEMI, 7 vs. 4%, 3 vs. 2%, respectively) [14]. From these results, we should recognize that TTS could be a life-threatening condition and needs to be monitored carefully, especially in the acute phase. In the present study, history of diabetes mellitus, β-blocker use before admission, and lower systolic blood pressure emerged as independent predictors of in-hospital cardiac complications. On the other hand, chest pain at onset was identified as a negative predictor of in-hospital cardiac complications, which is consistent with previous studies [2]. The majority of patients with dyspnea (56%) developed pulmonary edema

Table 2 Vital signs and cardiac catheterization results

	Overall ($n=154$)	Complications (+) ($n=61$)	Complications (−) ($n=93$)	p value
Heart rate (bpm)	92 ± 20	97 ± 21	89 ± 18	0.009
Systolic blood pressure (mmHg)	123 ± 29	110 ± 24	132 ± 30	< 0.001
LVEDP (mmHg)	21 ± 9	22 ± 9	20 ± 8	0.31
LVEF (%)	47 ± 13	41 ± 12	50 ± 13	< 0.001
LVOT gradient ≥ 15 mmHg[a]	29 (19%)	11 (19%)	18 (20%)	0.90
Mitral regurgitation grade 3 or 4	12 (8%)	5 (8%)	7 (8%)	0.88
Apical ballooning	85 (55%)	34 (56%)	51 (55%)	0.91
Coronary artery stenosis ≥ 75%	27 (18%)	12 (20%)	15 (16%)	0.57

LVEDP left ventricular end-diastolic pressure, *LVEF* left ventricular ejection fraction, *LVOT* left ventricular outflow tract

[a]LVOT gradient was measured in 149 patients

Table 3 Multiple logistic regression analysis

	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	p value	Odd ratio (95% CI)	p value
Dyslipidemia	0.45 (0.22–0.91)	0.02	0.66 (0.25–1.73)	0.39
Diabetes mellitus	2.78 (1.25–6.18)	0.01	2.92 (1.01–8.41)	0.04
Emotional stress	0.24 (0.08–0.74)	0.005	0.47 (0.11–2.02)	0.30
Physical stress	2.68 (1.38–5.23)	0.003	0.52 (0.18–1.50)	0.22
Chest pain	0.22 (0.11–0.45)	< 0.001	0.20 (0.07–0.55)	0.001
Dyspnea	2.35 (1.08–5.10)	0.03	1.22 (0.43–3.45)	0.71
β-Blockers	10.2 (1.20–87.2)	0.009	16.9 (1.57–181.7)	0.006
Heart rate	1.02 (1.01–1.04)	0.01	1.01 (0.99–1.03)	0.39
Systolic BP	0.97 (0.96–0.99)	< 0.001	0.97 (0.96–0.99)	0.001
LVEF	0.94 (0.92–0.97)	< 0.001	0.97 (0.94–1.01)	0.14

BP blood pressure, *CI* confidence interval, *LVEF* left ventricular ejection fraction

secondary to TTS, while only 16% of patients with chest pain showed pulmonary edema. In addition, patients without subjective symptoms tended to have more severe general status such as under sedation or just after resuscitation. These might be the reasons why chest pain was a negative predictor of in-hospital cardiac complications. All identified predictors are very useful for the management of TTS patients in the acute phase, because they can be obtained briefly and immediately on admission. Interestingly, the GRACE study demonstrated that a history of diabetes mellitus and prior use of oral β-blocker were independent predictors of heart failure secondary to ACS in analogy with our results in patients with TTS [15].

Although the definitive etiology of TTS is still unknown, previous studies have suggested that catecholamine might have a central role in developing and worsening TTS [16, 17]. Thus, β-blockers seem to be the most reasonable drug for treatment and prevention from the pathophysiological aspect. However, there are few data demonstrating the positive effect of β-blockers on TTS. Isogai et al. reported that β-blocker use in the acute phase of TTS had no beneficial effect on in-hospital mortality [18]. In addition, two meta-analyses failed to show a benefit of β-blockers in preventing the recurrence of TTS [19, 20]. In the present study, 7 patients (5%) suffered from TTS in spite of daily use of β-blockers for hypertension ($n=5$) or atrial fibrillation ($n=2$). Out of these 7 patients, 5 showed pulmonary edema and 1 patient experienced thromboembolism. Furthermore, multivariate analysis demonstrated that β-blocker use before admission was an independent predictor of in-hospital cardiac complications. There are two possible explanations for the association of β-blocker use before admission with in-hospital cardiac complications. First, negative inotropic effect of β-blockers might have a harmful impact on the hemodynamic status, which might suggest that we should consider quitting β-blockers, especially in patients with symptoms of acute heart failure. Second, patients developing TTS despite daily use of β-blockers might have a higher intrinsic catecholamine level at onset than patients without β-blockers before admission, which could lead to hemodynamic instability. However, further study is still needed to confirm this result, because the number of patients with β-blockers before admission in this study was relatively small.

In the present study, we demonstrated that diabetes mellitus was one of the independent predictors of in-hospital cardiac complications. Although the impact of diabetes mellitus on clinical outcomes in TTS has not yet been established, it is widely recognized that diabetes mellitus leads to some complications including nephropathy, neuropathy, and atherosclerosis. Actually, in this study, TTS patients with diabetes mellitus showed higher creatinine level (1.41 ± 1.96 vs. 0.84 ± 1.00 mg/dl, $p=0.02$) and higher prevalence of coronary artery stenosis (44 vs. 11%, $p<0.001$) than those without, which could explain the relationship between diabetes mellitus and worse in-hospital outcome.

In the present study, of the patients with in-hospital cardiac complications there was a higher prevalence of males, but not significant, compared to those without (21 vs. 12%, $p=0.11$). Although some previous studies have demonstrated that male patients had worse all-cause mortality [5, 21, 22], the impact of sex difference on in-hospital cardiac complications is still debated [2–4]. Murakami et al. reported that male sex was an independent predictor of in-hospital cardiac events including cardiovascular death, severe pump failure, and serious ventricular arrhythmia [23]. On the other hand, the International Takotsubo Registry revealed that male sex had a significant difference in univariate analysis; however, it was not an independent predictor of in-hospital cardiac complications after multivariate adjustment [6]. Of note, male patients more often have physical triggers [23]. Therefore, not only cardiac care, but also intensive management for underlying conditions would be needed.

There are some limitations in the present study. First, the number of patients was relatively small. Due to the retrospective nature of this study and patients' enrollment only from tertiary emergency centers, some selection bias might be present. However, our cohort seems to be pertinent, because the incidence of cardiac complications is comparable to that of previous studies [2, 3]. Nevertheless, current results should be interpreted carefully, because non-severe heart failure might be included in this study due to our definition of in-hospital cardiac complications. Second, we did not show laboratory data because there was substantial number of missing data. However, predictors identified in this study, which can be obtained immediately on admission, are more useful than laboratory data, because it might take a lot of time to obtain laboratory data depending on the centers' situation. Third, β-blocker use after admission was not taken into account in this study. We believe β-blocker use before admission is more important for predicting in-hospital complications, because β-blockers used broadly in Japan have a relatively long half-life and almost all cardiac complications occur in the very acute phase or even at onset. In addition, β-blocker use after admission might have a huge bias, because physicians do not use β-blockers in patients with apparent symptoms indicating acute heart failure.

In conclusion, in-hospital cardiac complications are observed in 40% of patients with TTS. Patients with cardiac complications more often needed catecholamine or intra-aortic balloon pumping, and longer hospital stay than those without. Lower systolic blood pressure on admission, history of diabetes mellitus, and β-blocker use before admission are independent predictors of in-hospital cardiac complications, while chest pain at onset was identified as a negative predictor of cardiac complications. Thus, to predict in-hospital

cardiac complications, we should obtain vital signs and patient's medical history carefully as soon as possible after admission.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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