Characterization of predictors of in-hospital cardiac complications of takotsubo cardiomyopathy: Multi-center registry from Tokyo CCU Network

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A B S T R A C T

Background: Takotsubo cardiomyopathy (TC) is an acute cardiac syndrome characterized by transient left ventricular dysfunction and relatively good prognosis after discharge. However, cardiac complications during hospitalization remain to be fully determined. We attempted to determine features characterizing patients with adverse clinical outcome by comparing those with cardiac complication and without cardiac complication during hospitalization.

Methods and results: We investigated 107 patients with TC from the Tokyo CCU Network database, comprising 67 cardiovascular centers in the metropolitan area during January 1 to December 31, 2010. Cardiac complications were defined as cardiac death, pump failure (Killip grade ≥ II), sustained ventricular tachycardia or fibrillation (SVT/VF), and advanced atrioventricular block (AVB). Cardiac complications were observed in 41 patients (37 pump failure complicated by 3 cardiac deaths and 2 SVT/VF and 2 AVB without pump failure), and there was no cardiac complication in the remaining 66 patients. There was no difference in age, peak creatinine kinase level, C-reactive protein level and ST elevation on electrocardiogram. Multiple logistic regression analysis showed that white blood cell count (p=0.039) and brain natriuretic peptide (p=0.001) were independent predictors of in-hospital adverse cardiac complications.

Conclusions: Cardiac complications are relatively high in patients with TC during hospitalization. High white blood cell count and brain natriuretic peptide level are associated with poor clinical outcome in patients with TC.

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Introduction

Takotsubo cardiomyopathy (TC) is one of the common cardiomyopathies featuring characteristic morphology on cardiac imaging [1–3]. TC usually has a good prognosis, but in rare instances, it may be associated with cardiac complications such as cardiac rupture, thrombus formation resulting in thromboembolic event, heart failure, various arrhythmias, and death [4,5]. However the whole nature of clinical presentation and hospital course remains ill-defined, because large clinical databases are lacking. Tokyo CCU Network database is an ongoing multicenter registry that prospectively collects information on emergency admissions to acute cardiac care facilities [6,7]. The database, comprising 67 large volume cardiovascular centers in the metropolitan area, provides us a unique opportunity to characterize fundamental features of the disease. This study sought to characterize the epidemiology and predictors of cardiac
complications during hospitalization with TC from Tokyo CCU Network database.

Methods

Inclusion criteria with TC

We defined TC according to the following 4 criteria which have been proposed by the Mayo Clinic, Rochester, MN, USA [8]. (1) Transient hypokinesis, akiness, or dyskinesis of the left ventricular midsegments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is 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 of cardiac troponin. (4) Absence of pheochromocytoma or myocarditis.

Study subjects

In 2010, 23,063 patients, including 4653 with acute myocardial infarction, 5326 with acute heart failure, and 918 with acute aortic dissection, were admitted to the 67 large-volume cardiovascular centers in the metropolitan area which participated in the Tokyo CCU Network. We examined 107 patients with TC from the Tokyo CCU Network database during January 1 to December 31, 2010.

Data acquisition

The following data on TC patients were collected: (1) Elapsed time from the onset to hospitalization. (2) Clinical profiles including chief complaint, age, preceding stresses, and past history of TC. (3) Initial vital signs such as systolic and diastolic blood pressure in the emergency room or cardiac care unit, arterial O2 saturation, heart rate, and Killip classification [9]. (4) Electrocardiogram on admission [10]. QT prolongation was defined as QTC ≥ 0.44 s. (5) Laboratory data on admission and peak creatinine kinase (CK) and its MB isozyme during hospitalization. (6) Echocardiographic findings on admission. Left ventricular ejection fraction (LVEF) was evaluated by modified Simpson method using echocardiography performed on admission. Left ventricular outflow tract obstruction was considered significant if more than 30 mmHg [11]. (7) Cardiac catheterization finding obtained from coronary angiography, left ventriculography, and endomyocardial biopsy if performed. (8) Arrhythmic events during hospitalization. (9) Therapeutic procedures during hospitalization, such as mechanical cardiorespiratory support and cardiovascular drugs during hospitalization. (10) In-hospital mortality.

Cardiac complications during hospitalization

Cardiac complications during hospitalization were defined as cardiac death, cardiac rupture, thromboembolism, pump failure (Killip grade ≥ II), sustained ventricular tachycardia or ventricular fibrillation (VT/VF), and advanced atrioventricular block (AVB). We attempted to characterize factors predicting clinical outcome by comparing between patients with cardiac complications and those without complications during hospitalization.

Statistical analysis

Data are expressed as mean ± SD. Differences between all variables were analyzed using Student’s t-test. Differences between categorical variables were analyzed using the chi-square test. A p-value <0.05 was considered significant. Stepwise multiple logistic regression analysis was performed to predict in-hospital cardiac complications.

Results

Data on 107 patients with TC were collected. Elapsed time from the onset to hospitalization was shorter than 24h in 81.8%, and 95.9% of the study population were admitted within 72h. There were 4 patients who presented with symptoms after surgical procedure (details unknown).

The main chief complaint was chest pain (54.2%). Almost all cases were preceded by physical (39.3%) or emotional (29.0%) stresses. Prior history of TC was noted in 5 patients. In recurrent cases, elapsed time from prior episode to the attack was 14 months, 42 months, and 14 months, respectively. In the remaining 2 cases, data were not available as to when prior episodes of TC occurred. In these recurrent cases, emotional stress was identified as a precipitating factor in 4 patients. Seventy patients (65.4%) showed Killip class I, and the remaining 37 patients (34.6%) showed class II or more (Table 1). There was ST segment elevation in 79 patients (73.8%), negative T in 77 patients (72.0%), and QT prolongation in 50 patients (46.7%).

There was a seasonal variation, showing 10 TC patients in February, 11 in March, 13 in September, 14 in October, and 12 in November (Fig. 1). Data were not available for 4 patients as to when TC occurred.

![Fig. 1](https://example.com/fig1.png) Seasonal distribution of onset of takotsubo cardiomyopathy is shown. There was a tendency for bimodal peaks in spring and autumn.
There was a mild elevation of creatinine kinase (338 ± 554 IU/l) and its MB fraction (27 ± 40 IU/l), while blood cell count (WBC, 9676 ± 4006/μl), and C-reactive protein (CRP, 2.19 ± 4.04 mg/dl) level on admission. Brain natriuretic peptide (BNP) level was also moderately increased (656 ± 1622 pg/ml). Blood urea nitrogen (BUN) was 23 ± 16 mg/dl, creatinine (Cr) was 1.49 ± 3.20 (including 2 hemodialysis patients). Aspartate aminotransferase was 52 ± 53 IU/l, alanine aminotransferase was 29 ± 26 IU/l, and total bilirubin was 0.82 ± 0.63 mg/dl. Cardiac troponin was measured in 93 cases, of whom 78 cases (83.9%) were positive.

Echocardiographic findings showed that LVEF was 54.1 ± 14.9%, left ventricular end-diastolic dimension was 43 ± 8 mm, end-systolic dimension was 29 ± 9 mm, and left atrial dimension was 33 ± 7 mm. Apical ballooning type was predominant (91.6%, n = 98), but mid-ventricular type (3.7%, n = 4), basal inverted type (2.8%, n = 3), and apical type (1.9%, n = 2) were also noted. Significant left ventricular outflow obstruction was noted in 4 patients, and moderate or more degree of mitral regurgitation was observed in 5 patients. There were 5 patients who exhibited pericardial effusion with no evidence of cardiac rupture.

Emergency catheterization was performed in 92 cases (86.0%). Significant coronary arterial stenosis was recognized in 9 patients, of whom single-vessel disease was present in 6 patients, double-vessel disease in 2 patients, and triple-vessel disease in 1 patient, although these coronary lesions did not account for the wall motion abnormality. There was no evidence suggesting plaque rupture. Left ventriculography was performed in only 59 cases. Provocation of coronary spasm using acetylcholine was attempted in only 2 cases, with positive in 1 case and negative in the remaining 1 case. Endomyocardial biopsy was not performed in any patients.

Atrial flutter or fibrillation was observed in 13 patients (12.1%). SVT/VF was noted in 3 patients (1 case with pump failure and 2 cases without pump failure). AVB was observed in 2 patients at the time of hospitalization, requiring permanent pacemaker implantation in 1 patient. During the hospital course, 19.6% of cases necessitated cardiac supportive therapies (inotropic agents, n = 16; pacing, n = 2; intra-aortic balloon pumping, n = 3) and 13.1% cases needed respiratory support therapies (mechanical ventilation, n = 7; non-invasive positive pressure ventilation, n = 7).

Nine patients (8.4%) died during the hospital course. There were 4 cardiovascular deaths (3.7%) including heart failure death in 2, death due to cardiogenic shock in 1, and death due to cerebral embolism in 1 (Table 2). In the remaining 5 patients, the primary causes of death were non-cardiovascular, but all cases were complicated by heart failure. WBC count tended to be higher in patients with cardiovascular death than those with non-cardiovascular death (14,183 ± 7118/μl vs. 6866 ± 3698/μl, p = 0.08).

Cardiac complications were observed in 41 patients, and there was no complication in the remaining 66 patients. Pump failure was noted in 37 patients. There were 2 patients with SVT/VF and 2 patients with AVB who did not have pump failure complications. Three cardiac deaths were observed in patients who had pump failure complications. Among them, 1 patient also had SVT complications. One patient with pump failure complications, died of cerebral embolism. There was no cardiac rupture.

Ninety-eight patients survived the hospital course. At discharge, angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers, beta-blocker, and diuretics were prescribed in 48.0%, 25.5%, and 20.4% of the study population, respectively. No digitalis or inotropic agents were given.

There was no difference in age (75 ± 10 years vs. 72 ± 11 years, p = 0.289), female gender (70.7% vs. 80.3%, p = 0.144), peak CK level (553 ± 710 IU/l vs. 486 ± 1024 IU/l, p = 0.780), CRP level (2.63 ± 3.75 mg/dl vs. 1.9 ± 4.25 mg/dl, p = 0.378), BUN/Cr (26.0 ± 9.6 vs. 29.2 ± 36.5, p = 0.53), and ST elevation on electrocardiogram (68.3% vs. 75.8%, p = 0.398), between patients with complications and those without complications. WBC (11,189 ± 4516/μl vs. 9020 ± 3352/μl, p = 0.005) and BNP (1125 ± 1245 pg/ml vs. 376 ± 764 pg/ml, p = 0.004) were higher in patients with cardiac complications than those without. LVEF was lower in patients with complications than those without (49.3 ± 15.4% vs. 56.6 ± 14.1%, p = 0.031) (Table 3). There was no difference in gender, LVEF, WBC, BNP, BUN/Cr, or CRP levels between patients with cardiac death and those without cardiac death.

The median value of WBC, BNP, and LVEF were 9050/μl, 203.7 pg/ml, and 56%, respectively. Stepwise multiple logistic regression analysis was performed using the median value of WBC, BNP, and LVEF. We found that higher WBC (odds ratio = 2.52, 95% CI = 1.05–6.06, p = 0.039) and BNP (odds ratio = 4.92, 95% CI = 1.97–12.3, p = 0.001) were independent predictors of cardiac complications during hospitalization (Table 4).

**Table 2**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Gender</th>
<th>Type</th>
<th>Preceding stress</th>
<th>Killip</th>
<th>Cause</th>
<th>Time to death</th>
<th>WBC (/μl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>Female</td>
<td>Apical</td>
<td>Dyspnea</td>
<td>II</td>
<td>Respiratory failure</td>
<td>13 days</td>
<td>7400</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>Female</td>
<td>Apical</td>
<td>None</td>
<td>II</td>
<td>Cerebral embolism</td>
<td>13 days</td>
<td>9600</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
<td>Female</td>
<td>Apical</td>
<td>Hypoxia</td>
<td>II</td>
<td>Intestinal pneumonia</td>
<td>56 days</td>
<td>8600</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>Male</td>
<td>Apical</td>
<td>Hydropsyemia</td>
<td>IV</td>
<td>Multiple organ failure</td>
<td>8 days</td>
<td>1400</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>Female</td>
<td>Apical</td>
<td>Infection</td>
<td>III</td>
<td>Sepsis</td>
<td>3 days</td>
<td>5600</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>Male</td>
<td>Apical</td>
<td>Emotional</td>
<td>IV</td>
<td>Cardiogenic shock</td>
<td>2 days</td>
<td>8330</td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>Female</td>
<td>Apical</td>
<td>None</td>
<td>IV</td>
<td>Heart failure</td>
<td>12 days</td>
<td>24000</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>Female</td>
<td>Apical</td>
<td>Emotional</td>
<td>IV</td>
<td>Heart failure</td>
<td>12 days</td>
<td>14800</td>
</tr>
<tr>
<td>9</td>
<td>76</td>
<td>Female</td>
<td>Apical</td>
<td>Hemodialysis</td>
<td>II</td>
<td>DIC</td>
<td>32 days</td>
<td>11330</td>
</tr>
</tbody>
</table>

Time, duration from occurrence of takotsubo cardiomyopathy to death; DIC, disseminated intravascular coagulation; WBC, white blood cell count.

**Discussion**

In this analysis of the database of TC collected from the Tokyo CCU Network annual report, we demonstrated that there was a considerable number of patients who experienced adverse clinical events during hospitalization. We found that WBC count on admission as well as plasma BNP level were independent predictors of adverse clinical outcome.

**Table 3**

<table>
<thead>
<tr>
<th>Cardiac complication</th>
<th>Present (n = 41)</th>
<th>Absent (n = 66)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75.2 ± 10.4</td>
<td>72.9 ± 11.6</td>
<td>0.289</td>
</tr>
<tr>
<td>Female</td>
<td>n = 29 (70.7%)</td>
<td>n = 53 (80.3%)</td>
<td>0.144</td>
</tr>
<tr>
<td>WBC (/μl)</td>
<td>11189 ± 4516</td>
<td>9020 ± 3352</td>
<td>0.005</td>
</tr>
<tr>
<td>Peak CK (IU/l)</td>
<td>553 ± 710</td>
<td>486 ± 1024</td>
<td>0.780</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>2.63 ± 3.75</td>
<td>1.9 ± 4.25</td>
<td>0.378</td>
</tr>
<tr>
<td>BUN/Cr</td>
<td>26.0 ± 9.6</td>
<td>29.2 ± 36.5</td>
<td>0.53</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>1125 ± 1245</td>
<td>376 ± 764</td>
<td>0.004</td>
</tr>
<tr>
<td>LVEF</td>
<td>49.3 ± 15.4</td>
<td>56.6 ± 14.1</td>
<td>0.030</td>
</tr>
<tr>
<td>ST elevation</td>
<td>n = 28 (68.3%)</td>
<td>n = 50 (75.8%)</td>
<td>0.398</td>
</tr>
</tbody>
</table>

WBC, white blood cell count; CK, creatinine kinase; CRP, C-reactive protein; BNP, brain natriuretic peptide level; BUN, blood urea nitrogen; LVEF, left ventricular ejection fraction on echocardiography.
Table 4
Independent predictors of in-hospital adverse cardiac complications.

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>2.52</td>
<td>1.05–6.06</td>
<td>0.039</td>
</tr>
<tr>
<td>BNP</td>
<td>4.92</td>
<td>1.97–12.3</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.27</td>
<td>0.07–1.05</td>
<td>0.059</td>
</tr>
</tbody>
</table>

WBC, white blood cell count; BNP, brain natriuretic peptide level; LVEF, left ventricular ejection fraction on echocardiography.

Epidemiology

Previous TC outcome data exhibited an increased incidence during summer (June, July, and August) in Italy, winter in Switzerland, and in April in France [12]. The Tokyo CCU Network database indicated there was an increased incidence both during the spring and autumn. Although there was a difference in the seasonal occurrence among various regions, the reason why there was such a difference cannot be explained properly. Further investigation is needed to confirm this issue.

Five patients (4.7%) showed recurrence of TC. Previous reports have shown that the percentage of recurrence ranged from 1.7% to 9.0% [13,14]. The recurrence of TC in four of the five patients was preceded by emotional stress. Unfortunately, data on prior medications before admission were not available in this Tokyo CCU Network database. The small number of patients who experienced recurrence and limited information on prior medications failed to allow meaningful statistical analysis of factors predicting the recurrence.

Nine patients (8.4%) died during their hospital stay for various reasons including four cardiovascular deaths (3.7%). The previous reports showed that the mortality rate during hospitalization ranged from 1.7% to 2.0% [13–15]. Overall mortality may be higher in clinical practice, since non-cardiac death also comprises a considerable part of in-hospital mortality in severely ill patients who experience TC. Actually, the mortality rate in the present study was relatively high compared with the previous reports. Tokyo CCU Network database included non-cardiac deaths, so the overall mortality was higher than the previous reports. However, most of non-cardiac deaths were precipitated by concomitant heart failure. Recently, Brinjikji et al. reported clinical profiles in a large number of patients with TC based on National Inpatient Database Samples 2008 to 2009. They found that in-hospital mortality was as high as 4.2%, and most of the deaths were associated with underlying critical illnesses [16]. TC seems to be associated with high mortality rates during hospitalization in the real world setting.

Inflammation in TC

Cardiovascular magnetic resonance imaging demonstrated the contribution of an inflammatory process in the acute setting and showed complete normalization of left ventricular function and inflammatory parameters (T2-weighted image) [15,17,18]. Otherwise, apart from their possible noxious role in the activation of the inflammatory response, catecholamines could also contribute to myocardial stunning in the absence of relevant myocardial perfusion abnormalities [19,20]. In this regard, the inflammatory process may play a role in the pathophysiology of TC. CRP may reflect acute inflammation, but the present study failed to show a relationship with in-hospital cardiac complications. Alternatively, an increase in WBC count may precede the CRP activation during the early phase of inflammation. We found that higher WBC count was associated with adverse clinical outcome, independently from cardiac function as reflected by BNP level. WBC count also tended to be higher in patients with cardiovascular death than those with non-cardiovascular death. There are numerous markers that reflect inflammation, such as proinflammatory cytokines, oxidative stress, etc. Although WBC count may be affected by various factors including preceding stress, this may be a simple conventional marker to reflect the severity of TC. In this registry, 7 patients who experienced infection were noted. However, the extent of leukocytosis was associated with TC itself in the predominant cases.

BNP level

Plasma BNP level is a well-accepted marker for cardiac function. The present study demonstrated this plasma level was moderately increased in the overall population, but there was a wide variation in its distribution. Plasma BNP may reflect mechanical wall stress induced by abrupt onset of TC, as well as cardiac dysfunction. In this study, 25.2% patients with higher BNP level experienced pump failure. As expected, we found that higher BNP level was associated with adverse clinical outcome. Morel et al. examined the relationship between plasma BNP level and other neurohormones as well as inflammatory markers, and found that there were close correlations among these parameters [19]. It is possible that sympathoadrenal activation during the early process of TC induces hypertrophic signal and inflammatory response as reflected by BNP and CRP levels [21], although an increase in plasma norepinephrine concentration during the early phase after onset is inconsistent in previous reports [22].

LV dysfunction

Cardiac dysfunction is a characteristic feature during the early process of TC. We found that pump failure was noted in 37 patients, and this complication was related directly or indirectly to in-hospital mortality. In fact, LVEF was lower in patients with cardiac complications than those without complications. However, multivariate analysis failed to show the significance of lower LVEF in predicting clinical outcome. Since plasma BNP level may be associated with LVEF [21], potential significance could have been abolished by the presence of BNP.

PredischARGE medications

Experimental studies have shown that combined alpha-and beta-blocker, beta-blocker with intrinsic sympathomimetic activity, and calcium channel blocker, azelnidipine, prevent stress-induced cardiac dysfunction in rats [23,24]. In cases in whom the left ventricular wall motion abnormalities remains, beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II type 1 receptor blockers are recommended [1]. In our registry, only 48.0% patients were given angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers, and 25.5% patients were given beta-blockers. Whether or not such medications affect clinical course after discharge remains to be determined.

Study limitations

First, not all patients underwent catheterization, so the diagnosis of TC was made according to the characteristic findings on electrocardiography and echocardiography in several cases. Second, WBC count may be affected by various factors, such as infection and preceding stress. Third, biopsy was performed in none of the study subjects. Cardiac magnetic resonance imaging in assessing the presence of myocarditis was performed in only four cases. Acute myocarditis also exhibits some degree of cellular infiltration on histopathology and interstitial inflammation on T2 imaging in cardiac magnetic resonance imaging, both of which mimic TC. Lastly, the present Tokyo CCU Network database included limited data during hospitalization.
Conclusions

In this report from the Tokyo CCU Network database, cardiac complications were relatively high during hospitalization, and a considerable number of patients died. High WBC count and BNP level are associated with poor clinical outcome in patients with TC. Long-term follow-up and factors influencing life expectancy are necessary to further clarify its clinical features.

References


