Impact of Malignancies in the Early and Late Time Course of Takotsubo Cardiomyopathy

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Background: Although the relationship between malignancies and catecholamine-induced myocardial stunning remains largely speculative, it has been suggested that the presence of cancer may lower the threshold for stress stimuli and/or may aggravate cardiac adrenoceptor sensitivity. We sought to investigate whether associations exist between a previous or current diagnosis of malignancy, diagnostic parameters during hospitalization and death in takotsubo.

Methods and Results: The 154 takotsubo patients were retrospectively identified between May 2008 and December 2014. Previous history of malignancy was identified in 44 patients (28.5%). Cardiac arrest was present at admission in 13 patients (8.4%). Intra-aortic balloon pump was inserted in 16 patients (10.4%). In patients with malignancy, higher B-type natriuretic peptide (BNP), leukocyte and C-reactive protein (CRP) peaks could be observed during the hospital phase. Initial impairment of left ventricular ejection fraction was negatively related to BNP, leukocyte, and CRP peaks. At a median follow-up of 364 days, all-cause death occurred in 41 patients (26.6%) and cardiac death in 12 patients (7.7%). Multivariate Cox regression analysis identified malignancy (hazard ratio 4.77 (1.02–22.17), leukocyte peak and age as independent predictors of cardiac death. Malignancy (2.62 (1.26–5.44), leukocyte peak (1.05 (1.01–1.08) and initial cardiac arrest (6.68 (2.47–18.01) were identified as independent predictors of overall mortality.

Conclusions: In the present takotsubo patients, the prevalence of malignancy was high and may have affected cardiovascular outcomes through the activation of inflammatory and neurohormonal mechanisms. (*Circ J* 2016; **80**: 2192–2198)

Key Words: Inflammation; Malignancy; Mortality; Takotsubo cardiomyopathy

Takotsubo cardiomyopathy can be broadly defined as a transient cardiomyopathy clinically sharing many features of myocardial infarction such as acute chest pain, ECG changes and troponin rise. Various sets of criteria have been proposed over time to standardize the diagnosis of takotsubo cardiomyopathy.^{1,2} Although no definitive agreement has been achieved, the presence of mostly reversible regional wall motion abnormalities that extend beyond a single epicardial vascular distribution and occurring in the absence of hemodynamically significant coronary obstructions appears to be the unifying feature.^{2,3}

A large body of evidence indicates that takotsubo cardiomyopathy tends to occur more frequently in women, in older patients, and in the presence of a history of emotional or physical

stress.⁴ Intriguingly, the prevalence of cancer history or new diagnosis appears to be higher in patients with takotsubo cardiomyopathy compared with age-matched populations.^{5–7} As takotsubo cardiomyopathy has been reported in association with several other clinical scenarios, such as epinephrine treatment or overdosing, trauma, acute medical or surgical illnesses such as shock and intracranial bleeding, and pheochromocytoma,⁸ a common pathophysiological mechanism involving the catecholaminergic system has been postulated.^{2,9–11} Although the relationship between malignancies and catecholamine-induced myocardial stunning remains largely speculative, it has been suggested that the presence of cancer may lower the threshold for stress stimuli and/or may aggravate cardiac adrenoceptor sensitivity.^{5,6} Whether, in patients with takotsubo cardiomy-

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Table 1. Clinical Characteristics of Takotsubo Patients

Patients, n	Takotsubo cardiomyopathy		P value
	Without malignancy	With malignancy	
	110	44	
Age (years)	67±13	68±10	0.571
Female	90 (81.8)	29 (65.9)	0.033
Arterial hypertension	73 (66.4)	21 (47.7)	0.032
Diabetes mellitus	29 (26.4)	9 (20.5)	0.442
Hyperlipidemia	45 (10.9)	12 (27.3)	0.113
Past tobacco use	22 (20)	16 (36.4)	0.033
Current tobacco use	26 (23.6)	10 (22.7)	0.904
Obesity	25 (22.7)	5 (11.4)	0.108
Presentation			
Chest pain	48 (43.6)	17 (38.6)	0.570
Dyspnea	42 (38.2)	25 (56.8)	0.035
Cardiac arrest	10 (9.1)	3 (6.8)	0.647
Syncope	4 (3.6)	1 (2.3)	0.666
IABP insertion	12 (10.9)	4 (9.1)	0.726
Amines	12 (10.9)	3 (6.8)	0.439
Dobutamine	5 (4.5)	1 (2.3)	0.510
Adrenaline	4 (3.6)	1 (2.3)	0.666
Noradrenaline	11 (10)	3 (6.8)	0.535
Emotional trigger	23 (20.9)	5 (11.4)	0.011
Physical stressor	48 (43.6)	31 (70.5)	0.011
Trigger unknown	39 (35.5)	8 (18.2)	0.011

IABP, intra-aortic balloon pump.

opathy, the presence of cancer correlates with worse ECG, and echocardiographic, and laboratory parameters at the time of presentation, and whether these variables predict all-cause and cardiac death in this population has not been explored. Therefore, the current study was designed to investigate whether associations exist between a previous or current diagnosis of malignancy, diagnostic parameters during hospitalization and death in patients with takotsubo cardiomyopathy.

Methods

Study Population

Patients with suspected takotsubo cardiomyopathy were identified from the 21,326 coronary angiograms recorded in the Cardiac Catheterization Laboratory database of the University Hospital of Strasbourg between May 2008 and December 2014. The database was queried using the key words “stress”, “takotsubo” or “catecholamine”. The diagnosis of takotsubo cardiomyopathy was made according to the Madias’ criteria.³ However, given the common underlying mechanism, we did not exclude patients with pheochromocytoma and intracranial bleeding. Patients with coronary stenosis >50% were included when transient left ventricular (LV) dysfunction could not be explained by transient or permanent coronary occlusion. Exclusion criteria comprised a diagnosis of acute coronary occlusion, percutaneous intervention, myocarditis, valve replacement during the hospital phase, and tachycardia-induced cardiomyopathy. Two cardiologists (M.G. and O.M.) reviewed all the cases and the diagnosis of takotsubo cardiomyopathy was made based on a consensus agreement after exclusion of other reversible causes of myocardial dysfunction (eg, myocarditis, tachycardia-induced cardiomyopathy). The study protocol was approved by the Institutional Review Board of the University

of Strasbourg. Retrospective consent was obtained from patients when alive at follow-up or from their relatives.

Clinical Assessment

At the time of the index event, a complete medical history was recorded. Because the entire recovery of malignancy, as cure of cancer without recurrence is difficult to establish, every history of malignancy was considered. 12-lead ECG and routine laboratory data, including a quantitative troponin I (TN-I), BNP, high-sensitivity C-reactive protein and leukocyte count were obtained serially. For the current study, analysis of the ECGs was performed by a cardiologist who was blind to the diagnosis of malignancy. The following parameters were collected: presence and number of Q waves, Q wave amplitude in millimeters, and sum of Q waves amplitude in millimeters. Multiplane coronary angiography was performed in all patients by radial or femoral approach using standard techniques. LV ejection fraction (EF) was calculated from planimetric evaluation of the end-diastolic and endsystolic volumes in the 30° right anterior oblique projection. 2D transthoracic echocardiographic studies were performed in all patients in a standard fashion to assess LV systolic function and wall motion abnormalities. Calculation of the LVEF was done in the 4-chamber view according to Simpson’s method.

Clinical Follow-up

After hospital discharge, follow-up was obtained for all patients using standardized telephone interviews with a cardiologist or another physician. In cases of death, the cause was ascertained by thorough review of all available clinical information at the time of death. Cardiac death was defined as any death with demonstrable cardiac cause or any death that was not clearly attributable to a noncardiac cause. Follow-up was stopped at 1,000 days.

Table 2. Electrocardiographic, Echocardiographic, Angiographic and Biological Parameters of Takotsubo Patients

	Takotsubo cardiomyopathy		P value
	Without malignancy	With malignancy	
Electrocardiogram			
Q waves, n	1.3±1.8	2.1±2.1	0.028
Q wave max amplitude (mm)	3.8±5.8	6.9±7.1	0.011
Q wave, sum of amplitudes (mm)	9±15	17±19	0.011
Wall motion distribution, n (%)			
Apical	66 (60)	30 (68.2)	0.628
Apical+other location	88 (80)	38 (86.4)	
Midventricular	26 (23.6)	7 (15.9)	
Other	18 (16.3)	7 (15.9)	
Ejection fraction (%)			
Angiography	37±11	34±10	0.161
Echo: initial	38±11	36±12	0.465
Echo: at discharge	54±10	54±10	0.806
Echo in-hospital change (discharge-initial)	18±10	21±10	0.382
Echo: at follow-up	62±7	66±5	0.162
Coronary stenosis >50%	8 (7.3)	3 (6.8)	0.921
Troponin I (μg/L)			
On admission	1.04 (0.35–3.65)	1.41 (0.16–5.16)	0.969
Peak	3.08 (1.30–7.55)	5.23 (0.95–12.89)	0.213
At discharge	0.41 (0.13–1.23)	0.23 (0.07–0.88)	0.340
BNP (ng/L)			
On admission	268 (82–986)	515 (149–987)	0.115
Peak	1,001 (363–1,989)	1,970 (950–3,836)	0.014
At discharge	455 (133–758)	450 (191–1,105)	0.403
Leukocyte count (10 ⁹ /L)			
On admission	11,460 (8,240–14,850)	11,000 (6,765–14,487)	0.560
Peak	12,810 (9,622–19,030)	16,075 (12,190–23,120)	0.017
At discharge	7,335 (5,875–9,182)	7,490 (6,110–11,000)	0.730
CRP (mg/L)			
On admission	10 (1–28)	33 (9–151)	0.001
Peak	57 (15–131)	129 (47–225)	0.001
At discharge	8 (1–21)	26 (6–57)	0.003

Data are expressed as mean ± SD or as median (25–75th interquartile range). BNP, B-type natriuretic peptide; CRP, C-reactive protein.

Statistical Analysis

Categorical variables are expressed as counts and percentages. Continuous variables are reported as mean ± SD or as median and interquartile range (25–75th) according to their distribution. Categorical variables were compared with chi-square test or Fisher's exact test. Continuous variables were compared with Mann-Whitney test. To determine the predictors of death, Cox regression analysis was performed. Associations between malignancies and occurrence of clinical outcomes were assessed by Kaplan-Meier analysis and log-rank test. Correlations were studied using Spearman Test. All tests were 2-sided. $P < 0.05$ was considered significant. Calculations were performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

A total of 190 patients were identified in the Cardiac Catheterization Laboratory database by our query. Of them, 154 met the inclusion and exclusion criteria and were included in the present analyses (Figure S1). Participants were divided into 2 groups

according to the presence of a history of malignancy. Their baseline demographic and clinical characteristics are reported in Table 1. At the time of the index event, a previous history of malignancy was identified in 44 patients (28.5%). Cardiac arrest was present at the time of admission in 13 patients (8.4%). Intra-aortic balloon pump (IABP) was inserted in 16 patients (10.4%). Female sex, history of arterial hypertension and emotional stress as the likely trigger event were more frequently recorded in patients without a history of malignancy, whereas the prevalence of past tobacco use and a physical trigger was higher in those with a positive cancer history.

The types of cancers are listed in Table S1 and the triggering events in Table S2. As detailed in Table 2, no differences between the 2 patient groups in initial LVEF, LVEF at hospital discharge, LVEF at follow-up or DLVEF during the hospital phase were present. The number of Q waves, maximum Q wave amplitude and sum of Q wave amplitudes were higher when a diagnosis of malignancy was present. The distribution of the various forms of takotsubo cardiomyopathy (apical, midventricular, and other types) was not substantially different between

the 2 subsets of patients. Laboratory parameters during the hospital phase are reported in [Table 2](#). Whereas no differences in baseline BNP and leukocyte count could be observed between groups, higher peak of BNP and leukocyte count were observed in takotsubo cardiomyopathy patients with malignancy. Likewise, baseline, peak and discharge CRP levels were higher in the malignancy subgroup. TN-I peak tended to be higher in the malignancy subgroup but the difference did not reach statistical significance. The initial LVEF was inversely related to peak BNP level ($r=-0.374$; $P<0.001$), leukocyte peak ($r=-0.237$; $P=0.005$) and CRP peak ($r=-0.223$; $P=0.013$). Conversely, no significant relationship between peak TN-I and initial LVEF was present ($r=-0.065$; $P=0.455$).

Clinical Outcomes

Outcomes were available for all patients with a median follow-up of 364 days (range, 79–878). Death from any cause occurred in 41 patients (26.6%) and cardiac death in 12 patients (7.7%). Death occurred during hospitalization in 25 patients (16.2%) and after hospital discharge in 16 patients (10.3%). No recurrence of takotsubo cardiomyopathy was observed. At follow-up, both all-cause death and cardiac death were higher in the subgroup with malignancy compared with patients without (45.5% vs. 19.1%; log-rank $P=0.001$ and 13.6% vs. 5.5% log-rank $P=0.052$) ([Figures A,B](#)). No effect of the type of stress on clinical outcome could be evidenced.

Predictors of Cardiac Death

By univariate Cox analysis, age, cardiac arrest at admission, IABP, history of malignancy, TN-I peak, leukocyte peak, and CRP peak were associated with cardiac death. In contrast, the type of takotsubo cardiomyopathy (apical vs. other forms), initial LVEF dysfunction, and the type of triggering event (mental vs. physical) did not correlate with death. On multivariate Cox regression analysis, cardiac arrest, history of malignancy, leukocyte count peak, and age remained as independent predictors of cardiac death ([Table 3](#)).

Predictors of All-Cause Death

By univariate Cox analysis, cardiac arrest at the time of admission, IABP, initial LVEF, history of malignancy, troponin peak, BNP peak, leukocyte peak, CRP peak and physical stressor were significant predictors of all-cause death. In contrast, the type of takotsubo cardiomyopathy did not correlate with death. On multivariate Cox regression analysis, cardiac arrest, history of malignancy, and leukocyte count peak remained as independent predictors of all-cause death ([Table 4](#)).

Discussion

The main findings of the present study are that, among patients presenting with takotsubo cardiomyopathy, those with a diagnosis of malignancy showed more marked ECG abnormalities; higher peak BNP and leukocyte levels, higher CRP on admission, at peak, and at discharge, and higher mortality rate. Furthermore, a diagnosis of malignancy was an independent predictor of cardiac and all-cause deaths. Thus, malignancies appear to significantly enhance neurohormonal activation and the inflammatory response during the acute phase of takotsubo cardiomyopathy and to be an independent predictor of early cardiac death and overall mortality during follow-up. In addition, our data confirm the high prevalence of malignancy in patients with this condition.

A number of clinical and experimental studies have inves-

Figure. Kaplan-Meier analysis for the probability of (A) overall survival and (B) cardiac survival according to malignancy in patients with takotsubo syndrome.

tigated the potential links between cancer, emotional stress, inflammation, and neurohormonal activation, particularly with regard to the sympathetic nervous system.^{5,6} The enhanced catecholamine release observed in various cancers may promote myocardial stunning, as suggested by the evidence of reversible cardiac dysfunction in pediatric patients with neuroblastoma, a primitive neural tumor often associated with elevated plasma catecholamine levels.^{12,13} Of interest, Lyon and coworkers have proposed that the effects of catecholamines on myocardial function are induced by a switch in the β_2 -adrenergic receptor (β_2 -AR) intracellular signaling from a G_s to G_i protein.¹⁰ Although this switch may be cardioprotective by reducing the proapoptotic effects of excessive β_1 -AR stimulation of the myocardium, it may also exert negative inotropic effects. Of note, inflammation may lead to activation of p38 mitogen-activated protein kinase,¹⁴ a downstream effector of the β_2 -AR

Table 3. Univariate and Multivariate Analyses for Prediction of Cardiac Death of Takotsubo Patients

	HR	95% CI	P value	HR	95% CI	P value
Age	1.05	0.99–1.10	0.065	1.11	1.03–1.2	0.006
Female	0.82	0.22–3.06	0.774			
Cardiac arrest	7.23	1.82–28.67	0.005	5.00	0.46–53.3	0.182
IABP	4.21	1.08–16.37	0.038	3.73	0.53–26.07	0.183
Initial LVEF	0.31	0.01–77.24	0.678			
Coronary stenosis >50%	0.04	0.01–7.98	0.533			
LVEF at discharge	1.47	0.01–4,878.61	0.925			
ΔEF	19.25	0.01–36.961	0.443			
Malignancy	3.09	0.97–9.82	0.056	4.77	1.02–22.17	0.046
Diabetes mellitus	1.45	0.43–4.83	0.544			
Troponin I peak	1.02	1.01–1.03	0.001	1.00	0.98–1.02	0.897
BNP peak	1.00	1.00–1.00	0.949			
Leukocyte peak	1.08	1.04–1.12	0.001	1.10	1.03–1.19	0.006
CRP peak	1.00	1.002–1.014	0.013			
Apical form	1.35	0.29–6.22	0.698			
Mental trigger	0.42	0.05–3.29	0.412			
Physical stressor	1.23	0.38–3.93	0.724			
Past tobacco use	1.16	0.31–4.40	0.819			

CI, confidence interval; HR, hazard ratio; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction. Other abbreviations as in Tables 1,2.

Table 4. Univariate and Multivariate Analyses for Prediction of All-Cause Death of Takotsubo Patients

	HR	95% CI	P value	HR	95% CI	P value
Age	1.01	0.98–1.04	0.286			
Female	0.98	0.46–2.06	0.960			
Cardiac arrest	5.80	2.72–12.39	0.001	6.68	2.47–18.01	<0.001
IABP	2.42	1.06–5.53	0.035	1.60	0.53–4.79	0.395
Initial LVEF	0.01	0.00–0.39	0.009	0.13	0.02–8.41	0.341
Coronary stenosis >50%	1.53	0.54–4.30	0.419			
LVEF at discharge	0.16	0.00–15.84	0.436			
ΔEF	26.92	0.55–131	0.097			
Malignancy	2.77	1.48–5.17	0.002	2.62	1.26–5.44	0.010
Diabetes mellitus	1.30	0.66–2.56	0.442			
Troponin I peak	1.01	1.00–1.02	0.002	0.99	0.97–1.05	0.175
BNP peak	1.00	1.00–1.01	0.007			
Leukocyte peak	1.05	1.03–1.08	<0.001	1.05	1.01–1.08	0.008
CRP peak	1.00	1.03–1.09	<0.001			
Apical form	1.40	0.58–3.35	0.442			
Mental trigger	0.62	0.24–1.59	0.325			
Physical stressor	2.12	1.10–4.10	0.025	1.13	0.48–2.63	0.776
Past tobacco use	1.07	0.52–2.20	0.850			

Abbreviations as in Tables 1–3.

signaling pathway,¹⁵ suggesting possible synergistic effects of stress and inflammation in the pathogenesis of takotsubo cardiomyopathy in cancer patients.

Our current findings of higher peak leukocyte counts and higher CRP levels in patients with malignancy compared with those without expands our previous work indicating that these inflammatory markers may be involved in the pathogenesis of takotsubo cardiomyopathy.¹⁶ In particular, our new data suggested that the presence of malignancy may promote inflammation, which in turn contributes to myocyte damage. Furthermore, as the levels of CRP in the patients with cancer were higher at baseline, at peak and at discharge, it is reasonable

to speculate that a sustained enhanced inflammatory status associated with malignancy may promote the onset of takotsubo cardiomyopathy. The presence of intramyocardial inflammatory activation in patients with takotsubo cardiomyopathy has been documented directly by myocardial biopsy studies,¹¹ as well as by technetium pyrophosphate imaging¹⁷ and by cardiac MRI.¹⁸ Of note, recent cardiac MRI data show that takotsubo cardiomyopathy is characterized by a state of intramyocardial edema secondary to a global LV inflammatory response, which is detectable early after the index event and persisting well beyond the resolution of segmental LV contractile dysfunction.¹⁹

Several additional mechanisms may underlie the relationship

between inflammatory response, neurohumoral activation, and myocardial damage observed in patients with takotsubo cardiomyopathy and malignancy. Cytokines and reactive oxygen species released by activated inflammatory cells could contribute directly to myocardial damage.²⁰ In rats, immobilization stress induces the production of heat shock protein 70 by the myocardium, a potent activator of the inflammatory response,²¹ and enhances atrial and B-type natriuretic peptide expression.²² Notably, catecholamines may promote an acute inflammatory response and leukocytosis. Consistent with this effect, we have previously shown a direct relationship between catecholamines and leukocyte levels in the acute phase of takotsubo cardiomyopathy.¹⁶

The high prevalence of malignancy in patients with takotsubo cardiomyopathy observed in the present cohort is in line with previous data from our group^{16,23} and from Burgdorf and coworkers.^{5,6} However, in a large international collaborative meta-analysis Pelliccia and coworkers reported a lower average prevalence of 10%, with a range from 4% to 29%.²³ This difference may be related, at least in part, to underreporting of a diagnosis of malignancy in patients hospitalized in a cardiology setting. The patients enrolled in the current study were admitted to both the cardiology unit and the critical care department with a large proportion of oncologic patients. Independent of the explanation, the elevated rate of malignancy observed in patients with takotsubo cardiomyopathy greatly exceeds the expected prevalence of cancer in age-matched populations in the United States (8.2%), Germany (11.2%) and combined European countries (7.8%).^{5,6} In France, data from the FRANCIM (French network of cancer registries) registry indicated a total prevalence of cancer of 6.4% for men and 5.3% for women. A high prevalence of malignancy in takotsubo cardiomyopathy has also been reported by El-Sayed and coworkers in large cohort of 24,701 patients.²⁴ In that study, the prevalence of malignancy was 14.4% in patients with takotsubo cardiomyopathy, compared with 10% and 8.8% in age-matched controls with myocardial infarction and orthopedic conditions, respectively.²⁴

Predictors of Death in Takotsubo Cardiomyopathy

Although previous retrospective studies of patients with takotsubo cardiomyopathy have suggested a significant mortality risk mostly in the early period (1–1.5%), with a low risk for recurrence or permanent damage,²⁵ and survival rates similar to age- and sex-matched populations,²⁶ recent data have challenged this notion.²⁷ In our cohort, cardiac death occurred in 7.8% of the patients, and all-cause death in 26.6%, with higher rates observed in the malignancy subgroup. In-hospital death (16.2%) was twice as high as recently reported by another French group (7.5%).²⁸ Patient's severity was also clearly highlighted by the high rates of initial cardiac arrest (8.4%) and of IABP implantation (10.3%). Recent investigations have demonstrated that the development of hypotension in the early stages of takotsubo cardiomyopathy is not associated with the degree of LV systolic dysfunction and heart rate, suggesting that other factors are the underlying determinants of the hemodynamic impairment.²⁹ The evidence in our cohort of a lack of a relationship between initial LVEF and cardiac death further supports the concept that the extent of myocardial stunning is not a predictor of cardiac death per se, and may represent a protective mechanism in the presence of a stressor event. Although elucidation of the complex interactions between inflammation and malignancy is beyond the scope of the present study, both parameters remained independent predictors of all-cause death and cardiac death. The present findings are consistent with recent reports from Japanese investigators that

showed higher in-hospital mortality rates, the deleterious impact of malignancy and inflammation on in-hospital mortality rates,³⁰ and the value of the leukocyte count and BNP level as independent predictors of death.³¹

Study Limitations

We based the diagnosis of takotsubo cardiomyopathy on new criteria proposed by Madias rather than the Mayo Clinic's criteria. However, the main difference relies on the recognition that takotsubo cardiomyopathy may occur in a variety of illness, including pheochromocytoma, acute coronary syndrome or intracranial bleeding, and it is unlikely to have significantly affected the overall characteristics of the cohort included in this study. As with similar evaluations of registry data, there are inherent limitations in this type of study, mainly related to known or unknown confounding factors. Inflammation evaluation was restricted to CRP and leukocyte measurements. Other parameters reflecting catecholamine release were not assessed. The effect of LV outflow tract obstruction on the extent of takotsubo could not be established. Owing to the retrospective nature of the study, mechanistic insights concerning the link between malignancy, adrenoceptor sensitivity and inflammation could not be investigated. Events were not adjudicated by an independent committee. Given the relatively low number of cardiovascular deaths recorded in this registry, the multivariate analysis should be interpreted with caution and the findings viewed as exploratory and/or hypothesis generating. Finally, the effect of other factors contributing to adverse outcome, such as unhealed cancer, chemotherapy, radiation and surgery, was not investigated.

Conclusions

In the present patients with takotsubo cardiomyopathy, the prevalence of malignancy was high and may have affected cardiovascular outcomes through the activation of inflammatory and neurohormonal mechanisms. Further study is necessary to confirm our findings in a large, multicenter cohort and to elucidate the mechanisms underlying the association between malignancy and takotsubo cardiomyopathy.

Conflicts of Interest

None.

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Supplementary Files

Supplementary File 1

Figure S1. N=21,326 coronary angiography between May 2008 and December 2014 (1,754 in 2008 / 2,752 in 2009 / 2,887 in 2010 / 3,207 in 2011 / 3,512 in 2012 / 3,468 in 2013 / 3,746 in 2014).

Table S1. Types of malignancy in takotsubo patients

Table S2. Identifiable precipitating factors of takotsubo patients

Please find supplementary file(s);
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