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【 ORIGINAL ARTICLE 】

# Gender Differences in the Circadian and Seasonal Variations in Patients with Takotsubo Syndrome: A Multicenter Registry at Eight University Hospitals in East Japan

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**Abstract:**

**Objective** The aim of this study was to clarify the circadian and seasonal variations in addition to identify sex-based differences in Japanese patients with Takotsubo syndrome (TTS).

**Methods** The authors conducted a retrospective observational study to analyse the differences between the groups based on sex.

**Patients** The patients were registered out of each institute registry of the acute coronary syndrome (ACS) which contains a total of 10,622 cases in eight academic hospitals in east Japan.

**Results** Data for 344 consecutive TTS (73 male and 271 female) were extracted from each hospital registry. In-hospital mortality was higher in the male group than in the female group (18% vs. 7%; p=0.005). With regard to the circadian variations in all study patients, TTS events occurred most often in the afternoon and least often during the night. Moreover, the patterns of circadian variations in the female and male groups were the same as that of all study patients. TTS events occurred most frequently in the autumn and least often in the spring in the whole study cohort. Moreover, the seasonal variation in the female group showed the same pattern as that of the whole cohort. However, there were no significant seasonal differences in the incidence of TTS in the male group.

**Conclusion** In a multicenter study in Japan, seasonal variation was observed in the female group but not in the male group. Circadian variation was observed in both groups. These results suggested that the pathogenesis and clinical features of TTS might therefore differ according to sex.

**Key words:** takotsubo syndrome, circadian variation, seasonal variation, gender differences

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## Introduction

Takotsubo syndrome (TTS), which is characterized by a transient reversible left ventricular dysfunction, was first reported in 1990 in Japan (1). Ninety percent of TTS patients are female and most are over 50 years old (2, 3). TTS can occur after several types of stressors (4, 5). In general, TTS in female patients is caused by emotional stressors, while TTS in male patients is caused by physical stressors. These patient characteristics have been established in many previous studies (6-8). However, there are few reports regarding circadian and seasonal variations in TTS patients. There is a lack of consensus about circadian (9-13) and seasonal variations in TTS (6, 9, 12, 14), most likely due to the small number of patients. As a result, controversy remains regarding the circadian and seasonal variations in patients with TTS. Furthermore, there have been no previous reports about sex-based differences in the circadian or seasonal variations. Given the difference in stressors between male and female TTS patients, there may be differences in the chronological variations between those groups of patients. The aims of this study were to elucidate the clinical features of sex-based differences in the circadian and seasonal variations in patients with TTS.

## Materials and Methods

### Study patients

The patients were registered from each institute registry of acute coronary syndrome (ACS) cases which contained a total of 10,622 cases at the 10 hospitals affiliated with eight medical schools in eastern Japan (the Cardiovascular Research Consortium-8 Universities: CIRC-8U: CIRC-8U: Iwate Medical University, Kitasato University, Tokai University, Dokkyo Medical University, Saitama Medical University, St. Marianna University, Teikyo University, and Kyorin University). The diagnostic criteria used to diagnose TTS were the Mayo Clinic diagnostic criteria (15). The present study protocol was approved by the ethics committee of each hospital.

### Baseline parameters and clinical outcomes

This was a retrospective observational study that analyzed the clinical characteristics of TTS patients. A unified patient registration sheet was used to acquire information such as the clinical history and examination data from the medical records. The types of triggers were classified as suggested by a previous study (5). Emotional triggers included a range of traumatic emotions including grief, interpersonal conflicts, fear, panic, anger, anxiety, and embarrassment. Physical stressors were defined as physical activities, medical conditions, traumatic injury, and surgery.

Cardiac catheterization and echocardiography data were registered in each facility. The left ventricular (LV) ejection fractions (LVEF) of the patients were measured using echocardiography on admission and were evaluated by the modified Simpson method or Teichholz method. Cardiac catheterization and coronary angiography were performed during the acute phase of admission, mainly on the day of admission. Significant coronary stenosis was defined by visual estimation according to the AHA (American Heart Association) classification (16). The method of classifying LV asynergy by left ventriculography (LVG) has been defined in a previous report (7). LV obstruction was defined as a peak-to-peak pressure gradient greater than 20 mmHg between the LV outflow (LVOT) and the LV apex. Regarding complications during hospitalization, severe pump failure was defined according to the Framingham criteria (17). Cardiogenic shock was defined according to the Killip classification (systolic blood pressure <90 mmHg or decrease in systolic blood pressure of 30 mmHg, a urine volume ≤20 mL/h) and catecholamine use for hypotension.

### Definition of circadian rhythm and seasonal variations

The time of symptom onset was categorized into four 6-h intervals (night: 12:00 to 5:59 AM; morning: 6:00 to 11:59 AM; afternoon: 12:00 to 5:59 PM; and evening: 6:00 to 11:59 PM) for the circadian analysis. The day of symptom onset was categorized into four 3-month intervals (January to March, April to June, July to September, and October to December).

### Statistical analysis

Continuous data are presented as the mean±standard deviation (SD). Categorical data were analyzed by the chi-squared test. The Mann-Whitney U test was used to determine statistically significant differences in non-parametric data between the two groups. Differences were considered significant if the p value was <0.05. The statistical analyses were performed using the SPSS for Windows software program, version 21.0 (Chicago, USA). Circadian rhythm and seasonal variations were evaluated by the chi-square goodness-of-fit test using the StatMate software program (Version 3.18, ATMS, Tokyo, Japan).

## Results

### Comparison between male and female patients

Out of 10,622 patients with ACS who were admitted to 10 hospitals belonging to CIRC-8U between May 1997 and December 2014, 344 consecutive patients (71.6±11.2 years of age, 73 male/271 female) were diagnosed with TTS. The clinical characteristics of the study patients are summarized in Table 1. There was no significant difference in age between the sexes. The incidence of smokers was significantly higher in the male group than in the female group, and the incidence of dyslipidaemia was higher in the female group than in the male group. Significant coronary stenosis had a

**Table 1. Baseline Clinical Characteristics.**

| | All patients (n=344) | Male (n=73) | Female (n=271) | p value |
|---|---|---|---|---|
| Age (years) | 71.6±11.2 | 71.8±10.4 | 71.5±11.4 | 0.899 |
| BMI (kg/m$^2$) | 21.3±3.9 | 20.9±3.1 | 21.5±4.1 | 0.783 |
| BSA (m$^2$) | 1.47±0.16 | 1.61±0.15 | 1.40±0.23 | <0.001 |
| Hypertension | 190/332 (57%) | 37/71 (52%) | 153/261 (59%) | 0.346 |
| Dyslipidemia | 83/333 (25%) | 11/71 (15%) | 72/262 (27%) | 0.044 |
| Diabetes mellitus | 55/332 (17%) | 14/70 (20%) | 41/262 (16%) | 0.371 |
| Current smoking | 47/283 (17%) | 17/57 (30%) | 30/226 (13%) | 0.005 |
| Medicines on admission | | | | |
| $\beta$-blockers | 19/299 (6%) | 6/61 (10%) | 13/238 (5%) | 0.212 |
| ACE inhibitors/ARB | 80/300 (27%) | 20/61 (33%) | 60/239 (25%) | 0.226 |
| Calcium blockers | 73/299 (24%) | 16/61 (26%) | 57/238 (24%) | 0.712 |
| Nitrovasodilators | 21/303 (7%) | 5/62 (8%) | 16/241 (7%) | 0.693 |
| Symptom | | | | |
| Chest pain | 166/343 (48%) | 31/73 (42%) | 135/270 (50%) | 0.292 |
| No symptom | 66/339 (19%) | 15/73 (21%) | 51/266 (19%) | 0.739 |
| Stressors | | | | |
| Physical stress | 162/325 (50%) | 45/70 (64%) | 117/255 (46%) | 0.007 |
| Emotional stress | 74/325 (23%) | 7/70 (10%) | 67/255 (26%) | 0.004 |
| Absence of stress | 89/325 (27%) | 18/70 (26%) | 71/255 (28%) | 0.764 |
| Vital signs | | | | |
| Systolic blood pressure (mm Hg) | 135.6±31.1 | 139.2±31.8 | 134.7±30.9 | 0.339 |
| Diastolic blood pressure (mm Hg) | 79.5±19.0 | 81.6±21.6 | 78.9±18.2 | 0.576 |
| Heart rate (bpm) | 94.3±24.9 | 103.3±28.2 | 91.9±23.5 | 0.004 |
| Body temperature (degree) | 36.6±1.1 | 36.9±1.3 | 36.5±1.1 | 0.066 |
| Laboratory data | | | | |
| White blood cell count (cells/μL) | 9,916±4,728 | 10,685±4,185 | 9,704±4,853 | 0.011 |
| Peak creatinine kinase (IU/L) | 783±2,109 | 799±1,838 | 779±2,180 | 0.065 |
| Peak creatinine kinase MB (IU/L) | 30.9±48.3 | 34.3±56.9 | 30.0±45.8 | 0.310 |
| C-reactive protein (mg/dL) | 3.3±6.2 | 5.6±7.1 | 2.7±5.7 | <0.001 |
| Creatinine (mg/dL) | 0.9±1.0 | 1.2±1.1 | 0.8±0.9 | <0.001 |
| ST elevation | 208/286 (73%) | 42/57 (74%) | 166/229 (72%) | 1.000 |
| LVEF (%) by TTE | 45.9±13.0 | 44.7±13.2 | 46.2±13.0 | 0.544 |
| LVEF (%) by left ventriculography | 46.6±11.8 | 44.5±11.7 | 47.0±11.8 | 0.122 |
| Coronary stenosis | 23/285 (8%) | 11/58 (19%) | 12/227 (5%) | 0.002 |
| Type of takotsubo syndrome by Cardiac catheterization | | | | |
| Apical type | 227/248 (91.5%) | 44/47 (93.6%) | 183/201 (91.0%) | 0.539 |
| Midventricular type | 9/248 (3.6%) | 1/47 (2.1%) | 8/201(4.0%) | |
| Basal type | 2/248 (0.8%) | 1/47 (2.1%) | 1/201 (0.5%) | |
| Focal type | 10/248 (4.0%) | 1/47 (2.1%) | 9/201 (4.5%) | |
| LV obstruction | 10/185 (5%) | 0/30 (0%) | 10/155 (6%) | 0.162 |

BMI: body mass index, BSA: body surface area, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, LVEF: left-ventricular ejection fraction, TTE: trans-thoracic echocardiography

higher prevalence in the male group than in the female group. Significant coronary stenosis was observed in a few patients, but these coronary lesions did not have any haemodynamic effects on the patients. The incidence of patients with an absence of any stress was 28%, and there was no significant difference in the absence of stress between the groups. However, the incidence of physical stress was significantly higher in the male group than in the female group (64% vs. 46%: p=0.007) and the incidence of emotional stress was significantly higher in the female group than in the male group (26% vs. 10%: p=0.004). Significant differences between the two groups were not observed regarding blood pressure or body temperature upon admission to the hospital. However, the heart rate, white blood cell count, C-reactive protein and creatinine upon admission were significantly higher in the male group than in the female group. The incidence of significant LV obstruction on cardiac catheterization was 6% in the female group, and no patients in the male group presented. Asynergy of the LVG was categorized as apical type (92%), mid-ventricular type (4%), basal type (1%) and focal type (4%). The proportions of the different LVG classes were not significantly different be-

**Table 2.** **In-hospital Complications and Outcome.**

| | All patients (n=344) | Male (n=73) | Female (n=271) | p value |
|---|---|---|---|---|
| Severe heart failure | 102/341 (30%) | 25/73 (34%) | 77/268 (29%) | 0.388 |
| Cardiogenic shock | 50/340 (15%) | 14/73 (19%) | 36/267 (13%) | 0.262 |
| Arrhythmia | | | | |
| Atrial fibrillation Atrial tachycardia | 33/340 (10%) | 7/73 (10%) | 26/267 (10%) | 1.000 |
| Ventricular tachycardia Ventricular fibrillation | 14/340 (4%) | 4/73 (5%) | 10/267 (4%) | 0.510 |
| Complete atrioventricular block Sick Sinus Syndrome | 7/340 (2%) | 1/73 (1%) | 6/267 (2%) | 1.000 |
| Left ventricular thrombus | 6/336 (2%) | 0/72 (0%) | 6/264 (2%) | 0.581 |
| Recurrence | 4/355 (1%) | 1/72 (1%) | 3/263 (1%) | 1.000 |
| Death | 31/341 (9%) | 13/71 (18%) | 18/270 (7%) | 0.005 |
| Cardiovascular death | 11/341 (3%) | 3/71 (4%) | 8/270 (3%) | 0.704 |
| Others | 20/341 (6%) | 10/71 (14%) | 10/270 (4%) | 0.003 |

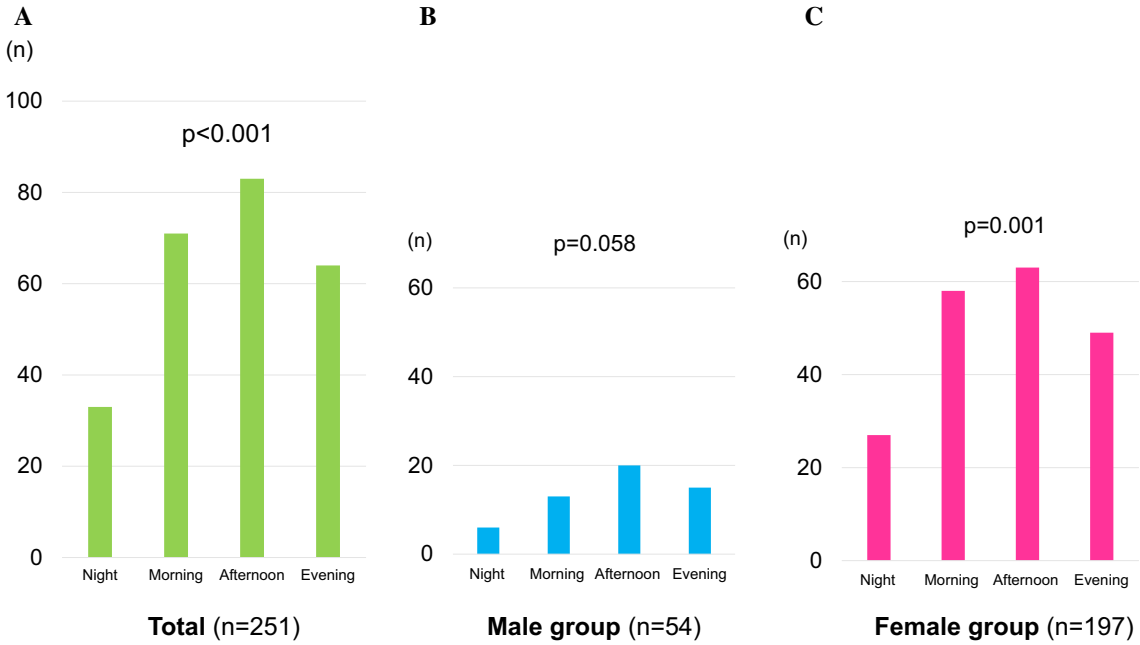


**Figure 1.** **Circadian variation in the study patients: TTS events were most frequent in the afternoon and least frequent during the night in whole study cohort (A). The pattern of circadian variations in the female and male groups were the same as that in the whole study cohort (B: the male group, C: the female group).**

tween the two groups.

### *In-hospital complications and outcomes*

The in-hospital complications and outcomes of the study patients are shown in Table 2. In-hospital mortality was significantly higher in the male group than in the female group (18% vs. 7%; p=0.005). The incidence of non-cardiac death was significantly higher in the male group than in the female group (14% vs. 4%; p=0.003).

### *Circadian variations*

Among all study patients, TTS events were most common in the afternoon and least common during the night (Fig. 1A). Moreover, the patterns of circadian variations in the female and male groups were the same as those in the whole study cohort (Fig. 1B: the male group, C: the female group). A Supplementary material showed the circadian rhythm for each trigger. There was less nighttime onset of any trigger. Interestingly, there was also circadian variation in cases with no or unknown stressors. Circadian variation in deaths was as follows: 0.8% at night, 3.2% in the morning, 2.8% during the afternoon, and 2.4% in the evening. As a result, in-hospital mortality was not significantly influenced by the onset time (p=0.955).

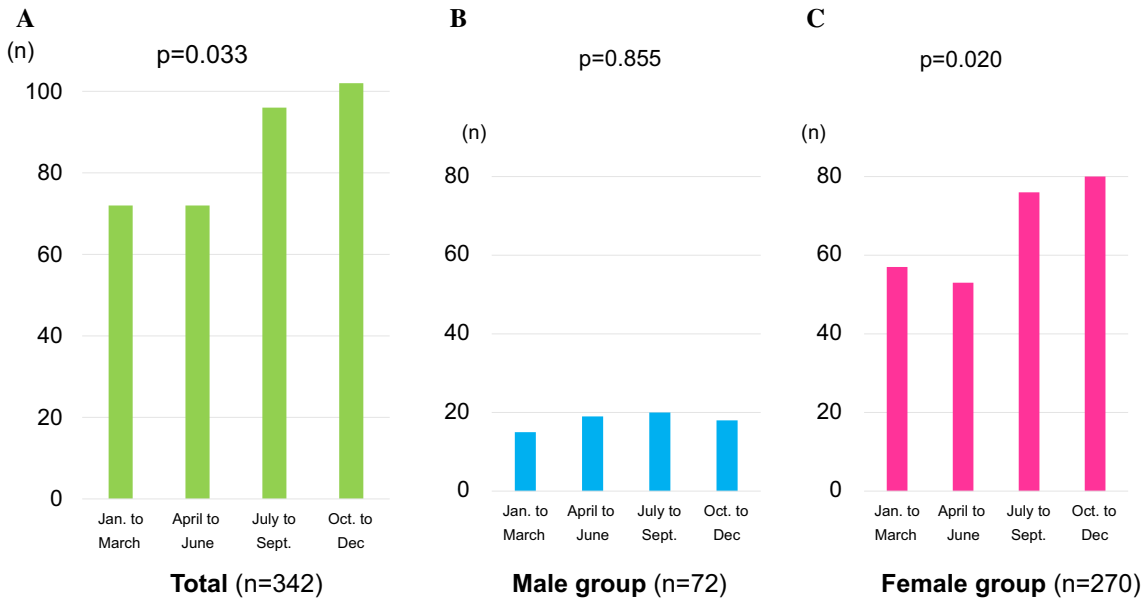


**Figure 2.** **TTS events occurred most frequently in the autumn and least frequently in the spring in the whole study cohort (A). Seasonal variations in the female group showed the same pattern as that in the whole study cohort. However, there was no significant seasonal variations in the incidence of TTS in the male group (B: the male group, C: the female group).**

### *Seasonal variations*

TTS events occurred most often in the autumn and least often in the spring in whole study cohort (Fig. 2A). Moreover, the seasonal variation in the female group had the same pattern as that of the whole study cohort. However, there was no significant difference in the incidence of TTS according to season in the male patients (Fig. 2B: the male group, C: the female group). In-hospital mortality was not significantly influenced by the season as indicated by the following data: 1.5% in spring, 2.9% in summer, 2.3% in autumn, and 2.3% in winter (p=0.771).

## Discussion

To the best of the authors' knowledge, this study is the first report of gender differences in both circadian and seasonal variations in patients with TTS. It is noteworthy that all patients in the cohort were of the same ethnicity.

The main results of this study can be summarized as follows. First, this study showed that the in-hospital mortality rate was higher in male patients than in female patients with TTS. Moreover, the cause of death in male patients was more frequently non-cardiac than cardiac, as has been found in previous reports. Second, in the whole study cohort, TTS events were most common in the afternoon and least common during the night. Regarding seasonal variation, the incidence of TTS was highest in the autumn and lowest in the winter and spring in the whole study cohort. Last, the circadian and seasonal variations in the female group were the same as those in the whole study cohort. There was no significant seasonal variation in the male group, although a nearly significant difference according to time of day was observed.

### *Male patients with takotsubo syndrome and physical stress*

As has been found in recent studies, in this study, the in-hospital mortality rate was significantly higher in the male group than in the female group (8, 18). Moreover, in the male group, the prevalence of physical stress was higher than that of emotional stress (8, 19), and the incidence of non-cardiac death was higher than that of cardiac death (8). The causes of non-cardiovascular death included cancer, infection, sepsis, surgical operation, cerebral hemorrhage, renal failure and gangrene of the foot. White blood cell counts, C-reactive protein and heart rate on admission were higher in the male group than in the female group because the inflammatory reaction is exacerbated by physical stressors. The mortality rate of TTS patients who had another disease before the onset of TTS in the hospital was significantly higher than that of patients without a pre-existing comorbidity (20), and the severity of the comorbidity was thought to be important. Moreover, in-hospital mortality was higher in this study than in the previous study. This is because we assessed data from university hospitals, which possibly treat a larger number of severe cases and patients with underlying diseases than community hospitals. Therefore, the number of physical triggering factors might have been higher in our cohort than in those of previous studies.

### *Circadian variation of TTS*

Previous reports about circadian variations in patients with TTS have obtained heterogeneous results. There were no circadian variations in the patients with TTS in a report from Australia (10). TTS events occurred most often in the

morning and least often in the evening in studies from Switzerland (11) and Italy (12), while they were most common in the afternoon and least common in the evening in a study from the United States (13). The reasons for these inconsistent results are associated with the fact that the divisions of time within a day varied, and the numbers of patients in the studies were small. Moreover, racial differences might also have affected the results. From Japan in 2007, there was a previous small report on circadian variations that summarized 50 cases of TTS (21). The classification of the onset time in that study was similar to that used in our study. There were no significant differences found in circadian variations because of the small number of cases. However, the incidence of onset times during the day was high. The prior study had similar results to those in the present study, which suggests that the onset time of TTS in Japan is most common in the afternoon (22).

### Catecholamine and circadian variation

Catecholamines directly or indirectly affect the brain, vascular system, coronary artery, and myocardium (23). When people are exposed to stressors, the hypothalamo-pituitary-adrenal axis is activated, and more epinephrine and norepinephrine are released. Estrogens reduce inotropic and chronotropic responses to catecholamines and protect the heart. Postmenopausal depletion may increase the catecholamine load (22). There are still many unclear points about the mechanism of TTS. However, the theory of sympathetic overactivity due to excess catecholamines is considered to be the most influential factor. The reason is that pheochromocytoma and acute brain injury are associated with TTS (23), and the catecholamine levels in the blood at the acute phase of TTS is higher than that of heart failure caused by ACS (24). A previous study reported that circadian variations differed between patients with TTS and those with ACS (13). The serum catecholamine levels are higher during activity than at rest (25). Circadian variations in the level of catecholamines might be related to the fact that TTS events are most common in the afternoon. Evaluating the difference in the catecholamine levels between the baseline and the peak after exposure to stressors might provide evidence regarding the underlying pathological mechanism and treatment of TTS. Depending on the sub-analysis of our study between circadian variation and the TTS trigger, it is also noteworthy that circadian variation was observed even in cases with or without any unknown stressors. Further study is needed to evaluate the relationship between triggers and circadian variations.

### Seasonal variations of TTS

There have been various reports about seasonal variations in patients with TTS. TTS events occurred most frequently in the summer in studies from Italy (12) and Germany (22), while a French group reported that the incidence of TTS events was highest in the winter and spring and the lowest in the summer (14). Further investigation is needed because the numbers of patients included in the studies from European countries were small. The study of 6,837 patients with TTS from the United States reported that TTS occurred most frequently in the summer, with a peak in July, and least frequently in the relatively cold seasons (6). The existing reports are from the Northern Hemisphere, and reports from the Southern Hemisphere are thus needed. TTS events were reported to be most common in the summer and autumn and least common in the winter and spring in the study of 4,306 patients with TTS in Japan, with data obtained from the diagnosis procedure combination (DPC) (22). The results of that study were similar to the results of our study, although there was insufficient diagnostic accuracy in the DPC study. The commonality of the results between the two studies suggests that TTS events in Japan occur most frequently in the autumn and least commonly in the winter and spring. The seasonal variation in the female group was similar to that in the whole study cohort. However, there was no significant difference in the incidence of TTS according to season among the male patients. One possible explanation is that TTS events in males are usually caused by physical stress, underlying disease or surgical operations. On the other hand, Japanese women may experience more stressors in autumn, as the stressors associated with human relationships at work and at home peak in the autumn. In another Japanese study, there was a significant difference in the proportion of males across all seasons (23). The analytic methodology in that study was different from the methodology used in our study. They analysed the changes in the sex ratio of TTS patients according to season. When we applied that analytical method to our data, there were no significant differences in the sex ratio according to season. The seasonal variations of TTS may be affected by not only racial differences but also by weather, temperature and atmospheric pressure, and therefore further studies are needed.

### Study limitations

There are several limitations associated with this study. First, this study was retrospective. However, the data used in this study was relatively reliable because they were collected from multiple academic hospitals. Second, the number of patients in this study was relatively small. In particular, the number of male patients was small, so the statistical power may be lacking. Another study with a large number of male patients is needed. Third, these data were all obtained from university hospitals, resulting in some institutional bias. It is possible that patients with TTS in general hospitals have different characteristics, so patient data need to be collected from various types of hospitals. Forth, Mayo clinic diagnostic criteria was used in this study. Further study in the future is needed using new diagnostic criteria. Finally, this study only included data from patients with broken heart syndrome, so it is also necessary to collect data from TTS patients with happy heart syndrome (24).

## Conclusion

In a multicenter study in Japan, seasonal variations were observed in the female group but not in the male group, while circadian variations were observed in both sexes. These results suggested that the pathogenesis and clinical features of TTS might differ according to sex.

Informed consent was obtained in the form of opt-out on the website.

**The authors state that they have no Conflict of Interest (COI).**

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