

Role of climatic factors in the incidence of Takotsubo syndrome: A nationwide study from 2012 to 2016

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Abstract

Aims This study aimed to investigate the influence of climatic factors on the onset of Takotsubo syndrome (TTS).

Methods and results We performed a retrospective nationwide study among patients registered in the Japanese Registry of All Cardiac and Vascular Diseases and Diagnosis Procedure Combination (JROAD–DPC) discharge database, between 2012 and 2016. Before the analysis, a multicentre validation study was conducted for assessing the accuracy of the JROAD–DPC classification for TTS. First, we investigated the seasonal variation of incidences of TTS. Second, we analysed the associations between the incidence of TTS and climatic factors using the hierarchical Poisson regression modelling, and we also investigated the associations between typhoon landfalls and hospitalization for TTS, using the fixed-effects conditional Poisson regression model. The sensitivity and specificity for diagnosis were 83% and 100%, respectively. Then we analysed 5643 patients with TTS. The mean patient age was 74 (standard deviation \pm 11) years; 79% were female. TTS was diagnosed significantly more frequently in the summer and early autumn. The incidence of TTS was related to higher temperatures; adjusted incidence rate ratios were 1.46 [95% confidence interval (CI): 1.33–1.60, $P < 0.01$] and 1.47 (95% CI: 1.34–1.62, $P < 0.01$) for temperatures of 20–25°C and $>25^\circ\text{C}$, respectively. The incidence rate ratio for the first 2 days after a typhoon landfall was 1.85 (95% CI: 1.07–3.19; $P = 0.03$).

Conclusions This study demonstrates distinct patterns of seasonal variation in the incidence of TTS, as well as a significant association between its onset and climatic factors, including typhoon landfalls.

Keywords Takotsubo syndrome; Climatic events; Typhoon; JROAD–DPC

Received: 12 October 2019; Revised: 1 May 2020; Accepted: 29 May 2020

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Introduction

Takotsubo syndrome (TTS), also referred to as ‘broken heart syndrome’, has been increasingly recognized as an acquired heart syndrome. It is prevalent in elderly women.¹ According to previous studies, TTS may represent 1–2% of all admissions for acute coronary syndromes (ACSs).^{2,3} There has been a marked increase in hospitalization rates for TTS in recent years⁴; the common triggers include stressful events such as emotional and physical duress.¹ TTS has been reported to be associated with sympathetic stimulation. However, the

pathophysiological mechanisms of TTS are not completely understood.⁵

Although cardiovascular events including ACS and stroke show well-defined seasonal variations and occur most frequently in the winter,^{6–8} the seasonal variations of TTS are much debated.^{9,10} In addition, the impact of climatic factors or natural disasters on the onset of TTS has not been explored.

The aim of this study was to investigate the seasonal and regional variations in TTS, as well as the short-term effects of climatic factors and typhoon landfalls, using a well-validated nationwide cardiovascular hospitalization database.

Methods

Validation of diagnosis procedure combination

Diagnosis procedure combination (DPC) is a case-mix patient classification system that is linked to payments at acute-care hospitals in Japan. It includes patients' data such as age, sex, main diagnosis code, drugs, diagnostic and therapeutic procedures, length of stay, and patient outcomes.

Prior to the main analysis, we validated the accuracy of the DPC codes for TTS by performing a multicentre study using chart review results as reference standards. Because the prevalence of TTS is very low,¹¹ we employed the nested case-control design among a cohort of patients aged 20 years and older who were admitted to one of the three acute-care hospitals with cardiovascular divisions in Japan.¹² These three hospitals that participate in the Japanese Registry of all Cardiac and Vascular Diseases and Diagnosis Procedure Combination (JROAD-DPC) system are 612-bed, 848-bed, and 992-bed hospitals in the Osaka, Kumamoto, and Nara prefectures, respectively.

The validation study cohort included all consecutive patients who were admitted to these three hospitals between 1 April 2012 and 31 March 2016. Full study population was defined as patients who were admitted at the three hospitals during the validation study period. Nested case-control samples were drawn from the full study population. The cardiologists systematically conducted chart reviews using the hospitalization registries, admission reports, and catheter reporting systems. TTS was defined according to the Mayo Clinic criteria.² Age-matched and sex-matched controls were obtained from the same study cohort using random sampling without replacement; the case-control ratio was 1:10. If any of the control subjects were diagnosed with TTS according to the Mayo Clinic criteria, new matched controls were randomly selected. Moreover, multiple hospitalizations of a single patient during the study period were each regarded as independent events.

Calculated measures of diagnostic accuracy included sensitivity, specificity, and positive and negative predictive values; estimated positive and negative predictive values in a full study cohort can be obtained by weighing the controls with the case-control sampling fraction. For example, positive predictive values were calculated with $(\text{number of true positives}) / [(\text{number of true positives}) + (1/\text{SF}) \times (\text{number of false positives})]$.¹²

Design and setting of the study

This cross-sectional study used the JROAD-DPC discharge database, which is a nationwide institutional registry managed by the Japanese Circulation Society.^{13,14} The JROAD-DPC constitutes the claims database in acute-care hospitals in Japan

and includes individual patient data including the diagnosis, visit date, location, and performed medical procedures; it encompasses all 47 prefectures in Japan. Among 1081 hospitals using the DPC system, 715 provided DPC data to the JROAD-DPC in 2015.

Patient selection

From the JROAD-DPC database, we extracted data of patients diagnosed with TTS by their attending physicians based on the *International Classification of Diseases*, tenth edition (ICD-10) code I518. Patients hospitalized with TTS between 1 April 2012 and 31 March 2016, aged 20 years or older, and who underwent coronary angiography were included. Patients who underwent percutaneous coronary intervention, were diagnosed with myocarditis (I40) or pheochromocytoma (D350), had planned admissions, and had TTS after hospital admissions were excluded.

Data regarding co-morbidities such as hypertension, diabetes mellitus, and dyslipidaemia in individuals were also retrieved from medical claims, on the basis of the ICD-10 codes. We obtained data on the patients' age, sex, admission and discharge dates, discharge status, prescribed medications, and use of circulation devices.

Weather information

Japan is an island country in East Asia and lies within the temperate zone. The northern and southern regions are in the subarctic and subtropical zones, respectively. There are four seasons in Japan, namely, spring (March–May), summer (June–August), autumn (September–November), and winter (December–February). We used climatic information from the Japan Meteorological Agency¹⁵; this included the average temperature, average atmospheric pressure, average humidity, and daily sunshine duration in each of the 47 prefectural capitals of Japan. Additionally, we focused on rapid climatic changes to verify whether physiological or emotional stresses caused by climatic events may affect the onset of TTS. While there were no large-scale disasters such as earthquakes, we obtained data regarding typhoon landfalls. The Japan Meteorological Agency defines a typhoon as a storm with maximum surface wind speeds exceeding 34 knots that occur in the Northwest Pacific Ocean or the South China Sea.¹⁶ The days on which typhoon landfalls occurred were extracted for each of the 47 prefectures in Japan.

Statistical analysis

Data were presented as mean and standard deviations and medians (inter-quartile range) for normally and

non-normally distributed continuous variables, respectively, and proportions for categorical variables.

The clinical endpoint was hospitalization for TTS. First, the dates of emergency admission were categorized into 12 intervals of 1 month each for seasonal analysis, and the number of annual TTS admissions was described by year. To compare the seasonality of TTS, we additionally obtained data of patients admitted for acute myocardial infarction (AMI) on the basis of ICD-10 codes (I21\$ and I22\$) on an emergency basis to the JROAD–DPC hospitals between 1 April 2012 and 31 March 2016; the incidences of TTS were compared with those of AMI. Second, the incidence rate and age-adjusted incidence rate by prefecture were analysed.

Third, we analysed the association between the incidence of TTS and climatic (including temperature, atmospheric pressure, humidity, and sunshine duration) and geographic factors. Daily mean temperatures were analysed in 5°C increments, while atmospheric pressure was divided into three categories on the basis of bimodality (small and large peaks). The remaining factors were uniformly distributed and divided into four categories. Hierarchical Poisson regression modelling was performed to evaluate the incidence of TTS, with each prefecture at the first level and patients at the second. Models included the mean temperature, mean atmospheric pressure, mean humidity, and sunshine duration. Results from these analyses were reported as incidence rate ratios (IRRs) with 95% confidence intervals (CIs). Moreover, we performed sensitivity analysis using another cut-off value to test the robustness of the effect estimates.

Finally, we analysed the association between typhoons and TTS admissions. A self-controlled case series design was used to evaluate the association between typhoon landfalls and hospitalization for TTS in each prefecture in Japan. To set the observation periods to 365 days, we obtained data on typhoon landfalls between 1 April 2013 and 31 March 2015. As described subsequently, we included patients who were admitted at least once for TTS during the exposure and observation periods. Because TTS is caused by acute stress events, the exposure period was defined as the interval between the day of typhoon landfall and the day after, while the observation period was defined as the interval from 365 before to 363 days after the exposure period. We used a fixed-effects conditional Poisson regression model and estimated the IRR for TTS hospitalizations during the risk period compared with the control period. In addition to the primary analysis, we considered other risk periods (the typhoon landfall day as well as Days 1 through 7, Days 3 through 7, 48 h before and including the index day, and the index date itself), and we limited the control period to 1 or 6 months before and after the risk periods. To accommodate the multiple testing problem, the Bonferroni correction was used to adjust the significance levels for each exposure period.

The STATA (version 14, Stata Corp., College Station, TX, USA) software package was used for all statistical analyses

in this study. All statistical tests were two-sided, and *P*-values ≤ 0.05 were considered statistically significant.

Ethics statement

The investigation conforms with the principles outlined in the Declaration of Helsinki (*Br Med J* 1964; ii: 177), and the study protocol was approved by the ethics committees of both the Japanese Circulation Society and the Nara Medical University (registration number: 1899). The requirement for individual informed consent was waived because all data were originally anonymized when provided by the DPC.

Results

Patient selection and characteristics

A total of 10 782 patients with TTS were identified at 834 hospitals between 1 April 2012 and 31 March 2016. Among them, 6959 who were ≥ 20 years old and underwent coronary angiography were included. Among these patients, 1316 were later excluded for various reasons (*Figure 1*); data from 5643 patients were finally analysed.

The baseline characteristics of the patients are shown in *Table 1*. The mean age (\pm standard deviation) was 74 ± 11 years, 79% were female, and the 30 day mortality rate was 4%. Hypertension, found in 43% of patients, was the most prevalent co-morbidity (*Table 1*).

FIGURE 1 Study flow chart; 5643 patients were analysed in the study. PCI, percutaneous coronary intervention; TTS, Takotsubo syndrome.

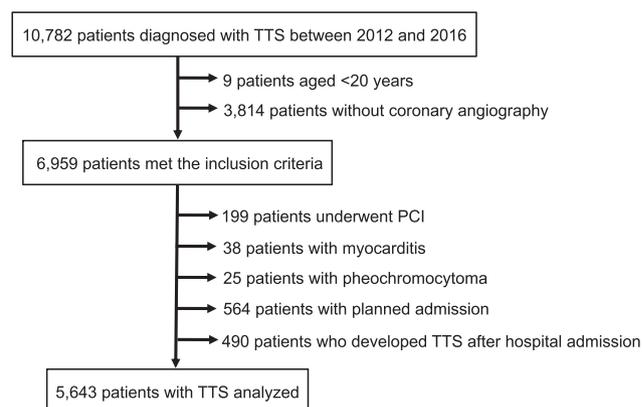


Table 1 Patient clinical characteristics

Age (years): mean \pm standard deviation	74 \pm 11
Female, <i>n</i> (%)	4465 (79)
Charlson co-morbidity score, median (IQR)	1 (1–2)
Co-morbidities, <i>n</i> (%)	
Hypertension	2439 (43)
Diabetes mellitus	787 (14)
Dyslipidaemia	1264 (22)
Ambulance use, <i>n</i> (%)	3388 (60)
Treatments during hospitalization, <i>n</i> (%)	
ACE/ARBs	2173 (39)
CCBs	1758 (31)
Beta-blockers	1811 (32)
Respirator	236 (4)
IABP	134 (2)
ECMO	24 (0.4)
Eight regions of Japan, <i>n</i> (%)	
Hokkaido	211 (4)
Tohoku	396 (7)
Kanto	1388 (25)
Cyubu	1119 (20)
Kinki	1089 (19)
Cyugoku	461 (8)
Shikoku	189 (3)
Kyushu	790 (14)
Length of hospital stay, median (IQR)	12 (8–19)
Death (30 days), <i>n</i> (%)	198 (4)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pumping; IQR, inter-quartile range

Validity of diagnosis procedure combination with Takotsubo syndrome

In the validation study, a total of 84 patients with TTS and 840 randomly selected controls were identified at the three hospitals. The 840 controls were selected out of 171 930 patients in a full study population. The prevalence of TTS in the entire study population ($n = 171\ 930$) was 0.05% (84/171 930). The

mean age of patients with TTS was 76 years; 78% of the patients were female.

The sensitivity and specificity of diagnosis were 0.83 and 1.0, respectively. The sampling fraction in the nested case-control sample was 0.005 (840/171 930). The estimated positive and negative predictive values of the entire study population calculated using the sampling fraction were 1.0 and 1.0, respectively (*Figure S1*).

Seasonal analysis

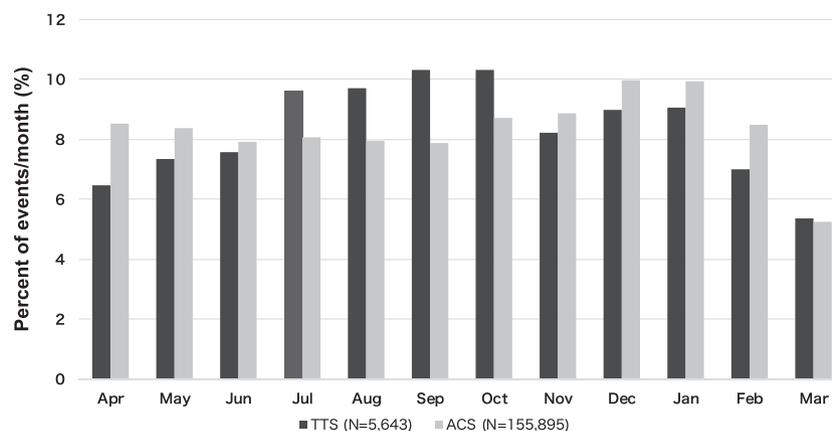
The annual incidence of TTS is shown in *Figure S2*. The annual number of TTS increased yearly. The total number of cases diagnosed with TTS was 1081 (19%), 1519 (27%), 1628 (29%), and 1415 (25%) in spring, summer, autumn, and winter, respectively. These data demonstrated that the onset of TTS was most frequent in the summer and autumn of each year.

To investigate the seasonal variations in the incidence of TTS, we identified patients who were hospitalized for AMI in the JROAD–DPC hospitals during the same period as those hospitalized for TTS. Among 163 817 patients diagnosed with AMI, 46 aged <20 years, 4423 with planned admissions and 1221 patients already suspected to have TTS were excluded; finally, 155 895 patients with AMI were compared with patients with TTS. The seasonal peak for TTS admissions was found to differ from that of AMI admissions; the latter peaked in the winter season (*Figure 2*).

Regional analysis

In each prefecture, the incidence rate per 100 000/year varied between 0.32 and 2.01 and between 0.37 and 2.66 according to crude and age-adjusted analyses, respectively.

FIGURE 2 The incidences of Takotsubo syndrome and acute coronary syndrome. The peak of incidence for TTS was most frequent in the summer and autumn, which is different from that of ACS, which was most frequent in winter. TTS, Takotsubo syndrome; ACS, acute coronary syndrome.



The incidence rate was higher in Western than Eastern Japan, even after age-standardized analysis (Figure S3).

Risk of Takotsubo syndrome in relation to climatic factors

The number of TTS admissions was found to increase with rising temperatures. Compared with days in which the average temperature was <0°C, the risk of TTS significantly increased during days in which the average temperature was higher than 20°C (unadjusted IRR: 1.46, 95% CI: 1.14–1.86, *P* < 0.0001 for temperatures of 20–25°C, and IRR: 1.43; 95% CI: 1.12–1.84, *P* < 0.001 for temperatures > 25°C). After confounding factors were adjusted, the IRRs were 1.46 (95% CI: 1.33–1.60, *P* < 0.0001) for temperatures of 20–25°C and 1.47 (95% CI: 1.34–1.62, *P* < 0.001) for temperatures > 25°C (Figure 3). Sensitivity analyses showed robust results when using the various cut-off points (Table S1).

Risk of Takotsubo syndrome after typhoon landfall

In Japan, we usually have typhoon landfalls in late summer and early autumn. Between 1 April 2013 and 31 March 2015, six typhoons made landfall in Japan and attacked a total of 38 prefectures. In the prefectures where the typhoon passed through, there were 2035 admissions for TTS during the risk (on the day of typhoon landfall and the next day) and control periods (between the interval from 365 before to 363 days after the exposure period). During the risk

period, a total of 13 TTS admissions were observed (0.17 admissions per day and each prefecture), and during the control period, 2022 TTS admissions were observed (0.09 admissions per day and each prefecture); the IRR for the risk period was 1.85 (95% CI: 1.07–3.19, *P* = 0.03). Subsequently, we altered risk periods and performed the same analysis. The IRR for the typhoon landing day was 2.84 (95% CI: 1.53–5.30, *P* < 0.001). Conversely, no significant increases were noted in the incidence on Days 1 through 7 (IRR: 1.79; 95% CI: 1.01–3.17, *P* = 0.05), Days 3 through 7 (IRR: 0.85; 95% CI: 0.53–1.35, *P* = 0.49), and 48 h before and including the index day (IRR: 1.71; 95% CI: 0.97–1.01, *P* = 0.07). Sensitivity analyses showed robust results in the various control periods (Table 2).

Discussion

Our nationwide study revealed the following significant findings: (i) the peak of TTS admission occurs during the summer and early autumn, which differs from that of AMI, and (ii) the onset of TTS is associated with higher temperatures and typhoon landfalls. Although a few previous studies have reported similar findings with regard to the seasonal variations in TTS, most of them are small sample sizes,^{10,17,18} and another relatively large cohort did not use validated data.⁹ To the best of our knowledge, this is the largest cohort study to investigate the role of climatic factors in the onset of TTS, using a well-validated nationwide cohort. Although it may be impossible to exactly identify the mechanism of TTS onset, our findings elucidate novel features that distinguish

FIGURE 3 The association between climatic factors and the incidence of Takotsubo syndrome. The risk of TTS significantly increased during days in which the average temperature was higher than 20°C. SD, standard deviation; IRR, incidence rate ratio.

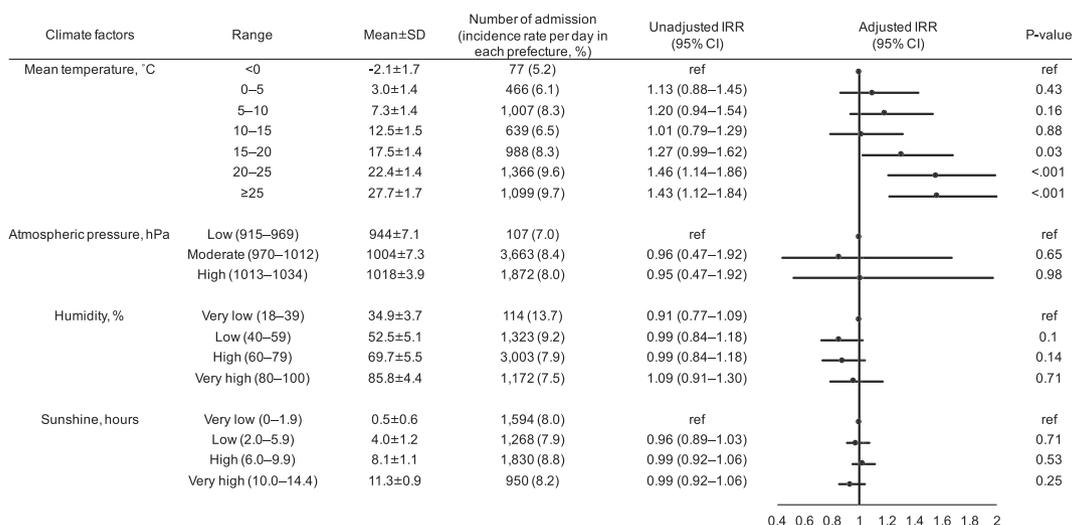


Table 2 Incidence ratios for Takotsubo syndrome after typhoon landfalls

	IRR (95% CI)	P-value
Risk period		
Day 1	2.84 (1.53–5.30)	<0.001*
Days 1–2	1.85 (1.07–3.19)	0.03
Days 1–7	1.79 (1.01–3.17)	0.05
Days 3–7	0.85 (0.53–1.35)	0.49
48 h before and including the Day 1	1.71 (0.97–1.01)	0.07
Sensitivity analysis with different control periods		
Control period limited to 6 months before and after typhoon	1.98 (1.15–3.42)	0.01
Control period limited to 1 month before and after typhoon	1.88 (1.08–3.29)	0.03

CI, confidence interval; IRR, incidence rate ratio.

*P-values were significant after adjustments using the Bonferroni correction.

TTS from AMI and identify climatic factors and natural events as potential triggers for TTS.

A few earlier studies reported seasonal variations in TTS admissions; the highest incidences have been observed in the summer and autumn.^{17,18} Similar findings were also noted in the Southern hemisphere; as demonstrated by Looi *et al.*, the onset of TTS in New Zealand was most frequent in summer.¹⁹ In our study, we found that the onset of TTS was associated with a higher daily mean temperature, after adjusting for other climatic factors; in addition, a high incidence rate was observed in Western Japan, which is warmer than Northern Japan. Our results therefore suggest that warmer weather may increase the frequency of onset of TTS.

Our study demonstrated that the peak of TTS incidence differed from that of AMI. This concurs with the findings of a previous relatively small cohort²⁰ and implies that the aetiologies of TTS and AMI are different. Additionally, the number of annual diagnosis of TTS was increasing yearly in Japan as in other countries.⁴ It may be because the diagnosis criteria are more accurate and because cardiologists are more aware of TTS.

We also found that typhoon landfalls were associated with the onset of TTS. Admissions for TTS were significantly higher on the day and immediately after the typhoon landfalls. There is considerable evidence that TTS often occurs after an acute emotional or physical trigger,²¹ and acute sympathetic stimulation is associated with the onset of TTS.^{22–24} Plasma catecholamine levels at presentation are reported to be higher among patients with emotional stress-induced TTS than among those with Killip Class III myocardial infarction.²⁵ Radical climatic events such as typhoon landfalls may be relating to activation of sympathetic nerve activity like emotional stress. Watanabe *et al.* showed that TTS increases after a great earthquake in Japan, and TTS may be caused by physical and psychological stresses.²⁶ Serious disasters such as earthquakes, which we did not have during the period we studied, may cause TTS by the same mechanisms as typhoon.

Typhoons often cause landfall in Japan between summer and autumn and are more common in Western Japan; this

corresponds with the admission patterns of TTS. However, during this study, there were only six typhoon episodes, not suggesting that only typhoon landfalls contribute to higher incidence of TTS in summer and autumn. Further studies are needed to evaluate the factors affecting the onset of TTS.

Limitations

Although our study used a nationwide validated registry to analyse the role of seasonal variations and climatic factors for the onset of TTS, there were notable limitations. First, the JROAD–DPC database only encompasses ~66% of the cardiovascular hospitals in Japan; this could have led to selection bias. However, we carried out an extra evaluation of data from the hospitals that participated in the JROAD–DPC in each prefecture and confirmed that the distribution of the number of onset of TTS was different from the distribution reported by the hospitals that provided the DPC data. Second, the number of patients hospitalized in March may have been underestimated, because a proportion of the records of patients hospitalized in the beginning of the Japanese calendar-based fiscal year may be missing. Third, we could not fully measure how much of the onset of TTS was reported alongside climatic factors such as high temperatures and typhoon landings. The magnitude and the extent of climatic trigger in all onsets of TTS remain unknown. Finally, we could not exclude other factors being related to the onset of TTS other than climate factors, and other potential factors linked to seasonal changes that may possibly underlie the increased risk of TTS, such as viral infections and air pollution, were not considered during analysis owing to the lack of data.

Conclusions

In this nationwide study, we found that TTS admissions peak during summer and early autumn. Moreover, the incidence of TTS is higher in Western Japan, and its onset is associated with higher temperatures and typhoon landfalls. These

findings suggest that climatic events are potential triggers for TTS. Further large-scale studies are needed to validate our findings and identify additional triggers for TTS.

Acknowledgement

We are deeply grateful to Yoko Sumita for preparing the datasets.

Conflict of interest

None declared.

Funding

None.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Validity of DPC diagnosis with Takotsubo syndrome. The case-control ratio was 1:10 (sampling fraction (SF) = 840/171,930 = 0.005). For example, the estimated negative predictive value (NPV) of a full study population can be calculated with $(840/SF) / (14 + 840/SF) 1.00$. Diagnostic accuracy was very high in TTS.

Figure S2. The annual incidences of Takotsubo syndrome. The onset of TTS was most frequent in the summer and autumn of each year.

Figure S3. Geographical distribution of Takotsubo syndrome. Figure A shows crude incidence rate and figure B shows age-standardised incidence rate in each prefecture. The incidence rate was higher in Western than in Eastern Japan.

Table S1. Sensitivity for the analyses of climatic factors and the incidence of Takotsubo syndrome

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