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ORIGINAL ARTICLE

In-hospital Takotsubo syndrome versus in-hospital acute myocardial infarction among patients admitted for non-cardiac diseases: a nationwide inpatient database study

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Abstract

Takotsubo syndrome (TTS) and acute myocardial infarction (AMI) occasionally occur during hospitalization for non-cardiac diseases. However, no study has compared the clinical characteristics between in-hospital TTS and AMI. Using the Diagnosis Procedure Combination database in Japan between 2010 and 2014, we retrospectively identified eligible inpatients who were admitted for non-cardiac diseases and developed TTS ($n=230$) or AMI ($n=611$) as an early in-hospital complication diagnosed by coronary angiography within 7 days after admission. We examined factors associated with developing in-hospital TTS or AMI using multivariable logistic regression. We also compared 30-day and overall in-hospital mortality between patients with TTS and AMI using 1:1 propensity score matching. Despite similar age (72.7 ± 12.4 vs. 72.8 ± 10.4 years), patients with TTS were more often female (63.5 vs. 32.9%) and underweight (24.8 vs. 14.1%) and were more likely to have had impaired activities of daily living (ADL) and impaired consciousness than those with AMI. Multivariable logistic regression analysis showed that female sex [adjusted odds ratio: 4.16 (95% confidence interval: 2.73–6.34)], impaired ADL [2.33 (1.18–4.60)], chronic pulmonary disease [3.33 (1.49–7.44)], and pneumonia [3.00 (1.81–4.98)] were associated with developing TTS relative to AMI, while overweight status, aortic disease, cerebrovascular disease, peripheral arterial disease, and dyslipidemia were associated with developing AMI relative to TTS. Propensity score-matched analysis (189 pairs) showed that 30-day in-hospital mortality was not significantly different between patients with TTS and AMI (15.3 vs. 19.0%, $p=0.41$), but overall in-hospital mortality was significantly lower in patients with TTS than in those with AMI (19.6 vs. 29.1%, $p=0.041$). This study suggests that although in-hospital TTS and in-hospital AMI are similarly likely to occur in older patients, in-hospital TTS is more likely to occur in female patients with impaired ADL and/or respiratory disease and carries a similar 30-day mortality risk but a lower overall in-hospital mortality risk compared with in-hospital AMI. Our results indicate the importance of differentiating TTS from AMI in hospital settings.

Keywords Takotsubo syndrome · Acute myocardial infarction · In-hospital complication · Non-cardiac disease · Mortality

Introduction

Takotsubo syndrome (TTS) is a cardiac dysfunction syndrome characterized by reversible ventricular dysfunction in the absence of culprit coronary artery disease [1–4]. TTS can be classified into primary TTS and secondary TTS. Primary TTS is generally defined as TTS caused by emotional stress or no identifiable stress, while secondary TTS is defined as TTS that is secondary to another medical condition, often occurring in hospital settings [1, 5–8]. More simply, TTS can also be classified according to the setting of TTS development: out-of-hospital TTS versus in-hospital TTS [9]. Out-of-hospital TTS often occurs in the absence of a critical medical disease, whereas in-hospital TTS occurs in

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the presence of chronic or acute comorbidities [9]. Previous studies have reported that secondary TTS and in-hospital TTS were associated with a higher mortality risk than were primary TTS and out-of-hospital TTS, respectively [5–9].

TTS is currently recognized as an important differential diagnosis of acute myocardial infarction (AMI). The treatment strategies differ between the two cardiac disorders [1, 2, 10–12]. Reperfusion therapy has been established as an effective treatment for AMI [10–12], whereas there is currently no evidence-based treatment for TTS because of a lack of randomized controlled trials [1, 2]. Previous studies have reported that both proportions of comorbidities and in-hospital mortality were significantly higher among patients who developed AMI after hospital admission (i.e., in-hospital AMI) than among those with out-of-hospital AMI [13–16], suggesting that different patient characteristics and prognoses were associated with in-hospital AMI, compared with out-of-hospital AMI. Although several studies have compared patient characteristics and outcomes between TTS and AMI as a whole (mainly out-of-hospital TTS versus out-of-hospital AMI) and showed that the prognosis of TTS was comparable with that of AMI [17, 18], no study has involved direct comparison of the clinical characteristics between in-hospital TTS and in-hospital AMI.

Thus, the present study aimed to compare patient characteristics and outcomes between in-hospital TTS and in-hospital AMI among patients admitted for non-cardiac diseases, using a national inpatient database in Japan.

Methods

Study design and data source

This nationwide retrospective cohort study in Japan used the Diagnosis Procedure Combination (DPC) database, which includes hospital administrative claim data and discharge abstracts. The details of the database have previously been described elsewhere [9, 19, 20]. For the DPC reimbursement system, attending physicians are required to record diagnosis data in discharge abstracts until the time of patient discharge. The DPC diagnosis data include up to 12 diagnoses (recorded with Japanese-text diagnoses and International Classification of Diseases, 10th Revision code [ICD-10] codes), including "main diagnosis," "admission-precipitating diagnosis," "most resource-consuming diagnosis," "second most resource-consuming diagnosis," "comorbidities already identified at admission," and "complications occurring after admission" in its discharge abstracts [9, 19, 20]. Although the DPC database partially corresponds to the Nationwide Inpatient Sample in the USA [8], it has several unique advantages. One advantage of the DPC database is that comorbidities already present at admission are clearly distinguished from complications that occur after admission.

The present study used data on 21 million inpatients from approximately 1000 hospitals collected from July 2010 to March 2014. Patients were followed up from the date of admission to the date of discharge. In general, lengths of hospital stay are longer in Japan than in other countries because hospitalized patients generally receive nursing care and rehabilitation as well as acute care during a single hospitalization [21]. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. This study was approved by the Institutional Review Board at The University of Tokyo. The requirement for informed consent was waived because of the anonymous nature of the data.

Patient selection

We identified an initial reason for admission for each patient using the "admission-precipitating diagnosis" in the discharge abstract. (ICD-10 codes and Japanese-text diagnoses used in this study are shown in "Appendix.") We also identified cases of in-hospital TTS and in-hospital AMI using the diagnoses of "complications occurring after admission" in the discharge abstract. We then selected patients who were admitted with a non-cardiac disease as the initial reason for admission and developed TTS or AMI as an in-hospital complication after admission. We excluded patients with in-hospital TTS who (i) were aged < 20 years, (ii) had coexisting pheochromocytoma or acute myocarditis, (iii) underwent coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) during hospitalization, and (iv) received both diagnoses of TTS and AMI. We also excluded patients with in-hospital AMI who (i) were aged < 20 years and (ii) received both diagnoses of TTS and AMI. For the main analysis of this study, we focused on the comparison of TTS and AMI as early in-hospital complications. We therefore selected patients who developed TTS or AMI after admission and underwent coronary angiography (CAG) within 7 days after admission (defined as the "main cohort").

Patient characteristics

We identified the following baseline characteristics: age; sex; body mass index (BMI) at admission; status of activities of daily living (ADL) at admission, calculated using the Barthel Index [22]; consciousness level at admission, measured using the Japan Coma Scale score; and comorbidities and atherosclerotic risk factors [hypertension, diabetes mellitus, dyslipidemia, and smoking history (including both current smoker and ex-smoker)] present at admission. BMI was categorized into five groups: < 18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal weight), 25.0–29.9 kg/m^2

(overweight), ≥ 30.0 kg/m^2 (obese), and missing data. The Barthel Index was categorized into the following six groups: 0–20, 25–45, 50–70, 75–95, 100, and missing data. The Japan Coma Scale score was categorized into four groups: 0 (alert), 1–3 (drowsy), 10–30 (somnolent), and 100–300 (comatose). The Japan Coma Scale score has been reported to have a good correlation with the Glasgow Coma Scale score [23].

In-hospital management

We collected the following data regarding in-hospital management: the hospitalization day of CAG, surgery performed under general anesthesia on or before the date of CAG, and intensive treatments given during hospitalization. Intensive treatments included catecholamine administration, intra-aortic balloon pumping (IABP), extracorporeal membrane oxygenation (ECMO), use of a ventricular assist device, and mechanical ventilation. For the AMI group, data on coronary revascularization during hospitalization were also collected.

Outcomes

The outcomes were 30-day in-hospital mortality and overall in-hospital mortality. The 30-day in-hospital mortality was defined as in-hospital all-cause deaths within 30 days after admission.

Statistical analyses

Categorical variables were compared using Fisher's exact test. Continuous variables were compared using Student's *t* test or the Mann–Whitney U test. Using the main cohort of this study, we examined the factors associated with the development of in-hospital TTS (vs. in-hospital AMI) using multivariable logistic regression models. Baseline variables with a *p* value of < 0.10 in the univariable analyses were selected as covariates in the multivariable logistic regression analysis. For the multivariable analyses, we created 20-copy datasets where missing data for BMI, the Barthel Index, and/or smoking history were imputed with plausible values using multiple imputation, and we obtained the pooled results from the multivariable logistic regression analyses in the 20-copy datasets based on Rubin's rule [24].

We performed a propensity score-matched analysis to compare outcomes between patients with in-hospital TTS and in-hospital AMI. A logistic regression model was created to estimate the propensity score for the development of in-hospital TTS (vs. in-hospital AMI) using patient characteristics as covariates. Nearest-neighbor matching was then performed based on the estimated propensity score within a caliper width of 0.2 times the pooled standard deviation of the propensity scores for the cohort. Balances of patient characteristics between the groups after propensity score matching were assessed by calculating standardized differences, for which a difference of < 0.10 was considered to indicate good balance. In this propensity score-matched cohort, we also performed subgroup analyses to compare overall in-hospital mortality between patients with TTS and AMI among subgroups of patients with cardiovascular risk factors [hypertension, diabetes mellitus, dyslipidemia, smoking history, or obesity (BMI of ≥ 30.0 kg/m^2)], with assessment of interactions between TTS/AMI and each risk factor.

Previous studies have shown that a certain proportion of patients with TTS were diagnosed without CAG in real-world clinical settings [25–27]; however, misdiagnosis of AMI as TTS can occur in such patients [27]. In the present study, the main cohort included only patients who underwent CAG to increase the specificity of the diagnoses of TTS and AMI. However, the analysis of this cohort may have been subject to selection bias. Thus, for the sensitivity analysis, we compared patient characteristics and outcomes between TTS and AMI using the "extended cohort," which included both patients who did and did not undergo CAG.

All hypothesis tests had a two-sided significance level of 0.05. All statistical analyses were conducted using IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA) and Stata/SE 14.0 (StataCorp, College Station, TX, USA).

Results

Study cohort

Figure 1 shows a flowchart of the patient selection for this study. For the main cohort, we identified 841 eligible patients hospitalized at 417 hospitals, including 230 (27.3%) with in-hospital TTS and 611 (72.7%) with in-hospital AMI. Figure 2 shows the non-cardiac diseases as initial reasons for admission in the main cohort. In the TTS group, respiratory disease (20.0%) was the leading reason for admission, followed by digestive organ disease (12.2%) and malignancy (10.9%). In the AMI group, malignancy (16.2%) was the leading reason for admission, followed by aortic/peripheral arterial disease (15.5%) and cerebrovascular disease (12.4%). The median length of stay in the main cohort was 25 days. The 1:1 propensity score matching created a cohort of 378 patients (189 pairs). The C-statistic of the propensity scores was 0.81.

Patient characteristics

Table 1 shows the patient characteristics in the main cohort and the propensity score-matched cohort. In the main cohort, patients with in-hospital TTS were more often female, had significantly lower BMIs, lower Barthel Indexes (i.e., more

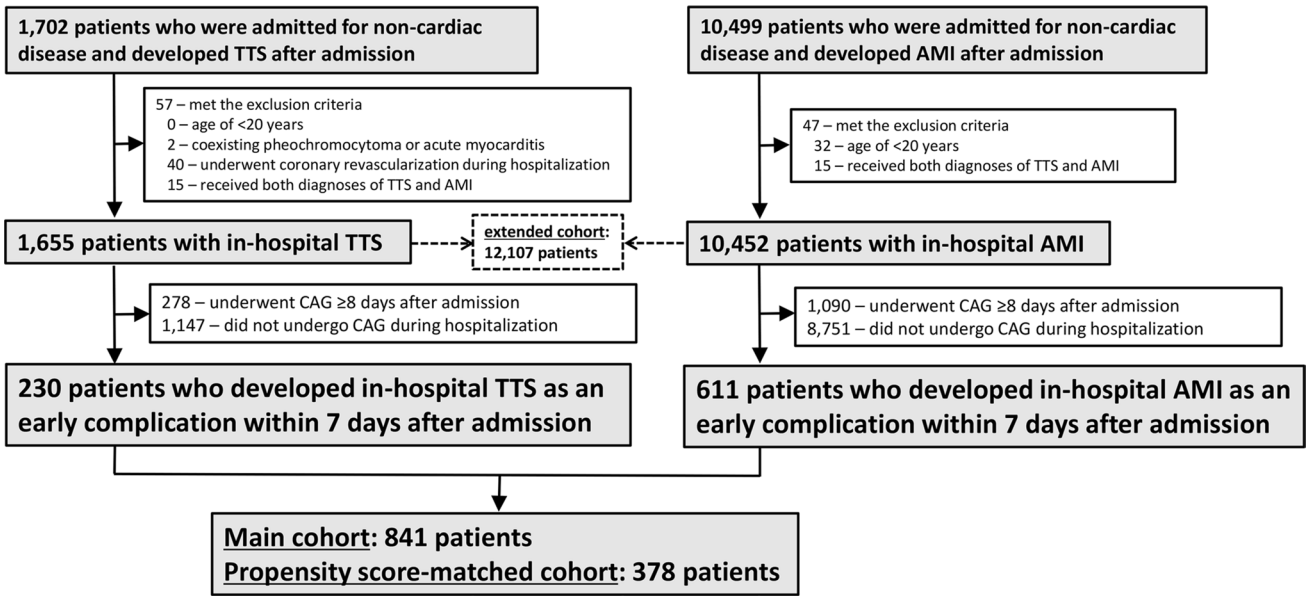

Fig. 1 Selection of study patients. *TTS* Takotsubo syndrome, *AMI* acute myocardial infarction, *CAG* coronary angiography

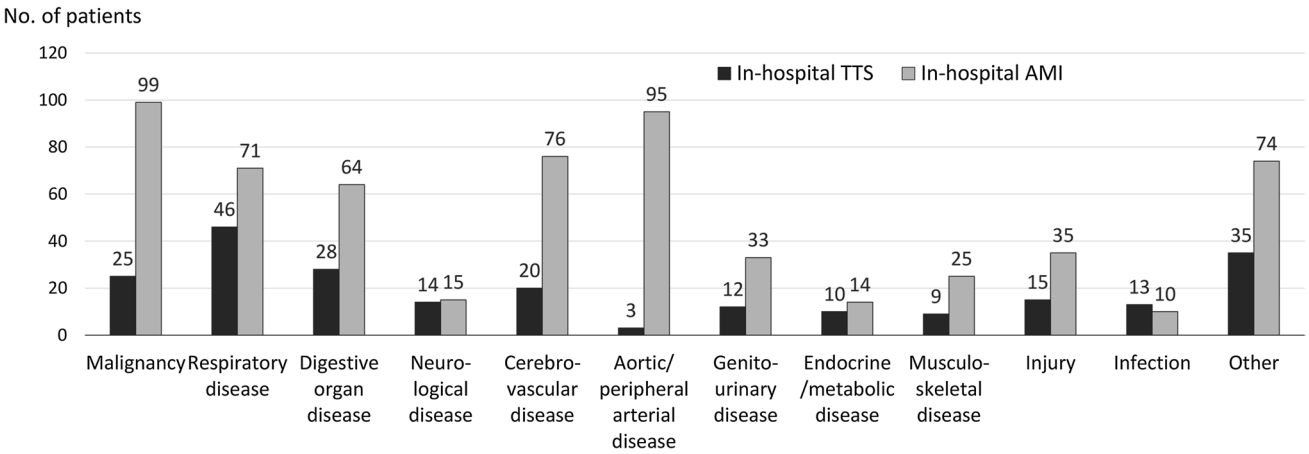

Fig. 2 Non-cardiac diseases as initial reasons for admission among the main cohort (230 patients with in-hospital TTS and 611 patients with in-hospital AMI). *TTS* Takotsubo syndrome, *AMI* acute myocardial infarction

impaired ADL), and higher Japan Coma Scale scores (i.e., lower consciousness levels) than those with in-hospital AMI. The proportions of several comorbidities coexisting at admission (chronic pulmonary disease, neurological disease, sepsis, pneumonia, and seizure/status epilepticus) were significantly higher among patients with in-hospital TTS than among those with in-hospital AMI. Conversely, the proportions of cerebrovascular disease, aortic disease, peripheral arterial disease, atherosclerotic risk factors, and chronic renal failure were significantly higher in patients with in-hospital AMI. In the propensity score-matched cohort, patient characteristics were well balanced between the two groups.

Factors associated with development of in-hospital TTS versus in-hospital AMI

Figure 3 shows the results of logistic regression models for the development of in-hospital TTS (vs. in-hospital AMI). Univariable analyses identified sex, BMI, the Barthel Index, the Japan Coma Scale score, 10 comorbidities, and four atherosclerotic risk factors as variables with p values of < 0.10. In the multivariable logistic regression analysis using these variables as covariates, female sex, a lower Barthel Index, chronic pulmonary disease, and pneumonia were significantly more likely to be associated with developing TTS relative to AMI, whereas an

Table 1 Patient characteristics in the main cohort and propensity score-matched cohort

	Main cohort ($N=841$)			Propensity score-matched cohort ($N=378$)			
	In-hospital TTS ($n=230$)	In-hospital AMI ($n=611$)	p value	In-hospital TTS ($n=189$)	In-hospital AMI ($n=189$)	p value	Standardized difference
Age: mean years ± SD	72.7 ± 12.4	72.8 ± 10.4	0.97	73.1 ± 12.2	73.5 ± 10.7	0.75	−0.033
Sex: female	146 (63.5)	201 (32.9)	< 0.001	111 (58.7)	111 (58.7)		0.0
Clinical conditions at admission							
Body mass index, kg/m^2			< 0.001			0.89	
< 18.5 (underweight)	57 (24.8)	86 (14.1)		40 (21.2)	46 (24.3)		−0.076
8.5–24.9 (normal weight)	116 (50.4)	329 (53.8)		101 (53.4)	103 (54.5)		−0.021
25.0–29.9 (overweight)	21 (9.1)	124 (20.3)		20 (10.6)	17 (9.0)		0.053
≥ 30.0 (obese)	6 (2.6)	22 (3.6)		6 (3.2)	5 (2.6)		0.031
Missing data	30 (13.0)	50 (8.2)		22 (11.6)	18 (9.5)		0.069
Barthel Index			< 0.001			0.87	
100	51 (22.2)	244 (39.9)		48 (25.4)	48 (25.4)		0.0
75–95	12 (5.2)	43 (7.0)		12 (6.3)	8 (4.2)		0.095
50–70	22 (9.6)	40 (6.5)		16 (8.5)	17 (9.0)		−0.019
25–45	15 (6.5)	37 (6.1)		14 (7.4)	17 (9.0)		−0.058
0–20	86 (37.4)	169 (27.7)		62 (32.8)	68 (36.0)		−0.067
Missing data	44 (19.1)	78 (12.8)		37 (19.6)	31 (16.4)		0.083
Japan Coma Scale score			< 0.001			0.99	
0 (alert)	152 (66.1)	481 (78.7)		132 (69.8)	134 (70.9)		−0.023
1–3 (drowsy)	40 (17.4)	81 (13.3)		33 (17.5)	33 (17.5)		0.0
10–30 (somnolent)	16 (7.0)	26 (4.3)		10 (5.3)	10 (5.3)		0.0
100–300 (comatose)	22 (9.6)	23 (3.8)		14 (7.4)	12 (6.3)		0.042
Comorbidities present at admission							
Malignancy	42 (18.3)	120 (19.6)	0.70	38 (20.1)	40 (21.2)	0.90	−0.026
Chronic pulmonary disease	16 (7.0)	21 (3.4)	0.037	9 (4.8)	9 (4.8)	1.0	0.0
Chronic liver disease	7 (3.0)	25 (4.1)	0.55	6 (3.2)	6 (3.2)	1.0	0.0
Chronic renal failure	16 (7.0)	87 (14.2)	0.003	15 (7.9)	15 (7.9)	1.0	0.0
Neurological disease	39 (17.0)	60 (9.8)	0.006	29 (15.3)	23 (12.2)	0.46	0.092
Psychiatric disease	10 (4.3)	13 (2.1)	0.096	7 (3.7)	9 (4.8)	0.80	−0.053
Sepsis	19 (8.3)	20 (3.3)	0.005	11 (5.8)	12 (6.3)	1.0	−0.022
Pneumonia	54 (23.5)	50 (8.2)	< 0.001	35 (18.5)	33 (17.5)	0.89	0.028
Cerebrovascular disease	34 (14.8)	131 (21.4)	0.032	32 (16.9)	28 (14.8)	0.67	0.058
Aortic disease	1 (0.4)	55 (9.0)	< 0.001	1 (0.5)	3 (1.6)	0.62	−0.10
Peripheral arterial disease	7 (3.0)	70 (11.5)	< 0.001	7 (3.7)	7 (3.7)	1.0	0.0
Acute gastrointestinal disease	13 (5.7)	34 (5.6)	1.000	13 (6.9)	12 (6.3)	1.0	0.021
Seizure/status epilepticus	6 (2.6)	2 (0.3)	0.007	2 (1.1)	2 (1.1)	1.0	0.0
Injury	21 (9.1)	48 (7.9)	0.57	19 (10.1)	21 (11.1)	0.87	−0.034
Atherosclerotic risk factors							
Hypertension	53 (23.0)	225 (36.8)	< 0.001	45 (23.8)	53 (28.0)	0.41	−0.097
Diabetes mellitus	49 (21.3)	192 (31.4)	0.004	44 (23.3)	44 (23.3)	1.0	0.0
Dyslipidemia	13 (5.7)	94 (15.4)	< 0.001	12 (6.3)	11 (5.8)	1.0	0.022
Smoking history			0.005			0.91	
Yes	59 (25.7)	228 (37.3)		47 (24.9)	50 (26.5)		−0.036
No	133 (57.8)	301 (49.3)		115 (60.8)	114 (60.3)		0.011
Missing data	38 (16.5)	82 (13.4)		27 (14.3)	25 (13.2)		0.031

Numbers are *n* (%), unless otherwise stated

TTS Takotsubo syndrome, *AMI* acute myocardial infarction, *SD* standard deviation

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, per 1-year increase	1.00 (0.99–1.01)	0.964	NA	NA
Sex: female (reference: male)	3.55 (2.58–4.87)	<0.001	4.16 (2.73–6.34)	<0.001
Body mass index at admission, kg/m^2				
<18.5 (underweight)	1.88 (1.27–2.79)	0.002	1.33 (0.84–2.10)	0.221
18.5–24.9 (normal weight)	Reference		Reference	
25.0–29.9 (overweight)	0.48 (0.29–0.80)	0.005	0.48 (0.26–0.86)	0.015
≥30.0 (obese)	0.77 (0.31–1.95)	0.587	0.89 (0.28–2.81)	0.846
Barthel Index at admission				
100	Reference		Reference	
75–95	1.34 (0.66–2.71)	0.423	1.29 (0.56–2.93)	0.549
50–70	2.63 (1.44–4.80)	0.002	2.33 (1.18–4.60)	0.015
25–45	1.94 (0.99–3.80)	0.053	1.45 (0.68–3.05)	0.333
0–20	2.43 (1.64–3.63)	<0.001	1.59 (0.96–2.63)	0.073
Japan Coma Scale score at admission				
0 (alert)	Reference		Reference	
1–3 (drowsy)	1.56 (1.03–2.38)	0.037	1.38 (0.80–2.36)	0.242
10–30 (somnolent)	1.95 (1.02–3.73)	0.044	1.21 (0.54–2.70)	0.648
100–300 (comatose)	3.03 (1.64–5.58)	<0.001	1.84 (0.82–4.12)	0.138
Malignancy	0.91 (0.62–1.35)	0.651	NA	NA
Chronic pulmonary disease	2.10 (1.08–4.10)	0.030	3.33 (1.49–7.44)	0.003
Chronic liver disease	0.74 (0.31–1.73)	0.480	NA	NA
Chronic renal failure	0.45 (0.26–0.79)	0.005	0.62 (0.33–1.16)	0.134
Neurological disease	1.88 (1.21–2.90)	0.005	1.41 (0.82–2.41)	0.211
Psychiatric disease	2.09 (0.90–4.84)	0.085	1.58 (0.59–4.20)	0.361
Sepsis	2.66 (1.39–5.08)	0.003	1.99 (0.92–4.33)	0.081
Pneumonia	3.44 (2.26–5.24)	<0.001	3.00 (1.81–4.98)	<0.001
Cerebrovascular disease	0.64 (0.42–0.96)	0.031	0.60 (0.36–0.99)	0.046
Aortic disease	0.04 (0.01–0.32)	0.002	0.07 (0.01–0.53)	0.010
Peripheral arterial disease	0.24 (0.11–0.54)	<0.001	0.39 (0.16–0.93)	0.035
Acute gastrointestinal disease	1.02 (0.53–1.96)	0.961	NA	NA
Seizure/status epilepticus	8.16 (1.63–40.71)	0.011	3.49 (0.59–20.61)	0.168
Injury	1.18 (0.69–2.02)	0.549	NA	NA
Hypertension	0.51 (0.36–0.73)	<0.001	0.73 (0.48–1.11)	0.136
Diabetes mellitus	0.59 (0.41–0.85)	0.004	0.80 (0.53–1.22)	0.304
Dyslipidemia	0.33 (0.18–0.60)	<0.001	0.48 (0.24–0.97)	0.040
Smoking history	0.59 (0.41–0.83)	0.003	1.28 (0.80–2.04)	0.301

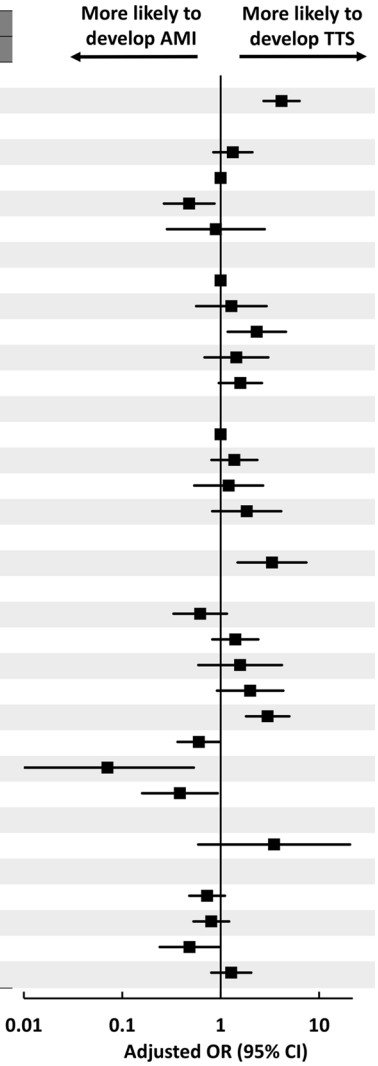

Fig. 3 Factors associated with the development of in-hospital TTS versus in-hospital AMI. Variables with a p value of < 0.10 in the univariable analyses were selected as covariates in the multivariable logistic regression analysis. *TTS* Takotsubo syndrome, *AMI* acute myocardial infarction, *OR* odds ratio, *CI* confidence interval, *NA* not applicable

overweight status, aortic disease, cerebrovascular disease, peripheral arterial disease, and dyslipidemia were significantly more likely to be associated with developing AMI relative to TTS.

In-hospital management

Table 2 shows in-hospital management in the main cohort and the propensity score-matched cohort. The proportion of patients who received IABP was significantly higher in the AMI than TTS group in the main cohort and propensity score-matched cohort. The proportion of patients who received ECMO was significantly higher in the AMI than TTS group in the main cohort, but the difference was not significant in the propensity score-matched cohort.

Mortality risk of in-hospital TTS versus in-hospital AMI

Table 3 shows in-hospital mortality in the main cohort and the propensity score-matched cohort. In both the main cohort and the propensity score-matched cohort, 30-day in-hospital mortality did not differ between the TTS and AMI groups, but overall in-hospital mortality was significantly lower in the TTS than in the AMI group. Subgroup analyses of the propensity score-matched cohort revealed no significant difference in overall in-hospital mortality between TTS and AMI among subgroups of patients with hypertension (13.3 vs. 18.9%, $p = 0.59$), diabetes mellitus (15.9 vs. 22.7%, $p = 0.59$), dyslipidemia (0.0 vs. 9.1%, $p = 0.48$), smoking history (14.9 vs. 24.0%, $p = 0.31$), or obesity (0.0 vs. 20.0%, $p = 0.45$), and there was no significant interaction in each

Table 2 In-hospital management in the main cohort and propensity score-matched cohort

	Main cohort ($N=841$)			Propensity score-matched cohort ($N=378$)		
	In-hospital TTS ($n=230$)	In-hospital AMI ($n=611$)	p value	In-hospital TTS ($n=189$)	In-hospital AMI ($n=189$)	p value
Hospitalization day of CAG performed			0.87			0.80
Day of admission	23 (10.0)	70 (11.5)		21 (11.1)	25 (13.2)	
Day 2	56 (24.3)	160 (26.2)		48 (25.4)	39 (20.6)	
Day 3	45 (19.6)	96 (15.7)		37 (19.6)	31 (16.4)	
Day 4	34 (14.8)	83 (13.6)		27 (14.3)	28 (14.8)	
Day 5	28 (12.2)	84 (13.7)		20 (10.6)	27 (14.3)	
Day 6	22 (9.6)	58 (9.5)		18 (9.5)	18 (9.5)	
Day 7	22 (9.6)	60 (9.8)		18 (9.5)	21 (11.1)	
Surgery under general anesthesia on or before the date of CAG	29 (12.6)	103 (16.9)	0.14	24 (12.7)	29 (15.3)	0.55
Intensive treatment during hospitalization						
Catecholamine	123 (53.5)	353 (57.8)	0.28	105 (55.6)	124 (65.6)	0.058
IABP	6 (2.6)	118 (19.3)	<0.001	4 (2.1)	33 (17.5)	<0.001
ECMO	3 (1.3)	33 (5.4)	0.007	1 (0.5)	5 (2.6)	0.22
Ventricular assist device	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–
Mechanical ventilation	105 (45.7)	275 (45.0)	0.88	90 (47.6)	97 (51.3)	0.54
Coronary revascularization						
Percutaneous coronary intervention	–	397 (65.0%)	–	–	116 (61.4)	–
Coronary artery bypass graft	–	14 (2.3%)	–	–	1 (0.5)	–

Numbers are *n* (%)

TTS Takotsubo syndrome, *AMI* acute myocardial infarction, *CAG* coronary angiography, *IABP* intra-aortic balloon pumping, *ECMO* extracorporeal membrane oxygenation

Table 3 In-hospital mortality in the main cohort and propensity score-matched cohort

	Main cohort ($N=841$)			Propensity score-matched cohort ($N=378$)		
	In-hospital TTS ($n=230$)	In-hospital AMI ($n=611$)	p value	In-hospital TTS ($n=189$)	In-hospital AMI ($n=189$)	p value
30-day in-hospital mortality	35 (15.2)	129 (21.1)	0.063	29 (15.3)	36 (19.0)	0.41
Overall in-hospital mortality	43 (18.7)	166 (27.2)	0.012	37 (19.6)	55 (29.1)	0.041

Numbers are *n* (%)

TTS Takotsubo syndrome, *AMI* acute myocardial infarction

subgroup (p for interaction = 0.78, 0.86, 0.40, 0.90, and 0.22, respectively).

Sensitivity analysis

For the sensitivity analysis, the extended cohort comprised 1655 patients with in-hospital TTS and 10,452 patients with in-hospital AMI (Fig. 1). Table 4 shows the patient characteristics and outcomes in the extended cohort. Almost all patient characteristics showed consistent results in terms of comparison between TTS and AMI, but the mortality risk was significantly higher in AMI.

Discussion

This retrospective study showed that (1) in-hospital TTS was more likely than in-hospital AMI to occur among female patients with poor general health and/or respiratory disease; (2) in-hospital AMI was more likely than in-hospital TTS to occur among overweight patients with vascular disease

Table 4 Patient characteristics and in-hospital mortality in the extended cohort

	In-hospital TTS ($n=1655$)	In-hospital AMI ($n=10,452$)	p value
Patient characteristics			
Age: mean years ± SD	75.4 ± 12.0	76.1 ± 11.7	0.016
Sex: female	1116 (67.4)	4201 (40.2)	< 0.001
Clinical conditions at admission			
Body mass index, kg/m^2			< 0.001
< 18.5 (underweight)	457 (27.6)	1910 (18.3)	
18.5–24.9 (normal weight)	776 (46.9)	5393 (51.6)	
25.0–29.9 (overweight)	153 (9.2)	1518 (14.5)	
≥ 30.0 (obese)	25 (1.5)	341 (3.3)	
Missing data	244 (14.7)	1290 (12.3)	
Barthel Index			< 0.001
100	318 (19.2)	3187 (30.5)	
75–95	80 (4.8)	658 (6.3)	
50–70	119 (7.2)	846 (8.1)	
25–45	115 (6.9)	662 (6.3)	
0–20	715 (43.2)	3469 (33.2)	
Missing data	308 (18.6)	1630 (15.6)	
Japan Coma Scale score			< 0.001
0 (alert)	998 (60.3)	7714 (73.8)	
1–3 (drowsy)	348 (21.0)	1681 (16.1)	
10–30 (somnolent)	138 (8.3)	585 (5.6)	
100–300 (comatose)	171 (10.3)	471 (4.5)	
Comorbidities present at admission			
Malignancy	329 (19.9)	2219 (21.2)	0.22
Chronic pulmonary disease	152 (9.2)	609 (5.8)	< 0.001
Chronic liver disease	61 (3.7)	372 (3.6)	0.78
Chronic renal failure	122 (7.4)	1118 (10.7)	< 0.001
Neurological disease	300 (18.1)	1437 (13.7)	< 0.001
Psychiatric disease	156 (9.4)	751 (7.2)	0.002
Sepsis	110 (6.6)	312 (3.0)	< 0.001
Pneumonia	344 (20.8)	1533 (14.7)	< 0.001
Cerebrovascular disease	371 (22.4)	2113 (20.2)	0.042
Aortic disease	16 (1.0)	341 (3.3)	< 0.001
Peripheral arterial disease	54 (3.3)	617 (5.9)	< 0.001
Acute gastrointestinal disease	85 (5.1)	457 (4.4)	0.16
Seizure/status epilepticus	30 (1.8)	48 (0.5)	< 0.001
Injury	150 (9.1)	1079 (10.3)	0.13
Atherosclerotic risk factors			
Hypertension	461 (27.9)	3299 (31.6)	0.003
Diabetes mellitus	295 (17.8)	2963 (28.3)	< 0.001
Dyslipidemia	102 (6.2)	1217 (11.6)	< 0.001
Smoking history			0.028
Yes	398 (24.0)	2801 (26.8)	
No	1029 (62.2)	6150 (58.8)	
Missing data	228 (13.8)	1501 (14.4)	
In-hospital mortality			
30-day in-hospital mortality	232 (14.0)	3071 (29.4)	< 0.001
Overall in-hospital mortality	410 (24.8)	4393 (42.0)	< 0.001

Numbers are *n* (%), unless otherwise stated

TTS Takotsubo syndrome, *AMI* acute myocardial infarction, *SD* standard deviation

and/or atherosclerotic risk factors; and (3) according to the propensity score-matched analysis, 30-day in-hospital mortality was not significantly different but overall in-hospital mortality was significantly lower in patients with TTS than with AMI.

To date, a limited number of studies have investigated patients who developed secondary/in-hospital TTS and in-hospital AMI. Four observational studies reported that, compared with primary TTS, secondary TTS showed worse prognoses in terms of mortality and cardiac complications [5–8]. Our previous study showed that in-hospital TTS was associated with more prevalent comorbidities and higher in-hospital mortality than was out-of-hospital TTS [9]. Four observational studies have investigated in-hospital AMI in the current era of reperfusion in the twenty-first century, showing that patients with in-hospital AMI had more frequent comorbidities and higher in-hospital mortality than did those with out-of-hospital AMI [13–16]. These previous studies provide useful information about the differences between the in-hospital onset type and the out-of-hospital onset type of each disease. However, existing studies have been unable to investigate the differences in patient backgrounds and outcomes between in-hospital TTS and in-hospital AMI in the same study setting.

In this study, approximately one-third of patients with in-hospital TTS were male in the main and extended cohorts, suggesting that male patients were more prevalent in this study than that in previous Western studies focusing on an overall TTS cohort (approximately 10%, including patients with out-of-hospital TTS and those with in-hospital TTS) [1, 5–8, 17, 28]. Asian ethnicity may be related to the high proportion of men among patients with TTS in this study because Japanese studies and a Korean study reported a higher proportion of men with TTS (20–40%) [9, 27, 29–31]. The inclusion of only patients with in-hospital TTS may also be related to the high proportion of men in this study because some previous studies have suggested that secondary/in-hospital TTS affects a higher proportion of men than does primary/out-of-hospital TTS [5, 8, 9].

Our findings suggest that female sex, poor general health, and respiratory disease are associated with developing in-hospital TTS compared with in-hospital AMI, whereas atherosclerotic diseases and conventional cardiovascular risk factors are associated with developing in-hospital AMI compared with in-hospital TTS. Although the mortality risk was different between the main cohort and the extended cohort, probably because the mortality risk differed between patients who did and did not undergo CAG [26, 27], the results of the patient characteristics in the extended cohort were consistent with those in the main cohort. Previous studies have shown that patients with pneumonia have a risk of developing cardiovascular disease, including AMI [32, 33]. However, no previous studies have investigated the risk of developing TTS in patients with pneumonia. In this study, pneumonia was significantly associated with developing TTS relative to AMI, suggesting that pneumonia is more strongly associated with the occurrence of in-hospital TTS than in-hospital AMI. Similarly, chronic pulmonary disease was significantly associated with developing TTS relative to AMI. Thus, physicians may need to be aware of TTS as a cardiovascular complication among patients hospitalized with respiratory disease.

Multivariable logistic regression analysis showed that several comorbidities (e.g., malignancy, neurological disease, sepsis, seizure/status epilepticus, hypertension, and diabetes mellitus) were not significantly associated with the development of TTS compared with AMI. However, these results should be interpreted with caution because the multivariable analysis only showed odds ratios and 95% confidence intervals of each comorbidity for the development of in-hospital TTS compared with in-hospital AMI. Thus, the multivariable analysis was not able to determine the impacts of comorbidities on the incidence of in-hospital TTS among the overall inpatient population. Previous studies reported that several comorbidities were associated with the incidence [8, 34, 35] and prognosis [9, 36–38] of TTS. Additionally, other studies found that TTS had a prognostic impact in patients with a specific comorbidity or treatment (e.g., those with severe sepsis [39] or receiving chemotherapy [40]). Thus, attending physicians should be aware of these comorbid conditions when diagnosing and treating TTS.

The propensity score-matched analysis of the present study showed that 30-day in-hospital mortality was not significantly different but overall in-hospital mortality was significantly lower in patients with TTS than with AMI. This may indicate a similar mortality risk between patients with TTS and AMI in the early phase, with a later reduction in the mortality risk of TTS even if potential confounding factors such as comorbidities are well balanced between the two groups. One reason for this may be the reversibility of subsequent cardiac dysfunction of TTS compared with AMI. Given the beneficial effect of reperfusion therapy on the prognosis of AMI, our result suggests that CAG should not be delayed for accurate differentiation between in-hospital TTS and in-hospital AMI and subsequent appropriate management.

Hypertension, diabetes mellitus, dyslipidemia, smoking history, and obesity are well-known cardiovascular risk factors. In the present study, these risk factors and atherosclerotic diseases were more prevalent in patients with in-hospital AMI than in those with in-hospital TTS. Thus, a patient's atherosclerotic background is more relevant to the risk of AMI than the risk of TTS. Meanwhile, the subgroup analyses showed no significant interaction of TTS or AMI with cardiovascular risk factors in terms of mortality. However,

the sample size of each subgroup was too small to examine the impact of risk factors; further data are needed.

Study limitations

Several limitations should be acknowledged in this study. First, this study was based on a secondary analysis of administrative data. Diagnoses from administrative data are generally less well validated than those from prospective studies. A validation study reported that diagnoses in the DPC data have high specificity (> 96%) but relatively low sensitivity (< 85%) [41]. This means that, in the present study, the diagnoses of TTS and AMI may have been susceptible to the underreporting of cases rather than overreporting. Second, the main and propensity score-matched cohorts in this study did not include patients with in-hospital TTS or AMI who did not undergo CAG. Thus, the results from the two cohorts may have limited generalizability. Meanwhile, the extended cohort included patients who did not undergo CAG for the diagnosis of TTS or AMI, but such patients would be more likely to have an inaccurate diagnosis of TTS or AMI than those diagnosed with CAG. Therefore, prospective cohort studies are warranted to further clarify the clinical features of in-hospital TTS and AMI. Third, data on patients' medical histories, symptoms, vital signs, and laboratory findings were unavailable in this study. We were therefore unable to compare the time course from onset to CAG, cardiac biomarkers, electrocardiographic findings (e.g., ST elevation), and echocardiographic findings (e.g., left ventricular ejection fraction and wall motion abnormality) between in-hospital TTS and in-hospital AMI. Fourth, data on cause of death were unavailable in this study. Previous studies have suggested that TTS carries a higher non-cardiac mortality risk than cardiac mortality risk because of coexisting disease [42, 43]. In addition, a recent study revealed that patients with the apical form of TTS showed lower cardiac mortality but higher non-cardiac mortality during hospitalization than those with anterior AMI [29]. Thus, the mortality risks for different causes of death (cardiac or non-cardiac) may have differed between in-hospital TTS and in-hospital AMI in this study. Finally, we were unable to compare the long-term outcomes between in-hospital TTS and in-hospital AMI because of a lack of data.

Conclusions

This retrospective study compared patient characteristics and outcomes between in-hospital TTS and in-hospital AMI among patients admitted for non-cardiac diseases. In-hospital TTS was more strongly associated with female sex, poor general health, and respiratory disease compared with in-hospital AMI. In-hospital AMI was more strongly associated with overweight status, vascular disease, and dyslipidemia compared with in-hospital TTS. The propensity score-matched analysis showed that 30-day in-hospital mortality was not significantly different between patients with TTS and AMI but that overall in-hospital mortality was significantly lower in patients with TTS than with AMI. Our results show that the differentiation of the two cardiac disorders in in-hospital settings is important for the appropriate management.

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Compliance with ethical standards

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

The following ICD-10 codes were used to identify diseases. Use of both a Japanese-text diagnosis and an ICD-10 code to identify a disease is designated by placing "with Japanese text" after the ICD-10 code.

Takotsubo syndrome (I42.8, I42.9, or I51.8 with Japanese text); acute myocardial infarction (I21.x); cardiac disease (I00.x–I02.x, I05.x–I15.x, I20.x–I28.x, I30.x–I52.x, C38.0, D15.1, Q20.x-Q24.x, T82.x, Z95.x, R57.0); malignancy (C00.x–C97 except for C38.0); respiratory disease (J00.x–J99.x); digestive organ disease (K00.x–K93.x); neurological disease (G00.x–G99.x); cerebrovascular disease (I60.x–I69.x); aortic disease (I70.0, I71.x, I74.0, I74.1, I79.0, I79.1); peripheral arterial disease (I70.1–I70.9, I72.x, I73.x, I74.2–I74.9, I77.x, I78.x, I79.2–I79.9); genitourinary disease (N00.x–N99.x); endocrine/metabolic disease (E00.x–E90.x); musculoskeletal disease (M00.x–M99.x); injury (S00.x–S99.x or T00.x–T14.x); infection (A00.x–B99.x); chronic pulmonary disease (I27.8, I27.9, J40.x–J45.x, J47.x, J60.x–J67.x, J68.4, J70.1, J70.3); chronic liver disease (B18.x, I85.x, I86.4, I98.2, K70.x, K71.x–K74.x, K76.6, K76.7); chronic renal failure (I12, I13, N18.x, T82.4, Z99.2); psychiatric disease (F00–F99); sepsis (A02.1, A40.x, A41.x); pneumonia (J12.x–J18.x, J69.0);

acute gastrointestinal disease (K25.0–K25.2, K25.4–K25.6, K26.0–K26.2, K26.4–K26.6, K27.0–K27.2, K27.4–K27.6, K28.0–K28.2, K28.4–K28.6, K63.1, K65.x, K92.2); seizure/status epilepticus (G41.9, R25.2, R25.8, R56.8); hypertension (I10.x, I15.x); diabetes mellitus (E10.x–14.x); dyslipidemia (E78.x); other diagnoses: in situ neoplasms, benign neoplasms, and neoplasms of uncertain behavior (D00.x–D48.x except for D15.1), diseases of the eye and adnexa (H00.x–H59.x), diseases of veins, lymphatic vessels, and lymph nodes (I80–I89), diseases of the skin and subcutaneous tissue (L00.x–L99.x), pregnancy, childbirth, and the puerperium (O00.x–O99.x), congenital malformations (Q00.x–Q18.x, Q25.x–Q99.x), symptoms, signs, and abnormal clinical and laboratory findings (R00.x–R99.x except for R57.0), or consequences of external causes (T15–T98 except for T82.x).

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