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ORIGINAL ARTICLE
Myocardial Disease

Takotsubo Syndrome in Older Men
— Clinical Characteristics Differ by Sex and Age —

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Background: Takotsubo syndrome (TTS) in male patients is under-studied, particularly in the older population.

Methods and Results: From 226 patients with TTS, 44 older male patients (prevalence rate: 19.5%, age: median 77 years) were compared with 182 older female patients (prevalence rate: 80.5%, age: median 80 years). Emotional triggers of TTS were less frequent (2% vs. 19%; P=0.007), whereas physical triggers were more frequent (75% vs. 58%; P=0.040) in older men than in women. Among physical triggers, serious respiratory infection was more common in older men than in women. As initial clues to the diagnosis, ECG T-wave inversion was more frequent (48% vs. 29%; P=0.018) and chest pain and/or dyspnea were less common (23% vs. 38%; P=0.050) in older men than in women. In total, 14 patients (6%) had cardiogenic shock and 41 (18%) had severe heart failure as complications, although there were no significant differences in the frequency of these complications between older men and women. Although cardiac death occurred in 3 female patients (1%) and noncardiac death in 3 male and 5 female patients (4%), there were no significant differences in death rate between older men and women.

Conclusions: Emotional triggers of TTS were extremely infrequent whereas physical triggers were common in older men. Although severe heart failure was common, there were no significant differences in the frequency of complications and in-hospital deaths between older men and women.

Key Words: Emotional triggers; Male patients; Older population; Physical triggers; Takotsubo syndrome

Takotsubo syndrome (TTS), initially reported in Japan in 1990,[1] is an acute heart failure syndrome characterized by transient systolic ventricular dysfunction usually of the apical and mid-ventricular segments.[2–5] Manifestation of TTS is usually precipitated by a triggering event, usually either acute emotional or physical stress.[3–7] The pathophysiology of TTS is not well understood, but there is increasing evidence that the transient ventricular dysfunction observed in TTS is related to acute sympathetic stimulation resulting in microvascular ischemia and dysfunction.[8] Since its original description, most studies have reported that TTS predominantly affects postmenopausal women;[3–7,9] its characterization in men is under-recognized and the older population with TTS is particularly under-studied.

Therefore, the aim of the present study was to investigate and clarify the clinical characteristics of TTS in older men.

Methods

Study Patients

From 341 consecutive patients diagnosed with TTS who were hospitalized at Chikamori Hospital between January 2008 and December 2022, data for 226 patients aged >60 years who underwent emergency coronary angiography and who did not have total occlusion of the coronary artery were analyzed in the present retrospective study. All patients underwent diagnostic evaluation during acute presentation and received appropriate and best possible management during hospitalization. The definition of TTS was based primarily on the revised version of the Mayo Clinic diagnostic criteria,[10,11] together with International Takotsubo (Inter TAK) diagnostic criteria for this condition,[3] as follows: (1) the presence of a transient regional wall motion abnormality of the left ventricle that extends a single epicardial vascular distribution; (2) no significant obstructive

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coronary artery disease; (3) the presence of new ECG abnormalities, either ST-segment elevation and/or T-wave inversion, or modest elevations in cardiac biomarker levels; and (4) no myocarditis. However, the presence of coronary artery disease per se was not considered as an exclusion criterion.

The patient cohort was divided into 2 groups according to sex and patient data were evaluated for baseline characteristics, factors triggering TTS, comorbidities, changes in 12-lead ECG, transient regional wall motion abnormality assessed by echocardiography, and in-hospital complications and outcomes. With regard to the factors triggering TTS, an emotional trigger was classified as a definite emotional stressor in the absence of accompanying serious illness before and/or at first presentation. Physical trigger was classified as presentation with serious illness or condition in the absence of coexisting emotional stressor. TTS was classified as apical, mid-ventricular, basal, or focal.[6] The transient regional wall motion abnormalities associated with TTS were evaluated by follow-up echocardiography, which usually revealed recovery of normal wall motion. Clinical data, ECG and echocardiographic features, and angiographic findings of the patients were independently reviewed by 2 investigators experienced in diagnosing TTS.

Table. Baseline Characteristics

	Total (n=226)	Sex		P value
		Male (n=44)	Female (n=182)	
Age (years)	80 (70–85)	77 (65–84)	80 (71–85)	0.075
Trigger				
Emotional	35 (15)	1 (2)	34 (19)	0.007
Physical	139 (62)	33 (75)	106 (58)	0.040
Infection	39 (17)	16 (36)	23 (13)	<0.001
Respiratory	23	11	12	<0.001
Urinary	9	3	6	0.284
Other	7	2	5	0.537
Stroke	8 (4)	0	8 (4)	0.157
Hemorrhage	1	0	1	0.622
Infarction	5	0	5	0.266
SAH	2	0	2	0.485
Fracture	26 (12)	2 (5)	24 (13)	0.107
Postoperative status	15 (7)	5 (11)	10 (5)	0.160
Respiratory disease	10 (4)	4 (9)	6 (2)	0.094
Convulsion	6 (3)	0	6 (2)	0.222
Other	35 (15)	6 (14)	29 (16)	0.705
No trigger	52 (23)	10 (23)	42 (23)	0.961
Vital signs				
Systolic BP (mmHg)	137 (120–160)	141 (117–160)	137 (120–160)	0.673
Diastolic BP (mmHg)	83 (70–97)	86 (66–102)	83 (70–98)	0.603
Heart rate (bpm)	90 (78–101)	93 (79–103)	89 (76–101)	0.929
Comorbidities				
Hypertension	138 (61)	31 (70)	107 (59)	0.154
Diabetes mellitus	56 (25)	14 (32)	42 (23)	0.228
Dyslipidemia	100 (44)	18 (41)	82 (45)	0.619
Current smoker	32 (14)	20 (45)	12 (7)	<0.001
Pulmonary disease	33 (15)	11 (25)	22 (12)	0.030
Malignant disease	41 (18)	15 (34)	26 (14)	0.002
Coronary artery disease	15 (7)	6 (13)	9 (5)	0.038
Stroke	52 (23)	10 (23)	42 (23)	0.961
Initial clue to diagnosis				
ECG	137 (61)	32 (73)	105 (58)	0.067
ST-segment elevation	94 (42)	20 (45)	74 (41)	0.563
T-wave inversion	74 (33)	21 (48)	53 (29)	0.018
QT prolongation	91 (40)	21 (48)	70 (38)	0.261
Other	6 (3)	0 (0)	6 (3)	0.222
Subjective symptoms	80 (35)	10 (23)	70 (38)	0.050
Chest pain	71 (31)	8 (18)	63 (35)	0.035
Dyspnea	9 (4)	2 (4)	7 (4)	0.831
Other	9 (4)	2 (4)	7 (4)	0.831

(**Table** continued the next page.)

	Total (n=226)	Sex		P value
		Male (n=44)	Female (n=182)	
Cardiac biomarkers				
hs-cTnT, peak (ng/mL)	0.39 (0.17–0.77)	0.3 (0.12–0.59)	0.40 (0.16–0.77)	0.648
CK-MB, peak (ng/mL)	25 (16–37)	19 (13–42)	25 (15–37)	0.083
BNP, on admission (pg/mL)	217 (87–617)	200 (60–361)	263 (102–766)	0.678
WBC, peak ($\times 10^2$)	101 (71–137)	110 (78–189)	99 (69–131)	<0.001
CRP, peak (mg/dL)	4.2 (0.4–10.6)	8.0 (1.3–15.1)	3.8 (0.3–9.7)	0.869
Regional wall motion abnormality				
Apical	184 (81)	32 (73)	152 (84)	0.099
Mid–Apex	131 (58)	23 (52)	108 (59)	0.394
Apex	53 (23)	9 (20)	44 (24)	0.601
Mid-ventricular	25 (11)	7 (16)	18 (10)	0.253
Basal	2 (1)	0 (0)	2 (1)	0.485
Focal	15 (7)	5 (11)	10 (5)	0.160
LVEF (%)	47 (40–53)	45 (39–50)	48 (41–54)	0.198
Acute intensive care treatment				
IABP	9 (4)	1 (2)	8 (4)	0.518
NIPPV	14 (6)	2 (5)	12 (7)	0.613
Temporary pacemaker	6 (3)	1 (2)	5 (3)	0.266
Medications during hospitalization				
ACEI/ARB	83 (37)	15 (34)	68 (37)	0.686
β-blocker	47 (21)	11 (25)	36 (20)	0.444
Ca-antagonist	66 (29)	15 (34)	51 (28)	0.427
Diuretics	70 (31)	11 (25)	59 (32)	0.340
Complications				
Cardiogenic shock	14 (6)	1 (2)	13 (7)	0.229
Heart failure	41 (18)	7 (16)	34 (19)	0.668
VT/VF	9 (4)	4 (9)	5 (3)	0.053
AF	9 (4)	2 (5)	7 (4)	0.831
In-hospital death				
Cardiac	3 (1)	0 (0)	3 (2)	0.391
Noncardiac	8 (4)	3 (7)	5 (3)	0.190

Unless indicated otherwise, data are given as the median (interquartile range), or n (%). P value: male vs. ≥female. ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker; AF, atrial fibrillation; BNP, B-type natriuretic peptide; BP, blood pressure; Ca, calcium; CK-MB, creatine kinase-MB; CRP, C-reactive protein; ECG, electrocardiogram; IABP, intra-aortic balloon pumping; LVEF, left ventricular ejection fraction; NIPPV, noninvasive positive pressure ventilation; VT/VF, ventricular tachycardia/ventricular fibrillation; WBC, white blood cell.

Diagnostic concordance between them was based primarily on the Mayo Clinic and Inter TAK diagnostic criteria[3,10,11] (i.e., the presence of typical ECG changes, echocardiographic transient regional wall motion abnormality and the absence of total occlusion of the coronary artery). When eligibility for inclusion was uncertain, cases were reviewed by all members of the research team to reach consensus. All in-hospital events were assessed on the basis of a chart review. The Killip classification was used to define the condition of heart failure and Killip class III–IV was defined as severe heart failure in the present study. Cardiogenic shock was defined as systolic blood pressure <90 mmHg refractory to fluid resuscitation with clinical and laboratory evidence of end-organ dysfunction.[12] Cause of death was classified as either cardiac or noncardiac.

All patients were managed in accordance with the Declaration of Helsinki and comprehensive consent for disclosed information of the hospital was assumed to be obtained from the patients. The present study protocol was approved by the ethics committee of the hospital.

Statistical Analysis

Continuous variables that were not normally distributed are presented as the median and interquartile range (IQR), and those with a normal distribution are presented as the mean±SD. Categorical variables are presented as frequencies. Categorical variables were compared using Chi-squared or Fisher's exact tests. Two-sided P<0.05 was considered statistically significant.

Results

Patients' Characteristics

Baseline patient characteristics are presented in the **Table**. Median patient age was 80 years (IQR; 70–85 years). Of the 226 patients who underwent coronary angiography, there were 44 men (19.5%) and 182 women (80.5%). Among them, 197 patients did not have significant coronary artery disease. Although 22 patients had single-vessel coronary artery disease, 6 patients had double-vessel disease and 1 patient had triple vessel disease, none had total occlusion of the coronary artery suggestive of acute coronary syndrome. Moreover, the possibility of acute coro-

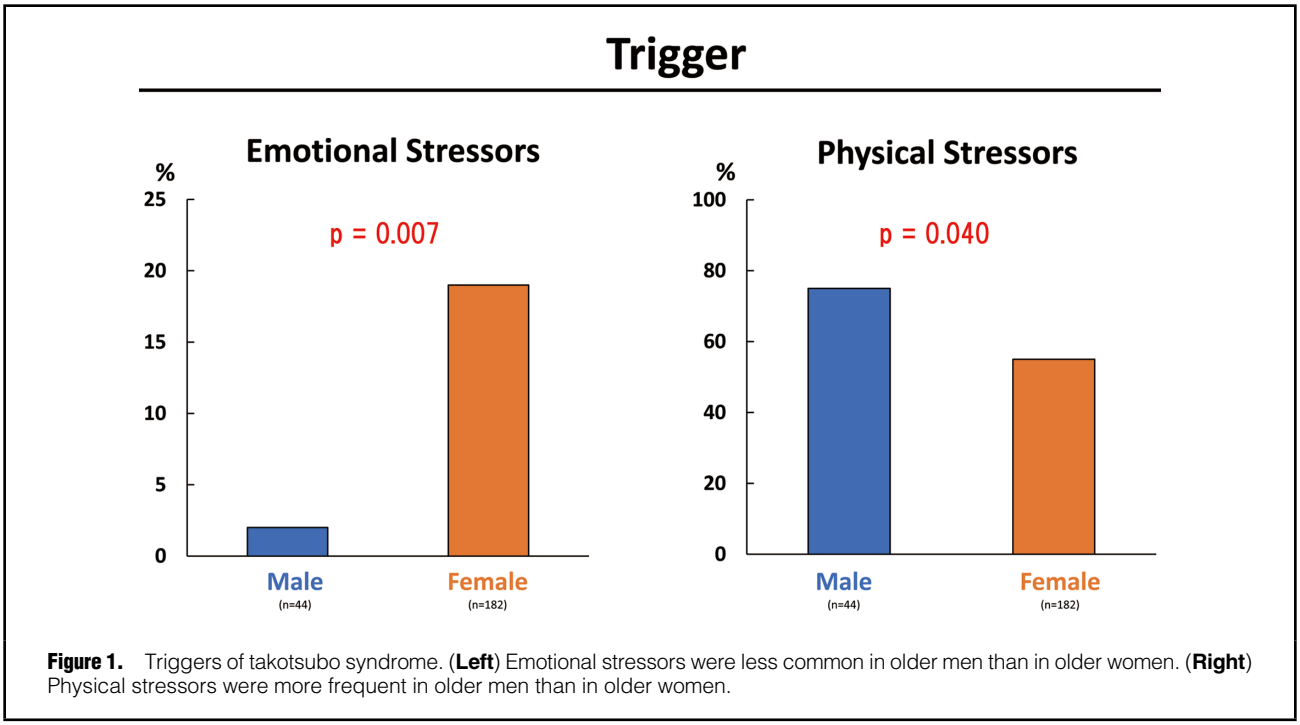

Figure 1. Triggers of takotsubo syndrome. (**Left**) Emotional stressors were less common in older men than in older women. (**Right**) Physical stressors were more frequent in older men than in older women.

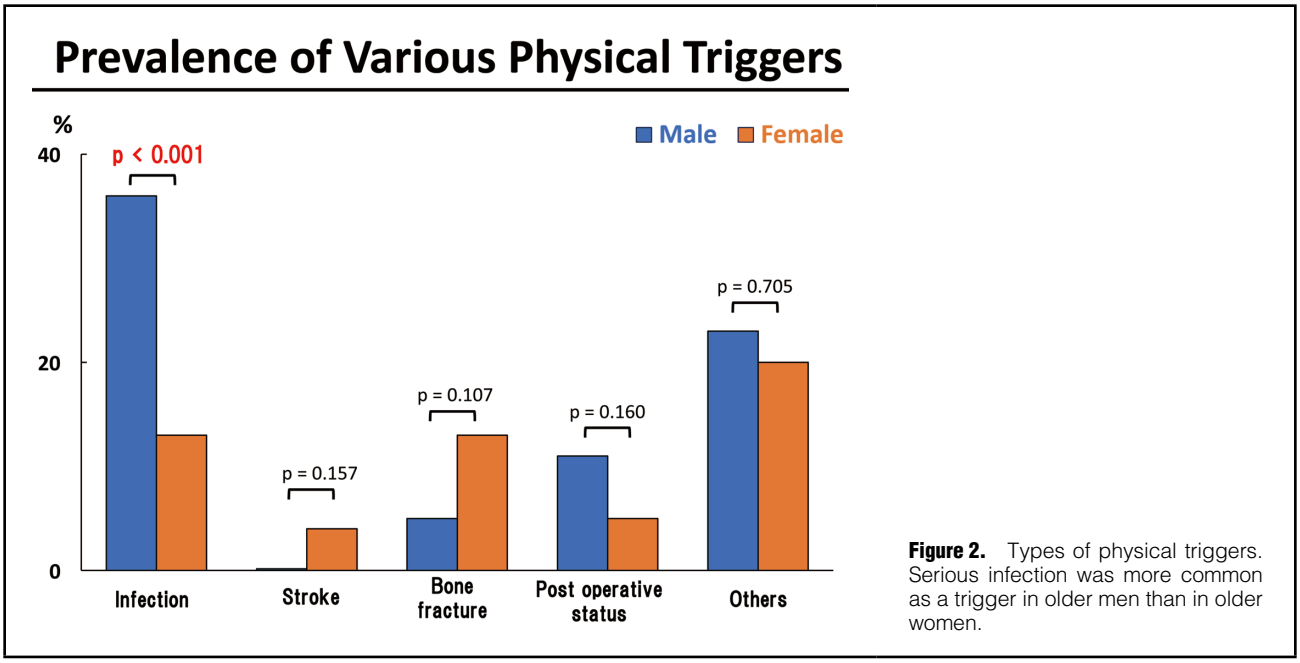

Figure 2. Types of physical triggers. Serious infection was more common as a trigger in older men than in older women.

nary syndrome was firmly excluded because of a total recovery in left ventricular wall motion abnormalities within a few weeks in all 29 patients. Acute myocarditis was also excluded based on the absence of significant elevation of myocardial biomarkers, including hs-cTnT and CK-MB, or inflammatory markers, as well as the total recovery in wall motion abnormalities.

Triggers of TTS

Preceding emotional and physical triggers of TTS were identified in 174 patients (77%); emotional triggers in 35 patients (15%) and physical triggers in 139 patients (62%). Emotional triggers were extremely less common in older men than in older women (2% vs. 19%; P=0.007; **Table**, **Figure 1**), but physical triggers were more frequently found in older men than in women (75% vs. 58%; P=0.040; **Figure 1**). Most of the physical triggers were acute critical illnesses, such as serious infection, stroke, and bone fracture. Serious infection, in particular respiratory infection, was more common in older men than in women (36% vs.

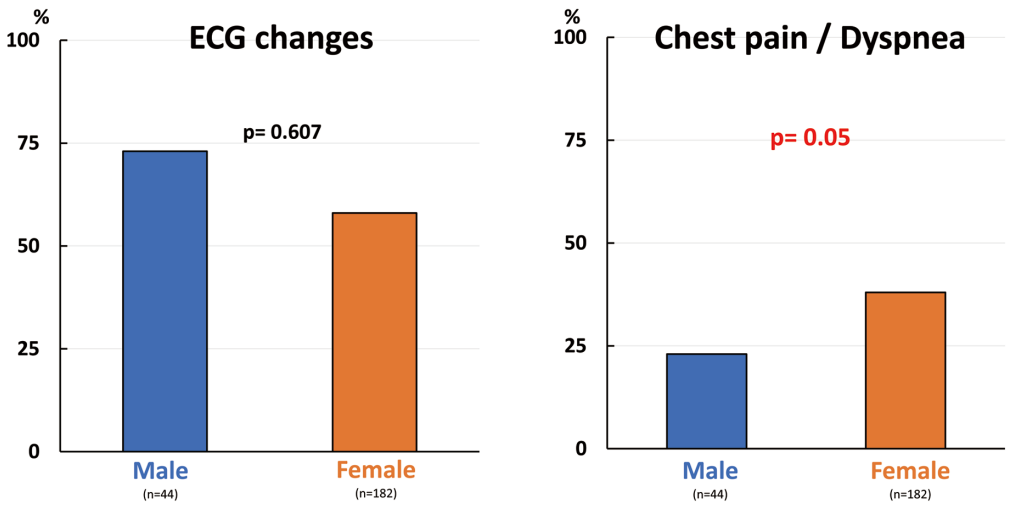

Figure 3. Initial clues to the diagnosis of takotsubo syndrome. (**Left**) Prevalence of ECG changes was similar in older men and older women. (**Right**) Prevalence of subjective symptoms including chest pain and/or dyspnea was lower in older men than in older women. Dx, diagnosis; ECG, electrocardiographic.

13%; P<0.001; **Table**, **Figure 2**). There were 52 patients (23%) in whom emotional and physical triggers of TTS were not identified.

Initial Clues to the Diagnosis of TTS

As initial clues to the diagnosis of TTS, 12-lead ECG changes, including ST-segment elevation, T-wave inversion and prolongation in the QT interval, and subjective symptoms such as chest pain and dyspnea were evaluated (**Table**). Of the 226 patients, 137 (61%) were initially suspected to have TTS based on ECG changes, and 80 patients (35%) were initially suspected to have TTS based on symptoms of chest pain and/or dyspnea. There were 9 other patients who were found to have TTS because of a modest elevation of hs-cTnT (2 patients) and echocardiographic regional wall motion abnormalities (7 patients). The 137 patients who were suspected to have TTS based on ECG changes also had subjective symptoms other than chest pain and/or dyspnea, mostly related to the acute critical illnesses at the time of admission. The 80 patients who were suspected to have TTS based on the presence of chest pain and/or dyspnea were later found to have ECG changes indicative of TTS. In addition, the percentage of patients suspected to have TTS based on subjective symptoms was significantly lower among older men than older women (23% vs. 38%; P=0.050; **Table**, **Figure 3**). Older men were more frequently found to have T-wave inversion as an initial ECG change than older women (48% vs. 29%; P=0.018; **Table**, **Figure 4**).

Transient Regional Wall Motion Abnormalities

Apical ballooning occurred in 184 patients (81%); 131 patients had somewhat broader apical ballooning extending to the mid-ventricular segment and 53 patients had ballooning limited to the apical segment; 42 patients (19%) had non-apical wall motion abnormalities: 25 with the mid-ventricular form, 15 with the focal form, and 2 with the basal form. There was no significant difference in the prevalence of apical ballooning between older men and women (73% vs. 84%). The prevalence of non-apical wall motion abnormalities also did not differ significantly between older men and women (27% vs. 16%). All these forms of abnormal left ventricular wall motion were transient and showed complete recovery at the time of patient discharge, with the exception of those patients who died during hospitalization.

Left ventricular ejection fraction (LVEF) was slightly reduced in total TTS population (47% [IQR: 40–53%]; **Table**). There was no significant difference in LVEF between older men (45% [IQR: 39–51%]) and women (48% [IQR: 41–54%]).

Comorbidities

Several comorbidities were more frequently found in older men than in older women, including current tobacco use (45% vs. 7%, P<0.001; **Table**), pulmonary disease (25% vs. 12%, P=0.030), malignant disease (34% vs. 14%, P=0.002), and coronary artery disease (13% vs. 5%, P=0.038).

Acute Intensive Care Treatment

A total of 9 patients were treated with intra-aortic balloon pumping (IABP), 14 patients with noninvasive positive pressure ventilation and 5 patients with a temporary pacemaker. There were no significant differences in the frequency of these intensive treatments between older men and women.

Medications

Details of medications used during the course of hospitalization, including angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, β-blockers, calcium

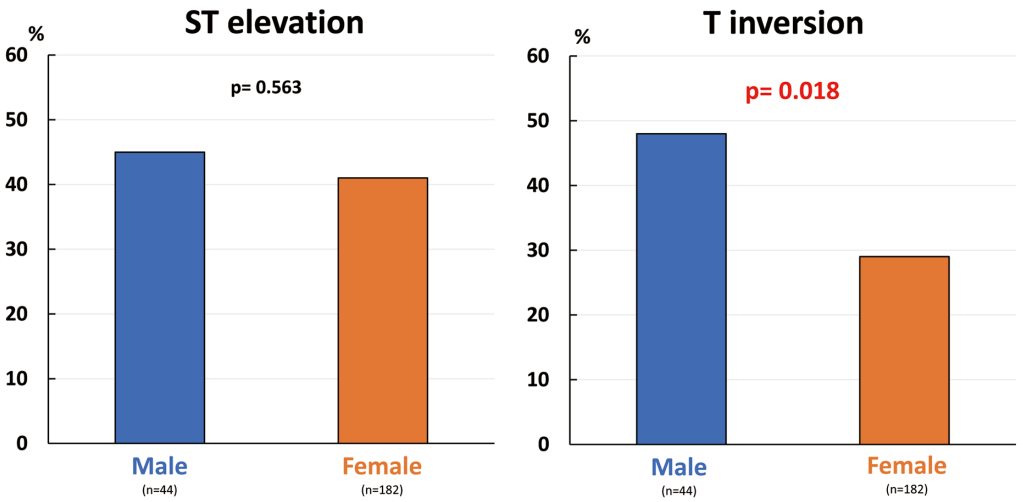

Figure 4. Initial ECG changes. (**Left**) ST-segment elevation was similarly found in older men and older women. (**Right**) T-wave inversion was more frequently found in older men than in older women.

antagonists, and diuretics, are shown in the **Table**. There were no significant differences in the prescription rate of these medications between older men and women.

Complications

Across the entire study cohort, 14 patients (6%) had cardiogenic shock and 41 patients (18%) had severe heart failure as complications (**Table**). There were no significant differences in the frequency of these complications between older men and women. Among all 226 patients, 18 (8%) experienced serious arrhythmic events: 9 patients experienced ventricular tachycardia and/or ventricular fibrillation and 9 patients experienced atrial fibrillation (**Table**). Although statistically not significant, ventricular tachycardia and/or ventricular fibrillation seemed more common in older men than in older women.

In-Hospital Outcomes

In-hospital outcomes for the entire cohort, as well as for older men and women separately, are shown in the **Table**. In-hospital deaths were recorded for 11 patients (5%): cardiac death in 3 patients (1%) and noncardiac death in 8 patients (4%). The rate of all-cause death was 7% in male patients and 5% in female patients. There were no significant differences in the frequency of in-hospital deaths between older men and women.

Discussion

This is the first study to focus on the clinical characteristics of older men with TTS and the main results are summarized as follows. Approximately 20% of the predominantly older TTS study population was male and, as the triggering event, emotional stress was extremely uncommon in older men with TTS than in older women with TTS. On the other hand, physical stress was more common in older men with TTS, compared with older women with TTS. In-hospital complications and deaths occurred at similar rates in older men and women.

A consistent observation in previous studies of TTS has been the marked predominance of postmenopausal women.[3–7,9] Approximately 90% of TTS cases occur in women, whereas men comprise approximately 10% of the TTS population.[13–15] Although the reason why older women are disproportionately affected is poorly understood, these observations can be explained in part by the influences of aging and sex on the sympathetic nervous system. Resting sympathetic nervous system activity seems to be particularly elevated in older women,[16] and the declining cardioprotective effects of estrogen may lead to a higher incidence of TTS in postmenopausal women, particularly during the episodes of a hypersympathetic response to stress with excessive catecholamine release.[17–20] The present study with 226 older adult patients (age: median 80 years [range 70–85 years]) revealed that the percentage of men among patients with TTS was approximately 20%. Although the reason for the higher proportion of men with TTS in the present study, as compared with studies in Western countries, is not known, the number of men seems higher in other studies from Asia. Murakami and colleagues reported 368 patents with TTS (age: median 76 years [range 67–82 years]) from the Tokyo CCU Network database and showed 22.8% of them were men.[21] Yoshizawa and colleagues also reported 344 patients with TTS (age: mean 71.6±11.2 years) and showed that 21.2% were men.[22] As in the present study, the average age of the patients from these studies from Japan is significantly older than that of the patients in studies from Western countries (Inter TAK Registry: mean age, 66.4±13.1 years;[6] The National Inpatient Sample database in the United States [2008–2009]: median age, 65.6 years [range 64.9–66.2 years][23]). It is possible that this age differ-

ence between Japan and Western countries could have led to the somewhat higher prevalence of men in the present study.

With regard to the prevalence of triggering stress, emotional triggers were extremely uncommon in older men whereas physical triggers were more common compared with women in the present study. Although previous studies have reported less frequent emotional triggers in men, ranging around 10–20%,[6,21,22,24] it is difficult to explain the extremely low prevalence of emotional triggers (2%) in the present study. It is possible that older age, relative to the TTS population in previous studies, may have contributed to a relatively lower prevalence of emotional triggers in men in the present study. Because of a lower resting sympathetic tone in older men compared with older women,[16] it may be postulated that the stronger noradrenergic stimulation caused by a physical trigger is needed to precipitate TTS in older men with their lower susceptibility. When physical triggers were further defined, serious infections such as pneumonia were more common in older men with TTS as compared with older women with TTS. A triggering stress was not identified in approximately one-quarter of the older men and women with TTS.

In the present study, in-hospital complications and deaths occurred at similar rates in older men and women with TTS, which is not in agreement with previous studies showing a high prevalence of in-hospital complications such as cardiogenic shock and serious arrhythmias as well as higher in-hospital deaths in men.[24] Lemor and colleagues reported a higher probability of acute complications and higher in-hospital mortality rate in men with TTS.[25] Templin and colleagues also reported higher mortality rates in younger men with physical triggers.[6] However, several recent studies indicated the importance of age-specific clinical characteristics of patients with TTS.[26,27] Thus, the association between age and the in-hospital outcomes in TTS should be taken into account. Cammann and colleagues examined age-specific differences in presentation and outcomes in TTS in 2,098 patients from the Inter TAK Registry and showed no significant difference in in-hospital mortality rates among different age groups.[27] At the same time, they found that younger patients were the sickest and were more likely to have in-hospital complications than older patients. More importantly, Templin and colleagues found that older age (>70 years) was associated with fewer in-hospital complications and all-cause deaths than younger age (<70 years).[6] The average age of men in previous studies (Inter TAK Registry: mean age, 62.9±13.1 years;[6] The National Inpatient Sample database in the United States (2006–2016): mean age, 61.6±16.2 years[25]), which reported higher in-hospital complications and mortality rate in men, was significantly younger than that of the men in the present study (median age, 77 years [range 65–84 years]). It is therefore possible that the older age of the men in the present study may have contributed to results differing from the several previous studies, leading to similar in-hospital complications and outcomes in the older men and women with TTS.

Sex-based differences among patients with TTS under long-term observation have been rarely reported. Recently, Arcari and colleagues reported in their retrospective study that the long-term mortality rate was similar in men and women, although they speculated the possibility that a minority of men with TTS might have worse outcomes than women.[24] However, the long-term prognosis in the older population with TTS remains unresolved. The results of the present study were also limited to in-hospital outcomes, so further studies on long-term prognosis are needed to clarity sex-based differences among older patients with TTS.

Study Limitations

This was a retrospective study performed in a single institution and thus suffers from inherent limitations. In addition, although the study enrolled 226 patients, including 44 older male patients, the number of the patients was modest compared with numbers in recent multicenter studies. However, this was the first study focusing especially on older men in TTS.

Conclusions

Approximately 20% of older patients with TTS were male, and an emotional trigger of TTS was extremely uncommon in older men, which is a new finding. Despite frequent presence of comorbidities and physical triggers in older men, in-hospital complications and deaths occurred in similar proportions of older men and women.

Acknowledgments

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Disclosures

None of the authors has conflicts of interest to disclose. This study did not receive any specific funding.

IRB Information

Ethics Committee of Chikamori hospital, Reference number: 368.

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