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Age-sex effect on in-hospital complications and mortality in patients with Takotsubo syndrome. Insights from the National Inpatient Sample

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Ethics approval and consent to participate: this study analyzed the National Inpatient Sample (NIS), a database produced by the Agency for Healthcare Research and Quality (AHRQ). Developed under the AHRQ Healthcare Cost and Utilization Project, the NIS includes administrative and demographic data from a 20% sample of inpatient hospitalizations in the United States, and has been compiled annually since 1988 through a partnership between multiple statewide data organizations to contribute all-payer healthcare utilization data annually. International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification diagnostic and procedural codes were used to identify the study population. Institutional review board approval is not needed, as all patient information was de-identified.

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Abstract

Age and sex differences in Takotsubo syndrome (TTS) are still a matter of debate. The present study aimed to evaluate the difference in cardiovascular (CV) risk factors, CV disease, in-hospital complications, and death within different sex-age groups. Using the National Inpatient Sample database between 2012 and 2016, 32,474 patients older than 18 years of age hospitalized with the primary diagnosis of TTS were identified. A total of 32,474 patients were enrolled; 27,611 (85.04%) were female. CV risk factors were higher in females, while CV diseases and in-hospital complications were significantly higher in males. The mortality in males was twice as high as that of female patients (9.83% *versus* 4.58%, p<0.01), and in the logistic regression model after adjustment for confounders, the odds ratio (OR) was 1.79, the confidence interval was 1.60-2.02, and p<0.01. After dividing the group based on age, in-hospital complications were inversely related to age in both sexes, and the length of in-hospital stay was double in the youngest group compared to the oldest one. Mortality increased progressively with age in both groups but was constantly higher in males for each age group. Multiple logistic regression analysis for mortality was performed for the two sexes separately and for the three age groups, considering the youngest one as the reference group. In females, the OR was 1.59 and 2.88, respectively, for groups 2 and 3; for males, the OR was 1.92 and 3.15, all of them statistically significant (p<0.01). In-hospital complications were more common in younger patients with TTS, particularly in males. Mortality was positively correlated with age for both sexes, but mortality was higher in males compared to females in all age groups.

Introduction

The clinical presentation of Takotsubo syndrome (TTS) is quite similar to acute coronary syndrome (ACS), representing 1-3% of all patients with ACS, 5-6% of females suspected to have ST-elevation myocardial infarction [1-3], and 0.02% of the in-hospital patients in the United States [4]. TTS is a disease with temporary ventricle motion abnormalities, in particular apical akinesis and basal hypercontractility, with regional wall motion abnormalities extending beyond a single epicardial vascular distribution, triggered by emotional or physical stress, often affecting postmenopausal women, and induced by a surge in catecholamines [5-9]. Initially considered a benign disease, TTS is currently known

to be associated with life-threatening complications, and mortality is reported to be double that of ACS, in particular for those patients with physical triggers [10,11]. Although the pathology is considered to be typical of elderly women, a great number of complications are described in younger patients and in males in particular [8,12-15]. Currently, the increase in diagnosis is the result of a growing awareness of the disease, especially in younger patients, even if sex and age distribution in terms of outcomes have not been studied in detail [16,17]. We aim to illustrate in-hospital complications and mortality in a large cohort of patients with TTS diagnoses according to sex and age distribution.

Materials and Methods

Study population

The National Inpatient Samples (NIS) Database, from the Healthcare Cost and Utilization Project, is the largest nationally publicly available inpatient care database in the United States. NIS was used for information on TTS hospitalization and outcomes in terms of in-hospital complications and mortality. In the present study, 32,474 patients (27,622 females, 85%, and 4856 males, 15%) admitted between 2012 and 2016 [18], older than 18 years of age, were identified with a diagnosis of TTS based on the International Statistical Classification of Diseases and Related Health Problems (ICD-9-CM) code (ICD-9: 429.83 and ICD-10: I51.81) [19]. All patients with a primary diagnosis of TTS were included in this study. Patients with ICD-9 codes for ACS as their primary admitting diagnosis were excluded.

The NIS database contains baseline demographics (age, sex, year of admission), clinically relevant comorbidities [smoking status, diabetes mellitus, hypertension, hyperlipidemia, history of myocardial infarction, history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), atrial fibrillation/flutter, peripheral artery disease, and sepsis], in-hospital procedures and complications (cardiogenic shock, cerebrovascular accidents, acute kidney injury, mechanical ventilation, mechanical support, length of stay), and mortality for each patient coded by ICD-9 and ICD-10 [19].

Statistical analysis

The cohort of patients was first divided by sex and then stratified according to age into three age groups (group 1 <50 years, group 2 51-74 years, and group 3 >75 years). Baseline demographic and health characteristics were compared between sexes by the Chi-square test and Student's *t*-test for binary and continuous variables, and by the Chi-square test and analysis of variance test to assess differences between the three groups. Multivariable logistic regression analysis was used to calculate estimated odds ratios (OR) and 95% confidence intervals (CI) for the association between sex and in-hospital mortality after adjusting for age, comorbidities, and in-hospital complications [cardiovascular (CV) risk factors and CV disease] and then the effect of combined sex and age group (2-tailed $p<0.001$). A second multivariable logistic regression analysis was performed by sex and age groups, considering the youngest group in each sex as the reference group. The association between TTS and mortality was analyzed using α. Statistical analyses were performed using SAS version 9.4 (SAS, Cary, NC, USA) and STATA version 16 (STATA Corp, College Station, TX, USA). All tests were conducted using an $\alpha=0.05$ as the probability for a type I error.

Results

A cohort of 32,474 patients older than 18 years with a primary diagnosis of TTS was identified, 85% females and 15% males (4856 patients), who were younger (64±16 *versus* 68±13 years, $p<0.001$). It was found that there was a progressive increase in in-hospital admissions over time, either in males or females (Figure 1).

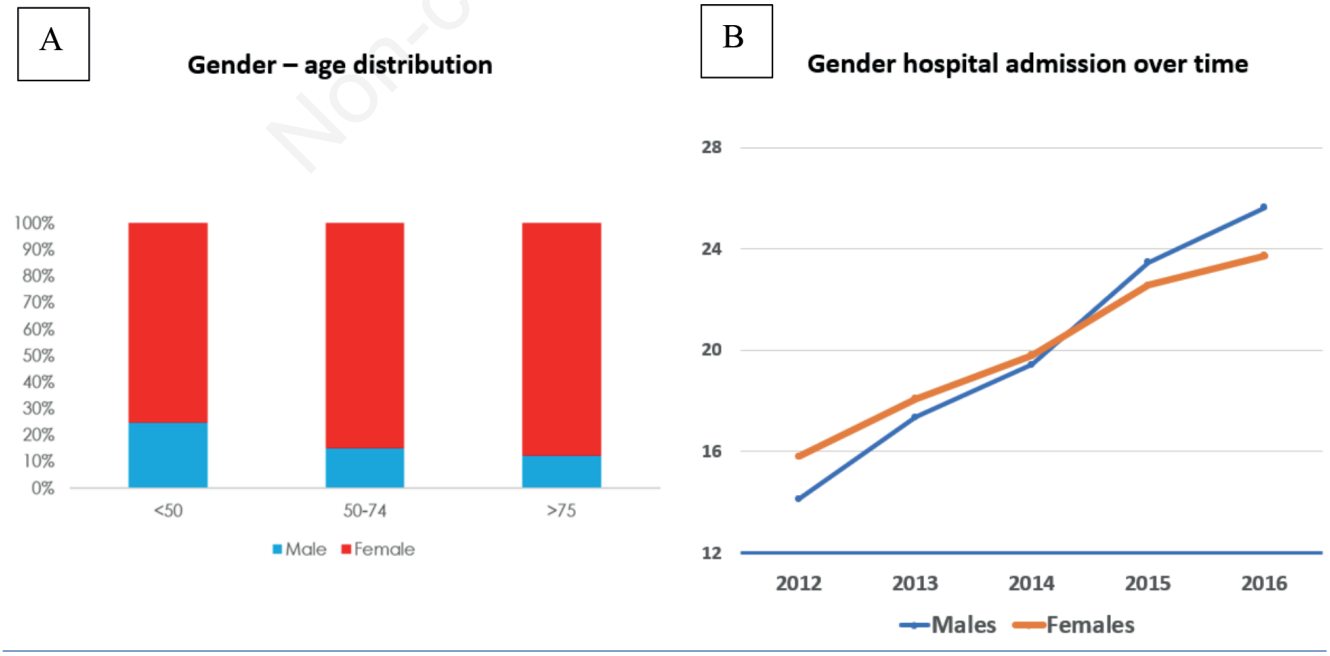

Figure 1. A) Sex-age distribution in patients with Takotsubo syndrome; B) hospital admission over time in males and females.

Males *versus* females' characteristics

CV risk factors, such as hyperlipidemia and hypertension, were significantly higher in females, while smoking was higher in males. There was no difference in diabetes among the sexes. All CV diseases (atrial fibrillation/flutter, CABG, PCI, and peripheral vascular disease) were significantly higher in males except for a history of myocardial infarction (Figure 2).

In-hospital complications were significantly higher in males, but mechanical support and mortality were almost double in males than in females (9.83% *versus* 4.58%, p<0.01) (Figure 3). The logistic regression model between males and females, after adjusting for

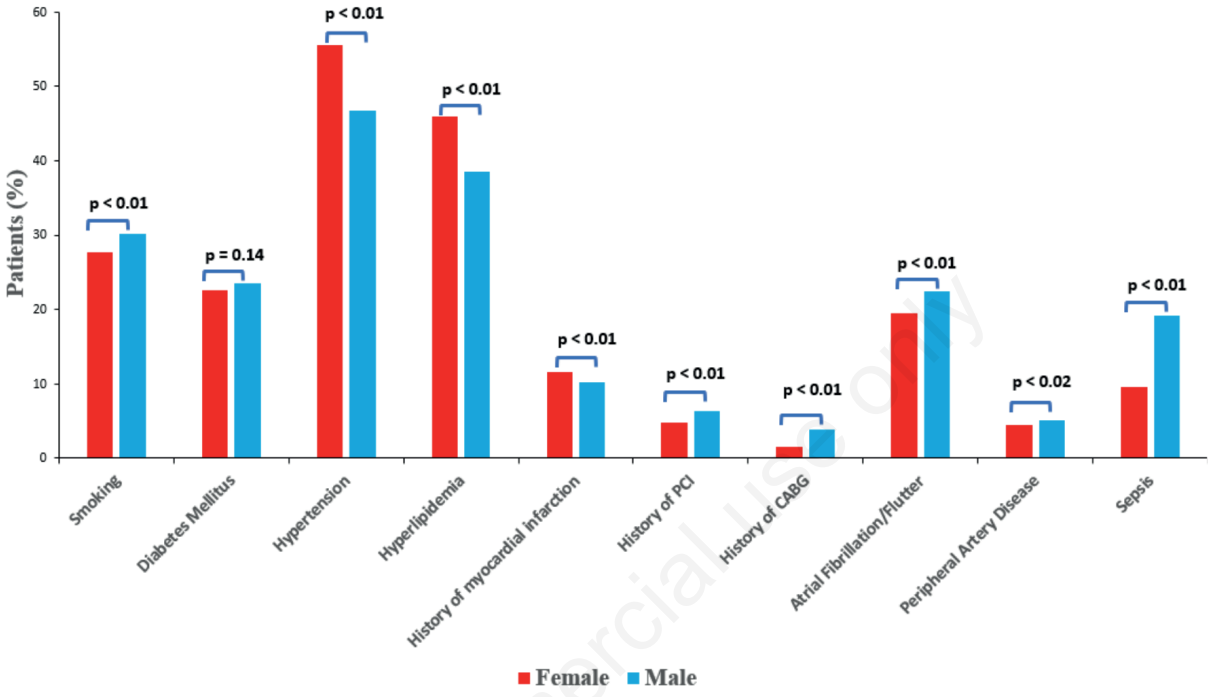

Figure 2. Cardiovascular risk factors and cardiovascular disease divided by sex. PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

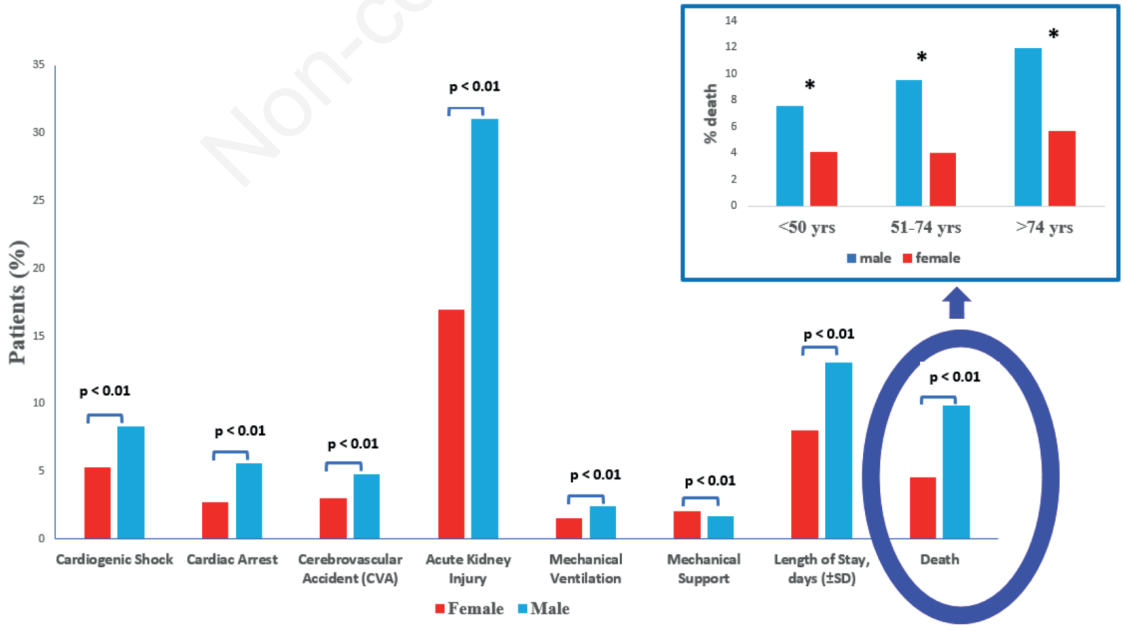

Figure 3. In-hospital complication. Small graph: difference in mortality between males and females for each age group; *p<0.01. SD, standard deviation.

age, CV risk factors, CV disease, and in-hospital complications showed that males still had significantly higher mortality (OR: 1.79; CI: 1.60-2.02, p<0.01).

Males and females divided by age

Males and females were divided by age: 10.86% <50 years old (group 1), 55.96% between 51-74 years old (group 2), and 33.18% >75 years old (group 3). In each age group, females were the most represented, and there was a progressive increase from group 1 to group 3: 75.5% in group 1, 85.2% in group 2, and 87.9% in group 3 (p<0.01).

CV risk factors and CV disease showed the same positive age relation in either males or females (Tables 1 and 2): diabetes, arterial hypertension, hyperlipemia, a history of myocardial infarction, a history of PCI, CABG, atrial fibrillation, and peripheral artery disease increased with age.

In-hospital complications

In males, in-hospital complications such as cardiac arrest, mechanical ventilation, and length of stay were inversely related to age, while acute kidney injury and death increased with age (Table 3). In females, cardiogenic shock, cardiac arrest, mechanical ventilation, mechanical support, and length of stay were more common in the younger group, while cerebrovascular accidents, acute kidney injury, and death increased significantly with age (Figure 3 and Table 4). In addition, males experienced more in-hospital mortality for each age group considered, compared to the corresponding female age group (Figure 3).

In the multiple logistic regression analysis, after full adjustment, mortality increased progressively with age, either in males or females, when compared to the youngest group considered the reference group (Tables 5 and 6).

Table 1. Baseline demographic and clinical characteristics for the male patients with Takotsubo syndrome.

	≤50 years	51-74 years	≥75 years	p value
n (%)	864 (17.79)	2695 (55.50)	1297 (26.71)	
Demographic characteristics				
Age, year (±SD)	38 (±9)	63 (±7)	82 (±5)	<0.01
Clinical characteristics				
Variables [n, (%)]				
Smoking	284 (32.87)	922 (34.21)	261 (20.12)	<0.01
Diabetes mellitus	105 (12.15)	637 (23.64)	499 (30.76)	<0.01
Hypertension	289 (33.45)	1,361 (50.50)	622 (47.96)	<0.01
Hyperlipidemia	174 (20.14)	1,035 (38.40)	663 (51.12)	<0.01
History of myocardial infarction	35 (4.05)	288 (10.69)	170 (13.11)	<0.01
History of PCI	14 (1.62)	166 (6.16)	127 (9.79)	<0.01
History of CABG	5 (0.58)	90 (3.34)	92 (7.09)	<0.01
Atrial fibrillation/flutter	64 (7.41)	533 (19.78)	495 (38.16)	<0.01
Peripheral artery disease	12 (1.39)	146 (5.42)	93 (7.17)	<0.01
Sepsis	167 (19.33)	522 (19.37)	240 (18.50)	0.80

SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Table 2. Baseline demographic and clinical characteristics for the female patients with Takotsubo syndrome.

	≤50 years	51 to 74 years	≥75 years	p value
n (%)	2661 (9.64)	15,475 (56.05)	9475 (34.32)	
Demographic characteristics				
Age, year (±SD)	42 (±7)	64 (±7)	82 (±5)	<0.01
Clinical characteristics				
Variables [n, (%)]				
Smoking	883 (33.18)	4,821 (31.15)	1,961 (20.70)	<0.01
Diabetes mellitus	387 (14.54)	3,557 (22.99)	2,278 (24.04)	<0.01
Hypertension	1,053 (39.57)	8,748 (56.53)	5,563 (58.71)	<0.01
Hyperlipidaemia	600 (22.55)	7,112 (45.96)	5,000 (52.77)	<0.01
History of myocardial infarction	192 (7.22)	1,740 (11.24)	1,253 (13.22)	<0.01
History of PCI	51 (1.92)	696 (4.50)	595 (6.28)	<0.01
History of CABG	13 (0.49)	205 (1.32)	188 (1.98)	<0.01
Atrial fibrillation/flutter	107 (4.02)	2,140 (13.83)	3,132 (33.06)	<0.01
Peripheral artery disease	35 (1.32)	606 (3.92)	577 (6.09)	< 0.01
Sepsis	317 (11.91)	1,459 (9.43)	860 (9.08)	< 0.01

SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Discussion

The results of the present paper are from one of the largest cohorts of patients (the NIS dataset) admitted with the primary diagnosis of TTS in the United States. The main findings are: i) patients less than 50 years of age were more likely to have in-hospital complications and a longer in-hospital stay, but ii) a lower mortality rate in comparison to the elderly subjects; iii) mortality was positively related to age in both sexes but always higher in males for each age group, including the youngest one.

TTS was described for the first time by a Japanese cardiologist 25 years ago, and since then it has been increasingly recognized [1-3,7]. Clinical presentation resembles acute myocardial infarction and shares similar in-hospital complications [20,21], but is typically characterized by transient systolic and diastolic dysfunction [22]. It is estimated that 4% of the patients admitted with symptoms of ACS are diagnosed as TTS, but the prevalence is likely higher due to misdiagnosis or not reporting [1,7,23]. It is known that TTS involves predominantly females, and more than 80% of them are older than 50 years of age. Currently, it is clear that both sexes, all ages, and ethnic groups are involved [24,25]. Although the number of young male patients with TTS is increasing, there is

Table 3. In-hospital complication and clinical outcome among male patients with Takotsubo syndrome.

Variables [n, (%)]	≤50 years	51 to 74 years	≥75 years	p value
Cardiogenic shock	81 (9.38)	230 (8.53)	92 (7.09)	0.14
Cardiac arrest	65 (7.52)	148 (5.49)	58 (4.47)	0.01
Cerebrovascular accident	42 (4.86)	117 (4.34)	73 (5.63)	0.20
Mechanical ventilation	319 (36.92)	821 (30.46)	269 (20.74)	<0.01
Mechanical support	21 (2.43)	66 (2.45)	29 (2.24)	0.92
Length of stay, days (±SD)	9.9 (±16)	9.7 (±14)	8.1 (±8)	<0.01
Acute kidney injury	263 (30.44)	803 (29.80)	442 (34.08)	0.02
Death	65 (7.54)	257 (9.54)	155 (11.95)	<0.01

SD, standard deviation.

Table 4. In-hospital complication and clinical outcome among female patients with Takotsubo syndrome.

Variables [n, (%)]	≤50 years	51 to 74 years	≥75 years	p value
Cardiogenic shock	169 (6.35)	860 (5.56)	429 (4.53)	<0.01
Cardiac arrest	160 (6.01)	402 (2.60)	196 (2.07)	<0.01
Cerebrovascular accident	85 (3.19)	401 (2.59)	341 (3.60)	<0.01
Mechanical ventilation	670 (25.18)	2,579 (16.67)	1,141 (12.04)	<0.01
Mechanical Support	55 (2.07)	259 (1.67)	115 (1.21)	<0.01
Length of stay, days (±SD)	7 (±10)	6 (±8)	6 (±6)	<0.01
Acute kidney injury	381 (14.32)	2,356 (15.22)	1,938 (20.45)	<0.01
Death	109 (4.10)	622 (4.02)	534 (5.64)	<0.01

SD, standard deviation.

Table 5. The risk of death among male patients after adjustment of the differences in the baseline demographic and health characteristics. Logistic regression model was used to adjust for the baseline characteristics and complications at the time of presentation.

Age	Odds ratio	95% confidence interval	p value
≤50 years	Reference	-	-
51 to 74 years	1.92	(1.39-2.65)	<0.01
≥75 years	3.15	(2.17-4.57)	<0.01

Table 6. The risk of death among female patients after adjustment of the differences in the baseline demographic and health characteristics. Logistic regression model was used to adjust for the baseline characteristics and complications at the time of presentation.

Age	Odds ratio	95% Confidence interval	p value
≤50 years	Reference	-	-
51 to 74 years	1.59	(1.25-2.02)	<0.01
≥75 years	2.88	(2.24-3.72)	<0.01

still relatively little knowledge for a full understanding of the differences among these groups [3,24,26].

In our cohort, the overall percentage of males was 15%, but they were 32% in the youngest group, and, overall, they were younger than females. In both sexes, there was a progressive increase in hospital admissions over time [14,20,27,28]. We found that in patients with TTS, in-hospital complications were higher in the younger groups in both sexes, in particular in males, as also reported by others [14,15,27]. The only in-hospital complication related to age in both sexes, besides death, was acute kidney injury, which is known to be 3- to 8-fold more frequent in patients older than 60 years with multifactorial etiology [29]. Moreover, acute kidney injury is independently associated with in-hospital mortality [30].

In the present study, as previously mentioned [6,9,14,31], there has been an increase in mortality with an increase in age in both sexes, but mortality was higher in males and, interestingly, was still higher in men and in the younger age group. Bertin *et al.,* in a group of TTS females, found more in-hospital complications in the younger patients, but mortality was higher in the older group [15]. Misumida *et al.,* in 22,818 patients with TTS from the NIS database (2010-2014), of whom 92% were female, found the same results [31]. The authors demonstrated that an increase in mortality was associated with higher comorbidities that likely precluded coronary angiography, which was, according to their results, one of the factors in favor of increased death. On the other hand, Cammann *et al.* [14] from the InterTAK registry, after dividing the population into three age groups, found no significant difference in death among them but rather in-hospital complications that were higher in the youngest ones. From a different NIS database period [26,31,32] death was constantly higher in males. These data were also confirmed by the work of Vincent *et al.,* who reported a 2.5-fold increase in in-hospital mortality in males [24], and the same results were described by Pérez-Castellanos *et al.* (4.4% males *versus* 0.2% females, $p<0.01$) [33]. Also, the International Multicenter GEIST Registry [25] reported higher mortality in males as the overall cohort or in the group where patients with TTS were matched with a control group. Murakami *et al*. [27], on the other hand, described a higher prevalence of in-hospital complications in their male group as all causes of death, while CV death was higher in females, though death was not statistically significant.

We need to consider several factors when considering why males had higher in-hospital complications and mortality. In terms of complications in the younger population, Cammann *et al*. hypothesized that the higher heart rate at presentation in their younger patients was the expression of extensive sympathetic stimulation, but the better outcome could be counterbalanced by a relatively "healthier status" [14]. Sympathetic stimulation and alterations in the autonomic nervous system are considered to be the background of TTS. The more favorable outcome in the younger population, in addition to lower CV risk factors and CV disease, could also be explained by the sympatholytic effect of estrogens [34,35] and prevent endothelial dysfunction [36]. High estrogen concentrations can be protective for pre-menopausal women, given the lower percentage of complications and eventually death on the one hand, but insufficient to protect the corresponding age-male group, who had a higher prevalence of in-hospital complications, supporting the theory of different responses to stress in the two sexes. Complications and death in males can also be determined by the inflammatory status that is reported to be higher in males [20,27] and an increased concentration of white blood cells was independently associated with CV death, suggesting that it could also be used to identify severe TTS [27]. Moreover, estrogens also protect against myocardial inflammation following myocardial infarction, as found in animal models [37]. In addition, the different stressors can play a role since TTS in males is caused mainly by physical triggers such as acute respiratory failure, cerebrovascular accidents, infections, and postoperative trauma, which means an underlined clinical pathology and a more fragile patient, while in females the stressor is more likely to be emotional [10,20]. Physical triggers have also been linked to higher norepinephrine levels in patients with TTS that might worsen TTS in males, who are otherwise less prone to develop the syndrome compared with their postmenopausal female counterparts.

We found that CV risk factors were higher in females, but CV diseases were higher in males, and they increased according to age in both sexes. This pathological background could play a role in short- and, in particular, long-term prognosis. Several studies reported that death is more common in patients with TTS and a higher prevalence of CV risk factors/disease [11,12], and these risk factors should be considered in the equation of a TTS patient's outcome [17,38,39]. This was also underlined by the InterTAK prognostic score [11], and by the factors related to the absence of early recovery [40]. Citro *et al.* reported the worst outcome in patients with TTS and biventricular involvement who also had higher comorbidities by the Charlson comorbidity index [6]. The same association was reported by Cammann *et al*. [14], who described an increased prevalence of hypertension, diabetes mellitus, hypercholesterolemia, chronic obstructive pulmonary disease, and cancer in elderly patients who had a relatively higher percentage of death. In our case, higher mortality in males could be in part explained by the higher prevalence of smoking and CV disease (CABG and PCI, atrial fibrillation/flutter, and peripheral artery disease), although the male group was significantly younger than females. This reflects sex differences in CV disease and might play a role in the TTS outcome. In males, CV risk profiles increase linearly over time as part of the atherosclerotic process. Females are protected during fertile age due to estrogen benefits, and CV risk factors and disease increase exponentially after menopause. Consequently, coronary syndrome is 3-4 times more common in men less than 60 years of age, while it is more common in women over 75 years of age [41].

This study has limitations previously reported by other authors who used the same NIS data set [26,31,32]. First of all, this is a retrospective study based on administrative data using ICD coding, and the accuracy of the diagnosis relies entirely on proper coding. Second, the NIS database does not give information on important clinical predictors such as laboratory data in general and cardiac biomarkers in particular; electrocardiographic and echocardiographic findings are also not available. Third, there are no reported clinical predictors like disease severity, left ventricular ejection fraction at baseline, or type of stressor. Fourth, specific medical management is not available, and finally, no long-term outcome is available. All of these points are listed in the previous NIS papers.

Conclusions

In conclusion, in-hospital complications were more common in the younger patients with TTS, particularly in males, but mortality was positively correlated with age for both sexes. Nevertheless, mortality was higher in males regardless of age, even after full adjustment for confounders. These data underline that CV risk factors and CV disease should be considered in the risk stratification of these patients. In particular, males, independent of age, are at higher risk for the worst in-hospital outcomes, including mortality, with the need for close monitoring.

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