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Cardiac arrhythmias and In-hospital mortality amongst patients with takotsubo cardiomyopathy: A retrospective study in an Italian population

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ABSTRACT

Background: Takotsubo cardiomyopathy (TTC) is an acute non-ischemic cardiomyopathy classically associated with an intense emotional or physiologic trigger. Data on the relationship between arrhythmias and mortality in TTC have been limited by small sample sizes. The aim of this study is to assess the impact of ventricular and atrial arrhythmias and advanced atrioventricular block on in-hospital mortality in a large inpatient population with TTC.

Methods: Data was obtained from the Italian National Healthcare System Databank from 2009 to 2016. Patients with TTC were identified using diagnosis codes and clinical characteristics were collected, with a primary outcome of mortality. Univariate and multivariate logistic regression analyses were used to identify significant predictors for mortality, and patients with TTC were further analyzed according to sex and age.

Results: There were 10,861 patients with TTC; 91.7% were women (9959) and the mean age was 70.7 +/− 11.9 years. The mortality rate was 2.2%; while 1.2% of patients had ventricular arrhythmias, 10.0% had atrial arrhythmias, and 1.3% had advanced atrioventricular block. Male sex, increased age and ventricular arrhythmias were predictors of mortality. In a sex-stratified analysis, ventricular arrhythmias and advanced age remained independent predictors for mortality in women.

Conclusion: In this large retrospective analysis, male sex and the presence of ventricular arrhythmias are strong predictors of mortality in patients hospitalized with TTC.

1. Introduction

Takotsubo cardiomyopathy (TTC) has become increasingly recognized as a type of non-ischemic cardiomyopathy, particularly in hospitalized patients, since it was first described in the 1990′s in Japan.[1] TTC is characterized by acute left ventricular systolic and diastolic dysfunction with transient wall motion abnormalities without a culprit coronary stenosis or other concurrent diagnoses including hypertrophic cardiomyopathy or myocarditis. *Takotsubo* refers to the traditional Japanese octopus pot, to depict the appearance of the left ventricle in most common form of TTC, with ballooning of the left ventricular apex and preserved function of the basal segments [1]. It is most commonly seen in elderly women and typically is associated with an intense emotional or physiologic trigger resulting in a sudden increase in adrenergic tone, although it has been described without an identifiable stressor as well [2–5]. The sudden rise in adrenergic tone is thought to cause microvascular dysfunction and myocardial stunning, however the pathogenesis of TTC remains controversial [6]. The clinical presentation of TTC along with the electrocardiogram (ECG) and cardiac biomarkers can be indistinguishable from that of an acute myocardial infarction, particularly upon initial presentation [2–7]. Angiographically, however, they are readily distinguished as TTC will demonstrate wall motion abnormalities, typically extending beyond a single epicardial vessel distribution, in the absence of culprit atherosclerotic coronary artery disease [3].

An important characteristic of TTC is the rapid, and often, complete recovery of left ventricular function once the acute phase of the syndrome has ended. This has led to the common belief that TTC is a relatively benign and reversible condition [8]. However, in-hospital mortality of patients with TTC has been demonstrated to be as high as 4.1%, predominantly as the result of cardiovascular

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causes [5,9]. In particular, life threatening arrhythmias (LTAs) have been reported to occur in 1.8% to 13.5% of hospitalized patients with TTC as well as an increased frequency of cardiogenic shock [5,10,11]. LTAs, including ventricular tachycardia, ventricular fibrillation, asystole, and pulseless electrical activity, have been associated with increased major adverse cardiovascular events (MACE), however these data have been limited by smaller sample sizes [9,12]. The largest of which included a recent analysis of the GEIST registry with 906 total patients with TTC demonstrated the adverse impact of ventricular arrhythmias and brady-arrhythmias on long-term and short-term outcomes [13]. In addition to LTA's, there is an increased risk of developing atrial arrhythmias in patients with TTC due to transient left atrial dysfunction in the acute phase of the disease [14]. Smaller studies have been conflicting with respect to the impact of atrial fibrillation on long-term and short-term mortality [15]. A single-center study of 114 patients with TTC demonstrated that nearly 1 out of 5 patients with TTC have atrial fibrillation with it being an independent risk factor of morality while a single-center study of 214 patients did not demonstrate such an impact [16,17]. The purpose of this study is to define the incidence of TTC in a large inpatient healthcare system and to further assess the impact of ventricular and atrial arrhythmias and advanced atrioventricular block on in-hospital mortality.

2. Methods

2.1. Study Population:

Data was obtained from the Italian National Healthcare System Databank (Banca dati SDO), which captures all patient hospital admissions in Italy and includes the following data: baseline patient demographics, admission type (emergency, urgent or elective), up to five primary and secondary diagnoses, up to five in-hospital interventions, length of hospital stay and status upon discharge. Data from 2009 to 2016 were queried and all patients with a primary diagnosis at discharge of TTC (ICD9 code 429.83) were identified for analysis.

2.2. Study variables

Following identification of patients with TTC, patient demographics, the length of hospitalization and the presence of arrhythmias were described according to ICD9 secondary diagnosis codes (see Supplementary Material). Atrial arrhythmias included atrial fibrillation and atrial flutter; ventricular arrhythmias included ventricular tachycardia, ventricular fibrillation, and ventricular flutter; while high degree block comprised complete heart block and second-degree atrioventricular block type II. Furthermore, subjects who suffered a cardiac arrest were also identified.

2.3. Outcomes:

The primary outcome was in-hospital mortality for the study group.

2.4. Statistical Analysis:

Continuous variables are shown as means with standard deviations while categorical variables are presented with frequency and percentages. A two-tailed p value of<0.05 defined statistical significance. Univariate logistic regression analyses were used to identify significant predictors for mortality. Secondarily, all significant univariate predictors for mortality were included in a multivariate logistic regression model using a stepwise approach to define independent predictors of mortality. Patients were subsequently categorized according to their sex and the relationship between patient each variable and inpatient mortality was evaluated in both men and women, separately. Patients were further stratified into age quartiles and the frequency of arrhythmias as well as mortality and length of stay were described within each quartile. Multivariate logistic regression analyses were used to identify predictors of mortality within each age stratum, as well. All statistical analyses were carried out using Stata 13.0 (StataCorp).

3. Results:

3.1. Study group

From 2009 to 2016, a total of 10,861 patients were identified with a diagnosis of TTC. The patient's clinical characteristics are described in Table 1. As expected, patients were predominantly women, comprising 91.7% of the overall cohort, and they tended to be older with an overall mean age of 70.7 +/- 11.9 years. The length of hospital stay was, on average, 8.3 +/- 8.6 days. The in-hospital mortality rate was 2.2% amongst the entire study population. The presence of atrial arrhythmias was markedly more common than ventricular arrhythmias. Nearly 10% of patients had atrial arrhythmias with atrial fibrillation representing the most prominent etiology. Conversely, 135 total patients had ventricular arrhythmias (ventricular tachycardia = 90, ventricular fibrillation = 43, ventricular flutter = 2), comprising 1.2% of the overall study population. Advanced atrioventricular block was identified in 1.3% of patients (136 patients), nearly three-quarters of which were due to complete heart block (108 patients) with the remainder due to second degree Mobitz II block.

3.2. Predictors of inpatient mortality

Male sex, advanced age, and the presence of ventricular arrhythmias were all univariate predictors of mortality in hospitalized patients with TTC (Table 2). Following multivariate analysis, they remained significant independent predictors of mortality (Table 3). Men had over two-fold increased odds of death (OR 2.32, CI 1.65–3.27, p < 0.001). Additionally, when examined as a

Table 1
Clinical Characteristics.

Characteristic	Overall Cohort (N = 10,861)
Age -years	70.7 +/−11.9
Female sex	9959 (91.7%)
Length of hospitalization - days	8.3 +/−8.6
Hypertension – no. (%)	2520 (23.2%)
Hyperlipidemia – no. (%)	1299 (12.0%)
Diabetes mellitus – no. (%)	731 (6.7%)
Chronic kidney disease – no. (%)	239 (2.2%)
Stage II – no. (%)	67 (28.1%)
Stage III– no. (%)	105 (43.9%)
Stage IV– no. (%)	38 (15.9%)
Stage V– no. (%)	29 (12.1%)
Obesity (BMI > 30) – no. (%)	118 (1.1%)
Ventricular Arrhythmias – no. (%)	135 (1.2%)
Ventricular fibrillation – no. (%)	43 (31.1%)
Ventricular flutter – no. (%)	2 (1.4%)
Ventricular tachycardia – no (%)	90 (66.6%)
Atrial Arrhythmias – no. (%)	1,083 (10.0%)
Atrial fibrillation – no. (%)	1032 (95.3%)
Atrial flutter – no. (%)	51 (4.7%)
Advanced Atrioventricular Blocks – no. (%)	136 (1.16%)
Second Degree Mobitz Type II – no. (%)	18 (13.2%)
Third Degree Heart Block – no. (%)	108 (86.8%)
In-hospital Outcomes	
Mortality – no. (%)	241 (2.2%)
Cardiac arrest – no. (%)	115 (1.05%)

Table 2
Clinical Predictors for Inpatient Mortality.

Variable	OR	p value	CI
Male sex	2.46	<0.001	1.76–3.46
Advanced age – per year	1.05	<0.001	1.04–1.06
Atrial Arrhythmias	1.28	0.20	0.80–1.81
Ventricular Arrhythmias	3.23	0.001	1.62–6.43
Advanced AVB	1.43	0.47	0.53–3.82

Table 3
Multivariate Analysis of Clinical Predictors for Inpatient Mortality.

Variable	OR	p value	CI
Male sex	2.32	<0.001	1.65 – 3.27
Advanced age – per year	1.05	<0.001	1.04–1.07
Ventricular Arrhythmias	2.92	0.003	1.45–5.90

continuous variable, each year of age was associated with 5% increased odds of death (OR 1.05, CI 1.04–1.07, p < 0.001). Patients with TTC who had a ventricular arrhythmia had a nearly three-fold increased odds of death when compared to those patients who had no such arrhythmia (OR 2.92, CI 1.45 – 5.90, p = 0.003). Interestingly, when examining the entire study population, neither the presence of atrial arrhythmias or high degree atrioventricular conduction block were independent predictors of inpatient mortality.

3.3. Sex-stratified analysis

Patients were subsequently categorized according to their sex and univariate predictors of inpatient mortality within each group were analyzed (Table 4a). Interestingly, age was a predictor of mortality in only women while there was no significant relationship between mortality and age in men. Each year was associated with 6% increased odds of inpatient mortality in women (OR 1.06, CI 1.04 – 1.08, p < 0.001). Similarly, the presence of atrial arrhythmias was associated with increased mortality in women (OR 1.50, CI 1.01 – 2.24, p = 0.049) while there was no significant relationship in men. Ventricular arrhythmias, on the other hand, was associated with a nearly three-fold increased odds of mortality in both women (OR 2.82, CI 1.22 – 6.50, p = 0.015) and men (OR 3.32, CI 0.94 – 11.67, p < 0.062), although this did not reach statistical significance in men. When examining the multivariate analysis (Table 4b), age remained a strong predictor of mortality in women. Ventricular arrhythmias remained a predictor of mortality in women (2.71, CI 1.16 – 6.32, p = 0.02) and men 3.11 (OR 3.11, CI 0.87 – 11.04, p = 0.07), although once again this did not reach statistical significance in men. The presence of high-degree atrioventricular block was not associated with increased mortality in men or women.

3.4. Age-stratified analysis

Patients were stratified according to age quartiles and their characteristics are described in Table 5. In-hospital mortality increased with each age quartile as patients ≤ 65 years had a mortality rate of 0.96% while those > 85 years had a mortality rate of 4.28%. The prevalence of male sex was highest in the oldest quartile, comprising 9.29% of the group. Length of hospital stay increased across all four groups as patients ≤ 65 years had a mean length of stay of 6.9 +/- 7.0 days while the mean length of stay in patients > 85 years was 9.7 +/- 7.4 days. The prevalence of atrial fibrillation increased in each age quartile with 16.69% of those > 85 years having atrial fibrillation. Similarly, the frequency of high-degree atrioventricular block increased with increasing age to a maximum prevalence of 2.15% of patients > 85 years. The prevalence of ventricular arrhythmias, on the other hand, was similar across all four quartiles, ranging from 1.10% – 1.40%.

Univariate and multivariate predictors of mortality for each quartile are described in Table 6a and 6b. Across the three younger age quartiles, both male sex and increasing length of stay were independent predictors of mortality. After multivariate analysis, the presence of ventricular arrhythmias was a significant predictor of mortality in patients between 75 and 85 years of age (OR 3.54, CI 1.37 – 9.17, p = 0.009) and trended towards being a significant predictor in patients older than 85 (OR 3.67, CI 0.79 – 17.07, p = 0.09). Regardless of the age quartile, neither atrial fibrillation or high-degree atrioventricular block were predictors of mortality.

4. Discussion

Our study of in-hospital mortality amongst patients with TTC provided several important findings. To the best of our knowledge, this is the largest retrospective study evaluating the impact of arrhythmias on inpatient mortality in patients with TTC as previous studies have been limited by small sample sizes and this is the largest analysis to demonstrate the impact of ventricular arrhythmias in this population [9,14,15]. From 2009 to 2016, there were 10,861 total patients hospitalized with a diagnosis of TTC identified in this Italian-based registry. Overall, the mortality rate of patients with TTC was 2.2% in our study population, with males being more likely to die. Furthermore, patients with TTC who experience ventricular arrhythmias have 2.5-fold increased odds of death.

The in-hospital mortality rate of 2.2% in this Italian-based registry is lower than that described in other large retrospective US-based studies, which demonstrated mortality rates up to 4.2% [5,9,18]. These differences may be secondary to distinctly different in-patient populations along with variances in comorbid conditions. We furthermore hypothesize that these other analyses may have more broadly included patients with alternative diagnoses with elevated mortality rates, such as acute coronary syndromes with spontaneous lysis of thrombus, myocarditis or other forms of non-ischemic cardiomyopathies. Male gender was a significant predictor of mortality in our study population, consistent with these prior US-based analyses. Interestingly, males with TTC were at increased risk of mortality regardless of their age, whereas increasing age was strongly associated with increased risk of mortality in women.

Table 4a
Univariate Clinical Predictors of In-hospital Mortality Stratified by Sex.

	Women			*Men*		
Variable	OR	p value	CI	OR	p value	CI
Age	1.06	<0.001	1.04–1.08	1.02	0.11	0.99–1.05
Atrial Arrhythmias	1.50	0.049	1.01–2.24	0.41	0.226	0.097–1.73
Ventricular Arrhythmias	2.82	0.015	1.22–6.50	3.32	0.062	0.94–11.67
Advanced AVB	1.85	0.215	0.69–4.97	0.51	<0.001	0.37–0.69

Table 4b
Multivariate Predictors of In-hospital Mortality Stratified by Sex.

	Women			*Men*		
Variable	OR	p value	CI	OR	p value	CI
Age	1.06	<0.001	1.04–1.08	1.02	0.08	0.99–1.05
Atrial Arrhythmias	1.08	0.69	0.72 – 1.63	0.35	0.16	0.08 – 1.51
Ventricular Arrhythmias	2.71	0.02	1.16 – 6.32	3.11	0.07	0.87 – 11.04
Advanced AVB	1.27	0.68	0.39 – 4.11	1.00	NS	NS

Table 5
Clinical characteristics stratified by age quartiles.

Variable	Age ≤ 65(n = 3010)	65 < Age ≤ 75(n = 3165)	75 < Age ≤ 85(n = 3566)	Age > 85(n = 1120)
In hospital mortality – no. (%)	29 (1.0%)	52 (1.6%)	106 (3.0%)	54 (4.3%)
Male sex – no. (%)	236 (7.9%)	240 (7.6%)	322 (9.0%)	104 (9.3%)
Length of stay – days	6.9 +/- 7.0	7.9 +/- 8.8	9.3 +/- 9.2	9.7 +/- 7.4
Atrial Arrhythmias – no. (%)	72 (2.4%)	280 (8.9%)	544 (15.3%)	187 (16.7%)
Atrial Fibrillation – no. (%)	65 (2.2%)	269 (8.5%)	520 (14.6%)	178 (15.9%)
Atrial Flutter – no. (%)	7 (0.2%)	11 (0.4%)	24 (0.7%)	9 (0.8%)
Ventricular Arrhythmias – no (%)	37 (1.2%)	35 (1.1%)	50 (1.4%)	13 (1.2%)
Ventricular Fibrillation – no. (%)	13 (0.4%)	11 (0.4%)	16 (0.5%)	3 (0.3%)
Ventricular Tachycardia – no. (%)	24 (0.8%)	24 (0.8%)	34 (1.0%)	10 (0.9%)
Advanced AVB – no.(%)	19 (0.6%)	37 (0.9%)	55 (1.5%)	24 (2.2%)
Second degree AVB – no. (%)	2 (0.07%)	12 (0.09%)	9 (0.25%)	4 (0.36%)
Complete AVB – no. (%)	17 (0.56%)	25 (0.79%)	46 (1.29%)	20 (1.79%)

Table 6a
Univariate Clinical Predictors of Mortality within Each Age Quartile.

Characteristic	Age ≤ 65(n = 3010)		65 < Age <≤ 75(n = 3165)		75 < Age ≤ 85(n = 3566)		Age > 85(n = 1120)	
	OR	p value	OR	p value	OR	p value	OR	p value
Male sex	3.12 (1.25–7.73)	0.014	5.20 (2.81–9.63)	0.0001	1.83 (1.07–3.16)	0.029	1.23 (0.52–2.96)	0.63
Atrial Arrhythmias	1.46 (0.20–10.90)	0.37	0.63 (0.20–2.02)	0.44	1.14 (0.60–1.90)	0.62	0.86 (0.40–1.86)	0.70
Ventricular Arrhythmias	2.92 (0.39–22.06)	0.299	1.78 (0.24–13.22)	0.58	3.76 (1.46–9.66)	0.006	3.70 (0.80–17.07)	0.090
Advanced AVB	1.00	NS	1.00	NS	2.69 (0.95 – 7.62)	0.062	1.00	NS

Table 6b
Multivariate Predictors of Mortality within Each Age Quartile.

Characteristic	Age ≤ 65(n = 3010)		65 < Age ≤ 75(n = 3165)		75 < Age ≤ 85(n = 3566)		Age > 85(n = 1120)	
	OR	p value	OR	p value	OR	p value	OR	p value
Male sex	3.05 (1.22–7.61)	0.016	5.20 (2.80–9.64)	<0.0001	1.79 (1.03–3.09)	0.037	1.21 (0.50–2.92)	0.66
Atrial Arrhythmias	1.45 (0.19–10.90)	0.71	0.60 (0.18–1.95)	0.41	1.12 (0.66–1.87)	0.66	0.84 (0.39–1.83)	0.67
Ventricular Arrhythmias	2.39 (0.30–18.4)	0.43	1.50 (0.19–11.53)	0.69	3.54 (1.37–9.17)	0.009	3.67 (0.79–17.07)	0.096
Advanced AVB	1.00	NS	1.00	NS	1.00	NS	1.00	NS

Overall, the prevalence of ventricular arrhythmias in our study population was 1.2%, significantly lower than US-based large retrospective analyses ranging from 3 to 5% and a recent analysis demonstrating a prevalence of 5.6% in a European-based patient population [5,13,19,20]. While these differences may ultimately be secondary to differences in clinical characteristics of the study populations, they may also be due to distinct differences in data collection, most notably in medical coding. The presence of ventricular arrhythmias was a powerful predictor of mortality in both univariate and multivariate analyses. When stratified by sex, ventricular arrhythmias were significant predictors of mortality in women and, although it did not meet statistical significance due to small samples sizes, trended towards significance in men, as well. Although the prevalence of ventricular arrhythmias was similar across all age groups, they were only a significant predictor of mortality in those subjects between the ages of 75 and 85 with a trend towards significance in those subjects older than 85, underscoring the risk of these arrhythmias in an older population. In addition to age, baseline left ventricular function and electrocardiographic abnormalities have been demonstrated to be strong predictors of mortality from ventricular arrhythmias in TTC [21]. Although, patient-specific management decisions could not be obtained from our database, this study underscores the importance of prompt recognition and treatment of individuals with ventricular tachyarrhythmias due to the high mortality associated with their presence in patients with TTC. Telemetry monitoring should be continued for all patients hospitalized with suspected TTC to aid in this prompt recognition of ventricular tachyarrhythmias.

Mechanistically, there are several potential etiologies for ventricular arrhythmias in patients with TTC with reentry in the substrate of underlying myocardial fibrosis being the most widely accepted [22]. Despite being a non-ischemic cardiomyopathy, myocardial fibrosis has been demonstrated on cardiac magnetic resonance (CMR) imaging in patients with TTC in the acute and subacute phases of the syndrome [23]. In addition, QT interval prolongation has been described in patients with TTC, thus a potential substrate for ventricular arrhythmias due to early afterdepolarization-induced triggered activity [22,24].

Atrial arrhythmias, on the other hand were prevalent in our study population, comprising 10.0% of the overall cohort. A recent metanalysis described the prevalence of atrial fibrillation in TTC ranging from 8.4 to 25.0%, depending upon the average age of the study population [15,25–29]. Acutely, atrial arrhythmias in TTC is thought to be the result of left atrial dysfunction as well as from a catecholaminergic surge [14,30]. Not surprisingly, consistent with epidemiologic studies, its prevalence increases with an aging population [31]. Atrial arrhythmias were an independent univariate predictor of increased mortality (OR 1.50, CI 1.01 – 2.24, p = 0.049) when specifically examining female subjects, however no such relationship existed in the multivariate analysis. Although a new diagnosis of atrial arrhythmias was unable to be distinguished from a pre-existing diagnosis in our analysis, we hypothesize that our findings highlight the strong impact of age on mortality in women with TTC rather than the isolated impact of atrial fibrillation. Although ventricular arrhythmias were associated with worse in-hospital outcomes, no such relationship was demonstrated when examining advanced atrioventricular block.

While the results of this study are compelling, there are several limitations in this large retrospective analysis that should be considered. First, the data source, the Italian National Healthcare System Databank, is dependent upon accurate physician and hospital billing codes for TTC and associated patient comorbidities. In addition, the data from the Italian National Healthcare System Databank does not provide longitudinal data and recurrent hospitalizations are considered unique patient encounters. Furthermore, as previously noted, the presence of pre-existing arrhythmias was unable to be discerned from new-onset arrhythmias and caution should be taken when interpreting a causal relationship between TTC and arrhythmias in the present study. Finally, specific data such as vital signs, left ventricular ejection fraction, laboratory results, procedural results, and concurrent medications were not available and could not be used as covariates in the analyses.

5. Conclusions:

In this large retrospective analysis, male sex and the presence of ventricular arrhythmias are strong predictors of mortality in patients hospitalized with TTC. Furthermore, atrial arrhythmias are associated with increased mortality in women. Further follow-up prospective studies are necessary to determine predictive nature of arrhythmias on long-term and short-term mortality in patients with TTC.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100608.

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