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# Burden of arrhythmias in patients with Takotsubo Cardiomyopathy (Apical Ballooning Syndrome)☆,☆☆

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ABSTRACT

*Introduction:* The objective of our study was to assess the burden of arrhythmias, the gender differences in occurrence of arrhythmias and the impact of these arrhythmias on hospitalization outcomes in patients with Takotsubo Cardiomyopathy (TTC).

*Methods:* TTC and various arrhythmias were identified using appropriate ICD-9-CM codes from Nationwide Inpatient Sample (NIS) discharge records 2006–2010. Length of hospital stay (LOS), in-hospital mortality and total charges were used to assess the impact of the arrhythmias on TTC hospitalization. All analyses were performed using SASv9.2 (Cary Institute Inc., Cary, NC).

*Results:* A total of 16,450 patients were included in the study and 26% ($n = 4296$) of patients had cardiac arrhythmias. Following arrhythmias were present in the descending order of frequency: atrial fibrillation (Afib) 6.9%, ventricular tachycardia (VT) 3.2%, atrial flutter (Afl) 1.9%, ventricular fibrillation and flutter 1%, paroxysmal supraventricular tachycardia (PSVT) 0.8%. Nearly two percent of the patients had sudden cardiac arrest (SCA). Males were more likely to have cardiac arrhythmias in general compared to females (OR: 1.5, 95% CI: 1.3–1.7, $p$-value 0.001). Occurrence of ventricular tachycardia (OR: 1.7, 95% CI: 1.3–2.2, $p$-value $< 0.001$) and sudden cardiac arrest OR: 1.6, 95% CI: 1.1–2.2, $p < 0.001$) were significantly higher in males. In contrast, Afib was significantly less in males compared to females (OR:0.8, 95% CI:0.6–0.9). Patients with arrhythmias had significantly longer length of stay, and increased cost of hospitalization and mortality.

*Conclusions:* Arrhythmias are present in nearly one-quarter of patients with TTC and worsen the outcome. While TTC has been established as a disease mainly of females, life threatening arrhythmias like VT and SCA are more common in males.



## 1. Introduction

Stress-induced cardiomyopathy, also called Takotsubo cardiomyopathy (TTC), is characterized by transient dysfunction of mid left ventricular segment with or without apical involvement and hyperkinesis of the basal segment in the absence of obstructive coronary artery disease. Although this condition was initially considered rare, it is now being increasingly reported and accounts for approximately 1–2% of all admissions for suspected acute coronary syndrome [1]. Cardiac arrhythmias, left ventricular outflow tract obstruction, pump dysfunction and thromboembolism are the major complications of TTC during the acute phase [2–4].

There have been some case reports in the literature describing the occurrence of various cardiac arrhythmias during the acute phase of TTC. This includes benign stable arrhythmia to life threatening ventricular arrhythmias, high degree AV block and sudden cardiac arrest [5,6]. Understanding the burden of arrhythmias in these patients is important in risk stratification, prognostication and prevention of any detrimental effect on hemodynamic status during the acute phase. The burden of these arrhythmias in TTC has not been systematically studied so far. The aims of the study were: i) to assess the burden of arrhythmias in patients with TTC from a nationwide inpatient database ii) investigate

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the gender differences in occurrence of arrhythmias in patients with TTC, and iii) impact of these arrhythmias on outcomes of TTC hospitalization.

## 2. Methods

### 2.1. Data and design

Healthcare Cost and Utilization Project - National Inpatient Sample (NIS) database was utilized to investigate the frequency of arrhythmias in patient with TTC. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 421.83 was used to identify patients aged ≥15 years discharged with TTC as primary diagnosis. A cumulative data from 2006 through 2010 were collected. Patients with acute coronary syndrome, ischemic heart disease or any other form of cardiomyopathy were excluded.

NIS is an administrative dataset created by the Agency for Healthcare Research and Quality from data contributed by participating states [7]. NIS database has been used to evaluate the epidemiology of TTC in the United States in the recent past [8]. The NIS data is the largest of all payer database (Medicare, Medicaid, private insurance and uninsured) of hospital inpatient stay available in United States (excluding the Federal, institutional and short term rehabilitation hospitals). Each individual hospitalization is de-identified and maintained in the NIS as a unique entry with 1 primary discharge diagnosis and up to 24 secondary diagnoses during that hospitalization. Each entry also contains information on demographic details including age, sex, race, insurance status, primary and secondary procedures (up to 14), hospitalization outcome, total charges and length of stay. The NIS contains all discharge data from 45 states, nearly representative of a 20-percent stratified sample of U.S. community hospitals. Weights provided with the NIS were then used to generate national as well as regional discharge-level estimates. Data from the NIS has been previously used to identify, track, and analyze national trends in health care utilization, patterns of major procedures, access, disparity of care, trends in hospitalizations, charges, quality and outcomes [9–11].

### 2.2. Health-facility related definitions

Facilities were considered to be teaching hospitals if they had an American Medical Association approved residency program, were a member of the Council of Teaching Hospitals, or had a fulltime equivalent interns and resident to patient ratio of 0.25 or higher. Hospital location (rural/urban) and teaching status were combined into a single variable in the NIS, thereby generating three sub-classes: teaching urban, non-teaching urban and rural. In the NIS, hospitals were divided into small, medium and large on the basis of their bed-size and the cut-points varied from region to region.

### 2.3. Patient related definitions

Demographic information included age, race and gender. Specific co-morbidities that can potentially affect the hospitalization outcomes like obesity, hypertension, diabetes, hyperlipidemia, sepsis, pneumonia, end stage renal disease, etc. were identified using ICD-9-CM codes (supplementary appendix Table 2). Many of these conditions have been reported to be associated with TTC [8,12]. Similarly, various forms of arrhythmias were identified using ICD-9-CM codes (supplementary appendix Table 1).

### 2.4. Outcome variables

We used length of hospital stay (LOS), in-hospital mortality and total charges to assess the impact of the arrhythmias in TTC hospitalization outcome.

### 2.5. Statistical analysis

All analyses were performed using SASv9.2 (Cary Institute Inc., Cary, NC). Survey procedures available within SAS were applied in the analysis, in order to take into account design features of the complex sample survey, like clustering, stratification and sampling weights. Therefore resulting estimates should be representative of the national inpatient admissions for TTC. Univariate tests were applied to compare either the means or proportions for the mentioned outcomes between patients with TTC with and without arrhythmias. These test consisted of Pearson chi-square test for categorical outcomes and simple linear regression for continuous outcomes, respectively. Level of significance (alpha) was set at 5%. All outcome variables that were significant in single-predictor analyses were included in the final multiple logistic regression models.

## 3. Results

A total of 16,450 patients were identified after rigorous inclusion and exclusion criteria. The baseline characteristics of patients with TTC have been presented in Table 1.

Among these subjects, 26% had cardiac arrhythmias ($n = 4296$), while rest 74% ($n = 12{,}154$) had no documented diagnosis of arrhythmia. Among the arrhythmias, the following were present in the descending order of frequency: atrial fibrillation (Afib) 6.9% ($n = 1142$), ventricular tachycardia (VT) 3.2% ($n = 522$), atrial flutter (Afl) 1.9% ($n = 319$), ventricular fibrillation and flutter (VF/VFl) 1% ($n = 170$), paroxysmal supraventricular tachycardia (PSVT) 0.8% ($n = 123$). Nearly two percent of the patients had sudden cardiac arrest (SCA) ($n = 311$). The terminal rhythm before such event was not available for further categorization. The overall burden of arrhythmias among patients with TTC has been shown in Fig. 1.

We further investigated the gender difference in association of these arrhythmias. 29.3% of the males had cardiac arrhythmias as opposed to 25.7% of females ($p = 0.001$). Similarly, sudden cardiac arrest occurred in 3% in males and 1.8% in females ($p = 0.000$). The gender-based difference in burden of arrhythmias in bivariate analysis has been shown in Fig. 2.

On multivariate logistic regression analysis, males were more likely to have cardiac arrhythmias in general compared to females (OR: 1.5, 95% CI: 1.3–1.7, $p$-value 0.001). Further, occurrence of ventricular tachycardia (OR: 1.7, 95% CI: 1.3–2.2, $p$-value < 0.001) and sudden cardiac arrest OR: 1.6, 95% CI: 1.1–2.2, $p < 0.001$) were also significantly higher in males compared to females. In contrast, Afib was significantly less in males compared to females (OR: 0.8, 95% CI: 0.6–0.9). There was no statistical difference in the incidence of VF/VFl between males and females (OR: 0.6, 95% CI: 0.29–1.1). PSVT was infrequent in both groups, with no statistical difference between the genders (OR: 0.5, 95% CI: 0.2–1.3). This has been shown in Fig. 3.

**Table 1**
Baseline characteristics of the patients with TTC with and without arrhythmia.

| | Total population | | With arrhythmia | | Without arrhythmia | |
|---|---|---|---|---|---|---|
| Characteristics | *N* | (%) | *N* | (%) | *N* | (%) |
| Total admission | 16,450 | 100 | 4296 | 100 | 12,154 | 100 |
| **Age** | | | | | | |
| **15 – 34** | 653 | 3.8 | 171 | 4 | 482 | 4 |
| **35 – 49** | 1980 | 12 | 363 | 8.5 | 1617 | 13.3 |
| **50 – 64** | 5423 | 33 | 997 | 23.2 | 4426 | 36.4 |
| **65 – 79** | 5744 | 34.9 | 1633 | 38.02 | 4111 | 34 |
| **≥80** | 2650 | 16.1 | 1132 | 26.4 | 1518 | 12.5 |
| **Sex** | | | | | | |
| **Male** | 1714 | 10.4 | 503 | 11.7 | 1211 | 10 |
| **Female** | 14,736 | 89.6 | 3793 | 88.3 | 10,943 | 90 |
| **Race** | | | | | | |
| **White** | 10,912 | 66.3 | 3020 | 70.3 | 7892 | 65 |
| **Black** | 947 | 5.8 | 190 | 4.4 | 757 | 6.2 |
| **Hispanic** | 682 | 4.1 | 146 | 3.4 | 536 | 4.4 |
| **Asian** | 318 | 2 | 81 | 1.9 | 237 | 2 |
| **Native American** | 69 | 0.4 | 20 | 0.5 | 49 | 0.4 |
| **Others** | 324 | 2 | 70 | 1.6 | 254 | 2.1 |
| **Unknown** | 3198 | 19.4 | 769 | 18 | 2429 | 20 |
| **Outcomes** | | | | | | |
| **Died** | 761 | 4.6 | 318 | 7.4 | 443 | 3.7 |
| **Hospital Type** | | | | | | |
| **Teaching** | 10,315 | 63 | 2676 | 62.3 | 7639 | 62.9 |
| **Non-teaching** | 5903 | 36 | 1565 | 36.4 | 4338 | 35.7 |
| **Unknown** | 232 | 1.4 | 55 | 1.3 | 177 | 1.5 |
| **Hospital Bed Size** | | | | | | |
| **Small** | 1181 | 7.2 | 310 | 7.2 | 871 | 7.2 |
| **Medium** | 3809 | 23.2 | 1087 | 25.3 | 2722 | 22.4 |
| **Large** | 11,228 | 68.3 | 2844 | 66.2 | 8384 | 69 |
| **Unknown** | 232 | | 55 | 1.3 | 177 | 1.5 |
| **Hospital Location** | | | | | | |
| **Rural** | 1213 | 7.4 | 300 | 7 | 913 | 7.5 |
| **Urban** | 15,005 | 91.2 | 3942 | 91.8 | 11,063 | 91 |
| **Unknown** | 232 | 1.4 | 54 | 1.3 | 178 | 1.5 |
| **Primary Payer** | | | | | | |
| **Medicare** | 8894 | 54.1 | 2799 | 65.2 | 6095 | 50.2 |
| **Medicaid** | 1117 | 6.8 | 236 | 5.5 | 881 | 7.3 |
| **Private Insurance** | 5230 | 31.8 | 1030 | 24 | 4200 | 34.6 |
| **Self-pay** | 679 | 4.1 | 133 | 3.1 | 546 | 4.5 |
| **No change** | 63 | 0.4 | 10 | 0.2 | 53 | 0.4 |
| **Other** | 446 | 2.7 | 88 | 2.1 | 358 | 2.9 |
| **Unknown** | 21 | 0.1 | 0 | 0 | 21 | 0.2 |