



Impact of left bundle branch block in Takotsubo Syndrome

Jose Lopez^{a,1,*}, Gustavo J. Duarte^{b,2}, Rosario A. Colombo^{c,3}, Andrea Folds^{a,4},
Fergie J. Losiniecki^{d,5}, Robert Chait^{d,6}

^a Department of Internal Medicine, HCA Florida Aventura Hospital, Aventura, FL, United States

^b Department of Medicine, Jacobi Medical Center/Albert Einstein College of Medicine, New York, NY, United States

^c Division of Cardiology, University of Miami Miller School of Medicine/Jackson Memorial Hospital, Miami, FL, United States

^d Division of Cardiology, University of Miami Miller School of Medicine/JFK Medical Center, Atlantis, FL, United States

ARTICLE INFO

Keywords:

Takotsubo Cardiomyopathy
Takotsubo Syndrome
Left Bundle Branch Block
Left Ventricular Dyssynchrony
Ventricular Arrhythmogenesis

ABSTRACT

Background: Left bundle branch block (LBBB) causes left ventricular dyssynchrony, and its presence with concomitant left ventricular dysfunction has been proven to play a synergistic role, worsening ventricular function. Our study seeks to further explore the association between LBBB and various in-hospital outcomes in patients with takotsubo syndrome (TTS).

Methods: The national inpatient sample was queried from 2016 to 2019 to identify all admissions with a primary diagnosis of TTS. International classification of diseases, tenth revision codes were used to divide patients based on the presence or absence of LBBB. Multivariate regression analysis was performed to assess the effect of LBBB among all the pre-specified outcomes.

Results: A total of 26,615 admissions were included in the analysis. Admissions with LBBB were more likely to be older (72.2 vs. 66.2 years) and have a higher burden of comorbidities. The presence of a LBBB was associated with ventricular arrhythmias (OR = 1.97, 95% CI 1.08–3.61, $p = 0.028$) but not with sudden cardiac arrest (SCA), acute heart failure, cardiogenic shock, and all-cause intra-hospital mortality.

Conclusions: Intraventricular dyssynchrony appears to play a significant role in ventricular arrhythmogenesis and SCA, as several trials have demonstrated that cardiac resynchronization therapy alone without defibrillator function reduces the rate of ventricular arrhythmias and SCA in patients with heart failure with systolic dysfunction and a widened QRS complex. The most likely mechanism of arrhythmia development in TTS is related to the elevated plasma levels of catecholamines and their proarrhythmic effects in the ventricular myocardium.

1. Introduction

Takotsubo syndrome (TTS) is a transient syndrome characterized by

left ventricular regional systolic dysfunction that predominantly affects post-menopausal women. It can present with chest pain, electrocardiographic changes, and elevation of cardiac enzymes that mimic acute

* Corresponding author at: 3619 NE 207th St, Aventura, FL 33180.

E-mail address: jlopezmd191@gmail.com (J. Lopez).

¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Contributed to the study question, study design, statistical analysis, and manuscript writing.

² This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Contributed to the creation of figures and manuscript writing.

³ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Contributed to the process of manuscript writing and providing expert review.

⁴ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Contributed to the process of manuscript writing and creation of tables.

⁵ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Contributed to the process of manuscript writing and providing expert review.

⁶ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Contributed by the process of manuscript writing and providing expert review.

myocardial infarction without evidence of obstructive coronary artery disease or plaque rupture.[1] Patients with TTS usually recover within 1–4 weeks without significant complications.[2] However, the risk of severe complications is similar to patients with acute coronary syndromes and is associated with increased mortality, particularly in men.[3–5] Though rare, ventricular arrhythmias and mechanical complications confer an elevated mortality risk in TTS.[6,7].

Left bundle branch block (LBBB) has been described as an independent predictor of major cardiac adverse events in patients with coronary artery disease.[8] LBBB causes left ventricular mechanical dyssynchrony, and its presence with concomitant left ventricular dysfunction has been proven to play a synergistic role, worsening ventricular dynamics and cardiac function.[9] In fact, LBBB has been reported as an independent risk factor for all-cause mortality and sudden cardiac arrest (SCA) at one year in patients with chronic heart failure (HF).[10] However, little is known regarding the effects of LBBB in TTS. A small descriptive study found that LBBB had no effect on all-cause mortality during admission but was independently associated with several complications in patients admitted with TTS.[11].

Our study seeks to further explore the association between LBBB and various in-hospital outcomes in patients with TTS to generate possible hypotheses and guide future prospective studies.

2. Methods

2.1. Database

The National Inpatient Sample (NIS) is part of the Healthcare Cost and Utilization Project (HCUP) and is maintained by the Agency for Healthcare Research and Quality (AHRQ).[12] The NIS contains information on all inpatient stays (not individual patients) in 48 states plus the District of Columbia, representing approximately 98% of the United States population, excluding rehabilitation and long-term acute care hospitals.[12] Unweighted, it contains data from more than 7 million hospital stays each year, and weighted, it estimates more than 35 million hospitalizations nationally.[12] Each observation in the NIS contains a primary diagnosis, up to 39 secondary diagnoses, and up to 25 procedure codes depending on the year.[12] All discharge diagnoses and procedures were identified using the International Classification of Diseases, 10th edition (ICD-10) codes.[13] The AHRQ made these data available to the principal author via the HCUP. Institutional Review Board approval was pursued but not required due to the publicly available nature of this de-identified database.

2.2. Study design

We queried the NIS from January 1, 2016, to December 31, 2019, to identify a cohort of all adult admissions (greater than 18 years of age) with a diagnosis of TTS. Hospitalizations with a diagnosis of TTS were defined in this study as a primary diagnosis of Takotsubo Syndrome using the ICD-10 code I51.81. In addition, admissions with a primary diagnosis of TTS who did not have a diagnostic catheterization and those that underwent percutaneous coronary intervention and coronary artery bypass graft during the index hospitalization were excluded from the study to improve the specificity of the diagnosis. The sample was further stratified into 2 study groups: admissions with and without a diagnosis of LBBB. LBBB was abstracted from the database as a secondary diagnosis, which means it was either diagnosed during the index admission or diagnosed on a previous clinical encounter. A diagnosis of LBBB was identified using the ICD-10 code I44.7. The NIS contains information on patients' demographics, social habits, household income, hospital length of stay (LOS), hospital size, hospital type, and several other variables.[14] The rest of the clinical variables were identified using the ICD-10 codes, and the Elixhauser comorbidity index (use of 31 comorbid indicators to predict in-hospital mortality and 30-day readmission data) was calculated as a separate variable.[13,15] A list of the variables and

their respective ICD-10 codes used in the study can be found in **Supplementary Table 1**.

2.3. Outcomes

The primary endpoint was the occurrence of ventricular arrhythmias and SCA during the index admission. Secondary endpoints included acute HF, acute kidney injury, cardiogenic shock, all-cause in-hospital mortality, and non-routine discharge during the index admission.

2.3.1. Statistical analysis

National estimates were obtained using the discharge-level weight variable (DISCWT) provided by the HCUP. Weighted data were used for all statistical analyses. Missing values were excluded from the analysis. Categorical variables were compared using the Chi-square test and are described using frequency with percentages. Continuous variables were compared using the student's *t*-test and are reported as mean (\pm SD) if their distribution was normal or compared using the Mann–Whitney *U* test and reported as median (interquartile range [IQR]) if their distribution was skewed. Multivariable logistic and linear regression analysis was conducted to assess the association of LBBB with all previously specified endpoints. Variables used in the regression model building were either selected from the dataset as provided variables or abstracted with the ICD-10 codes or from the Elixhauser comorbidity index. The variables used for the regression model include admission year, age, sex, race/ethnicity, primary payer status, socioeconomic stratum, hospital location, hospital teaching status, diabetes without chronic complications, diabetes with chronic complications, liver disease, coagulopathies, fluid and electrolyte disturbances, pulmonary hypertension, chronic HF, chronic kidney disease, primary hypertension, primary hypertension with chronic complications, peripheral vascular disease, hyperlipidemia, chronic obstructive pulmonary disease, BMI \geq 25 Kg/m², coronary artery disease, valvular disease, ethanol use, tobacco use, illicit drug use, hypothyroidism, hyperthyroidism, human immunodeficiency virus, underweight, malnutrition, obstructive sleep apnea, prior stroke, cancer without metastasis, metastatic cancer, psychotic disorders, and the Elixhauser comorbidity index. Furthermore, in the regression model for ventricular arrhythmias we excluded all admissions with ICD placed as this could introduce significant bias. Variables were selected into the multivariate regression model if they were statistically significant ($p < 0.10$) in the univariate analysis screening. In addition, we forced variables that are well established to affect outcomes based on prior research. Logistic regression results are represented as adjusted odds ratios (ORs) and their respective 95% Confidence Intervals (CIs). Linear regression results are expressed as beta coefficients (Coef.) and their respective 95% CIs. Statistical analysis was performed using STATA/BE 17.0 (StataCorp, College Station, TX). *P*-values < 0.05 were considered statistically significant. The checklist for working with the NIS was used to ensure the appropriateness of data analysis as recommended by AHRQ.[16].

3. Results

3.1. Patient characteristics at index admission

A total of 32,590 adult admissions with a primary diagnosis of Takotsubo Syndrome were identified. Of these, only 26,615 admissions met the selection criteria and were included in the final analysis (Fig. 1). The mean age of the sample was 66.4 ± 12.5 years. As seen in Fig. 2, the number of admissions with a diagnosis of TTS increased each year slightly during the study period, from 6,420 admissions in 2016 to 7,155 admissions in 2019, representing an 11.5% increase over the study timeframe. Females represented 90.7% of the entire study population without significant differences between both study groups. The sample was predominantly white (83.1%), with more admissions in the non-LBBB group being black than in the LBBB group (6.8% vs. 2.1%).

Table 1
Baseline characteristics of patients with a diagnosis of Takotsubo Cardiomyopathy with and without left bundle branch block.

Baseline characteristics	Left Bundle Branch Block Absent (n = 25,660)	Left Bundle Branch Block Present (n = 955)	Total (n = 26,615)	p-value
Age, years (Mean, SD)	66.2 (12.5)	72.2 (10.1)	66.4 (12.5)	<0.001
Sex (n, %) ^a				0.335
Male	2,410 (9.4)	70 (7.3)	2,480 (9.3)	
Female	23,240 (90.6)	885 (92.7)	24,125 (90.7)	
Race (n, %) ^b				0.120
White	20,490 (82.9)	840 (89.8)	21,330 (83.1)	
Black	1,690 (6.8)	20 (2.1)	1,710 (6.7)	
Hispanic	1,435 (5.8)	50 (5.4)	1,485 (5.8)	
Asian or Pacific Islander	395 (1.6)	10 (1.1)	405 (1.6)	
Native American	135 (0.6)	0 (0.0)	135 (0.5)	
Other	580 (2.4)	15 (1.6)	595 (2.3)	
Calendar year (n, %)				0.020
2016	6,220 (24.2)	200 (20.9)	6,420 (24.1)	
2017	6,325 (24.7)	175 (18.3)	6,500 (24.4)	
2018	6,300 (24.6)	240 (25.1)	6,540 (24.6)	
2019	6,815 (26.6)	340 (35.6)	7,155 (26.9)	
Insurance type (n, %) ^c				<0.001
Medicare	14,985 (59.8)	710 (75.1)	15,695 (60.3)	
Medicaid	2,285 (9.1)	55 (5.8)	2,340 (9.0)	
Private Insurance	6,990 (27.9)	155 (16.4)	7,145 (27.5)	
Self-Pay	820 (3.3)	25 (2.7)	845 (3.3)	
Teaching status (n, %) ^d				0.349
Teaching	19,030 (74.2)	680 (71.2)	19,710 (74.1)	
Non-teaching	6,630 (25.8)	275 (28.8)	6,905 (25.9)	
Hospital Location (n, %) ^e				0.268
Rural	1,300 (5.07)	65 (6.8)	1,365 (5.1)	
Urban	24,360 (94.9)	890 (93.2)	25,250 (94.9)	
Median household income (n, %) ^d				0.122
0-25th percentile	6,085 (24.0)	155 (16.5)	6,240 (23.8)	
26th-50th percentile	6,570 (26.0)	270 (28.7)	6,840 (26.1)	
51st-75th percentile	6,830 (27.0)	280 (29.8)	7,110 (27.1)	
76th-100th percentile	5,825 (23.0)	235 (25.0)	6,060 (23.1)	
Comorbidities (n, %) ^e				0.472
HTN, uncomplicated ^e	11,280 (44.0)	395 (41.4)	11,675 (43.9)	
HTN, complicated ^e	3,660 (14.3)	185 (19.4)	3,845 (14.5)	0.047
Diabetes Mellitus without chronic complications	4,730 (18.4)	225 (23.6)	4,955 (18.6)	0.074
Diabetes Mellitus with chronic complications	1,820 (7.1)	125 (13.1)	1,945 (7.3)	0.002
Hyperlipidemia	865 (3.4)	40 (4.2)	905 (3.4)	0.541
Coronary artery disease	11,350 (44.2)	515 (53.9)	11,865 (44.6)	0.008

Table 1 (continued)

Baseline characteristics	Left Bundle Branch Block Absent (n = 25,660)	Left Bundle Branch Block Present (n = 955)	Total (n = 26,615)	p-value
Carotid artery stenosis	230 (0.9)	20 (2.1)	250 (0.9)	0.092
PVD ^f	1,730 (6.7)	95 (10.0)	1,825 (6.9)	0.085
BMI ≥ 25 Kg/m ² ^g	3,310 (12.9)	115 (12.0)	3,425 (12.9)	0.728
Hypothyroidism	4,795 (18.7)	255 (26.7)	5,050 (19.0)	0.006
Hyperthyroidism	120 (0.5)	0 (0.0)	120 (0.5)	0.341
Chronic heart failure	955 (3.7)	50 (5.2)	1,005 (3.8)	0.281
Chronic Kidney Disease	2,055 (8.0)	115 (12.0)	2,170 (8.2)	0.045
HIV ^h	10 (0.04)	0 (0.00)	10 (0.04)	0.785
Valvular disease	3,005 (11.7)	155 (16.2)	3,160 (11.9)	0.061
Atrial fibrillation & flutter	3,295 (12.8)	160 (16.8)	3,455 (13.0)	0.115
Prior PPM ⁱ	570 (2.2)	15 (1.6)	585 (2.2)	0.547
Prior ICD ^j	105 (0.4)	10 (1.1)	115 (0.4)	0.187
COPD ^k	5,430 (21.1)	170 (17.8)	5,600 (21.0)	0.256
Obstructive Sleep Apnea	1,205 (4.7)	50 (5.2)	1,255 (4.7)	0.731
Pulmonary Hypertension	1,180 (4.6)	80 (8.4)	1,260 (4.7)	0.016
Prior ischemic stroke	1,885 (7.4)	95 (10.0)	1,980 (7.4)	0.175
Liver disease	835 (3.3)	30 (3.1)	865 (3.3)	0.931
Coagulopathy	930 (3.6)	30 (3.1)	960 (3.6)	0.724
Solid tumor without metastasis	610 (2.4)	20 (2.1)	630 (2.4)	0.634
Metastatic Cancer	285 (1.1)	15 (1.6)	300 (1.1)	0.555
Underweight	850 (3.3)	20 (2.1)	870 (3.3)	0.353
Malnutrition	1,015 (4.0)	40 (4.2)	1,055 (4.0)	0.871
Ethanol	1,085 (4.2)	10 (1.1)	1,095 (4.1)	0.030
Tobacco	4,025 (15.7)	55 (5.8)	4,080 (15.3)	<0.001
Illicit drugs	940 (3.7)	35 (3.7)	975 (3.7)	0.999

^a There were a total of 10 admissions missing sex identification;
^b There were a total of 955 admissions missing race identification;
^c There were a total of 590 admissions missing insurance information;
^d Median household income national quartile for patient ZIP Code;
^e Hypertension;
^f Peripheral Vascular Disease;
^g Body Mass Index;
^h Human Immunodeficiency Virus;
ⁱ Permanent Pacemaker;
^j Implantable cardioverter-defibrillator;
^k Chronic Obstructive Pulmonary Disease.

Admissions with LBBB were more likely to be older (72.2 years for patients with LBBB vs. 66.2 years for patients without LBBB), have complicated hypertension, diabetes mellitus, coronary artery disease, chronic HF, chronic kidney disease, peripheral vascular disease, pulmonary hypertension, prior stroke, valvular disease, hypothyroidism, and atrial fibrillation or atrial flutter. Conversely, they were less likely to have chronic obstructive pulmonary disease, ethanol use, and tobacco use. A detailed list of baseline characteristics is summarized in [Table 1](#).

3.2. Outcomes

[Table 2](#) and [Fig. 3](#) depict outcomes rates during index admission and the multivariate-adjusted ORs for the aforementioned specified outcomes. Ventricular arrhythmias occurred in 1,100 (4.1%) admissions and SCA in 405 (1.5%) admissions. The cohort with LBBB had higher rates of ventricular arrhythmias (6.8% for admissions with LBBB vs.

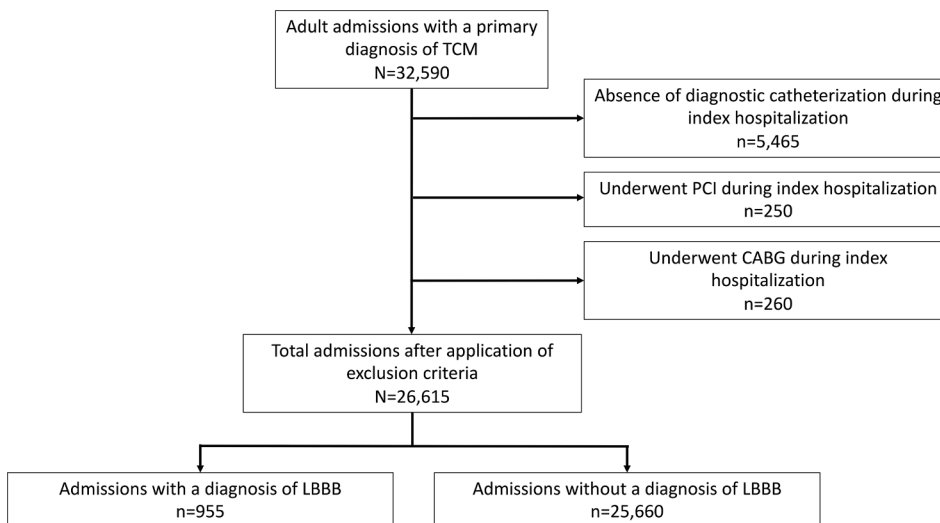


Fig. 1. Flowchart showcasing participant selection criteria. TTS, Takotsubo Syndrome. LBBB, Left Bundle Branch Block. PCI, Percutaneous Coronary Intervention. CABG, Coronary Artery Bypass Graft.

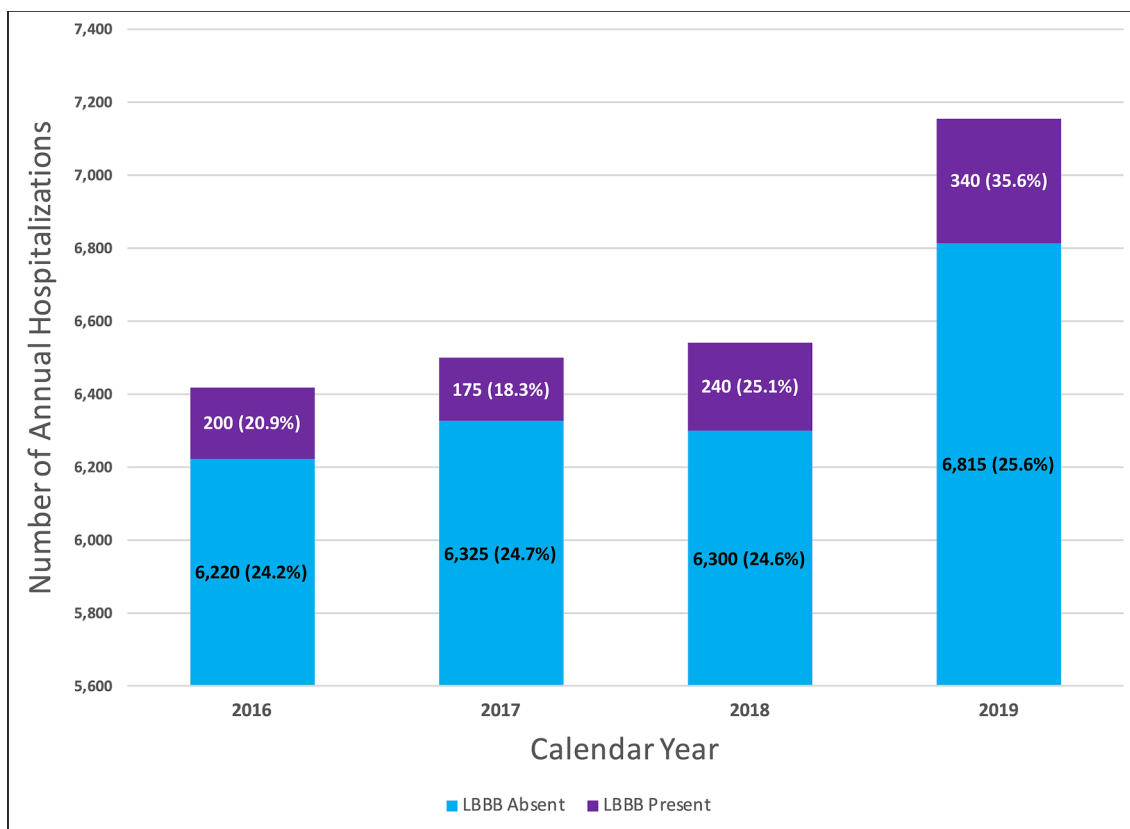


Fig. 2. Trends in LBBB prevalence of nationwide hospitalizations for Takotsubo Syndrome. LBBB, Left Bundle Branch Block.

4.0% for admissions without LBBB), acute HF (25.1% vs. 19.3%), and acute kidney injury (12.0% vs. 8.5%). Both study groups did not significantly differ between SCA, cardiogenic shock, and non-routine discharge. Overall, the all-cause in-hospital mortality rate for the study population was 1.2% (n = 325).

3.2.1. Multivariate regression analysis

After multivariate adjustment, the presence of a LBBB in TTS was associated with higher odds of ventricular arrhythmias (OR = 1.90, 95% CI 1.01–3.57, p = 0.045). Variables associated with higher odds of

ventricular arrhythmias included acid-base and electrolyte disturbances (OR = 2.31, 95% CI 1.71–3.12, p < 0.001), coagulopathies (OR = 1.74, 95% CI 1.01–2.98, p = 0.044), and valvular disease (OR = 1.63, 95% CI 1.10–2.42, p = 0.016). Conversely, comorbidities associated with lesser odds of ventricular arrhythmias include age in years at admission (OR = 0.98, 95% CI 0.97–0.99, p = 0.026), female sex (OR = 0.47, 95% CI 0.31–0.69, p < 0.001), and uncomplicated primary hypertension (OR = 0.53, 95% CI 0.38–0.73, p < 0.001).

After multivariate adjustment, TTS complicated by the presence of an LBBB was not associated with SCA (OR = 1.80, 95% CI 0.55–5.89, p

Table 2
Adjusted Comparative Outcomes Among Admissions with TCM and presence of a LBBB Versus Absence of a LBBB.

Outcomes	LBBB Present (n = 955)	LBBB Absent (n = 25,660)	OR	95% CI	p value
Ventricular arrhythmias*	60 (6.81)	1,015 (4.03)	1.90	1.01–3.57	0.045
SCA	15 (1.57)	390 (1.52)	1.80	0.55–5.89	0.331
Acute heart failure	240 (25.13)	4,940 (19.25)	1.23	0.83–1.82	0.307
AKI	115 (12.04)	2,170 (8.46)	1.26	0.76–2.11	0.377
Cardiogenic shock	40 (4.19)	1,185 (4.62)	0.79	0.38–1.66	0.534
In-hospital mortality	10 (1.05)	315 (1.23)	0.47	0.10–2.24	0.344
Non-routine discharge	195 (20.42)	4,795 (18.76)	0.78	0.53–1.16	0.223

Values are as n (%) unless otherwise indicated. TCM, takotsubo cardiomyopathy; LBBB, left bundle branch block; SCA, sudden cardiac arrest; AKI, acute kidney injury; CI, confidence interval; OR, odds Ratio. * 105 admissions with prior ICD placement were excluded. In this subgroup, there were a total of 25,555 admissions. 945 in the LBBB group and 1,015 without LBBB.

= 0.331), acute HF (OR = 1.23, 95% CI 0.83–1.82, p = 0.307), acute kidney injury (OR = 1.26, 95% CI 0.76–2.11, p = 0.377), cardiogenic shock (OR = 0.79, 95% CI 0.38–1.66, p = 0.534), all-cause in-hospital mortality (OR = 0.47, 95% CI 0.10–2.24, p = 0.344), and non-routine discharge (OR = 0.78, 95% CI 0.53–1.16, p = 0.223). Variables that were significant in the multivariate regression analysis for all specified outcomes can be seen in the **Supplementary Table 2**.

3.3. Predictors of all-cause in-hospital mortality after multivariate adjustment

The multivariate regression analysis identified several predictors of all-cause in-hospital mortality among patients with TTS and LBBB. In this cohort, the variables associated with higher mortality included race other than White, Black, Hispanic, Asian or Pacific Islander, and Native American (OR = 6.23, 95% CI 2.43–16.02, p < 0.001), self-payer status (OR = 3.40, 95% CI 1.03–11.26, p = 0.045), teaching hospital status (OR = 2.71, 95% CI 1.20–6.16, p = 0.017), cardiac arrhythmias (OR = 2.53, 95% CI 1.40–4.57, p = 0.002), neurological disorders (OR = 3.27, 95% CI 1.65–6.48, p = 0.001), liver disease (OR = 6.38, 95% CI 2.53–16.07, p < 0.001), metastatic cancer (OR = 3.63, 95% CI

1.08–12.19, p = 0.037), and fluid and electrolyte disorders (OR = 2.64, 95% CI 1.44–4.82, p = 0.002).

4. Discussion

In this retrospective observational study of more than 26,000 admissions with TTS, we evaluated the association between LBBB and various in-hospital outcomes. We found a significant association between LBBB and ventricular arrhythmias in patients with TTS without a significant association between SCA, acute HF, acute kidney injury, cardiogenic shock, and death during the index admission. In addition, there was no association of LBBB with hospital length of stay and non-routine discharge in TTS admissions.

Our study found that patients with TTS and accompanying LBBB were more likely to be older and have a higher burden of comorbidities than those without LBBB, including but not limited to chronic HF, coronary artery disease, hypertension, and valvular disease. These findings are consistent with previous studies, which have shown that the prevalence of LBBB increases with age and is associated with underlying cardiovascular disease.[17–20] This association is more likely a result of underlying cardiovascular disease, as LBBB is known to result from slow, progressive degeneration of the cardiac conduction system from conditions that contribute to myocardial fibrosis.[21] In addition, there was a steady increase in the annual number of TTS hospitalizations over the study period, possibly relating to increased clinical recognition and awareness of the condition.

It is well known that patients with HF are at high risk for ventricular tachyarrhythmias, and as many as one-third of patients with symptomatic HF with reduced ejection fraction (HFrEF) have ventricular dyssynchrony.[22] Intraventricular dyssynchrony appears to play a significant role in ventricular arrhythmogenesis and SCA, as several trials have demonstrated that cardiac resynchronization therapy alone without defibrillator function reduces the rate of ventricular arrhythmias and SCA in patients with HFrEF and impaired conduction velocity represented by a widened QRS complex.[23,24] The mechanism for this improvement remains unclear, but it is hypothesized to be related to hemodynamic improvement from ventricular synchrony resulting in decreased arrhythmogenesis.[25–27] It has been proposed that intra-ventricular mechanical dyssynchrony may be linked with ventricular arrhythmogenesis due to abnormal mechanical and subsequent abnormal electrical activation of the myocardium resulting in electrical heterogeneity in patients with HF; however, no causative relationship between these conditions has been firmly established.[27] In patients with TTS, an association between LBBB and ventricular arrhythmias and SCA has been previously observed, but poorly studied.[28] In our

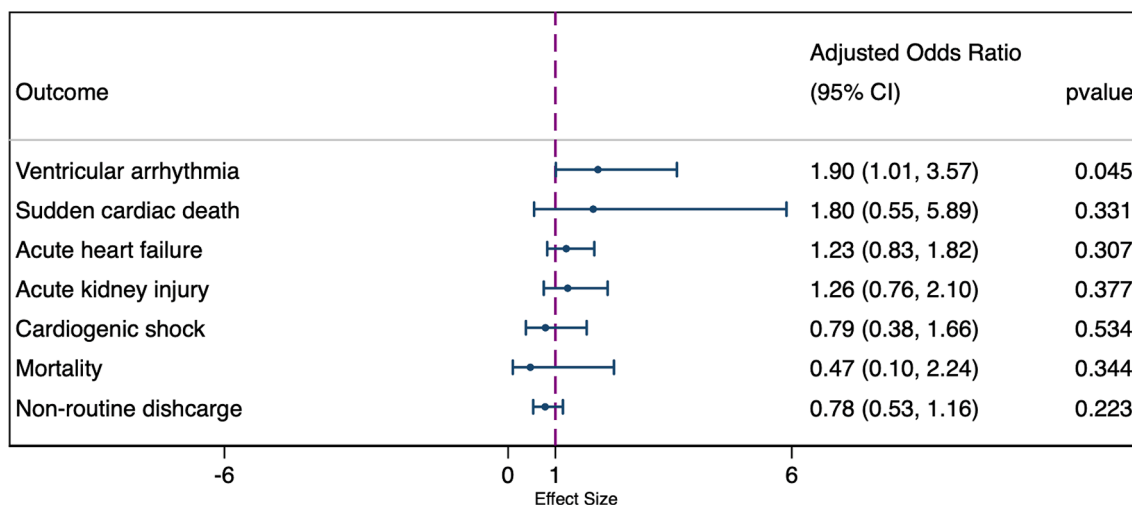


Fig. 3. Adjusted odds ratio for all specified outcomes among patients with Takotsubo Syndrome and left bundle branch block.

analysis, we found that the presence of LBBB is associated with higher odds of ventricular arrhythmias when adjusting for multiple variables; however, we found no significant association with SCA. This discrepancy may be due to limitations in our database making us unable to prospectively follow patients for SCA following hospital discharge. Although there is biological plausibility for patients with TTS and a LBBB to have a higher risk for arrhythmogenesis and resultant ventricular arrhythmias based on the mechanistic similarities with HF patients, this association has not been adequately studied. Our results indicate that VAs, although an important complication, are less frequent in TTS than in post-myocardial infarction patients as compared to patients in the SEARCH-MI and MADIT-II registries.[29,30] Increased sympathetic activity and elevated plasma levels of catecholamines have been implicated in the pathogenesis of TTS by means of direct myocardial stunning and toxicity.[31–33] It may thus be reasonable to consider a possible mechanism of arrhythmia development in TTS being related to elevated plasma levels of catecholamines and their proarrhythmic effects in the ventricular myocardium.

Ventricular conduction delay is known to cause electrical and mechanical ventricular dyssynchrony and, thus, worse systolic function, which could lead to acute organ damage from decreased perfusion. A previous study using the NIS found an association between TTS with LBBB and ventricular arrhythmias, SCA, cardiogenic shock, and acute HF, but not with all-cause in-hospital mortality during admission.[11] Our study aimed to expand upon these findings analyzing a significantly larger sample size and it did not find any association between LBBB and acute HF, acute kidney injury, cardiogenic shock, all-cause mortality, and hospital length of stay during the index admission in patients with TTS after multivariate adjustment.[9].

4.1. Limitations

Since the NIS is derived from administrative data, it carries inherent limitations. Information such as clinical symptoms, laboratory results, vital signs, data on HF etiology, ejection fraction, functional class, and medications are not available. Furthermore, the temporal relationship between LBBB occurrence and TTS and whether LBBB resolved or persisted after onset and resolution of TTS is not recorded in the database. It was also not possible to determine from the database whether LBBB was diagnosed on the current admission or on a previous clinical encounter. Accuracy of diagnoses depend on the medical provider's coding, and particular diagnoses may be under-coded or even miscoded to a greater degree. In our study, undercoding might be a particular issue with the diagnosis of LBBB. In addition, it is essential to recognize that the unit of observation in the NIS is an admission and not an individual patient. This means that the same patient could represent several observations in the database, and it is not possible to track patients after their discharge. Even though a clinical registry or cohort study would solve these constraints, they do not provide the national scale of information that the NIS provides. Therefore, it is paramount to understand these limitations and how the data is obtained to interpret the results from NIS data correctly.

5. Conclusion

In conclusion, our study found a significant association between LBBB and ventricular arrhythmias in patients with TTS, which should be further explored with prospective trials to determine the mechanism and the role of LBBB as a predictor of ventricular arrhythmias and sudden cardiac death and its possible function in prognostication among this population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Acknowledgement

Author JL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JL contributed to developing the clinical question and design of the study. JL, GD, RAC, FJR, AF, and RC contributed substantially to the manuscript's interpretation, literature research, writing, and manuscript revisions.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2022.101123>.

References

- [1] A. Dias, I.J. Núñez Gil, F. Santoro, J.E. Madias, F. Pelliccia, N.D. Brunetti, E. Salmoiraghi-Blotcher, S.W. Sharkey, I. Eitel, Y.J. Akashi, I. El-Battrawy, E. Franco, I. Akin, M. Jaguszewski, D. Dawson, V.M. Figueredo, L.C. Napp, T. E. Christensen, K. Hebert, I. Ben-Dor, Y. Ozaki, H.M. García-García, A.H. Kajita, T. Akasaka, S. Kurisu, A. Lerman, R. Waksman, Takotsubo syndrome: State-of-the-art review by an expert panel-Part 1, Published online 20 (1) (2019) 70–79.
- [2] H.Z. Amin, L.Z. Amin, A. Pradipta, Takotsubo Cardiomyopathy: a brief review, *J Med Life*. 13 (1) (2020) 3–7.
- [3] C. Templin, J.R. Ghadri, J. Diekmann, L.C. Napp, D.R. Bataiosu, M. Jaguszewski, V. L. Cammann, A. Sarcon, V. Geyer, C.A. Neumann, B. Seifert, J. Hellermann, M. Schwyzer, K. Eisenhardt, J. Jenewein, J. Franke, H.A. Katus, C. Burgdorf, H. Schunkert, C. Moeller, H. Thiele, J. Bauersachs, C. Tschöpe, H.-P. Schultheiss, C. A. Laney, L. Rajan, G. Michels, R. Pfister, C. Ukena, M. Böhm, R. Erbel, A. Cuneo, K.-H. Kuck, C. Jacobshagen, G. Hasenfuss, M. Karakas, W. Koenig, W. Rottbauer, S. M. Said, R.C. Braun-Dullaeus, F. Cuculi, A. Banning, T.A. Fischer, T. Vasankari, K.E. J. Airaksinen, M. Fijalkowski, A. Rynkiewicz, M. Pawlak, G. Opolski, R. Dworakowski, P. McCarthy, C. Kaiser, S. Osswald, L. Galiuto, F. Crea, W. Dichtl, W.M. Franz, K. Empen, S.B. Felix, C. Delmas, O. Lairez, P. Erne, J.J. Bax, I. Ford, F. Ruschitzka, A. Prasad, T.F. Lüscher, Clinical features and outcomes of takotsubo (stress) cardiomyopathy, *N Engl J Med*. 373 (10) (2015) 929–938.
- [4] L.T. Vincent, J. Grant, B. Ebner, J. Maning, P. Montana, O. Olorunfemi, N.I. Olarte, E. de Marchena, M. Munagala, R. Colombo, Effect of Gender on Prognosis in Patients With Takotsubo Syndrome (from a Nationwide Perspective), *Am J Cardiol*. 162 (2022) 6–12.
- [5] L. Arcari, I.J. Núñez-Gil, T. Stiermaier, I. El-Battrawy, F. Guerra, G. Novo, B. Musumeci, L. Cacciotti, E. Mariano, P. Caldarola, G. Parisi, R. Montisci, E. Vitale, M. Scalfani, M. Volpe, M. Corbi-Pasqual, M. Martínez-Selles, M. Almedro-Delia, A. Sionis, A. Urbarri, I. Akin, H. Thiele, N.D. Brunetti, I. Eitel, F. Santoro, Gender differences in takotsubo syndrome, *J. Am. Coll. Cardiol*. 79 (21) (2022) 2085–2093.
- [6] A. Vijiñac, V. Ploscaru, R.G. Vataescu, The Great Myocardial Mimic - Takotsubo Syndrome, *Maedica*. 15 (1) (2020) 111–121.
- [7] MECHANICAL COMPLICATIONS OF TAKOTSUBO CARDIOMYOPATHY: A SYSTEMATIC REVIEW. Accessed May 15, 2022. [https://www.jacc.org/action/showCitFormats?doi=10.1016/S0735-1097\(22\)01546-7](https://www.jacc.org/action/showCitFormats?doi=10.1016/S0735-1097(22)01546-7).
- [8] B. Hesse, L.A. Diaz, C.E. Snader, E.H. Blackstone, M.S. Lauer, Complete bundle branch block as an independent predictor of all-cause mortality: report of 7,073 patients referred for nuclear exercise testing, *Am. J. Med.* 110 (4) (2001) 253–259.
- [9] O.A. Smiseth, J.M. Aalen, Mechanism of harm from left bundle branch block, *Trends Cardiovasc Med*. 29 (6) (2019) 335–342.
- [10] S. Baldasseroni, C. Opasich, M. Gorini, D. Lucci, N. Marchionni, M. Marini, C. Campana, G. Perini, A. Deorsola, G. Masotti, L. Tavazzi, A.P. Maggioni, Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure, *Am. Heart J*. 143 (3) (2002) 398–405.
- [11] D. Ludhwani, M. Rahaby, V. Patel, S. Jamil, A. Kedzia, C. Wu, Implications of Left Bundle Branch Block in Takotsubo Cardiomyopathy: propensity Match Analysis from the National Inpatient Sample, *Cardiol. Ther.* 8 (2) (2019) 253–265.
- [12] Healthcare Cost and Utilization Project (HCUP). NIS Overview. Agency for Healthcare Research and Quality, Rockville. Published September 2021. Accessed April 4, 2022. <https://www.hcup-us.ahrq.gov/nisoverview.jsp>.
- [13] World Health Organization (WHO). International Classification of Diseases (ICD). World Health Organization (WHO). Accessed April 9, 2022. <http://www.who.int/standards/classifications/classification-of-diseases>.
- [14] Agency for Healthcare Research and Quality, Rockville. NIS Description of Data Elements. Healthcare Cost and Utilization Project (HCUP). Published October 2021. Accessed May 2022. <https://www.hcup-us.ahrq.gov/db/nation/nis/nisdde.jsp>.
- [15] C. van Walraven, P.C. Austin, A. Jennings, H. Quan, A.J. Forster, A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data, *Med. Care*. 47 (6) (2009) 626–633.
- [16] Healthcare Cost and Utilization Project (HCUP). Checklist for working with the NIS. Agency for Healthcare Research and Quality, Rockville, MD. Published

- October 2021. Accessed April 10, 2022. <https://www.hcup-us.ahrq.gov/db/nation/nis/nischecklist.jsp>.
- [17] J.F. Schneider, H.E. Thomas Jr, B.E. Kreger, P.M. McNamara, W.B. Kannel, Newly acquired left bundle-branch block: the Framingham study, *Ann. Intern. Med.* 90 (3) (1979) 303–310.
- [18] Y. Siegman-Igra, J.H. Yahini, U. Goldbourt, H.N. Neufeld, Intraventricular conduction disturbances: a review of prevalence, etiology, and progression for ten years within a stable population of Israeli adult males, *Am. Heart J.* 96 (5) (1978) 669–679.
- [19] R.G. Hiss, L.E. Lamb, Electrocardiographic findings in 122,043 individuals, *Circulation.* 25 (6) (1962) 947–961.
- [20] L.D. Ostrander, R.L. Brandt, M.O. Kjelsberg, F.H. Epstein, Electrocardiographic findings among the adult population Of a total natural community, tecumseh, MICHIGAN. *Circulation.* 31 (6) (1965) 888–898.
- [21] N.Y. Tan, C.M. Witt, J.K. Oh, Y.M. Cha, Left Bundle Branch Block: Current and Future Perspectives, *Circ. Arrhythm Electrophysiol.* 13 (4) (2020), e008239.
- [22] F.A. McAlister, J. Ezekowitz, N. Hooton, B. Vandermeer, C. Spooner, D.M. Dryden, R.L. Page, M.A. Hlatky, B.H. Rowe, Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review, *JAMA.* 297 (22) (2007) 2502.
- [23] A.J. Moss, W.J. Hall, D.S. Cannom, H. Klein, M.W. Brown, J.P. Daubert, N.A. M. Estes, E. Foster, H. Greenberg, S.L. Higgins, M.A. Pfeffer, S.D. Solomon, D. Wilber, W. Zareba, Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events, *N Engl J. Med.* 361 (14) (2009) 1329–1338.
- [24] M.R. Bristow, L.A. Saxon, J. Boehmer, S. Krueger, D.A. Kass, T. De Marco, P. Carson, L. DiCarlo, D. DeMets, B.G. White, D.W. DeVries, A.M. Feldman, Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure, *N Engl. J. Med.* 350 (21) (2004) 2140–2150.
- [25] S.L. Higgins, P. Yong, D. Scheck, M. McDaniel, F. Bollinger, M. Vadecha, S. Desai, D.B. Meyer, Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy, *J. Am. Coll. Cardiol.* 36 (3) (2000) 824–827.
- [26] J.G.F. Cleland, J.-C. Daubert, E. Erdmann, N. Freemantle, D. Gras, L. Kappenberger, L. Tavazzi, The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure, *N Engl. J. Med.* 352 (15) (2005) 1539–1549.
- [27] V. Kutyifa, A.-C. Pouleur, D. Knappe, A. Al-Ahmad, M. Gibinski, P.J. Wang, S. McNitt, B. Merkely, I. Goldenberg, S.D. Solomon, A.J. Moss, W. Zareba, Dyssynchrony and the Risk of Ventricular Arrhythmias, *JACC: Cardiovascular Imaging.* 6 (4) (2013) 432–444.
- [28] S. Vallabhajosyula, G.W. Barsness, J. Herrmann, N.S. Anavekar, R. Gulati, A. Prasad, Comparison of Complications and In-Hospital Mortality in Takotsubo (Apical Ballooning/Stress) Cardiomyopathy Versus Acute Myocardial Infarction, *Am. J. Cardiol.* 132 (2020) 29–35.
- [29] M. Santini, M. Russo, G. Botto, M. Lunati, A. Proclemer, B. Schmidt, A. Erdogan, E. Helmling, W. Rauhe, M. Desaga, E. Santi, M. Messier, G. Boriani, Clinical and arrhythmic outcomes after implantation of a defibrillator for primary prevention of sudden death in patients with post-myocardial infarction cardiomyopathy: the survey to evaluate arrhythmia Rate in High-risk MI patients (SEARCH-MI), *Europace.* 11 (4) (2008) 476–482.
- [30] A.J. Moss, A. Vyas, H. Greenberg, R.B. Case, W. Zareba, W.J. Hall, M.W. Brown, S. A. McNitt, M.L. Andrews, Temporal aspects of improved survival with the implanted defibrillator (MADIT-II), *Am. J. Cardiol.* 94 (3) (2004) 312–315.
- [31] I.S. Wittstein, D.R. Thiemann, J.A.C. Lima, K.L. Baughman, S.P. Schulman, G. Gerstenblith, K.C. Wu, J.J. Rade, T.J. Bivalacqua, H.C. Champion, Neurohumoral features of myocardial stunning due to sudden emotional stress, *N Engl. J. Med.* 352 (6) (2005) 539–548.
- [32] H.M. Nef, H. Mollmann, S. Kostin, C. Troidl, S. Voss, M. Weber, T. Dill, A. Rolf, R. Brandt, C.W. Hamm, A. Elsasser, Tako-Tsubo cardiomyopathy: intraindividual structural analysis in the acute phase and after functional recovery, *Eur. Heart J.* 28 (20) (2007) 2456–2464.
- [33] M. Gianni, F. Dentali, A.M. Grandi, G. Sumner, R. Hiralal, E. Lonn, Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review, *Eur. Heart J.* 27 (13) (2006) 1523–1529.