Impact of left bundle branch block in Takotsubo Syndrome

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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 a higher risk of intraventricular 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 myocardial infarction.
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 dysynchrony, 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 with ICD placed as this could introduce significant bias. Variables were selected into the multivariate regression model if they were statistically significant at the 0.05 level. 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, %)               |                                             |                                           |                    | 0.335   |
| Male                     | 2,410 (9.4)                                 | 70 (7.3)                                  | 2,480 (9.3)        |         |
| Female                   | 23,240 (90.6)                               | 885 (29.2)                                | 24,125 (90.7)      |         |
| Race (n, %)              |                                             |                                           |                    | 0.120   |
| White                    | 20,490 (82.9)                               | 840 (88.9)                                | 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)          |         |
| 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)          | 0.020   |
| Calendar year (n, %)     |                                             |                                           |                    |         |
| 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, %)    |                                             |                                           |                    | <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, %)   |                                             |                                           |                    | 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, %) |                                             |                                           |                    | 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, %)     |                                             |                                           |                    |         |
| HTN, uncomplicated e     | 11,280 (44.0)                               | 395 (41.4)                                | 11,675 (43.9)      | 0.472   |
| HTN, complicated f       | 3,660 (14.3)                                | 185 (19.4)                                | 3,845 (14.5)       | 0.047   |
| Diabetes Mellitus without chronic complications g | 4,730 (18.4) | 225 (23.6) | 4,955 (18.6) | 0.074  |
| Diabetes Mellitus with chronic complications g | 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  |                                             |                                           |                    |         |
| PV D                     | 230 (0.9)                                   | 20 (2.1)                                  | 250 (0.9)          | 0.092   |
| BMI ≥ 25 Kg/m² c         |                                             |                                           |                    | 0.728   |
| Hyperlipidemia           |                                             |                                           |                    | 0.006   |
| Hyperthyroidism          |                                             |                                           |                    | 0.341   |
| Chronic heart failure    |                                             |                                           |                    | 0.281   |
| Chronic Kidney Disease   |                                             |                                           |                    | 0.045   |
| HIV g                    |                                             |                                           |                    | 0.785   |
| Valvular disease         |                                             |                                           |                    | 0.061   |
| Atrial fibrillation & flutter |                         |                                           |                    | 0.115   |
| Prior PPM h              |                                             |                                           |                    | 0.175   |
| Prior ICD i              |                                             |                                           |                    | 0.931   |
| COPD k                   |                                             |                                           |                    | 0.724   |
| Obstructive Sleep         |                                             |                                           |                    | 0.731   |
| Apnea                    |                                             |                                           |                    |         |
| Pulmonary Hypertension   |                                             |                                           |                    |         |
| Prior ischemic stroke    |                                             |                                           |                    |         |
| Liver disease            |                                             |                                           |                    |         |
| Coagulopathy             |                                             |                                           |                    |         |
| Solid tumor without metastasis |             |                                           |                    |         |
| Metastatic Cancer        |                                             |                                           |                    |         |
| Underweight              |                                             |                                           |                    |         |
| Malnutrition             |                                             |                                           |                    |         |
| Ethanol                  |                                             |                                           |                    |         |
| Tobacco                  |                                             |                                           |                    |         |
| 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.
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
cardiac arrest; AKI, acute kidney injury; CI, confidence interval; OR, odds Ratio. TCM, takotsubo cardiomyopathy; LBBB, left bundle branch block; SCA, sudden kidney injury (OR = 0.331), acute HF (OR = 1.23, 95% CI 1.08–1.29, 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 dysynchrony.[22] Intraventricular dysynchrony 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 intraventricular mechanical dysynchrony 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

### Table 2

| Outcomes                          | LBBB Present (n = 955) | LBBB Absent (n = 25,660) | OR 95% CI       | p value |
|-----------------------------------|------------------------|--------------------------|-----------------|---------|
| Ventricular arrhythmias           | 60 (6.81)              | 1,015                    | 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                    | 4,940                    | 1.23 0.83–1.82  | 0.307   |
| AKI                               | 115                    | 2,170                    | 1.26 0.76–2.11  | 0.377   |
| Cardiogenic shock                 | 40 (4.19)              | 1,185                    | 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                    | 4,795                    | 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.

Fig. 3. Adjusted odds ratio for all specified outcomes among patients with Takotsubo Syndrome and left bundle branch block.
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 dys synchrony 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 multivariable 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 mis-coded 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.

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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 writing, writing, and manuscript revisions.

Appendix A. Supplementary material

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