



Occurrence, mortality and predictors of complicated cardiac perforation in patients with CRT-D: Based on the National Inpatient Sample registry

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ABSTRACT

Background: Cardiac Resynchronization Therapy Defibrillator (CRT-D) has been one of the most important therapies for patients with cardiomyopathy over the last decades. Cardiac perforation occurs infrequently but can be fatal. The occurrence of cardiac perforation after CRT-D implantation has not been studied well. The aim of study is to investigate the occurrence, mortality and predictors of cardiac perforation in patients receiving CRT-D during the index hospitalization.

Methods: Data were obtained from the National Inpatient Sample, the largest all-payer inpatient dataset in the United States. Patients who received CRT-D from 2002 to 2012 were identified using ICD-9 codes. Multivariate analyses were used to identify predictors of cardiac perforation. Complications including in-hospital death and cardiac perforation were identified using ICD-9 codes.

Results: A total of 77,827 patients with CRT-D implantation were included into our analysis. After the CRT-D implantation, the in-hospital and rate of cardiac perforation was between 0.24 and 0.48% and had increased significantly ($p = 0.02$). Although occurrence of cardiac perforation is rare (0.32%), the mortality was 10.6% among those patients with cardiac perforation. In Multivariate analysis identified female as independent risk factors for cardiac perforation (OR: 2.628, 95% CI 1.926–3.585, $p < 0.0001$).

Conclusion: Despite rapid progress of the tools and skills for CRT-D implantation, the occurrence of cardiac perforation has not improved. While cardiac perforation is rare, it carries the highest rate of mortality, especially in female patients. Implanting physicians should be familiar with the comorbidities and patient demographics that put them at a higher risk for complications.

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1. Introduction

Cardiac resynchronization therapy (CRT) has been one of the most important advanced heart failure therapies that reduce all-cause mortality, death from progressive heart failure, and symptoms of heart failure and improve left ventricular (LV) systolic function [1–6]. After FDA approval in 2001, the number of Cardiac Resynchronization Therapy Defibrillator (CRT-D) implantations has increased. From 2002 to 2012, >500,000 patients received a CRT-D and >75,000 received a cardiac resynchronization therapy pacemaker (CRT-P) in the United States alone [7].

Most patients who undergo implantable cardioverter defibrillator (ICD) or CRT-D implantation have cardiomyopathy with reduced LV systolic function and are at risk for significant complications including

cardiogenic shock and death. Average in-hospital mortality in patients who underwent CRT was reported from 0.3% to 1.0% [8,9]. Cardiac tamponade is a potentially fatal complication and can lead to significant morbidity and mortality. However, the occurrence, mortality and predictors of cardiac tamponade in CRT-D recipients in a large cohort have not been studied well.

Hypothetically, the increased experience of implantation along with progression of the techniques and tools for implantation would have made the procedure easier and safer, as a result the complication rate should have been lower than previously reported.

Herein, we report on the rate of complicated cardiac perforation after CRT-D implantation using data from the National Inpatient Sample (NIS) registry from 2002 to 2012.

2. Methods

2.1. Data source

Data was collected from the NIS registry, the largest public all-payer inpatient care database representing >95% of the United States (US) inpatient population [10]. NIS is the largest all-payer inpatient database in the US and contains a 20% stratified sample of all

Abbreviations: CRT, Cardiac Resynchronization Therapy; LV, left ventricle; CRT-D, Cardiac Resynchronization Therapy Defibrillator; CRT-P, Cardiac resynchronization therapy pacemaker; ICD, Implantable cardioverter defibrillator; CS, coronary sinus; US, United States; NIS, National Inpatient Sample; PPM, permanent pacemaker; CIED, Cardiac Implantable Electronic Device; IQR, interquartile range; NCDR, National Cardiovascular Data Registry.

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discharges from US nonfederal short-term general hospitals, subspecialty hospitals, and public hospitals, which are stratified based on the number of beds, ownership, hospital teaching status, US region, and state. National estimates can be calculated using sampling weights provided by the NIS. This de-identified database has been previously described and used in studies examining temporal trends and safety of various procedures [11–14]. The data includes primary and secondary admission diagnoses, primary and secondary procedures, admission and discharge status, demographic information such as sex, age, race and ethnicity, zip-code derived median income, and length of stay. Hospital demographic information included hospital region, teaching status, ownership type, and bed size. Institutional review board approval and informed consent were not required for this study, as all data collection was derived from a de-identified administrative database.

2.2. Study design

We analyzed patients hospitalized with a primary diagnosis of CRT implantation from 2002 to 2012 using the International Classification of Diseases, Ninth Edition (ICD 9) codes of CRT-D implantation (00.51). We excluded patients who underwent CRT-P (00.50), who underwent upgrade to CRT-D (00.52) and those who received generator exchange of the CRT-D (00.53, 00.54). Patients who underwent implantation of any type of permanent pacemaker (PPM) device (ICD-9-CM procedure code 00.50, 00.53), upgrade to CRT-D (00.52), replacement of any type of PPM device (37.85, 37.86, 37.87, 37.88, 37.89) or insertion or replacement of PPM leads (ICD-9-CM procedure codes 37.76, 37.77) were also excluded from the analysis.

In-hospital mortality and the rate of major complications were identified using the corresponding ICD-9-CM diagnosis code. In this study, we defined complicated cardiac perforation as pericardial effusion with hemopericardium, cardiac tamponade or surgical intervention. In ICD-9 code, complicated cardiac perforation was identified by hemopericardium (423.0), cardiac tamponade (423.3), pericardiocentesis (procedure code 37.0), cardiomy and pericardiomy (37.10, 37.11 and 37.12) during the index admission. CRT-D patients undergoing concomitant major cardiac procedures known to cause perforation were excluded. Those invasive procedures include diagnostic coronary angiogram, coronary revascularization, catheter ablation, and open-heart surgery except for cardiomy and pericardiomy.

To examine trends and in-hospital complications of patients undergoing CRT-D procedures, other complications were also investigated. To identify pneumothorax, the ICD codes for iatrogenic pneumothorax (512.1), post-operative pneumothorax (512.2) and traumatic pneumothorax (860) were used. Postoperative hemorrhage requiring transfusion was identified with the codes 998.11, 998.12 or 285.1 and 99.01 to 99.09. Lead revision was identified by ICD-9-CM procedure codes 37.75 and 37.79. These ICD-9-CM codes have been consistent during this time period, thereby allowing the analysis of longitudinal trends in the data for prevalence of PPM implantations.

The ICD-9-CM codes used to identify each of these diagnoses and procedures are listed in Supplemental Table 1.

Patient who were younger than 18 years old or older than 90 years old were excluded. Patients with missing information regarding age, gender and mortality were also excluded.

2.3. Predictors

We used the NIS variables to identify patient age, sex, and race. We divided age into 5 subgroups: 18 to 34 years of age, 35 to 49 years of age, 50 to 64 years of age, 65 to 79 years of age, and ≥ 80 years of age. A facility was considered to be a teaching hospital if it had an American Medical Association approved residency program, was a member of the Council of Teaching Hospitals, or had a full-time equivalent ratio of interns and residents to patients of 0.25 or higher. Hospital location (rural/urban) and bed size were also recorded.

2.4. Statistical analysis

We used the weights provided with the NIS to determine national estimates of the number of yearly admissions. Chi square test was used to compare categorical variables between patients with and without complications. Hierarchical mixed-effects logistic regression models were generated to identify the independent multivariate predictors of post procedural complications. Two-level hierarchical models (with patient-level factors nested within hospital-level factors) were created with the unique hospital identification number incorporated as random effects within the model. We included hospital-level variables such as hospital bed size, hospital region (Northeast, South, Midwest, with West as referent), teaching vs. non-teaching hospital, and patient level variables such as age, sex, median household income, and primary payer (with Medicare/Medicaid considered as referent). Hospital identification was introduced as a random effect in the model to account for the effect of hospital clustering. We used SAS software, version 9.4, for all analyses (SAS Institute Inc., Cary, North Carolina). Univariate and distributional analyses included measures of central tendency, kurtosis, and skew. A p value of 0.05 was considered significant.

3. Results

3.1. Baseline clinical characteristics

A total of 268,394 CRT-D implantations were included into our analysis. The number of CRT-D implantation steadily increased from 2002 to

2006 followed by a significant decline until 2012 (Supplemental Fig. 1). Demographics of patients undergoing CRT-D implantation are shown in Table 1. Our results showed that at least one complication occurred in 12,008 of the 268,394 CRT-D implantations performed, resulting in overall complication rate of 4.5%. More than 51.0% of CRT-D recipients were between the age of 65 and 79 years old, 72.7% were performed on male patients, and 61.3% were performed on white subjects. Most CRT-D implantations (72.9%) were performed in large hospitals, hospitals located in urban area (89.3%), and in teaching hospitals (57.0%). Median length of stay was 1 day (1–5 days).

3.2. Trends of in-hospital complications and mortality

The trends of each complication and in-hospital mortality between the year 2002 and 2012 are depicted in Table 2. The mortality after CRT-D implantation has not changed significantly and was 0.66% during the entire duration. The occurrence of cardiac perforation has also increased significantly, and the occurrence was 0.48% in 2012, which was the highest between 2002 and 2012.

Fig. 1 shows the number of each complications and the mortality following the complications. Although the number of cardiac perforations had the second lowest complication rate, the mortality rate is the highest among all complications. Lead revision was the most common complication but carried the lowest mortality risk.

3.3. Characteristics of patients with cardiac perforation

Overall, 870 patients (0.32%) developed cardiac perforation. Compared with patients without cardiac perforation, patients with cardiac perforation were more often women. While only 27% of CRT-D recipients were female, about half (49%) patients who developed cardiac perforation were female. In addition, patients with cardiac perforation were more likely black and Medicaid. Regarding comorbidities, patients with cardiac perforation likely to have higher rates of pulmonary circulation disorders, fluid and electrolyte disorders and coagulopathies, but lower rate of diabetes. Patients with cardiac perforation showed a higher in-hospital mortality (10.60 vs. 0.63 $p < 0.0001$), longer hospital stay (Median 8 days [interquartile range (IQR): 4 to 14 days] vs. 1 day [IQR: 1 to 5 days]; $p < 0.001$) and higher hospital cost (Median \$157,919 [IQR:\$ 83,519 to 148,449] vs. \$111,134 [IQR: \$11,614 to 215,961,146,964]; $p < 0.001$). In addition, patients with cardiac perforation were less likely discharged to home (56.48% vs. 84.93%, $p < 0.0001$). Overall, 92 out of 870 patients (10.6%) who developed cardiac perforation died during admission, which was >16 times higher than the number of CRT-D recipients without cardiac perforation (0.63%) ($p < 0.001$).

3.4. Independent predictors of cardiac perforation

Table 3 demonstrated the multivariate analysis for cardiac perforation. After multivariable adjustment, female was associated with higher odds of cardiac perforation (odds ratio [OR]: 2.628; 95% confidence interval [CI]: 1.926 to 3.585; $p < 0.001$). Fluid and electrolyte disorders and coagulopathy were also associated with higher odds of cardiac perforation (OR: 2.818; 95% CI: 1.922 to 4.130; $p < 0.001$, OR:2.127; 95% CI: 1.141 to 3.965; $p = 0.0176$, respectively). Diabetes was associated with lower odds for cardiac perforation (OR: 0.681; 95% CI: 0.471 to 0.985; $p = 0.0411$).

4. Discussion

Using the NIS of US hospital records, we investigated outcomes, especially cardiac perforation after de novo CRT-D implantation between 2002 and 2012. The major findings are the following: First, the rates of cardiac perforation have been 0.24–0.48% and did not decrease over time. Second, patients with cardiac perforation showed in-hospital

Table 1
Demographics of patients with and without cardiac perforation.

	Overall	No cardiac perforation	Cardiac perforation	p value
Patient-level variables	268,394	267,524 (99.68%)	870 (0.32%)	
Ages in years, %				
18–34	0.80	0.80	1.17	
35–49	5.11	5.10	4.98	
50–64	23.50	23.42	25.58	0.4347
65–79	51.00	51.02	49.49	
≥80	19.56	19.56	18.77	
Sex, %				
Male	72.74	72.58	50.78	<0.001
Female	27.26	27.10	49.22	
Race, %				
White	61.32	61.32	62.11	
Black	8.41	8.40	11.54	
Hispanic	4.81	4.81	5.51	0.0010
Others	3.30	3.30	2.68	
Missing	22.16	22.17	18.15	
Comorbidities, %				
Charlson/Deyo comorbidity index*				
0 or 1	35.61	35.59	41.05	
>2 and ≤4	57.86	57.87	52.40	0.0028
≥5	6.53	6.53	6.56	
Comorbidities, %				
Obesity	7.11	7.12	5.29	0.1042
Hypertension	52.74	52.73	54.69	0.498
Diabetes mellitus	31.59	31.61	25.56	0.0001
Chronic pulmonary disease	19.54	19.54	19.90	0.9162
Peripheral vascular disorders	7.84	7.84	8.24	0.8631
Pulmonary circulation disorders	0.19	0.18	1.00	0.0269
Fluid & electrolyte disorders	9.76	9.71	22.70	<0.0001
Other neurological disorders	2.16	2.16	2.79	0.4193
Coagulopathy	2.71	2.70	7.78	<0.0001
Hospital bed size, %				
Small	8.64	8.64	6.59	
Medium	17.97	17.98	15.75	0.0307
Large	72.90	72.89	77.06	
Hospital region, %				
Northeast	20.54	20.56	16.75	
Midwest or north central	26.24	26.25	23.81	0.0004
South	37.19	37.18	39.42	
West	16.03	16.01	20.02	
Hospital location, %				
Rural	3.15	3.16	1.01	<0.0001
Urban	89.35	89.36	88.05	
Hospital teaching status, %				
Nonteaching	35.48	35.49	33.01	0.0004
Teaching	57.02	57.02	56.05	
Missing	7.50	7.49	10.94	
Median household income, %				
0–25th percentile	25.12	25.12	25.78	
26–50th percentile	25.95	25.95	26.00	0.8134
51–75th percentile	24.53	24.55	23.23	
76–100th percentile	21.74	21.73	22.70	
Primary payer, %				
Medicare	72.46	72.24	68.48	
Medicaid	4.63	4.61	6.75	0.0075
Private including HMO	20.01	20.00	21.90	
Self-pay/no charge/other	2.79	2.90	2.87	
Outcomes				
In-hospital mortality, %	0.66	0.63	10.60	<0.0001
Median length of stay, days, (interquartile range)	1 (1–5)	1(1–5)	8(4–14)	<0.0001
Median cost, \$, (interquartile range)	111,251 (83,591–148,449)	111,134 (83,490–148,207)	157,919 (116,144–215,961)	<0.0001
Disposition among survivors, %				
Home	84.85	84.93	56.48	<0.0001
Facility/others	15.15	15.07	43.52	

mortality of 10.6%. Third, female sex was identified as independent factors that increased the odds of developing cardiac perforation.

4.1. Complication risk after CRT-D implantation

In our analysis, the overall complication rate was 4.5%. Although definition of complications is not consistent among studies, complication

risks after ICD and CRT-D implantation has been reported to be 3–8% [8,14,16–24]. In addition, most study showed that CRT-D recipients had higher risk for major or minor complications compared to ICD or permanent pacemaker recipients [17,25].

Post-operative cardiac complication (ICD-9 code 997.1) was not included in our analysis because it is difficult to tell the complication was really caused by the implantation procedure, due to the lack of

Table 2
Trends of each complication and in-hospital mortality.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Overall	p value
Mortality	0.66	0.72	0.98	0.75	0.64	0.47	0.67	0.63	0.58	0.71	0.45	0.66	0.0701
Any complications	2.87	3.66	3.97	3.43	4.65	4.62	4.85	4.72	4.97	4.62	5.37	4.47	0.008
Any complications & mortality	3.53	4.63	4.85	4.06	5.15	5.01	5.46	5.33	5.43	5.18	5.61	5.03	0.0053
Major complications	2.5	1.87	1.88	1.87	1.75	1.85	2.01	2.07	2.28	2.36	2.45	2.01	0.2736
Major complications & mortality	3.16	2.51	2.80	2.55	2.34	2.26	2.65	2.68	2.76	2.92	2.74	2.60	0.7301
Postoperative hemorrhage requiring transfusion	1.04	0.58	0.58	0.51	0.50	0.60	0.66	0.77	0.80	1.06	0.98	0.68	0.1232
Accidental puncture, other vascular complications	0	0.57	0.48	0.35	0.42	0.50	0.46	0.49	0.29	0.30	0.40	0.42	0.5849
Pneumothorax	1.45	1.00	1.02	1.14	0.99	0.99	1.13	0.97	1.14	1.01	1.01	1.05	0.4604
Cardiac perforation	0	0.36	0.28	0.24	0.28	0.26	0.34	0.36	0.43	0.36	0.48	0.32	0.02
Infection	0.37	0.65	0.78	0.45	0.58	0.26	0.18	0.21	0.12	0.17	0.21	0.36	0.0117
Wound disruption	0	0.13	0.13	0.05	0.04	0.03	0.13	0.06	0.02	0.13	0.13	0.08	0.4331
Lead revision	0	0.44	0.61	0.67	1.75	2.01	1.87	1.86	2.20	1.68	1.89	1.53	0.0157

specific definition. This is likely the main reason that the overall complication rate was lower than other studies using the NIS data (6.11%) [26].

4.2. Occurrence of cardiac perforation

In our analysis, 870 patients (0.32%) developed cardiac perforation. The occurrence of cardiac perforation in patients CIED (Cardiac Implantable Electronic Device) recipients has been reported to be 0.1–0.7% [17,21–24,26,27]. Using the NIS, Cheung et al. reported the occurrence of cardiac perforation in patients receiving de novo CRT-D as 0.4%, which is consistent with our result [24]. In the NIS, the occurrence of cardiac perforation in patients after pacemaker implantation was reported to be 0.28% and slightly lower than those with CRT-D [27]. NCDR study by Hsu et al. reported the occurrence of cardiac perforation in patients with defibrillator (ICD or CRT-D) as 0.14%. In their analysis, although CRT-D was not independent predictor for cardiac perforation, CRT-D was more prevalent in patients with cardiac perforation. Generally, CRT-D recipients require more pacing leads than pacemaker and ICD recipients, and that likely to be associated with the higher complication rates [18]. A large Danish cohort showed that the occurrence of major complication was the 2.6 times higher in patients with CRT-D than dual chamber pacemaker [25].

4.3. The high mortality after cardiac perforation

The mortality rate of patients who developed cardiac perforation was 10.6% and 16 times higher compared with those without cardiac tamponade. In recent study analyzing NIS, the mortality after cardiac perforation among recipients with permanent pacemaker was reported to be 6.8% [27]. Based on NCDR database, Hsu et al. reported the crude risk of in-hospital death in defibrillator (ICD or CRT-D) patients with cardiac perforation to be 5.6% [22]. This is the first time, to our knowledge, that in-hospital mortality following cardiac perforation in CRT-D recipients has been investigated on a large data base. The higher mortality after cardiac perforation in patients with CRT-D can be a reflection of a sicker population that is prone to perforation. In dilated cardiomyopathy, the muscle wall would become stretched and thin, that likely contribute to the higher rate of cardiac perforation.

4.4. Predictors for cardiac perforation

Multivariate analysis revealed that women were associated with higher rate of cardiac perforation. Female gender has been reported to be associated with higher occurrence of cardiac perforation compared to male [16,25,27,28]. This suggests that women may have anatomy characteristics that pose greater technical challenges, such as a thinner

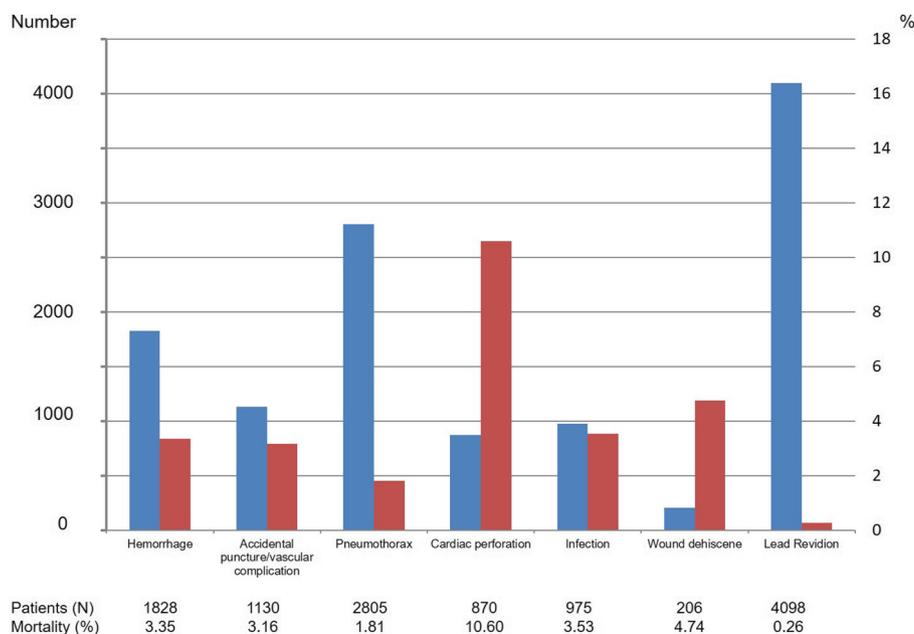


Fig. 1. Occurrence of complication (blue) and in-hospital mortality (red) after each complication.

Table 3
Multivariate analysis for cardiac perforation after CRT-D implantation.

	Odds ratio	95% CI	p value
Age			
18–34	Referent		
35–49	0.721	0.145–3.583	0.6894
50–64	0.956	0.221–4.123	0.9515
65–79	0.947	0.214–4.188	0.9424
≥80	0.887	0.195–4.031	0.8769
Female	2.628	1.926–3.585	<0.001
Emergency/urgent admission	1.081	0.917–1.275	0.8431
Income			
1st quartile	Referent		
2nd quartile	1.083	0.705–1.663	0.7150
3rd quartile	0.949	0.596–1.512	0.8270
4th quartile	1.327	0.830–2.122	0.2367
Payer status			
Medicare	Referent		
Medicaid	1.811	0.906–3.622	0.0930
Private insurance	1.108	0.684–1.797	0.6768
Self-pay	0.738	0.224–2.435	0.6177
Hospital bed size			
Small	Referent		
Medium	1.000	0.449–2.228	0.9981
Large	1.257	0.628–2.517	0.5186
Hospital region			
Northeast	Referent		
Midwest	1.018	0.562–1.842	0.9542
South	1.310	0.748–2.292	0.3451
West	1.407	0.661–2.996	0.3753
Teaching hospital	1.147	0.761–1.729	0.5122
Obesity	0.747	0.372–1.499	0.4144
Hypertension	1.095	0.796–1.507	0.5778
Diabetes	0.681	0.471–0.985	0.0411
CHF	1.966	0.928–4.165	0.0776
Chronic lung disease	0.860	0.579–1.277	0.4537
Peripheral vascular disease	1.379	0.808–2.353	0.2384
Pulmonary Circulation Disorders	0.854	0.908–7.472	0.8866
Fluid and electrolyte disorders	2.818	1.922–4.130	<0.0001
Neurological disorder	1.419	0.609–3.303	0.4172
Coagulopathy	2.127	1.141–3.965	0.0176

RV wall and smaller blood vessel diameter, which may predispose them to adverse events. Anatomical disadvantage for LV lead placement and higher chance of coronary venous dissection in women have also been reported [16,29]. Patients with congestive heart failure are likely to have dilated left and right ventricles, and those findings might be related to overall frailty that affords susceptibility to complications.

In our analysis, patients with coagulopathy were associated with higher rate of cardiac perforation. In patients receiving pacemakers, liver disease and impaired coagulation were identified as independent predictors of cardiac tamponade [27]. They speculated that impaired coagulation, as well as intrinsic cirrhosis are potential mechanisms that are partly responsible for the increased rate of tamponade in patients with pacemaker implants. The same theory would apply for CRT-D recipients in our analysis. Conversely diabetes mellitus was associated with lower odds of cardiac perforation. Interestingly this is consistent with a previous report from NCDR data analysis [22]. Epicardial fat thickness was reported to be higher in patients with diabetes [30] and increased thickness of epicardial fat tissue induced by diabetes mellitus may be protective against cardiac perforation and myocardial wall puncture. Although temporary transvenous pacemaker installation and steroid use were reported as independent risk factors in patients with CIED implantations, those risk factors were not investigated in our study [31].

4.5. Study limitations

Although the NIS represents the largest study of CRT implantation to date, there are several limitations. First, the NIS is an administrative database, which carries the risk of errors arising from coding inaccuracies.

Second, this study is retrospective study and selection bias can happen. Although increasing number of patients receiving CRT-D implantations at outpatient, our data is limited to inpatient procedure. Third, our study reports incidences of in-hospital cardiac perforations among CRT-D recipients and complications that occurred after hospital discharge could not be captured. However, previous studies have shown that most complications after implantable cardiac device implantation, including cardiac tamponade, occur before discharge and our findings would not differ significantly from the actual incidence of those complications [21,32]. Fourthly, the NIS database does not contain any information regarding the type of leads (active vs. passive), size, or device manufacturer of the PPM devices, and therefore, the associations between these factors and the occurrence of cardiac perforations could not be investigated. Lastly, the recent introduction of quadripolar LV leads has demonstrated a reduction easy deliverability and lower rate of phrenic nerve injury which would affect the rate of complications including cardiac perforations [33].

5. Conclusions

Our study represents real-world experience in a large population of patients undergoing CRT-D implantation in the U.S. from 2002 to 2012. Although occurrence of cardiac perforation is low (0.32%), the mortality was 10.6% among those patients with cardiac perforation. Female was found to be independently associated with a greater odds of cardiac perforation and implanting physicians should be aware that.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.05.018>.

Declaration of Competing Interest

HK: None
 AE: None
 OL: None
 RC: None
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