



ORIGINAL ARTICLE

Trends, burden, and impact of arrhythmia on cardiac amyloid patients: A 16-year nationwide study from 1999 to 2014

Ameesh Isath MBBS¹  | Ashish Correa MBBS² | Gregory P. Siroky MD²  |
Stuthi Perimbeti MBBS, MPH¹ | Selma Mohammed MD⁴ |
C. Anwar A. Chahal MBChB, PhD, MRCP^{3,5} | Deepak Padmanabhan DM^{3,6} |
Davendra Mehta MD, PhD²

¹Department of Medicine, Mount Sinai St. Luke's and Mount Sinai West, New York, NY, USA

²Department of Cardiology, Mount Sinai St. Luke's, New York, NY, USA

³Department of Cardiovascular Medicine, Mayo Clinic, Jacksonville, FL, USA

⁴Department of Cardiovascular Medicine, MedStar Washington Hospital Center, Washington, DC, USA

⁵University of Pennsylvania, Philadelphia, PA, USA

⁶Sri Jayadeva Institute of Cardiovascular Sciences and Research, Cardiology, Bengaluru, Karnataka, India

Correspondence

Davendra Mehta, Mount Sinai St. Luke's, 1111 Amsterdam Ave, New York, NY 10025, USA.

Email: davendra.mehta@mountsinai.org

Abstract

Background: Patients with cardiac amyloidosis (CA) have increased mortality, which can be explained in part by an increased risk of arrhythmias. The burden of arrhythmias in CA, their predictors, and impact on in-hospital outcomes remains unclear. The role of implantable cardioverter-defibrillators (ICD) in this population is also uncertain.

Methods: We queried the National Inpatient Sample (NIS) using ICD-9-CM codes 277.39 and 425.7 to identify CA. Twelve common arrhythmias were extracted using appropriate, validated ICD-9-CM codes. ICD implantation was identified using procedure ICD-9 codes 37.94 to 37.98, 00.51 and 00.54.

Results: There were a total of 145,920 CA hospitalizations between 1999 and 2014 in the United States and 56,199 (38.5%) of them were associated with arrhythmias. The prevalence of arrhythmias remained relatively constant from 41.5% in 1999 to 40.2% in 2014. The most common arrhythmia was atrial fibrillation (25.4%). In-patient mortality was significantly higher in CA patients with arrhythmias (10.4% vs 6.5%, $P < .001$). ICD implantation was performed in 1,381 (0.94%) patients with CA and analysis revealed an incremental trend in implantation over the study period (0.48% in 1999 to 0.65% in 2014). In-hospital mortality was significantly lower in patients who underwent ICD implantation (3.7% vs 8%; $P = .0078$). CA patients with arrhythmias also had an increased cost of hospitalization and length of stay ($\$65,046 \pm 1,079$ vs $\$53,322 \pm 687$ and 8.3 ± 0.1 vs 7.4 ± 0.1 days, respectively; $P < .0001$).

Conclusion: Cardiac arrhythmias are common in patients with CA and are associated with worse in-hospital outcomes, increased length of stay, and cost of hospitalization.

KEYWORDS

arrhythmias, cardiac amyloidosis, national inpatient sample

Davendra Mehta is the senior author.

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1 | INTRODUCTION

Cardiac amyloidosis (CA) is one of the most common infiltrative cardiomyopathies and is an increasingly recognized cause of heart failure with preserved or reduced ejection fraction.¹ Its pathophysiology is attributed to an abnormal deposition of misfolded protein, known as amyloid fibrils, in the cardiac tissue.² There are multiple forms of amyloidosis, however, cardiac involvement is primarily due to deposition of either immunoglobulin light chains (AL) or transthyretin (ATTR).³

The prevalence of arrhythmias in CA has been described in a few studies to date, though atrial and ventricular arrhythmias (VA) seem to be fairly common.⁴⁻⁸ The exact mechanism of arrhythmias in CA is poorly defined and likely multifactorial. Reentrant circuits and triggered activity are possible mechanisms given the particular toxic effect of light chains on the myocardium in the AL variant. Amyloid fibril deposition leading to impaired relaxation with elevated filling pressures resulting in atrial dilation which can predispose to atrial arrhythmias such as atrial fibrillation (AF).^{6,9,10} Previous studies have also demonstrated the co-relation of pathological atrial amyloid deposits to AF.^{9,11} Limited retrospective studies have also demonstrated that VAs are common in CA and associated with increased mortality.^{4,5} The independent effect of arrhythmias on mortality in these patients is still under investigation, with recent data indicating a larger role than previously thought.⁵

Despite the high risk of cardiovascular mortality in patients with CA, implantation of implantable cardioverter defibrillators (ICD) in these patients is not widespread. Observational data presented by Kristen et al suggest that ICDs do not improve survival¹². There is also a high 1-year mortality in patients with CA, thereby excluding them from ICD implantation based on guidelines. However, data are now emerging that the VAs may indeed have a role in sudden cardiac death (SCD) in CA (especially the AL variant) and patients may benefit from device therapy.^{8,13,14} Furthermore, as therapies for CA improve, life-expectancy of these patients will undoubtedly improve.

While arrhythmias in CA is being increasingly recognized, there are limited data on the trends, predictors, and clinical impact of arrhythmias in a large, real-world population. We investigated the trends and burden of cardiac arrhythmias in patients with CA. In doing so we aim to describe the clinical predictors of arrhythmia, impact of arrhythmias on in-hospital outcomes, trends in the use, and role of ICD therapy in CA patients with arrhythmia along with measures of health care utilization.

2 | METHODS

2.1 | Data source

Our study was conducted utilizing Healthcare Cost and Utilization Project (HCUP)—Nationwide Inpatient Sample (NIS) dataset from 1999 through 2014 which is available publicly online.¹⁵ The NIS

represents 95% of the United States (US) hospitalizations from 44 states participating in HCUP, provides a stratified sample of 20% of discharges and includes up to 8 million hospital discharges per year, making it the largest all-payer inpatient dataset in the US. The NIS database has been demonstrated to correlate well with other discharge databases in the US and has been validated in various studies to provide reliable estimates of admissions within the US.¹⁶ Data collection methods and administration of NIS are detailed.¹⁷ The NIS database also provides the total expenses associated with each hospital which are then converted to cost estimates using the group average all-payer in-hospital cost information from the detailed reports by hospitals to the Centers for Medicare and Medicaid Services. All costs and charges were adjusted for annual inflation rates on the basis of consumer price index data available from the Bureau of Labor Statistics.

2.2 | Study population

We included hospitalizations with a diagnosis of cardiac amyloidosis based on International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 277.39 and 425.7. Twelve common arrhythmias were identified using ICD-9-CM codes (Supplementary Table S1). ICD implantation was identified using the ICD-9-CM code 37.94 to 37.98; 00.51; 00.54. The ICD-9-CM codes used to identify each of these diagnoses and procedures are listed in Supplementary Table S1.

2.3 | Definition of variables

NIS variables were used to identify age, sex, and race (Whites, African American, Hispanics or other). The severity of comorbid conditions was defined using the Deyo modification of the Charlson Comorbidity Index (CCI).¹⁸ This index contains 17 comorbid conditions with differential weights. The score ranges from 0 to 33, with higher scores corresponding to greater burden of comorbid diseases.

2.4 | Statistical analysis

Statistical Analysis System (SAS) 9.4 (SAS Institute Inc) was used for all analyses and a *P* value of <.05 was considered statistically significant. Since the HCUP database approximates only 20% stratified sample of US hospitals, it is recommended to obtain weighted numbers to calculate regional and national estimate. The discharge weights provided by the Agency for Healthcare Research and Quality were applied.¹⁵ The hazard ratios were adjusted for age, sex, CCI, and race. Chi-square test was used for categorical variables, and for non-normal distributed continuous variables such as length of stay, Student's *t* test was used. Logistic regression models were generated to identify the independent multivariate predictors for arrhythmias and ICD implantation.

3 | RESULTS

There was a total of 145,920 hospitalizations due to CA between 1999 and 2014 in the United States. There was a steady increase in the number hospitalizations for CA with an approximately fivefold increase from 3330 in 1999 to 17 755 in 2014 (Figure 1).

Among the 145 920 CA hospitalizations, 56,199 (38.5%) had concomitant cardiac arrhythmias. The yearly prevalence of arrhythmias remained relatively stable from 41.5% in 1999 to 40.2% in 2014.

The most common arrhythmia was AF (25.4%) followed by ventricular tachycardia (VT) (5.1%) (Figure 2). Ventricular fibrillation contributed to the majority of the inpatient mortality (47.3%), followed by ventricular tachycardia (13.8%) (Figure 3).

Table 1 compares the baseline demographics, comorbidities, and hospitalization characteristics of the two groups (CA hospitalizations with and without arrhythmias). The median age of the patients with arrhythmias was 73 years [Interquartile range (IQR) 63-81] and for patients without arrhythmias was 69 years [IQR 57-74] ($P < .0001$).

The majority of the patients with arrhythmias were men (64%) and the study group was predominantly white population (59.8% in patients with arrhythmia and 56.4% in patients without arrhythmia). CA patients with arrhythmias had more thyroid disease (20.6% vs 15.9%), heart failure (59.3% vs 33.2%), and renal failure (33.3% vs 30.6%), but had less hypertension (29.7% vs 34.7%) and diabetes mellitus (22.7% vs 26%) ($P < .0001$). There was no significant difference in the CCI between the groups.

Table 2 demonstrates independent factors associated with an increased risk of arrhythmias. Heart failure and thyroid disorders were noted to be independent predictors for arrhythmias in patients with CA. Women had a lower risk of arrhythmias when compared to men (Hazard ratio (HR) [95% Confidence interval (CI)]; 0.56[0.43-0.72]. African Americans and Hispanics had lower risk of arrhythmias compared to white patients (HR [95%CI]; 0.83[0.79-0.87], 0.76[0.69-0.82], respectively).

CA patients with arrhythmias were associated with a 34% increased risk of inpatient mortality compared to those patients

FIGURE 1 Trends of cardiac amyloidosis from 1999 to 2014. Figure 1 describes the annual number of CA diagnosis from 1999 to 2014 with an increasing trend. CA, cardiac amyloidosis

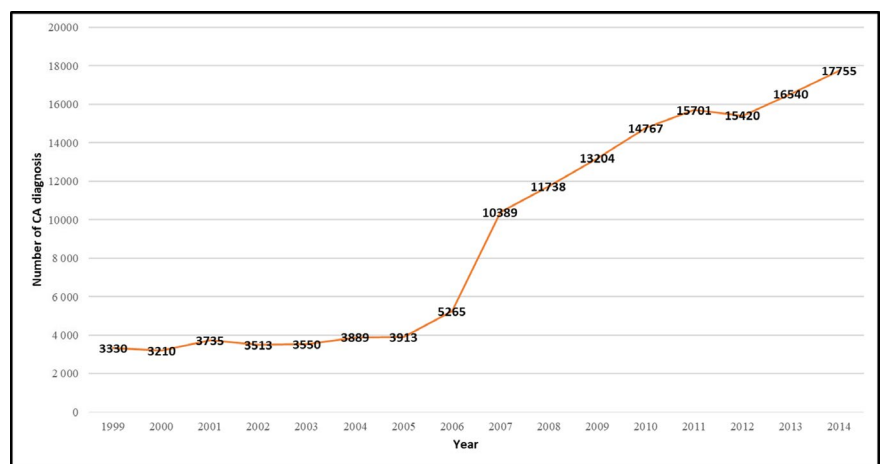
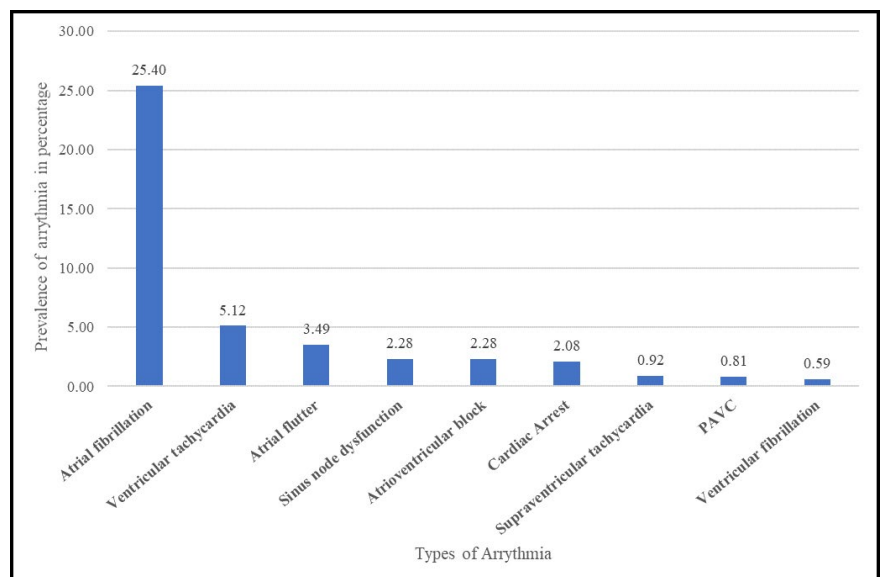


FIGURE 2 Types of Arrhythmias in Cardiac amyloidosis. Figure 2 demonstrates the distribution of the types of arrhythmias in cardiac amyloidosis with most common being atrial fibrillation (Legend as above). PAVC, premature atrial/ventricular complex



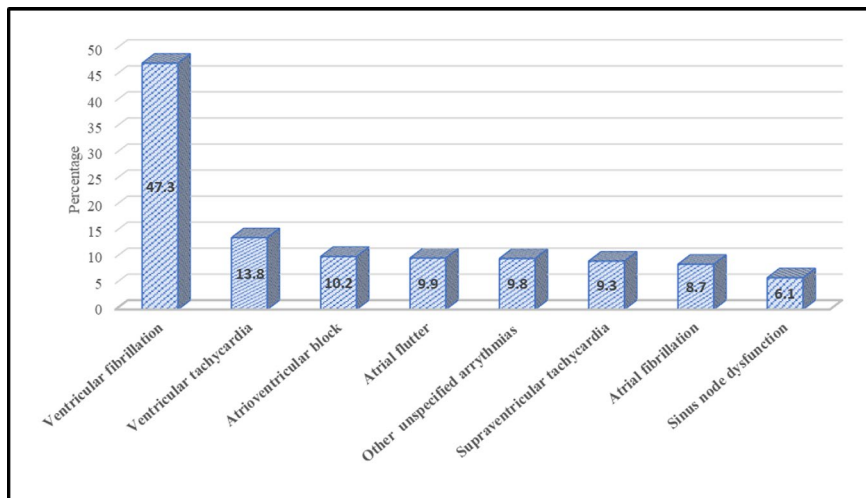


FIGURE 3 In-hospital Mortality by Arrhythmia type. Figure 3 describes inpatient mortality based on type of arrhythmia

without arrhythmias (HR [95%CI]; 1.34[1.23-1.46]). Cardiogenic shock and the need for mechanical circulatory support was also significantly higher in the arrhythmia group (2.4% vs 0.7% and 0.6% vs 0.2%, respectively). CA patients with arrhythmias were also associated with a significantly higher rate of ICD implantation (HR [95%CI]; 14.05[9.25-21.34]) and pacemaker implantation (HR [95%CI]; 11.44[8.49-15.39]). (Table 3) Subgroup analysis of outcomes of atrial and ventricular arrhythmias are as shown in Table 4.

Among CA patients with arrhythmias, the cumulative length of stay was higher when compared with patients without arrhythmia (8.3 ± 0.1 vs 7.4 ± 0.1 days, respectively; $P < .0001$) with an increased cost of hospitalization ($\$65,046 \pm 1079$ vs $\$53,322 \pm 687$, $P < .0001$).

A subgroup analysis of patients with the most common arrhythmia, atrial fibrillation was performed. The annual prevalence of AF among patients with CA remained consistent from 27.5% ($n = 916$) in 1999 to 27.4% ($n = 4875$) in 2014. Inpatient mortality was significantly higher in CA patients with AF (10.4% vs 6.5%, $P < .0001$). Furthermore, cardiogenic shock was significantly higher in amyloidosis patients with AF (2.1% vs 1.2%, $P < .001$), but the use of mechanical circulatory support was not significantly different between the groups. (0.42% vs 0.35%, $P = .375$). In addition, implantation of pacemakers was also noted to be higher in CA patients with AF compared to patients without AF (2.8% vs 1.2%, $P < .0001$). The baseline demographics and co-morbidities was similar to that of the total arrhythmia group. CA patients with AF suffered more from diseases of the thyroid (22.5% vs 16.1%), heart failure (62.9% vs 36.5%) and renal failure (34.7% vs 30.5%), but less from hypertension (29.3% vs 34.0%) and diabetes mellitus (23.2% vs 25.2%) ($P < .0001$). There was no significant difference in the CCI between the groups.

Of the 149,520 CA patients, 1,381 (0.94%) underwent ICD implantation with an increasing trend toward ICD implantation over the years [0.48% in 1999 to 0.65% in 2014, $p_{\text{trend}} = 0.0292$]. Heart failure was an independent predictor for ICD implantation in patients with CA (HR [95%CI]; 4.14[3.11-5.5]). (Table 5) CA patients who underwent ICD implantation during their hospital stay had a lower in-patient hospital mortality compared to those who did not receive an ICD (3.7% vs 8%, $P < .0078$).

4 | DISCUSSION

The salient findings of our study are as follows: (a) cardiac arrhythmias are common in patients with CA, with AF being the most common; (b) cardiac arrhythmias complicating CA were associated with worse in-hospital outcomes, increased length of stay, and higher cost of hospitalization; and (c) the rate of ICD implantation has been increasing over time and is associated with improved short term mortality in patients with CA.

Falk et al showed that complex ventricular and supraventricular arrhythmias are common in patients with CA on ambulatory electrocardiography and despite the relatively low mortality in this study, 33% patients with more complex arrhythmias suffered from sudden cardiac death.⁶ This has been demonstrated in other studies, with a prevalence of VAs documented as high as 27% in patients with CA.^{14,19,20} However, no large-scale registries or studies examined the burden of arrhythmias in cardiac amyloidosis. The NIS database is a very well validated and nationally representative database which provides population level information that is generalizable to the whole US population. As such, our study provides useful information in this regard by analyzing nationally representative data.

AF is the most common arrhythmia in cardiac amyloidosis with a prevalence of up to 20%–60% in prior studies.^{13,21,22} Our study in a larger subset of patients with CA found a prevalence of 25.4%. AF in CA patients can occur due to elevated left ventricular (LV) and atrial filling pressures secondary to LV diastolic dysfunction as a result of either amyloid fibril deposition within the myocardium or direct atrial myocardial toxicity from the amyloid deposition.^{9,11} Previous studies have shown that the presence of AF does not have a significant impact on mortality in CA,^{13,23} but can increase the risk of stroke, precipitate heart failure, or result in inappropriate therapies in patients being considered for ICD implantation. However, in a larger real-world population over 16 years, our study demonstrated that patients with AF were associated with increased short-term mortality (10.4% vs 6.5%, $P < .0001$). In our study, arrhythmias in patients admitted with

TABLE 1 Baseline characteristics of patients with Cardiac amyloidosis based on presence or absence of arrhythmia

Variables	Arrhythmias		P value
	Yes	No	
No. of observation, unweighted	11 333	18 103	
No. of observation, weighted	56 199	89 721	
Age, median (IQR)	73(63-81)	69(58-78)	<.0001
Men	64%	53.9%	.0288
Race/Ethnicity			<.0001
White	59.8%	56.4%	
Black	17.8%	18.2%	
Hispanic	4.9%	6.5%	
Other	4.2%	4.8%	
Chronic obstructive pulmonary disease	0.23%	.26%	.711
Coronary artery disease	0.11%	.11%	.065
Hypertension	29.7%	34.7%	<.0001
Peripheral vascular disease	0.76%	.93%	.1657
Thyroid disorders	20.6%	15.9%	<.0001
Diabetes mellitus	22.7%	26%	<.0001
Obesity	4.7%	4.8%	.4802
Congestive heart failure	59.3%	33.2%	<.0001
Heart Failure with preserved EF	14.8%	7.7%	<.0001
Renal failure	33.3%	3.6%	<.0001
Liver disease	1.58%	1.57%	.9393
Hyperlipidemia	20.9%	23.9%	.4435
Smoking	4.3%	6.6%	<.0001
Charlson comorbidity score			.0515
0-1	35.7%	34.1%	
2-3	14.4%	14.2%	
≥4	50.1%	51.4%	
Expected primary payer			<.0001
Medicare	70.6%	63.8%	
Medicaid	5.3%	7.7%	
Private	19.8%	23.7%	
Others	4.3%	4.6%	
Median household income in quartile			<.0001
1st quartile	21.3%	23.4%	
2nd quartile	23.1%	23.8%	
3rd quartile	24.8%	24.8%	
4th quartile	30.7%	27.9%	

Bold *P* values are significant (*P* < .05).

Abbreviations: EF, ejection fraction; IQR, interquartile range.

CA were associated with significantly worse clinical outcomes. In-hospital mortality was more frequent in the arrhythmia cohort (10.4% vs 6.5%, HR 1.34, *P* < .0001) and was highest among

TABLE 2 Independent predictors of arrhythmias in patients with cardiac amyloidosis

Variables	Hazard ratio	95% CI	P value
Female	0.56	0.43 0.72	<.0001
Diabetes mellitus	0.94	0.90 0.98	.0064
Thyroid disorders	1.32	1.26 1.38	<.0001
Congestive heart failure	1.76	1.69 1.82	<.0001
Race (reference- White)			
Black	0.83	0.79 0.87	<.0001
Hispanic	0.76	0.699 0.82	<.0001
Other	0.78	0.72 0.86	<.0001
Chronic obstructive pulmonary disease	0.86	0.576 1.27	.44
Hypertension	1.06	1.023 1.10	.0021
Renal dysfunction	0.98	0.939 1.01	.20
Smoking history	0.87	0.796 0.95	.0019
Charlson comorbidity index (≥2 compared against 0)	0.77	0.742 0.80	<.0001

Bold *P* values are significant (*P* < .05).

those who experienced VAs. This is in keeping with previous studies which demonstrated the prevalence of VAs in CA and associated mortality.^{5,20} Sayed et al demonstrated that loop recorders implanted in patients with CA demonstrated bradycardia as the most common cause of death; however, the study only included 20 patients.²⁴ Our study demonstrated 4% of patients had sinus node dysfunction which was associated with 6.1% of inpatient mortality.

In the aforementioned study by Falk et al,⁶ 62% of patients with heart failure related to CA had complex arrhythmias compared to 43% without heart failure. They also demonstrated that amyloid deposition could be detected in the thyroid gland of 50%–80% of patients with amyloidosis. However, the relationship between thyroid disorders and cardiac amyloidosis remains unclear. Our study revealed that coexisting heart failure and thyroid disorders are associated with a higher risk of arrhythmias, however, the use of amiodarone in patients with CA could be a potential confounder for the development of thyroid disorders and unfortunately, could not be assessed with this database. Furthermore, women were found to be at a decreased risk of arrhythmias (HR: 0.56, *P* < .0001). The reason for this remain unclear, but Hornsten et al demonstrated that men have more pronounced septal thickness which could play a role in increased prevalence of supraventricular arrhythmias.⁷

A few studies have shown that SCD death from arrhythmias is common in AL cardiomyopathy.²⁰ However, the prognosis of AL amyloidosis is poor, with less than 12 months survival after diagnosis, which is a relative contraindication to ICD implantation.

Clinical outcomes	Arrhythmias		Hazard Ratio (95% CI)	P value
	Yes	No		
In-patient mortality	10.4%	6.49%	1.34 (1.23-1.46)	<.0001
Cardiogenic shock	2.4%	0.7%	2.86 (2.31-3.5)	<.0001
Mechanical circulatory support	0.6%	0.2%	2.36 (1.59-3.51)	<.0001
Pacemaker placement	3.9%	0.2%	11.44 (8.49-15.39)	<.0001
ICD placement	2.2%	0.15%	14.05 (9.25-21.34)	<.0001

TABLE 3 Clinical impact of arrhythmia in patients admitted with cardiac amyloidosis

Furthermore, Kristen et al and Lin et al separately demonstrated that ICD therapy in CA for primary prevention did not improve long term survival, however, the studies did show that ICDs were associated with a high rate of appropriate device therapy, suggesting that ICD implantation may have some beneficial effects.^{12,25}

Over the last decade, with the advent of new therapies for CA, patients can achieve large reductions in the circulating light chains and as a result the prognosis of the disease has significantly improved.^{26,27} Furthermore, more recent data demonstrated the effectiveness of ICD implantation in a subset of patients with increased risk of arrhythmias, especially in patients whose life expectancy is greater than 1 year. Varr et al demonstrated successful ICD therapy in 80% of the patients with CA indicating that ICDs may indeed play a significant role in improving survival in patients with CA.⁵

Our study demonstrates that the use of ICD therapy in CA has significantly increased from 0.48% in 1999 to 0.65% in 2014 which can be postulated to be as a result of improving therapies and thus survival of patients with CA. To date, there have been no prior studies demonstrating a mortality benefit from ICD therapy in CA patients

despite the aforementioned successful ICD therapies. Our study demonstrated the improvement in in-hospital mortality among CA patients (HR [95%CI]; 0.35 [0.19-0.65]) after adjusting for co-morbidities. However, it is to be noted that the long-term benefit of ICD therapy could not be assessed using this database and further prospective studies are needed to evaluate the role of ICDs given recent advances in the management of CA and improving prognosis.^{28,29}

Our study also looked at gender difference and social disparities in the prevalence of ICD implantation in patients with CA. Previous studies have demonstrated that race- and gender-related disparities often persist over years when it comes to in the use of novel procedures.³⁰ Women had a 44% lower likelihood of ICD implantation compared to men, however, there was no significant racial differences in the rates of ICD implantation. These disparities are in concordance with previous studies which demonstrated race and sex disparities in ICD utilization rates.^{31,32} Our study did demonstrate the lower likelihood of arrhythmias in women compared with men, however, the disparity in ICD therapy can be related to other patient- and provider-related factors which needs further studies to fully understand.

TABLE 4 Subgroup analysis of clinical impact on patients admitted for cardiac amyloidosis based on atrial vs ventricular focus of arrhythmia

Clinical outcomes	Ventricular arrhythmias		P value
	Yes	No	
In-patient mortality	16.13%	7.51%	<.0001
Cardiogenic shock	5.68%	1.17%	<.0001
Mechanical circulatory support	1.63%	0.30%	<.0001
Pacemaker placement	4.00%	1.54%	<.0001
ICD placement	9.34%	0.46%	<.0001
Clinical outcomes	Atrial arrhythmias		P value
	Yes	No	
In-patient mortality	8.90%	7.65%	.0003
Cardiogenic shock	2.07%	1.17%	<.0001
Mechanical circulatory support	0.47%	0.33%	.0998
Pacemaker placement	3.07%	1.16%	<.0001
ICD placement	1.37%	0.79%	<.0001

TABLE 5 Independent predictors of patients with cardiac amyloidosis undergoing ICD implantation

Variables	Hazard ratio	95% CI	P value
Female	0.56	0.43 0.72	<.0001
Diabetes mellitus	1.04	0.785 1.379	.784
Congestive heart failure	4.145	3.11 5.525	<.0001
Race (reference- White)			
Black	1.109	0.819 1.501	.5038
Hispanic	0.629	0.33 1.196	.157
Other	0.897	0.496 1.622	.7193
Chronic obstructive pulmonary disease	0.856	0.576 1.272	.4412
Hypertension	1.134	0.873 1.474	.3463
Obesity	1.104	0.632 1.929	.7286
Liver disease	0.581	0.188 1.798	.3461
Renal dysfunction	0.648	0.493 0.853	.002
Smoking history	1.171	0.683 2.008	.5656

Bold P values are significant ($P < .05$).

5 | LIMITATIONS

This study has certain limitations, most of these are characteristic of studies derived from administrative databases. First, the burden of arrhythmias was estimated using the NIS database which is an administrative database based on coding and is well known to be at risk of coding errors. Also, we were unable to validate individual ICD-9-CM codes which affects the sensitivity and specificity of the codes.

Second, the NIS database is only based on hospital discharge data and thus does not include from ambulatory clinic or emergency department data. Furthermore, there is no access to patient-level information. Third, we are unable to study important data like ejection fraction, laboratory values, or medication use as the NIS database lacks such data. Fourth, NIS database uses "unique admission" as the unit of analysis and thus patients may be represented more than once in case of repeated admissions. Finally, therapies for cardiac amyloidosis are constantly evolving with more novel treatments not being reflected in our study.

However, these limitations may be compensated for by the various strengths of the NIS database. The NIS is well validated and representative of the national population and has our study has good generalizability to the US population. The huge sample size of the NIS database increases the power of the study and allows to compensate for residual confounders which could not be assessed.

6 | CONCLUSION

The number of hospitalizations with cardiac amyloidosis is increasing over time, with a significant proportion of patients with CA manifesting cardiac arrhythmias. Cardiac arrhythmias complicating CA are associated with worse in-hospital outcomes, requirement of additional procedures, increased length of stay, and cost of hospitalization.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

ORCID

Ameesh Isath  <https://orcid.org/0000-0002-7992-8113>

Gregory P. Siroky  <https://orcid.org/0000-0002-8604-7218>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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