Impact of Arrhythmias on Hospitalizations in Patients With Cardiac Amyloidosis

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Cardiac involvement in amyloidosis is associated with a poor prognosis. Data on the burden of arrhythmias in patients with cardiac amyloidosis (CA) during hospitalization are lacking. We identified the burden of arrhythmias using the National Inpatient Sample (NIS) database from January 2016 to December 2017. We compared patient characteristics, outcomes, and hospitalization costs between CA patients with and without documented arrhythmias. Out of 5,585 hospital admissions for CA, 2,020 (36.1%) had concurrent arrhythmias. Propensity-score matching for age, sex, income, and co-morbidities was performed with 1,405 CA patients with arrhythmias and 1,405 patients without. The primary outcome of all-cause mortality was significantly higher in CA patients with arrhythmia than without(13.9% vs 5.3%, p-value <0.001). Atrial fibrillation (AF) was the most common (72.2%) arrhythmia in CA patients with concurrent arrhythmia. The secondary outcomes of AF-related mortality (11.95% vs 9.16%, p-value = 0.02) and acute and acute on chronic as heart failure (HF) exacerbation (32.38% vs 24.91%, p-value <0.0001) were significantly higher in CA and concurrent arrhythmia compared with CA patients without. The total length of hospital stay (6[3 to 12] vs 5[3 to 10], p-value <0.001) and cost of hospitalization were ($ 15,086[7,813 to 30,373] vs $ 12,219[6,865 to 23,997], p-value = 0.001) were significantly greater among CA with arrhythmia compared with those without. These data suggest that the presence of arrhythmias in CA patients during hospital admission is associated with a poorer prognosis and may reflect patients with a higher risk of HF exacerbation and mortality. **(Am J Cardiol 2021;143:125−130)**

Systemic amyloidosis is caused by the deposition of insoluble amyloid fibrils in the extracellular space of tissues, which leads to progressive organ failure and death. The 2 most common sources of amyloid fibrils are plasma cell-derived monoclonal proteins, amyloid light-chain (AL), or hepatic-derived transthyretin (ATTR). Cardiac infiltration with AL and ATTR (cardiac amyloidosis, CA) typically manifests with symptoms of congestive heart failure and/or arrhythmias and is associated with a relatively poorer prognosis compared with patients with involvement of other organs.[1−3] Cardiac involvement is associated with cardiac arrhythmias such as atrial fibrillation (AF), ventricular arrhythmias, bradyarrhythmia from infiltration of the native conduction system, and sudden cardiac death.[4,5] There is a paucity of data regarding the frequency of arrhythmias and related outcomes in patients hospitalized with CA. This study aimed to evaluate the burden of arrhythmias and outcomes in hospitalized patients with CA.

Methods

A population-based sample of 5,585 CA related hospitalizations in patients aged >18 with or without arrhythmias was analyzed in a retrospective manner from 2016 to 2017 using the National inpatient sample (NIS) database (**Figure 1**). The NIS is the largest publicly available all-payer inpatient care database in the United States. Weighted, it estimates data on more than 35 million hospital stays nationally. It was set in motion by the Healthcare Cost and Utilization Project (HCUP) through a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality (AHRQ). Its large sample size is ideal for developing national and regional estimates

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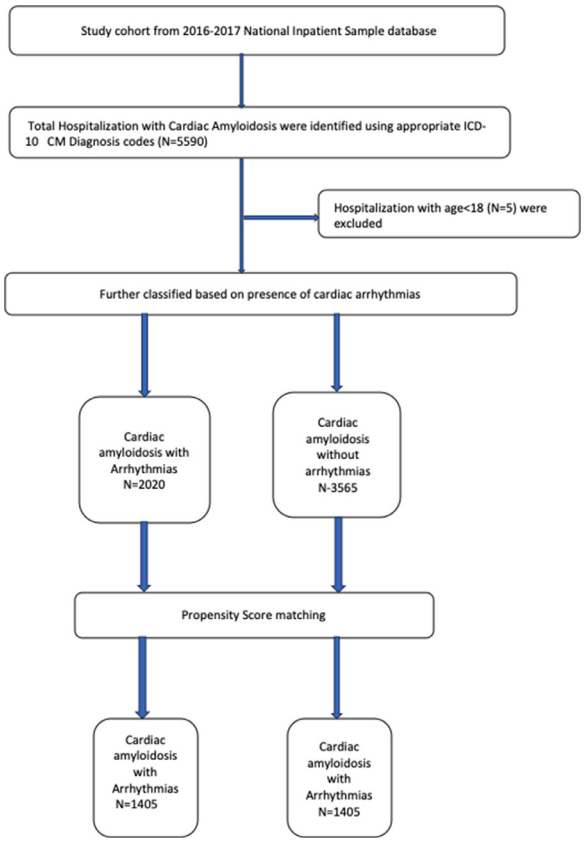

Figure 1. Patient selection and study design; This figure illustrates patient selection and study design.

and enables analyses of rare conditions, uncommon treatments, and special populations. Due to the nature of the study having deidentified hospitalizations, it did not require approval from the institutional review board. The RECORD statement for the checklist of items required was included in **Supplementary Table 1**.

Patients >18 years old admitted with a principal diagnosis of CA between January 2016 and December 2017 were identified using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code E 85.4. The cohort was further stratified into 2 study groups: Patients with arrhythmias versus those without arrhythmias. The prevalence of different arrhythmia was analyzed using appropriate ICD10-CM codes (**Supplementary table**). Both groups were compared for baseline demographics, hospital characteristics, co-morbidities, and outcomes. Most hospital-level characteristics were directly extracted as provided in the NIS, whereas the Elixhauser Comorbidity Index was used to identify co-morbid disorders. The primary outcome was all-cause in-hospital mortality. Secondary outcomes included AF-related mortality, new-onset acute HF or acute on chronic HF exacerbation, length of stay (LOS), and total hospital charges.

Categorical variables were presented as the numbers and percentages using the Chi-square test. Numerical variables were presented as the median and Interquartile range (IQR) and were compared using the Wilcoxon test. All tests were reciprocal, and a p-value of <0.05 was set as a level of significance. Discharge weights provided by the HCUP were applied to get the national estimates. We created matched cohorts using propensity score matching to balance out the differences in baseline characteristics and co-morbidities between the 2 groups. After logistic regression, propensity matching was performed using a one-to-one scheme without replacement using the nearest number matching. Subsequently, the absolute standardized difference with an acceptable difference being <10% was calculated between the groups. We have followed the methodology for analysis recommended by the NIS-HCUP and included in **Supplementary Table**.[6,7] All statistical analysis was performed with SAS 9.4 (SAS Institute, Inc, Cary, North Carolina).

Results

A total of 5,585 hospital admissions with CA were included in the analysis (**Figure 1**). Among this cohort, 2,020 (36.1%) had concurrent arrhythmia compared with 3,565 (63.8%), who had no concurrent arrhythmias. CA hospitalizations were more common in older patients (>75 years, 54.5% in CA with arrhythmia and 41.6% CA without arrhythmia, p <0.0001), Caucasians (65.2% in CA with arrhythmia and 64.3% CA without arrhythmia, p <0.0001), and those on Medicare (77.2% vs 70.1%, p <0.0001). Similar results were found even after propensity-matched analysis. Hospitalizations with CA who developed arrhythmias were more likely to be older (>75 years of age, 54.5% vs 41.6%, p <0.0001) and male (61.6% vs 46.6%, p <0.0001) (**Table 1**).

Before matching, there were significant differences in the co-morbidities among both groups. Hospitalizations with CA who had concurrent arrhythmias had a higher frequency of co-morbidities including HF (63.4% vs 24.3%, p <0.0001), cardiogenic shock (8.4% vs 1.1%, p <0.0001), valvular heart disease (14.6% vs 5%, p <0.0001), previous myocardial infarction (8.4% vs 3.1%, p <0.0001), peripheral vascular disease (4.7% vs 2.8%, p = 0.0002), pulmonary hypertension (3.2% vs 0.7%, p < 0.0001), as well as chronic kidney disease (35.4% vs 24.9%, p < 0.0001). After the propensity score-matched analysis, each group included 1,405 hospitalizations, and there was a <10% difference between all the variables, including co-morbidities (**Table 2**).

We found that all-cause mortality was significantly higher in patients with CA hospitalized with concurrent arrhythmias compared to those without (13.9% vs 5.3%, p-value <0.0001). Among all arrhythmias, AF was most common (72.2%), followed by ventricular tachycardia (14.9%), atrial flutter (9.6%), supraventricular tachycardia (7.5%), and ventricular fibrillation (1.8%). We also found that 5.7% of CA hospitalizations developed cardiac arrest and that 1.4% developed complete heart block (**Figure 2**).

AF-related mortality (11.95% vs 9.16%, p value = 0.02) and combined acute (acute on chronic) HF exacerbation (32.38% vs 24.91%, p value <0.0001) were significantly higher in patients with CA hospitalizedwith concurrent arrhythmia. Finally,the total length of hospital stay (6[3 to 12] vs 5[3 to 10], p value <0.001) and cost of health care ($ 15,086[7,813 to 30,373] vs $ 12,219[6,865 to 23,997], p value = 0.001) were significantly greater among CA

Table 1
Demographics and baseline characteristics of cardiac amyloidosis hospitalizations

	Arrhythmia		
	Yes (N = 2020)	No (N = 3565)	p Value
Age range (years)			<0.0001
≥18-<45	2.2%	3.1%	
≥45-<55	2.5%	7.8%	
≥55-<65	13.6%	18.4%	
≥65-≤75	27.2%	29%	
>75	54.5%	41.6%	
Gender			<0.0001
Male	61.6%	46.6%	
Female	38.4%	53.4%	
Race			<0.0001
White	65.2%	64.3%	
Black	24.4%	21.6%	
Hispanic	5.6%	5.9%	
Asian/PI	1.3%	3.2%	
Native American	0.3%	0.4%	
Other	2.9%	4.6%	
Types of admission			0.33
Elective	11.6%	12.5%	
Non-elective	88.3%	87.5%	
Primary Payer			<0.0001
Medicare	77.2%	70.1%	
Medicaid	2.9%	5.6%	
Private	17.6%	21%	
Others	2.2%	3.2%	
Income Quartile			<0.0001
0 to 25	20.8%	24.5%	
26 to 50	30.9%	22.6%	
51 to 70	22.4%	25.2%	
76 to 100	25.9%	27.6%	
Comorbidities			
Obesity	4.9%	5.5%	0.40
Obstructive sleep apnea	12.9%	6%	<0.0001
Hypertension	66.3%	67.9%	0.24
Hyperlipidemia	45%	43.2%	0.18
Diabetes Mellitus	7.4%	8.8%	0.06
Hypothyroidism	17.1%	13.9%	0.001
Congestive heart failure	63.4%	24.3%	<0.0001
Cardiogenic shock	8.4%	1.1%	<0.0001
Chronic obstructive pulmonary disease	11.6%	11.6%	0.99
Chronic kidney disease	35.4%	24.9%	<0.0001
Pulmonary hypertension	3.2%	0.7%	<0.0001
Smoker (Tobacco use disorder)	1.7%	7%	<0.0001
Alcohol use	0.9%	1.9%	0.005
Drug abuse	0.2%	1.5%	<0.0001
Valvular Heart disease.	14.6%	5%	<0.0001
Electrolyte imbalance.	41.6%	30.4%	<0.0001
Coagulopathy.	10.4%	9.3%	0.16
Prior myocardial infarction	8.4%	3.1%	<0.0001
Peripheral vascular disease	4.7%	2.8%	0.0002
Hospital Characteristics			
Hospital bed-size			<0.0001
Small	9.4%	7.1%	
Medium	23.5%	17.4%	
Large	67.1%	75.5%	
Hospital Region			0.002
Northeast	28.7%	29.7%	
Midwest	23.5%	22.6%	
South	28.2%	31.6%	
West	19.5%	16.1%	
Hospital Location			<0.0001
Rural	1.2%	3.5%	
Urban non-teaching	8.2%	12.1%	
Urban Teaching	90.6%	84.4%	

Categorical variables presented as percentages.

Table 2
Demographics and baseline characteristics of cardiac amyloidosis hospitalizations after propensity match

	Arrhythmia		
	Yes (N = 1405)	No (N = 1405)	Standardized difference %
Age range (years)			5.63
≥18-<45	2.8%	1.4%	
≥45-<55	2.1%	5.7%	
≥55-<65	15.3%	14.6%	
≥65-≤75	27.4%	29.5%	
>75	52.3%	48.7%	
Gender			2.16
Male	57.6%	58.7%	
Female	42.3%	41.3%	
Types of admission			9.77
Elective	11.4%	14.6%	
Non-elective	88.6%	85.4%	
Race			5.31
White	67.3%	65.1%	
Black	20.6%	23.5%	
Hispanic	6.8%	3.9%	
Asian/PI	1.8%	2.5%	
Native American	0.4%	0.7%	
Others	3.2%	4.3%	
Primary payer			2.42
Medicare	75.1%	76.2%	
Medicaid	3.9%	3.9%	
Private	18.5%	17.4%	
Others	2.5%	2.5%	
Income quartile			0.00
0 to 25	22.4%	27.8%	
26 to 50	30.9%	22.8%	
51 to 70	21.7%	22.1%	
76 to 100	24.9%	27.4%	
Comorbidities			
Obesity	4.9%	4.6%	1.64
Obstructive sleep apnea	9.2%	6.4%	10.0
Hypertension	66.2%	65.8%	0.76
Hyperlipidemia	46.6%	44.8%	3.58
Diabetes Mellitus	7.5%	8.9%	5.33
Hypothyroidism	14.5%	15.3%	1.98
Congestive heart failure	50.9%	47.3%	7.78
Cardiogenic shock	4.9%	2.5%	11.6
Chronic obstructive pulmonary disease	11%	11%	0.00
Chronic kidney disease	32%	30.2%	3.92
Pulmonary hypertension	1.4%	1.8%	2.56
Smoker (Tobacco use disorder)	2.5%	2.8%	1.70
Alcohol use	1.1%	1.4%	2.97
Drug abuse	0.4%	0.4%	0.00
Valvular Heart disease.	9.9%	8.9%	3.72
Electrolyte imbalance.	37%	34.5%	5.23
Coagulopathy.	10.7%	12.1%	4.72
Prior myocardial infarction	4.9%	6.8%	7.56
Peripheral vascular disease	3.2%	2.5%	3.87
Hospital characteristics			
Hospital bed-size			3.92
Small	7.8%	9.9%	
Medium	22.1%	20.2%	
Large	70.1%	69.7%	
Hospital region			0.98
Northeast	29.9%	28.8%	
Midwest	19.9%	20.6%	
South	29.9%	32.7%	
West	20.3%	17.8%	
Hospital location			3.50
Rural	1.1%	1.4%	
Urban non-teaching	8.5%	9.2%	
Urban Teaching	90.4%	89.3%	

Categorical variables presented as percentages.

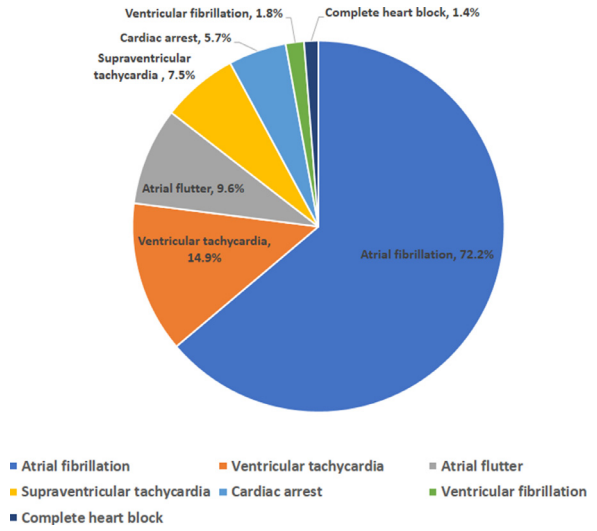

Figure 2. Spectrum of arrhythmias in cardiac amyloidosis; This figure illustrates the frequency of different arrhythmias in hospitalizations with cardiac amyloidosis.

hospitalizations with arrhythmia compared with those without (**Table 3**).

Discussion

Our analysis of 5,585 hospitalizations with CA revealed the following findings; (1) Arrhythmias in patients with CA hospitalizations were associated with increased in-hospital mortality, acute heart failure exacerbations, increased length of stay, and hospitalization costs; (2) AF was identified as the most frequent arrhythmia among hospitalizations with CA.

An increased prevalence of AF among patients with CA echoes trends observed in previous observational studies, particularly among elderly patients.[4,8] Atrial involvement is suspected to arise due to progressive atrial wall infiltration as well as infiltration and thickening of the ventricular walls. Subsequently, ventricular remodeling results in impaired relaxation and elevated filling pressures that ultimately predispose to atrial enlargement and atrial arrhythmias.[9,10] In one study, atrial arrhythmias were found in up to 20% of patients with familial transthyretin amyloid neuropathy without apparent CA.[11] Atrial arrhythmias are more common with ATTR-CA (up to 70%), probably related to the older age of presentation.[8] Beta-blockers and calcium channel blockers are poorly tolerated in CA due to its negative chronotropic effect where compensatory heart rate response is the primary driver of cardiac output in this restrictive cardiomyopathy making rate control more challenging.[12,13] Consequently, a rhythm control strategy is usually considered over a rate control strategy, mainly with catheter ablation.[14–16]

Given the cardiomyopathy, ventricular arrhythmias are also common, especially in AL-CA, and are associated with poor prognosis.[17] Sudden cardiac death has been one of the most common causes of mortality in patients with CA.[18] Implantable Cardioverter Defibrillator (ICD) placement in CA and its impact on mortality benefit has been debatable considering poor prognosis and short life expectancy associated with CA.[19,20]

The onset of congestive HF due to CA has been independently correlated with poor prognosis and increased mortality in both ATTR and AL CA.[21,22] Our analysis revealed a statistically significant increase in HF exacerbations and all-cause mortality events in CA patients with concurrent arrhythmias. Arrhythmias in CA have not been associated directly with all-cause mortality. However, arrhythmias, including AF, are known precipitators of HF exacerbations and may indirectly contribute to increased all-cause mortality. Similarly, HF exacerbation can also aggravate AF, which leads to a vicious cycle. Patients with concurrent HF and AF have a worse prognosis and higher mortality irrespective of ejection fraction.[8,23,24]

There are several limitations of the study due to the inherent shortcomings of the NIS database. We could not differentiate the type of cardiac amyloid. NIS is an administrative claim-based database that uses ICD codes for diagnosis susceptible to the inherent miscoding among diagnoses and procedural codes. However, when available, the authors used authenticated codes from literature laid out by HCUP/AHRQ to identify the ICD-10-CM codes for a particular diagnosis or procedure. NIS collects data on inpatient discharges with each admission treated as an independent event. NIS samples are not designed to follow patients longitudinally; therefore, long-term outcomes could not be assessed. All the data were from an administrative inpatient discharge database, which may lead to abstruse confounding and also explain the observed differences in outcomes. However, the NIS is a large and nationally representative database that allows us to generalize

Table 3
Outcomes in cardiac amyloidosis hospitalizations with and without arrhythmias

Outcomes	Arrhythmia		p Value
	Yes	No	
All-cause in-hospital mortality (%)	13.9%	5.3%	<0.0001
*AF mortality (%)	11.95%	9.16%	0.02
#Acute heart failure (%)	32.38%	24.91%	<0.0001
Mean length of stay (days)	6 (3-12)	5 (3-10)	0.0007
Mean hospital cost ($)	15086 (7813-30373)	12219 (6865-23997)	0.001

* AF mortality = mortality caused by atrial fibrillation in cardiac amyloidosis hospitalizations.
# Acute heart failure = frequency of acute and acute on chronic heart failure exacerbation.
Categorical variables presented as percentages.
Continuous variables presented as Median (IQR)

findings and utilize it as a reference tool for how the real-world data looks like. The order of occurrence of amyloidosis and atrial fibrillation in the present sample cannot be determined due to the cross-sectional nature of the database. Finally, the present analysis did not account for diagnostic and management strategies, provided the limitation of the database.

In conclusion, in-hospital mortality was significantly higher for CA hospitalizations with concurrent arrhythmias. AF is the most frequent arrhythmia seen and is associated with significantly higher odds of mortality. Moreover, patients with CA and arrhythmia have a higher risk of acute HF exacerbation. These ultimately lead to a higher burden on hospital resources and translate into the increased length of stay and hospitalization costs. Further prospective studies are required to determine if more aggressive rhythm controlling strategies are merited in these patients in order to reduce such poor outcomes.

Credit Author Statement

Thakkar: Conceptualization; Methodology; Visualization; Writing- Original draft preparation. Patel: Conceptualization; Methodology; Software; Writing- Original draft preparation. Chowdhury: Conceptualization; Methodology; Writing- Original draft preparation. Patel: Methodology; Software. Kumar: Methodology; Software; Validation; Writing- Reviewing and Editing. Arora: Conceptualization; Methodology. Zahid: Conceptualization. Goel: Conceptualization. Barssoum: Conceptualization. Jain: Methodology. AbouEzzeddine: Conceptualization; Methodology; Supervision. DeSimone: Conceptualization; Methodology; Supervision. Baibhav: Conceptualization; Methodology; Supervision. Rao: Conceptualization; Methodology; Supervision. Deshmukh: Conceptualization; Methodology; Supervision.

Disclosures

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.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.024.

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