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Burden and trends of arrhythmias in hypertrophic cardiomyopathy and its impact of mortality and resource utilization

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Abstract

Background: Hypertrophic cardiomyopathy (HCM) accounts for significant morbidity and mortality worldwide. Arrhythmias are considered the main cause of mortality, however, there is paucity of data relating to trends of arrhythmia and associated outcomes in HCM patients.

Methods: Nationwide Inpatient Sample from 2003 to 2014 was analyzed. HCM related hospitalizations were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) code 425.1 and 425.11 in all diagnosis fields.

Results: Overall, there was an increase in number of hospitalizations related to arrhythmias among HCM patients from 7784 in 2003 to 8380 in 2014 (relative increase 10.5%, $P < 0.001$). The increase was most significant in patients ≥ 80 years and those with higher comorbidity burden. Atrial fibrillation (AF) was the most frequently occurring arrhythmia however atrial flutter (AFL) witnessed the highest rise during the study period. In general, there was a down trend in mortality with the greatest reduction occurring in patients with ventricular fibrillation/flutter (VF/VFL). The mean length of stay was higher if patients had arrhythmia, which led to increased cost of care from $16105 in 2003 to $19310 in 2014 (relative increase 22.9%, $P < 0.001$).

Conclusion: There is overall decline in HCM related hospitalizations but rise in hospitalization among HCM patients with arrhythmias. HCM with arrhythmia accounts for significant inpatient mortality coupled with prolonged hospital stay and increased cost of care. However, there is an encouraging downtrend in the mortality most likely because of improved clinical practice, cardiac screening and primary and secondary prevention strategies.

KEYWORDS
arrhythmias, atrial fibrillation, cost trend, hypertrophic cardiomyopathy, outcomes

1 | INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a complex genetically transmitted disease with variable clinical expression.[1,2] Since its initial presentation more than 50 years ago, HCM is considered as a major cause of sudden cardiac death (SCD), heart failure (HF), AF and stroke.[3,4] HCM often takes insidious clinical course, and early detection may be beneficial for prevention of significant morbidity and mortality in high-risk patients. Consequently, there is an ever growing effort to study the frequency of HCM in the general population.[5]

However, most of the natural history data of HCM are derived from regional cohorts,[6–8] and thus comprehensive assessment of disease in various age groups and patients with different ethnicity remains incomplete. More importantly, there is paucity of epidemiological information with regards to HCM and concomitant arrhythmia, which is the main trigger for mortality in these patients. To fill this knowledge gap, we studied the temporal trends in HCM related hospitalization in the United States (US), while keeping the main focus on patients with HCM and associated burden of arrhythmia. This study also covers the important aspects of disease burden in terms of inhospital mortality, comorbidities, length of hospital stay (LOS) and cost of caring during the hospitalization.

2 | METHODS

We acquired data using Nationwide Inpatient Sample (NIS) from the year 2003 to 2014. NIS is the largest database of hospital inpatient stays in the United States (US), generated by the Agency for Healthcare Research and Quality (AHRQ). This database accounts for approximately up to 8 million discharges each year; and has been used in the past for ascertainment, tracking, and assessment of national trends in health care provision, access, major procedures related outcomes, disparity of care, hospitalizations rates, and analysis of health care economics and quality control measures.[9–12] Each individual hospitalization in NIS is deidentified and kept as a unique entry with one primary discharge diagnosis and < 29 secondary diagnoses during that hospitalization. Internal validity of the database is maintained by performing annual data quality assessments, while the external validity of this database is evaluated by comparing with the National Hospital Discharge Survey from the National Center for Health Statistics, American Hospital Association Annual Survey Database, and the MedPAR inpatient data from the Centers for Medicare and Medicaid Services.[13]

In this cross sectional study, we studied all hospitalizations from 2003 to 2014 using the ICD-9 codes 425.1 and 425.11 for hypertrophic cardiomyopathy (HCM) in all diagnosis fields. We included all the subjects ≥ 18 years. To study the baseline characteristics, we excluded subjects with missing information, such as, age, gender, admission or discharge date, and inpatient mortality status. For the purpose of potential confounder identification, both patient- and hospital-level variables were included. The severity of comorbid conditions was defined using Deyo modification of Charlson comorbidity index[14] (Table S1). 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. We identified heart failure and renal failure using "cm_" variables provided by NIS. We defined arrhythmias as codiagnosis of any of any of these specific rhythm disorders: Atrial fibrillation, Atrial Flutter, Supraventricular tachycardia, Ventricular Fibrillation/Flutter, or Ventricular Tachycardia. These specific arrhythmias were identified using ICD-9 codes in any diagnosis field (Table S2). We defined teaching hospitals if they were accredited with an American Medical Association approved residency program, were a member of the Council of Teaching Hospitals, or had a full-time equivalent intern and resident-to-patient ratio of 0.25. We estimated the cost of hospitalizations by merging NIS data with cost to- charge ratios available from the Healthcare Cost and Utilization Project. The cost of each inpatient stay was calculated by multiplying the total hospital charge with the cost to charge ratio. The adjusted cost for each year was calculated in terms of the 2011 cost after adjusting for inflation according to the latest consumer price index data released by the US government on January 16, 2013.[15,16] This methodology is in line with prior studies.[17] Exponential trend line was used to represent the trend in total cost from 2003 to 2014.

All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, North Carolina), which accounts for the complex survey design and clustering. Since NIS represents a 20% stratified random sample of US hospitals, analyses were performed using hospital-level discharge weights provided by the NIS, to obtain national estimates of HCM hospitalization. For categorical variables like annual change in HCM hospitalization rate and inhospital mortality, we used Chi-square test of trend for proportions using the Cochrane Armitage test.[18] Differences between categorical variables were tested using the chi-square test, and differences between continuous variables were tested using the student's *t* test. All the analyses were performed at 5% significance level.

3 | RESULTS

3.1 | HCM hospitalization, demographics and comorbidities

A total of 225 618 hospitalizations with HCM as the discharge diagnosis were analyzed from 2003 to 2014 (59.72% to ≥ 65 years of age, 63.4% females, 62.1% whites). Among which, 90 940 had

TABLE 1 Baseline characteristics of HCM patient with and without arrythmias

	Arrhythmia			
	No	Yes	Overall	*P*-value
Index hospitalization with HOCM	134 678	90 940	225 618	<0.001
Patient level variables				
Age, y (%)				<0.001
18-49	18.2	12.1	15.8	
50-64	25.3	23.5	24.5	
65-79	31.6	35.9	33.4	
≥80	24.9	28.5	26.4	
Race (%)				<0.001
White	58.6	67.3	62.1	
Black	14.0	8.4	11.8	
Hispanics	4.3	3.7	4.1	
Other	23.1	20.6	22.1	
Gender (%)				<0.001
Male	34.0	40.6	36.6	
Female	66.0	59.5	63.4	
Deyo/Charlson Score[b] (%)				<0.001
0	30.3	26.6	28.8	
1	29.4	30.7	29.9	
≥2	40.4	42.8	41.3	
Comorbidities (%)				
Codiagnosis of Heart failure[a]	29.2	44.7	35.4	<0.001
Renal failure/Electrolyte abnormality[a]	12.4	13.9	13.0	<0.001
Median household income category for patient's zip code[c] (%)				<0.001
1. 0-25th percentile	26.5	22.0	24.7	
2. 26-50th percentile	25.8	25.4	25.7	
3. 51-75th percentile	23.8	25.2	24.4	
4. 76-100th percentile	23.9	27.4	25.3	
Primary Payer (%)				<0.001
Medicare/ Medicaid	68.9	71.6	70.0	
Private including HMO[f]	25.0	24.4	24.8	
Self-pay/no charge/other	5.9	3.9	5.1	
Hospital characteristics				
Hospital bed size[d] (%)				<0.001
Small	11.2	11.0	11.1	
Medium	22.5	21.6	22.1	
Large	66.3	67.4	66.8	
Hospital teaching status[e] (%)				<0.001
NonTeaching	44.8	43.6	44.3	
Teaching	54.9	56.2	55.4	
Admission type (%)				<0.001
NonElective	78.4	80.0	79.0	
Elective	21.7	20.0	21.0	

(Continues)

TABLE 1 (Continued)

	Arrhythmia			
	No	Yes	Overall	*P*-value
Admission day (%)				<0.001
Weekdays	81.6	80.1	81.0	
Weekend	18.4	19.9	19.0	
In hospital Mortality (%)	2.9	4.6	3.6	<0.001
Length of stay (Mean ± Std dev), days	5.46 ± 0.04	6.53 ± 0.06	5.89 ± 0.04	<0.001

Abbreviation: Iqr, Interquartile range.
[a]Variables are AHRQ comorbidity measures.
[b]Charlson/Deyo Comorbidity index (CCI) was calculated as per Deyo classification.
[c]Represents a quartile classification of the estimated median household income of residents in the patients ZIP Code, derived from ZIP Code-demographic data obtained from Claritas. The quartiles are identified by values of 1 to 4, indicating the poorest to wealthiest populations. Because these estimates are updated annually, the value ranges vary by year. https://www.hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nrdnote.jsp
[d]The bed size cutoff points divided into small, medium, and large have been done so that approximately one-third of the hospitals in a given region, location, and teaching status combination would fall within each bed size category. https://www.hcup-us.ahrq.gov/db/vars/hosp_bedsize/nrdnote.jsp
[e]A hospital is considered to be a teaching hospital if it has an AMA-approved residency program, is a member of the Council of Teaching Hospitals (COTH) or has a ratio of full-time equivalent interns and residents to beds of 0.25 or higher. https://www.hcup-us.ahrq.gov/db/vars/hosp_ur_teach/nrdnote.jsp
[f]HMO: Health Maintenance Organization.

coexisting arrhythmias. Compared to HCM patients without arrhythmias, those with arrhythmias were older (64.4% vs 56.6% ≥ 65 years of age), had higher burden of comorbidities (42.78% vs 40.36% with charlson comorbidity index ≥ 2), consisted of higher proportion of Males (40.55% vs 33.98%) and White subjects (67.32% vs 58.56%). Those with arrhythmias had higher median household income (52.6% vs 47.7% above 50th percentile), and Medicare/Medicaid coverage (71.6% vs 68.9%). Additionally, subjects with arrhythmias were more frequently admitted to large hospitals (67.4% vs 66.3%) with teaching affiliation (56.2% vs 54.9%), had higher proportion of admissions over weekend (19.9% vs 18.4%) and were admitted emergently (80% vs 78.4 %). Significantly higher prevalence of heart failure (44.7% vs 29.2%) and renal failure (13.9% vs 12.4%) were noted among HCM patients with arrhythmias. Our study noted higher mortality among patients with arrhythmias compared to those without arrhythmias (4.6% vs 2.9%). [*P*-value significant for all values, Table 1].

3.2 | Trends of arrhythmia in HCM patients

In a total of 90 940 HCM patients with arrhythmia, there was an increase in the number of hospitalizations from 7784 in 2003 to 8380 in 2014 (relative increase 10.5%). The magnitude of rise in arrhythmia was observed in the following age groups (Table 2) in descending order: ≥ 80 years (relative increase 23.2%, $P < 0.001$), 50–64 years (relative increase 20%, $P < 0.001$), 65–79 years (relative increase 19%, $P < 0.001$) and 18–49 (relative increase 17.1%, $P < 0.001$). The relative rates of increment over the years were higher for males (relative increase 22.19%, $P < 0.001$) and Hispanics (relative increase 40.1%, $P < 0.001$) among gender and race groups respectively. Our study noted a higher rise in the prevalence of arrhythmias among patients with charlson comorbidity index ≥ 2 (relative increase 20.47%), lower socioeconomic class (relative increase 25.75%), no insurance coverage relative increase 67.25%), admitted to nonteaching facilities (relative increase 19.52%) or in mid-west (relative increase 22.42%). HCM patients admitted over weekday or having nonurgent hospitalizations had higher increment in arrhythmias compared to those who had weekend or urgent admissions respectively. HCM patients with renal failure witnessed greater rise in prevalence of compared to those without renal failure. (Relative increase 50.64%) [*P*-value significant for all trends].

3.3 | Trends of specific arrhythmias among HCM patients

Among HCM subjects, 40.3% of patients had a wide range of arrhythmia at presentation. Specifically, AF (34.1%) was the most commonly reported arrhythmia followed by ventricular tachycardia (6.7%) and atrial flutter (4.4%). Across all the arrhythmias, AFL showed the maximum increase in prevalence across the study period (relative increase 65.7%, $P < 0.001$), followed by VT (relative increase 30.1%, $P < 0.001$), VT/VFL (relative increase 26.7%, $P < 0.001$) and AF (relative increase 22.1%, $P < 0.001$) (Figure 1).

3.4 | Mortality trends among HCM patients with arrhythmias

Although inhospital mortality was higher in HCM patients with concomitant arrhythmia, there was a significant decline in mortality in patients with arrhythmia from 6.2 % in 2003 to 3.4 % in 2014 (relative decrease 22.82%, *P*-trend < 0.001). Mortality rate was higher in patients ≥ 80 years age (7.4%), females (5.5%), and black population (4.64%) among HCM patients with arrhythmias. Mortality was slightly lesser in teaching hospitals than nonteaching hospitals (4.4%

TABLE 2 Trend of prevalence of any arrhythmia in hospitalized HCM patients

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Overall	P-trend	Relative change
Patients with HOCM (N)	20 494	18 841	18 954	19 852	17 770	18 191	19 611	18 401	18 749	17 765	18 045	18 945	225 618		-6.5
Patients with Arrhythmias in HOCM Population (N)	7784	7374	7003	7649	6857	6874	8102	7344	7724	7770	8080	8380	90 940		10.5
Age, Y (%)															
18–49	28.4	29.6	29.0	28.1	27.2	30.2	33.5	32.9	35.0	31.2	33.6	33.3	31.0	<0.001	17.1
50–64	34.5	37.9	34.9	37.0	37.1	37.2	39.9	36.7	39.7	44.0	39.1	42.6	38.6	<0.001	20.0
65–79	41.3	42.7	39.5	39.7	43.8	39.4	44.5	44.4	41.7	48.1	48.8	47.8	43.4	<0.001	19.0
≥80	40.9	40.7	39.8	44.3	40.3	40.6	44.5	42.3	46.1	45.6	52.8	48.0	43.6	<0.001	23.2
Race (%)															
White	42.1	43.2	39.4	42.1	42.3	40.3	45.2	42.8	44.2	46.6	47.4	47.5	43.7	<0.001	15.1
Black	28.2	29.2	23.1	29.2	23.5	29.4	24.9	30.7	27.6	30.2	36.3	29.6	28.8	<0.001	18.9
Hispanics	29.7	33.6	31.8	41.0	31.0	36.5	32.8	31.8	42.1	36.7	39.5	49.5	36.8	<0.001	40.1
Other	33.5	35.0	36.3	35.5	37.3	35.5	39.9	36.2	40.6	42.8	41.6	43.8	37.4	<0.001	28.1
Gender (%)															
Male	41.3	42.1	41.6	40.5	42.4	42.1	45.6	44.2	48.4	50.8	47.7	48.2	44.6	<0.001	22.2
Female	36.4	37.6	34.4	37.4	36.3	35.4	38.7	37.3	37.0	39.5	42.9	41.8	37.8	<0.001	15.5
Deyo/Charlson Score [b] (%)															
0	32.9	37.6	35.7	34.9	34.7	35.7	41.4	35.9	39.0	41.2	39.2	40.8	37.2	<0.001	19.9
1	40.8	39.1	38.5	41.4	42.5	39.7	41.8	40.0	41.3	43.4	44.8	44.9	41.3	<0.001	11.8
≥2	40.0	40.7	36.5	39.2	38.7	37.9	40.9	42.4	42.4	45.3	47.4	45.5	41.7	<0.001	20.5
Median household income category for patient's zip code [c] (%)															
1. 0-25th percentile	32.1	33.0	35.3	30.7	37.3	33.8	37.9	35.2	36.4	39.1	41.1	40.1	36.0	<0.001	25.8
2. 26-50th percentile	37.4	38.5	35.3	40.1	37.1	35.5	40.8	39.4	42.6	43.4	45.9	44.2	40.0	<0.001	22.9
3. 51-75th percentile	38.4	43.9	35.3	39.5	38.7	39.6	42.1	40.4	44.4	44.0	46.0	48.7	41.8	<0.001	22.6
4. 76-100th percentile	44.7	41.4	35.3	44.1	41.9	41.3	44.5	45.6	42.3	48.7	46.6	45.2	43.8	<0.001	12.9
Primary Payer (%)															
Medicare/ Medicaid	39.5	40.8	38.2	39.1	39.4	38.0	42.0	39.7	42.2	44.6	46.5	44.9	41.2	<0.001	17.2
Private including HMO	34.8	36.5	36.3	39.8	39.4	38.4	41.3	42.4	40.0	42.6	41.6	43.0	39.7	<0.001	21.3
Self-pay/no charge/other	23.9	26.3	21.1	24.4	23.8	31.5	34.7	30.7	33.6	37.2	36.7	36.9	30.5	<0.001	67.3

(Continues)

TABLE 2 (Continued)

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Overall	P-trend	Relative change
Hospital characteristics															
Hospital bed size [d] (%)															
Small	42.2	37.7	33.0	38.4	36.8	39.3	46.1	39.4	39.9	42.2	40.7	42.4	39.9	<0.001	10.5
Medium	34.0	41.8	32.5	37.6	38.1	36.6	38.7	40.2	42.7	43.5	44.4	43.6	39.4	<0.001	27.2
Large	38.7	38.5	38.9	39.0	39.1	37.9	41.7	39.9	40.9	44.1	45.6	45.0	40.7	<0.001	18.2
Hospital teaching status[e] (%)															
NonTeaching	36.3	39.5	37.2	38.9	39.8	37.4	40.0	40.9	39.7	42.7	45.3	43.9	39.7	<0.001	19.5
Teaching	39.9	38.8	36.6	38.3	37.5	38.3	42.6	39.0	42.2	44.4	44.5	44.3	40.9	<0.001	17.5
Admission type (%)															
NonElective	38.5	40.0	38.2	38.7	38.9	38.1	41.6	40.3	41.8	44.0	45.6	44.8	40.8	<0.001	18.2
Elective	35.8	36.2	32.3	37.8	37.4	36.5	40.4	38.6	39.3	43.2	41.7	42.2	38.4	<0.001	22.7
Admission Day (%)															
Weekdays	37.5	38.7	36.1	37.8	38.7	37.3	40.5	39.8	40.9	43.3	44.6	43.8	39.9	<0.001	19.9
Weekend	40.3	41.0	40.6	41.3	38.2	39.8	45.4	40.5	42.4	45.8	45.7	46.1	42.2	<0.001	15.3
Comorbidities (%)															
Heart failure[a]															
Yes	50.1	48.8	47.7	48.0	51.8	46.6	49.2	50.5	51.0	53.8	56.7	54.3	50.8	<0.001	13.4
No	31.7	34.2	31.3	33.7	32.1	33.5	37.2	33.9	35.9	37.8	36.7	37.4	34.5	<0.001	18.5
Renal failure/Electrolyte abnormality[a]															
Yes	37.4	41.0	32.4	40.9	40.3	38.0	41.1	41.4	43.6	45.0	51.4	49.6	43.1	<0.001	50.6
No	37.8	39.0	37.3	38.2	38.3	37.8	41.4	39.7	40.7	43.5	43.3	43.1	39.9	<0.001	16.3

a, c, d, e, f, g = Same as Table 1.

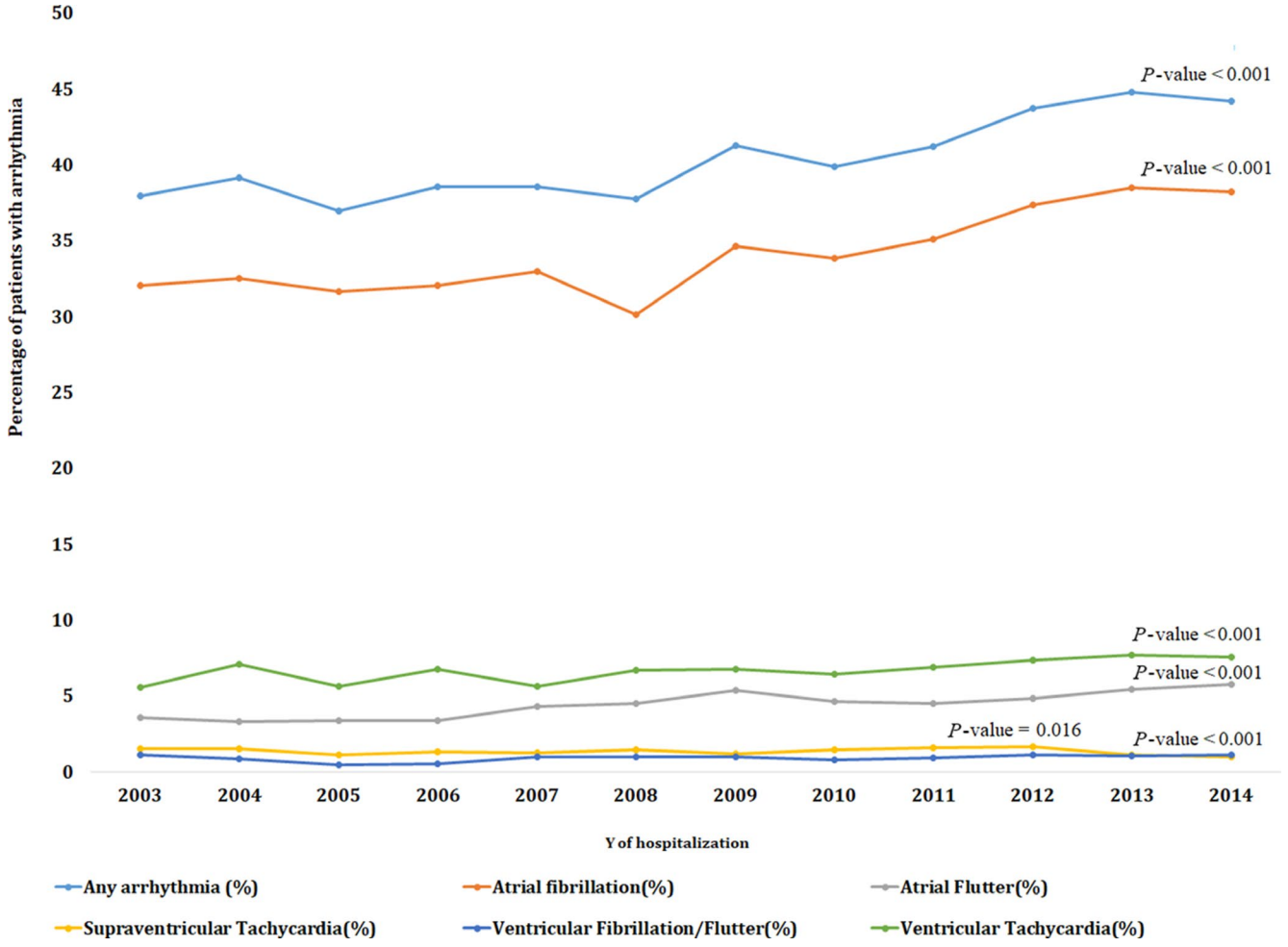

FIGURE 1 Trends of overall and specific arrhythmias in hypertrophic cardiomyopathy (HCM) patients

vs 4.8%, *P* < 0.001); conversely, mortality rates were higher in West region hospitals (5.6%) and in patients with Medicare/Medicaid insurance (5.3%). Mortality was higher for patients carrying HF (9.5%) and renal failure (8.1%) as comorbid diagnosis compared to those who did not have these comorbidities. Trends of mortality in specific subgroups of HCM patients with arrhythmias are shown in Table 3.

Among specific arrhythmias in HCM patients, highest mortality was observed in patients with VF/VFL (18.3 %), AF and VT (4.5%) and atrial flutter (4.1%).However, there was a gradual reduction in arrhythmia specific mortality, and statistically significant reduction occurred in VF/VFL (relative decrease 44.5%, *P*-trend < 0.001) and AF (relative decrease 29.3%, *P*-trend < 0.001) (Table 4).

3.5 | Cost trends (USD) in HCM patients with arrhythmias

Among HCM patients with arrhythmias, after adjustment for inflation, HCM hospitalization with arrhythmia claimed $17599 as total mean cost of care, with a significant rise from $16105 in 2003 to $19310 in 2014 (relative increase 22.9%, *P*-trend < 0.001). This represents an absolute increment in annual national cost from 125 million dollars in 2003 to 162 million dollars in 2014 (relative increase 34.5%, *P*-trend < 0.001). Trends in cost of care among different subgroups of HCM patients are presented in Table S3.

Overall mean cost of HCM hospitalization was consistently higher if patients had any type of arrhythmia compared to no arrhythmia ($20522 vs $15636). Across all arrhythmias, the mean cost of care was highest if subjects had VF/VFL ($39108) and ventricular tachycardia ($28996), while, the increase in trend of cost of care was highest for supraventricular tachycardia throughout the study period (relative increase 45.4%, *P*-trend < 0.04) **(**Table 5**).** Arrhythmia specific trend in length of hospitalization is shown in Table S4.

4 | DISCUSSION

In this study of contemporary data of HCM related hospitalization in USA, we report that over 11 years (2003-2014), there was an increase in hospitalization rates in patients with HCM and concurrent arrhythmia. Patients 65 years of age or older were admitted most frequently. Overall in HCM, females were dominant over males, and thus had comparatively a higher prevalence of mortality and LOS, however we noted higher prevalence of

TABLE 3 Trends of mortality based on demographics and comorbidities of hospitalized HCM patients

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Overall	*P*-value	relative change
Patients with Arrhythmias and HOCM	7784	7374	7003	7649	6857	6874	8102	7344	7724	7770	8080	8380	90 940	<0.001	10.5
Overall mortality in HOCM (%)															
Patients without arrhythmia	3.5	3.0	2.6	2.2	2.9	3.9	2.7	3.2	3.2	2.7	2.5	2.2	2.9	0.001	−14.2
Patients with Arrhythmia	6.2	5.3	4.0	4.5	4.6	4.1	5.3	4.7	5.0	3.9	4.3	3.4	4.6	<0.001	−22.8
Age, y (%)															
18–49	5.8	0.6	1.7	1.7	0.6	0.5	1.4	2.1	2.7	0.6	3.0	2.1	1.9	0.239	−10.5
50–64	1.4	3.0	2.2	4.2	2.2	2.3	3.6	2.2	3.3	2.8	2.2	2.7	2.7	0.539	21.8
65–79	5.6	5.8	3.9	3.7	5.0	3.1	5.5	4.9	4.1	4.0	4.7	3.1	4.5	<0.001	−22.6
≥80	9.7	8.0	6.1	6.5	7.6	8.2	8.7	8.2	8.5	6.4	5.9	5.1	7.4	<0.001	−21.4
Race (%)															
White	5.7	4.4	3.7	4.4	4.8	3.8	5.6	4.8	5.2	4.0	4.0	3.3	4.5	<0.001	−14.9
Black	3.6	7.1	6.3	6.3	4.7	6.0	2.9	5.4	4.4	2.1	5.2	3.0	4.6	0.003	−67.6
Hispanics	13.1	5.0	5.2	1.9	0.0	0.0	8.2	0.0	4.4	3.7	4.0	4.4	4.0	0.066	−27.9
Other	7.4	7.0	4.1	4.4	4.7	5.0	4.5	5.0	4.2	4.2	4.9	4.3	5.1	<0.001	−27
Gender (%)															
Male	5.2	3.0	2.3	3.4	3.8	2.9	3.7	3.3	3.3	2.2	3.2	3.3	3.3	0.009	−15.3
Female	6.7	6.6	5.1	5.1	5.2	4.9	6.4	5.7	6.2	5.2	5.0	3.5	5.5	<0.001	−23.2
Deyo/Charlson Score[b] (%)															
0	2.3	2.8	1.8	1.3	1.6	1.5	2.1	1.6	1.5	0.8	2.4	1.1	1.8	<0.001	−38.1
1	6.0	3.9	3.4	3.1	5.5	4.2	4.1	3.0	3.5	2.2	3.6	3.0	3.8	<0.001	−32.4
≥2	9.3	8.9	6.5	8.1	5.9	5.7	8.4	7.5	7.7	6.3	5.4	4.6	6.9	<0.001	−32.8
Median household income category for patient's zip code[c] (%)															
1. 0-25th percentile	6.9	3.4	6.1	5.0	4.3	4.5	5.0	4.5	4.9	4.5	2.8	2.7	4.5	<0.001	−34.9
2. 26-50th percentile	7.8	5.5	4.0	3.8	5.3	4.7	5.4	6.0	5.7	3.5	4.5	3.4	4.9	<0.001	−23.7
3. 51-75th percentile	5.8	5.6	4.4	4.5	5.2	3.6	6.8	3.7	6.2	3.3	5.6	3.4	4.9	0.021	−18.0
4. 76-100th percentile	4.4	5.8	1.5	4.4	4.1	4.0	3.6	5.0	3.0	4.4	4.1	3.9	4.0	0.526	−4.8
Primary payer (%)															
Medicare/ Medicaid	6.7	5.9	5.0	5.0	5.6	5.0	6.2	5.6	6.2	4.1	4.9	3.8	5.3	<0.001	−23.7
Private including HMO [x]	3.6	3.7	0.8	2.9	1.7	2.1	3.6	2.9	1.5	2.3	2.5	2.3	2.5	0.103	−16.8
Self-pay/no charge/other	11.7	2.2	5.3	3.9	5.4	1.4	2.2	2.9	3.4	8.6	3.6	2.9	4.1	0.169	−23.1

(Continues)

TABLE 3 (Continued)

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Overall	*P*-value	relative change
Hospital characteristics															
Hospital bed size[d] (%)															
Small	7.5	3.1	2.5	3.8	3.5	4.9	6.9	1.3	7.6	2.6	2.5	2.8	4.1	0.001	−21.7
Medium	4.5	4.6	4.2	5.3	4.2	4.0	4.3	8.1	5.4	4.3	5.7	2.8	4.7	0.868	3.6
Large	6.4	5.9	4.1	4.3	4.9	4.0	5.2	4.3	4.4	3.9	4.1	3.8	4.6	<0.001	−28.1
Hospital teaching status[e] (%)															
NonTeaching	6.4	5.3	3.3	4.6	4.7	4.2	6.3	5.2	5.4	4.2	4.4	3.3	4.8	0.008	−17.4
Teaching	5.9	5.3	4.8	4.4	4.5	4.0	4.5	4.2	4.7	3.7	4.2	3.4	4.4	<0.001	−28.3
Admission type (%)															
NonElective	6.9	5.8	4.6	4.9	4.9	4.4	5.4	5.1	5.1	4.3	4.3	3.4	4.9	<0.001	−29.0
Elective	3.3	3.2	1.2	2.4	3.4	2.7	4.6	3.0	4.2	2.2	4.2	3.5	3.2	0.018	32.6
Admission day (%)															
Weekdays	6.0	5.2	4.2	4.0	4.8	4.0	5.0	3.8	4.3	3.5	4.7	3.5	4.4	<0.001	−23.2
Weekend	6.9	5.8	3.2	6.1	4.0	4.4	6.3	8.2	7.5	5.5	2.3	3.0	5.3	0.002	−20.9
Comorbidities (%)															
Heart failure[a]															
No	4.8	4.3	3.1	3.2	3.1	2.6	3.8	3.3	4.4	3.2	3.5	2.6	3.5	<0.001	−17.9
Yes	14.1	9.9	7.6	10.2	10.2	11.9	12.7	11.0	7.7	7.0	7.0	6.7	9.5	<0.001	−33.2
Renal failure/Electrolyte abnormality[a]															
No	5.2	3.9	2.2	2.9	3.2	2.5	2.6	2.6	2.3	1.6	1.9	1.4	2.8	<0.001	−50.6
Yes	11.6	9.8	9.5	8.1	7.5	7.4	10.0	8.5	8.7	7.1	7.0	5.9	8.1	<0.001	−31.9

a, c, d, e, f, g = Same as Table 1.

TABLE 4 Trends of mortality as per specific arrhythmia in hospitalized HOCM patients

Arrhythmia specific mortality trend (%)	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Overall	P-trend	Relative change
Any arrhythmia[a]															
Yes	6.2	5.3	4.0	4.5	4.6	4.1	5.3	4.7	5.0	3.9	4.3	3.4	4.6	<0.001	-22.8
No	3.5	3.0	2.6	2.2	2.9	3.9	2.7	3.2	3.2	2.7	2.5	2.2	2.9	<0.001	-14.2
Atrial fibrillation[a]															
Yes	6.2	5.4	4.2	4.9	4.5	3.5	4.7	4.7	4.8	4.1	3.8	3.2	4.5	<0.001	-29.3
No	3.7	3.1	2.6	2.2	3.1	4.1	3.3	3.4	3.4	2.7	3.0	2.4	3.1	0.3	-8.8
Atrial Flutter[a]															
Yes	4.8	5.4	3.0	3.5	4.6	2.4	4.8	4.9	2.7	4.6	3.6	4.6	4.1	0.753	-6.3
No	4.5	3.8	3.1	3.1	3.5	4.0	3.7	3.8	3.9	3.1	3.3	2.6	3.5	<0.001	-17.6
Supraventricular Tachycardia[a]															
Yes	4.8	3.2	2.2	0.0	4.6	9.1	9.2	5.4	0.0	3.4	2.4	0.0	3.7	0.128	-39.1
No	4.5	3.9	3.1	3.1	3.5	3.9	3.7	3.8	4.0	3.2	3.3	2.8	3.6	<0.001	-16.2
Ventricular Fibrillation/Flutter[a]															
Yes	29.6	23.5	10.3	23.2	25.6	20.2	15.7	9.9	27.6	4.9	20.5	7.1	18.3	<0.001	-44.5
No	4.2	3.7	3.1	3.0	3.3	3.8	3.6	3.8	3.7	3.2	3.1	2.7	3.4	<0.001	-15.1
Ventricular Tachycardia[a]															
Yes	5.3	2.9	2.2	3.7	4.7	6.3	7.3	3.0	4.8	4.6	5.0	3.8	4.5	0.123	16
No	4.4	4.0	3.2	3.1	3.5	3.8	3.5	3.9	3.8	3.1	3.2	2.7	3.5	<0.001	-19.5

[a]Other primary diagnosis: derived from appropriate ICD 9CM code mentioned in Table S2.

TABLE 5 Trends of cost of care as per specific arrhythmia in hospitalized HOCM patients

Arrhythmia specific Mean Cost in USD ($)	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Overall	P-trend	Relative change
Any arrhythmia[a]															
Yes	19 680	19 141	19 917	19 060	18 856	18 311	22 041	19 807	21 989	21 124	22 866	22 430	20 522	<0.001	18.3
No	13 962	14 733	14 555	14 552	14 585	16 492	16 589	15 912	16 288	16 944	16 858	16 843	15 636	<0.001	22.1
Atrial fibrillation[a]															
Yes	19 032	18 435	18 673	17 820	18 073	16 451	20 344	18 457	20 888	19 740	20 697	19 494	19 080	0.004	10.8
No	14 729	15 498	15 549	15 557	15 316	17 497	18 070	16 948	17 390	18 183	18 838	19 196	16 836	<0.001	29.3
Atrial Flutter[a]															
Yes	22 173	23 056	26 017	21 394	22 194	19 548	26 785	26 297	26 173	24 299	31 845	32 120	25 676	0.006	38.2
No	15 882	16 240	16 195	16 104	15 967	17 065	18 408	17 058	18 238	18 477	18 841	18 513	17 229	<0.001	20.2
Supraventricular Tachycardia[a]															
Yes	16 817	20 349	14 331	18 376	15 763	18 385	26 159	26 776	18 756	27 442	15 708	26 444	20 443	0.039	45.4
No	16 094	16 398	16 560	16 251	16 225	17 164	18 776	17 332	18 585	18 623	19 596	19 239	17 562	<0.001	22.6
Ventricular Fibrillation/Flutter[a]															
Yes	31 412	53 413	50 984	33 983	35 657	25 231	35 173	35 095	38 938	56 450	29 302	46 546	39 108	0.509	2.5
No	15 938	16 177	16 361	16 185	16 040	17 103	18 684	17 310	18 403	18 306	19 444	19 002	17 401	<0.001	22.5
Ventricular Tachycardia[a]															
Yes	29 163	27 746	26 301	25 967	27 644	26 409	28 526	25 035	30 910	30 311	34 154	33 461	28 996	0.004	20.0
No	15 403	15 604	15 958	15 576	15 544	16 481	18 153	16 961	17 674	17 842	18 329	18 154	16 788	<0.001	21.1

[a]Other primary diagnosis: derived from appropriate ICD 9CM code mentioned in Table S2.

arrhythmias associated with HCM among male patients compared to females. AF was the most commonly reported arrhythmia and AFL exhibited a substantial increase in prevalence compared to all other arrhythmias. Compared to HCM patients without arrhythmias, inhospital mortality was significantly higher in those with arrhythmia, with VF related SCD as the main contributor in mortality. However, there was a trend towards reduction in mortality throughout the study periods, and in fact the highest mortality reduction occurred in VF victims. The mortality was significantly higher in patients carrying codiagnosis of HF and renal failure. The cost of care increased significantly over the entire study duration, and admissions with renal failure and HF claimed for the highest cost of care. Insignificant reduction in length of stay was noted during study period (Table S2).

Besides endorsing various former studies, these observations highlight some new epidemiological trends in HCM patients. Higher prevalence of HCM among women has been consistently reported in prior reports,[3,6,19] however, exponential growth among male patients who had concomitant arrhythmia has not been demonstrated before. On the same note, historically HCM is known to be more strongly associated with Blacks,[20] while on contrary, we found higher prevalence of disease in Whites and increment in hospitalization rates among Hispanics. These observations show the contrasting patterns to historical trends[2,5,8] and clearly demonstrate the evolving penetration of the disease in the general population, affecting patients from both genders and various racial origins. Additionally, we noted that HCM patients admitted non-emergently (vs emergently) or during weekdays (vs weekends) had higher increment in arrhythmias over years. This population simply represents healthier subgroup who have more room to develop arrhythmias with increasing age and comorbidities.

Although, HCM can present from infancy to old age,[21] it is considered to be prevalent in young and middle age groups[22] with most patients surviving to advanced ages (>80 years)[23,24]. Our study reports lesser mortality in relatively younger age groups and more admission rates among old age patients. These findings validate some of the recently published reports.[25,26] Maron et al[25] reported that among 1001 cohorts (30-59 years), the 5 and 10 year survival rates (confined to HCM related mortality) were 98% and 94%, respectively. The enhanced survival in HCM patients reflects evolution of HCM related treatment strategies and continuum of improved medical practices leading to early cardiac surveillance in high-risk patients.[4,27–29] Detection of high-risk candidates through improved risk stratification algorithm and diligent application of professional guidelines has led to a more reliable selection of patients who are likely to get mortality benefit from intra cardiac defibrillators (ICDs).[30–32] For instance, in a study by Maron et al,[25] out of 56 high-risk patients, 33 survived sudden cardiac death (SCD) due to ICD; whereas, SCD occurred in patients who declined ICDs or could not receive prophylactic ICDs. The more frequent use of ICD in right set of candidates along with robust medical care explain the negative trend seen in mortality, with the highest reduction noticed in VF related SCD.

SCD is the most common cause of death in HCM; whereas, HF is reported to be the most common comorbid condition and second most common perpetuator of mortality in these patients.[2,33] These findings have been consistently shown in various regional based studies.[5,26,31] The data utilized from three regional tertiary centers (744 patients) ranked HF as second most common cause of mortality (36%) after SCD.[26] In another analysis of 956 cohorts (follow-up: 69 ± 45 months), HF related death was second most frequent cause of mortality (21 patients)[5] following SCD. Interestingly, the more recent emerging data represent evolving epidemiological trends and hint towards equilibration of HF with SCD as major contributor of mortality.[25,34] Maron et al showed that at 7.2 ± 5.2 years of follow-up, the mortality rate was 0.23 % per person -year in 1000 HCM patients,[25] which was equivalent to mortality rate of SCD (0.23% per person-year). This paradigm shift is explainable by the extended use of ICD for both primary and secondary prevention of SCD.[26–28,30] Encouragingly, we observed a significant decline in HF related death (relative decrease: 33.2 %, $P < 0.001$) from 2003 to 2014.

AF is the most commonly associated supraventricular arrhythmia in HCM.[35] In analysis of Italian and US cohorts, AF was found be a strong predictor of mortality in HCM (odds ratio (OR): 3.7; $P < 0.002$) secondary to severe HF related death.[35] This risk was greater in patients < 50 years of age with left ventricular outlet obstruction. Another Japanese study showed that incidence of AF was most important predictor of cardiovascular mortality in HCM patients.[36] These findings from our analysis are supported by results published in previous studies. Consistent with general reduction in mortality, AF related mortality in HCM has also reduced due to previously discussed better clinical practices which have led to extended longevity in these subsets of patients.

Our study explored the cost burden associated with management of HCM patients with arrhythmias, noting approximately 34.5% rise during the study period. Despite no significant change in the length of hospitalization, healthcare burden significantly rose during the study period approximating 160 million USD per annum. This overwhelming rise in cost of care not only reflects the increasing utilization of expensive technologies such as catheter ablation and devices in the management of these high-risk subjects but also points towards the growing prevalence of arrhythmias in HCM patients. In the context of ever growing burden on public health and its associated cost of care, these observations are alarming and deserve serious consideration.[37]

5 | LIMITATIONS

This study has limitations inherent to administrative databases. Although administrative databases are increasingly used for representing the scientific information, such studies are prone to errors secondary to coding inaccuracies. HCM and related comorbidities

were diagnosed based on administrative codes. Therefore, there is a possibility that we might have missed some information, leading to under estimation of the number of hospitalizations. Given the nature of the data, we could only examine inhospital mortality; hence, the study lacks the assessment of long-term follow-up outcomes.

6 | CONCLUSION

Our study reports rise in hospitalization as a result of arrhythmias in HCM patients as well as concurrent increase in mortality and resource utilization over study period. We believe that this study represents new epidemiological trends. Furthermore, inclusion of a "real-world" large sample size and the absence of selection bias have strengthened the validity of the outcomes.

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CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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