

# Predictors, Burden, and the Impact of Arrhythmia on Patients Admitted for Acute Myocarditis



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**A significant proportion of patients with acute myocarditis experience sudden cardiac death presumably due to cardiac arrhythmia. In this study, we explore the burden, the predictors of arrhythmia in acute myocarditis and the association between arrhythmias and adverse in-hospital outcomes. After evaluating the frequency of various tachyarrhythmias and bradyarrhythmia in myocarditis population, we built a logistic model to determine the independent predictors of arrhythmias in myocarditis and a 1:1 propensity-matched analysis to examine the impact of arrhythmias. Overall, cardiac arrhythmias were identified in 33.71% of the hospitalized myocarditis cases. Ventricular tachycardia and atrial fibrillation were most common arrhythmias. There were increased odds of in-hospital mortality, cardiogenic shock, use of mechanical circulatory support, pacemaker implantation, and nonroutine hospital discharges in the arrhythmia cohorts. Length of stay and cost of hospitalization were also significantly higher. A significant proportion of patients with myocarditis have cardiac arrhythmias. As the occurrence of arrhythmias in myocarditis is associated with worse outcomes, it may be important to risk stratify patient to identify those who will benefit from early intervention. Published by Elsevier Inc. (Am J Cardiol 2019;123:139–144)**

Accumulating evidence indicates that a significant proportion of patients with acute myocarditis experience major cardiovascular events including sudden cardiac death (SCD), acute heart failure, chronic cardiomyopathy with significant arrhythmia risk.<sup>1</sup> In a single center study, authors attributed up to 8.6% of SCD to myocarditis.<sup>2</sup> Another study reported that in most cases of SCD resulting from myocarditis, there was evidence of acute inflammation, which often involves the conduction system.<sup>3</sup> Although the pathogenesis of SCD in myocarditis continues to present a major challenge to clinicians, there are indications to suggest that various arrhythmias might play significant role. While previous studies have focused on incidence of SCD in myocarditis, the arrhythmic burden and its pathogenetic impact on SCD in acute myocarditis is often overlooked. There exists only circumstantial evidence to suggest the possible association between arrhythmia and myocarditis, many of which are case reports and based on patients' experience in single centers with limited number of cases.<sup>4–10</sup> As a result, the impact as well as the

prognostic implications of arrhythmia on myocarditis remains unknown. Against this background, we evaluated the burden and clinical predictors of arrhythmia in acute myocarditis population; and the association between arrhythmias and adverse in-hospital outcomes. Recognizing potential predictors of arrhythmias in acute myocarditis will provide physicians with useful insight in risk-stratifying patients for early interventions.

## Method

Our study was conducted utilizing data from the 2007 through 2014 Healthcare Cost and Utilization Project (HCUP)—Nationwide Inpatient Survey Dataset (NIS). The NIS is a yearly survey of 20% of every admission from more than 4,000 hospitals and across over 30 states in the US and the District of Columbia.<sup>11</sup> The NIS has been validated in numerous studies to provide reliable estimates of admissions within the U.S.<sup>12,13</sup> Methods of data collection and administration of the NIS are detailed.<sup>14</sup> National estimates were generated using weights provided by Agency for Healthcare Research and Quality (AHRQ). We identified hospitalizations for aged 18 years or older with a discharge diagnosis of myocarditis using International Classification of Diseases, Ninth Revision; Clinical Modification (ICD-9-CM) codes [Supplemental Table 1](#). Arrhythmias were identified using ICD-9-CM codes ([Supplemental Table 1](#)). These codes have been used to determine national estimates in prior studies on NIS database.<sup>15</sup> We compared the outcomes between myocarditis hospitalization with or without arrhythmias. Our primary outcome was in-hospital mortality; secondary outcomes as detailed in [Supplemental Table 1](#). We estimated the cost of each inpatient stay by

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See page 144 for disclosure information.

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Table 1  
Baseline characteristics of patients with myocarditis by arrhythmia in the United States—unmatched

Variables	Total	Arrhythmias		p Value
		Yes	No	
No. of observation, unweighted	6,624	2,232 (33.71%)	4,393 (66.29%)	
No. of observation, weighted	32,107	10,844	21,329	
Age, mean (SD)	43.89 (17.83)	48.76 (18.10)	41.41 (17.18)	<0.0001
Women	38.66%	42.58%	36.67%	<0.0001
Race/Ethnicity				<0.0001
White	59.51%	62.68%	57.89%	
Black	13.45%	13.83%	13.26%	
Hispanic	8.73%	6.25%	9.99%	
Asia	18.32%	17.25%	18.86%	
Chronic obstructive pulmonary disease	14.38%	16.48%	13.32%	0.0004
Coronary artery disease	15.63%	18.61%	14.12%	<0.0001
Alcohol abuse	3.88%	4.25%	3.70%	0.263
Prior cerebrovascular disease	1.60%	2.10%	1.35%	0.018
Hypertension	31.76%	36.31%	29.45%	<0.0001
Peripheral vascular disease	2.46%	3.49%	1.94%	0.0001
Rheumatoid arthritis/collagen vascular diseases	3.17%	3.43%	3.04%	0.373
Hyperthyroidism	0.57%	0.91%	0.39%	0.006
Diabetes mellitus	11.92%	13.79%	10.97%	0.001
Obesity	11.72%	12.75%	11.20%	0.064
Deficiency anemia	13.11%	15.22%	12.04%	0.0004
Electrolyte derangement	28.26%	35.19%	24.73%	<0.0001
Congestive heart failure	37.68%	50.60%	31.11%	<0.0001
Coagulation disorder	8.63%	11.46%	7.19%	<0.0001
Renal failure	7.12%	9.40%	5.96%	<0.0001
Liver disease	2.36%	2.32%	2.38%	0.889
Valvular heart disease	5.24%	7.11%	4.29%	<0.0001
Smoking	26.91%	25.05%	27.85%	0.016
Weekend admission	24.67%	22.60%	25.71%	0.005
Endomyocardial biopsy	3.21%	4.85%	2.38%	<0.0001
Elixhauser score				<0.0001
0 - 1	48.38%	40.36%	52.45%	
2 - 3	32.62%	35.18%	31.32%	
≥ 4	19.00%	24.45%	16.23%	
Hospital bed size				0.445
Small	10.75%	11.32%	10.45%	
Medium	25.51%	22.92%	22.30%	
Large	66.74%	65.75%	67.25%	
Expected primary payer				<0.0001
Medicare	17.88%	23.53%	15.02%	
Medicaid	14.02%	13.86%	14.11%	
Private	52.97%	49.07%	54.94%	
Others	15.13%	13.54%	15.94%	
Median household income in quartile				0.0006
1 <sup>st</sup> quartile	22.85%	21.69%	23.43%	
2 <sup>nd</sup> quartile	24.24%	21.80%	25.48%	
3 <sup>rd</sup> quartile	25.27%	26.69%	24.55%	
4 <sup>th</sup> quartile	27.64%	29.81%	26.54%	
Hospital region				0.299
Northeast	26.56%	27.78%	25.93%	
Midwest	22.26%	21.93%	22.43%	
South	31.62%	31.81%	31.54%	
West	19.56%	18.49%	20.10%	
Teaching status				0.152
Rural	7.43%	7.16%	7.57%	
Urban, nonteaching	34.30%	32.76%	35.08%	
Urban, teaching	58.27%	60.08%	57.35%	

Obesity was defined by ICD-9-CM codes: 278.0, 278.00, 278.01.

multiplying the total hospital charge with cost-to-charge ratios.<sup>16</sup> To account for the effect of inflation on hospital charges, we used data from the Bureau of Labor Statistic's

medical care component of the Consumer Price Index (CPI) and presented the data in 2017 US dollars.<sup>17</sup> The severity of co-morbidities was quantified using the

Elixhauser co-morbidity index. We used propensity score matching to generate a matched cohort in whom patients with versus without arrhythmia. We built a multivariable logistic regression model with arrhythmia as the outcome variable and all baseline variables listed in [Table 1](#), as well as weekend admission status, year of admission, and elective as covariates. Using a 1-to-1 greedy matching protocol as described in prior studies,<sup>18</sup> we matched 9,257 hospitalizations with arrhythmias with 9,262 without arrhythmia. After the matching, we examined standardized differences (SD) for each variable between the 2 groups to assess the efficacy of the propensity score model. Standardized difference, all < 10% after matching indicates successful matching. As a sensitivity analysis, we examined the impact of arrhythmias on the outcomes of acute myocarditis after excluding the patients with had only conduction disturbances—bundle branch block, atrioventricular block, and Wolff-Parkinson-White (WPW) pattern ([Supplemental Table 3](#)). All the data extraction and analyses was done with Statistical Analysis System (SAS V.9.4) and p values are 2-sided with a significance threshold of < 0.05. For categorical variables, chi-square tests were used, and for non-normal distributed continuous variables such as length of stay, Wilcoxon–Mann–Whitney test was used. Stepwise backward logistic regression models with a p value of 0.3 for entry into the model were built to determine the independent predictors of arrhythmias in myocarditis. We excluded all the missing variables from the analysis, and did a complete case analysis given that observations are missing at random. Binary outcomes were modelled with binomial logistic regressions. For discrete numeric overdispersed count distribution variable—length of stay—Generalized linear model with negative binomial function was used and with gamma function was employed for total hospital cost. As recommended by HCUP, analyses were

performed in Statistical Analysis System with appropriate statements to account for the complex clustered sampling methodology.<sup>16,19</sup>

## Results

There was an estimated total of 32,107 acute myocarditis hospitalizations between 2007 and 2014 in the United States. Of these, 10,844 (33.71%) had arrhythmias. [Table 1](#) lists the comparison of patients and hospital characteristics with and without arrhythmias. Baseline characteristics were significantly different among the cohorts. Patients with arrhythmias were older, had significantly higher rates of major co-morbidities. The proportion of endomyocardial biopsy (EMB) performed was significantly higher in the arrhythmias cohorts compared with those without. The results are summarized in [Table 1](#). [Figure 1](#) shows the arrhythmia burden in myocarditis. Overall, cardiac arrhythmias were identified in 33.71% of the hospitalized myocarditis cases. The most common form of arrhythmias was atrial fibrillation (26.90%) followed by ventricular tachycardia (22.34%).

[Table 2](#) demonstrates the independent factors associated increased risk of arrhythmias, comorbidities such as hyperthyroidism, increasing age, and higher socio-economic status were found to be independently associated with greater odds of arrhythmias. Conversely, Hispanics and Western US region were associated with lower odds of arrhythmias. After 1:1 propensity-matched analysis, baseline characteristics were well matched in both groups as delineated in [Table 2](#). There were increased odds of in-hospital mortality, cardiogenic shock, use of mechanical circulatory support, pacemaker implantation, ICD placement, catheter ablation, cardioversion, and nonroutine hospital discharge in arrhythmia cohorts compared with those without. Length of stay

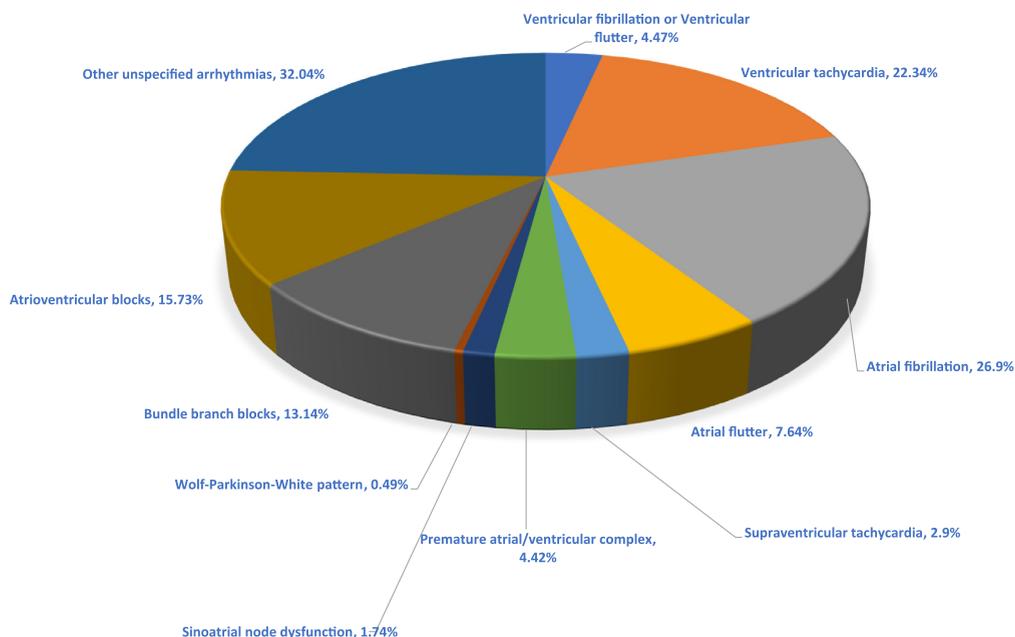


Figure 1. Types of arrhythmias in acute myocarditis. Overall, cardiac arrhythmias were identified in 33.71% of the hospitalized acute myocarditis cases.

Table 2  
Independent predictors of arrhythmias in patients with myocarditis in the United States between 2007 and 2014

Variables	Adjusted OR		95% CI	p Value
Hyperthyroidism	2.154	1.052	4.409	0.0357
Obesity	1.308	1.090	1.570	0.0039
Age, every 5 years increase	1.021	1.016	1.025	<0.0001
Electrolyte derangement	1.446	1.255	1.666	<0.0001
Deficiency anemia	1.170	0.977	1.400	0.0875
Congestive heart failure	1.923	1.698	2.178	<0.0001
Race/Ethnicity				
White (ref.)				
Black	1.032	0.863	1.234	0.0899
Hispanic	0.704	0.560	0.886	0.0025
Asia	0.972	0.827	1.143	0.3746
Chronic obstructive pulmonary disease	1.141	0.964	1.351	0.1254
Coagulopathy	1.561	1.271	1.918	<0.0001
Weekend admission	0.876	0.767	1.000	0.0499
Peripheral vascular disease	1.387	0.976	1.970	0.0677
Valvular heart disease	1.557	1.210	2.004	0.0006
Alcohol abuse	1.251	0.926	1.689	0.1443
Smoking history	0.917	0.802	1.048	0.2037
Hospital region				
Northeast (ref.)				
Midwest	0.857	0.723	1.015	0.7556
South	0.895	0.763	1.049	0.5866
West	0.751	0.630	0.896	0.0097
Expected primary payer				
Medicare (ref.)				
Medicaid	1.216	0.959	1.541	0.2247
Private	1.067	0.886	1.285	0.3152
Others	1.208	0.953	1.529	0.2567
Median household income in quartile				
1 <sup>st</sup> quartile (ref.)				
2 <sup>nd</sup> quartile	0.996	0.840	1.181	0.0118
3 <sup>rd</sup> quartile	1.272	1.075	1.506	0.0227
4 <sup>th</sup> quartile	1.310	1.104	1.556	0.0047

The following variables did not meet the entry criterion of p value <0.3 for entry into model: previous percutaneous coronary intervention, coronary artery disease, previous cerebrovascular disease, gender, rheumatologic and/or collagen vascular disorder, diabetes, hypertension, chronic liver disease, and chronic renal failure.

Obesity was defined by ICD-9-CM codes: 278.0, 278.00, 278.01.

and cost of hospitalization were significantly higher in arrhythmia group respectively (Supplemental Table 2 and Table 3). Similar results were obtained after excluding the hospitalizations with only conduction disturbances (Supplemental Table 3). The most common arrhythmia in those that experienced in-hospital mortality was ventricular tachycardia (23.74%; Supplemental Figure 2).

## Discussion

The salient findings in our study are: (1) A significant proportion of patients with myocarditis have cardiac arrhythmias with atrial fibrillation and ventricular tachycardia being the most common (2) Increasing age and increased co-morbidity burden are associated with greater odds of developing arrhythmias in acute myocarditis. (3) Cardiac arrhythmias complicating myocarditis is associated with worse in-hospital outcomes, increased length of stay, and cost of hospitalization.

Though cardiac arrhythmia especially ventricular tachyarrhythmia has only been reported in some case reports and single-center studies,<sup>6–10</sup> there are no previous large-scale

studies that examine the burden of arrhythmias in acute myocarditis. Using a nationally representative sample, we found that approximately 34% of patients admitted for myocarditis had arrhythmias during their hospitalization. This is similar to the result of previous case series where arrhythmias was reported in up to 40% of patients with myocarditis<sup>1</sup> some of which may manifest as SCD. The exact mechanism of arrhythmias in acute myocarditis is unknown. However, myocardial<sup>20</sup> cell death with resulting fibrosis, autoimmune-mediated cell damage, proarrhythmic effects of cytokines, and unmasking of preexisting cardiomyopathy have been postulated as possible mechanisms.<sup>1,3</sup> Ventricular arrhythmia and other abnormal cardiac rhythm have long been implicated in the pathogenesis of SCD in varieties of structural heart diseases.<sup>20,21</sup> In our study, there was 50% increase odds of in-hospital mortality among patients with acute myocarditis complicated with arrhythmias compared with those without. In a nationwide-retrospective study of SCD, myocarditis accounted for about 6% of SCD.<sup>22</sup> However, in another on the etiology of SCD among young army recruits, myocarditis was identified in up to 20% of cases.<sup>23</sup> Though the incidence of SCD in acute

Table 3  
Clinical impact of arrhythmia in patient admitted for myocarditis in the United States

Outcome variables	Arrhythmia		OR/*MR (95% CI)	p Value
	Yes	No		
In-patient mortality	6.89%	4.45%	1.59 (1.20, 2.13)	0.0015
Acute myocardial infarction	12.16%	13.82%	0.85 (0.71, 1.03)	0.096
Cardiogenic shock	14.91%	10.63%	1.46 (1.20, 1.78)	0.002
Mechanical circulatory support	8.79%	5.01%	1.81 (1.40, 2.34)	<0.0001
Cardiac tamponade	1.12%	1.06%	1.03 (0.56, 1.92)	0.914
Pericardiocentesis	0.90%	0.61%	1.41 (0.67, 2.96)	0.369
Vascular complication requiring surgery	1.18%	0.64%	1.81 (0.89, 3.67)	0.099
Ischemic stroke	2.29%	2.25%	0.98 (0.64, 1.49)	0.922
Acute respiratory failure	0.84%	0.34%	2.25 (0.92, 5.53)	0.076
Post-op DVT/PE	3.18%	2.55%	1.24 (0.85, 1.81)	0.273
Pacemaker placement	7.50%	0.43%	19.09 (9.30, 39.16)	<0.0001
ICD placement	4.94%	0.57%	8.80 (4.70, 16.44)	<0.0001
Catheter ablation	1.23%	0.05%	23.22 (3.13, 172.39)	0.002
Cardioversion	2.05%	0.05%	39.31 (5.38, 287.19)	0.0003
Acute kidney injury	23.33%	21.71%	1.07 (0.92, 1.26)	0.381
Acute kidney injury requiring dialysis	3.27%	3.45%	1.03 (0.72, 1.46)	0.887
Nonroutine home discharge	34.50%	29.50%	1.27 (1.11, 1.46)	0.0008
Cost	\$36, 623	\$26, 535	1.38 (1.22, 1.57)	<0.0001
Length of stay	8.51 days	6.83 days	1.25 (1.13, 1.38)	<0.0001

OR represents odds ratio (with 95% CI).

ICD: implantable cardioverter-defibrillator.

DVT/PE: Deep venous thrombosis/pulmonary embolism.

\* MR: Mean ratio for Length of stay and cost.

myocarditis complicated by arrhythmia vary widely in these studies presumably due to difference in the population under study, the significant risk of SCD in these studies underscores the importance of accessing the burden of arrhythmia both as a critical step in prevention of SCD and as a window to targeting those who may benefit from early ICD placement.

We found that increasing age and presence of co-morbidities are associated with greater odds of developing arrhythmias in acute myocarditis. The influence of age on the development of arrhythmias may be related to age-related changes in the conduction system with associated fibrosis.<sup>24</sup> The aging heart is particularly predisposed to the inflammatory changes in myocarditis. As expected, factors which predispose to cardiac arrhythmias tend to increase the risk of development of arrhythmias in patients admitted with myocarditis. Electrolyte abnormalities at admission increase the burden of arrhythmias in myocarditis as they tend to predispose to arrhythmias. Our studies revealed that coexisting heart failure, as well as valvular heart disease is associated with a higher risk of arrhythmias. Prior studies categorized heart failure in myocarditis as high risk for arrhythmias.<sup>25</sup> It is interesting to note that patients with hyperthyroidism have double the odds to develop arrhythmias compared with those without hyperthyroidism. As pointed out by Anakwe et al, hyperthyroidism causes cardiac dysfunction through hyperdynamic circulation, tachyarrhythmias, or the less recognized autoimmune myocarditis.<sup>26</sup> Expectedly, EMB was performed more among those with arrhythmias (4.85% vs 2.38%). Similar relationship was found by Ammirati et al who reported EMB performed in 39.8% of patients with complicated acute myocarditis compared with 2.8% in uncomplicated myocarditis.<sup>27</sup> Fewer EMB was done in our cohort compared with

the Italian cohorts where it was reported that 12.6% of the patients had EMB performed.<sup>27</sup> This observed difference most likely reflects variations in physician practices and available resources. There is increasing attention to the role of noninvasive cardiac magnetic resonance imaging in the prognostication of acute myocarditis.<sup>28</sup>

We found that patients admitted with myocarditis who had arrhythmias while on admission have poorer clinical outcomes. In-hospital mortality is more frequent in the arrhythmias cohort in the current study (6.89% vs 4.45%, odds ratio 1.59,  $p = 0.0015$ ). The proportion of in-hospital mortality was highest among those who experienced ventricular tachycardia. This is in keeping with previous studies which found that ventricular arrhythmias and heart failure predicted mortality. In an Italian registry, in-hospital mortality and heart transplant was found in 11.9% of the study population and was seen only in those with complicated myocarditis defined as heart failure or ventricular arrhythmias.<sup>27</sup> The increased mortality among those with arrhythmias may be due to increased risk of SCD and difficult to treat arrhythmias.

Our study has the following limitations: First, the use of NIS database which is an administrative database, to estimate the burden arrhythmias among patients presenting with acute myocarditis is well known to be at risk of coding errors.<sup>29</sup> As an example, a significant proportion of arrhythmias were unspecified. However, the database is still able to provide important information regarding the burden of arrhythmias in myocarditis. Second, the NIS does not provide data on other important measures like ejection fraction, medication use, thus, we are unable to study the impact of these clinical indicators on the outcome of arrhythmias in acute myocarditis.

Despite these limitations, our study remains the first to evaluate the burden, predictors and outcome of arrhythmias

in the United States using a nationally representative database. Also, our rigorous statistical method such as the propensity-matched analysis ensures that we adjusted adequately for the effects of known confounders.

In conclusion, cardiac arrhythmia is common in myocarditis, noted in 33.71% of patients with myocarditis. The increasing number of comorbidities and advancing age are important associations with the occurrence of cardiac arrhythmias. As the occurrence of arrhythmias in myocarditis is associated with worse outcomes as exemplified in this current study, it will be important to risk stratify patient to identify those who will benefit from early intervention.

## Disclosures

Authors have no disclosures.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.amjcard.2018.09.017](https://doi.org/10.1016/j.amjcard.2018.09.017).

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