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ORIGINAL RESEARCH

Frequency of Arrhythmias and Postural Orthostatic Tachycardia Syndrome in Patients With Marfan Syndrome: A Nationwide Inpatient Study

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BACKGROUND: Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder affecting multiple systems, particularly the cardiovascular system. The leading causes of death in MFS are aortopathies and valvular disease. We wanted to identify the frequency of arrhythmia and postural orthostatic tachycardia syndrome, length of hospital stay, health care–associated costs (HAC), and in-hospital mortality in patients with MFS.

METHODS AND RESULTS: The National Inpatient Sample database from 2005 to 2014 was queried using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes for MFS and arrhythmias. Patients were classified into subgroups: supraventricular tachycardia, ventricular tachycardia (VT), atrial fibrillation, atrial flutter, and without any type of arrhythmia. Data about length of stay, HAC, and in-hospital mortality were also abstracted from National Inpatient Sample database. Adjusted HAC was calculated as multiplying HAC and cost-to-charge ratio; 12 079 MFS hospitalizations were identified; 1893 patients (15.7%) had an arrhythmia; and 4.9% of the patients had postural orthostatic tachycardia syndrome. Median values of length of stay and adjusted HAC in VT group were the highest among the groups (VT: 6 days, $18 975.8; supraventricular tachycardia: 4 days, $11 906.6; atrial flutter: 4 days, $11 274.5; atrial fibrillation: 5 days, $10431.4; without any type of arrhythmia: 4 days, $8336.6; both P=0.0001). VT group had highest in-patient mortality (VT: 5.3%, atrial fibrillation: 4.1%, without any type of arrhythmia: 2.1%, atrial flutter: 1.7%, supraventricular tachycardia: 0%; P<0.0001) even after adjustment for potential confounders (without any type of arrhythmia versus VT; odds ratio [95% CI]: 3.18 [1.62–6.24], P=0.001).

CONCLUSIONS: Arrhythmias and postural orthostatic tachycardia syndrome in MFS were high and associated with increased length of stay, HAC, and in-hospital mortality especially in patients with VT.

Key Words: cardiac arrhythmia ■ hospitalization ■ Marfan syndrome ■ postural orthostatic tachycardia syndrome ■ ventricular arrhythmia

Marfan syndrome (MFS) is an autosomal dominant, multi-system connective tissue disorder, caused by mutations in the fibrillin 1 gene (*FBN1*). Pathogenic variants in *FBN1* cause a dysregulation in the formation of microfibrils and of transforming growth factor-beta, which lead to morphological changes in the cardiovascular, musculoskeletal, and ocular systems.[1,2] Clinically, MFS is characterized by thoracic aortic

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CLINICAL PERSPECTIVE

What Is New?

- Overall burden of inpatient arrhythmia in Marfan syndrome (MFS) is high compared with the general non-Marfan population; the most common arrhythmia was atrial fibrillation. Mortality was highest in those with ventricular tachycardia.
- Postural orthostatic tachycardia syndrome is recognized in joint hypermobility syndromes and non-Marfan connective tissue disease.
- We identified 4.9% patients with MFS had postural orthostatic tachycardia syndrome which is novel and not previously reported.

What Are the Clinical Implications?

- The association between arrhythmias, postural orthostatic tachycardia syndrome, and connective tissue disorders are not clearly understood at present and may be underdiagnosed in the MFS population.
- In patients hospitalized with MFS with arrhythmias, the mean length of hospital stay was 4 days and mean health care–associated cost was $12184.98.
- Screening patients with MFS for arrhythmias in the outpatient setting may be a cost-effective method to prevent unnecessary complications and hospitalization in this population.

Nonstandard Abbreviations and Acronyms

AFL	atrial flutter
HAC	health care-associated cost
MFS	Marfan syndrome
POTS	postural orthostatic tachycardia syndrome
SVT	supraventricular tachycardia
WA	without any type of arrhythmia

aneurysm and/or dissection, ectopia lentis, and systemic features.[3,4] MFS has a prevalence of 1 per 5000 individuals worldwide, regardless of sex, race or ethnicity, or geographical location.[2,5,6] The leading causes of death in patients with MFS are cardiovascular complications, mainly aortopathies (aortic dissection and rupture).[5–7] Valvular heart disease also contributes to morbidity in MFS. However, the frequency and prevalence of arrhythmias (including postural orthostatic tachycardia syndrome [POTS]), length of hospital stay (LOS), health care–associated costs (HAC) and in-hospital mortality in patients with MFS are unknown.

Given the rarity of MFS, "big data" studies are well-suited for its investigation as sample sizes larger than single center samples can be identified, and tertiary referral bias can be minimized. Thus, we sought to determine the frequency of arrhythmias and POTS, describe comorbidities, and determine whether these impact the LOS in hospital, HAC, and in-hospital mortality, using the number of hospitalizations found in the database.

METHODS

The data underlying this article are available in the article and in its online supplementary material.

Database

The study was conducted using the National Inpatient Sample (NIS) data set (of the Health Care Utilization and Project Data Set) between January 1, 2005 to December 31, 2014. Briefly, the NIS data set includes in-patient care from all-payer hospitals and is the largest inpatient data set in the United States including 20% of community hospitals. Each entry contains information on the demographics, primary procedures, hospitalization outcome (ie, in-hospital mortality), total HAC, and LOS of patients. The data correlate with other hospitalization discharge databases in the United States.[7] The information is stored with safeguards to protect the privacy of patients, physicians, and hospitals involved. The NIS data were analyzed using the *International Classification of Diseases, Ninth Edition, Clinical Modification* (*ICD-9-CM*) to identify the number of patients with arrhythmias. This study was considered exempt from Institutional Review Board approval because Healthcare Cost and Utilization Project-NIS contain only publicly available deidentified patient information.

Patients

The patients with MFS were identified using *ICD-9-CM* codes as shown in Table S1. Patients with MFS were divided into adult patients (≥18 years old) and young patients (<18 years old). Patients with MFS were classified into 5 subgroups based on the presence/absence and type of arrhythmia detected: supraventricular tachycardia (SVT), ventricular tachycardia (VT), atrial fibrillation (AF), atrial flutter (AFL), and without any arrhythmia (WA). Patients with multiple arrhythmias during inpatient stay and a history of orthostatic hypotension were excluded from this study as shown in Figure 1. There have been previous studies[8,9] that indicated pregnancy can increase the frequency of arrhythmias in patients with MFS and non-MFS; however, from the 36 pregnant females with MFS who were identified in the database, all of them did not have any type of arrhythmia identified during this study period.

Abstracted Data

Data on the patient's age (in years), HAC (US Dollars, $), LOS (days), and in-hospital deaths for these patients were extracted from the NIS database. We included baseline patient-level characteristics: race or ethnicity [Whites, Non-Hispanic Blacks, Hispanics, and others (Asians, American Indian/Alaska natives, Native Hawaiian/Other Pacific Islander)], sex, and health insurance type (Medicare, Medicaid, private, self-pay, and others). We also included variables for hospital-level factors: region Northeast (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, Pennsylvania, and New Jersey), Midwest (Wisconsin, Michigan, Illinois, Indiana, Ohio, Missouri, North Dakota, South Dakota, Nebraska, Kansas, Minnesota, and Iowa), South (Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida, Kentucky, Tennessee, Mississippi, Alabama, Oklahoma, Texas, Arkansas, and Louisiana), and West (Idaho, Montana, Wyoming, Nevada, Utah, Colorado, Arizona, New Mexico, Alaska, Washington, Oregon, California, and Hawaii), and hospital size (small, medium, and large sizes). The bed size was categorized by 3 quantile range, which was based on the region the hospital was located (Northeast/Midwest/South/West), area of the hospital (urban or rural), teaching status of the hospital, and the existence of comorbidities (using the Elixhauser comorbidity software) in the patients were also included. The primary reason for admission was defined using the *ICD-9-CM* code. To estimate the cost of hospitalization more accurately, the NIS data were merged with cost-to-charge ratios available from the Healthcare Cost and Utilization Project. We estimated the adjusted HAC of each in-patient stay by multiplying the total hospital charge with cost-to-charge ratios.

Statistical Analysis

The data are shown as median (interquartile range; IQR), number (%), standardized beta (β), odds ratio (OR) 95% CI and coefficient (95% CI). Continuous variables were analyzed by Kruskal–Wallis test after the Kolmogorov–Smirnov test and Bonferroni correction methods as post hoc tests. Binary variables were analyzed using Fisher exact test. Dichotomous outcomes (eg, in-patient mortality) were modeled with logistic regressions adjusting for demographic factors such as race or ethnicity, income level, insurance status, and hospital-level factors (ie, hospital bed size and hospital region). Discrete numeric variables with an overdispersed distribution (ie, LOS) and continuous variables with a skewed spread (ie, adjusted HAC) were modeled with multiple regression analysis (ordinary least-squares linear regression models), which were adjusted for similar covariates as above. Multiple regression analysis, except for evaluation of adjusted

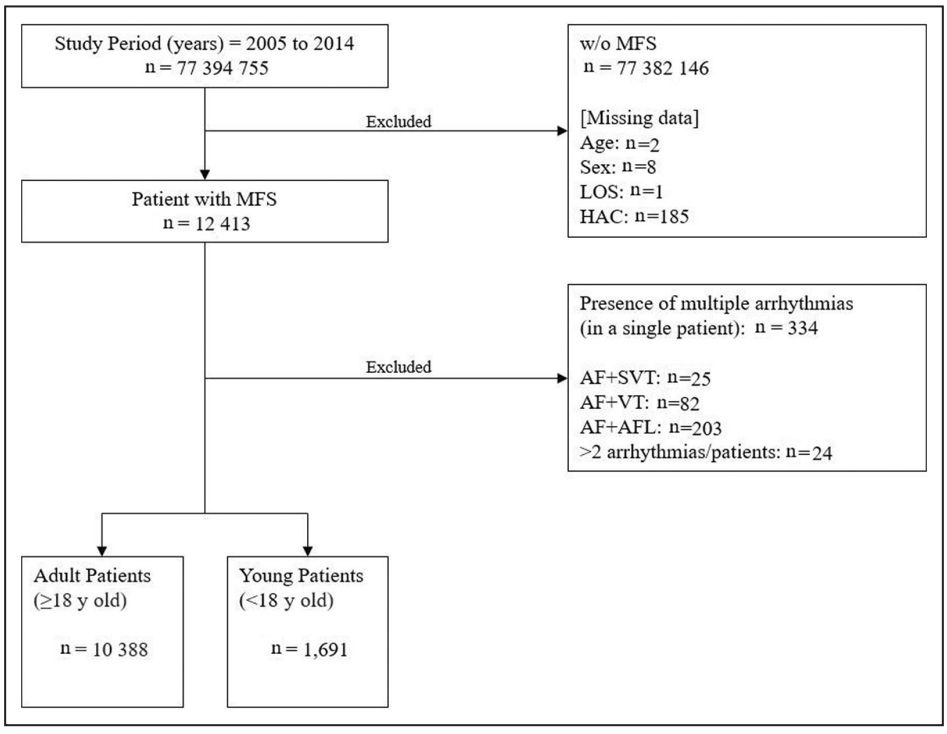

Figure 1. Patient flowchart.
AF indicates atrial fibrillation; AFL, atrial flutter; HAC, health care–associated cost; LOS, length of hospital stay; MFS, Marfan syndrom; SVT, supraventricular tachycardia; and VT, ventricular tachycardia.

HAC, were adjusted using 3 models (Model 1: sex, age, LOS, type of arrhythmia, hospital region, and hospital size; Model 2: Model 1+race or ethnicity and health insurance; Model 3: Model 2+POTS, anticoagulants, and existence of comorbidities). In addition to the multiple regression analysis, inverse-probability-weighted regression adjustment was used for estimation with control for confounding. The included variables for adjustment were sex, age, hospital region, hospital size, type of race or ethnicity, and existence of comorbidities. All data extraction and analyses were done using STATA version 15.1 (Stata-Corp, TX, USA). A 2-tailed *P* value of <0.05 was considered as statistically significant.

Table 1. Baseline Characteristics of Patients With MFS

	All MFS	WA	AF	VT	AFL	SVT	*P* value
No. (%)	12 079 (100.0)	10 186 (84.2)	1542 (12.8)	189 (1.6)	118 (1.0)	44 (0.4)	…
Age, y	39 (25–53)	35 (23–50)	57 (47–66)†	44 (32–54)*,†	51 (35–61)†	36 (24–50)*,†	0.0001
Male sex, n (%)	6799 (56.3)	5630 (55.3)	957 (62.1)	114 (60.3)	76 (64.4)	22 (50.0)	<0.0001
POTS, n (%)	597 (4.9)	465 (4.6)	98 (6.4)	17 (9.0)	≤10 (N/A)	≤10 (N/A)	<0.0001
Anticoagulants, n (%)	1693 (14.0)	1236 (12.1)	402 (26.1)	24 (12.7)	≤30 (N/A)	≤10 (N/A)	<0.0001
Race or ethnicity, n (%)							
White	7612 (75.1)	6270 (73.4)	1123 (86.5)	119 (72.6)	75 (80.7)	25 (71.4)	
Black	1280 (12.6)	1141 (13.4)	98 (7.5)	29 (17.7)	≤10 (N/A)	≤10 (N/A)	
Hispanic	791 (7.8)	731 (8.6)	39 (3.0)	11 (6.7)	≤10 (N/A)	≤10 (N/A)	
Other*	448 (4.4)	398 (4.7)	39 (3.0)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	<0.0001
Comorbidities, n (%)							
CHF	717 (5.9)	453 (4.5)	242 (15.7)	12 (6.4)	≤10 (N/A)	≤10 (N/A)	<0.0001
CPD	1907 (15.8)	1559 (15.3)	293 (19.0)	28 (14.8)	≤20 (N/A)	≤10 (N/A)	0.008
Diabetes	704 (5.8)	534 (5.2)	155 (10.1)	11 (5.8)	≤10 (N/A)	≤10 (N/A)	<0.0001
Hypertension	4112 (34.0)	3241 (31.8)	746 (48.4)	62 (32.8)	48 (40.7)	15 (34.1)	<0.0001
Liver diseases	173 (1.4)	145 (1.4)	23 (1.5)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	0.86
Obesity	450 (3.7)	357 (3.5)	68 (4.4)	16 (8.5)	≤10 (N/A)	≤10 (N/A)	0.002
Renal failure	545 (4.5)	403 (4.0)	125 (8.1)	12 (6.4)	≤10 (N/A)	≤10 (N/A)	<0.0001
Mitral valve prolapse	1351 (11.2)	1085 (10.7)	220 (14.3)	24 (12.7)	≤20 (N/A)	≤10 (N/A)	0.001
Devices, n (%)							
Pacemaker	89 (0.7)	42 (0.4)	36 (2.3)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	<0.0001
ICD	52 (0.4)	26 (0.3)	≤10 (N/A)	16 (8.5)	≤10 (N/A)	≤10 (N/A)	<0.0001
CRT-D	18 (0.2)	≤10 (N/A)	11 (0.7)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	<0.0001
CRT-P	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	0.009
@Health insurance, n (%)							
Medicare/Medicaid	5928 (49.2)	4926 (48.5)	837 (54.4)	93 (49.2)	51 (43.2)	21 (47.7)	
Private	4943 (41.0)	4160 (40.9)	630 (40.9)	72 (38.1)	61 (51.7)	20 (45.5)	
Others	1187 (9.8)	1082 (10.6)	72 (4.7)	24 (12.7)	≤10 (N/A)	≤10 (N/A)	<0.0001
Region, n (%)							
Northeast	2284 (18.9)	1928 (18.9)	293 (19.0)	34 (18.0)	≤20 (N/A)	≤20 (N/A)	
Midwest	3056 (25.3)	2548 (25.0)	419 (27.2)	48 (25.4)	30 (25.4)	11 (25.0)	
South	4389 (36.3)	3718 (36.5)	545 (35.3)	75 (39.7)	39 (33.1)	12 (27.3)	
West	2350 (19.5)	1992 (19.6)	285 (18.5)	32 (16.9)	≤40 (N/A)	≤10 (N/A)	0.52
Hospital size, n (%)							
Small	1335 (11.1)	1149 (11.3)	163 (10.6)	12 (6.4)	≤10 (N/A)	≤10 (N/A)	
Medium	2568 (21.4)	2154 (21.2)	352 (22.9)	41 (21.8)	≤20 (N/A)	≤10 (N/A)	
Large	8126 (67.6)	6842 (67.4)	1020 (66.5)	135 (71.8)	91 (77.8)	38 (86.4)	0.01

AF indicates atrial fibrillation; AFL, atrial flutter; CHF, chronic heart diseases; CPD, chronic pulmonary diseases; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; ICD, implantable cardioverter defibrillator; MFS, Marfan syndrome; POTS, postural orthostatic tachycardia syndrome; SVT, supraventricular tachycardia; VT, ventricular tachycardia; and WA, without any type of arrhythmia.

@=The variable has missing data.

Vs. AF: †*P*<0.0001; vs. AFL: †*P*<0.0001; vs. VT: **P*<0.05, †*P*<0.0001; vs. SVT: **P*<0.05, †*P*<0.0001.

*Other refers to Asian, American Indian/Alaska native, Native Hawaiian/Other Pacific Islander.

RESULTS

Frequency of Arrhythmias

In total, 12 079 hospitalizations in patients with MFS were identified from the NIS over the 10-year study period (Figure 1). The median (IQR) age and prevalence of arrhythmias were 39 (25–53) years and 15.8%, respectively (Table 1). Of the patients who were included, 4.9% of patients had POTS (Table S2). The most prevalent arrhythmia in adult patients was AF (14.8%) followed by VT (1.7%), AFL (1.1%), and SVT (0.4%) as shown in Table S3. Among adult patients stratified by arrhythmia, those in the AF group were the oldest, and those with AFL were more likely to be male (64.6%). The frequency of POTS and mitral valve prolapse in adult patients were 543 (5.2%) and 1119 (10.8%), respectively. The most prevalent comorbidity was hypertension (38.9%) followed by chronic pulmonary diseases, mitral valve prolapse, chronic heart failure (CHF), diabetes, renal failure, obesity, and liver diseases. Children had significantly less frequency of POTS (3.3%), CHF (2.5%), chronic pulmonary diseases (11.4%), and hypertension (4.1%) than adult patients; conversely mitral valve prolapse was higher in children (13.7%) in our data set (Table S4). Arrhythmias in patients with MFS with POTS were AF 465 (4.6%) and VT 94 (6.4%) whilst AFL and SVT were statistically insignificant (Table S3).

Primary Reason for Admission

The rate of admission for the patients with MFS ranged from 0.01% to 0.02% during 2005 to 2014 and the estimated rates of patients with MFS and arrythmias such as AF, VT, SVT, and AFL ranged from 0.002% to 0.003% (Table S5). For admissions of adult patients with MFS, the most frequent race or ethnicity of patients with MFS admitted regardless of arrhythmia group were of White descent (Table S3). Also, the estimated rates of adult patients with MFS and arrythmias ranged from 0.002% to 0.004% (Table S5). The most frequent cardiac related reason for admission for adult patients with MFS were thoracic aortic dissection followed by thoracic aortic aneurysm and AF, while the most frequent cardiac related reason for admission in young patients with MFS was thoracic aortic aneurysm (Table S6 and S7). Pneumonia and pneumothoraces were also high in not only adult patients but also in young patients as the primary reason for admission (Table S8).

Length of Stay in Hospital

Overall, LOS in the patients with MFS with VT was longest among the different subgroups followed by those with AF and AFL (WA: 4.0 [2.0–7.0] days, AF: 5.0 [2.0–8.0] days, AFL: 4.0 [1.0–10.0] days, VT: 6.0 [3.0–12.0] days, SVT: 4.0 [2.0–9.0] days; P=0.0001) (Figure 2). After the adjustments for potential confounders, the presence of AF, VT, and AFL were significant factors for prolonged LOS (AF: β=0.05, P<0.0001; VT: β=0.04, P<0.0001; AFL: β=0.05, P<0.0001) (Table 2). In the adult patients with MFS, the median (IQR) LOS was 4.0 (2.0–7.0) days (WA: 4.0 [2.0–7.0] days, AF: 5.0 [2.0–8.0] days, AFL: 4.0 [2.0–8.0] days, VT: 6.0 [3.0–12.0] days, SVT: 4.0 [1.5–10.0] days; P=0.0001) (Figure S1). In the multivariable analysis, the adult patients with MFS with AF, VT, and AFL were admitted longer than those WA. Younger male patients with MFS were also admitted longer than older female patients with MFS (Table S9). An estimation using inverse-probability-weighted regression adjustment showed presence of AF, VT, and AFL were significant predictors for lengthening of hospitalization (Table S10). Furthermore, adult patients with MFS with CHF, obesity, and chronic renal failure were admitted longer than those without them. In the young patients with MFS group, the significant predictors for prolonged hospitalization were increasing age, AFL, and CHF (Table S11). The LOS for patients with MFS with POTS was 4 (2.0–7.0) days (Table S2 and Figure 3).

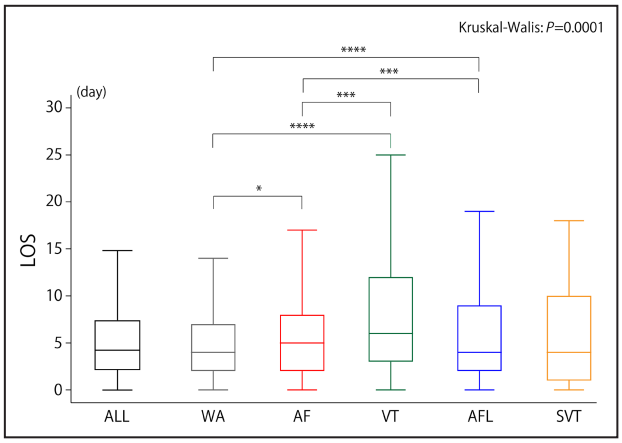

Figure 2. Length of hospital stay.
We compared the differences among the arrhythmia groups (ie, without any type of arrhythmia, atrial fibrillation, ventricular tachycardia, atrial flutter, and supraventricular tachycardia). AF indicates atrial fibrillation; AFL, atrial flutter; ALL, total number of Marfan Syndrome patients in this study; LOS, length of hospital stay; SVT, supraventricular tachycardia; VT, ventricular tachycardia; and WA, without any type of arrhythmia. *P<0.05, ***P<0.001, ****P<0.0001.

Health Care–Associated Costs

The adjusted HAC in patients with MFS with VT was the highest among the different subgroups (WA: $8336.6 [$4304.1–19263.2], AF: $10431.4 [$5129.4–25592.5], AFL: $11274.5 [$5406.8–50073.7], VT: $18975.8 [$7381.2–43512.1], SVT: $11906.6 [$6057.9–39707.9] days; P=0.0001) (Figure 4) After the

Table 2. Predictors for Length of Hospital Stay

	Model 1		Model 2		Model 3	
	β	*P* value	β	*P* value	β	*P* value
Female sex	−0.03	0.003	−0.03	0.001	−0.03	0.003
Age, y	−0.07	<0.0001	−0.06	<0.0001	−0.08	<0.0001
POTS	…	…	…	…	−0.005	0.61
Anticoagulants	…	…	…	…	−0.04	<0.0001
Arrhythmia						
WA	(ref.)	…	(ref.)	…	(ref.)	…
AF	0.05	<0.0001	0.05	<0.0001	0.05	<0.0001
VT	0.05	<0.0001	0.04	<0.0001	0.04	<0.0001
AFL	0.04	<0.0001	0.05	<0.0001	0.05	<0.0001
SVT	0.002	0.83	0.0005	0.96	0.002	0.85
Region						
Northeast	(ref.)	…	(ref.)	…	(ref.)	…
Midwest	−0.06	<0.0001	−0.04	0.001	−0.05	<0.0001
South	−0.01	0.29	−0.007	0.57	−0.01	0.30
West	−0.04	0.002	−0.03	0.007	−0.03	0.007
Hospital size						
Small	(ref.)	…	(ref.)	…	(ref.)	…
Medium	0.02	0.19	0.01	0.35	0.01	0.33
Large	0.06	<0.0001	0.05	<0.0001	0.05	<0.0001
Race or ethnicity						
White	…	…	(ref.)	…	(ref.)	…
Black	…	…	0.02	0.04	0.01	0.27
Hispanic	…	…	0.02	0.02	0.02	0.04
Other*	…	…	0.009	0.38	0.008	0.41
Health insurance						
Medicare/Medicaid	…	…	(ref.)	…	(ref.)	…
Private	…	…	−0.03	0.003	−0.02	0.04
Others	…	…	−0.04	<0.0001	−0.04	<0.0001
Comorbidities						
CHF	…	…	…	…	0.07	<0.0001
CPD	…	…	…	…	0.009	0.38
Diabetes	…	…	…	…	−0.006	0.53
Hypertension	…	…	…	…	0.02	0.04
Liver diseases	…	…	…	…	−0.002	0.82
Obesity	…	…	…	…	0.02	0.02
Renal failure	…	…	…	…	0.04	<0.0001
Mitral valve prolapse	…	…	…	…	−0.03	0.001

The β is standardized beta.

Model 1: Sex, age, type of arrhythmia, hospital region, and hospital size; Model 2: Model 1+type of race or ethnicity and health insurance; Model 3: Model 2+ POTS, anticoagulants, and existence of comorbidities. AF indicates atrial fibrillation; AFL, atrial flutter; CHF, chronic heart disease; CPD, chronic pulmonary diseases; POTS, postural orthostatic tachycardia syndrome; ref., reference group for Beta-standardization test; SVT, supraventricular tachycardia; VT, ventricular tachycardia; and WA, without any type of arrhythmia.

*Other refers to Asian, American Indian/Alaska native, Native Hawaiian/Other Pacific Islander.

adjustments for potential confounders, the presence of AF, VT, and AFL were significant factors for increased adjustment HAC (AF: β=0.03, *P*<0.0001; VT: β=0.05, *P*<0.0001; AFL: β=0.03, *P*<0.0001) (Table 3). For adult patients with MFS, the median (IQR) was $8548.0 [$4533.5–19225.3]. Adult patients with MFS with VT had the highest adjusted HAC among the groups (VT: $18570.4 [$7381.2–42403.6]; AF: $10397.6 [$5129.0–25535.6]; AFL: $11274.5 [$5406.8–47788.1], SVT: $12684.2 [$6482.0–45909.5]; WA: $8130.3 [$4387.6–17641.4], *P*=0.0001) (Figure S2). Multivariable analysis showed adult patients with MFS with AF, VT, AFL, and

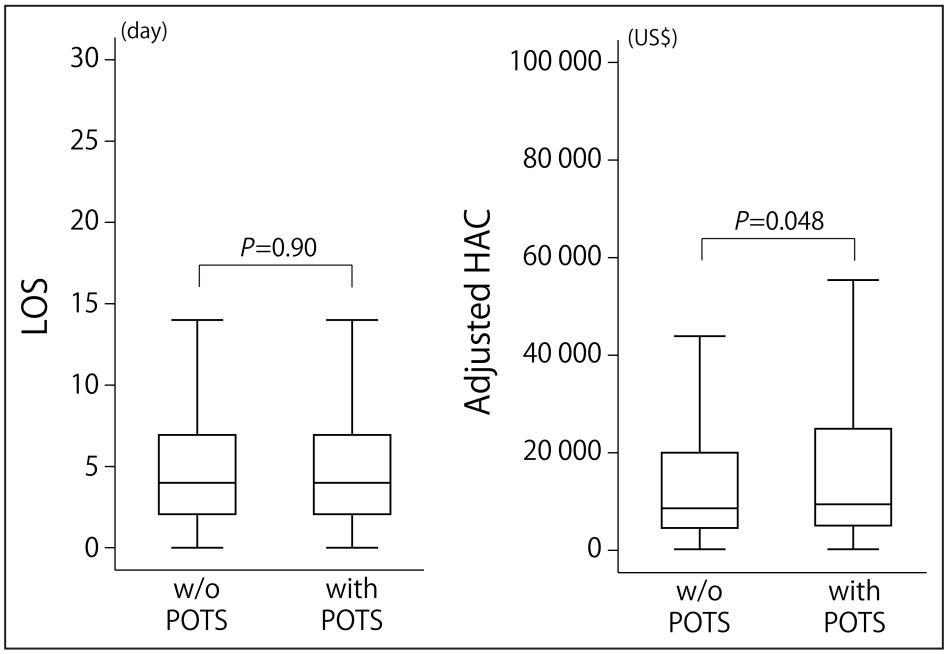

Figure 3. LOS and HAC for patients with POTS.
HAC indicates health care–associated cost; LOS, length of hospital stay; and POTS, postural orthostatic tachycardia syndrome.

SVT resulted in significantly higher adjusted HAC than those WA (Table S12). The multivariable analysis also showed that male sex, and presence of hypertension and obesity were significant predictors to increased adjusted HAC for these patients. In the young patients, female sex, high age, and presence of AFL, SVT, CHF, and mitral valve prolapse were significant predictors for higher adjusted HAC (Table S11). Among the different groups, the type of health insurance used, and hospital size were significantly different. An estimation using inverse-probability-weighted regression adjustment also showed adjusted HAC in patients with MFS with AF, VT, and AFL were significantly higher than those WA (Table S10). The adjusted HAC for patients with MFS with POTS was $9425 [$4881.1–25144.3] (Table S2 and Figure 3) which is lower compared with the adjusted HAC for patients with arrhythmias.

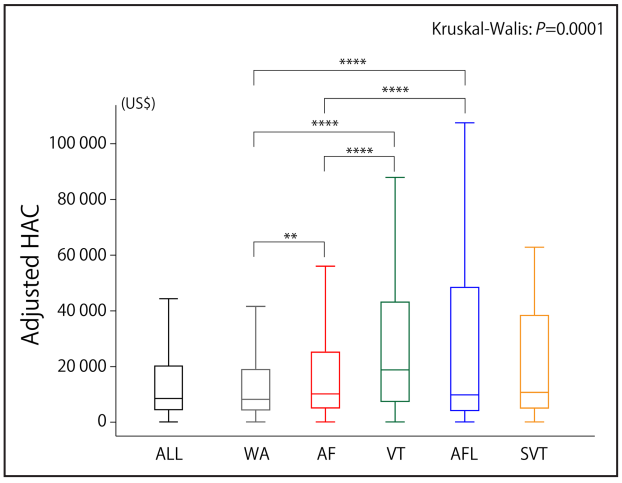

Figure 4. Adjusted HACs.
We compared the differences among the arrhythmia groups (ie, without any type of arrhythmia, atrial fibrillation, ventricular tachycardia, atrial flutter, and supraventricular tachycardia). AF indicates atrial fibrillation; AFL, atrial flutter; ALL, total number of Marfan Syndrome patients in this study; HAC, health care–associated cost; SVT, supraventricular tachycardia; VT, ventricular tachycardia; and WA, without any type of arrhythmia. **P<0.01, ****P<0.0001.

In-Hospital Mortality

Overall, in-hospital all-cause mortality for patients with MFS with VT was the highest among the different subgroups followed by the patients with AF, WA, and AFL (5.3%, 4.1%, 1.7%, and 1.7%; respectively, P<0.0001) (Figure 5). The trends remained the same after adjustment for potential confounders (VT: OR [95% CI]: 2.75 [1.22–5.42], P=0.01; AF: OR [95% CI]: 1.96 [1.36–2.83], P<0.0001) (Table 4). In the adult patients with MFS, the all-cause in-hospital mortality was 2.1%. For the adult patients with MFS with VT, the frequency of all-cause mortality in-hospital was 4.5%, which is the highest among the different subgroups (P<0.0001) (Figure S3). Adult patients with MFS WA, with AF and with AFL had in-hospitals deaths of 1.7%, 4.1%, and 1.8%, respectively. None of the adult patients with MFS with SVT died during their admission. Regarding predictors of in-hospital death, the multivariable analysis

Table 3. Predictors for Adjusted Health Care–Associated Cost

	Model 1		Model 2		Model 3	
	β	*P* value	β	*P* value	β	*P* value
Female sex	−0.02	0.006	−0.02	0.004	−0.02	0.002
Age, y	−0.03	<0.0001	−0.02	0.04	−0.02	0.04
LOS	0.67	<0.0001	0.67	<0.0001	0.67	<0.0001
POTS	…	…	…	…	0.002	0.78
Anticoagulants	…	…	…	…	−0.03	<0.0001
Arrhythmia						
WA	(ref.)	…	(ref.)	…	(ref.)	…
AF	0.02	0.001	0.02	0.003	0.03	<0.0001
VT	0.04	<0.0001	0.05	<0.0001	0.05	<0.0001
AFL	0.03	<0.0001	0.03	<0.0001	0.03	<0.0001
SVT	0.01	0.03	0.01	0.11	0.01	0.12
Region						
Northeast	(ref.)	…	(ref.)	…	(ref.)	…
Midwest	−0.01	0.18	−0.01	0.26	−0.01	0.26
South	−0.05	<0.0001	−0.04	<0.0001	−0.04	<0.0001
West	0.08	<0.0001	0.09	<0.0001	0.09	<0.0001
Hospital size						
Small	(ref.)	…	(ref.)	…	(ref.)	…
Medium	−0.03	0.001	−0.04	0.002	−0.04	0.001
Large	0.004	0.71	0.004	0.70	0.005	0.66
Race or ethnicity						
White	…	…	(ref.)	…	(ref.)	…
Black	…	…	0.01	0.10	0.01	0.16
Hispanic	…	…	0.01	0.11	0.01	0.10
Other*	…	…	0.03	<0.0001	0.03	<0.0001
Health insurance						
Medicare/Medicaid	…	…	(ref.)	…	(ref.)	…
Private	…	…	0.08	<0.0001	0.08	<0.0001
Others	…	…	0.01	0.23	0.009	0.24
Comorbidities						
CHF	…	…	…	…	−0.02	0.007
CPD	…	…	…	…	0.005	0.46
Diabetes	…	…	…	…	−0.00004	1.00
Hypertension	…	…	…	…	0.02	0.03
Liver diseases	…	…	…	…	−0.00009	0.99
Obesity	…	…	…	…	0.02	0.002
Renal failure	…	…	…	…	0.006	0.43
Mitral valve prolapse	…	…	…	…	0.20	0.008

Model 1: Sex, age, length of hospital stay, type of arrhythmia, hospital region, and hospital size; Model 2: Model 1+type of race or ethnicity and health insurance; Model 3: Model 2+POTS, anticoagulants and existence of comorbidities. AF indicates atrial fibrillation; AFL, atrial flutter; CHF, chronic heart disease; CPD, chronic pulmonary diseases; LOS, length of hospital stay; POTS, postural orthostatic tachycardia syndrome; ref., reference group for Beta-standardization test; SVT, supraventricular tachycardia; VT, ventricular tachycardia; and WA, without any type of arrhythmia.

*Other refers to Asians, American Indian/Alaska natives, Native Hawaiian/Other Pacific Islander.

showed that adult patients with MFS with AF and VT were significantly more likely to die (during their admission) than those WA (Table S13). Moreover, male sex and the presence of CHF, chronic liver disease, hypertension, and renal failure were significant predictors for in-hospital death. Also, the presence of VT was a significant predictor for in-hospital mortality in young patients with MFS (Table S11). The presence of VT was a significant predictor for in-hospital death on estimation using inverse-probability-weighted regression

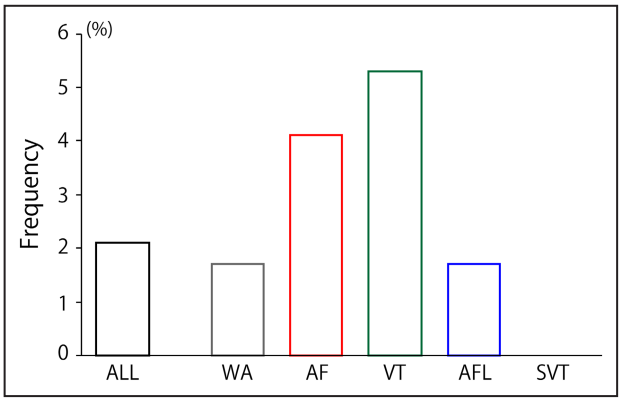

Figure 5. Frequency of in-hospital mortality.
We compared the differences among the arrhythmia groups (ie, without any type of arrhythmia, atrial fibrillation, ventricular tachycardia, atrial flutter, and supraventricular tachycardia). AF indicates atrial fibrillation; AFL, atrial flutter; ALL, total number of Marfan Syndrome patients in this study; SVT, supraventricular tachycardia; VT, ventricular tachycardia; and WA, without any type of arrhythmia.

adjustment (Table S10). There were no observable differences between the in-hospital mortality for patients with MFS with and without POTS (P=0.14) (Table S2).

DISCUSSION

This study has several important and novel findings. First, AF was the most frequent arrhythmia (12.8% in all patients with MFS, 14.8% in adult patients with MFS only) with a median age of 57 years, SVT being the least frequent arrhythmia, and occurred in those of younger age. Second, the most common primary cardiac related reason for admission for adult patients during this study period was because of thoracic aortic dissection. Third, patients with MFS with VT had the longest LOS, highest adjusted HAC, and the highest percentage of in-hospital deaths. Lastly, 4.9% of patients with MFS had POTS, which is an unreported association.

AF is the most common sustained arrhythmia in the United States (affecting 2.7 to 6.1 million people with annual health care cost between $6 to $26 billion) with male preponderance, a prevalence of 3% (adults ≥20 years, increasing with age) and is commonly associated with comorbidities such as hypertension, CHF, coronary artery disease, obesity, diabetes, and renal failure.[6,10] This could explain why the most frequent arrhythmia in patients with MFS is also AF which is consistent with previous studies on MFS and related heart diseases (valve and aortic heart diseases).[10–12] However, the frequency of AF in our study group is markedly higher than that expected based on data in the general population of the same mean age of 57 (IQR, 47–66) years (observed 14.8% in MFS versus 5% expected).[10] Patients with MFS may start developing AF (and other arrhythmias) secondary to the underlying structural heart disease that they may have and/or because of MFS pathology itself. Table S14 contains the comparison studies of the frequency and outcomes of arrhythmias in patients with MFS in relation with the general population.

The primary reason for admission was because of cardiac causes (excluding arrhythmias), of which 38.4% was attributable to disease of the aorta. It is important to note that the mortality rate increases in patients developing more comorbidities, as they grow older, have a poorer preadmission performance status, pre-existing structural heart, and coronary artery disease, had previous failed (surgical) interventions and unsuccessful cardioversion/ablations attempts. The complications and progress of these diseases also increase the rate of mortality. However, the cause(s) of death in each of the individual patients with MFS were unidentified.

The LOS of patients with MFS with arrhythmias compared with those without any type of arrhythmia differed by 1 to 3 days at most (from the upper limit of those WA). Those with VT had the longest LOS and highest adjusted HAC. This may be because of interventions such as anti-arrhythmic medication and/or direct current cardioversion used to treat the VT, the need for additional investigative modalities, admission onto the coronary care unit/intensive care unit, and further interventions such as the implantation of a pacemaker/implantable cardioverter defibrillator. Patients with MFS with comorbidities had a longer LOS and higher adjusted HAC than those without. This was probably because of the complications that may have developed secondary to the comorbidities, thus increasing adjusted HAC and LOS; however, the exact cause(s) for this is difficult to ascertain because of limitations of the NIS database. We must also consider patients on palliative care or who have advanced care plans in place that would limit the interventions given or not given.

The frequency of all-cause mortality in-hospital in adult patients with MFS with VT was 4.5% which is the highest value among the different subgroups (Figure 5). Although none of the patients with MFS with SVT died during the admission, the frequency of all-cause hospital mortality in adult patients with MFS WA, with AF, and with AFL were 1.7%, 4.1%, and 1.8%, respectively. Regarding predictors of in-hospital death, the multivariable analysis showed that patients with AF or VT were significantly more likely to die in the admission than those WA (Table 4). Moreover, male sex and existence of CHF, liver disease, hypertension, and renal failure were significant predictors for in-hospital death. In MFS, it has been established that aortic emergencies such as aortic dissection and aortic rupture are the

Table 4. Predictors for In-Hospital Mortality

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Female sex	0.73 (0.56–0.94)	0.02	0.72 (0.55–0.96)	0.02	0.74 (0.55–0.98)	0.04
Age, y	1.01 (1.00–1.01)	0.10	1.00 (1.00–1.01)	0.30	1.01 (1.00–1.01)	0.24
POTS	…	…	…	…	1.00 (1.00–1.00)	0.20
Anticoagulants	…	…	…	…	0.58 (0.37–0.92)	0.02
Arrhythmia						
WA	(ref.)	…	(ref.)	…	(ref.)	…
AF	2.09 (1.51–2.90)	<0.0001	2.16 (1.52–3.08)	<0.0001	2.16 (1.50–3.11)	<0.0001
VT	3.00 (1.55–5.79)	0.001	3.33 (1.72–6.48)	<0.0001	3.18 (1.62–6.24)	0.001
AFL	0.90 (0.22–3.68)	0.88	1.16 (0.28–4.77)	0.84	1.22 (0.30–5.06)	0.78
SVT†	N/A	…	N/A	…	N/A	…
Region						
Northeast	(ref.)	…	(ref.)	…	(ref.)	…
Midwest	0.79 (0.52–1.19)	0.27	0.97 (0.61–1.52)	0.88	0.95 (0.60–1.50)	0.82
South	1.27 (0.89–1.80)	0.19	1.30 (0.90–1.88)	0.16	1.27 (0.88–1.84)	0.20
West	1.14 (0.76–1.71)	0.53	1.14 (0.75–1.75)	0.54	1.11 (0.73–1.71)	0.63
Hospital size						
Small	(ref.)	…	(ref.)	…	(ref.)	…
Medium	0.92 (0.58–1.45)	0.71	0.99 (0.60–1.62)	0.96	0.97 (0.59–1.60)	0.91
Large	0.92 (0.62–1.38)	0.69	1.01 (0.65–1.56)	0.98	1.01 (0.65–1.57)	0.98
Race or ethnicity						
White	…	…	(ref.)	…	(ref.)	…
Black	…	…	1.27 (0.85–1.88)	0.24	1.13 (0.75–1.70)	0.56
Hispanic	…	…	1.28 (0.76–2.14)	0.35	1.28 (0.76–2.15)	0.36
Other*	…	…	1.47 (0.81–2.69)	0.21	1.47 (0.80–2.70)	0.21
Health insurance						
Medicare/Medicaid	…	…	(ref.)	…	(ref.)	…
Private	…	…	0.73 (0.54–0.99)	0.04	0.78 (0.58–1.06)	0.12
Others	…	…	0.86 (0.53–1.38)	0.52	0.91 (0.56–1.47)	0.70
Comorbidities						
CHF	…	…	…	…	2.00 (1.32–3.03)	0.001
CPD	…	…	…	…	0.73 (0.49–1.09)	0.13
Diabetes	…	…	…	…	0.51 (0.26–0.99)	0.048
Hypertension	…	…	…	…	0.71 (0.52–0.98)	0.03
Liver diseases	…	…	…	…	2.08 (0.98–4.39)	0.056
Obesity	…	…	…	…	1.50 (0.83–2.72)	0.18
Renal failure	…	…	…	…	2.52 (1.63–3.89)	<0.0001
Mitral valve prolapse	…	…	…	…	0.56 (0.32–0.97)	0.04

Model 1: Sex, age, type of arrhythmia, hospital region, and hospital size; Model 2: Model 1+types of race or ethnicity and health insurance; Model 3: Model 2+postural orthostatic tachycardia syndrome, anticoagulants, and existence of comorbidities. AF indicates atrial fibrillation; AFL, atrial flutter; CHF, chronic heart diseases; CPD, chronic pulmonary diseases; OR, odds ratio; POTS, postural orthostatic tachycardia syndrome; ref., reference group for Beta-standardization test; SVT, supraventricular tachycardia; VT, ventricular tachycardia; and WA, without any type of arrhythmia.

*Other refers to Asian, American Indian/Alaska native, Native Hawaiian/Other Pacific Islander.

†Since there were no recorded deaths for patients with MFS with SVT, we are unable to calculate the odds ratio and 95% CI for in-hospital death of these patients.

leading cause of early mortality in these patients.[6,12–17] Surgical repair remains the mainstay treatment to reduce morbidity and mortality although the use of medication such as angiotensin II receptor blockers, and beta blockers as well as implantable devices as preventative methods are still considered.[11–14,17] There are many complications that may occur perioperatively, one of them being arrhythmias [Table S6 and S7].

As compared with our data, Hiratzka et al[14] and the 2014 ESC Guidelines[12,13] reported that complications

from open surgical approaches can cause ventricular arrhythmias (1%–5%) and VT and VF are common complications after composite valve graft insertion (19%–21% risk). They also found that VT and VF can be potentiated by undiagnosed myocardial infarction and inadequate myocardial protection during surgery (from "coronary button" reattachment problems, which are usually apparent during operation or shortly thereafter). They noted that severe hypothermia (during descending aortic open surgical and endovascular repair surgeries) can potentiate arrhythmias, particularly AF and VF.

Lastly, 4.9% of adult patients with MFS had POTS and of these 95.1% did not have any history of arrhythmia. The LOS of these patients differed by 1–3 days at most (from the upper limit of those WA). POTS has been associated with conditions causing peripheral autonomic denervation and connective tissue disorders (Joint hypermobility syndrome, Ehlers-Danlos syndrome), chronic fatigue syndrome, autoimmune disorders, and deconditioning. It usually affects young female patients and symptoms vary from mild to severely incapacitating disease.[18–26] However, the association with MFS and POTS is to the best of our knowledge unreported. Orthostatic hypotension is well recognized and postulated to be attributable to tall asthenic posture, low muscle mass, and autonomic dysregulation.[27] In a study conducted by Peters et al,[28] about 70.7% of patients with MFS reported a sensation of dizziness which may be attributable to low blood pressure secondary to dysautonomia, poor venous return to the heart, deconditioning, and/or cardiac abnormalities (ie, aortopathy, heart failure). The authors did not report POTS and thus our study findings that 4.9% of MFS have POTS is novel and warrants further investigation. Figure 6 groups the frequency of arrhythmia, LOC, adjusted HAC, and in-hospital deaths into a summarized illustration.

Strengths and Limitations

There are several strengths to our study including a large sample size for a rare disease, with reliable "real world" data reflective of national private, not-for-profit, and academic practices, which enhance generalizability. This is also the first study to report impact of arrhythmia on outcomes in MFS and the first reporting an association with POTS. To echo our previous thoughts and discussions, the main limitation is that detailed individual patient information such as laboratory, echocardiographic and wide genome data were not obtainable via the NIS database. This makes it difficult to ascertain whether the results obtained were true to 12 079 unique patients, which is a well-recognized limitation of the NIS. There may have been several overlaps in terms of readmissions, multiple comorbidities, and multiple reasons for admission. It is also difficult to ascertain whether some if not all these patients had multiple arrhythmias during a single or multiple admission, or whether they had surgery in their previous admission. Also, it is important to note that the primary (reason) diagnosis for these patients with MFS is the initial differential diagnosis submitted to the NIS database. These initial diagnoses may have evolved

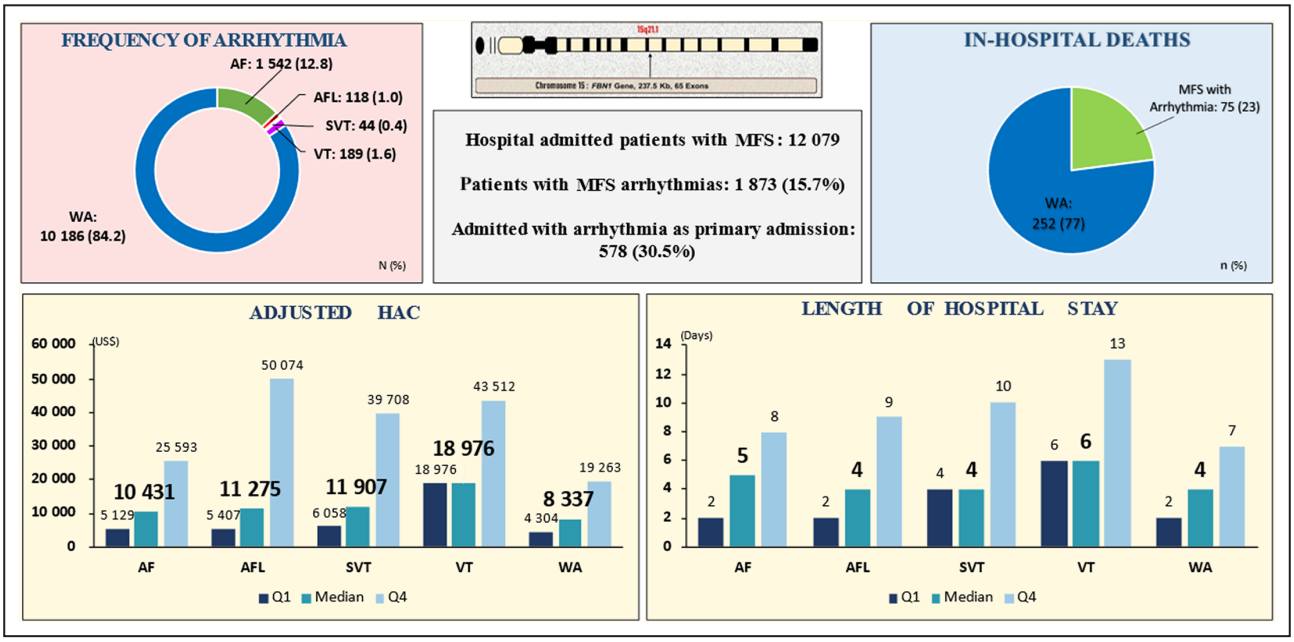

Figure 6. Frequency, LOS, HAC, and outcomes of arrhythmias in patients with MFS from 2005 to 2014, in the United States.
AF indicates atrial fibrillation; AFL, atrial flutter; HAC, health care–associated cost; LOS, length of hospital stay; and MFS, Marfan syndrome; SVT, supraventricular tachycardia; VT, ventricular tachycardia; and WA, without any type of arrhythmia.

throughout the patient stay and may entirely be different to the actual (final) diagnosis. Not forgetting that there is the possibility of misdiagnosis and underdiagnosis of conditions (including arrhythmia and POTS) at different levels of care.

To date, there are not many large register data relating MFS to arrhythmia, therefore it is difficult to ascertain whether there are any obvious trends to the disease. Also, because of limitations surrounding the practice of coding, we were not able to genuinely appreciate whether the different subtypes of arrythmias (paroxysmal, persistent, permanent AF) were primary or whether they developed post-surgery in these patients. With large data sets, it is also difficult to ascertain whether the arrythmias evolved from paroxysmal to persistent during the study period. There is also the possibility of misdiagnoses or findings not documented during these admissions which can affect data entry. Also, the median (IQR) number of patients with MFS per (admitted into) hospital was 2 (1–3) patients. This is because of the large number of hospitals included in the database (as compared with the fewer number of patients with MFS). Another limitation is that we were unable to show actual values for in-hospital mortality for patients with MFS with POTS because of personal protection data issues, while the differences in the rate of in-hospital mortality between patients with MFS with and without POTS were not observable.

The management (or lack of) and complications of these arrhythmias would have contributed to the LOS and HAC; however, the exact details of this could not be ascertained via the NIS database. The risk of these limitations is further amplified by the long duration undertaken in this study (2005 to 2014; 10 years).

CONCLUSIONS

The burden of inpatient arrhythmia, especially VT, in MFS is high and is associated with increased mortality and HAC compared with patients with MFS WA, and the general non-MFS population. Although the prevalence of arrhythmia in the MFS community is lower than that of aortic diseases, it is still a major complication that can shorten the lifespan of these patients, increase LOC and HAC if not recognized and managed early. Screening patients with MFS for arrhythmias in the outpatient setting may be a cost-effective method to prevent unnecessary complications and hospitalization that is associated with arrhythmias in this population, given the advent of end-user ECG and activity monitors. The association between arrhythmias, POTS, and connective tissue disorders are not clearly understood at present, but with time and technological advancements, we may be able to understand the pathophysiology and connection of these diseases to better guide management of these patients.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Tables S1–S14
Figures S1–S3
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