

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; 12079 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, \$18975.8; 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

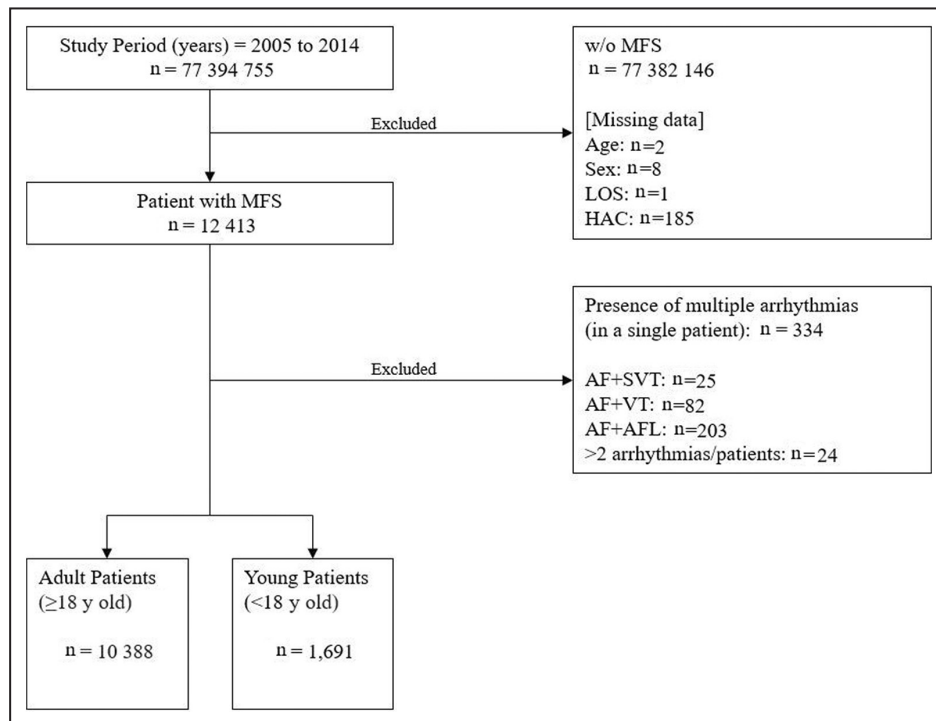


Figure 1. Patient flowchart.

AF indicates atrial fibrillation; AFL, atrial flutter; HAC, health care–associated cost; LOS, length of hospital stay; MFS, Marfan syndrome; 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	<i>P</i> 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 arrhythmias 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 arrhythmias 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; $P=0.0001$)

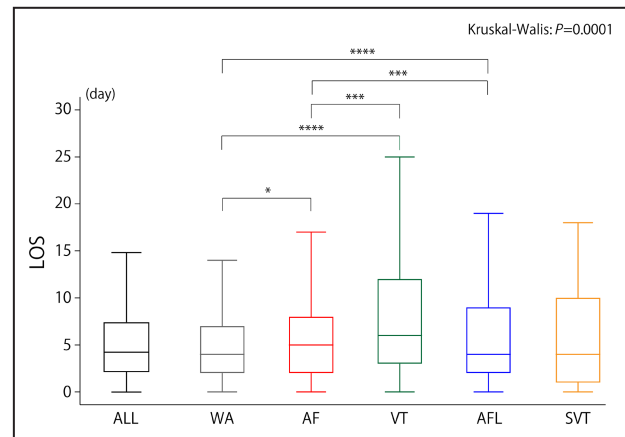


Figure 2. Length of hospital stay.

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. * $P<0.05$, *** $P<0.001$, **** $P<0.0001$.

(Figure 2). After the adjustments for potential confounders, the presence of AF, VT, and AFL were significant factors for prolonged LOS (AF: $\beta=0.05$, $P<0.0001$; VT: $\beta=0.04$, $P<0.0001$; AFL: $\beta=0.05$, $P<0.0001$) (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).

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: $\beta=0.03$, $P<0.0001$; VT: $\beta=0.05$, $P<0.0001$; AFL: $\beta=0.03$, $P<0.0001$) (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

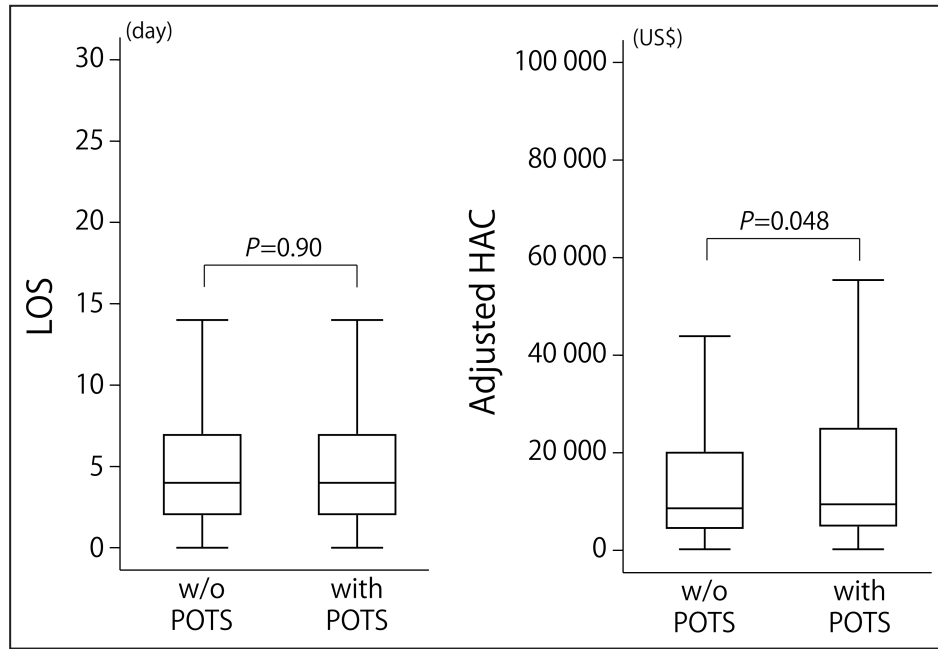


Figure 3. LOS and HAC for patients with POTS. HAC indicates health care–associated cost; LOS, length of hospital stay; and POTS, postural orthostatic tachycardia syndrome.

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.

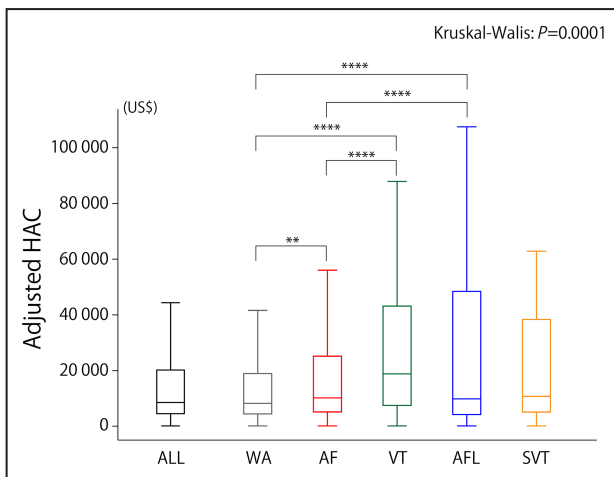


Figure 4. Adjusted HACs. We compared the differences among the arrhythmia groups (ie, without any type of arrhythmia, atrial fibrillation, ventricular tachycardia, atrial flutter, and supraventricular tachycardia). AF indicates atrial fibrillation; AFL, atrial flutter; ALL, total number of Marfan Syndrome 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-hospital 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	<i>P</i> value	β	<i>P</i> value	β	<i>P</i> 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

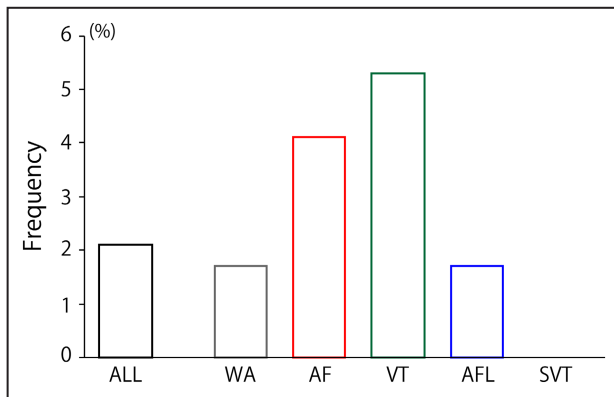


Figure 5. Frequency of in-hospital mortality.

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 al¹⁴ 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

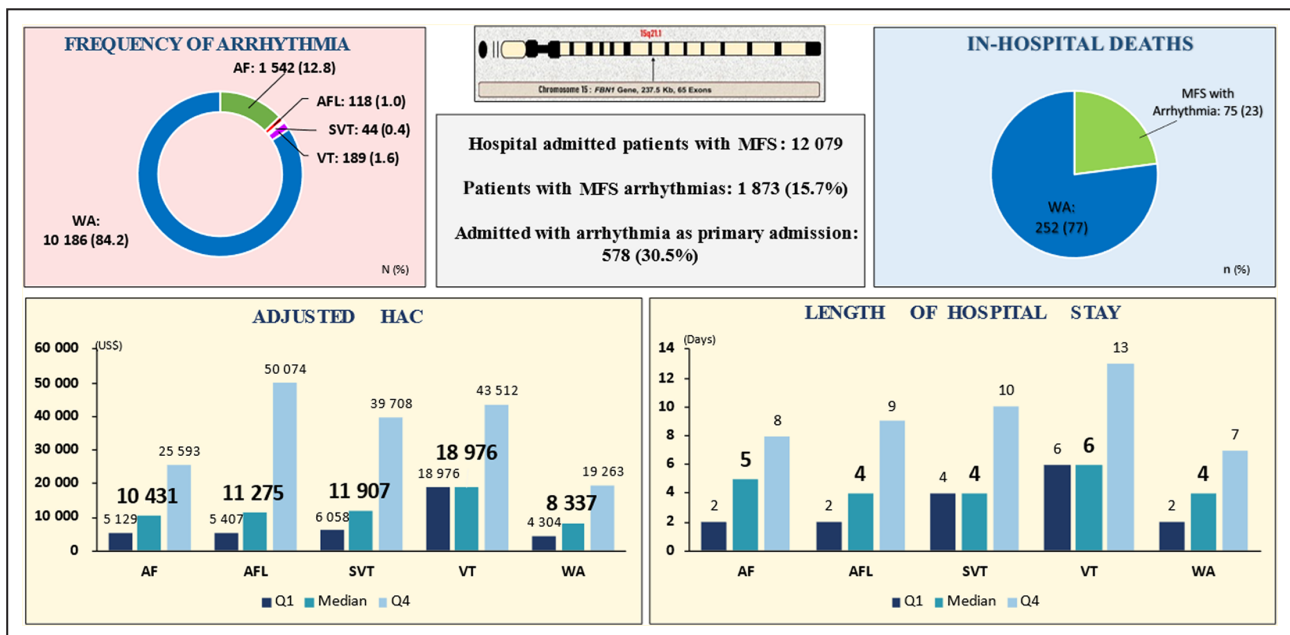


Figure 6. Frequency, LOS, HAC, and outcomes of arrhythmias in patients with MFS from 2005 to 2014, in the United States. AF indicates atrial fibrillation; AFL, atrial flutter; HAC, health care–associated cost; LOS, length of hospital stay; and MFS, Marfan syndrome; SVT, supraventricular tachycardia; 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 arrhythmias (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 arrhythmias 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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Supplemental Material

Tables S1–S14
 Figures S1–S3
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SUPPLEMENTAL MATERIAL

Table S1: ICD-9 Codes for Identification of Any Comorbidities and Therapies

ICD-9-CM- CODES OF MARFAN SYNDROME	
759.82	Marfan syndrome
ICD-9-CM- CODES OF ARRHYTHMIAS	
427.31	Atrial fibrillation
427.1	Paroxysmal ventricular tachycardia
427.32	Atrial flutter
427.0	Paroxysmal supraventricular tachycardia
ICD-9-CM- CODES OF DEVICES	
37.70	Initial insertion of lead [electrode], not otherwise specified (PM)
37.71	Initial insertion of transvenous lead [electrode] into ventricle (PM)
37.72	Initial insertion of transvenous leads [electrodes] into atrium and ventricle (PM)
37.73	Initial insertion of transvenous lead [electrode] into atrium (PM)
37.74	Insertion or replacement of epicardial lead [electrode] into epicardium (PM)
37.75	Revision of lead [electrode] (PM)
37.76	Replacement of transvenous atrial and/or ventricular lead(s) [electrode] (PM)
37.80	Insertion of permanent pacemaker, initial or replacement, type of device not specified (PM)
37.81	Initial insertion of single-chamber device, not specified as rate responsive (PM)
37.82	Initial insertion of single-chamber device, rate responsive (PM)
37.83	Initial insertion of dual-chamber device (PM)
37.85	Replacement of any type pacemaker device with single-chamber device, not specified as rate responsive (PM)
37.86	Replacement of any type of pacemaker device with single-chamber device, rate responsive (PM)
37.87	Replacement of any type pacemaker device with dual-chamber device (PM)
37.89	Revision or removal of pacemaker device (PM)
37.94	Implantation or replacement of automatic cardioverter/ defibrillator, total system (ICD)
37.95	Implantation of automatic cardioverter/defibrillator lead(s) only (ICD)
37.96	Implantation of automatic cardioverter/defibrillator pulse generator only (ICD)
37.97	Replacement of automatic cardioverter/defibrillator lead(s) only (ICD)
37.98	Replacement of automatic cardioverter/defibrillator pulse generator only (ICD)
00.50	Implantation of cardiac resynchronization pacemaker without mention of defibrillation, total system (CRT-P)
00.53	Implantation or replacement of cardiac resynchronization pacemaker pulse generator only (CRT-P)
00.51	Implantation of cardiac resynchronization defibrillator, total system (CRT-D)
00.54	Implantation or replacement of cardiac resynchronization defibrillator pulse generator device only (CRT-D)
ICD-9-CM- CODES OF POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME	
427.89	Other specified cardiac dysrhythmias
ICD-9-CM- CODES OF MITRAL VALVE PROLAPSE	

424.0	Mitral valve disorders
746.6	Congenital mitral insufficiency
ICD-9-CM- CODES OF USE OF ANTICOAGULANTS	
V58.61	Long-term (current) use of anticoagulants
ICD-9 CODES FOR IDENTIFICATION OF ANY COMORBIDITIES	
CHF	398.91, 428.0-428.9
CPD	490-492.8, 493.00-493.92, 494-494.1, 495.0-505, 506.4
Diabetes Mellitus	250.00-250.33, 648.00-648.04, 249.00-249.31
Hypertension	401.1, 401.9, 642.00-642.04, 401.0, 437.2, 642.20-642.24, 402.00, 402.10, 402.90, 405.09, 405.19, 405.99, 402.01, 402.11, 402.91, 403.00, 403.10, 403.90, 405.01, 405.11, 405.91, 642.10-642.14, 403.11, 403.91, 404.00, 404.10, 404.90, 404.01, 404.11, 404.91, 404.02, 404.12, 404.92, 404.03, 404.13, 404.93, 642.70-642.74, 642.90-642.94
Liver Diseases	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.40-571.49, 571.5, 571.6, 571.8, 571.9, 572.3, 572.8, V427
Obesity	278.0, 278.00, 278.01, 278.03, 649.10-649.14, V853.0-V853.9, V854.1-V854.5, V855.4, 793.91
Renal Failure	585.3, 585.4, 585.5, 585.6, 585.9, 586, V420, V451, V560-V563.2, V568, V451.1-V451.2
Mitral Valve Prolapse	424.0, 746.6

ICD-9-CM = International classification of diseases, ninth edition, clinical modification, PM = Pacemaker, ICD = Implantable cardioverter defibrillator, CRT-P = Cardiac resynchronization therapy with pacemaker, CRT-D = Cardiac resynchronization therapy with defibrillator, CHF = Congestive heart failure, CPD = Chronic pulmonary diseases

Table S2: Baseline Characteristics of MFS Patients with POTS

	w/o POTS	with POTS	P-value
Number (%)	11,482 (95.1)	597 (4.9)	-
Age, years	39.0 (25.0-53.0)	41.0 (27.0-54.0)	0.008
Male, N (%)	6,461 (56.3)	338 (56.6)	0.90
Anticoagulants, N (%)	1,614 (14.1)	79 (4.7)	0.63
In-hospital death, N (%)	245 (2.1)	≤10 (N/A)	0.14
Length of stay, day	4.0 (2.0-7.0)	4.0 (2.0-7.0)	0.90
Medical costs, \$US			
Net value	25,373.5 (12,331.0-60,901.0)	29,203.0 (13,134.0-70,139.0)	0.053
Adjusted value	8,617.4 (4,422.9- 20,220.4)	9,425.0 (4,881.1-25,144.3)	0.048
@ Ethnicity, N (%)			
White	7,239 (75.1)	373 (76.9)	
Black	1,226 (12.7)	54 (11.1)	
Hispanic	763 (7.9)	28 (3.5)	
Other	418 (4.3)	30 (6.7)	0.06
Co-Morbidities, N (%)			
CHF	700 (6.1)	17 (2.4)	<0.0001
CPD	507 (5.0)	90 (4.7)	0.69
Diabetes mellitus	570 (5.0)	27 (3.8)	0.18
Hypertension	382 (4.8)	215 (5.2)	0.31
Liver diseases	591 (5.0)	≤10 (N/A)	0.48
Obesity	581 (5.0)	16 (3.6)	0.18
Renal failure	578 (5.0)	19 (3.5)	0.12
Mitral valve prolapse	489 (4.6)	108 (8.0)	<0.0001
Arrhythmias, N (%)			
AF	1,444 (12.6)	465 (4.6)	
VT	172 (1.5)	98 (6.4)	
AFL	108 (0.9)	≤10 (N/A)	
SVT	37 (0.3)	≤10 (N/A)	<0.0001
Devices, N (%)			
PM	71 (0.6)	18 (3.0)	<0.0001
ICD	592 (4.9)	≤10 (N/A)	0.11
CRT-D	596 (4.9)	≤10 (N/A)	0.60
CRT-P	596 (4.9)	≤10 (N/A)	0.60
@Health insurance, N (%)			
Medicare/Medicaid	5,673 (49.5)	255 (42.7)	
Private	4,674 (40.8)	269 (45.1)	
Others	1,114 (9.7)	73 (6.2)	0.003
Region, N (%)			
Northeast	2,169 (18.9)	115 (19.3)	
Midwest	2,891 (25.2)	165 (27.6)	
South	4,173 (36.3)	216 (36.2)	
West	2,249 (19.6)	101 (16.9)	0.32
Hospital size, N (%)			
Small	1,272 (11.1)	63 (4.7)	
Medium	2,445 (21.4)	123 (4.8)	
Large	7,717 (67.5)	409 (5.0)	0.81

@ = The variable has missing data

POTS = Postural orthostatic tachycardia syndrome, N = Number, CHF = Chronic heart diseases, CPD = Chronic pulmonary diseases, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia, PM = Pacemaker, ICD = Implantable cardioverter defibrillator, CRT-D = Cardiac resynchronization therapy with defibrillator, CRT-P = Cardiac resynchronization therapy with pacemaker

Table S3: Baseline Characteristics for Adult MFS Patients

	All Adults	WA	AF	VT	AFL	SVT	P-value
Number (%)	10,388 (100.0)	8,527 (82.1)	1,536 (14.8)	179 (1.7)	110 (1.1)	36 (0.4)	-
Age, years	43.0 (31.0-55.0)	40.0 (29.0-52.0) *†	57.0 (47.0-66.0) § ‡	45.0 (35.0-54.0)	51.0 (39.0-62.0) †	39.5 (29.5-52.0)	0.001
Male, N (%)	5,891 (56.7)	4,737 (55.6)	953 (62.0)	110 (61.5)	71 (64.6)	20 (55.6)	<0.0001
POTS, N (%)	543 (5.2)	414 (4.9)	97 (6.3)	16 (8.9)	≤10 (N/A)	≤10 (N/A)	<0.0001
Anticoagulants, N (%)	1,660 (16.0)	1,205 (14.1)	401 (26.1)	24 (13.4)	≤30 (N/A)	≤10 (N/A)	<0.0001
@Ethnicity, N (%)							
White	6,756 (77.3)	5,425 (75.6)	1,120 (86.6)	117 (75.0)	70 (82.4)	24 (80.0)	
Black	1,107 (12.7)	971 (13.5)	98 (7.6)	26 (16.7)	≤10 (N/A)	≤10 (N/A)	
Hispanic	521 (6.0)	470 (6.6)	39 (3.0)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	
Other	354 (4.1)	307 (4.3)	37 (2.9)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	<0.0001
Comorbidities, N (%)							
CHF	699 (6.7)	437 (5.1)	242 (15.8)	11 (6.2)	≤10 (N/A)	≤10 (N/A)	<0.0001
CPD	1,715 (16.5)	1,369 (16.1)	292 (19.0)	27 (15.1)	≤20 (N/A)	≤10 (N/A)	0.06
Diabetes Mellitus	697 (6.7)	527 (6.2)	155 (10.1)	11 (6.2)	≤10 (N/A)	≤10 (N/A)	<0.0001
Hypertension	4,042 (38.9)	3,172 (37.2)	745 (48.5)	62 (34.6)	48 (43.6)	15 (41.7)	<0.0001
Liver diseases	170 (1.6)	143 (1.7)	23 (1.5)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	0.87
Obesity	440 (4.2)	347 (4.1)	68 (4.4)	16 (8.9)	≤10 (N/A)	≤10 (N/A)	0.01
Renal failure	542 (5.2)	400 (4.7)	125 (8.1)	12 (6.7)	≤10 (N/A)	≤10 (N/A)	<0.0001
Mitral valve prolapse	1,119 (10.8)	860 (10.1)	218 (14.2)	20 (11.2)	≤20 (N/A)	≤10 (N/A)	<0.0001
Devices, N (%)							
PM	85 (0.8)	39 (0.5)	36 (2.3)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	<0.0001
ICD	47 (0.5)	22 (0.3)	≤10 (N/A)	15 (8.4)	≤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)	0.006
@Health insurance, N (%)							
Medicare/Medicaid	5,185 (50.0)	4,197 (49.3)	836 (54.5)	88 (49.2)	≤50 (N/A)	≤20 (N/A)	
Private	4,125 (39.8)	3,356 (39.4)	626 (40.8)	70 (39.1)	57 (51.8)	16 (44.4)	

Others	1,057 (10.2)	956 (11.2)	71 (4.6)	21 (11.7)	≤10 (N/A)	≤10 (N/A)	<0.0001
Region, N (%)							
Northeast	1,957 (18.8)	1,612 (18.9)	292 (19.0)	32 (17.9)	≤20 (N/A)	≤10 (N/A)	
Midwest	2,696 (26.0)	2,194 (25.7)	416 (27.1)	46 (25.7)	≤30 (N/A)	≤10 (N/A)	
South	3,741 (36.0)	3,079 (36.1)	544 (35.4)	73 (40.8)	≤40 (N/A)	≤10 (N/A)	
West	1,994 (19.2)	1,642 (19.3)	284 (18.5)	28 (15.6)	≤30 (N/A)	≤10 (N/A)	0.44
Hospital size, N (%)							
Small	1,108 (10.7)	924 (10.9)	163 (10.7)	≤10 (N/A)	≤10 (N/A)	≤10 (N/A)	
Medium	2,178 (21.1)	1,769 (20.8)	349 (22.8)	≤40 (N/A)	≤20 (N/A)	≤10 (N/A)	
Large	7,055 (68.2)	5,796 (68.3)	1,017 (66.5)	128 (71.9)	84 (77.1)	30 (83.3)	0.04

@ = The variable has missing data

vs. AF: * P<0.0001; vs. VT: ¶ P<0.05, § P<0.0001; vs. AFL: || P<0.0001; vs. SVT: † P<0.05, ‡ P<0.0001

MFS = Marfan syndrome, WA = without any type of arrhythmia, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia, N = Number, POTS = Postural orthostatic tachycardia syndrome, CHF = Chronic heart diseases, CPD = Chronic pulmonary diseases, PM = Pacemaker, ICD = Implantable cardioverter defibrillator, CRT-D = Cardiac resynchronization therapy with defibrillator, CRT-P = Cardiac resynchronization therapy with pacemaker

Table S4: Comparison between Young and Adult Patients

	<18 years	≥18 years	P-value
Number (%)	1,691	10,388	-
Age, years	11.0 (0.0-15.0)	43.0 (31.0-55.0)	<0.0001
Male, N (%)	908 (53.7)	5,891 (56.7)	0.02
POTS, N (%)	56 (3.3)	543 (5.2)	0.001
Anticoagulants, N (%)	33 (2.0)	1,660 (16.0)	<0.0001
In-hospital death, N (%)	34 (2.0)	218 (2.1)	0.93
Length of stay, day	4.0 (2.0-8.0)	4.0 (2.0-7.0)	0.09
Medical costs, \$US			
Net value	28,050.0 (10,507.0-82,493.0)	25,323.5 (12,580.0-58,303.0)	0.10
Adjusted value	9,911.2 (3,781.5-30,713.0)	8,548.0 (4,533.5-19,225.3)	0.02
® Ethnicity, N (%)			
White	856 (61.5)	6,756 (77.3)	
Black	173 (12.4)	1,107 (12.7)	
Hispanic	270 (19.4)	521 (6.0)	
Other	94 (6.8)	354 (4.1)	<0.0001
Co-Morbidities, N (%)			
CHF	18 (2.5)	699 (6.8)	<0.0001
CPD	192 (11.4)	1,715 (16.5)	<0.0001
Diabetes mellitus	≤10 (N/A)	≤700 (N/A)	<0.0001
Hypertension	70 (4.1)	4,042 (38.9)	<0.0001
Liver diseases	≤10 (N/A)	≤170 (N/A)	<0.0001
Obesity	≤10 (N/A)	≤440 (N/A)	<0.0001
Renal failure	≤10 (N/A)	≤550 (N/A)	<0.0001
Mitral valve prolapse	232 (13.7)	1,119 (10.8)	<0.0001
Arrhythmias, N (%)			
AF	≤10 (N/A)	1,536 (14.8)	
VT	≤10 (N/A)	179 (1.7)	
AFL	≤10 (N/A)	110 (1.1)	
SVT	≤10 (N/A)	36 (0.4)	<0.0001
Devices, N (%)			
PM	≤10 (N/A)	85 (0.8)	0.009
ICD	≤10 (N/A)	47 (0.5)	0.36
CRT-D	≤10 (N/A)	18 (0.2)	0.09
CRT-P	≤10 (N/A)	≤10 (N/A)	0.32
® Health insurance, N (%)			
Medicare/Medicaid	743 (43.9)	5,185 (50.0)	
Private	818 (48.4)	4,125 (39.8)	
Others	130 (11.0)	1,057 (10.2)	<0.0001
Region, N (%)			
Northeast	327 (19.3)	1,957 (18.8)	
Midwest	360 (21.3)	2,696 (26.0)	
South	648 (38.2)	3,741 (36.0)	
West	356 (21.1)	1,994 (19.2)	0.001
Hospital size, N (%)			
Small	227 (13.5)	1,108 (10.7)	
Medium	390 (23.1)	2,178 (21.1)	
Large	1,071 (63.5)	7,055 (68.2)	<0.0001

@ = The variable has missing data

N = Number, POTS = Postural orthostatic tachycardia syndrome, CHF = Chronic heart diseases, CPD = Chronic pulmonary diseases, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia, PM = Pacemaker, ICD = Implantable cardioverter defibrillator, CRT-D = Cardiac resynchronization therapy with defibrillator, CRT-P = Cardiac resynchronization therapy with pacemaker

Table S5: Estimations of Patients with Marfan Syndrome who were Admitted

(A) All MFS Patients

All Patients with MFS					All Patients with MFS and Arrhythmia				
Year	N of MFS Admissions	Total Hospital Admissions	% of MSF Admissions	Estimated Hospital Prevalence	Year	N of MFS Admissions	Total Hospital Admissions	% of MSF Admissions	Estimated Hospital Prevalence
2005	1,095	7,995,048	0.01	1 in 7,301	2005	1,095	7,995,048	0.002	1 in 63,960
2006	1,063	8,074,825	0.01	1 in 7,596	2006	1,063	8,074,825	0.002	1 in 57,268
2007	1,028	8,043,415	0.01	1 in 7,824	2007	1,028	8,043,415	0.002	1 in 52,571
2008	1,271	8,158,381	0.02	1 in 6,419	2008	1,271	8,158,381	0.002	1 in 40,997
2009	1,284	7,810,762	0.02	1 in 6,083	2009	1,284	7,810,762	0.003	1 in 39,250
2010	1,256	7,800,441	0.02	1 in 6,210	2010	1,256	7,800,441	0.003	1 in 38,616
2011	1,316	8,023,590	0.02	1 in 6,097	2011	1,316	8,023,590	0.003	1 in 34,734
2012	1,265	7,296,968	0.02	1 in 5,768	2012	1,265	7,296,968	0.003	1 in 36,124
2013	1,222	7,119,563	0.02	1 in 5,826	2013	1,222	7,119,563	0.003	1 in 34,394
2014	1,279	7,071,762	0.02	1 in 5,529	2014	1,279	7,071,762	0.003	1 in 30,221
Total	12,079	77,394,755	0.02	1 in 6,407	Total	12,079	77,394,755	0.002	1 in 40,885

(B) Adult MFS Patients only

All Patients with MFS					All Patients with MFS and Arrhythmia				
Year	N of MFS Admissions	Total Hospital Admissions	% of MSF Admissions	Estimated Hospital Prevalence	Year	N of MFS Admissions	Total Hospital Admissions	% of MSF Admissions	Estimated Hospital Prevalence
2005	882	6,550,434	0.01	1 in 7,427	2005	123	6,550,434	0.002	1 in 53,256
2006	903	6,712,893	0.01	1 in 7,434	2006	138	6,712,893	0.002	1 in 48,644
2007	893	6,639,401	0.01	1 in 7,435	2007	149	6,639,401	0.002	1 in 44,560
2008	1,107	6,840,196	0.02	1 in 6,179	2008	196	6,840,196	0.003	1 in 34,899
2009	1,115	6,546,273	0.02	1 in 5,871	2009	199	6,546,273	0.003	1 in 32,896
2010	1,080	6,545,343	0.02	1 in 6,061	2010	194	6,545,343	0.003	1 in 33,739
2011	1,179	6,834,910	0.02	1 in 5,797	2011	227	6,834,910	0.003	1 in 30,110
2012	1,062	6,142,504	0.02	1 in 5,784	2012	199	6,142,504	0.003	1 in 30,867
2013	1,061	5,993,894	0.02	1 in 5,649	2013	205	5,993,894	0.003	1 in 29,239
2014	1,106	5,950,391	0.02	1 in 5,380	2014	231	5,950,391	0.004	1 in 25,759
Total	10,388	64,756,239	0.02	1 in 6,234	Total	1,861	64,756,239	0.003	1 in 34,796

MFS = Marfan Syndrome

Table S6: Primary Reasons for Admission

	ICD-9	N (%)		ICD-9	N (%)
Cardiac		2,625 (47.4)			
<i>Primary Rhythm</i>		578	<i>Aorta</i>		1,007
Paroxysmal Ventricular Tachycardia	427.1	63	Aortic valve	424.1	90
Atrial Fibrillation	427.31	280	Abdominal Aortic dissection	441.02	74
Atrial Flutter	427.32	70	Thoracic Aortic Dissection	441.01 441.03	428
Cardiac Dysrhythmias	427.89	100	Thoracic Aortic Aneurysm	441.2	249
Atrioventricular Nodal Block	426	13	Aortic dissection	441	21
Paroxysmal Atrial Tachycardia	427.1	17	Abdominal Aortic Aneurysm	441.4	71
Ventricular Fibrillation	427.41	13	Thoracoabdominal AA without rupture	441.7	39
Sinoatrial Node dysfunction	427.81	22	Thoracic aortic ectasia	447.71	11
<i>Mitral</i>		127	Congenital aortic abnormality	747.29	24
Mitral valve (unspecified)	424	105	<i>Coronary Artery</i>		127
Mitral regurgitation	396.3	22	Myocardial Infarction	410.X	67
<i>Cardiomyopathy</i>		31	Coronary (native vessel) atherosclerosis	414.01	60
Primary Cardiomyopathy	425.4	16	<i>Heart Failure</i>		305
Atrial septal (secundum) defect	745.5	15	Congestive Heart Failure	428	161
<i>Others</i>		101	Systolic Heart Failure	428.2X	116
Pericardial disease	423.9	21	Vascular		321 (5.8)
Functional disturbances following cardiac surgery	429.4	≤10	Intracerebral Hemorrhage	431	23
Infective Endocarditis	421	33	Subdural Hemorrhage	432.1	38
Malfunction prosthetic heart valve	996.02	≤20	Intracerebral Infarction	435.9	108
Mitral/Aortic Valve insufficiency	396.3	22	Iliac artery aneurysm	442.2	≤15
Pulmonary		618 (11.2)	Lower extremity aneurysm	442.3	≤10
Pneumonia	486	278	Subclavian Aneurysm	442.82	16
Pneumothoraces	512.8	173	Lower limb DVT	453.41	30
Pulmonary embolism	415.9	63	Cerebral Arterial Occlusion (not otherwise specified with infarction)	434.91	83
Acute Respiratory Failure	518.81	61	Syncope and collapse	780.2	103
Acute and chronic Resp. failure	518.84	43	Dizziness and giddiness	780.4	19

Neurological		123 (2.2)	Obstetrics		372 (6.7)
Epilepsy	345.X	66	Single Live born in hospital without mention of cesarean delivery or section	V30.00	132
Convulsions	780.39	57	Single Live born in hospital with cesarean delivery or section	V30.01	144
Musculoskeletal/Connective Tissue Disease		624 (11.3)	Unspecified delivery	678.91	96
Idiopathic Scoliosis	737.3	122	Other/ Unspecified		737 (13.3)
Marfan syndrome	759.82	502	Septicemia	38.9	147
			Rehabilitation	V57.89	153
			Chest pain	786.5X	437

ICD = International Classification of Diseases, N = Number, Resp. = Respiratory, AA = Aortic aneurysm, DVT: Deep vein thrombosis

Table S7: Primary Reasons for Admission for Adult MFS Patients

	ICD-9	N (%)		ICD-9	N (%)
Cardiac		1,981 (49)			
<i>Primary Rhythm</i>		449 (11.1)	<i>Aorta</i>		938(23.1)
Paroxysmal Ventricular Tachycardia	427.1	40	Aortic valve	424.1	84
Atrial Fibrillation	427.31	205	Abdominal Aortic dissection	441.02	72
Atrial Flutter	427.32	36	Thoracic Aortic Dissection	441.01	267
				441.03	150
Cardiac Dysrhythmias	427.89	86	Thoracic Aortic Aneurysm	441.2	223
Atrioventricular Nodal Block	426.0	≤15	Aortic dissection	441.0	21
Paroxysmal Atrial Tachycardia	427.1	40	Abdominal Aortic Aneurysm	441.4	66
Ventricular Fibrillation	427.41	≤10	Thoracoabdominal AA without rupture	441.7	38
Sinoatrial Node dysfunction	427.81	21	Thoracic aortic ectasia	447.71	≤10
<i>Mitral</i>		105 (2.6)	Congenital aortic abnormality	747.29	≤20
Mitral valve (unspecified)	424.0	88	<i>Coronary Artery</i>		125 (3.1)
Mitral regurgitation	396.3	17	Myocardial Infarction	410.X	67
<i>Cardiomyopathy</i>		13 (0.3)	Coronary (native vessel) atherosclerosis	414.01	58
Primary Cardiomyopathy	425.4	13	<i>Heart Failure</i>		271 (6.7)
Atrial septal (secundum) defect	745.5	≤10	Congestive Heart Failure	428.0	139
			Systolic Heart Failure	428.2X	106
<i>Others</i>		80 (2)	Diastolic Heart Failure	428.3X	26
Pericardial disease	423.9	20	Vascular		269 (6.6)
Functional disturbances following cardiac surgery	429.4	≤10	Intracerebral Hemorrhage	431	19
Infective Endocarditis	421.0	30	Subdural Hemorrhage	432.1	38
Malfunction prosthetic heart valve	996.02	≤15	Intracerebral Infarction	434.1	≤10
				435.9	65
Mitral/Aortic Valve insufficiency	396.3	17	Iliac artery aneurysm	442.2	13
Pulmonary		490 (12.1)	Lower extremity aneurysm	442.3	≤10
Pneumonia	486	222	Subclavian Aneurysm	442.82	16
Pneumothoraces	512.8	112	Lower limb DVT	453.41	30
Pulmonary embolism	415.9	61	Cerebral Arterial Occlusion (not otherwise specified with infarction)	434.91	79
Acute Respiratory Failure	518.81	55	Syncope/pre-syncope		105 (2.6)
Acute and chronic Resp. failure	518.84	40	Syncope and collapse	780.2	89
Neurological		96 (2.4)	Dizziness and giddiness	780.4	16
Epilepsy	345.X	50	Other/ Unspecified		700(17.3)
Convulsions	780.39	46	Septicemia	038.9	134
Musculoskeletal/Connective Tissue Disease		411 (10.1)	Rehabilitation	V57.89	148
Idiopathic Scoliosis	737.30	26	Chest pain	786.5X	418
Marfan syndrome	759.82	385			

ICD = International Classification of Diseases, N = Number, Resp. = Respiratory, AA = Aortic aneurysm, DVT: Deep vein thrombosis

Table S8: Primary Reasons for Admission for Young MFS Patients

	ICD-9	N (%)		ICD-9	N (%)
Cardiac		30 (7.7)			
<i>Primary Rhythm</i>		11 (2.8)	<i>Aorta</i>		19 (4.9)
Paroxysmal Ventricular Tachycardia	427.1	≤10	Aortic valve	424.1	≤10
Atrial Fibrillation	427.31	≤10	Abdominal Aortic dissection	441.02	≤10
Atrial Flutter	427.32	≤10	Thoracic Aortic Dissection	441.01	≤10
				441.03	≤10
Cardiac Dysrhythmias	427.89	11	Thoracic Aortic Aneurysm	441.2	19
Atrioventricular Nodal Block	426.0	≤10	Aortic dissection	441.0	≤10
Paroxysmal Atrial Tachycardia	427.1	≤10	Abdominal Aortic Aneurysm	441.4	≤10
Ventricular Fibrillation	427.41	≤10	Thoracoabdominal AA without rupture	441.7	≤10
Sinoatrial Node dysfunction	427.81	≤10	Thoracic aortic ectasia	447.71	≤10
<i>Mitral</i>			Congenital aortic abnormality	747.29	≤10
Mitral valve (unspecified)	424.0	≤10	<i>Coronary Artery</i>		
Mitral regurgitation	396.3	≤10	Myocardial Infarction	410.X	≤10
<i>Cardiomyopathy</i>			Coronary (native vessel) atherosclerosis	414.01	≤10
Primary Cardiomyopathy	425.4	≤10	<i>Heart Failure</i>		
Atrial septal (secundum) defect	745.5	≤10	Congestive Heart Failure	428.0	≤10
<i>Others</i>			<i>Vascular</i>		
Pericardial disease	423.9	≤10	Intracerebral Hemorrhage	431	≤10
Functional disturbances following cardiac surgery	429.4	≤10	Subdural Hemorrhage	432.1	≤10
Infective Endocarditis	421.0	≤10	Intracerebral Infarction	434.1	≤10
				435.9	≤10
Malfunction prosthetic heart valve	996.02	≤10	Iliac artery aneurysm	442.2	≤10
Mitral/Aortic Valve insufficiency	396.3	≤10	Lower extremity aneurysm	442.3	≤10
Pulmonary		114 (29.2)	Subclavian Aneurysm	442.82	≤10
Pneumonia	486	54	Lower limb DVT	453.41	≤10
Pneumothoraces	512.8	60	Cerebral Arterial Occlusion (not otherwise specified with infarction)	434.91	≤10
Pulmonary embolism	415.9	≤10	Syncope/pre-syncopal		12 (3.1)
Acute Respiratory Failure	518.81	≤10	Syncope and collapse	780.2	12
Acute and chronic Resp. failure	518.84	≤10	Dizziness and giddiness	780.4	≤10
Neurological		26 (6.6)	Other/ Unspecified		14 (3.6)
Epilepsy	345.X	15	Septicemia	038.9	≤10
Convulsions	780.39	11	Rehabilitation	V57.89	≤10
Musculoskeletal/Connective Tissue Disease		195 (49.9)	Chest pain	786.5X	14
Idiopathic Scoliosis	737.30	96			
Marfan syndrome	759.82	99			

ICD = International Classification of Diseases, N = Number, Resp. = Respiratory, AA = Aortic aneurysm, DVT: Deep vein thrombosis

Table S9: Predictors for Length of Hospital Stay for Adult MFS Patients

	Model 1		Model 2		Model 3	
	β	P-value	β	P-value	β	P-value
Female	-0.04	<0.0001	-0.05	<0.0001	-0.05	<0.0001
Age	0.02	0.03	0.02	0.04	0.007	0.58
POTS	-	-	-	-	-0.01	0.31
Anticoagulants	-	-	-	-	-0.05	<0.0001
Arrhythmia						
WA	(ref.)	-	(ref.)	-	(ref.)	-
AF	0.05	<0.0001	0.05	<0.0001	0.05	<0.0001
VT	0.06	<0.0001	0.05	<0.0001	0.05	<0.0001
AFL	0.03	<0.0001	0.04	0.001	0.04	<0.0001
SVT	0.009	0.38	0.007	0.52	0.009	0.41
Region						
Northeast	(ref.)	-	(ref.)	-	(ref.)	-
Midwest	-0.08	<0.0001	-0.06	<0.0001	-0.07	<0.0001
South	-0.02	0.07	-0.01	0.31	-0.02	0.13
West	-0.04	0.004	-0.03	0.02	-0.03	0.01
Hospital size						
Small	(ref.)	-	(ref.)	-	(ref.)	-
Medium	0.005	0.72	0.007	0.66	0.008	0.61
Large	0.07	<0.0001	0.06	<0.0001	0.06	<0.0001
Ethnicity						
White	-	-	(ref.)	-	(ref.)	-
Black	-	-	0.02	0.053	0.01	0.37
Hispanic	-	-	0.01	0.20	0.01	0.29
Other	-	-	0.01	0.20	0.01	0.22
Health insurance						
Medicare/Medicaid	-	-	(ref.)	-	(ref.)	-
Private	-	-	-0.01	0.19	-0.004	0.71
Others	-	-	-0.03	0.006	-0.03	0.02
Co-Morbidities						
CHF	-	-	-	-	0.06	<0.0001
CPD	-	-	-	-	0.02	0.08
Diabetes mellitus	-	-	-	-	-0.01	0.37
Hypertension	-	-	-	-	0.02	0.11
Liver diseases	-	-	-	-	0.0007	0.95
Obesity	-	-	-	-	0.03	0.002
Renal failure	-	-	-	-	0.05	<0.0001
Mitral valve prolapse	-	-	-	-	-0.03	0.001

Model 1: sex, age, type of arrhythmia, hospital region, and hospital size; Model 2: Model 1 + types of ethnicity and health insurance; Model 3: Model 2+ POTS, anticoagulants, and existence of co-morbidities

The β is standardized beta.

MFS = Marfan Syndrome, POTS = Postural orthostatic tachycardia syndrome, WA = without any type of arrhythmia, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia, CHF = Chronic heart diseases, CPD = Chronic pulmonary diseases

Table S10: Associations between Arrhythmias and LOS, HAC and Outcomes Estimated by Treatment-effect with Inverse-probability-weighted regression Adjustment

	Length of stay		Adjusted HAC		In-hospital death	
	Coef, (95%CI)	P-value	Coef, (95%CI)	P-value	Coef, (95%CI)	P-value
WA	(ref.)	-	(ref.)	-	(ref.)	-
AF	0.51 (-0.07 to 1.08)	0.08	5,927.9 (2,922.8 to 8,932.4)	<0.0001	0.006 (-0.003 to 0.015)	0.17
VT	2.87 (1.31 to 4.44)	<0.0001	24,400.7 (13,210.2 to 35,591.2)	<0.0001	0.075 (0.022 to 0.128)	0.006
AFL	11.04 (2.42 to 49.66)	0.01	42,336.4 (15,769.1 to 68,903.8)	0.002	-0.006 (-0.024 to 0.012)	0.50
SVT	0.32 (-4.03 to 4.68)	0.89	8,150.7 (-19,275.6 to 35,577.1)	0.56	-	-

Adjusted variables were sex, age, hospital region, hospital size, type of ethnicity and existence of co-morbidities.

*Since there were no SVT patients with hospital death, the risk for in-hospital death was not calculated.

HAC = Health-associated cost, Coef. = Coefficient, CI = Confidence interval, WA = without any type of arrhythmia, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia

Table S11: Predictors for Length of Hospital Stay, HAC and Outcomes for Young MFS Patients

	Length of stay		Adjusted HAC		In-hospital death	
	β	P-value	β	P-value	OR (95%CI)	P-value
Female	-0.009	0.74	0.01	0.61	0.86 (0.38-1.92)	0.71
Age	-0.21	<0.0001	0.07	0.001	0.80 (0.72-0.90)	0.81
Length of stay	-	-	0.71	<0.0001	-	-
POTS	0.03	0.24	0.006	0.78	1.00 (1.00-1.00)	0.81
Anticoagulants	-0.02	0.52	-0.009	0.64	N/A	N/A
Arrhythmia						
WA	(ref.)	-	(ref.)	-	(ref.)	-
AF	-0.005	0.84	0.006	0.74	N/A	N/A
VT	0.01	0.61	-0.004	0.85	17.8 (1.38-231.30)	0.03
AFL	0.09	0.001	0.07	<0.0001	N/A	N/A
SVT	-0.01	0.69	0.05	0.008	N/A	N/A
Region						
Northeast	(ref.)	-	(ref.)	-	(ref.)	-
Midwest	0.02	0.46	0.03	0.27	0.35 (0.05-2.25)	0.27
South	0.01	0.69	-0.02	0.55	0.90 (0.31-2.64)	0.85
West	-0.02	0.60	0.08	0.002	1.39 (0.42-4.54)	0.59
Hospital size						
Small	(ref.)	-	(ref.)	-	(ref.)	-
Medium	0.04	0.26	-0.07	0.01	0.60 (0.13-2.69)	0.50
Large	0.05	0.20	-0.09	0.002	0.80 (0.22-2.92)	0.73
Ethnicity						
White	(ref.)	-	(ref.)	-	(ref.)	-
Black	0.02	0.41	-0.005	0.81	1.11 (0.31-3.98)	0.88
Hispanic	0.03	0.34	-0.007	0.76	1.98 (0.71-5.54)	0.20
Other	-0.002	0.95	-0.02	0.32	2.18 (0.55-8.73)	0.27
Health insurance						
Medicare/Medicaid	(ref.)	-	(ref.)	-	(ref.)	-
Private	-0.02	0.49	0.05	0.02	1.49 (0.59-3.80)	0.40
Others	-0.03	0.35	0.04	0.03	0.70 (0.15-3.38)	0.66
Co-Morbidities						
CHF	0.17	<0.0001	0.04	0.045	9.68 (1.52-61.88)	0.02
CPD	0.005	0.85	0.03	0.19	N/A	N/A
Diabetes Mellitus	-0.02	0.56	-0.008	0.69	N/A	N/A
Hypertension	0.03	0.21	0.02	0.21	N/A	N/A
Liver diseases	-0.05	0.08	-0.006	0.75	3.70 (0.12-109.63)	0.45
Obesity	0.01	0.67	0.01	0.54	N/A	N/A
Renal failure	0.009	0.72	0.007	0.71	99.22 (2.61-3773.51)	0.01
Mitral Valve prolapse	0.004	0.88	0.08	<0.0001	0.93 (0.19-4.44)	0.93

HAC = Health-associated cost, MFS = Marfan Syndrome, POTS = Postural orthostatic tachycardia syndrome, WA = without any type of arrhythmia, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia, CHF = Chronic heart diseases, CPD = Chronic pulmonary diseases

Table S12: Predictors for Adjusted Healthcare-associated Cost for Adult MFS Patients

	Model 1		Model 2		Model 3	
	β	P-value	β	P-value	β	P-value
Female	-0.02	0.01	-0.02	0.003	-0.02	0.002
Age	-0.03	<0.0001	-0.02	0.004	-0.03	0.005
Length of stay	0.66	<0.0001	0.66	<0.0001	0.66	<0.0001
POTS	-	-	-	-	0.002	0.81
Anticoagulants	-	-	-	-	-0.04	<0.0001
Arrhythmia						
WA	(ref.)	-	(ref.)	-	(ref.)	-
AF	0.03	<0.0001	0.03	0.002	0.03	<0.0001
VT	0.04	<0.0001	0.04	<0.0001	0.04	<0.0001
AFL	0.03	<0.0001	0.02	0.002	0.03	0.002
SVT	0.02	0.01	0.01	0.06	0.01	0.06
Region						
Northeast	(ref.)	-	(ref.)	-	(ref.)	-
Midwest	-0.02	0.052	-0.02	0.07	-0.02	0.07
South	-0.06	<0.0001	-0.05	<0.0001	-0.05	<0.0001
West	0.09	<0.0001	0.09	<0.0001	0.09	<0.0001
Hospital size						
Small	(ref.)	-	(ref.)	-	(ref.)	-
Medium	-0.02	0.10	-0.02	0.09	-0.02	0.09
Large	0.03	0.005	0.03	0.02	0.03	0.02
Ethnicity						
White	-	-	(ref.)	-	(ref.)	-
Black	-	-	0.02	0.053	0.01	0.01
Hispanic	-	-	0.02	0.04	0.02	0.04
Other	-	-	0.04	<0.0001	0.04	<0.0001
Health insurance						
Medicare/Medicaid	-	-	(ref.)	-	(ref.)	-
Private	-	-	0.08	<0.0001	0.08	<0.0001
Others	-	-	0.00009	0.99	-0.0007	0.94
Co-Morbidities						
CHF	-	-	-	-	-0.03	<0.0001
CPD	-	-	-	-	-0.0002	0.98
Diabetes mellitus	-	-	-	-	0.003	0.76
Hypertension	-	-	-	-	0.02	0.04
Liver diseases	-	-	-	-	-0.0006	0.94
Obesity	-	-	-	-	0.02	0.003
Renal failure	-	-	-	-	0.004	0.63
Mitral Valve prolapse	-	-	-	-	0.005	0.55

Model 1: sex, age, LOS, type of arrhythmia, hospital region, and hospital size; Model 2: Model 1 + types of ethnicity and health insurance; Model 3: Model 2 + POTS, anticoagulants and existence of co-morbidities

The β is standardized beta.

MFS = Marfan Syndrome, POTS = Postural orthostatic tachycardia syndrome, WA = without any type of arrhythmia, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia, CHF = Chronic heart diseases, CPD = Chronic pulmonary diseases

Table S13: Predictors for In-Hospital Mortality for Adult MFS Patients

	Model 1		Model 2		Model 3	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Female	0.68 (0.51-0.90)	0.008	0.68 (0.50-0.92)	0.01	0.69 (0.51-0.95)	0.02
Age	1.02 (1.01-1.03)	<0.0001	1.01 (1.00-1.02)	0.006	1.02 (1.00-1.03)	0.005
POTS	-	-	-	-	1.00 (1.00-1.00)	0.18
Anticoagulants	-	-	-	-	0.59 (0.38-0.94)	0.03
Arrhythmia	-	-	-	-	-	-
WA	(ref.)	-	(ref.)	-	(ref.)	-
AF	1.88 (1.35-2.61)	<0.0001	1.94 (1.36-2.77)	<0.0001	1.96 (1.36-2.83)	<0.0001
VT	2.49 (1.20-5.18)	0.01	2.71 (1.29-5.66)	0.008	2.57 (1.22-5.42)	0.01
AFL	0.91 (0.22-3.75)	0.90	1.18 (0.28-4.87)	0.82	1.26 (0.30-5.26)	0.75
*SVT	N/A	-	N/A	-	N/A	-
Region						
Northeast	(ref.)	-	(ref.)	-	(ref.)	-
Midwest	0.82 (0.53-1.27)	0.38	1.03 (0.63-1.66)	0.92	1.02 (0.63-1.66)	0.92
South	1.30 (0.89-1.91)	0.17	1.33 (0.90-1.92)	0.15	1.30 (0.87-1.94)	0.19
West	1.08 (0.69-1.69)	0.73	1.11 (0.70-1.76)	0.67	1.08 (0.67-1.72)	0.75
Hospital size						
Small	(ref.)	-	(ref.)	-	(ref.)	-
Medium	0.86 (0.53-1.40)	0.55	0.97 (0.57-1.66)	0.82	0.97 (0.57-1.66)	0.91
Large	0.89 (0.58-1.36)	0.58	0.99 (0.62-1.59)	0.98	1.01 (0.63-1.62)	0.98
Ethnicity						
White	-	-	(ref.)	-	(ref.)	-
Black	-	-	1.31 (0.86-2.00)	0.21	1.19 (0.77-1.85)	0.42
Hispanic	-	-	0.88 (0.43-1.83)	0.73	0.90 (0.43-1.88)	0.19
Other	-	-	1.40 (0.70-2.78)	0.34	1.08 (0.67-1.72)	0.75
Health insurance						
Medicare/Medicaid	-	-	(ref.)	-	(ref.)	-
Private	-	-	0.77 (0.56-1.07)	0.12	0.83 (0.59-1.15)	0.26
Others	-	-	1.00 (0.60-1.66)	1.00	1.05 (0.63-2.78)	0.85
Co-Morbidities						
CHF	-	-	-	-	1.84 (1.20-2.82)	0.005
CPD	-	-	-	-	0.80 (0.53-1.20)	0.28
Diabetes Mellitus	-	-	-	-	0.49 (0.25-0.96)	0.04
Hypertension	-	-	-	-	0.71 (0.52-0.97)	0.03
Liver diseases	-	-	-	-	1.91 (0.86-4.25)	0.11
Obesity	-	-	-	-	1.62 (0.89-2.93)	0.11
Renal failure	-	-	-	-	2.35 (1.52-3.66)	<0.0001
Mitral Valve prolapse	-	-	-	-	0.58 (0.32-1.06)	0.08

Model 1: sex, age, type of arrhythmia, hospital region, and hospital size; Model 2: Model 1 + types of ethnicity and health insurance; Model 3: Model 2 + POTS, anticoagulants, and existence of co-morbidities

MFS = Marfan Syndrome, POTS = Postural orthostatic tachycardia syndrome, WA = without any type of arrhythmia, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia, CHF = Chronic heart diseases, CPD = Chronic pulmonary diseases

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

Table S14: Study Comparison of Frequency and Outcomes of Arrhythmias in MFS Patients vs General Population

	Wafa et al [Current Study]	Khurshid et al [29]	Mah et al [5]	Chamberlain et al [11]	Feinberg et al [30]	Go et al. [31]	Chugh et al [32]	Aggarwal A, et al [33]	Granada et al [34]	Garson et al [35]
Study Period (years)	2005 to 2014	2018	2007 to 2011	2000 to 2010	1995	1996-1997	1980-2010	1983 to 2016	1991-1995	1985
Sample size (N)	12,079	502,627	274	3,344	USA population	17974	Compilation of 184 studies worldwide	977	58,820	380
Mean age of patient (years)	39	58	11	72.6	75	75	n/a	34	72	1-25 years old
Male distribution	56.3%	45.6%	45.1%	52%	50% (40% after 75 years old)	70%	62%	64.7%	62%	Not specified
AF frequency (%)	12.8 of sample population	3.11 per 1000 person-years; 95% CI: 3.05-3.17)	n/a	88% of sample population had positive EKG findings of AF. Incidence rates per 1000 population standardized to the age and sex distribution of the USA population in 2010 were 2.99-3.23	2.3% in people >40 years old 5.9% in people >65 years old Estimated 2.2 million people in the USA with AF	Estimated 2.3 million people in the USA have AF (prevalence of 0.95%)	Estimated 33.5 million people in the world have AF (prevalence: 569.5 per 100,000 population in men, 359.9 per 100,000 population in women	15.6 of sample population	181 new case of AFL identified: 58% from them had at least one episode of AF	n/a

Other Arrhythmia frequency (N, [%])	AFL: 118 [1.0] SVT: 44 [0.4] VT: 189 [1.6] WA: 10,186 [84.2]	Bradyarrhythmia: 0.89 per 1000 person-years; 95% CI: 0.86-0.92. Conduction system disease: 1.06 per 1000 person-years; 95% CI: 3.05-2.17. SVT: 0.51 per 1000 person-years; 95% CI: 0.48-0.53. Ventricular Arrhythmias: 0.57 per 1000 person-years; 95% CI: 0.55-0.60.	Significant Ventricular ectopic: 20 [7] Supraventricular ectopic: 13 [5] VE and SVE: 2 [1]	Atrial Flutter 4%	n/a	n/a	n/a	n/a	Atrial Flutter: 181 new cases (incidence 88/100,000 persons per year 2.5 times more common in men	Mean onset of AFL was 10.3 years old; 60% of patients had repaired congenital heart disease, 13% palliated congenital heart disease, 8% unoperated congenital heart disease, 8% otherwise normal heart, 6% cardiomyopathy, 4% rheumatic heart disease and 2% other lesions
Antiarrhythmic therapy use	n/a	n/a	n/a	n/a	n/a	n/a	n/a	70% of patients (10% for catheter ablation)	n/a	Amiodarone+ Digoxin + Quinidine= 53% eliminated AFL Digoxin alone = 44% eliminated AFL

										Propranolol alone = 21% eliminated AFL
Length of inpatient hospital stay (days)	AF: 5 [2-8] AFL: 4 [2-9] SVT: 4 [4-10] VT: 6 [6-13] WA: 4 [2-7]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Healthcare acquired cost of AF (US\$)	\$25,608.0 [\$12,365.0-61,373.0]	n/a	n/a	\$6 to 26 billion	n/a	n/a	n/a	n/a	n/a	n/a
Mortality (N, [%])	AF : 63 [4.1] AFL : 2 [1.7] SVT : 0 [0] VT : 10 [5.3] WA : 252 [2.1]	n/a	At follow up (3 years): 0%	*Standardized mortality ratio First 30 days 19.4 (95% CI: 17.3-21.7) 31 to 90 days 4.2 (95% CI: 3.5-5.0) 91 to 365 days 1.5 (95% CI: 1.3-1.7)	n/a	n/a	2-fold (95% UI, 2.0-2.2) increase in mortality in women and 1.9-fold (95% UI, 1.8-2.0) increase in mortality in both men and women Disability-adjusted-life-years; an increase of 18.8% (95%	22.4%	n/a	At follow up (mean 6.5 years): 17% of patients did not survive

								UI, 15.8-19.3) in men and 18.9% (95%UI, 15.8-23.5) in women.			
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USA = United states of America, AF = Atrial fibrillation, CI = Confidence interval, EKG = Electrocardiogram, AFL = Atrial flutter, SVT = Supraventricular tachycardia, VT = Ventricular tachycardia, WA = without any type of arrhythmia, VE = Ventricular ectopic, SVE = Supraventricular ectopic

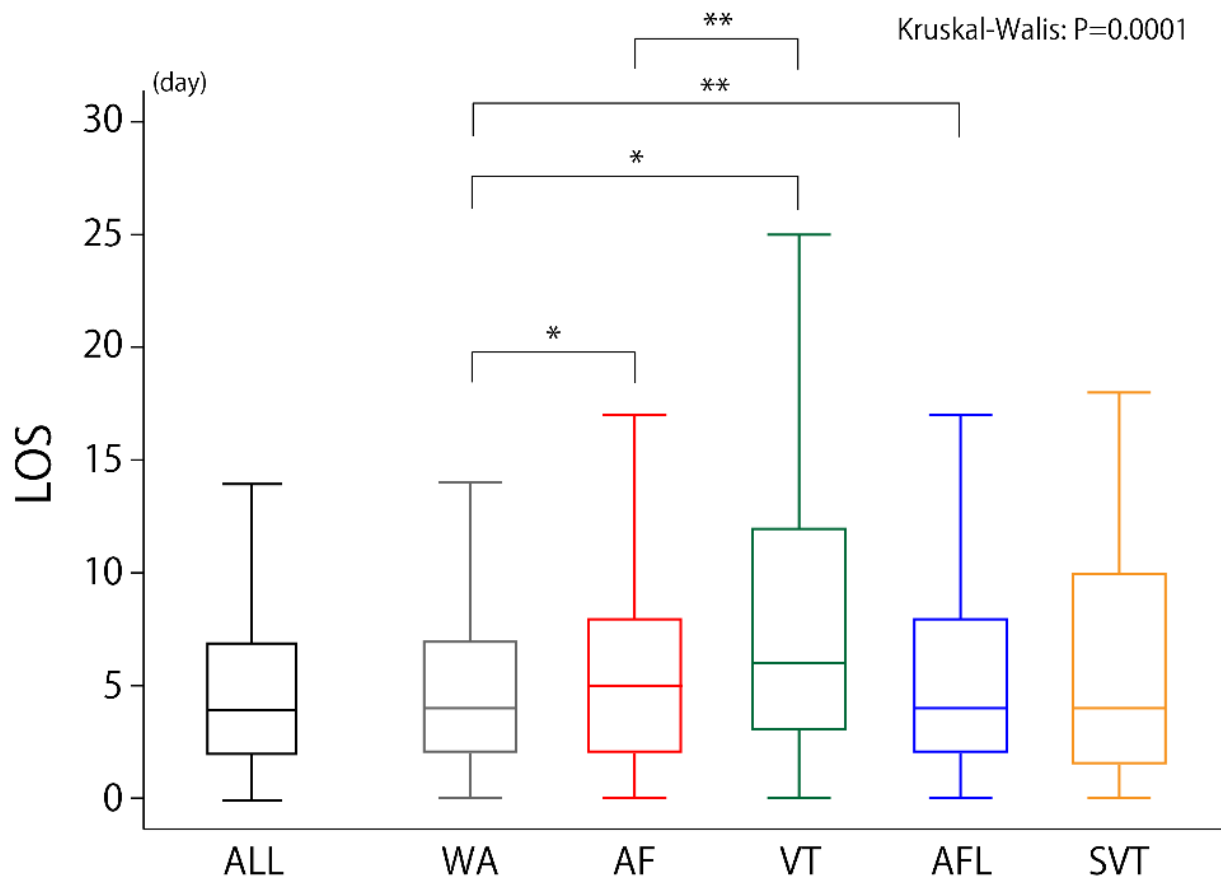


Figure S1 Length of Stay in Hospital for Adult MFS Patients

We compared the differences among the arrhythmia groups (i.e., WA, AF, VT, AFL, and SVT)

*: $P < 0.05$, ***: $P < 0.001$, ****: $P < 0.0001$

LOS = Length of (hospital) stay, WA = without any type of arrhythmia, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia

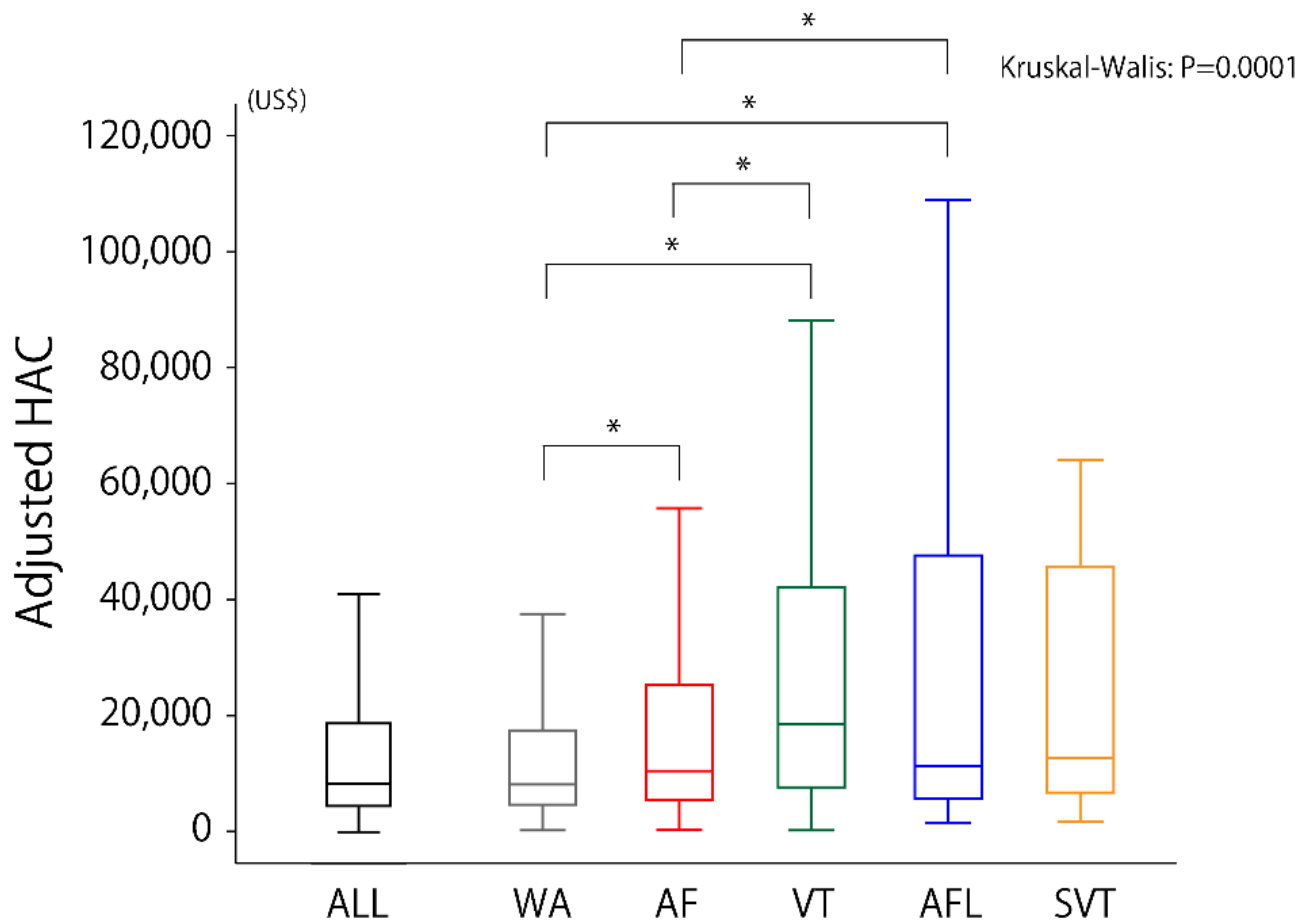


Figure S2 Adjusted Healthcare-Associated Costs for Adult MFS Patients

We compared the differences among the arrhythmia groups (i.e., WA, AF, VT, AFL, and SVT)

*: P<0.05, ***: P<0.001, ****: P<0.0001

HAC = Healthcare-associated cost, WA = without any type of arrhythmia, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia

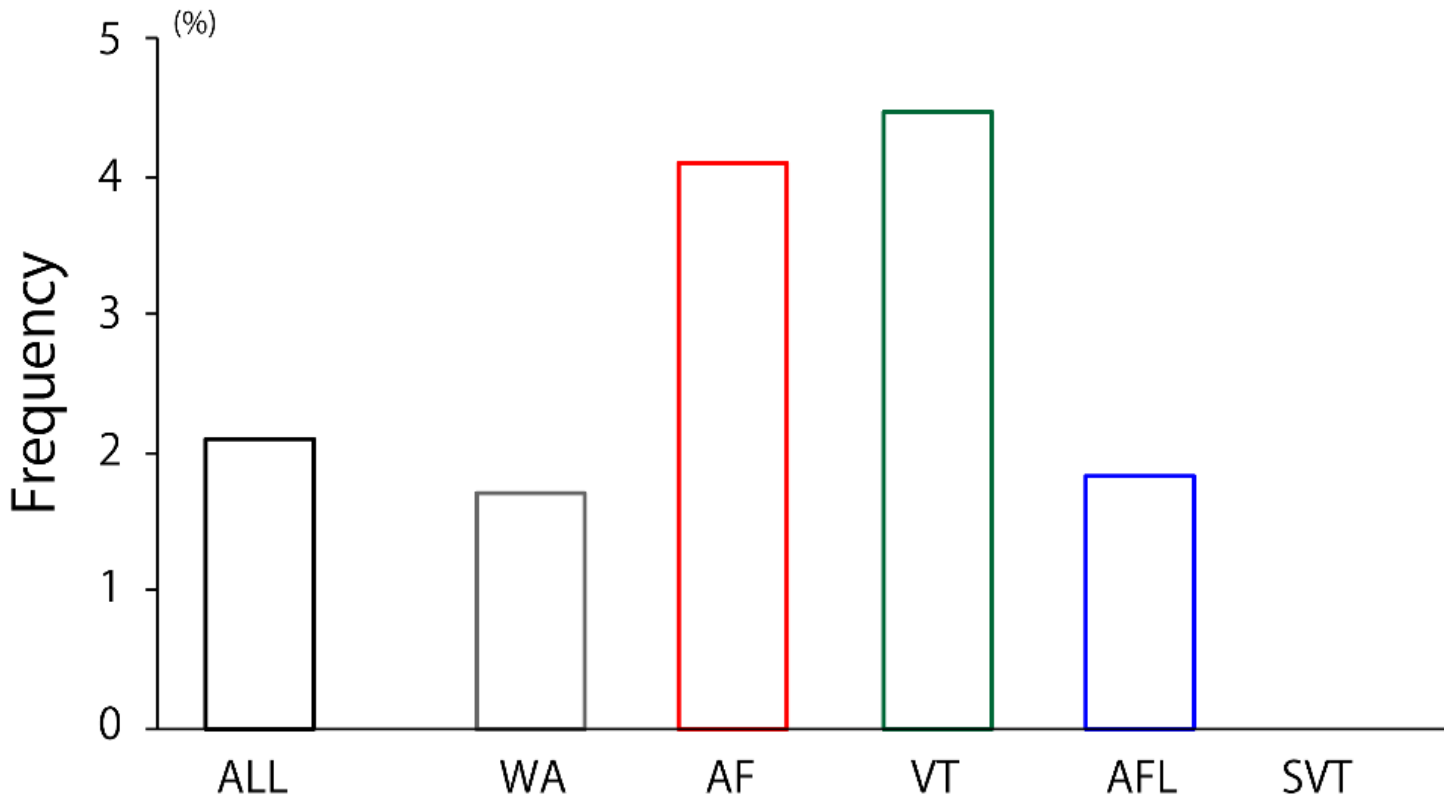


Figure S3 Frequency of In-Hospital Mortality for Adult MFS Patients

WA = without any type of arrhythmia, AF = Atrial fibrillation, VT = Ventricular tachycardia, AFL = Atrial flutter, SVT = Supraventricular tachycardia