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Prevalence and in-hospital mortality during arrhythmia-related admissions in adults with tetralogy of Fallot

Alexander C. Egbe *, Saraschandra Vallabhajosyula, Rahul Vojjini, Keerthana Banala, Maria Najam, Faizan Faizee, Fouad Khalil, Muhammad Wajih Ullah, Abhishek J. Deshmukh

Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN 55905, United States of America

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ABSTRACT

Background: Although outcomes of arrhythmia diagnosis have been described in ambulatory tetralogy of Fallot (TOF) patients, these have not been studied in hospitalized patients. The purpose of this study was to determine the prevalence and in-hospital mortality due to arrhythmias in TOF patients based on a review of the National Inpatient Sample database.

Methods: Admissions in adult TOF patients (2000–2014) were categorized as arrhythmia-related admission (ARA) or non-arrhythmia-related admission (NRA) based on arrhythmia diagnostic codes.

Results: Of 18,353 admissions, 5071 (27.6%) were ARA. The most common arrhythmias were atrial fibrillation (15.5%), atrial flutter (8.4%) and ventricular tachycardia (8.2%), and the prevalence of overall ARA as well as specific arrhythmia types increased over time. In-hospital mortality for ARA was 5.4%, and decreased over time. Arrhythmia diagnosis was an independent predictor of in-hospital mortality (odds ratio [OR] 1.63, 1.34–2.01, $p = 0.001$). Similarly, atrial fibrillation (OR 1.49, 1.18–1.89, $p = 0.001$) and ventricular tachycardia (OR: 2.01, 1.55–2.98, $p = 0.001$) were independent predictors of in-hospital mortality. Compared to small bed-size hospital, ARA in large hospital bed-size hospital was associated with a lower in-hospital mortality (OR 0.71, 0.53–0.96, $p = 0.03$).

Conclusion: Atrial fibrillation was the most common arrhythmia in hospitalized TOF patients, and arrhythmia diagnosis (specifically atrial fibrillation and ventricular tachycardia) was an independent predictor of in-hospital mortality, while admission to a large bed-size hospital was associated with a lower risk of in-hospital mortality. Further studies are required to determine if a more proactive approach to arrhythmia management in the ambulatory TOF population will reduce hospitalizations and mortality.

1. Introduction

Atrial and ventricular arrhythmias affect 11–25% and 9–22% of adults with repaired tetralogy of Fallot (TOF) respectively, and the prevalence vary depending on the demographics of the study population [1–3]. TOF patients have reduced longevity compared to the general population, and the median survival is about 50 years [1,3–5]. The most common causes of death are end-stage heart failure and arrhythmia/sudden cardiac death [1,3–5]. Atrial arrhythmia is a risk factor for heart failure hospitalization and mortality in both the congenital and acquired heart disease populations [6–9]. Therapies that reduce arrhythmia burden have been shown to reduce the risk of heart failure hospitalization and mortality in patients with acquired heart disease [10,11], and logically we should expect a similar survival benefit in the congenital heart disease population.

A recent single center study reported that atrial fibrillation was the most common atrial arrhythmia among TOF patients, and it was an independent risk factor for heart failure hospitalization and all-cause mortality [12]. The study also showed that rhythm control therapy for atrial fibrillation was associated with lower risk of heart failure hospitalization and mortality in that cohort [12]. Since arrhythmia prevalence and clinical outcomes vary with population demographics [1–3], it is unknown how the results of this single center study reflect the outcomes in other centers. A previous study reported national estimates of hospitalization in adult TOF patients [13]. However this study did not provide data about the types of arrhythmias during hospitalization or the risk of mortality in patients admitted because of arrhythmias. Such data are important because they would provide a clearer assessment of the relationship between the different arrhythmia

Abbreviations: TOF, tetralogy of Fallot; NIS, National (Nationwide) Inpatient Sample; HCUP, Healthcare Cost and Utilization Project; ICD-9CM, International Classification of Diseases 9 Clinical Modification; ARA, arrhythmia-related admissions; NRA, non-arrhythmia-related admissions; OR, odds ratio; CI, confidence interval.

* Corresponding author at: Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, United States of America.
E-mail address: egbe.alexander@mayo.edu (A.C. Egbe).

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types and the risk of hospitalization and mortality. Understanding this relationship is an important step towards formulating therapies to reduce the prevalence and mortality due to arrhythmias in the TOF population. The purpose of this study was therefore to determine the prevalence, temporal trends, and in-hospital mortality due to arrhythmia in TOF patients based on a review of the National (Nationwide) Inpatient Sample (NIS) database.

2. Methods

2.1. Study population, variables and outcomes

The NIS is the largest all-payer database of hospital inpatient stays in the United States. NIS contains discharge data from a 20% stratified sample of community hospitals and is a part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality [14]. Information regarding each discharge includes patient demographics, primary payer, hospital characteristics, principal diagnosis, up to 24 secondary diagnoses, and procedural diagnoses.

Using the HCUP-NIS data from 2000 to 2014, we performed a retrospective review of adult patients (>18 years) admitted with a primary or secondary diagnosis of TOF (International Classification of Diseases 9 Clinical Modification [ICD-9CM] code 745.2) [13,15]. Consistent with prior literature, arrhythmias were identified with the following ICD-9CM codes – atrial fibrillation 427.31, atrial flutter 427.32, supraventricular tachycardia 427.0, ventricular fibrillation 427.41 and ventricular tachycardia 427.1 [16,17]. Use of direct-current cardioversion and catheter ablation for arrhythmias was identified using procedure codes of ICD-9CM 99.61 and 37.34 respectively as reported in previous studies [17,18]. Patient characteristics (age, sex, and race, socio-economic status, primary payer) and hospital characteristics (teaching status and location, bed-size, and region) associated with each discharge were identified from the HCUP-NIS database. The Deyo's modification of Charlson Comorbidity Index was used to identify the burden of co-morbid diseases (Supplementary Table 1) [13,19]. The admissions were categorized as arrhythmia-related admission (ARA) if any of the arrhythmia ICD-9CM codes were listed as primary or secondary diagnosis. The admissions without any of the arrhythmia ICD-9CM codes were categorized as non-arrhythmia-related admission (NRA).

The primary outcome was the prevalence and temporal trends of ARA during the 15-year study period. Secondary outcome was the incidence and temporal trends of in-hospital mortality for ARA. Exploratory analysis was performed to determine if the hospital characteristics (hospital bed-size) was a predictors of in-hospital mortality for ARA. In order to assess temporal trends, we divided the study period into tertiles: early era (2000–2004), mid era (2005–2009) and late era (2010–2014).

2.2. Statistical analysis

As recommended by HCUP-NIS, survey procedures using discharge weights provided with HCUP-NIS database were used to generate national estimates. Chi-square test, *t*-test and One-Way Analysis of Variance tests were used for between-group comparisons as appropriate. Multivariate hierarchical logistic regression analysis was used to determine the adjusted risk of in-hospital mortality during ARA, using NRA as the referent group. Logistic regression analysis was also used to determine the adjusted risk of in-hospital mortality for ARA due to atrial fibrillation, atrial flutter and ventricular tachycardia, using NRA as the referent group. Risk factors for supraventricular tachycardia and ventricular fibrillation were not assessed because of small sample size. These logistic regression models were constructed with purposeful selection of statistically ($p < 0.20$) and clinically relevant variables such as age, sex, admission year, primary payer status, socio-economic stratum, hospital characteristics, comorbidities, acute organ failure, cardiac arrest, cardiac procedures, and non-cardiac interventions. For the exploratory analysis to determine the association between hospital bed-size and in-hospital morality among ARA, the small bed-size hospital category was used as the referent group. All comparisons were reported using odds ratios (OR) with 95% confidence intervals (CI). Two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS v25.0 (IBM Corp, Armonk NY).

3. Results

3.1. Prevalence of arrhythmia-related admissions in adults with TOF

During the period between January 1, 2000 and December 31, 2014, there were an estimated 18,353 admissions in adults with TOF diagnosis, of which 5071 (27.6%) were ARA. The baseline characteristics of the cohorts with ARA and NRA are presented in Table 1. As expected, the ARA had higher rates of cardiac arrest (2.1% vs. 0.9%), use of coronary angiography (13.4% vs. 8.4%), right heart catheterization (11.1% vs. 7.2%), respiratory failure requiring endotracheal intubation (7.9% vs. 4.2%) and hemodialysis (1.2% vs. 0.3%) (all $p < 0.001$).

Among the ARA, direct current cardioversions and catheter ablations were performed in 242 (4.8%) and 345 (6.8%) respectively. The ARA were more likely to occur in the large bed-size hospitals (large 75%, medium 19%, and small 6%, $p < 0.001$), and in the urban teaching hospitals (urban teaching hospital 72%, urban non-teaching hospital 22%, and rural hospital 6%, $p < 0.001$). Atrial fibrillation was the most common arrhythmia type (atrial fibrillation 2839 [15.5%], atrial flutter 1550 [8.4%], supraventricular tachycardia 271 [1.5%], ventricular tachycardia 1510 [8.2%], and ventricular fibrillation 252 [1.4%], $p < 0.001$). The 15-year temporal trends of arrhythmia prevalence are presented in Supplementary Fig. 1. There was a temporal increase in the prevalence of ARA from the early through the late eras (22.1% vs 33.5% vs 35%, $p < 0.001$). For the specific arrhythmia types, there was a temporal increase in the prevalence of atrial fibrillation (early era 704 [12.6%], mid era 1026 [16.1%], and late era 1109 [17.4%], $p < 0.001$); atrial flutter (early era 408 [7.3%], mid era 564 [8.8%], and late era 578 [9%], $p = 0.001$), and ventricular tachycardia (early era 398 [7.1%], mid era 549 [8.6%], and late era 563 [8.8%], $p = 0.002$), Fig. 1.

3.2. In-hospital mortality during arrhythmia-related admissions

The clinical outcomes of the cohorts with ARA and NRA are presented in Table 2. Compared to the NRA, ARA was associated with a higher unadjusted risk of in-hospital mortality (5.4% vs 2.5%; OR 2.21, 95%CI 1.88–2.61, $p < 0.001$). There was a temporal decrease in in-hospital mortality for ARA from early through the late era (early era 6.4%, mid era 5.5% and late era 4.6%, $p < 0.001$), Fig. 2.

In a multivariable hierarchical logistic regression analysis for in-hospital mortality, arrhythmia diagnosis was an independent predictor of in-hospital mortality (OR 1.63, 95%CI 1.34–2.01, $p = 0.001$). Similarly, atrial fibrillation (OR 1.49, 95%CI 1.18–1.89, $p = 0.001$) and ventricular tachycardia (OR: 2.01, 95%CI 1.55–2.98, $p = 0.001$) were independent predictors of in-hospital mortality. Using the small bed-size hospital category as referent group, exploratory analysis showed that ARA in large hospital bed-size hospital was associated with a lower risk of in-hospital mortality (OR 0.71, 95%CI 0.53–0.96, $p = 0.03$).

4. Discussion

Based on the review of a nationally representative database of hospital admissions, we showed that ARA comprised 28% of all hospital admissions in adults with TOF, and the most common arrhythmias were atrial fibrillation (16%), atrial flutter (8.4%), and ventricular tachycardia (8.2%). There was a temporal increase in the proportion of ARA between

Table 1
Baseline characteristics of tetralogy of Fallot admissions stratified by presence of arrhythmias.

Characteristic		Tetralogy of Fallot cohort ($N = 18,353$)			Arrhythmia only cohort ($N = 5071$)			
		Arrhythmias (N = 5071)	No arrhythmias ($N = 13,282$)	p	Atrial ($N = 3389$)	Ventricular ($N = 1217$)	Both ($N = 465$)	p
Age (years)		44 (33–55)	33 (25–44)	<0.001	46 (37–57)	38 (27–47)	45 (37–56)	<0.001
Female sex		45.2	56.7	<0.001	47.4	42.2	37.4	<0.001
Race	White	73.2	67.8	<0.001	72.6	74.1	75.6	<0.001
	Black	12.9	12.8		12.9	13.0	12.0	
	Others	13.9	19.4		14.5	12.9	12.4	
Primary payer	Medicare	32.7	26.3	<0.001	47.4	42.2	37.4	<0.001
	Medicaid	18.1	26.8		47.4	42.2	37.4	
	Private	40.4	37.8		47.4	42.2	37.4	
	Others	9.0	8.8		9.3	9.7	3.3	
Quartile of median household income for zip code	0-25th	23.3	23.8	0.38	24.5	19.7	24.2	<0.001
	26th–50th	25.8	25.9		25.7	26.2	26.2	
	51st-75th	25.8	26.5		26.6	24.1	24.4	
	75th–100th	25.0	23.8		23.3	29.9	25.3	
Hospital teaching status and location	Rural	6.0	8.9	<0.001	7.6	2.3	4.1	<0.001
	Urban non-teaching	22.1	24.5		24.8	17.7	13.3	
	Urban teaching	72.0	66.5		67.6	80.0	82.6	
Hospital bedsize	Small	6.3	11.7	<0.001	7.8	3.7	1.7	<0.001
	Medium	19.2	20.6		20.1	17.7	17.2	
	Large	74.5	67.7		72.1	78.6	81.1	
Hospital region	Northeast	18.9	22.2	<0.001	18.7	18.0	23.0	0.14
	Midwest	22.6	20.5		23.2	21.1	22.4	
	South	35.5	37.4		35.0	37.6	33.8	
	West	22.9	19.9		23.1	23.3	20.9	
Charlson Comorbidity Index	0–3	84.4	92.0	<0.001	82.6	92.4	76.8	<0.001
	4–6	13.5	6.5		14.8	6.8	21.3	
	≥7	2.1	1.6		2.6	0.8	1.9	
Prior cardiac procedures	Pacemaker	7.4	4.6	<0.001	8.7	5.6	3.2	<0.001
	Defibrillator	12.6	4.4	<0.001	9.1	15.3	30.3	<0.001
	Valve replacement	8.5	7.3	0.004	9.0	8.5	5.2	0.02

Legend: represented as percentage or median (interquartile range).

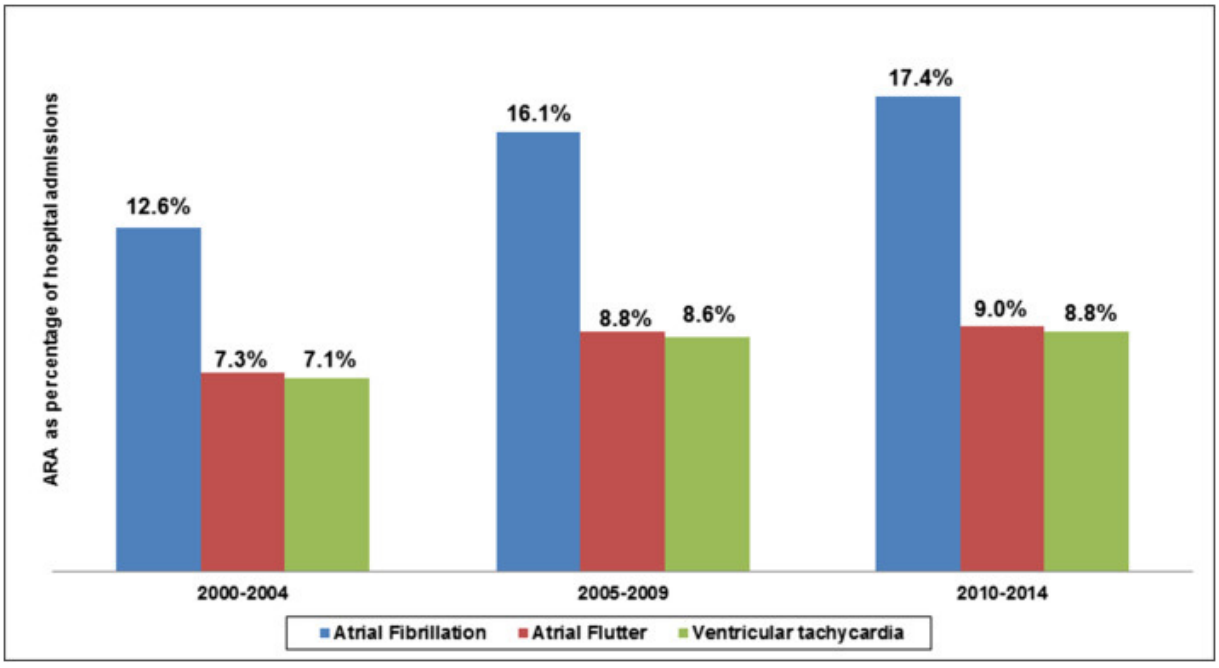

Fig. 1. Bar chart comparing arrhythmia-related admissions (ARA) prevalence for atrial fibrillation, atrial flutter and ventricular tachycardia between the different eras. $p < 0.05$ for all comparisons.

eras, likely a reflection of an *older and sicker* population. Although we observed a temporal decline in in-hospital mortality for ARA, in-hospital mortality during ARA was still >60% higher compared to NRA even in the late era (4.6% vs 2.8%). Having an arrhythmia diagnosis (specifically atrial fibrillation and ventricular tachycardia) was an independent predictor of in-hospital mortality, while ARA to large

Table 2
Clinical outcomes of tetralogy of Fallot admissions stratified by presence of arrhythmias.

Characteristic		Tetralogy of Fallot cohort (N = 18,353)			Arrhythmia only cohort (N = 5071)			
		Arrhythmias (N = 5071)	No arrhythmias (N = 13,282)	*p*	Atrial (N = 3389)	Ventricular (N = 1217)	Both (N = 465)	*p*
In-hospital mortality		5.4	2.5	<0.001	4.8	7.5	4.9	0.001
Length of stay (days)		4 (2–8)	3 (2–6)	<0.001	4 (2–8)	4 (2–7)	5 (3–8)	0.24
Median hospitalization costs (x1000 US dollars)		30 (12–86)	18 (9–42)	<0.001	23 (11–59)	51 (18–142)	43 (23–98)	<0.001
Discharge disposition	Home	75.5	79.5	<0.001	73.8	79.8	76.6	<0.001
	Hospital transfer	5.4	4.9		5.6	5.9	2.0	
	SNF	7.1	6.8		7.1	4.5	13.8	
	Home with HHC	11.4	7.9		12.7	9.0	7.5	
	AMA	0.7	0.9		0.7	0.8	0.0	

Legend: represented as percentage or median (interquartile range).
Abbreviations: AMA: against medical advice; HHC: home health care; SNF: skilled nursing facility; US: United States.

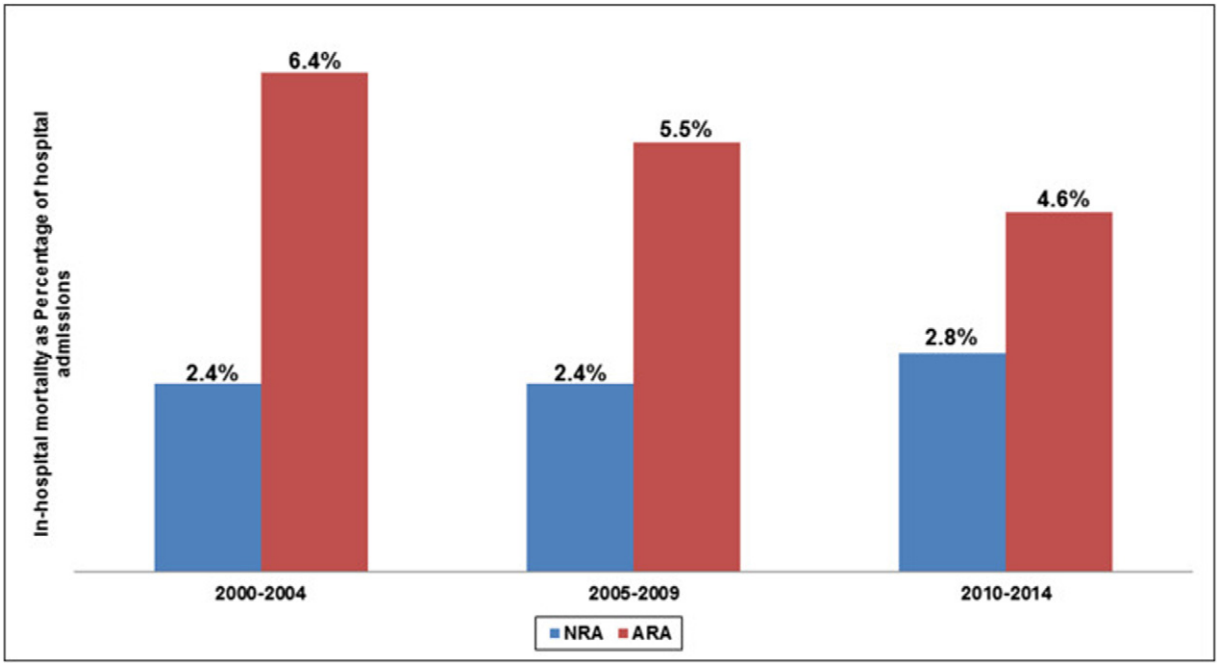

Fig. 2. Bar chart comparing between-era difference in in-hospital mortality. ARA: arrhythmia-related admission; NRA: Non-arrhythmia-related admission. $p < 0.001$ for ARA.

bed-size hospital was associated with a lower risk of in-hospital mortality. These results demonstrate that arrhythmia is an important determinant of clinical outcomes in the TOF population.

The prevalence of arrhythmias in adults with TOF has been described [1–3,20]. In a multicenter study of 556 ambulatory adult TOF patients, the prevalence of atrial and/or ventricular arrhythmia was 30%, and the most common arrhythmias were atrial flutter in 12%, atrial fibrillation in 7% and ventricular tachycardia in 14% [2]. In contrast to this multicenter study that was conducted in ambulatory patients, our study was based on an in-patient sample, but the estimates of arrhythmia prevalence were concordant between the two studies. A noteworthy difference was that atrial fibrillation was the most common arrhythmia in our study, in contrast to atrial flutter as the predominant arrhythmia in prior studies [1–3,20]. We speculate that the predominance of atrial fibrillation in this cohort reflects an older age and a greater burden of co-morbidities as shown by the median age of 44 years and higher Charlson Comorbidity Index in the current study. In support of our speculation, cohort studies conducted in older patient cohorts have also shown that atrial fibrillation is the predominant arrhythmia after the fourth decade of life [3].

Atrial and ventricular arrhythmias are known risk factors for mortality in TOF patients [1,20], hence the results of the current study were not unexpected. However, it is still sobering to note that arrhythmia was the primary or secondary diagnosis in >1 in 4 admissions in TOF patients. More importantly, arrhythmia diagnosis increased the odds of in-hospital mortality by 50% even after adjustment for differences in baseline characteristics. While in-hospital mortality during ARA declined over time likely reflecting an improvement in care, the rising prevalence of ARA and the excess mortality associated with ARA clearly show that arrhythmia management is an important unmet need in this population.

In this study, a majority of the ARA occurred in large bed-sized hospital (75% in large bed-sized hospital vs 25% in medium and small bed-sized hospital), and admissions that occurred in large bed-sized hospital was associated with a lower risk of in-hospital mortality. The guidelines for management of adults with congenital heart disease

recommend that adults with moderate/complex congenital heart disease should receive care in tertiary care centers with multidisciplinary expertise to deal with the comorbidities and healthcare needs of this unique population [21,22]. Such multidisciplinary expertise are typically available in the large bed-size hospitals. The lower in-hospital mortality for ARA in the large bed-sized hospital observed in this study suggests better in-hospital outcomes, and therefore supports the recommendation for specialist care in adults with congenital heart disease.

4.1. Clinical implications and future directions

Although we cannot infer causality from a cross-sectional study, one cannot help but wonder if interventions aimed at reducing arrhythmia burden in the ambulatory patients will potential reduce hospitalization and mortality in TOF patients with atrial arrhythmias. In a recent cohort study from the Mayo Clinic, 415 TOF patients were followed for a median 13 years, and among these patients, 88 (21%) had a history of atrial fibrillation [12]. Incident heart failure hospitalization was 4-folds higher in the patients with atrial fibrillation compared to the rest of the cohort (16% vs 4%), and atrial fibrillation was an independent risk factor for heart failure hospitalization and mortality. Among the 88 patients with history of atrial fibrillation, 69% received rhythm control therapy (catheter ablation and or class I/III antiarrhythmic drug) while 31% received rate control therapy. Rhythm control therapy was associated with lower risk of incident hospitalization and all-cause mortality [12]. It is important to note that the above study was an observational study which is prone to bias and confounding. Unfortunately there are no randomized studies comparing clinical outcomes between types of antiarrhythmia therapy in patients with congenital heart disease. In the context of the current study which highlights the prognostic implications of arrhythmias in TOF patients, there is a great need for prospective multicenter studies to explore the optimal antiarrhythmia therapy to potentially reduce hospitalization and mortality in this population.

4.2. Limitations

The NIS is an administrative database and relies on diagnostic codes which do not provide much information about disease severity within a particular diagnosis. We defined ARA as an admission with arrhythmia diagnosis code as the primary or secondary diagnosis, and hence arrhythmia may just be a 'by-stander' and not the main reason for the admission. The type of antiarrhythmia therapy received during hospitalization was not available for review. Additionally the NIS contains data of specific admissions, and not specific patients, and hence there are no follow-up data after hospital discharge. As a result we cannot determine readmissions over time. TOF patients with documented sustained ventricular tachycardia typically undergo defibrillator implantation because of high risk of sudden cardiac death [21,22]. We were unable to determine how many of the patients without defibrillators might have appropriate indications for defibrillator implantation, hence making it difficult to interpret the relationship between ventricular tachycardia and in-hospital mortality in the study. The NIS database does not contain information about prior surgical history such as age at the time of TOF repair, all data about acuity of admission. These factors limited inference that can be drawn from this study. Notwithstanding, the NIS database is ideal for hypothesis-generating studies such as this.

5. Conclusions

ARA account for 1 in 4 admissions in the TOF patients, and atrial fibrillation is the most common type of arrhythmia in this inpatient sample. Having an arrhythmia diagnosis (specifically atrial fibrillation and ventricular tachycardia) was an independent predictor of in-hospital mortality, while admission to a large bed-size hospital was associated with a lower risk of in-hospital mortality. The current study emphasizes the deleterious effect of arrhythmia on clinical outcomes in this population, and also highlights important knowledge gaps about the optimal arrhythmic therapy that will provide optimal long-term outcomes. The data also suggest better in-hospital outcomes for admission to large bed-sized hospitals. Further studies are required to determine if a more proactive approach to arrhythmia management in the ambulatory TOF population will reduce hospital admissions, and whether managing more of the ARA in large bed-size hospitals will improve survival in these patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.09.001.

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Declaration of competing interest

None.

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