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ORIGINAL ARTICLE

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Arrhythmia burden and related outcomes in Eisenmenger syndrome

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Abstract

Background: Patients with Eisenmenger syndrome have a shorter lifespan than the general population. A significant proportion develop arrhythmia and some, sudden death.

Objective: The aims of this study were to characterize the frequency, type and effects of arrhythmias in adult patients with Eisenmenger's syndrome and to identify risk factors for arrhythmias.

Methods: This retrospective study included patients aged $\geq$ 18 years of age with Eisenmenger's syndrome from three institutions. Arrhythmias were noted from electrocardiograms and Holter study reviews.

Results: A total of 167 patients, 96 females, 63 males (gender not available in 9 patients) were included in this study. The mean age was 38 $\pm$ 9 years (range: 18–63 years) with a majority in NYHA functional class II or III (57% and 32% respectively). Twenty-eight patients (17%) had significant tachyarrhythmia: paroxysmal supraventricular tachycardia (8 patients, 29%), atrial fibrillation (6 patients, 21%), atrial fibrillation and flutter (2 patients, 7%), nonsustained ventricular tachycardia (6 patients, 21%) and sustained ventricular tachycardia (6 patients, 21%). Among the entire study group, 26 patients (16%) were currently on antiarrhythmic therapy and 77 patients (49%) were on advanced therapies for pulmonary hypertension. Down syndrome was present in 78 patients (46%). There were 21 (13%) documented deaths, of which 8 (5%) were sudden death. Patients with arrhythmia were older [$P = .01$] and were more likely to have atrioventricular valvar regurgitation [Odds ratio: 4.33]. Advanced pulmonary hypertension therapy was associated with decreased all-cause mortality in logistic regression analysis [odds ratio: 0.31], while antiarrhythmic therapy was associated with sudden death [odds ratio: 6.24].

Conclusions: Arrhythmias are common among patients with Eisenmenger syndrome occurring in around 1 in 5 individuals and are associated with all-cause mortality and sudden death.

KEYWORDS

adult congenital heart disease, arrhythmias, congenital heart disease, Eisenmenger syndrome, pulmonary hypertension, sudden cardiac death

1 | INTRODUCTION

The detailed pathophysiology of Eisenmenger syndrome (ES) was first described in 1958 by Dr. Paul Wood.[1] Additionally Wood also reported on the natural history of ES, observing that there was a significant diminishment in clinical status in the 2nd and 3rd decades attributable to the development of intrapulmonary arterial thromboses, further increasing pulmonary vascular resistance, and limiting pulmonary blood flow. Subsequent studies in the late 90s surprisingly demonstrated that survival had not changed significantly as compared with these early observations made by Wood 3 decades earlier.[2,3] However, more recent longitudinal cohort studies support the notion that modern supportive therapies and advanced pulmonary hypertension drugs have been associated with improved survival. [4–7]

Arrhythmia as a manifestation of cardiovascular morbidity has long been recognized in ES. Relatively little data exists however giving us specific insight into the prevalence, risk factors for, and outcomes associated with arrhythmia in ES. Indeed, there are to our knowledge no prior publications focusing specifically on arrhythmia outcomes in ES. Earlier more general outcomes studies suggest that sudden cardiac death related to ventricular arrhythmias may be a significant contributor to the mortality.[5] The aims of this study therefore were to characterize the frequency, type and characterize the possible impact of arrhythmias on the outcome of patients in a moderately large cohort of adult patients with ES and to identify potential risk factors for arrhythmia in this population.

2 | METHODS

2.1 | Study design

This was a retrospective chart review that included patients under routine clinical surveillance at one of the three study sites [Southampton University Hospital, United Kingdom (n = 60); Research committee of the Japanese Society of Pediatric Cardiology and Cardiovascular Surgery (n = 110) and Royal Victoria Hospital, Belfast, Northern Ireland (n = 10)]. De-identified data from electronic hospital databases collected prior to 2011 for clinical care purposes were used to identify patients in the three study sites beginning from patient's 18th birthday to latest follow-up or death which spanned from 2001 to 2011. Patients with a diagnosis of ES and ≥ 18 years of age were included in the study. Patients with ES were identified based on clinical documentation. ES was defined as a clinical syndrome of cyanosis in the presence of a large nonrestrictive intracardiac or extracardiac communication due to the reversal of shunt flow to be from right to left in the absence of obstruction to the pulmonary flow at any level. In patients with single ventricle physiology, the diagnosis of pulmonary hypertension was based on increased pulmonary vascular resistance during cardiac catheterization. Patient demographic and clinical characteristics (NYHA functional class, hemoglobin level and saturation) were collected from the latest available follow-up documentation. Presence of ventricular dysfunction and atrioventricular (AV) valvar regurgitation was noted from the most recent echocardiogram. The QRS duration and corrected QT (QTc) interval were calculated based on the last available electrocardiograms (ECG). A QRS duration greater than 110 milliseconds (msec) was considered to be prolonged. The QT interval was corrected to obtain the QTc using the Bazet's formula (normal QTc: < 440 msec). Arrhythmias were diagnosed based on ECG obtained during clinical visits or on 24 hour Holter monitoring. The study was approved and the need for informed consent waived by the institutional review board at the Southampton General Hospital, and at Cincinnati Children's Hospital Medical Center.

2.2 | Congenital heart disease

Patients with patent ductus arteriosus (PDA), atrial septal defect (ASD) and ventricular septal defect (VSD) were classified as having simple congenital heart disease (CHD). The rest of the CHD were grouped as complex. Complex CHDs were further defined as atrioventricular septal defects (AVSD), cono-truncal anomalies (tetralogy of Fallot, truncus arteriosus and transposition of great arteries), single ventricle physiology and combined defects (for those with two or more defects).

2.3 | Arrhythmia characteristics and risk-factors

Significant tachyarrhythmias were classified as supraventricular tachycardia (SVT), nonsustained ventricular tachycardia (VT) and sustained VT. Greater than three premature ventricular complexes were considered to be VT. VT lasting for <30 seconds was considered to be non-sustained. SVT was further subclassified as atrial fibrillation, atrial fibrillation and flutter and paroxysmal SVT. Isolated premature ventricular or atrial complexes were not included in this study. Patient demographics and clinical characteristics were analyzed for predictors of arrhythmias, death from all causes and sudden death. Sudden death was defined as death within a short time of onset of new symptoms, that is, <24 hours. Sudden death due to severe infection, trauma, intoxication, and other conditions which were readily explainable by a noncardiac cause were excluded. Dysfunction of the subpulmonary or the single ventricle was classified as mild, moderate and severe based on the echocardiographic documented report.

2.4 | Statistics

Summary statistics were denoted as means ± SD, or frequencies and percentages. Bivariate statistical comparisons were made between groups using chi-square type analyses, or Student's *t* tests. Logistic regression analysis was done to determine independent predictors of three outcomes: any arrhythmia, death from all causes, and sudden death. The list of potential independent predictors for each outcome included variables which had a *P* value of .10 or less on bivariate analysis. A *P* value of .05 or less was considered to be statistically significant.

3 | RESULTS

Out of a total of 180 patients, 10 patients had insufficient data and 3 patients had died prior to 18 years of age and were excluded. Hence a

TABLE 1 Type of congenital heart disease among all patients and those with arrhythmias

Congenital heart disease	All patients (%) (N = 167)	Patients with arrhythmias (%) (N = 28)	% of Patients with arrhythmias in CHD group
Simple CHD	86 (52%)	10 (36%)	12%
Patent ductus arteriosus	15 (9%)	2 (7%)	13%
Atrial septal defect	15 (9%)	3 (11%)	20%
Ventricular septal defect	56 (34%)	5 (18%)	9%
Complex CHD	81 (49%)	18 (64%)	22%
Atrioventricular septal defect	43 (26%)	7 (25%)	16%
Single ventricle physiology	23 (14%)	9 (32%)	39%
Combined defects	10 (6%)	0 (0%)	10%
Cono-truncal anomalies	5 (3%)	2 (7%)	40%

Abbreviation: CHD: congenital heart disease.

total 167 patients were included in the study. There was an almost equal number of simple and complex CHDs, with VSDs and AVSDs being the most common in each group respectively (Table 1). The majority of the patients were young adults with an age range of 18–63 years (Table 2). The mean resting saturation in this patient population was 85% ± 7%. Close to half of the entire study group had Down syndrome, and they were younger (mean age: 35 ± 7 years) than the rest of the patients (mean age: 38 ± 9 years; $P = .003$). A majority of the patients had a NYHA functional class of II or III, with documented subpulmonary ventricular dysfunction in approximately 1/4th of the

TABLE 2 Patient demographics and clinical characteristics

Patient characteristics	All patients (N = 167)	Patients without arrhythmias (N = 139)	Patients with arrhythmias (N = 28)	% Patients with arrhythmias in subgroup	*P* value
Age (Mean ± SD) years	38 ± 9	37 ± 9	44 ± 9		.01
Females (%) [N = 158]	96 (60%)	78 (60%)	17 (61%)	18%	.9
Complex heart disease	81 (49%)	63 (45%)	18 (64%)	22%	.1
Functional class [N = 134]					.2
I	10 (7%)	9 (8%)	1 (4%)	10%	
II	76 (57%)	63 (58%)	13 (52%)	17%	
III	43 (32%)	34 (31%)	9 (36%)	21%	
IV	5 (4%)	2 (1.85)	3 (12%)	60%	
Hemoglobin (g/dl) [N = 93]	18.8 ± 3	18.8 ± 3	17.8 ± 3		.8
Oxygen saturation (%) [N = 93]	85% ±7%	86% ±8%	83% ± 7%		.4
Down syndrome	78 (46%)	75 (53%)	3 (11%)	4%	<.0001
Age (Mean ± SD) years	35 ± 7	35 ± 7	37 ± 7		
Electrocardiographic parameters					
QRS duration (mean ± SD) [msec] [N = 143]	102 ± 20	101 ± 20	118 ± 20		.3
QRS > 110 msec	48 (34%)	35 (39%)	13 (52%)	27%	.04
QTc duration (mean ± SD) [N = 139]	428 ± 25	430 ± 32	423 ± 27		.3
QTc > 440 msec	27 (29%)	24 (29%)	3 (13%)	11%	1
Congestive heart failure therapy [N=157]	72 (45%)	58 (44%)	14 (50%)	19%	.55
Ventricular dysfunction [N = 166]	37 (22%)	26 (19%)	11 (39%)	30%	.4
AV valve regurgitation [N = 148]	71 (48%)	53 (43%)	18 (72%)	25%	.01
Severity of AV valve regurgitation [N = 135]					.005
None	64 (47%)	58 (52%)	6 (24%)	9%	
Mild	54 (40%)	43 (40%)	11 (44%)	20%	
Moderate	13 (7%)	7 (7%)	6 (24%)	46%	
Severe	4 (3%)	2 (2%)	2 (8%)	50%	
Medications					
Disease targeting therapy [N = 157]	77 (49%)	68 (51%)	9 (38%)	12%	.4
Anti-arrhythmics [N = 164]	26 (16%)	6 (4%)	20 (67%)	78%	<.0001
Mortality					
Deceased	21 (13%)	12 (9%)	9 (30%)	43%	.004
Sudden death	8 (5%)	4 (3%)	4 (14%)	50%	.04
Age at death (mean ± SD) years	32 ± 12	30 ± 8	37 ± 15		

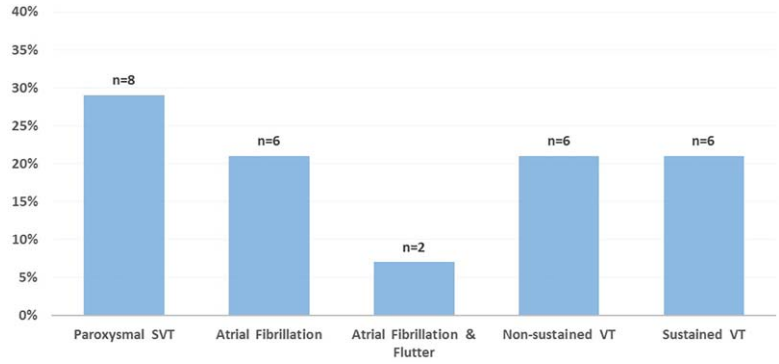


FIGURE 1 Arrhythmias in patients with Eisenmenger syndrome. Abbreviations: VT, ventricular tachycardia; SVT, supraventricular tachycardia

patients. Corrected QT interval (QTc) measured in patients with normal QRS duration was found to be prolonged in 29%. At the time of the last follow up, half of the patients were on advanced therapy for pulmonary hypertension and 26 patients (16%) on antiarrhythmic therapy. At the time of data collection, 21 patients were deceased, of which 8 patients were documented to have had sudden death. Among the patients with sudden death, three patients had documented evidence of ventricular fibrillation.

There was documented evidence of arrhythmias in 28 patients (17%), with supraventricular tachycardia (SVT) accounting for more than half of the arrhythmias (Figure 1). Patients with arrhythmias were more likely to have complex congenital heart disease especially single ventricle physiology (Table 1); however, this was not statistically significant (Table 3). Patients with arrhythmias were significantly older ($P = .01$) compared to the entire study group. These patients were comparable to the entire group in several other demographic and clinical characteristics including saturation (Table 2), except for a negative association with Down syndrome and a positive association with AV valve regurgitation and prolonged QRS duration. Further subgroup analysis also revealed an association with increasing severity of AV valve regurgitation. Antiarrhythmic therapy use was associated with worse NYHA functional class (class III/IV, 13, 27% vs class I/II, 9, 11%; OR: 3.2, 95% CI: 1.2–8.1). There was a trend towards more arrhythmias in worse functional class, however this was not statistically significant.

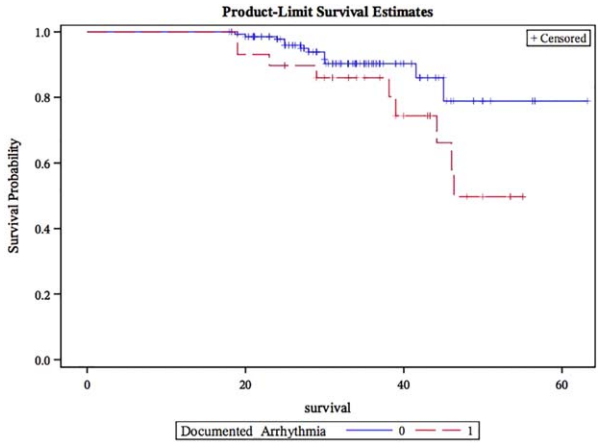
TABLE 3 Risk factors for arrhythmia, death from all causes and sudden death

Risk factors	Death from all causes: *P* value	Sudden death: *P*-value
Disease characteristics		
Complex CHD	.1	.48
Absence of Down syndrome	.04	.07
Clinical characteristics		
Functional class	.0003	.44
Congestive heart failure	.06	.14
Ventricular dysfunction	.76	.36
AV valve regurgitation	.29	.35
Severity AV valve regurgitation	.6	.18
Documented arrhythmia	.004	.03
Electrocardiographic parameters		
QRS duration	.84	.74
QRS > 110 msec	1	1
QTc duration	.25	.66
QTc > 440 msec	.43	.51
Medications		
DTT	.09	.28
Anti-arrhythmics	.005	.02

Abbreviations: AV, atrioventricular; CHD, congenital heart disease; DTT, disease targeting therapy.

Table 3 shows a summary of the association between arrhythmias, death from all causes and sudden death and various risk factors by bivariate analysis. While mortality was negatively associated with Down syndrome there was a positive association between death due to all cause and worse NYHA functional class (NYHA), history of arrhythmia and the need for antiarrhythmic therapy. Figure 2 illustrates the survival curve and the mortality risk for subjects with arrhythmias. The mean survival was 43 ± 0.6 years among patients without arrhythmia compared to 42 ± 1.5 years among those with arrhythmias. There was a trend towards early death in patients with arrhythmia, however this was not statistically significant ($P = .073$). Although there was a trend towards increased all-cause mortality among those with arrhythmias on antiarrhythmic therapy (10, 40%) compared to those with arrhythmias not on antiarrhythmic therapy (1, 10%), this was not statistically significant ($P = .2$, not shown in Table 3). Both documented arrhythmias and the need for antiarrhythmic medications were associated with sudden death. Subgroup analysis comparing supraventricular to ventricular arrhythmias did not reveal any statistically significant difference with respect to their association with sudden death. There was no specific difference on comparing isolated atrial fibrillation to other arrhythmias in regards to all-cause mortality and sudden death.

In logistic regression analysis, Down syndrome was negatively associated and AV valve regurgitation was positively associated with arrhythmia (Table 4, see Tables A1–A3 in Appendix for detailed statistical output). Both Downs syndrome and history of advanced pulmonary hypertension therapy were negatively associated with mortality and the need for antiarrhythmic therapy was positively associated with sudden death. Given the significant associations found with Down syndrome, characteristics of patients with Down syndrome was compared with those without Down syndrome. This revealed that



Age (Years)	No Arrhythmia	Arrhythmia
20	132	27
25	104	24
30	76	21
35	42	16
40	24	11
45	12	7
50	4	4
55	2	1

FIGURE 2 Survival analysis comparing patients with and without history of arrhythmias. The results of the survival analyses show a statistically nonsignificant (*P* value: .073) trend toward excess deaths in the arrhythmia patients as they age, compared to the patients without arrhythmia (N = 138)

patients with Down syndrome tended to be younger (mean age: 35 ± 7 years compared to mean age: 38 ± 9 years of the entire group) which was statistically significant ($P = .003$) and were less likely to be on antiarrhythmic therapy ($P < .0001$) and advanced pulmonary hypertension therapy ($P < .005$). Further details on the logistic regression analysis are provided in Appendix A.

4 | DISCUSSION

In this moderately large retrospective multi-center study of arrhythmia outcomes in ES patients, arrhythmias affected roughly a fifth of patients. These arrhythmias were predominantly supraventricular in origin (paroxysmal supraventricular tachycardia, atrial fibrillation, and atrial flutter) and were more prevalent in those with AV valve regurgitation while those with Down syndrome appeared relatively protected from arrhythmia. Arrhythmias were associated with all-cause mortality and sudden cardiac death.

Recent studies have challenged the previously and long held notion of decreased mortality risk associated with ES when compared to patients with other types of pulmonary hypertension.[6] Without advanced pulmonary hypertension therapies, the 10-year mortality has been reported to be 30% to as high as 70%.[6,7]Heart failure and sudden cardiac death emerge as the most common cause of death among patients with ES in recent studies. Though hemoptysis has been a significant cause of death in earlier studies it is now significantly less common and indeed in the recent German National Register study, it was not reported as an important cause of mortality.[1,4,7] This study also delineated other less common causes of death such as peri-operative mortality, infection, malignancy and pulmonary embolism.[7] Although sudden death has been identified as a significant contributor to the mortality and arrhythmias have been implicated in such mortality, studies focusing specifically on arrhythmia outcomes have been lacking.[2,7] The mean survival in the present series was 43 years with a trend towards worse survival in patients with arrhythmia. It is possible that with longer follow up time that this trend might represent a statistically significant association.

Daliento et al., studied 188 patients with ES retrospectively and reported arrhythmias in 23% of their patients based on routine ECGs and Holter reports.[2] The higher prevalence could be attributed to the inclusion of supraventricular ectopy which were not included in the present study. Similar to their study supraventricular arrhythmia was the most common type of arrhythmia in our group. In the present series atrioventricular valve regurgitation was associated with an increased risk of arrhythmia, presumably due to associated atrial enlargement and atrial myocardial stretch. There is limited information available on the genesis of arrhythmias in patients with ES. Semizel et al., found increased dispersion of repolarization and decreased heart rate variability among patients with ES.[8] Abnormal dispersion of repolarization as measured by QT dispersion has been related to ventricular inhomogeneity and was found by Semizel et al. to positively correlate with pulmonary-systemic resistance ratios.[9] It is plausible that abnormal myocardial hypertrophy and fibrosis in patients with ES might result in ventricular inhomogeneity which is likely to be arrhythmogenic. In fact recent studies by cardiac MRI have demonstrated myocardial fibrosis in patients with ES using late gadolinium enhancement.[10] Chronic cyanosis and abnormal pressure loading conditions in patients with Eisenmenger syndrome are thought to lead to abnormal myofibroblast activity and fibrosis.[10] Alterations in cardiac conduction and conduction blocks secondary to interstitial collagen deposition have been thought to induce arrhythmias and lead to sudden cardiac death.[11] More recently there has been interest in the role of fibroblast induced

TABLE 4 Statistically significant findings of logistic regression analysis

Any arrhythmia	1. Down syndrome, $P = .003$; odds ratio: 0.06 (CI: 0.01–0.28) 2. AV valve regurgitation, $P = .004$; odds ratio: 4.33 (CI:1.59–11.74)
Death from all causes	1. Down syndrome, $P = .03$; odds ratio: 0.3 (CI: 0.1–0.9) 2. DTT, $P = .03$; odds ratio: 0.31 (CI: 0.11–0.91)
Sudden death	1. Antiarrhythmic therapy, $P = .01$; odds ratio: 6.24 (CI: 1.45–26.88)

Abbreviations: AV, atrioventricular; CI, confidence interval; DTT, disease targeting therapy.

alterations in connexin hemichannels (connexons). These hemichannels are located and function at the cellular gap junctions, and thought to be another potential and potent arrhythmogenic factor.[12] The significant association with an older age and arrhythmias in our study could also be secondary increased presence of fibrosis, although future prospective studies are needed to validate this hypothesis.

The risk of arrhythmias seems to be low among patients with Down syndrome upon univariate and multivariate analysis. There could be several factors contributing to this. First, patients with Down syndrome were younger than the overall cohort, which might play a protective role against arrhythmias. Second, it is plausible that palpitations and other symptoms associated with arrhythmias might be less reported by patients with Down syndrome leading to decreased identification of arrhythmias in this population. Finally, one could speculate that the absence of an active lifestyle in some patients with Down syndrome could potentially cause less triggering of arrhythmias. Further studies are clearly needed to characterize the role of Down syndrome biology on the risk and consequences of arrhythmias in congenital heart disease.[13] Prolonged QRS duration was a risk factor for arrhythmia only by univariate analysis. Of the 49 patients with prolonged QRS duration, the majority (33 patients, 67%) had complex CHD. Diller et al., had also demonstrated a higher mortality risk for ES patients with prolonged QRS duration, presumably secondary to malignant arrhythmias.[5] QRS duration may be prolonged in the presence prior ventricular surgery, enlarged ventricles, and myocardial fibrosis. Prolonged QRS duration is a well-studied predictor of ventricular arrhythmias in patients with repaired tetralogy of Fallot, where its absolute duration as well as rate of progression has been demonstrated to mark greater ventricular tachycardia burden and sudden cardiac death risk.[14,15]

History of poor NYHA functional class, arrhythmia and the need for antiarrhythmic therapy were risk factors for mortality in this study, while Down syndrome appeared to provide survival benefit upon univariate analysis. In a previous study of 134 patients with ES, 44.8% had Down syndrome. In this cohort, survival in Down syndrome was not significantly different from those without Down syndrome.[5,17] We believe that the protective effects of Down syndrome in the present study, is likely to be confounded by the relatively younger age of Down syndrome patients in this dataset. The relationship between antiarrhythmic therapy and outcome in the present study may be a reflection of worse overall patient status as evident by its association with worse NYHA functional class.

Patients on advanced pulmonary hypertension therapy appeared to have lower all-cause mortality in the present study. These observations were substantiated in a number of prior studies[4,5] including the recent German national registry.[7,16] However, it is possible that patients on these medications might have received improved overall care and this is a potential confounder in multi-institutional studies. History of arrhythmia and the need for antiarrhythmic therapy predicted sudden death in the present series. These results are in accordance with data from a large series of 25,790 CHD subjects investigating sudden cardiac death.[18] In this study, of the 171 patients who had sudden death due to proven or presumed arrhythmia, 33 patients had Eisenmenger syndrome. When compared to matched controls without SCD, patients with ES who sustained SCD were more likely to be on antiarrhythmic therapy. Ventricular dysfunction, prolonged QRS duration, heart failure medications and heart failure symptoms were also associated with SCD in this study, which we did not observe in our patient cohort. As previously stated, the need for antiarrhythmic therapy might be a representation of an overall poor clinical status and could also indicate worse arrhythmia burden. Although lower oxygen saturation is a poor prognostic sign, this was not associated with all-cause mortality, sudden death or arrhythmias in this study.

5 | LIMITATIONS

The present study's results should be interpreted within the framework of the limitations of a retrospective study. Several biases were potentially introduced. The centers involved were tertiary referral centers, and hence the patients could represent the worse end of the spectrum of ES. The total number of patients was limited, and therefore the strength of statistical association was found lacking in some cases. The diagnosis of ES was based on clinical designation and assessment of the specialist adult congenital heart physician. The available data did not allow us to accurately determine the diagnostic modality used for diagnosing ES. It is possible that in the single ventricle group, or those with common mixing, that ES may have been over diagnosed. The duration and further characterization of arrhythmias such as PSVT was not available. The absence of information regarding the onset of arrhythmias, indication of antiarrhythmic therapy, interventions for arrhythmias such as ablation, specific antiarrhythmic medication and heart failure medication are limiting factors of this study. Six patients without documented arrhythmias were on antiarrhythmic therapy, this likely reflects inadequate data regarding arrhythmias in a minority of the patients. Finally sudden death was based on clinical documentation and not based on autopsy results.

6 | CONCLUSIONS

Supraventricular arrhythmias are common among patients with ES, specifically those with significant AV-valve regurgitation. The use of advanced therapy for pulmonary hypertension was advantageous in this cohort argues for greater and possibly earlier use of these therapies. Similarly the association between the presence of arrhythmia and greater mortality risk warrant careful evaluation, including hemodynamic and possible electrical evaluation to help with further risk stratification and to find targets of effective therapy. Future long term studies needs to specifically address the potential association between arrhythmias and all-cause mortality.

CONFLICTS OF INTEREST

There are no conflicts of interest or industry relationships to disclose

AUTHOR CONTRIBUTIONS

Data analysis/interpretation, statistics, drafting article, approval of article: Baskar

Concept/design, data collection, approval of article: Horne

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APPENDIX

TABLE A1 Logistic regression analysis of predictors of any arrhythmia

Predictor	β	SE	*P*	Odds ratio	CI	Model AUC
Intercept	2.3	0.4	<.0001			.82
Down syndrome	−1.4	0.39	.0003	0.061	(0.01, 0.28)	
AV valve regurgitation	0.73	0.38	.004	4.3	(1.6, 11.7)	

AV, atrioventricular.

TABLE A2 Logistic regression analysis of predictors of death from all causes

Predictor	β	SE	*P*	Odds ratio	CI	Model AUC
Intercept	2.2	0.34	<.0001			0.68
Down syndrome	−0.6	0.28	.03	0.30	(0.10, 0.90)	
DTT	−0.58	0.271	.004	0.31	(0.11, 0.91)	

TABLE A3 Logistic regression analysis of predictors of sudden death

Predictor	β	SE	*P*	Odds ratio	CI	Model AUC
Intercept	2.6	0.4	<.0001			0.68
Antiarrhythmic therapy	0.92	0.37	.014	0.061	(1.4, 26.9)	