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Outcomes in adults with congenital heart disease and heterotaxy syndrome: A single-center experience

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Abstract

Background: Heterotaxy syndrome (HS) is a condition in which the thoracoabdominal organs demonstrate an abnormal lateral arrangement and is often associated with congenital heart disease (CHD). Little is known about the adult HS population with CHD.

Objective: To describe the outcomes and sociodemographics of the adult CHD population with HS.

Methods: Records of patients 18 years of age or older with diagnoses of both CHD and HS at Texas Children's Hospital from 1964 to 2018 were reviewed.

Results: Sixty-two patients met inclusion criteria. Median age was 22.7 [IQR 19.6-30.0] years; 26 (42%) were female; and 13 (21%) of patients had a gap in care of >3 years. Median follow-up time in adulthood was 2.9 [IQR 1.3-8.2] years. Forty-three (69%) of patients had single ventricle heart disease, 31 (71%) of whom completed Fontan circulation. A total of 36 interventions occurred in 24 patients which included 16 cardiac catherization interventions, 13 electrophysiology-related procedures, and 18 surgical procedures including 2 orthotopic heart transplants. The median age for death or heart transplant was 45.3 (95%CI 34.3-56.1) years. Heart failure-free survival was 80.8 ± 5.2%, 58.7 ± 11.0%, and 31.1 ± 15.7% at 20, 30, and 40 years old, respectively. Cerebrovascular accident-free survival was 84.3 ± 5.1%, 54.2 ± 11.3%, and 40.6 ± 14.5% at 20, 30, and 40 years old, respectively. Tachyarrhythmia-free survival was 54.0 ± 7.1%, 29.2 ± 8.3%, and 19.5 ± 9.7% at 20, 30, and 40 years old and bradyarrhythmia-free survival was 66.0 ± 6.3%, 41.7 ± 9.4%, and 33.4 ± 10.6% at ages 20, 30, and 40 years, respectively.

Conclusions: At a tertiary referral center, adult patients with CHD and HS have high rates of comorbidities and early death or heart transplant. Longitudinal surveillance and further exploration into factors associated with improved survival in this population are warranted.

KEYWORDS

adult congenital heart disease, asplenia, Fontan circulation, heterotaxy syndrome, isomerism, polysplenia, single ventricle

Abbreviations: ACHD, adult congenital heart disease; CHD, congenital heart disease; CVA, cerebrovascular accident; HF, heart failure; HS, heterotaxy syndrome; HS-AS, heterotaxy syndrome with asplenia; HS-PS, heterotaxy syndrome with polysplenia; ICD, implantable cardioverter-defibrillator; OHT, orthotopic heart transplant; PLE, protein-losing enteropathy; PM, pacemaker.

1 | INTRODUCTION

Heterotaxy syndrome (HS) is a condition in which the thoracoabdominal organs demonstrate abnormal lateral arrangement and is frequently associated with complex congenital heart disease (CHD). Cardiovascular comorbidities are high and mortality in early childhood is estimated at ~10% or more, even in the current era.[1-4] Fortunately, the evolution of surgical techniques and perioperative care has enabled patients born with CHD and HS to survive into adulthood.[3,5]

Adult congenital heart disease (ACHD) patients now outnumber children with CHD, and complex ACHD is one of the most rapidly growing subpopulations.[6] Data regarding sociodemographic distributions and clinical outcomes in adult patients with CHD and HS have not been previously reported, leaving clinicians to rely on inferences from pediatric data, experience with similar adult physiologies, and anecdotal experience when managing these patients. Therefore, we sought to describe the sociodemographic profiles and clinical outcomes of the ACHD population with HS.

2 | METHODS

This study was approved by the Baylor College of Medicine Institutional Review Board. We performed a retrospective chart review of patients at Texas Children's Hospital between 1964 and 2018. Inclusion criteria included: age 18 years or older at time of any encounter within the date range, diagnoses of both HS (as previously defined[7]) and CHD. Exclusion criteria included: patients with situs inversus totalis or without thoracoabdominal laterality defect and patients with patent foramen ovale as the only cardiac diagnosis without abnormal cardiac rhythm. Beyond thoracoabdominal laterality defects, HS was further categorized based on splenic anatomy. Bronchial, atrial appendage, abdominal, and/or situs were determined based on cross-sectional imaging (computed tomography or magnetic resonance imaging), operative reports, or abdominal ultrasound in the case of splenic anatomy. Beyond HS and cardiac anatomy, collected clinical data included time of last follow-up, death or heart transplant, interventions and age at interventions and comorbid conditions including heart failure (HF), cerebrovascular accidents (CVAs), and arrhythmias. Clinical diagnosis and evidence of disease process was necessary for inclusion for comorbid medical conditions. Collected sociodemographic data included age, sex, race/ethnicity, educational and job attainment, marital status, parental status, and insurance status as available in the medical record. The date on which a comorbid condition was first diagnosed was recorded as the time of onset. Patients were considered lost to follow-up (LTFU) if they were not seen in our medical system for ≥3 years.

2.1 | Patient outcome characteristics

2.1.1 | Cardiac

Patients were defined as having HF if the diagnosis was assigned by the primary cardiologist or critical care attending in conjunction with evidence of ventricular dysfunction on imaging studies and/or the patient was prescribed HF medications. A diagnosis of pulmonary vein obstruction was confirmed by cardiac catheterization or cross-sectional imaging. Patients were defined as having cyanosis if they received the diagnosis from their primary cardiologist and had oxygen saturations of ≤ 90% in an otherwise stable state of health.

Patients were defined as having a tachyarrhythmia or bradyarrhythmia if given a diagnosis by their primary cardiologist or critical care attending and had confirmatory electrocardiographic studies. Tachyarrhythmias included atrial arrhythmias including supraventricular tachycardia, ectopic atrial tachycardia, intra-atrial re-entrant tachycardia, and atrial flutter/fibrillation. Additionally, nonsustained and sustained ventricular tachycardias were included in the tachyarrhythmia group. Bradyarrhythmias included symptomatic sinus bradycardia, atrioventricular block, and sinus node dysfunction which received a pacemaker (PM). For arrhythmia survival analysis, arrhythmia burden was considered only at time of onset of first arrhythmia type; cumulative arrhythmia burden was not factored into analysis.

2.1.2 | Noncardiac

Patients were defined as having pulmonary hypertension if the diagnosis was assigned by the primary cardiologist/critical care attending in conjunction with a documented mean pulmonary artery pressure ≥25 mm Hg on cardiac catheterization. Patients were defined as having a CVA if they presented with clinical stroke-like symptoms and had confirmatory brain imaging studies or received a diagnosis of transient ischemic attack by a neurologist.

2.1.3 | Imaging confirmation

Data from transthoracic echocardiograms, transesophageal echocardiograms, and cardiac magnetic resonance imaging demonstrating systolic ventricular function and atrioventricular valve and semilunar valve regurgitation were included if these studies were performed within 3 months of last cardiac follow-up. Data regarding renal and hepatic function were very limited in the medical record and were therefore not included.

2.2 | Data analysis

Statistical analyses were performed with SPSS (SPSS Inc, Chicago, IL) software or SAS software, version 9.4 (SAS Institute Inc, Cary, NC, USA). Data were reported as frequency (n) with proportion (%), or median with interquartile range (IQR, 25th-75th percentile). A denominator was reported in instances where limitations in the dataset prevented description of the entire cohort. Continuous variables were compared using Student's t test for normally distributed data or Wilcoxon rank-sum for data for nonnormally distributed data. Statistical analysis included survival analysis by Kaplan-Meier curves and univariate Cox regression models with time-dependent covariates; orthotopic heart transplant (OHT) was considered a

TABLE 1 Anatomy by heterotaxy classification in adults with congenital heart disease

	Polysplenia n (%)	Asplenia n (%)	NOS n (%)
Splenic anatomy	18 (29.0)	29 (46.8)	15 (24.2)
Atrial anatomy			
LA Isomerism	5 (83.3)	1 (9.1)	3 (33.3)
RA Isomerism	0 (0)	5 (45.5)	3 (33.3)
Usual	1 (16.7)	1 (9.1)	2 (22.2)
Mirror image	0 (0)	3 (27.2)	1 (11.1)
Ambiguous	0 (0)	1(9.1)	0 (0)
Bronchial Anatomy			
Bilateral hyparterial	6 (75.0)	0 (0)	3 (75.0)
Bilateral eparterial	0 (0)	10 (71.4)	0 (0)
Usual	1 (12.5)	2 (14.3)	0(0)
Mirror image	1 (12.5)	2 (14.3)	1 (25.0)
Right sided stomach	11 (61.1)	14 (56.0)	5 (33.3)
Dextro or mesocardia	5 (27.8)	4 (14.3)	8 (53.3)
Cardiac anatomy			
AVSD	12 (66.7)	21 (72.4)	10 (66.7)
VSD and/or ASD	4 (22.2)	3 (10.3)	4 (26.7)
Mitral atresia	0 (0)	3 (10.3)	0 (0)
DILV	1 (5.6)	1 (3.4)	1 (6.7)
Tricuspid atresia	0 (0)	1 (3.4)	0 (0)
Parachute mitral valve	1 (5.6)	0 (0)	0 (0)
Ventricular status			
Single V	10 (55.6)	26 (90.0)	7 (46.7)
BiV	8 (44.4)	3 (10.0)	7 (46.7)
1.5 V	0 (0)	0 (0)	1 (6.7)
Ventricular dominance			
LV	10 (58.8)	5 (17.2)	9 (60.0)
RV	4 (23.5)	16 (55.2)	1 (6.7)
No dominant	1 (5.9)	5 (17.2)	3 (20.0)
Unknown	2 (11.8)	3 (10.3)	2 (13.3)
TAPVR	1 (5.9)	11 (37.9)	3 (21.4)
Pulmonary outflow tract obstruction	10 (55.6)	28 (96.6)	7 (46.7)
Systemic outflow tract obstruction	3 (16.7)	0 (0)	2 (13.3)

Abbreviations: ASD, atrial septal defect; AVSD, atrioventricular septal defect; DILV, double-inlet left ventricle; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TAPVR, total anomalous pulmonary venous return; V, ventricle; VSD, ventricular septal defect.

nonsurvival event. Proportions for categorical variables were compared using chi-square test. Statistical significance was defined as *P* value ≤.05.

3 | RESULTS

3.1 | Heterotaxy classification

Among the 62 patients who met inclusion criteria for the study, 18 (29.0%) had heterotaxy syndrome with polysplenia (HS-PS) and 29 (46.7%) patients had heterotaxy syndrome with asplenia (HS-AS). Of the remaining patients, 6 (9.7%) had a single, morphologically normal spleen and the other 9 (14.5%) patients had inadequate imaging to define the splenic anatomy; therefore, these patients were categorized in the heterotaxy syndrome not otherwise specified group. The anatomical characteristics of adult patients with HS are listed in Table 1. The segmental anatomy patterns seen in the cohort were varied (Figure S1).

3.2 | Sociodemographics

The sociodemographic characteristics of the patient cohort are seen in Table 2. The racial/ethnic makeup is reflective of the local community served by our center. Documentation was inadequate to

TABLE 2 Sociodemographics of adults with congenital heart disease and heterotaxy syndrome

Characteristics	Median [IQR], n (%)
Age (yrs)	22.7 [19.6-30.0], n = 62
Sex (Female)	26 (41.9)
Status	
Alive	37 (60.0)
Dead or Heart transplant	12 (19.3)
Lost to follow-up	13 (21.0)
Follow-up time after 18 years of age (yrs)	2.9 [1.3-8.2]
Age at death or heart transplant	28.8 [21.0-35.9], n = 12
Race/ethnicity	
Non-Hispanic White	29 (48.3)
Non-Hispanic Black	7 (11.7)
Hispanic	24 (40.0)
Other/unknown	2 (3.2)
Did not complete high school	5/43 (11.6)
Bachelor's degree or higher level of education in patients 24 yrs of age or older	11/17 (64.7)
Job or attending school	36/41 (87.8)
Married	14/53 (26.4)
Had child(ren)	4/49 (8.2)
Any smoking (tobacco)	3/49 (6.1)
Any drug use	3/39 (7.7)
Insurance status	
None	7/52 (11.3)
Public insurance	16/52 (24.2)
Private insurance	29/52 (46.8)

quantify alcohol intake, but no patients had a diagnosis of alcoholism. Three men fathered children and one woman with HS-AS and Fontan circulation successfully carried a pregnancy to term; no offspring were noted to have CHD or HS.

3.3 | Clinical profile

The clinical characteristics of adults with CHD and HS at last clinic visit are depicted in Table 3. No genetic test results were found in our patient population. There was no evidence of volvulus occurring in adulthood for any patient.

3.3.1 | Interventions

A total of 36 interventions occurred in 24 patients after age 18. There were 16 interventions in the cardiac catherization laboratory at a median age of 24.5 [IQR 21.1-28.1] years including: angioplasty or stenting of an artery or vein (n = 7), device or coil placement to occlude a shunt or collateral (n = 5), pericardiocentesis (n = 2), catheter-mediated thrombolysis (n = 1), and Fontan fenestration creation (n = 1). There were 13 electrophysiology related procedures at a median age of 22.3 [IQR 20.2-29.5] years including: radiofrequency ablation (n = 4), lead placement and PM upgrade to a pacemaker/implantable cardioverter-defibrillator (PM-ICD) (n = 1), and pulse generator changes (n = 8). There were 18 surgical procedures other than sternal wire removal/revision at a median age of 22.6 [IQR 20.5-27.0] years. The surgical procedures included: epicardial PM/PM-ICD placement (separate from Fontan conversion procedure) or surgical lead revision (n = 6), pulmonary artery plication or augmentation (n = 2), Maze procedure (separate from Fontan conversion procedure) (n = 1), systemic atrioventricular valve replacement (n = 2), placement of a descending aorta to pulmonary artery anastomosis (Potts shunt) (n = 1), Fontan conversion procedure (n = 2), single-stage Fontan circulation completion (n = 1), Kawashima procedure (n = 1), and OHT (n = 2).

3.3.2 | Single ventricles

Of the 43 patients with single ventricle CHD, 71% received Fontan circulation completion. One patient had protein-losing enteropathy (PLE); no patients had plastic bronchitis. Among single ventricle patients not palliated to Fontan circulation, palliative procedures included Blalock-Taussig shunt (n = 3), central (aorta to pulmonary) shunt (n = 1), direct anastomosis of pulmonary artery to ascending aorta (Waterston shunt) (n = 2), pulmonary artery band and Blalock-Taussig shunt (n = 1), superior cavopulmonary anastomosis with bidirectional Glenn (n = 2) and Kawashima (n = 1), and no surgical intervention (n = 2).

3.3.3 | Mortality or cardiac transplant

Pretransplant mortality occurred in 10 patients. Among the patients who died, the causes of death were: postoperative complications after surgery (n = 1), HF (n = 3), sudden cardiac death (n = 2), complications from PLE (n = 1), complications from a massive CVA (n = 1), and unknown cause (n = 2). No patients received a durable, implantable mechanical circulatory support device. Two patients underwent OHT at ages 20 and 22 years old; one patient died 1 day after his transplant due to postoperative complications and the other patient survived his transplant and was transferred to an adult institution for post-OHT management. The age of transplant-free survival was 45.3 (95%CI 34.3-56.1) years, with overall transplant-free survival of 98.1 ± 1.9%, 83.5 ± 6.5%, and 54.2 ± 13.1% at ages 20, 30, and 40s years, respectively (Figure 1). Among all anatomic and demographic factors, only cardiac systemic outflow obstruction neared a transplant-free survival disadvantage (Log-rank P = .06). Ventricular status and HS type were not associated with a survival disadvantage (Log-rank P = .32 (Figure S2) and Log-rank P = .61 (Figure S3), respectively). A diagnosis of pulmonary hypertension was not associated with transplant-free survival in adulthood (HR 1.20, 95%CI 0.31-4.73, P value =.790). The study was underpowered to adequately assess the effect of pulmonary vein obstruction on survival.

TABLE 3 Clinical profile of adults with congenital heart disease and heterotaxy syndrome

Characteristics	Median [IQR], n (%)
BMI	22.5 [19.4-26.7], n = 61
Obese (BMI > 30)	10/61 (16.4)
Underweight (BMI ≤ 18.5)	11/61 (18.0)
Completed Fontan circulation (Percentage of single ventricles to complete FC)	31 (50.0)/(72.1)
Age at Fontan completion (years)	9.0 [4.0-14.7], n = 31
Arrhythmias	
None	18/58 (31.0)
Tachyarrhythmia (atrial or ventricular)	17/58 (29.3)
Bradyarrhythmia	8/58 (13.8)
Both	15/58 (25.9)
Pacemaker (PM)	24 (39.3)
Age at PM implantation (years)	6.6 [0.5-21.6], n = 23
Heart failure	17/57 (29.8)
Pulmonary hypertension	7/55 (12.7)
Pulmonary vein obstruction	4/56 (7.1)
Cerebrovascular accident	13/58 (22.4)
Cyanosis	14/56 (25.0)
Protein losing enteropathy	1/59 (1.7)
Findings on imaging studies	
> mild systemic AV valve regurgitation	16/54 (29.6)
> mild systemic ventricular systolic dysfunction	16/54 (29.6)
> mild aortic valve regurgitation	1/54 (1.8)
Medication use	
Diuretic	20/59 (33.9)
Betablocker (including carvedilol)	17/59 (28.8)
Other antiarrhythmic	16/59 (27.1)
Digoxin	14/59 (23.7)
ACE-I/ARB	37/59 (61.7)
Aspirin	33/59 (55.0)
Anticoagulation	10/59 (16.9)
Pulmonary hypertension medicine	3/59 (5.1)
Psychiatric medication	10/59 (16.9)
Regular antibiotic prophylaxis	28/59 (47.5)

3.3.4 | Heart failure

HF was diagnosed in 17/57 (29.8%) patients, and 7 had the diagnosis at or before the age of 18 years old. Among patients with HF, 6 (35.3%) had Fontan circulation. Adults with CHD and HS with HF present at age 18 were more likely to die or receive OHT with time to outcome of 2.6 (95%CI 1.9-3.3) years vs 17.3 (95%CI 13.5-21.1) years (Log-rank $P < .001$). A diagnosis of HF was associated with a survival disadvantage (HR 17.57, 95%CI 3.59-87.9, P value <.001). The median age of HF-free survival for the entire cohort was 32.6 (95%CI 27.0-38.1) years, with HF-free survival of 80.8 ± 5.2%, 58.7 ± 11.0%, and 31.1 ± 15.7% at ages 20, 30, and 40 years, respectively (Figure 2).

3.3.5 | Arrhythmias

At age 18, 24/52 (46.2%) had no arrhythmia, 13/52 (25%) had tachyarrhythmia, 9/52 (17.3%) had bradyarrhythmia, and 6/52 (11.5%) had both a tachyarrhythmia and bradyarrhythmia burden.

Bradyarrhythmias

Thirteen of 58 (22.4%) patients had sinus node dysfunction and 6/58 (10.3%) patients had atrioventricular block requiring PM therapy. Presence of bradyarrhythmia was not associated with a transplant-free survival disadvantage compared to no arrhythmia (HR 1.52, 95%CI 0.43-5.40, P value =.516). The age of bradyarrhythmia-free survival was 28.1 (95%CI 19.3-36.8) years, with bradyarrhythmia-free

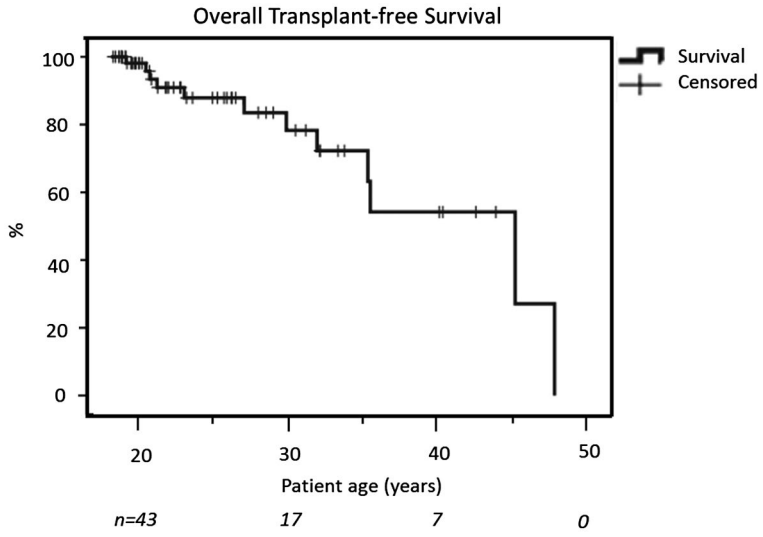

FIGURE 1 Kaplan-Meier analysis of transplant-free survival in adults with congenital heart disease and heterotaxy syndrome

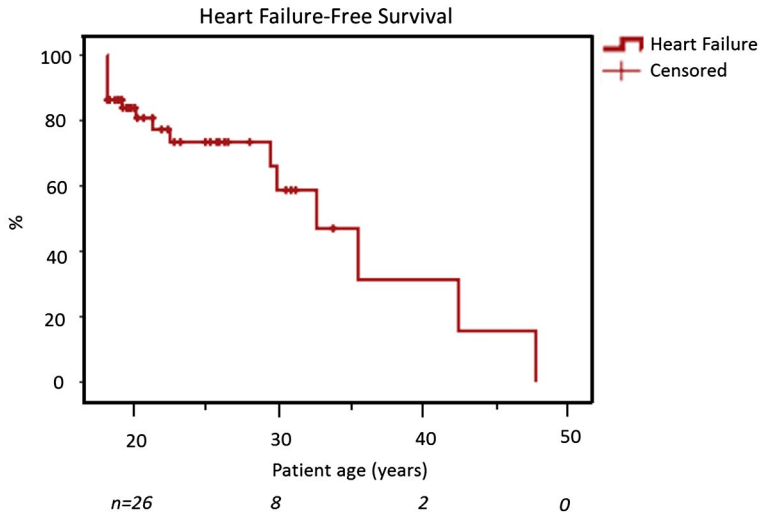

FIGURE 2 Kaplan-Meier analysis of heart failure-free survival

survival of 66.0 ± 6.3%, 41.7 ± 9.4%, and 33.4 ± 10.6% at ages 20, 30, and 40 years, respectively (Figure 3).

Tachyarrhythmias

Eleven of 58 (19.0%) patients had sustained or nonsustained ventricular tachycardia, 20/58 (34.5%) patients had atrial fibrillation or intra-atrial reentrant tachycardia, and 14/58 (24.1%) patients had supraventricular tachycardia with some patients experiencing more than one type of tachyarrhythmia. Patients with tachyarrhythmia had a survival disadvantage (HR 6.48, 95%CI 1.41-29.75, *P* value =.016). The median age of tachyarrhythmia-free survival was 21.2 (95%CI 18-26.1) years, with tachyarrhythmia-free survival of 54.0 ± 7.1%, 29.2 ± 8.3%, and 19.5 ± 9.7% at ages 20, 30, and 40 years, respectively (Figure 3).

Bradyarrhythmias or tachyarrhythmias

The presence of a bradyarrhythmia or tachyarrhythmia arrhythmia at age 18 was not associated with a survival disadvantage (Log-rank *P* = .595). There was no difference in survival when comparing bradyarrhythmia to tachyarrhythmia (Log-rank *P* = .421). Survival analysis for patients with both tachyarrhythmias and bradyarrhythmias was not performed due to the variable onset of bradyarrhythmias and tachyarrhythmias in each patient.

3.3.6 | Cerebrovascular accidents

CVAs occurred in 13/58 (22.4%) patients, with 7 patients experiencing a CVA before the age 18 years old. A history of CVA before the age 18 years trended toward a survival disadvantage (Log-rank *P* = .06). A diagnosis of CVA in adulthood was associated with a transplant-free survival disadvantage (HR 7.97, 95%CI 1.93-32.99, *P* value =.004). The median age of CVA-free survival for the entire cohort was 33.5 (95% CI 26.1-40.8) years, with CVA-free survival of 84.3 ± 5.1%, 54.2 ± 11.3%, and 40.6 ± 14.5% at ages 20, 30, and 40 years, respectively (Figure 4).

3.3.7 | Era effect

Era effect of the cohort was compared by partitioning patients based on date of birth; the 20 patients born before 1/1/1985 were considered "early era" and compared to the 42 patients born on or after

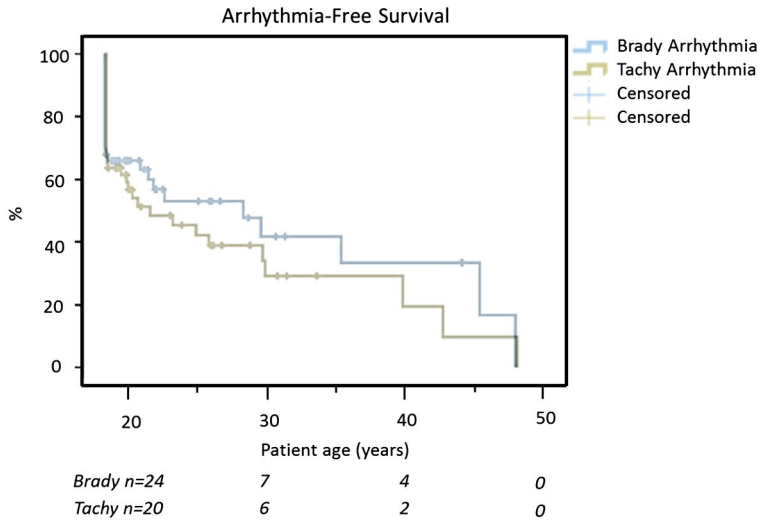

FIGURE 3 Kaplan-Meier analysis of tachyarrhythmia-free and bradyarrhythmia-free survival

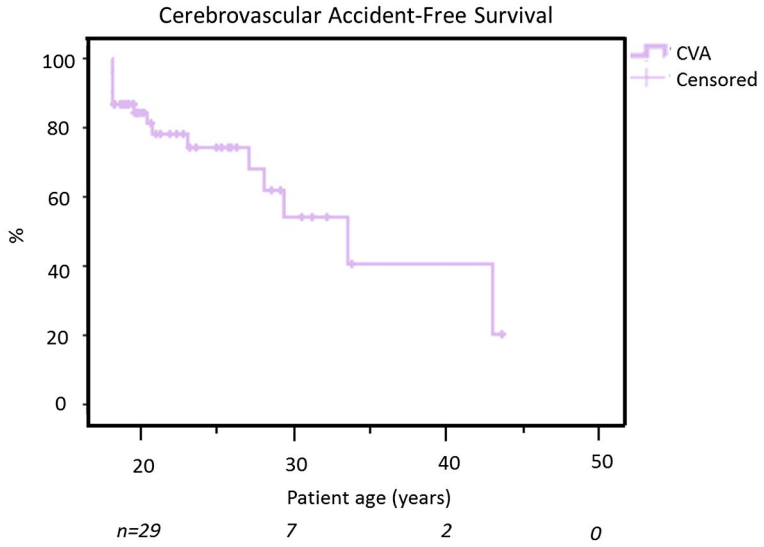

FIGURE 4 Kaplan-Meier analysis of cerebrovascular accident-free survival

1/1/1985 who were considered "late era." Race/ethnicity differed with late era having a higher composition of Hispanic patients (50% compared to 15%, P = .024). Age at first intervention (excluding PM) was different between groups (P = .004). In the early era group, first intervention was performed between birth and 1 year of age in 56.3%, between years of age 1-13 in 18.8% and after age 13 in 25.0%. In the late era group, first intervention was performed between birth and 1 year of age in 75.6%, between years of age 1-13 in 24.3% and after age 13 in 0.0%. Compared to the early era, late era patients had earlier median age (years) of Fontan completion (6.3 vs 15.0, P = .002) and PM implantation (4.6 vs 22.7, P = .027). There were no significant differences in other factors including anatomy, percentage of patients completing Fontan circulation or receiving a PM. There was no era-dependent association with transplant-free survival (Log-rank P = .847).

4 | DISCUSSION

To our knowledge, this is the first study to examine the clinical outcomes and sociodemographic characteristics in adults with CHD and HS. The results demonstrate these patients have a heavy burden of complex CHD and cardiac comorbidities and are at risk for early death or OHT. Over one third of patients in this complex patient population required at least one procedure after 18 years of age. Despite significant cardiac disease, adults with CHD and HS are able to accomplish many important life milestones including obtaining higher education, full-time employment, marriage, and becoming parents.

HSs are often discussed in terms of isomerism, a situation in which paired structures on opposite sides of the left-right axes of the body are symmetrical mirror images of each other.[7] In general, right isomerism is analogous to HS-AS syndrome and left isomerism is analogous to HS-PS. However, perhaps >20% of patients with HS will possess discordant findings which can confound categorization into either right or left isomerism.[8] There are ongoing debates and controversies regarding the concept of isomerism and how to describe cases with an abnormal arrangement of the body organs.[7,9,10] In this study, patients were categorized by splenic anatomy (absent, multiple or singular with normal morphology) because data on atrial morphology were unavailable on most patients.

Given what is known about HS and severity of disease in the pediatric literature, it may not be surprising that the data from this study suggest the adult cohort has a difficult cardiovascular outlook with a median survival for adults with CHD and HS of only ~54% at 40 years of age. Our cohort had a heavy burden of single ventricle heart disease, the majority of whom were palliated to Fontan circulation. Some studies of patients with Fontan circulation have shown patients with HS are at higher risk for poor outcomes compared to those without.[3,11] The burden of clinically apparent lymphatic dysfunction was low in this study: no patients had plastic bronchitis, and only one had PLE. The single patient with PLE in this study received the diagnosis in childhood which reinforces similar previous findings that susceptible patients will generally present in childhood.[11]

An interesting finding was that no congenital anatomic factors (Table 1), including ventricular status and HS type, were associated with decreased survival. Additionally, in the pediatric literature, patients with HS-PS tend to have better outcomes compared to those with HS-AS.[5] A potential confounder is that patients with particularly difficult anatomic substrates may be auto-selected out of this adult-only study cohort. The data show an overall heavy burden of cardiovascular co-morbidities with few differences between different anatomic factors. The relatively even distribution of cyanosis, HF, arrhythmia, and CVA regardless of ventricular status or HS type may help to explain our findings. An in-depth analysis of single ventricle HS patients (including evaluation for multiorgan dysfunction) was not within the scope of the present study but remains an important area of research.

Unsurprisingly, a diagnosis HF was associated with a worse prognosis for adult patients with CHD and HS. The high proportion of patients with an early onset (over 40% by age 30 years) of HF in this group is concerning. The dearth of utilization of advanced HF services for adult HS population is likely multifactorial including disease and anatomy complexity, unanticipated early demise, and unfamiliarity with anatomy and technically difficult operations. Much work remains in this important domain and patients with HS deserve a special focus.

The arrhythmia burden for patients with HS is well described in the pediatric literature[12]; this is the first study to describe the prevalence of arrhythmias in adult patients with HS. The majority of patients had a tachyarrhythmia and/or bradyarrhythmia by age 30 years and nearly all patients developed tachyarrhythmia before 50 years of age and the presence of tachyarrhythmia. Tachyarrhythmia may be an indicator of worsening atrioventricular valve or ventricular function and may warrant further clinical investigation.

In this study, over one fifth of adults with CHD and HS experienced a clinically significant CVA by the time of their most recent follow-up. Though some patients had a CVA in childhood, a significant proportion had an event after age 18. The etiology of CVA is likely multifactorial as most patients have known risk factors including surgical interventions, ventricular dysfunction, arrhythmias, and right to left shunts. Given that we were looking at associations between HS and comorbidities, we did not investigate the relationship between CVA and arrhythmia in this study. The subject of CVA prevention is an important area of investigation for the care of adults with CHD; further investigation in the HS and other cohorts are important future directions for research.[13]

The improvement in care through the decades for patients with CHD has allowed even the most anatomically complex to survive childhood. Because the advances in care for CHD have been iterative, the differences seen when comparing "era effect" of the HS cohort are probably expected. The results demonstrate a higher rate of first intervention in the neonatal period in patients born after 1985 which is very likely due to the improvement in early diagnosis, neonatal management, and additional technical capabilities available to surgeons and interventionalists. Ongoing surveillance and study of adult patients with CHD and HS is essential because interventions in childhood allow survival but, as demonstrated in this study, patients are burdened with residual lesions and important cardiovascular comorbidities.

Patients with HS are thought to be functionally asplenic and therefore at risk for infection. The study was not designed to evaluate vaccination status and history of medication use, including antibiotics but no deaths were known to be related to sepsis or meningitis. Evaluation of the frequency of hospitalization and outcomes related to bacterial infections in adult patients with HS is warranted. Another frequently encountered dilemma in the pediatric patient with HS is the issue of intestinal malrotation.[14,15] No patients had evidence of developing volvulus in adulthood; this study was not designed to evaluate the role of prophylactic Ladd's procedure in this patient population, but this could be a fruitful avenue for a future research direction.

Though the comorbidity burden and mortality are significant in the adult HS population with CHD, these patients often achieve important life goals. The majority of patients achieved a 4-year college degree which exceeds the educational attainment of the general US population.[16] This may be surprising given the known neurodevelopmental issues in patients with complex CHD.[17] Nearly all patients possessed a full-time job and most had health insurance. A large portion of patients were married, and some became parents with no known CHD in the offspring. These intelligent and productive patients will require guidance from their primary cardiologist on cardiovascular disease status and monitoring as well as appropriately set expectations given the difficult long-term outlook for this cohort. It is our hope that outcomes in adults with CHD and HS will benefit from the continued strive for improvement in perioperative management, increased availability of ventricular assist devices and other advanced HF services, as well as enhanced awareness of the need for lifelong care.

5 | LIMITATIONS

This study was limited by the retrospective nature of data acquisition. An inherent selection bias may be present in our results as we only studied patients who survived until age 18 or had disease significant enough to require referral to our center. Our results are

limited by number of patients included in this study and variable follow-up. Several patient data sets were incomplete with some study variables unavailable for analysis. All survival analysis was limited to univariate analysis due to the lack of comprehensive outcomes in this small data set. Further, the statistical analysis presented in the paper should be interpreted in the context of the aforementioned limitations; the limited patient numbers and variable follow-up may contribute less sensitivity and may not detect differences that may exist should a larger cohort with longer and more consistent follow-up be studied. Similarly, hazard ratios may be exaggerated, and it should be noted all have wide confidence intervals.

Patients may have shorter time to outcome than expected due to the nature of our tertiary care referral center; likely patients may not be referred until after they develop comorbid conditions, possibility at advanced stages. Further, patients may be less likely to follow-up if they are asymptomatic which may contribute to the acuity of the studied cohort. This study may overestimate the percentage of patients with ACHD and HS with health insurance because, in general, clinic follow-up is facilitated by having health insurance. Difficulties in obtaining insurance may account for the high rates of patients who were LTFU, as patients who are uninsured may not have been seen in our system. Because insurance is often obtained from employers, the percentage of patients who had a full-time job may also be overestimated for similar reasons. Furthermore, the demographics for educational level achieved may be similarly skewed because a higher level of education may facilitate employment with healthcare benefits. Larger, multi-institutional studies are warranted to confirm the findings in this manuscript.

6 | CONCLUSION

This is the first study to examine outcomes in adults with CHD and HS. This cohort has a heavy burden of complex CHD and comorbidities, with patients at risk for early death or OHT regardless of congenital anatomy, HS type, or surgical palliation pathway. Factors associated with a lower transplant-free survival, by univariate analysis, include HF, CVA, and tachyarrhythmia. Cardiac transplantation was uncommon in this population. Longitudinal surveillance and further exploration into factors associated survival in adults with CHD and HS is warranted.

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AUTHOR CONTRIBUTIONS

Christopher R. Broda: design, data analysis, drafting article, and statistics. Katherine B. Salciccioli: data analysis and critical review. Keila N. Lopez: data analysis, statistics, and critical review. Peter R. Ermis: data analysis and critical review. Douglas S. Moodie: concept, data analysis, and critical review. Heather A. Dickerson: concept, data analysis, and critical review.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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