Long-term survival and center volume for functionally single-ventricle congenital heart disease in England and Wales

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Kate L. Brown, MPH, MD,[a] Qi Huang, PhD,[b] Elena Hadjicosta, PhD,[b] Anna N. Seale, MD, MRCP,[c] Victor Tsang, FRCS,[a] David Anderson, FRCS,[d] David Barron, MD, FRCS,[c] Hannah Bellsham-Revell, MD,[d] Christina Pagel, PhD,[b] Sonya Crowe, PhD,[b] Ferran Espuny-Pujol, PhD,[b] Rodney Franklin, MD, FRCP,[e] and Deborah Ridout, MSc[f]

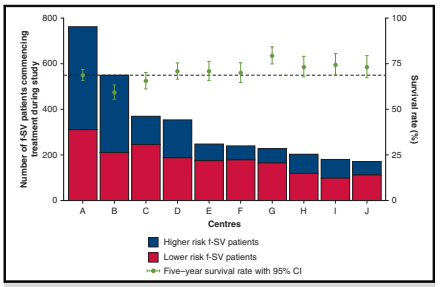
ABSTRACT

Objectives: Long-term survival is an important metric for health care evaluation, especially in functionally single-ventricle (f-SV) congenital heart disease (CHD). This study's aim was to evaluate the relationship between center volume and long-term survival in f-SV CHD within the centralized health care service of England and Wales.

Methods: This was a retrospective cohort study of children born with f-SV CHD between 2000 and 2018, using the national CHD procedure registry, with survival ascertained in 2020.

Results: Of 56,039 patients, 3293 (5.9%) had f-SV CHD. Median age at first intervention was 7 days (interquartile range [IQR], 4, 27), and median follow-up time was 7.6 years (IQR, 1.0, 13.3). The largest diagnostic subcategories were hypoplastic left heart syndrome, 1276 (38.8%); tricuspid atresia, 440 (13.4%); and double-inlet left ventricle, 322 (9.8%). The survival rate at 1 year and 5 years was 76.8% (95% confidence interval [CI], 75.3%-78.2%) and 72.1% (95% CI, 70.6%-73.7%), respectively. The unadjusted hazard ratio for each 5 additional patients with f-SV starting treatment per center per year was 1.04 (95% CI, 1.02-1.06), $P < .001$. However, after adjustment for significant risk factors (diagnostic subcategory; antenatal diagnosis; younger age, low weight, acquired comorbidity, increased severity of illness at first procedure), the hazard ratio for f-SV center volume was 1.01 (95% CI, 0.99-1.04) $P = .28$. There was strong evidence that patients with more complex f-SV (hypoplastic left heart syndrome, Norwood pathway) were treated at centers with greater f-SV case volume ($P < .001$).

Conclusions: After adjustment for case mix, there was no evidence that f-SV center volume was linked to longer-term survival in the centralized health service provided by the 10 children's cardiac centers in England and Wales. (J Thorac Cardiovasc Surg 2023;166:306-16)



Functionally single ventricle (f-SV) center volume by complexity and 5-year survival. High-risk f-SV subtypes are (unbalanced) AVSD and HLHS.

CENTRAL MESSAGE

In the centralized service provided for children with f-SV hearts in England, we found no evidence for a relationship between center volume and long-term survival after adjusting for case mix.

PERSPECTIVE

The survival rate for patients with f-SV disease at 1 year and 5 years was 76.8% (95% CI, 75.3%-78.2%) and 72.1% (95% CI, 70.6%-73.7%), respectively. After adjusting for risk factors, there was no evidence that center volume was associated with long-term survival, ie, HR, 1.01 (95% CI, 0.99-1.04) $P = .28$. Greater-volume centers tended to treat children with more complex disease (HLHS, Norwood pathway).

From the [a]Great Ormond Street Hospital Biomedical Research Centre and Institute of Cardiovascular Science, [b]Clinical Operational Research Unit, and [f]Population, Policy and Practice Programme, Great Ormond Street Institute of Child Health, University College London, London, United Kingdom; [c]Paediatric Cardiology and Cardiothoracic Surgery, Birmingham Women's and Children's Hospital National Health Service Foundation Trust and Institute of Cardiovascular Science, University of Birmingham, Birmingham, United Kingdom; [d]Paediatric Cardiology, Evelina London Hospital, London; and [e]Paediatric Cardiology, Royal Brompton and Harefield National Health Service Foundation Trust, London, United Kingdom.

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Data Availability Statement: The study dataset is available only with the required approvals in place from the National Institute for Cardiac Outcomes Research (NICOR) and the National Congenital Heart Diseases Audit, the UK Health Research Authority including Research Ethics Committee Approval, and Confidentiality Advisory Group Approval and the approval of NHS Digital for use of the life status data.

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Address for reprints: Qi Huang, PhD, Clinical Operational Research Unit, University College, London, WC1H 0BT, United Kingdom (E-mail: Qi_Huang@ucl.ac.uk).

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Abbreviations and Acronyms

AVSD = atrioventricular septal defect
CAG = Confidentiality Advisory Group
CHD = congenital heart disease
CI = confidence interval
DILV = double inlet left ventricle
f-SV = functionally single ventricle
HLHS = hypoplastic left heart syndrome
HR = hazard ratio
IQR = interquartile range
NCHDA = National Congenital Heart Diseases Audit
NHS = National Health Service
ONS = Office of National Statistics

Scanning this QR code will take you to the table of contents to access supplementary information.

A systematic review of long-term survival in congenital heart disease (CHD) identified only 16 population-based studies worldwide.[1] These 16 studies considered patients born in earlier eras, and therefore findings may not reflect recent evolutions in treatment. Moreover, the sparsest were reports of long-term outcome for patients with functionally single-ventricle (f-SV) disease. Recognizing an evidence gap, we previously used the National Congenital Heart Diseases Audit (NCHDA) to explore longer-term survival for patients who received any interventional treatments for hypoplastic left heart syndrome (HLHS)[2,3] and other forms of definite functionally univentricular heart.[4] Analysis of long-term survival can take account of treatment across the whole patient journey, which is important in the management of f-SV, given the late mortality risks[5,6] and need for serial surgeries.[7] Some studies from North American and European CHD registry data have supported a hypothesis that greater-volume centers have better early surgical outcomes.[8-11] Among center-volume studies, there has been a special focus on the Norwood operation.[9,10] As far as we are aware, no population-based studies of center volume and longer-term outcome have been undertaken. In this study, we aimed to evaluate risk factors for longer-term survival for all types of f-SV CHD in England and Wales during the era when the mandatory national audit was in place and then to explore the relationship between center volume and long-term survival. Notably, CHD services are provided by the National Health Service (NHS) in the United Kingdom, and the NHS has always taken a regional approach to the provision of specialized services such as pediatric cardiac surgery. As such, CHD services are centralized to 10 specialist centers in England and Wales; nonetheless, the case volume for the subset of patients with f-SV disease varies across these centers.[12]

METHODS

Study Design

This was a retrospective cohort study based on the NCHDA, with survival status from the Office of National Statistics (ONS).

Study Questions

We sought to explore the following 2 questions: (1) What are the important case mix variables for longer-term survival in patients who received any interventional treatment for f-SV? (2) What is the relationship between the volume of practice within individual centers and (adjusted) longer-term survival for children who received any interventions for f-SV?

Data Sources

We used all records of cardiac surgical procedures and interventional catheters performed in England and Wales between April 1, 2000, and March 31, 2018. During this period, data submission to the NCHDA was mandatory, subject to external data validation, and had approval from the relevant regulatory authorities for using patient-identifiable data. Patient vital status (dead or alive) was provided at the point of hospital discharge by NCHDA, who obtained this information from treating centers. The age at death for any patient who had died was taken from death certification data provided by the ONS. For surviving patients, we received from ONS their age when this status was confirmed (November 2020). Any patients who were discharged alive and who had missing life status with ONS were deemed lost to follow-up and were censored at their most recent discharge age provided by NCHDA.

To note, as the NCHDA is a procedure-based dataset, patients who did not undergo any surgical or interventional cardiac procedures do not appear in the dataset. Patient procedures were grouped as described previously[2-4] as stage 1 (Norwood, hybrid, isolated arch repair, pulmonary arterial banding, systemic-to-pulmonary arterial shunt); stage 2, comprehensive stage 2; and stage 3 (Fontan) and additional surgery/interventional catheters.

Data Approvals

The study was approved by the NCHDA Research Committee and the NHS Healthcare Quality Improvement Partnership (application number 18-CON-04), the Stanmore NHS Research Ethics Committee (research ethics committee number 18/LO/1688), and the Health Research Authority Confidentiality Advisory Group (CAG) (CAG number 17/CAG/0071), which permits the use of registry data for specific research purposes without consent.

Inclusions

We included patients with f-SV CHD, as defined in Table 1,[2-4,7,13-15] who were born between April 2000 and March 2018.

Exclusions

We excluded patients born before April 2000, to ensure a dataset in which the complete procedure history was present. We excluded patients from overseas, Scotland, and Northern Ireland, because life status data are collected by ONS for patients from England and Wales only. Based on agreement from 2 clinicians (K.B., R.F.), we excluded 178 patients,

TABLE 1. Definition of patients with f-SV CHD

f-SV disease types	Definition of CHD type
Classic HLHS	CHD with a small left ventricle, left-sided valvar stenosis or atresia, normally related great arteries, and no common atrioventricular junction[13] based on diagnostic and procedure codes as reported previously.[2,3]
Functionally univentricular heart (FUH)	CHD with double-inlet atrioventricular connection (both DILV and DIRV); absence of 1 atrioventricular connection (non-HLHS mitral atresia and tricuspid atresia); a common atrioventricular valve and only 1 completely well-developed ventricle (AVSD); only 1 fully well-developed ventricle and atrial isomerism as detailed previously.[4,14,15]
Other major primary congenital heart diagnoses with f-SV circulation	CHDs in which due to the presence of a hypoplastic ventricle or a straddling atrioventricular valve, the management pathway entailed staged palliative procedures for f-SV[2-4,7] and no procedures indicative of a biventricular circulation (pulmonary atresia intact ventricular septum, Ebstein malformation of the tricuspid valve, and congenitally corrected transposition).

f-SV, Functionally single ventricle; *CHD*, congenital heart disease; *HLHS*, hypoplastic left heart syndrome; *FUH*, functionally univentricular heart; *DILV*, double-inlet left ventricle; *DIRV*, double-inlet right ventricle; *AVSD*, atrioventricular septal defect.

97 who on closer inspection were found to have biventricular heart disease and 81 who had infeasible procedure sequence or clinically significant missing data, which meant that a reliable patient history could not be ascertained.

Outcomes

The primary study outcome was long-term survival.

f-SV Center Volume

We defined "center volume" as the number of new patients with f-SV disease starting their first cardiac procedure per year within the center as a continuous variable. Ten specialist pediatric cardiac hospitals in England and Wales are deidentified in our dataset and indicated by the letters A-J. An 11th hospital where there was small volume practice that ceased in 2010 was removed from the analysis. Most patients, N = 3146 (95.7%), did not change their hospital during their treatment pathway. For the N = 143 patients (4.3%) who changed their hospital, we assigned their hospital and year to that of their stage 1 operation, or stage 2 if there was no stage 1, or stage 3 operation if there was no stage 1 or 2.

Risk Factors

The data extract included the following variables, which have been defined (where applicable) for use in national audit in the United Kingdom[16]: sex, age at procedure (we used age at first cardiac procedure), antenatal diagnosis (yes, no, unknown), congenital extracardiac comorbidities (eg, genetic syndrome, major congenital anomaly of any organ outside the heart),[17] prematurity (birth at gestation less than 37 weeks), and additional cardiac risk factors (this only includes echocardiographic measures of impaired ventricular function and echocardiographic or cardiac catheterization measures of pulmonary hypertension).[17] In addition, the following procedure-based risk factors were derived at the first cardiac surgery procedure after birth: acquired comorbidities (the presence of an acquired complication related to CHD, eg, necrotizing enterocolitis, renal failure),[17] increased severity of illness (a need for preoperative ventilation or presence of pre-operative shock),[17] and low weight (<2.5 kg). We calculated weight-for-age z-scores based on British Growth Reference[18] and considered those outside the range of +5 and –8 to be clinically anomalous and their weight treated as missing.

Statistical Methods

We explored the number of patients treated at each hospital in total and by year. We created f-SV subgroups for which there were at least 100 patients, combining rarer conditions into an "other f-SV' group," using a hierarchical approach (HLHS, f-SV with atrial isomerism, double-inlet left ventricle [DILV], tricuspid atresia, mitral atresia without HLHS, unbalanced atrioventricular septal defect [AVSD], pulmonary atresia without other complex features but with f-SV and "other f-SV").

Survival analysis was conducted using the Kaplan–Meier approach, with the primary outcome of death representing failure. Data quality for diagnosis, procedures, weights, and survival status are of excellent quality from the year 2000; however, data quality for certain clinical variables (antenatal diagnosis, severity of illness, and acquired and congenital comorbidities) was poor initially and improved after 2009 (when the processes for data quality were changed[19]) Therefore, we included a time factor in the models (pre/post-2009). We explored important aspects of case mix using the χ^2 test for trend considering the time eras of 2000-2008 and 2009-2018 separately.

We explored the relationship between case mix and f-SV center volume as a continuous variable using 2-sample *t*-test. We explored the distribution of the risk factors within the key diagnostic subgroups. One-way analysis of variance and χ^2 test were performed to test the independence between clinical subgroups and other risk factors when appropriate.

We used multiple imputation by logistic regression to address missing values for low weight (2.0%), including all risk factors from the Cox model except for time interaction terms. We noted missing values for antenatal diagnosis (4.8%) and explored the case mix and outcomes among the missing patients, after which we chose to treat the missing antenatal diagnosis patients as a separate group.

Univariable or multivariable Cox regression models were performed to investigate the association between the patient's survival time and center volume adjusted for the prespecified risk factors of interest. Interaction term between the covariate and follow-up time was considered if the proportional hazards assumption was not met (ie, test of proportional hazard assumption using Schoenfeld residuals $P < .05$). A sensitivity analysis was performed by removing the 2 risk factors that were most poorly populated for data quality in the early era for NCHDA before 2009 from the Cox models (increased severity of illness and acquired comorbidity at the time of the first operation).

Given that previous studies found better outcomes with the Norwood operation in greater-volume centers,[9,20-23] we hypothesized that the effect of center volume on survival is different based on diagnosis subtypes and based on the stage one pathway of surgical management. These hypotheses were tested by fitting 2 separate multivariable Cox regression models that considered interactions between center volume and (1) diagnosis subtypes and (2) stage 1 pathway. All statistical analyses were performed with Stata 15 software (StataCorp LP).

RESULTS

Study Population

From the population of 56,039 patients in NCHDA, 3293 (5.9%) patients with f-SV met our inclusion criteria, as

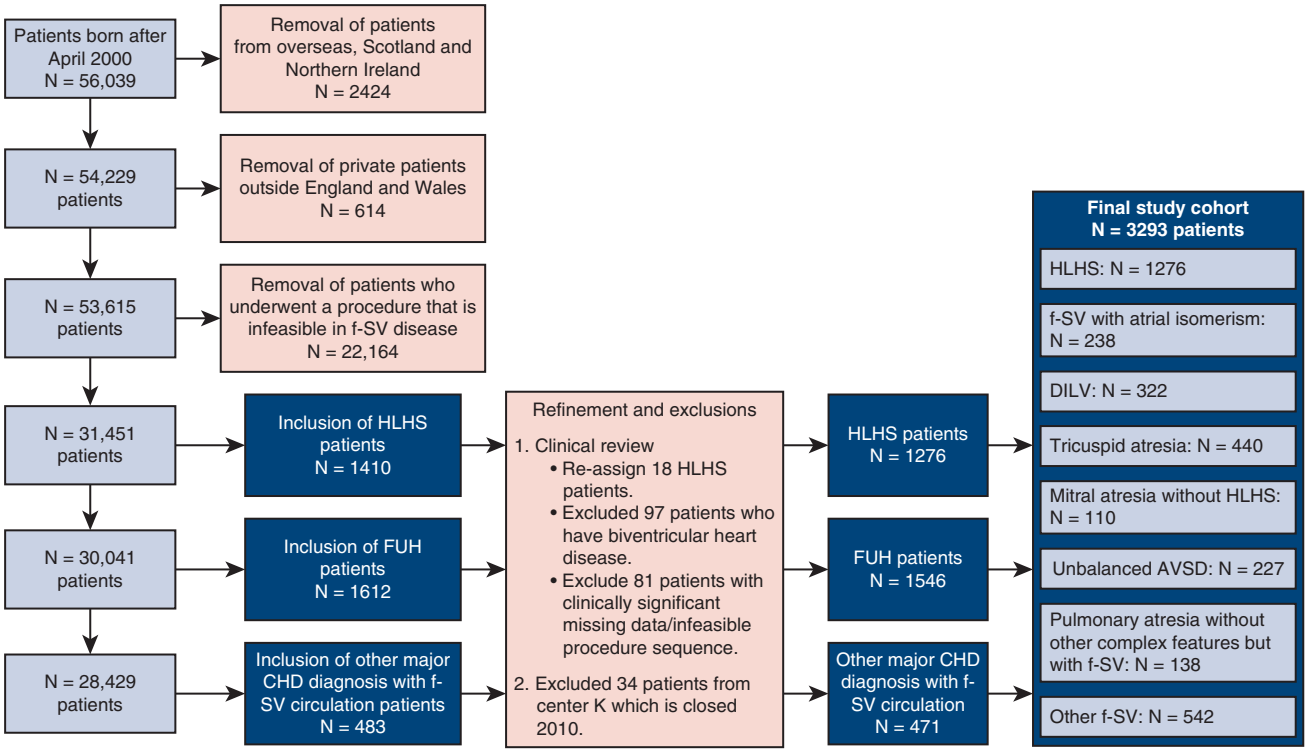

FIGURE 1. Inclusions and exclusions during the case-ascertainment process. The process of case ascertainment of the study cohort of 3293 patients with functionally single-ventricle (*f-SV*) disease from the National Congenital Heart Diseases Audit (NCHDA) data set with specific exclusions stated at each step. *HLHS*, Hypoplastic left heart syndrome; *DILV*, double-inlet left ventricle; *FUH*, functionally univentricular heart[4]; *AVSD*, atrioventricular septal defect; *CHD*, congenital heart disease.

shown in Figure 1. The median age at first cardiac procedure was 7 (interquartile range [IQR], 4, 27) days, 1930 (58.6%) were male, 2449 (74.4%) were antenatally diagnosed, 548 (16.6%) had a congenital noncardiac condition, 195 (5.9%) had premature birth, and 234 (7.1%) had an additional cardiac risk factor. At the time of the first cardiac procedure, 330 (10.0%) had weight <2.5 kg, 159 (4.8%) had an acquired comorbidity, and 384 (11.7%) were critically ill. We show the case mix by diagnostic subgroups in Table 2.

Surgical Pathway and Survival Rates

Of 3293 patients with f-SV, 2867 (87.1%) had a stage 1 operation (postoperative mortality 13.9%, defined as within hospitalization), and 426 (13%) did not undergo a stage 1 procedure, either they did not reach stage 1, 77 (2.3%), or they skipped stage 1 altogether, 349 (10.6%). Given the high risk of the Norwood and Hybrid stage 1 types, we display the proportion of patients with these surgical pathways by f-SV subtype in Figure 2, where we also list the proportions with each stage 1 type. In total, 2426 (73.7%) patients had a stage 2 operation, of which 165 (6.8%) were comprehensive stage 2 procedures (postoperative mortality 3.2%), and 1557 (47.3%) patients had a stage 3 (Fontan type) operation (postoperative mortality 1.4%). Among 3293 patients with f-SV, only 48 (1.46%) had a heart transplant, 14 (0.4%) after Fontan stage.

The median follow-up time in the study cohort was 7.6 (IQR, 1.0, 13.3) years, and maximum 20.6 years. The overall 1-year and 5-year survival rates (95% CI) for the cohort were 76.8% (75.3%-78.2%) and 72.1% (70.6%-73.7%) respectively. We present the Kaplan–Meier curves and survival rates by f-SV subtype in Figure 3 and Table 3: the lowest 5-year survival rates (95% CI) were for unbalanced AVSD, 56.1% (49.9%-63.0%), and HLHS, 56.7% (54.0%-59.5%), and the highest 5-year survival rates were for pulmonary atresia, 92.7% (88.5%-97.2%), and DILV, 90.5% (87.3%-93.8%).

Changes Over Time

We include details of the number of patients starting surgical treatment for f-SV by year, which was reasonably constant, and by center (Figure E1), survival at ages 1 and 5 years by year (Figure E2), and risk factors by year (Table E1 and Figure E3).

When we evaluated changes in case mix based on birth before/after the start of 2009, we found significant increases over time (and no decreases) in the following: antenatal

TABLE 2. Distribution or frequencies of risk factors by clinical subtypes of f-SV disease

Risk factor	HLHS (N = 1276)	f-SV with atrial isomerism (N = 238)	DILV (N = 322)	Tricuspid atresia (N = 440)	Mitral atresia without HLHS (N = 110)	Unbalanced AVSD (N = 227)	Pulmonary atresia without other complex features but with f-SV (N = 138)	Other f-SV (N = 542)
Median [Q1, Q3] (range)								
Center volume*	27 [17, 40] (7, 60)	19 [13, 31] (4, 60)	20 [15, 30] (5, 60)	18 [14, 27] (3, 60)	17 [12, 27] (6, 60)	20 [14, 36] (4, 60)	19 [13, 31] (5, 60)	20 [14, 31] (3, 60)
Age at the first cardiac procedure, d*	5 [4, 7] (1, 194)	13 [6, 83] (1, 4156)	14 [6, 65] (1, 2857)	20 [6, 66] (1, 3237)	11 [4, 30] (1, 3232)	14 [6, 64] (1, 2291)	5 [4, 8] (1, 2400)	15 [6, 84] (1, 2400)
n (%)								
Recent data, born from April 2009 onwards	649 (50.9)	128 (53.8)	173 (53.7)	230 (52.3)	60 (54.5)	124 (54.6)	71 (51.4)	262 (48.3)
Sex male*	801 (62.8)	130 (54.6)	181 (56.2)	256 (58.2)	66 (60.0)	99 (43.6)	85 (61.6)	312 (57.6)
Additional cardiac risk factor*	112 (8.8)	17 (7.1)	17 (5.3)	18 (4.1)	11 (10)	25 (11)	5 (3.6)	29 (5.4)
Antenatal diagnosis*	940 (73.7)	201 (84.5)	256 (79.5)	357 (81.1)	96 (87.3)	162 (71.4)	94 (68.1)	343 (63.3)
Congenital noncardiac comorbidity*	179 (14.0)	69 (29)	27 (8.4)	59 (13.4)	32 (29.1)	69 (30.4)	15 (10.9)	98 (18.1)
Premature birth†	54 (4.2)	12 (5)	20 (6.2)	33 (7.5)	7 (6.4)	24 (10.6)	13 (9.4)	32 (5.9)
Low-weight baby <2.5 kg (at the first cardiac procedure)*	156 (12.2)	17 (7.1)	19 (5.9)	46 (10.5)	14 (12.7)	26 (11.5)	16 (11.6)	44 (8.1)
Acquired comorbidity (at the first cardiac procedure)	69 (5.4)	10 (4.2)	10 (3.1)	22 (5)	3 (2.7)	15 (6.6)	9 (6.5)	21 (3.9)
Increased severity of illness (at the first cardiac procedure)*	203 (15.9)	20 (8.4)	23 (7.1)	48 (10.9)	14 (12.7)	24 (10.6)	13 (9.4)	39 (7.2)

Test of independence between f-SV subtypes and risk factors: one-way analysis of variance and χ^2 test were performed as appropriate. Low weight <2.5 kg includes imputed data. Missing data in antenatal diagnosis have been excluded. *HLHS*, Hypoplastic left heart syndrome; *f-SV*, functionally single ventricle; *DILV*, double-inlet left ventricle; *AVSD*, atrioventricular septal defect; *Q1 and Q3*, first and third quantiles. *Q1, Q3, Significance level (*P* value): .001. †.01.

diagnosis (early era, 44.4%-80.7%, $P < .001$; late era, 82.1%-89.8%, $P = .02$); additional noncardiac comorbidities (early era, 5.4%-19.1%; $P < .001$); HLHS or unbalanced AVSD (late era, 42.5%-58.1%, $P = .002$); severity of illness at first procedure (early era, 1.2%-2.6%, $P = .025$; late era, 16.4%-23.3%, $P < .001$); premature birth (late era, 5.0%-7.0%, $P = .007$); and acquired comorbidity (early era, 0.6%-2.1%, $P = .013$; late era, 5%-4.7%, $P = .006$). The unadjusted hazard ratio (HR) for mortality for the recent era was 0.90 (95% CI, 0.79-1.02), $P = .12$, and the adjusted HR for the recent era was 0.87 (95% CI, 0.75-1.01), $P = .07$, indicating a possible trend toward better survival.

Risk Factors for Mortality

Table 3 shows the multivariable HR with 95% CI for patients with f-SV. The most important mortality risk was f-SV subtype, where we found that, compared with HLHS, all f-SV subgroups except for unbalanced AVSD had lower adjusted mortality risk. Patients with antenatal diagnosis (HR, 1.51; 95% CI, 1.25-1.83), low weight (<2.5 kg; HR, 1.66; 95% CI, 1.38-2.00), acquired comorbidity (HR, 1.85; 95% CI, 1.44-2.37), and increased severity of illness (HR, 1.42; 95% CI, 1.17-1.73) at first operation all had greater risk of mortality ($P < .001$).

Although the adjusted risk of death was lower for f-SV with isomerism, DILV, pulmonary atresia, and "other f-SV," the time interaction term indicated that this risk increased as children got older. As an example, in the adjusted Cox model, the HRs for f-SV isomerism and its follow-up time interaction terms are 0.61 and 1.21, respectively. So, compared with the reference group HLHS, the mortality risk for patients with f-SV isomerism at follow-up times of birth, 1 year, and 5 years was 39% lower, 26% lower, and 58% higher.

Older age at first procedure was linked to lower adjusted mortality HR, 0.47 (95% CI, 0.32-0.68), $P < .001$, although this risk increased over time: HR, 1.06 (95% CI, 1.03-1.09), $P < .001$. The presence of congenital noncardiac comorbidity, although nonsignificant in the multivariable model, showed significant increased risk with time HR, 1.11 (95% CI, 1.04-1.18), $P < .001$: the mortality risk for patients with congenital noncardiac comorbidity at follow-up times of birth, 1 year, and 5 years is 7% lower, 3% higher, and 57% higher than those with no congenital comorbidities.

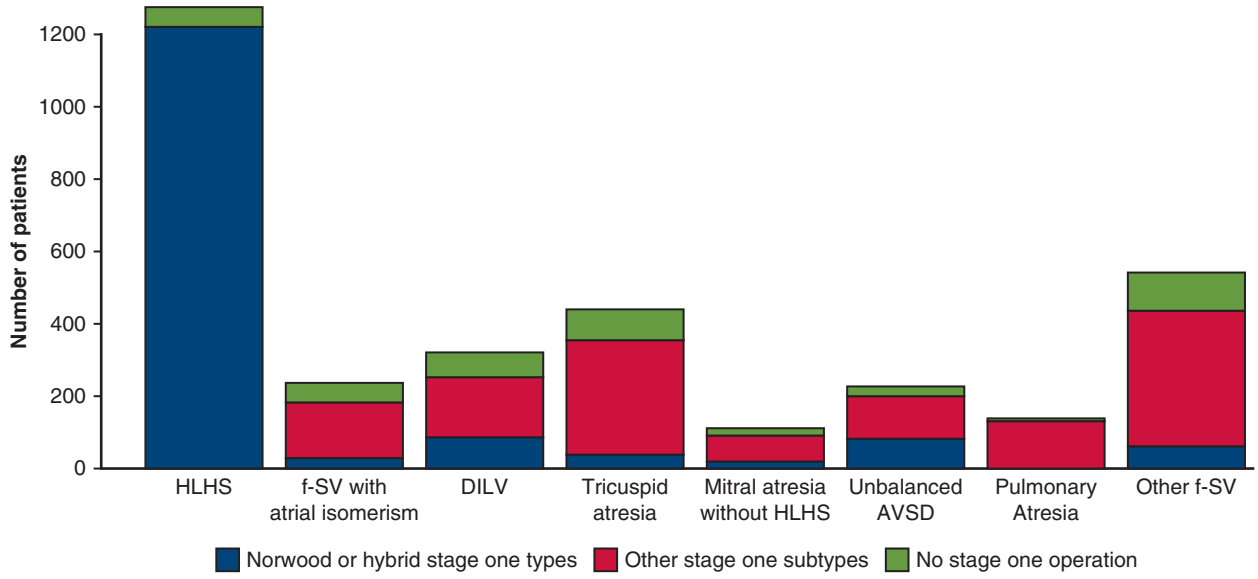

FIGURE 2. Number of patients by clinical subtypes of functionally single ventricle (*f-SV*) disease and stage 1 operation subtypes. Of 2867 patients who had a stage 1 operation, 1399 (48.8%) were Norwood-type operations, 141 (4.9%) were hybrid procedures for HLHS, 160 (5.6%) were isolated arch repairs (with or without pulmonary arterial banding), 807 (28.1%) were procedures to secure pulmonary blood flow, for example, arterial shunt operations, and 364 (12.7%) were isolated pulmonary arterial banding procedures. In 4 patients, the stage 1 type was unclear due to poor coding. The *bar chart* shows that the majority of greater-risk stage 1 subtypes of Norwood and hybrid were undertaken, as expected, in the HLHS group. A minority 426 (13%) of patients with f-SV did not undergo a stage 1 procedure; either they did not reach stage 1, 77 (2.3%), or they skipped stage 1 altogether, 349 (10.6%). *HLHS*, Hypoplastic left heart syndrome; *DILV*, double-inlet left ventricle; *AVSD*, atrioventricular septal defect.

f-SV Center Volume and Longer-Term Survival

The median f-SV center volume was 21 new patients treated per year (IQR, 15, 35), with a minimum number of 5 and a maximum number of 60 new patients treated per year in any center over the study period. The lowest-volume center contributed 170 patients and the highest-volume center contributed a total of 762 patients. The distribution of patients by center per year, was reasonably consistent (Figure E1).

As shown in Figure 4, the greater risk f-SV subgroups (HLHS and unbalanced AVSD) ($P < .001$), and correspondingly the Norwood and hybrid procedures ($P < .001$) were much more likely to be undertaken at centers with high f-SV case volume ($P < .001$), and there was weak evidence that centers with greater f-SV volume were more likely to treat babies with low weight ($P = .09$). Conversely, greater f-SV volume centers were less likely to treat babies with premature birth ($P = .01$). The other case mix variables that we identified in our study were not linked to f-SV center volume.

In the univariable analysis, we found that greater f-SV center volume (HR expressed per 5 patients) was associated with greater mortality, HR, 1.04 (95% CI, 1.02-1.06), $P < .001$. In the multivariable analysis, however, we found that the effects of f-SV center volume disappeared, after all the identified important case mix variables were considered in the model: the HR for f-SV center volume was 1.01 (95% CI, 0.99-1.04) $P = .28$.

We include the results of 2 separate multivariable Cox regression models that considered interactions between f-SV center volume and (1) diagnosis subtypes and (2) stage 1 pathway types. We found no evidence for better survival with greater f-SV volume between diagnosis subtypes ($P = .08$) or between different stage 1 pathways ($P = .11$). The adjusted HRs for f-SV center volume (scaled by 5 patients) for these 2 factors are shown in Tables E2 and E3.

DISCUSSION

Summary of Our Findings

Our population-based study of children born with f-SV and managed with operative treatment in England and Wales between 2000 and 2018 found that longer-term survival, based on a median follow-up time of 7.6 years, was strongly linked to f-SV subtypes, with poorer outcomes for HLHS or unbalanced AVSD and variables linked to the first cardiac procedure of low weight, increased severity of illness, and acquired comorbidity. We found that the risk of mortality increased over time for f-SV with isomerism, DILV, pulmonary atresia, and "other f-SV" relative to HLHS and with increased age at first procedure or additional noncardiac comorbidities (vs not). The number of

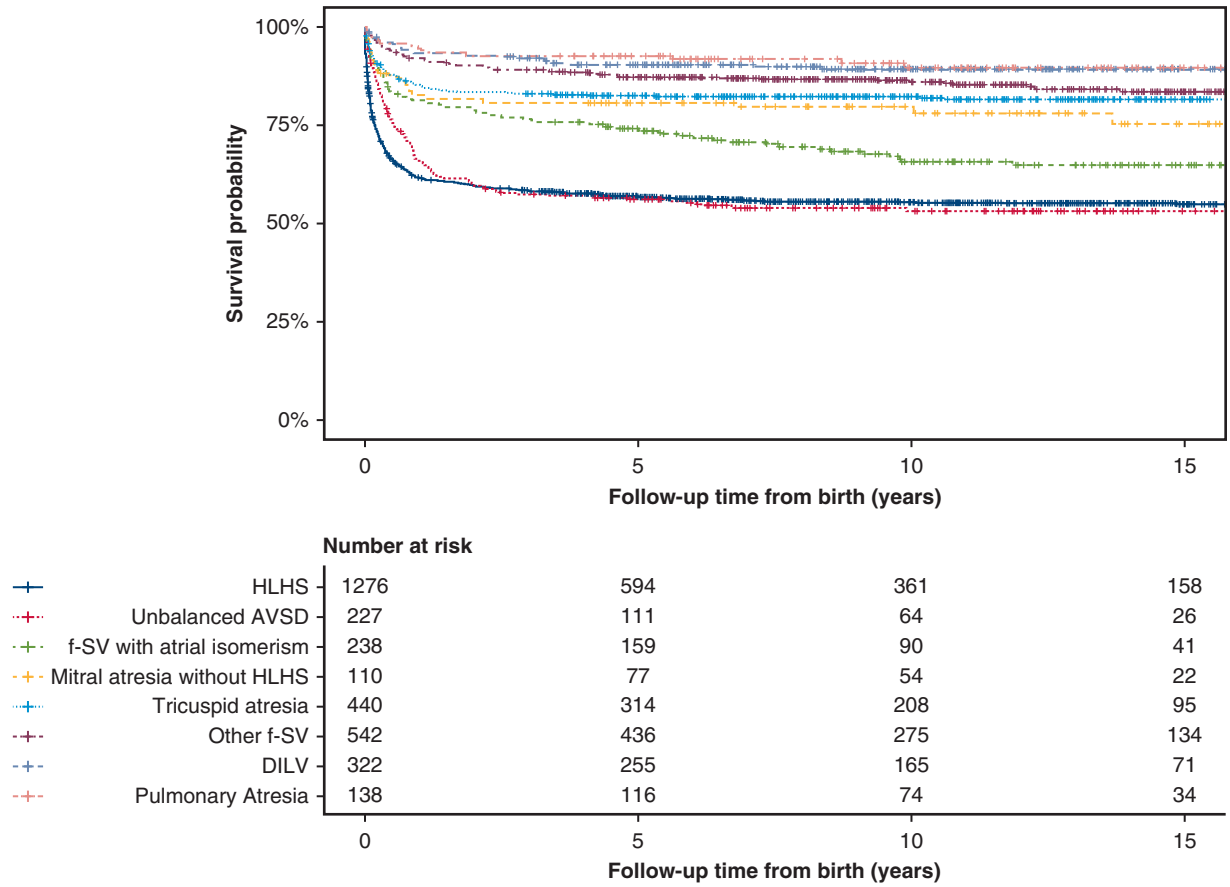

FIGURE 3. Kaplan–Meier survival curves for each clinical subtype of f-SV disease. The lowest 5-year survival rates (95% CI) were for unbalanced AVSD, 56.1% (49.9%-63.0%) and HLHS, 56.7% (54.0%-59.5%), and the greatest 5-year survival rates were for pulmonary atresia 92.7% (88.5%-97.2%) and DILV 90.5% (87.3%-93.8%). *HLHS*, Hypoplastic left heart syndrome; *f-SV*, functionally single ventricle; *DILV*, double-inlet left ventricle; *AVSD*, atrioventricular septal defect.

children starting treatment for f-SV disease was reasonably constant over time, but there was some evidence that the case mix for the f-SV population undergoing surgery has become more complex, and there was strong evidence for greater rates of antenatal diagnosis for f-SV disease over time. In the centralized service for treatment of CHD in England and Wales, a great proportion of the most complex types of f-SV disease were directed into centers undertaking a greater volume of f-SV practice, particularly affecting HLHS as the largest single subgroup, and patients operated at <2.5 kg. Conversely, patients who were born prematurely, who were more likely to have non-HLHS types of f-SV disease (pulmonary atresia), were more likely to be treated at centers with a low volume of f-SV practice. After adjustment for case mix, we found no statistically significant relationship between f-SV center volume and survival. When we specifically interrogated the relationship between f-SV center volume and outcome for the high-risk subgroup of HLHS, and for patients undergoing the Norwood stage 1 pathway, we found no evidence for an interaction between center volume and survival.

The Context for Our Study Findings

Previous studies have reported links between greater center volume and better early surgical survival,[11] especially for the Norwood operation,[9,20-23] and in a subset of studies for surgical neonates.[24,25] The relationship between f-SV center volume and postoperative mortality can be explored based on the Pediatric Heart Network's Single Ventricle Reconstruction (SVR) Trial, which included stage 1 surgeries between 2005 and 2008, with a rate of stage 1 in-hospital death or transplant of 7% to 39% across 14 trial sites.[26] The primary report of the SVR Trial found differences with shunt type by center volume, with greater-volume centers favoring the modified Blalock–Taussig shunt and lower-volume centers favoring the right ventricle-to-pulmonary arterial (Sano) shunt.[26] The 3-year follow-up from the SVR Trial found that an annual surgeon volume of fewer than 5 Norwood operations per year was linked to greater risk of death, HR, 1.73 (95% CI, 1.05-2.85), $P = .03$.[27] These findings support the hypothesis that for patients with f-SV, centers with greater volume of practice may achieve better outcomes for the Norwood pathway.

TABLE 3. Risk factors and survival outcomes in patients with f-SV disease

Risk factor	Median [Q1, Q3]	Range	Risk factors in Cox model	Univariable hazard ratio (95% CI)	Multivariable hazard ratio (95% CI)
Center volume	21 [15, 35]	(5, 60)	Center volume (per 5 patients)	1.04 (1.02-1.06)*	1.01 (0.99-1.04)
Age at first cardiac procedure, d	7 [4, 27]	(1, 5165)	Age at the first cardiac procedure, y	0.25 (0.16-0.38)*	0.47 (0.32-0.68)*
			Age at first procedure × follow-up time	1.10 (1.07-1.14)*	1.06 (1.03-1.09)*

	Frequency (%)	5-y survival rate % (95% CI)	Risk factors in Cox model	Univariable hazard ratio (95% CI)	Multivariable hazard ratio (95% CI)
Era					
Recent: born after April 2009	1697 (51.5%)	73.1 (70.9-75.1)	Recent: born after April 2009	0.90 (0.79-1.02)	0.87 (0.75-1.01)
Early: born before April 2009	1596 (48.5%)	71.1 (68.8-73,3)	Early: born before April 2009 (Ref)		
f-SV subtype					
HLHS	1276 (38.8%)	56.7 (54.0-59.5)	HLHS (Ref)		
f-SV with atrial isomerism	238 (7.24%)	74.2 (68.9-80.0)	f-SV with any type of atrial isomerism	0.44 (0.33-0.58)*	0.61 (0.45-0.81)†
			f-SV with atrial isomerism × follow-up time	1.30 (1.19-1.41)*	1.21 (1.11-1.31)*
DILV	322 (9.8%)	90.5 (87.3-93.8)	DILV	0.14 (0.09-0.20)*	0.19 (0.12-0.28)*
			DILV × follow-up time	1.26 (1.12-1.42)*	1.20 (1.07-1.34)†
Tricuspid atresia	440 (13.4%)	82.5 (79.1-86.2)	Tricuspid atresia	0.33 (0.26-0.42)*	0.41 (0.32-0.52)*
Mitral atresia without HLHS	110 (3.3%)	80.8 (73.7-88.5)	Mitral atresia	0.33 (0.21-0.53)*	0.47 (0.31-0.71)†
			Mitral atresia × follow-up time	1.20 (1.03-1.40)†	
Unbalanced AVSD	227 (6.9%)	56.1 (49.9 63.0)	Unbalanced AVSD	0.84 (0.67-1.08)	1.09 (0.88-1.36)
			Unbalanced AVSD × follow-up time	1.14 (1.02-1.27)†	
Pulmonary atresia without other complex features but with f-SV	138 (4.2%)	92.7 (88.5-97.2)	Pulmonary atresia	0.12 (0.06-0.23)*	0.14 (0.07-0.26)*
			Pulmonary atresia × follow-up time	1.27 (1.07-1.49)†	1.22 (1.04-1.44)‡
Other f-SV	542 (16.5%)	87.3 (84.6-90.2)	Other f-SV	0.18 (0.14-0.24)*	0.25 (0.18-0.33)*
			Other f-SV × follow-up time	1.28 (1.17-1.40)*	1.22 (1.12-1.32)*
Sex					
Male	1930 (58.6%)	73.3 (71.4-75.3)	Male	0.89 (0.79-1.01)	0.90 (0.79-1.02)
Female	1363 (41.4%)	70.4 (68.0-72.9)	Female (Ref)		
Additional cardiac risk factor					
Additional cardiac risk	234 (7.1)	67.4 (61.7-73.7)	Additional cardiac risk	1.08 (0.84-1.40)	0.95 (0.73-1.12)
			Additional cardiac risk × follow-up time	1.17 (1.09-1.26)*	1.16 (1.08-1.26)*
No additional cardiac risk	3059 (92.9)	72.5 (70.9-74.1)	No additional cardiac risk (Ref)		
Antenatal diagnosis					
Antenatal diagnosis	2449 (74.4%)	72.7 (70.9-74.5)	Antenatal diagnosis	1.58 (1.32-1.89)*	1.51 (1.25-1.83)*
Without antenatal diagnosis	684 (20.8%)	81.3 (78.4-84.3)	Without antenatal diagnosis (Ref)		
Missing data	160 (4.8%)	20.3 (14.6-28.3)	Missing data	6.66 (5.21-8.53)*	5.60 (4.31-7.29)*
Congenital noncardiac comorbidity					
Congenital noncardiac comorbidity	548 (16.6%)	70.5 (66.7-74.4)	Congenital noncardiac comorbidity	0.97 (0.81-1.17)	0.93 (0.77-1.13)
			Congenital noncardiac comorbidity × follow-up time	1.13 (1.06-1.20)*	1.11 (1.04-1.18)*

(Continued)

TABLE 3. Continued

	Frequency (%)	5-y survival rate % (95% CI)	Risk factors in Cox model	Univariable hazard ratio (95% CI)	Multivariable hazard ratio (95% CI)
Without congenital noncardiac comorbidity	2745 (83.4%)	72.5 (70.8-74.2)	Without congenital noncardiac comorbidity (Ref)		
Prematurity					
Premature birth	195 (5.9%)	66.4 (60.1-73.4)	Premature birth	1.20 (0.94-1.55)	1.05 (0.81-1.38)
Full term	3098 (94.1%)	72.5 (70.9-74.1)	Full term (Ref)		
Low weight baby (below 2.5 kg) at the first cardiac procedure					
Below 2.5 kg	336 (10.2%)	52.9 (47.5-58.2)	Below 2.5 kg	2.06 (1.73-2.44)*	1.66 (1.38-2.00)*
Above 2.5 kg	2957 (89.8%)	74.3 (72.6-76.0)	Above 2.5 kg (Ref)		
Acquired comorbidity at the first cardiac procedure					
Acquired comorbidity	159 (4.8%)	55.3 (48.1-63.6)	Acquired comorbidity	1.90 (1.50-2.40)*	1.85 (1.44-2.37)*
Without acquired comorbidity	3134 (95.2%)	73.0 (71.4-74.6)	Without acquired comorbidity (Ref)		
Increased severity of illness at the first cardiac procedure					
Increased severity of illness	384 (11.7%)	61.2 (56.4-66.3)	Increased severity of illness	1.60 (1.34-1.90)*	1.42 (1.17-1.73)*
Without increased severity of illness	2909 (88.3%)	73.6 (72.0-75.2)	Without increased severity of illness (Ref)		

Distribution or frequencies of risk factors with 5-year survival rates for patients with f-SV disease displayed with the results of the Cox proportional-hazards models. Low weight <2.5 kg includes imputed data. Interpretation of coefficients for covariates with time-varying interaction term. Consider x as a categorical covariate and the hazard regression coefficients for x and the time interaction term x × follow-up time (years from birth) are expressed as β and γ, respectively. The estimation of $\beta + \gamma \times$ follow-up time represents the change in the expected log of the hazard ratio relative to the reference. In the table, we report the baseline hazard ratio and time-changing hazard ratio by exp (β) and exp (γ). A value of exp (γ) larger than 1 indicates the mortality risk will increase with time, compared with the reference group, and vice versa. *Q1 and Q3*, First and third quantiles; *CI*, confidence interval; *f-SV*, functionally single ventricle; *HLHS*, hypoplastic left heart syndrome; *DILV*, double-inlet left ventricle; *AVSD*, atrioventricular septal defect. *Significance level (*P* value): .001. †.01 ‡.05.

In contrast to these studies, we did not find a relationship between f-SV center volume and longer-term survival after adjustment for risk factors. The UK CHD service has been highly centralized for the last 2 decades, is commissioned at national level, and the audit of postoperative outcomes is mandatory. Importantly, there are no low-volume (defined as <150 total CHD surgeries per year)[11] centers: in contrast to the recently reported median case volume of 170 per year in STS-CHSD, the contemporary median case volume in NCHDA is 305 per year.[28]

Implications of Our Findings

There has been a move toward centralization of CHD services in Europe, since concentrations of patients might help programs to build up expertise, not just in surgical skills, but in postoperative management. We studied longer-term survival of patients with f-SV; hence, our primary outcome incorporates the combined impacts of perioperative care associated with serial interventions and postdischarge interstage events.[5,29,30] An interesting example of "within-country centralization" demonstrated in our study is that among the patients with f-SV, we found a diversion of the most complex patients, those with HLHS, into centers with the highest numbers of patients with f-SV, favoring the development of concentrations of specific expertise within these centers. We note that, in the United Kingdom, public reporting of postoperative outcomes is mandatory, and this policy might have encouraged the development of referral pathways between centers with less experience in the management high-risk patients, to centers with more experience. Highly developed multidisciplinary expertise and collaborative learning are beneficial for CHD outcomes[31] and could be part of the explanation for our findings. Then, conversely, the centers with lower volume of f-SV practice (none of which were overall "low-volume centres"[5]) were more likely to manage, and hence develop, experience, with patients born premature with f-SV, especially those with pulmonary atresia, who in the United Kingdom might wait for surgery for a period of weeks on prostaglandin infusion before first intervention. Our findings reflect an era in which the case mix for f-SV became more complex, although this trend may have leveled off in the most recent era.

Study Limitations

As with any registry-based study, the retrospective analysis of an observational dataset holds inherent limitations and is limited by data quality. Perhaps the most important limitation is that our findings reflect practice in England

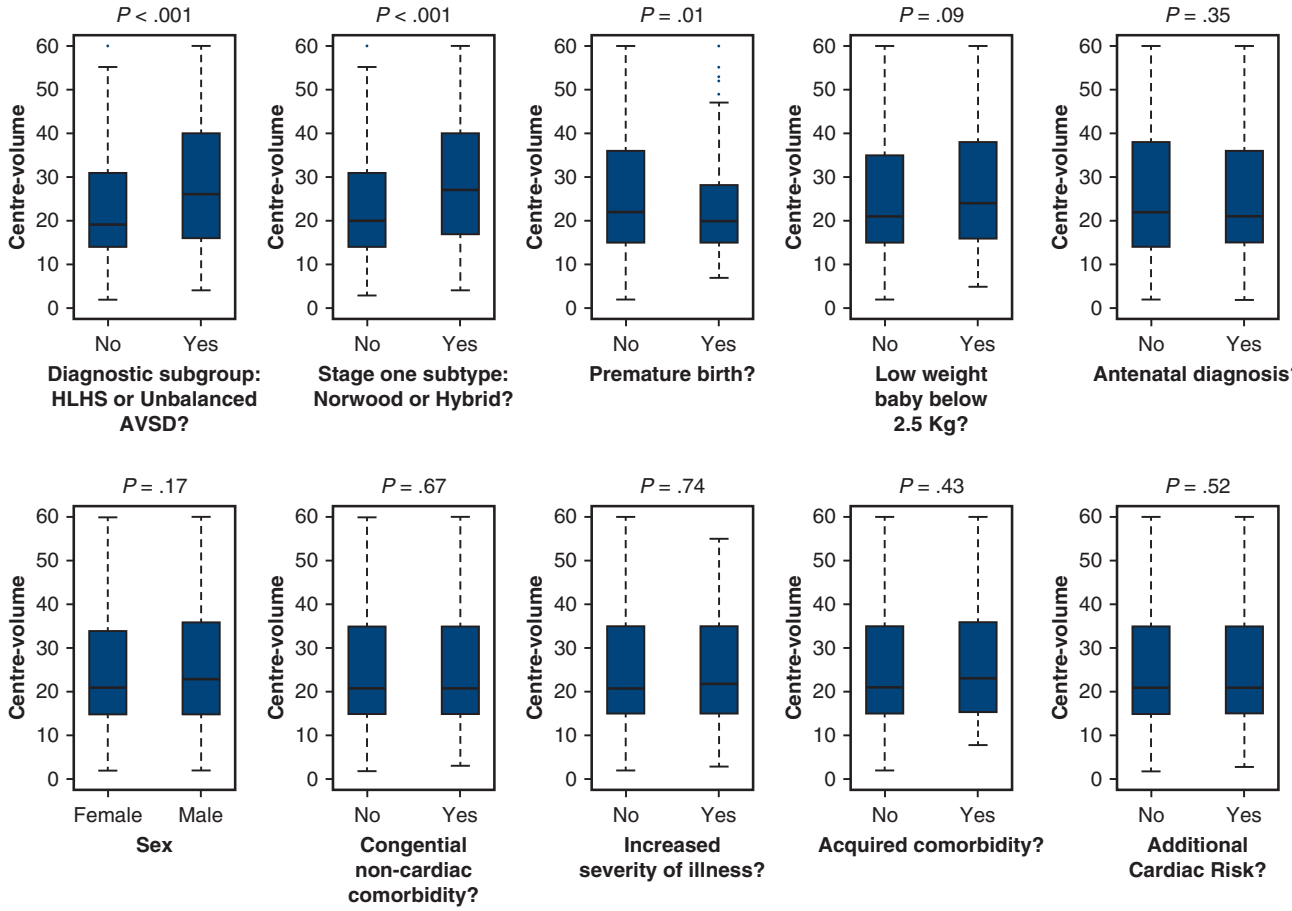

FIGURE 4. Association between center volume and categorical risk factors. The *box plots* indicate that the patients with more complex f-SV (HLHS, Norwood pathway) were treated at centers with greater f-SV case volume ($P < .001$). Conversely, patients born premature were more likely to be treated at centers with low center volume ($P = .01$). Two-sample *t*-test performed. All boxplots show the median (*horizontal black line*), interquartile range (*solid bars*), 1.5× interquartile range (*dotted vertical lines*), and outliers (*extra dots*). *HLHS*, Hypoplastic left heart syndrome; *AVSD*, atrioventricular septal defect.

and Wales. At patient level, we took an inclusive approach; hence, we included patients with unusual treatment pathways and hence some could have been misgrouped due to coding ambiguities. Only patients who underwent at least 1 postnatal procedure are captured in the NCHDA. Nonetheless, inclusion of patients who underwent any cardiac intervention provides a more complete picture than exclusive focus on specific procedures. Transplantation was a relatively rare occurrence in the study cohort and, informed by patient/parent views, we did not treat transplantation as an end point; hence, children who survived after transplantation are included in the number of survivors.

The data quality for the preoperative noncardiac risk variables in NCHDA improved after 2009 due to process changes at the audit. Although as mentioned, we added an era effect to the Cox regression models for this reason, this only partially accounts for this limitation. A sensitivity test was performed by removing the 2 covariates for which early data were poorest (severity of illness and acquired comorbidity) from the Cox model, and, in doing so, the overall results did not change. There was missing data for antenatal diagnosis (N = 160), and patients missing this variable had the greatest death rate (5-year of survival 20.3%), and most were patients before 2004 (N = 141, 88%) and had HLHS (N = 104, 63%). Considering the missingness was unlikely to be at random, imputation was not performed and a category of "missing" in antenatal diagnosis was added in the Cox regression model.

Finally, we note that although we present the outcome of longer-term survival, which is a strength given the novelty of the information, we acknowledge that a range of other important outcomes are not captured (morbidity, quality of life, neurodevelopmental outcome).

CONCLUSIONS

Within the service for CHD care in England and Wales, which has been centralized for the last 2 decades with mandatory public reporting of postoperative outcomes, we found no significant relationship between f-SV center volume and longer-term survival after adjustment for important

risk factors. This may partially reflect within-country referral of babies with HLHS to centers with greater volumes of f-SV practice. The f-SV subtype, severity of illness at first intervention, and associated comorbidities are the most important determinants of long-term survival. Increasing risk of mortality over time among certain groups emphasizes the importance of long-term multidisciplinary follow-up.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: congenital heart disease, Fontan, hypoplastic left heart syndrome, outcomes

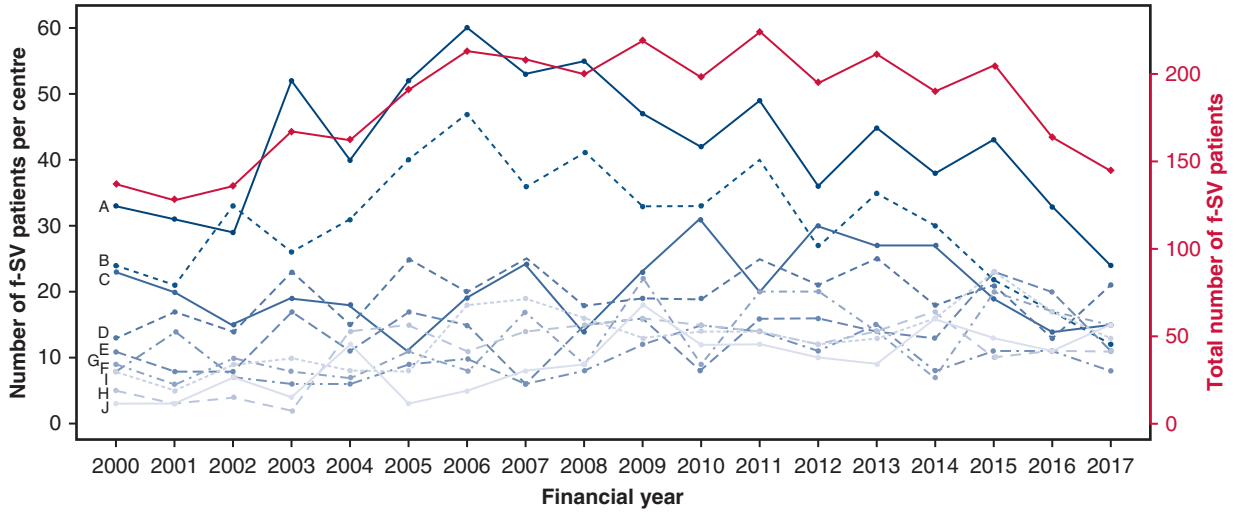

FIGURE E1. The number of functionally single ventricle (*f-SV*) patients per center commencing by years.

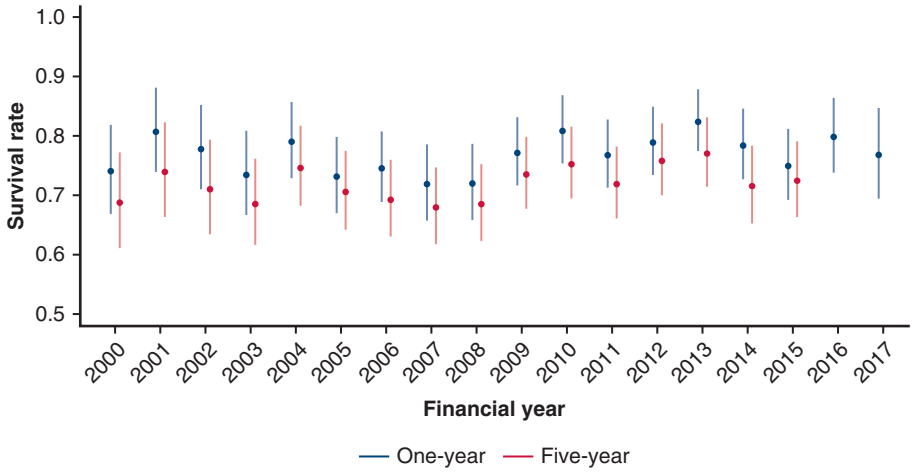

FIGURE E2. One-year and 5-year survival rates with 95% CI of patients with functionally single ventricle (f-SV) disease by birth year.

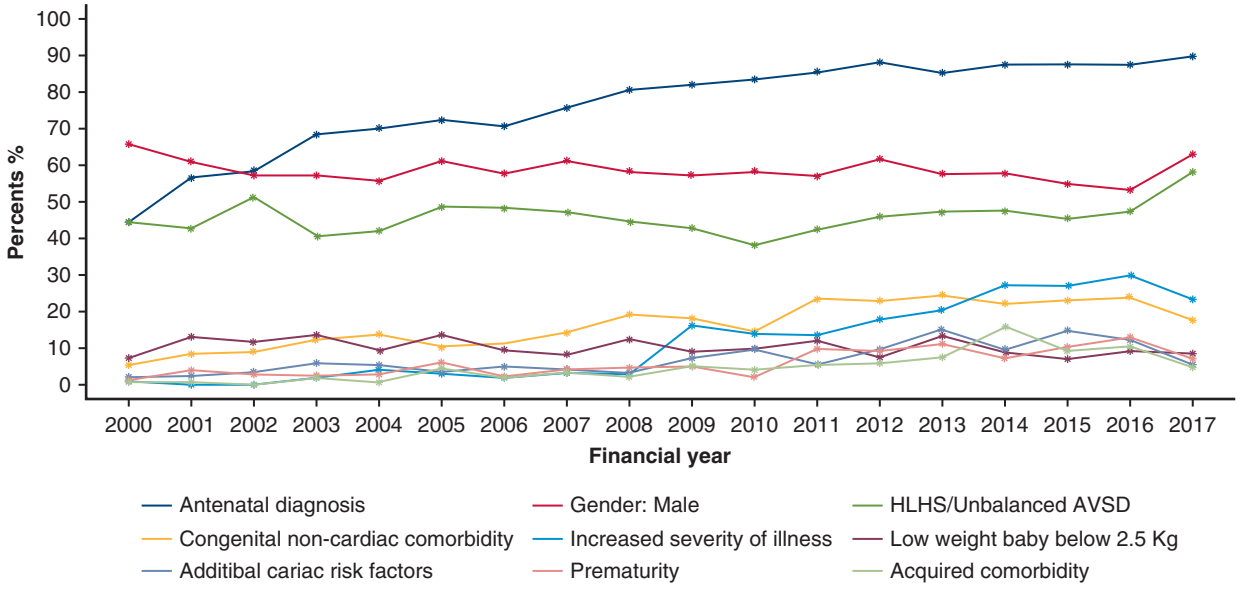

FIGURE E3. Percentage of categorical risk factors by year of birth. The following procedure-based risk factors were derived at the first cardiac surgery procedure after birth: acquired comorbidities, increased severity of illness, and low weight <2.5 kg. Low weight <2.5 kg includes imputed data. Missing values are excluded for N = 160 (4.9%) antenatal diagnosis. *HLHS*, Hypoplastic left heart syndrome; *AVSD*, atrioventricular septal defect.

TABLE E1. Percentage of categorical risk factors by year of birth

	Percentage % of risk factors by birth year (financial year)																		*P* value*	
Risk factors	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Early era	Recent era
Antenatal diagnosis	44	57	58	69	70	72	71	76	81	82	83	86	88	85	88	88	88	90	<.001	.02
Sex: male	66	61	58	57	56	61	58	61	58	57	59	57	62	58	58	55	53	63	.44	.88
HLHS/unbalanced AVSD	45	43	51	41	42	49	48	47	45	43	38	43	46	47	48	45	47	58	.54	.002
Congenital noncardiac comorbidity	5	8	9	12	14	10	11	14	19	18	15	23	23	25	22	23	24	18	<.001	.18
Increased severity of illness	1	0	0	2	4	3	2	3	3	16	14	14	18	20	27	27	30	23	.03	<.001
Low-weight baby <2.5 kg	8	13	12	15	9	14	10	8	12	9	10	12	8	13	9	7	9	9	.79	.43
Additional cardiac risk factors	2	2	3	6	5	4	5	4	3	7	10	6	10	15	10	15	12	5	.35	.11
Prematurity	1	4	3	2	3	6	2	4	5	5	2	10	9	11	7	10	13	7	.08	.007
Acquired comorbidity	1	1	0	2	1	5	2	3	2	5	4	6	6	8	16	9	10	5	.01	.006

The following procedure-based risk factors were derived at the first cardiac surgery procedure after birth: acquired comorbidities, increased severity of illness and low weight <2.5 kg. Low weight <2.5 kg include imputed data. Missing values are excluded for N = 160 (4.9%) antenatal diagnosis. *HLHS*, Hypoplastic left heart syndrome; *AVSD*, atrioventricular canal defect. *χ^2 test performed for testing trend in early ear (2000-2008) and recent era (2009-2019).

TABLE E2. The results of interaction between center volume and diagnosis subtypes of f-SV disease

f-SV subtype	Adjusted hazard ratio for center volume (95%CI)
HLHS	0.99 (0.96-1.02)
f-SV with atrial isomerism	1.08 (0.99-1.17)
DILV	0.90 (0.78-1.04)
Tricuspid atresia	1.10 (1.01-1.19)
Mitral atresia without HLHS	1.08 (0.92-1.26)
Unbalanced AVSD	1.04 (0.97-1.11)
Pulmonary atresia without other complex features but with f-SV	1.01 (0.82-1.26)
Other f-SV	1.02 (0.94-1.10)

The results have been reparametrized, and we report the hazard ratio for center volume in f-SV subtype with 95% CI. Hazard ratio has been adjusted using the same stated set of risk factors in Table 3. No evidence for better survival with greater f-SV volume between diagnosis subtypes was found (Wald test $P = .08$). *f-SV*, Functionally single ventricle; *CI*, confidence interval; *HLHS*, hypoplastic left heart syndrome; *DILV*, double-inlet left ventricle; *AVSD*, atrioventricular septal defect.

TABLE E3. The results of interaction between center volume and stage 1 operation subtype

Stage 1 subtype	Adjusted hazard ratio for center volume (95%CI)
Norwood	1.00 (0.97-1.03)
Coarctation/interrupted arch repair	0.96 (0.84-1.09)
Hybrid	1.05 (0.94-1.16)
Securing pulmonary blood flow	1.03 (0.97-1.10)
Protecting pulmonary vascular bed from excessive flow	1.13 (1.04-1.23)
No stage 1 operation	1.01 (0.94-1.09)

The results have been reparametrized and we report the hazard ratio for center volume in stage 1 subtype with 95% CI. No evidence for better survival with greater f-SV volume between different stage 1 pathways was found (Wald test $P = .11$). Hazard ratio has been adjusted using the same stated set of risk factors in Table 3 except for the f-SV subgroup risk factors. Missing values are excluded for N = 4 stage 1 subtypes. *CI*, Confidence interval.