Significant mortality, morbidity and resource utilization associated with advanced heart failure in congenital heart disease in children and young adults

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Background Children with congenital heart disease (CHD) are at risk for advanced heart failure (AHF). We sought to define the mortality and resource utilization in CHD-related AHF in children and young adults.

Methods All hospitalizations in the Pediatric Health Information System database involving patients ≤21 years old with a CHD diagnosis and heart failure requiring at least 7 days of continuous inotropic support between 2004 and 2015 were included. Hospitalizations including CHD surgery were excluded.

Results Of 465,482 CHD hospitalizations, AHF was present in 2,712 (0.6%) [58% infant, 55% male, 30% single ventricle]. AHF therapies frequently used included extracorporeal membrane oxygenation (ECMO) (15%) and cardiac transplant (16%). Ventricular assist device (VAD) support was rare (3%), although VAD use significantly increased from 2004 to 2015 ($P < .0010$). Hospital mortality in CHD with AHF was 26%, with higher mortality associated with single ventricle heart disease (OR 1.64, 95% CI 1.23-2.19; $P = .0009$), infancy (OR 1.71, 95% CI 1.17-2.5; $P = .0057$), non-white race (OR 1.28, 95% CI 1.04-1.59; $p=0.0234$), and chronic complex comorbidities (OR 1.76, 95% CI 1.34-2.30; $P < .0001$). Over the 11-year study period, despite the significant increase in CHD-related AHF hospitalizations ($P < .0001$), hospital mortality improved ($P = .0011$). Median hospital costs were $252,000, a 6-fold increase above those without AHF, and was primarily driven by hospital length of stay ($P < .0001$).

Conclusion AHF in children with CHD in uncommon but increasing and is associated with significant morbidity, mortality and resource utilization. Approximately 1 in 5 children do not survive to hospital discharge. Many risk factors for mortality may not be modifiable, and further study is needed to identify modifiable risk factors and improve care for this complex population. (Am Heart J 2019;209:9-19.)

Heart failure in children is a complex pathophysiologic state associated with high morbidity and mortality and can arise from a variety of diseases including cardiomyopathy, myocarditis and congenital heart disease (CHD).[1,2] Symptoms of heart failure in children include poor growth, feeding difficulties and exercise intolerance and can be associated with significant comorbidities, such as arrhythmias, pulmonary hypertension or respiratory failure. Heart failure in children results in approximately 14,000 hospitalizations annually in the United States with median hospital charges of $72,000 per admission.[3] Management of advanced pediatric heart failure continues to evolve as newer medical and mechanical support therapies are being developed.

With continued advancements in the management of CHD, survival over the past several decades has improved.[4] As a result, outcomes of CHD are shifting towards management of long-term morbidity associated with surgical palliation. In particular, patients with CHD are at increased risk for heart failure due to a variety of factors, including ongoing pressure or volume overload

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compounded by anatomic abnormalities, myocardial perfusion injury and/or conduction abnormalities.[5]

Most of the data and guidelines for the management of pediatric heart failure are derived from patients with dilated cardiomyopathy.[6-10] While this represents an important subset of heart failure, and is some respects analogous to adult heart failure patients, the majority of pediatric patients with heart failure do not have an underlying cardiomyopathy. CHD-related heart failure comprises nearly 70% of pediatric heart failure admissions in United States.[1] However, there are limited data on this population of children with CHD and advanced heart failure (AHF) in terms of morbidity, mortality and resource utilization.[11] Therefore, the primary aim of this study is to describe AHF in children with CHD and test the hypothesis that age, underlying heart disease, and comorbidities are associated with in-hospital mortality. Secondary aims include analyzing the association between AHF and morbidity and resource utilization, defined by hospital length of stay (LOS) and hospital cost.

Methods

Data source

Data for this study were obtained from the Pediatric Health Information System (PHIS) database. PHIS is an administrative and billing database that contains inpatient, emergency department, ambulatory surgery, and observation data from not-for-profit, tertiary care pediatric hospitals in the United States.[12] The 49 children's hospitals that contribute data to PHIS are affiliated with the Children's Hospital Association (CHA, formerly known as the Child Health Corporation of America, Lenexa, KS), a business alliance of children's hospitals. Data quality and reliability are assured through a joint effort between the CHA and participating hospitals. Participating hospitals provide discharge/encounter data including demographics, diagnoses, procedures, and charges. Data are de-identified at the time of data submission, and data are subjected to a number of reliability and validity checks before being included in the database. Details about the PHIS database have been reported previously.[12,13] The Institutional Review Board of the Children's Hospital of Philadelphia deemed this study exempt from review under 45 CFR 46.102(f), as patient data were de-identified. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Study design and definitions

We performed a multi-institutional, retrospective cohort review of the PHIS database for all hospitalizations of patients ≤21 years old between January 1, 2004 and October 31, 2015. All *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis and procedural codes for each patient's hospitalization was reviewed. Patients were defined as having AHF if they also had an *ICD-9* diagnosis of heart failure and at least seven days of continuous inotropic support during hospitalization. Patients who underwent CHD surgery during hospitalization were excluded to prevent inclusion of patients requiring transient peri-procedure inotropic support. The inotropic requirement was included in our definition of advanced heart failure to ensure a high severity group of patients was appropriately captured. Patients with heart failure on inotropic support who died prior to seven days were excluded. Patients who underwent heart transplantation were included only if they received inotropic support for at least seven days prior to transplantation. Inotropic medications included were epinephrine, norepinephrine, dopamine, dobutamine, and milrinone.

The primary outcome was in-hospital mortality and hospital costs. Secondary outcomes included use of AHF support including extracorporeal membrane oxygenation (ECMO) and ventricular assist device (VAD), cardiac transplantation, hospital LOS, intensive care unit (ICU) LOS.

We examined patient and hospital characteristics as covariates. These included age, gender, race, CHD group, acute comorbidities, and complex chronic conditions (CCC). Hospital characteristics included geographical region, and center CHD volumes. We identified comorbidities and classified CHD into three groups hierarchically: single ventricle complex CHD, non-single ventricle complex CHD, and simple CHD, using *ICD-9-CM* (See Supplement 1). These acute comorbidities included respiratory failure, acute renal failure, sepsis, and stroke.

CCCs were defined as medical conditions that can be reasonably expected to last at least 12 months and that involve either several different organ systems or 1 organ system severely affected enough to require specialty pediatric care and some period of hospitalization in a tertiary care center. Given that the majority of CHD patients should have a CCC for cardiovascular disease, the CCC for cardiovascular disease was not included in this analysis. To identify whether an individual was diagnosed with a CCC, we used a previously published classification scheme based on *ICD-9-CM*.[14]

Center CHD volume was determined by dividing the total number of CHD discharges by overall months of study duration per site (last hospitalization discharge date minus first hospital discharge date divided by 30). The 1st quartile is the lowest quartile of CHD discharges/month, and the 4th quartile is the highest quartile of CHD discharges/month.

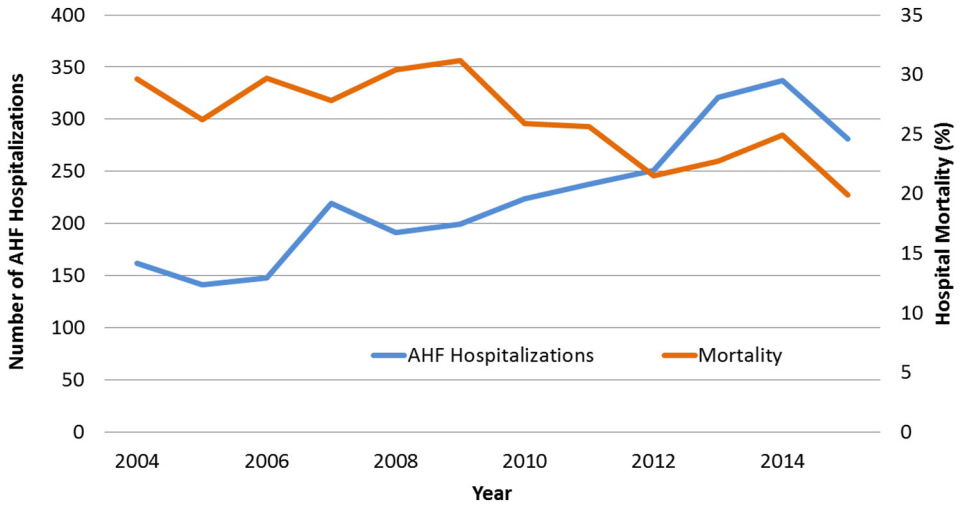
The wage and price index (published annually in the Federal Register) adjusted charges for each unit of service, and annual hospital- and department-specific ratio of cost-to-charge (RCC) were obtained from PHIS.

Table I. Patient demographic and clinical characteristics

	AHF (n = 2712)	No AHF (n = 462,770)	*P*
Age, years, n (%)			<.0001
<1	1587 (58.5)	300,338 (64.9)	
1-12	792 (29.2)	133,741 (28.9)	
13-21	331 (12.2)	28,692 (6.2)	
Male, n (%)	1486 (54.8)	251,747 (54.4)	.7134
Nonwhite, n (%)	1039 (38.3)	174,927 (37.8)	.6022
Cardiac diagnosis, n (%)			<.0001
Non-Complex 2V	632 (23.3)	207,321 (44.8)	
Complex 2V	1269 (46.8)	206,858 (44.7)	
Single V	808 (29.8)	49,054 (10.6)	
Acute comorbidities, n (%)			
Respiratory failure	1017 (37.5)	30,543 (6.6)	<.0001
Acute renal failure	610 (22.5)	12,958 (2.8)	<.0001
Sepsis	881 (32.5)	52,756 (11.4)	<.0001
Stroke	217 (8.0)	6,016 (1.3)	<.0001
Center volume, CHD discharge/month, n (%)			.0354
<40	198 (7.3)	37,022 (8.0)	
40-79	477 (17.6)	89,777 (19.4)	
80-119	816 (30.1)	134,666 (29.1)	
>120	1220 (45.0)	201,305 (43.5)	
Center region, n (%)			<.0001
Midwest	575 (21.2)	114,304 (24.7)	
Northeast	504 (18.6)	76,820 (16.6)	
South	1044 (38.5)	171,688 (37.1)	
West	835 (21.7)	99,496 (21.5)	

AHF indicates advanced heart failure; CHD, congenital heart disease. Data expressed as % for categorical variables, *P* values reflect comparisons between AHF and No AHF at admission.

Figure 1



Trends of number of AHF hospitalizations and hospital mortality, 2004-2015. Trend test for number of AHF hospitalizations ($P < .0001$). Trend tests for mortality ($P = .0011$).

Adjusted hospital costs were calculated by multiplying the adjusted charge by the relevant RCC then further inflated to 2015 US dollars using the medical care services component of the Consumer Price Index.[15] Costs for each day of hospitalization were summarized into the following categories: room and board, pharmacy, laboratory, clinical services (e.g., respiratory, rehabilitative services, etc.), supply, and imaging. Adjusted overall cost and total costs for each category were calculated for each patient as the sum of the daily costs during the hospitalization.

Table II. Characteristics and unadjusted outcomes among hospitalizations with advanced heart failure

	All AHF (n = 2712)	Non-complex 2V (n = 651)	Complex 2V (n = 1259)	Single V (n = 802)	*P*
Characteristics					
Acute comorbidities, n (%)					
Respiratory failure	1017 (37.5)	282 (43.3)	427 (33.9)	307 (38.3)	.0003
Acute renal failure	610 (22.5)	141 (21.7)	264 (20.9)	204 (25.4)	.0498
Sepsis	881 (32.5)	263 (41.9)	369 (29.3)	239 (29.8)	<.0001
Stroke	217 (8.0)	55 (8.4)	73 (5.8)	88 (10.9)	<.0001
CCC categories, n (%)					
Neurologic	369 (13.6)	113 (18.1)	149 (11.8)	99 (12.3)	.0007
Respiratory	445 (16.4)	133 (21.2)	194 (15.4)	115 (14.4)	.0016
Renal	453 (16.7)	100 (15.9)	204 (16.2)	143 (17.8)	.5816
Gastrointestinal	728 (26.9)	176 (28.1)	283 (22.5)	255 (31.8)	<.0001
Hematologic or Immunologic	222 (8.2)	50 (8.0)	107 (8.5)	62 (7.7)	.7719
Metabolic	328 (12.1)	86 (13.7)	149 (11.8)	87 (10.9)	.2773
Other Congenital or Genetic	475 (17.5)	174 (27.8)	210 (16.7)	86 (10.7)	<.0001
Malignancy	68 (2.5)	28 (4.4)	23 (1.8)	18 (2.3)	.0038
Neonatal	336 (12.4)	162 (25.8)	128 (10.2)	45 (5.6)	<.0001
Technology Dependence	1372 (50.6)	319 (50.9)	589 (46.8)	448 (55.8)	.0005
Number CCCs, n (%)					<.0001
0	914 (33.7)	144 (22.9)	491 (39.0)	275 (34.3)	
1	835 (30.8)	181 (28.8)	369 (29.3)	275 (34.3)	
2	518 (19.1)	147 (23.4)	210 (16.7)	156 (19.5)	
Outcomes					
Mortality, n (%)	688 (25.6)	179 (28.6)	286 (22.7)	223 (27.8)	.0055
ECMO, n (%)	414 (15.3)	110 (17.5)	199 (15.8)	101 (12.6)	.2569
VAD, n (%)	88 (3.2)	26 (4.2)	37 (2.9)	24 (3.0)	.3384
Transplant, n (%)	427 (15.7)	61 (9.7)	164 (13.0)	200 (24.9)	<.0001
Hospital length of stay (days), median (IQR)	38 (20-75)	41 (22-82)	34 (18-63)	42 (20-86)	<.0001
ICU length of stay (days), median (IQR)	26 (13-55)	32 (16-65)	24 (13-48)	26 (12-58)	<.0001
30-day readmission, n (%)	351 (17.4)	58 (12.9)	170 (17.5)	121 (20.9)	.0039
30-day AHF readmission, n (%)	66 (3.3)	11 (2.5)	28 (2.9)	27 (4.7)	.0856

AHF indicates advanced heart failure; CCC, chronic complex conditions; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; VAD, ventricular assist device. Data expressed as count (%) for categorical variables, median (interquartile range) for continuous variables, *P* values reflect comparisons between AHF and No AHF at admission.

Statistical analysis

Demographic and clinical data are expressed as number with percent or as median value with interquartile range (IQR), as appropriate. Comparisons of characteristics between patients with AHF and patients without AHF or among CHD groups were assessed with Chi-squares tests or with the Wilcoxon rank sum tests/the Kruskal-Wallis tests, as appropriate. We performed the trend analyses using Cochran-Armitage tests for rates and generalized linear models with a log link and gamma distribution for hospital costs.

To assess the association of patient's demographic and clinical characteristic with hospital mortality, we fitted multilevel logistic regression models including pertinent patient demographic and clinical characteristic variables, with a random intercept to account for the clustering of observations within hospitals. Variables in the multivariable regression included age in years, gender, race, CHD groups, and acute comorbidities, number of CCCs, VAD, ECMO, transplantation, geographical area, and hospital CHD volumes.

To assess the association of patient's demographic and clinical characteristic with total hospital costs, we fitted multivariable generalized linear models. Generalized linear models with a log link and gamma distribution were used to calculate unadjusted and adjusted cost ratios with corresponding 95% CI. We used all co-variables in previous multilevel logistic regression models and LOS. Robust variance estimates were obtained using generalized estimating equation methods with an exchangeable correlation matrix to account for clustering by hospital. All data management and statistical analyses were performed using SAS (version 9.4, SAS Institute, Inc., Cary, NC). A two-sided *P*-value <.05 was used as the threshold for statistical significance.

Results

Patient and center characteristics

A total of 465,482 CHD-related hospitalizations from 49 centers were included with patient and center characteristics shown in Table I. AHF was present in 2,712 (0.6%) hospitalizations with an almost two-fold increase throughout the study period from 2004 to 2015 (Figure 1, Supplement 2). Although infants comprised the largest proportion of patients overall, there were more

Table III. Risk factors for mortality in advanced heart failure

Characteristics	Unadjusted mortality, %	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age (years)					
<1	28.7	2.14 (1.53-2.97)	<.0001	1.71 (1.17-2.48)	.0057
1-12	23.3	1.62 (1.14-2.31)	<.0001	1.43 (0.97-2.13)	.0683
13-21	16.6	Reference	-	Reference	-
Gender					
Male	25.7	Reference	-	Reference	-
Female	25.8	1.04 (0.86-1.25)	.7663	1.02 (0.83-1.25)	.8602
Race					
White	23.2	Reference	-	Reference	-
None-white	29.6	1.35 (1.11-1.64)	.0035	1.28 (1.04-1.59)	.0234
Cardiac Disease					
Non-complex 2V	28.6	Reference	-	Reference	-
Complex 2V	22.7	0.73 (0.58-0.92)	.0086	0.97 (0.75-1.25)	.7928
Single V	27.8	0.98 (0.77-1.25)	.8631	1.64 (1.23-2.19)	.0009
Acute Comorbidities					
No respiratory failure	21.9	Reference	-	Reference	-
Respiratory failure	31.9	1.69 (1.39-2.04)	<.0001	1.47 (1.19-1.82)	.0007
No acute renal failure	20.3	Reference	-	Reference	-
Acute renal failure	44.2	3.24 (2.61-4.01)	<.0001	2.63 (2.06-3.35)	<.0001
No sepsis	19.8	Reference	-	Reference	-
Sepsis	37.8	2.25 (1.86-2.73)	<.0001	1.74 (1.40-2.17)	<.0001
No stroke	24.9	Reference	-	Reference	-
Stroke	34.3	1.64 (1.19-2.25)	<.0001	1.16 (0.80-1.68)	.4237
Number CCCs					
0	15.1	Reference	-	Reference	-
1	27.4	2.13 (1.66-2.73)	<.0001	1.76 (1.34-2.30)	<.0001
2	31.9	2.67 (2.03-3.51)	<.0001	1.87 (1.38-2.53)	<.0001
≥3	38.4	3.49 (2.64-4.63)	<.0001	2.14 (1.56-2.93)	<.0001
Advanced cardiac support					
ECMO No	22.3	Reference	-	Reference	-
ECMO Yes	44.2	2.80 (2.21-3.55)	<.0001	2.45 (1.87-3.21)	<.0001
VAD No	25.6	Reference	-	Reference	-
VAD Yes	28.4	1.20 (0.75-2.00)	.4569	1.48 (0.78-2.79)	.2116
Transplantation No	29.3	Reference	-	Reference	-
Transplantation Yes	6.3	0.16 (0.11-0.25)	<.0001	0.10 (0.06-0.16)	<.0001
Center volume by quartile					
Quartile 1	25.9	Reference	-	Reference	-
Quartile 2	23.2	0.63 (0.33-1.23)	.1728	0.63 (0.32-1.25)	.1771
Quartile 3	22.8	0.65 (0.35-1.23)	.1797	0.69 (0.36-1.35)	.2765
Quartile 4	28.5	0.78 (0.42-1.44)	.4204	0.84 (0.44-1.61)	.5979
Center region					
Midwest	22.6	Reference	-	Reference	-
Northeast	25.7	1.14 (0.66-1.97)	.6352	1.19 (0.63-2.23)	.5838
South	28.9	1.45 (0.95-2.22)	.0871	1.17 (0.71-1.91)	.5324
West	22.9	0.91 (0.56-1.48)	.6949	0.87 (0.52-1.45)	.5786

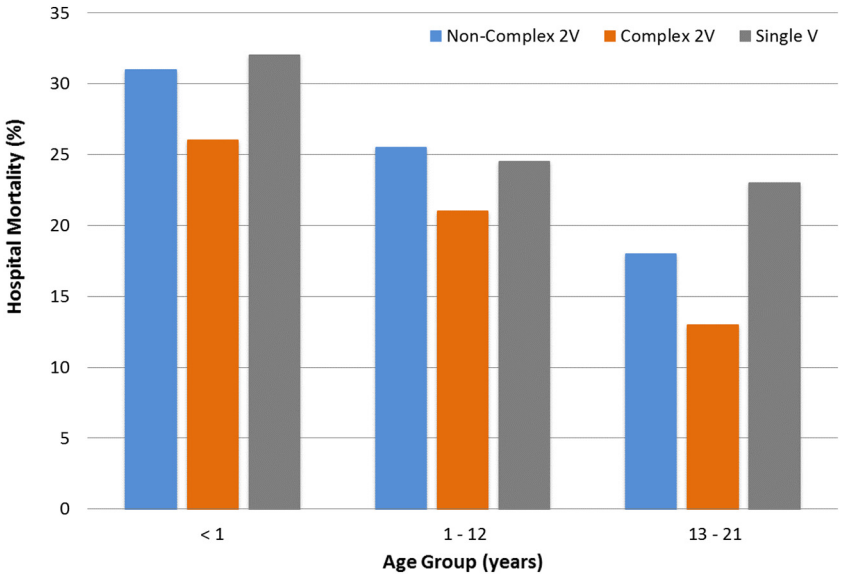
CCC indicates chronic complex conditions; IQR, interquartile range; CI, confidence interval. ECMO, extracorporeal membrane oxygenation; VAD indicates ventricular assist device.

adolescents and single ventricles with AHF compared to those without AHF. Approximately one-third of patients with AHF had acute non-cardiac comorbidities and over two-thirds had at least one CCC (Table II). Fifty percent of CHD patients with AHF were considered technology dependent. Over three-fourths of AHF-related hospitalizations occurred at large volume centers, defined as greater than 80 CHD discharges per month.

In-hospital mortality

Unadjusted outcomes in AHF are described in Table II. In-hospital mortality for children with CHD and AHF was 26%, compared to only 4% in those without AHF ($P<.0001$). Despite increasing incidence of AHF hospitalizations during the study period, mortality significantly improved over time ($P<.0001$, Figure 1, Supplement 2). Factors associated with mortality in AHF on multivariable analysis included non-white race, infancy, single ventricle, need for ECMO support, and presence of acute or chronic complex comorbidities (Table III, Figure 2). Conversely, heart transplantation was protective against mortality. VAD support was not associated with improved survival. Center volume was not associated with survival.

Figure 2



Unadjusted AHF mortality by age group and CHD complexity. * indicates $P < .05$ for comparison between complex 2v and single v. There was no significant difference between other groups.

Resource utilization

AHF was associated with significantly longer hospital and ICU LOS compared to those without AHF ($p<0.001$ for both), with median hospitalizations lasting greater than one month (Table II). Thirty-day readmission rate was 17%. Of those, 19% were for AHF. Advanced HF support utilization, including ECMO, VAD and transplant, significantly increased during the study period (Table IV). Single ventricle patients were less likely to receive ECMO support but more likely to receive cardiac transplantation, as VADs were rarely used in any CHD. However, VAD utilization significantly increased during the study period from 0.6% to 7.5% ($P<.0001$).

Hospital costs

Hospital costs were significantly greater in patients with AHF compared to those without (median $252,243 [IQR $122,493-486,134] vs. $44,133 [$19,535-98,615]; $P<.001$). Hospital costs for AHF significantly increased during the study period despite improvement in AHF mortality (Figure 3). Higher hospital costs were associated with infancy, longer LOS, use of advanced cardiac support, and presence of comorbidities (Table V). Notably, CHD disease complexity, including single ventricle, was not associated with differences in hospital cost. Among patients admitted with CHD for > 7 days, AHF was associated with higher costs across all charge categories compared to patients without AHF (Figure 4).

Discussion

To our knowledge, this is the first study to comprehensively evaluate outcomes and resource utilization in children with CHD-related heart failure. Although AHF in children with CHD is uncommon, the incidence is increasing and is associated with high morbidity, mortality and utilization of advanced cardiac therapies. More than 1 in 5 children with CHD and AHF will not survive to hospital discharge. Most risk factors for morality are not modifiable, including single ventricle physiology, infancy, non-white race and CCCs, necessitating the need for further study to identify other modifiable risk factors such as acute comorbidities.

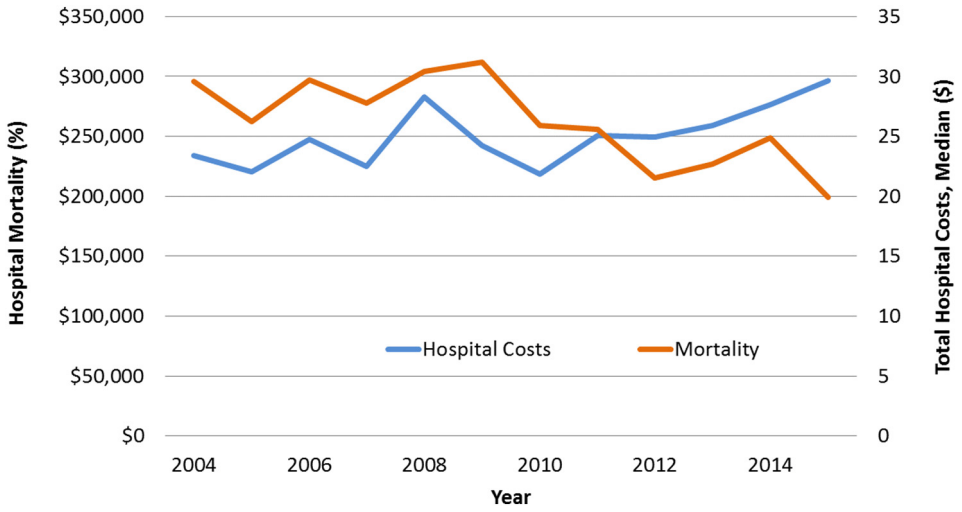
Heart failure in patients with CHD can be due to volume or pressure overload conditions related to palliative repairs or residual lesions that result in ventricular dysfunction.[5,16] Fontan palliation has previously been identified as high-risk for late ventricular dysfunction with 40% of Fontan patients exhibiting clinical heart failure by 16 years.[17,18] Heart failure management in CHD, particularly single ventricle patients, remains an area of ongoing study due to limited evidence for CHD-related heart failure management.[2,4,19] Currently most CHD-related heart failure data are extrapolated from non-congenital adult heart failure guidelines.[20,21] Therefore, studies analyzing outcomes and management of pediatric patients with heart failure and CHD are needed to develop best practices for this complex population. Our study begins to address this by

Table IV. Trend in resource utilization and hospital costs in advanced heart failure from 2004 to 2015

Year	Readmission, %	ECMO, %	VAD, %	Transplant, %	Total Hospital Costs, Median (IQR)
2004	20.3	9.3	0.6	11.7	$233,762 (137,171-392,357)
2005	21.3	9.2	0.7	9.2	$220,125 (118,465-359,814)
2006	16.3	18.2	3.4	15.5	$247,160 (121,688-385,597)
2007	17.2	12.3	2.3	14.2	$225,173 (116,410-489,873)
2008	12.0	16.2	2.1	19.9	$282,689 (135,918-508,480)
2009	18.2	11.6	3.0	11.1	$242,299 (110,282-496,737)
2010	15.1	11.2	2.2	15.2	$218,193 (101,717-385,658)
2011	14.7	18.5	2.5	15.9	$250,589 (136,882-494,750)
2012	21.3	11.6	1.6	15.5	$249,676 (121,682-486,134)
2013	18.1	16.8	4.1	12.8	$258,801 (134,236-563,623)
2014	20.9	20.5	5.0	17.8	$276,629 (130,217-558,717)
2015	13.3	20.3	7.5	24.6	$296,605 (133,404-615,731)

Trend tests for readmission ($P = .8170$); for ECMO ($P < .0001$); for VAD ($P < .0001$); for transplant ($P = 0.0009$); for total hospital costs ($P < .0001$).

Figure 3



Trends of hospital mortality and total hospital costs among patients with AHF, 2004-2015. Trend tests for total hospital costs ($P < .0001$). Adjusted hospital costs were adjusted using the cost-to-charge ratio and inflated to 2015 US dollars.

better defining this population and identifying factors associated with AHF. These patients have frequent comorbidities with over one-third having at least one acute comorbidity during hospitalization and over two-thirds having at least one chronic complex comorbidity. Over 50% of the cohort was chronically technologically dependent, a factor that reflects the complexity of this unique population.

Despite an increasing incidence of CHD-related AHF hospitalizations over the past decade, mortality rates are improving. Nevertheless, in-hospital mortality for CHD-related AHF is strikingly high at 26%, which is six-fold greater than those without AHF. Factors associated with mortality included infancy, single ventricle physiology and presence of acute and chronic comorbidities. Although most of these factors are non-modifiable, acute comorbidities may represent an opportunity to improve survival by identifying techniques for preventing acute complications such as sepsis.

There was a racial difference in survival in our cohort with non-white race associated with 1.3 greater risk for death compared to white after adjusting for patient-level factors. These data highlight a significant health care disparity that is consistent with previous studies in CHD. Oster et al. reported lower post-operative mortality after CHD surgery among non-Hispanic white patients compared to other races that persisted even after adjusting for differences in access to care, and Collins et al. described higher infant mortality in patients with CHD who were African-American compared to non-Hispanic white.[22,23]

Table V. Factor associated with total hospital costs

Characteristics	Total hospital cost, Median (IQR)	Unadjusted cost Ratio (95% CI)	*P*	Adjusted cost Ratio (95% CI)	*P*
Age (years)					
<1	$278,614 ($143,817-$526,430)	Reference	-	Reference	-
1-12	$234,044 ($101,717-$456,364)	0.84 (0.77-0.91)	<.0001	0.94 (0.90-0.99)	.0173
13-21	$171,536 ($73,726-$351,918)	0.65 (0.58-0.72	<.0001	0.92 (0.87-0.99)	.0170
Gender					
Male	$245,152 ($116,410-$468,264)	Reference	-	Reference	-
Female	$261,844 ($133,613-$508,971)	1.01 (0.94-1.08)	.7594	0.99 (0.95-1.03)	.6799
Race					
None-white	$254,472 ($129,623-$508,946)	Reference	-	Reference	-
White	$251,231 ($119,974-$475,973)	1.00 (0.93-1.08)	.9980	0.99 (0.95-1.03)	.4736
Cardiac Disease					
Non-complex 2V	$273,094 ($143,480-$500,547)	Reference	-	Reference	-
Complex 2V	$228,180 ($116,672-$433,202)	0.87 (0.79-0.95)	.0022	1.02 (0.97-1.07)	.3852
Single V	$271,392 ($117,043-$569,945)	1.10 (0.99-1.21)	.0580	1.03 (0.97-1.09)	.2798
Acute comorbidities					
Respiratory failure No	$207,615 ($100,705-$408,344)	Reference	-	Reference	-
Respiratory failure Yes	$336,342 ($171,053-$638,054)	1.53 (1.42-1.65)	<.0001	1.18 (1.13-1.23)	<.0001
Acute renal failure No	$217,907 ($105,281-$420,920)	Reference	-	Reference	-
Acute renal failure Yes	$403,991 ($207,615-$723,671)	1.62 (1.49-1.76)	<.0001	1.23 (1.17-1.29)	<.0001
Sepsis No	$195,284 ($96,859-$382,435)	Reference	-	Reference	-
Sepsis Yes	$386,597 ($212,680-$687,338)	1.73 (1.61-1.86)	<.0001	1.13 (1.08-1.17)	<.0001
Stroke No	$241,815 ($118,641-$461,314)	Reference	-	Reference	-
Stroke Yes	$422,417 ($206-$734,881)	1.45 (1.27-1.65)	<.0001	1.04 (0.97-1.12)	.2924
Number CCCs					
0	$159,989 ($79,515-$308,868)	Reference	-	Reference	-
1	$241,887 ($122,732-$444,258)	1.41 (1.29-1.53)	<.0001	1.13 (1.08-1.19)	<.0001
2	$340,885 ($162,250-$640,522)	1.84 (1.67-2.03)	<.0001	1.22 (1.15-1.30)	<.0001
≥3	$446,560 ($239,244-$766,640)	2.30 (2.07-2.54)	<.0001	1.29 (1.21-1.37)	<.0001
Length of Hospital Stay (days, quartiles)*					
1st (6–19)	$77,848 ($46,214-$119,974)	Reference	-	Reference	-
2nd (20-37)	$170,111 ($120,058-$249,612)	2.13 (1.99-2.26)	<.0001	1.94 (1.84-2.06)	<.0001
3rd (38-73)	$311,854 ($226,843-$434,225)	3.70 (3.47-3.95)	<.0001	3.06 (2.88-3.24)	<.0001
4th (74-601)	$689,209 ($466,017-$1,042,092)	8.69 (8.15-9.26)	<.0001	6.61 (6.20-7.03)	<.0001
Advanced cardiac support					
ECMO No	$215,487 ($107,266-$428,377)	Reference	-	Reference	-
ECMO Yes	$486,134 ($304,008-$794,989)	1.84 (1.67-2.03)	<.0001	1.60 (1.52-1.69)	<.0001
VAD No	$241,880 ($119,966-$458,993)	Reference	-	Reference	-
VAD Yes	$796,570 ($512,592-$1,143,175)	2.45 (2.02-2.97)	<.0001	1.37 (1.23-1.53)	<.0001
Transplantation No	$211,433 ($105,261-$422,417)	Reference	-	Reference	-
Transplantation Yes	$478,029 ($312,085-$803,721)	1.92 (1.75-2.11)	<.0001	1.26 (1.19-1.34)	<.0001
Center volume by quartile					
Quartile 1	$254,101 ($133,954-$432,071)	Reference	-	Reference	-
Quartile 2	$217,815 ($109,819-$393,825)	0.93 (0.76-1.15)	.5267	1.22 (1.09-1.36)	.0003
Quartile 3	$259,990 ($107,780-$517,078)	1.11 (0.93-1.35)	.2553	1.16 (1.03-1.29)	.0103
Quartile 4	$258,736 ($138,255-$512,729)	1.15 (0.96-1.39)	.1256	1.15 (1.04-1.27)	.0072
Center region					
Midwest	$260,997 ($119,717-$559,176)	Reference	-	Reference	-
Northeast	$222,348 ($106,425-$448,887)	0.87 (0.77-0.98)	.0164	0.83 (0.78-0.90)	<.0001
South	$274,984 ($140,464-$485,807)	0.94 (0.86-1.05)	.2455	1.01 (0.95-1.07)	.7216
West	$221,306 ($109,819-$452,634)	0.86 (0.78-0.96)	.0089	0.93 (0.88-0.99)	.0181

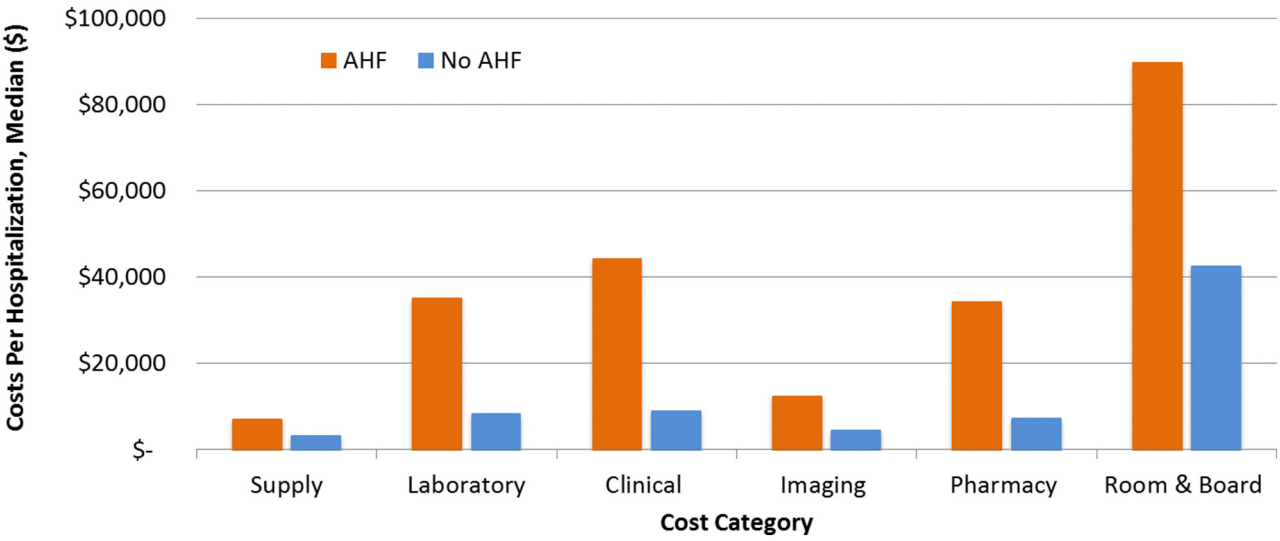
CCC indicates chronic complex conditions; IQR, interquartile range; CI, confidence interval. ECMO, extracorporeal membrane oxygenation; VAD indicates ventricular assist device.

This finding in our CHD population with AHF certainly warrants further study to better elucidate factors driving this health care disparity.

Although other studies have shown a relationship between center volume and outcomes after congenital heart surgery, our analysis did not show a survival advantage based on hospital volume.[24] However, most patients with AHF were treated in larger volume centers, so referral patterns likely impact the relationship between center volume and mortality. Nevertheless, further studies may be helpful to identify other care models that influence outcomes in children with CHD and heart failure.

Regarding use of advanced cardiac support in CHD, our study demonstrated a continual increase over the past

Figure 4



Advanced heart failure hospital costs by cost category. All charge categories had $P < .0001$ for AHF versus no AHF ≥7 day hospitalization. AHF = advanced heart failure.

decade. However, among the various advanced heart failure support strategies (ECMO, VAD, transplant), transplant was the only therapy associated with improved survival. VAD support is rarely utilized in CHD compared to other causes of pediatric heart failure such as cardiomyopathy, so evaluating the impact of VAD on pediatric heart failure outcomes in CHD remains challenging due to small patient size for adequately powered studies. Our VAD data in CHD are similar to reports from the PediMACS database of pediatric VAD utilization and is largely related to several factors including the anatomic challenges of VADs in CHD, particularly single ventricle disease.[19] Advances in surgical techniques and VAD technology may enable an increasing role for mechanical support in pediatric CHD, including in single ventricle patients.[25-28] In our study population, VADs were used in only 3% of cases but there was an increasing trend in utilization that may represent an important opportunity to develop effective strategies to improve outcomes in this high-risk population.

Furthermore, AHF in CHD is associated with significant resource utilization. Most AHF hospitalizations exceeded 1 month, generated hospital costs over $250,000, which was a six-fold increase above the non-AHF cohort, and readmissions within 30 days were frequent. This is significant because over 70% of all pediatric heart failure admissions are due to CHD.[3] Furthermore, hospital costs for pediatric heart failure hospitalizations are significantly greater than adult heart failure hospitalizations, have been steadily increasing over time, and will continue to contribute to high medical expenditures.[3,29] Our study in CHD-related AHF is consistent with this previous data, demonstrating an increase in hospital costs over the past decade. Factors associated with increased hospital costs in CHD-related include prolonged LOS, frequent comorbidities, infancy status and use of advanced cardiac support. Based on charge categories, AHF was associated with increased resource utilization across all areas of care, including laboratory, pharmacy, imaging and clinical services. As cost-effectiveness becomes an increasing driver in high-value care, ongoing study is needed to help optimize resource utilization. Possible strategies to reduce costs may include developing evidence-based guidelines, identifying modifiable risk factors to prevent hospital acquired infection, and developing strategies to decrease hospitalization duration, readmission rates and complications.[30-34] Additional study evaluating center variation in pediatric heart failure management may also help elucidate factors to help improve outcomes in this complex population. These strategies may not only decease resource utilization but may also improve overall outcomes, including mortality.

Limitations

This study is subject to the limitations inherent to all observational, retrospective database analyses. The data collection obtained from 49 US children's hospitals provides a multi-institutional perspective on outcomes to help account for the likely variation in heart failure management. However, these data are obtained from a subset of institutions and may not be representative of

care in non-participating academic or community hospitals. Additionally, the seven day inotropic support requirement as an inclusion criteria may result in a selection bias towards a more acutely ill cohort of patients, limiting the generalizability of the data to the broader cohort of CHD with heart failure. However, this inclusion criteria was selected to ensure a high enough severity of heart failure was sufficiently capture for our analysis.

The PHIS database is a large administrative database in which that the accuracy of diagnoses and procedures relies on accurate *ICD-9-CM* coding by participating institutions. Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals, and data are subjected to a number of reliability and validity checks before being included in the database. However, inaccurate or incomplete *ICD-9* coding may result in misreporting and affect outcome analysis.[35] Furthermore, PHIS does not collect physician professional fees so hospital costs, which is a limitation of cost analysis using the PHIS dataset.

Conclusion

Children with CHD-related AHF represent a high-risk population associated with significant morbidity, mortality and resource utilization. Approximately 1 in 5 children do not survive to hospital discharge. This is the first study to characterize this population and associated outcomes and resource utilization. Many risk factors for mortality may not be modifiable, and further study is needed to identify modifiable risk factors and improve care for this complex population.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.11.010.

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