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REVIEW ARTICLE

Impact of Medical Interventions and Comorbidities on Norwood Admission for Patients with Hypoplastic Left Heart Syndrome

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Abstract

The purpose of these analyses was to determine how specific comorbidities and medical interventions impact risk of inpatient mortality in those with hypoplastic left heart syndrome undergoing Norwood procedure. The secondary aims were to determine the impact of these on billed charges, postoperative length of stay, and risk of cardiac arrest. Admissions from 2004 to 2015 in the Pediatric Health Information System database with hypoplastic left heart syndrome and Norwood procedure were identified. Admission characteristics, patient interventions, and the presence of comorbidities were captured. A total of 5,138 admissions were identified meeting inclusion criteria. Of these 829 (16.1%) experienced inpatient mortality, and 352 (6.7%) experienced cardiac arrest. The frequency of inpatient mortality did not significantly change over the course of the study era. The frequency of cardiac arrest significantly decreased from 7.4% in 2004 to 4.3% in 2015 ($p=0.04$). The frequency of pharmacologic therapies, particularly vasoactive use, decreased as the study period progressed. Regression analyses demonstrated a significant association between cardiac arrest and inpatient mortality with arrhythmias, acute kidney injury, and pulmonary hypertension. Similarly, regression analyses demonstrated a significant association between increase in billed charges and length of stay with year of surgery, presence of heart failure, syndromes, and acute kidney injury. For patients with hypoplastic left heart syndrome undergoing the Norwood procedure, the frequency of pharmacologic therapies and cardiac arrest has decreased over time. There are significant associations between acute kidney injury, arrythmias, and pulmonary hypertension with cardiac arrest and mortality.

Keywords Hypoplastic left heart syndrome · Norwood procedures · Congenital heart surgery · Congenital heart disease

Introduction

Hypoplastic left heart syndrome (HLHS) is a group of clinical entities characterized by hypoplasia of the left heart structures and systemic outflow tract obstruction. The term was first used by Noonan and Nadas in 1958 [1]. The Norwood procedure with a modified Blalock-Taussig shunt or a right ventricle to pulmonary artery conduit are the main options for stage 1 surgical palliation for patients born with this condition [2, 3]. The period after the Norwood procedure is considered to be a high-risk period as many complications could arise [4]. Although risk factor identification after the Norwood procedure has increased over the years, most data focus on demographic, preoperative, and surgical risk factors [5–8]. There is limited information regarding the association of medical interventions such as the type of vasoactive agent selected with clinical outcomes. Therefore, the purpose of these analyses was to use data from a national

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database to help determine how specific comorbidities and medical interventions impact risk of inpatient mortality in those with hypoplastic left heart syndrome undergoing Norwood procedure. Secondary aims were to determine the impact of these specific comorbidities, interventions, and medications on billed charges, postoperative length of stay, and risk of cardiac arrest.

Methods

As this study utilized deidentified data from a national database, no consents were obtained by the authors of this study. This study is in concordance with the Helsinki declaration.

Pediatric Health Information System Database

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. The 53 hospitals that contribute data to PHIS are affiliated with the Children's Hospital Association (Lenexa, KS), a business alliance of children's hospitals. Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, procedures, and charges. Data are deidentified at the time of data submission, and data are subjected to several reliability and validity checks before being included in the database.

Admission Identification

Pediatric health information systems database data from 2004 to 2015 were utilized for this study. Data from these years were utilized as ICD-9 codes as the identifiers.

Firstly, admissions with hypoplastic left heart syndrome were identified. Of these admissions, those under 2 months of age were then further identified. Next, a Norwood procedure was then identified. As there is no single ICD-9 code for a Norwood procedure, a Norwood procedure was considered to be done when an arch repair and either Blalock-Taussig shunt or right ventricle to pulmonary artery conduit placement was done at the same intervention. Thus, the inclusion criteria for admissions for this study were: (1) diagnosis of hypoplastic left heart syndrome; (2) pediatric admissions under 2 months of age; (3) Norwood procedure identified by arch repair done concomitantly with Blalock-Taussig shunt placement or right ventricle to pulmonary artery conduit. Any admissions not meeting these criteria were excluded. From this point forward, the word "admission" will be used to refer to admissions meeting these inclusion criteria unless otherwise specified.

Admission Characteristics

Several data points were captured for each of the included admissions. Age of admission, gender, year of admission were captured for all admissions. Postoperative length of stay, billed charges, and inpatient mortality were also recorded for all admissions. Any use of "mortality" from here on after will refer to inpatient mortality during the admission of interest.

The presence of specific congenital malformations of the heart were captured using the ICD-9 codes outlined in supplementary Table 1. The presence of specific cardiac surgeries during the admissions were also captured using the ICD-9 codes outlined in supplementary Table 1.

The presence or absence of the following comorbidities was recorded as well: heart failure, tachyarrhythmia, bradyarrhythmia, acute kidney injury, pulmonary hypertension, hypothyroidism, and the presence of syndromes.

Severity of illness measures include the comorbidities listed above. Clinical or laboratory data such as near infrared spectroscopy, serum lactate, or venous saturation were not available for use.

The presence of the following interventions was recorded: need for peritoneal dialysis, continuous renal replacement therapy, peritoneal dialysis, extracorporeal membrane oxygenation.

The presence of the following medications was recorded: epinephrine, norepinephrine, dopamine, dobutamine, milrinone, vasopressin, sodium bicarbonate, calcium chloride, calcium gluconate, angiotensin converting enzyme inhibitor, beta blocker, alpha blocker, aspirin, warfarin, heparin, sildenafil, and inhaled nitric oxide. These were selected as they represent agents frequently used in the postoperative setting and are captured in the database.

Statistical Analyses

Continuous variables were described as median and range, while categorical variables were described as absolute frequency and percentage. Analyses of continuous variables across groups were conducted using a Mann–Whitney *U* test, while analyses of categorical variables were conducted using a Fisher exact test.

First, the frequency of interventions and medications was quantified by year. This was done to determine trends of use of various interventions throughout the era. An ANOVA was completed to compare variables on year-by-year trend over the study period. Additionally, the frequency of cardiac arrest and inpatient mortality were also quantified by year.

Next a series of regression analyses was conducted. Separate logistic regression analyses were conducted with cardiac arrest and mortality as the dependent variables and the comorbidities, interventions, and medications being included as independent variables. Next, separate linear regression analyses were conducted with billed charges and postoperative length of stay as the dependent variables and with the same independent variables as the prior mentioned regressions. All regressions were conducted as backwards stepwise regressions with 20 iterations using the likelihood ratio selection method. For the logistic regressions, the results are reported as odds ratio with 95% confidence interval, while for the linear regressions, the results are reported as beta-coefficient and p value.

All statistical analyses were conducted using SPSS, Version 23.0. A p value of less than 0.05 was considered statistically significant. Any use of the word "significant" throughout this manuscript implies statistical significance unless otherwise specified.

Results

Cohort Information

A total of 5,138 admissions were identified meeting the inclusion criteria outlined above. Of these a total of 829 (16.1%) experienced inpatient mortality. Of these 5,138 admissions, 352 (6.7%) experienced cardiac arrest. Median billed charges for admissions with survival to discharge were US$422,58 compared to US$743,851 for admissions that experienced inpatient mortality ($p < 0.01$). Median postoperative length of stay for admissions with survival to discharge was 26.0 days compared to 19.0 days in admissions that experienced inpatient mortality ($p = 0.15$) (Table 1).

Clinical Outcomes by Year

The frequency of cardiac arrest decreased significantly over the course of the study era. In 2004, the cardiac arrest frequency was 7.4%. This increased and decreased over the study era and was ultimately 4.3% in 2015 ($p = 0.04$) (Table 2).

The frequency of inpatient mortality did not significantly change over the course of the study era. It was 17.9% in 2004 compared to 15.8% in 2015 ($p = 0.06$) (Table 2).

Medications by Year

The following medications were used in significantly decreasing frequency when frequency of use was compared between all the years from 2004 to 2015: epinephrine (92.1 to 71.8%, $p < 0.01$), dopamine (87.1 to 52.3%, $p < 0.01$), dobutamine (31.3 to 2.5%, $p < 0.01$), milrinone (88.9 to 71.5%, $p < 0.01$), vasopressin (10.0 to 6.5%, $p < 0.01$), sodium bicarbonate (68.9 to 48.9%, $p < 0.01$), sodium chloride (70.8% versus 42.1%), sodium gluconate (63.4 to 40.6%, $p < 0.01$), angiotensin converting enzyme inhibitor (51.1% versus 36.8%, $p < 0.01$), alpha blocker (16.1 to 11.1%, $p < 0.01$), heparin (46.8 to 21.4%, $p < 0.01$) (Table 3).

The following medications were used in significantly increasing frequency when frequency of use was compared between 2004 and 2015: beta blocker (5.5 to 12.1%, $p < 0.01$) and inhaled nitric oxide (1.3 to 10.8%, $p < 0.01$) (Table 3).

With respect to aspirin there was a statistically significant change. Between 2004 and 2015 the frequency had decreased but between 2004 and 2014 there was a general increase in the use (Table 3).

No significant difference was noted in the frequency of use of norepinephrine, warfarin, and sildenafil (Table 3).

Regression Analyses, Billed Charges

Regression analyses demonstrated the following were associated with a significant increase in billed charges: year of surgery, heart failure, presence of a syndrome, bradyarrhythmia, tachyarrhythmia, acute kidney injury, pulmonary hypertension, dopamine, milrinone, inhaled nitric oxide, nicardipine, aspirin, right ventricle to pulmonary artery conduit (in comparison to Blalock-Taussig shunt), cardiac arrest, and extracorporeal membrane oxygenation.

The following were associated with a significant decrease in billed charges: epinephrine, norepinephrine, sodium bicarbonate, calcium gluconate, calcium chloride, sildenafil, steroids, angiotensin converting enzyme inhibitor, sodium

Table 1 Differences in billed charges and postoperative length of stay between those who survived to discharge and those who experienced inpatient mortality

	Survived to discharge	Inpatient mortality	Odds ratio	p value
Billed charges (USD)	$422,583	$743,851	–	< 0.01
Postoperative LOS[a] (days)	26.0 (0 to 574.0)	19.0 (0 to 397.0)	–	0.15

[a]LOS, length of stay

Data are shown as median (range)

Table 2 Admissions and clinical outcomes by year

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total	*p* value
Total admissions	380	427	432	473	484	448	384	423	449	434	481	323	5138	
Cardiac arrest	29 (7.6)	38 (8.9)	39 (9.0)	26 (5.5)	24 (5.0)	24 (5.4)	29 (7.6)	28 (6.6)	28 (6.2)	41 (9.4)	32 (6.7)	14 (4.3)	352 (6.7)	0.04
Inpatient mortality	68 (17.9)	80 (18.7)	85 (19.7)	73 (15.4)	77 (15.9)	73 (16.3)	71 (18.5)	71 (16.8)	52 (11.6)	62 (14.3)	66 (13.7)	51 (15.8)	829 (16.1)	0.06

Data are shown as *n* (%)

nitroprusside, and continuous renal replacement therapy (Tables 4 and 5).

Regression Analyses, Postoperative Length of Stay

Regression analyses demonstrated the following were associated with a significant increase in postoperative length of stay: heart failure, presence of a syndrome, bradyarrhythmia, tachyarrhythmia, acute kidney injury, pulmonary hypertension, nicardipine, aspirin, cardiac arrest, extracorporeal membrane oxygenation.

The following were associated with a significant decrease in postoperative length of stay: epinephrine, norepinephrine, dopamine, sodium bicarbonate, calcium gluconate, calcium chloride, steroids, angiotensin converting enzyme inhibitor, alpha blocker, and sodium nitroprusside (Tables 4 and 5).

Regression Analyses, Cardiac Arrest

Regression analyses demonstrated the following were associated with a significant increase in the odds of cardiac arrest: bradyarrhythmia, tachyarrhythmia, vasopressin, sodium nitroprusside, and continuous renal replacement therapy.

The following were associated with a significant decrease in the odds of cardiac arrest: more recent year of surgery, sodium bicarbonate, calcium chloride, steroids, angiotensin converting enzyme inhibitor, alpha blocker, aspirin, and right ventricle to pulmonary artery conduit (in comparison to Blalock-Taussig shunt) (Tables 4 and 5).

Regression Analyses, Inpatient Mortality

Regression analyses were associated with a significant increase in the odds of inpatient mortality: bradyarrhythmia, tachyarrhythmia, acute kidney injury, pulmonary hypertension, norepinephrine, dopamine, vasopressin, steroids, peritoneal dialysis, continuous renal replacement therapy, cardiac arrest, and extracorporeal membrane oxygenation.

The following were associated with a significant decrease in the odds of inpatient mortality: more recent year of surgery, hypothyroidism, calcium chloride, angiotensin converting enzyme inhibitor, nicardipine, and aspirin (Tables 4 and 5).

Discussion

This study characterizes the frequency of medical interventions and pharmacologic therapies during the Norwood admission for children with hypoplastic left heart syndrome and attempts to model the impact of these on various admission characteristics.

Table 3 Use of medications by year

	2004 $n=380$)	2005 ($n=427$)	2006 ($n=432$)	2007 ($n=473$)	2008 ($n=484$)	2009 ($n=448$)	2010 ($n=384$)	2011 ($n=423$)	2012 ($n=449$)	2013 ($n=434$)	2014 ($n=481$)	2015 ($n=323$)	p value
Epinephrine	350 (92.1)	396 (92.7)	407 (94.2)	431 (91.1)	431 (89.0)	402 (89.7)	347 (90.4)	398 (94.1)	427 (95.1)	396 (91.2)	391 (81.3)	232 (71.8)	< 0.01
Norepinephrine	33 (8.7)	36 (8.4)	42 (9.7)	56 (11.8)	50 (10.3)	47 (10.5)	31 (8.1)	37 (8.7)	47 (10.5)	52 (12.0)	44 (9.1)	32 (9.9)	0.65
Dopamine	331 (87.1)	372 (87.1)	371 (85.9)	383 (81.0)	372 (76.9)	331 (73.9)	286 (74.5)	315 (74.5)	328 (73.1)	276 (63.6)	276 (57.4)	169 (52.3)	< 0.01
Dobutamine	119 (31.3)	110 (25.8)	105 (24.3)	82 (17.3)	57 (11.8)	38 (8.5)	42 (10.9)	28 (6.6)	30 (6.7)	20 (4.6)	19 (4.0)	8 (2.5)	< 0.01
Milrinone	338 (88.9)	386 (90.4)	411 (95.1)	444 (93.9)	459 (94.8)	414 (92.4)	360 (93.8)	403 (95.3)	420 (93.5)	389 (89.6)	403 (83.8)	231 (71.5)	< 0.01
Vasopressin	38 (10.0)	17 (4.0)	35 (8.1)	33 (7.0)	45 (9.3)	41 (9.2)	22 (5.7)	42 (9.9)	41 (9.1)	51 (11.8)	61 (12.7)	21 (6.5)	< 0.01
Sodium bicarbonate	262 (68.9)	302 (70.7)	296 (68.5)	304 (64.3)	317 (65.5)	289 (64.5)	241 (62.8)	262 (61.9)	290 (64.6)	273 (62.9)	243 (50.5)	158 (48.9)	< 0.01
Calcium chloride	269 (70.8)	323 (75.6)	303 (70.1)	323 (68.3)	299 (61.8)	277 (61.8)	216 (56.3)	255 (60.3)	284 (63.3)	228 (52.5)	197 (41.0)	136 (42.1)	< 0.01
Calcium gluconate	241 (63.4)	258 (60.4)	250 (57.9)	266 (56.2)	248 (51.2)	238 (53.1)	201 (52.3)	211 (49.9)	227 (50.6)	229 (52.8)	212 (44.1)	131 (40.6)	< 0.01
ACE inhibitor	194 (51.1)	216 (50.6)	215 (49.8)	266 (56.2)	263 (54.3)	248 (55.4)	172 (44.8)	180 (42.6)	192 (42.8)	191 (44.0)	196 (40.7)	119 (36.8)	< 0.01
Beta blocker	21 (5.5)	22 (5.2)	40 (9.3)	34 (7.2)	51 (10.5)	36 (8.0)	44 (11.5)	47 (11.1)	52 (11.6)	62 (14.3)	71 (14.8)	39 (12.1)	< 0.01
Alpha blocker	61 (16.1)	81 (19.0)	126 (29.2)	97 (20.5)	86 (17.8)	69 (15.4)	63 (16.4)	75 (17.7)	25 (5.6)	59 (13.6)	66 (13.7)	36 (11.1)	< 0.01
Aspirin	242 (63.7)	285 (66.7)	289 (66.9)	336 (71.0)	386 (79.8)	350 (78.1)	315 (82.0)	335 (79.2)	338 (75.3)	304 (70.0)	349 (72.6)	190 (58.8)	< 0.01
Warfarin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.02)	0 (0.0)	0.65
Heparin	178 (46.8)	162 (37.9)	170 (39.4)	161 (34.0)	188 (38.8)	170 (37.9)	128 (33.3)	148 (35.0)	169 (37.6)	139 (32.0)	125 (26.0)	69 (21.4)	< 0.01
Sildenafil	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	(0.4)	1 (0.3)	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0.72
Inhaled nitric oxide	5 (1.3)	15 (3.5)	23 (5.3)	31 (6.6)	39 (8.1)	36 (8.0)	26 (6.8)	23 (5.4)	31 (6.9)	41 (9.4)	41 (8.5)	35 (10.8)	< 0.01

Data are shown as n (%)

Table 4 Results of regression analyses

	Billed charges (USD)	Postoperative length of stay (days)	Cardiac arrest	Inpatient mortality
Year	39,121*	0.12	0.93 (0.90 to 0.97)*	0.91 (0.88 to 0.94)*
Heart failure	92,754*	6.16*	1.38 (0.92 to 2.08)	1.43 (0.98 to 2.08)
Isomerism	− 62,438*	0.35	1.41 (0.77 to 2.58)	1.10 (0.62 to 1.94)
Syndrome	225,763*	11.70*	070 (0.39 to 1.26)	1.52 (0.99 to 2.34)
Bradyarrhythmia	232,036*	9.35*	I1.54 (1.06 to 2.23)*	1.70 (1.19 to 2.43)*
Tachyarrhythmia	218,012*	10.13*	1.41 (1.03 to 1.92)*	1.38 (1.03 to 1.86)*
Acute kidney injury	326,265*	8.78*	1.23 (0.91 to 1.67)	2.51 (1.92 to 3.28)*
Pulmonary hypertension	269,810*	6.35*	1.07 (0.66 to 1.73)	1.88 (1.24 to 2.86)*
Hypothyroidism	50,292	8.83	1.71 (0.83 to 3.54)	0.34 (0.14 to 0.80)*
Epinephrine	− 374,612*	− 19.65*	0.66 (0.43 to 1.02)	1.14 (0.75 to 1.74)
Norepinephrine	− 119,640*	− 3.60*	1.04 (0.73 to 1.48)	1.47 (1.07 to 2.02)*
Dopamine	53,433*	− 3.38*	0.96 (0.70 to 1.31)	1.44 (1.09 to 1.91)*
Dobutamine	− 37,661	− 2.36	1.09 (0.78 to 1.51)	1.31 (0.98 to 1.75)
Milrinone	220,142*	2.21	1.44 (0.91 to 2.29)	0.93 (0.64 to 1.36)
Vasopressin	− 67,468	− 2.67	1.60 (1.03 to 2.48)*	2.40 (1.69 to 3.41)*
Sodium bicarbonate	− 353,443*	− 20.93*	0.62 (0.44 to 0.86)*	0.99 (0.72 to 1.36)
Calcium gluconate	− 121,818*	− 7.77*	0.95 (0.72 to 1.26)	0.96 (0.75 to 1.22)
Calcium chloride	− 91,622*	− 8.97*	0.57 (0.43 to 0.77)*	0.73 (0.55 to 0.96)*
Sildenafil	− 704,232*	− 37.09*	–	0.73 (0.55 to 0.96)*
Inhaled nitric oxide	274,045*	2.33	1.31 (0.85 to 2.00)	2.04 (1.41 to 2.95)*
Steroids	− 195,418*	− 13.13*	0.69 (0.49 to 0.96)*	0.95 (0.73 to 1.24)
ACE Inhibitor	− 138,552*	− 3.07*	0.65 (0.50 to 0.84)*	0.22 (0.18 to 0.28)*
Beta blocker	− 53,783	1.17	0.91 (0.62 to 1.33)	0.98 (0.69 to 1.37)
Alpha blockade	− 14,441	− 6.08*	0.70 (0.49 to 0.99)*	1.24 (0.93 to 1.65)
Nicardipine	303,929*	11.87*	1.58 (0.91 to 2.74)	0.54 (0.30 to 0.98)*
Sodium nitroprusside	− 128,549*	− 3.16*	1.54 (1.18 to 1.97)*	1.12 (0.89 to 1.40)
Aspirin	70,057*	6.97*	0.64 (0.50 to 0.83)*	0.21 (0.17 to 0.26)*
Warfarin	− 125,911	1.09	–	–
Sano (vs BT shunt)	82,786*	1.60	0.67 (0.51 to 0.88)*	0.73 (0.58 to 0.93)*
Peritoneal dialysis	− 69,280	− 2.70	1.17 (0.75 to 1.84)	2.07 (1.38 to 3.10)*
CRRT	− 341,364*	− 23.81*	1.87 (1.01 to 3.50)*	2.64 (1.33 to 5.22)*
Cardiac arrest	164,571*	8.34*	–	1.80 (1.31 to 2.47)*
ECMO	349,733*	6.63*	–	8.85 (7.03 to 11.14)*

Data are shown as beta-coefficient or odds ratio (95% confidence interval)

*Statistically significant findings

Of interest, is that most pharmacologic therapies were used in decreasing frequency as the study period progressed. This likely represents advancements in surgical technique, cardiopulmonary bypass, perfusion strategy, and postoperative care. Nearly every vasoactive agent, the only exception being norepinephrine, had a significant decrease in use over the study period. The frequency of calcium supplementation, angiotensin converting enzyme inhibitor, alpha blocker, sodium bicarbonate and heparin also all decreased. Despite this, the frequency of cardiac arrest and inpatient mortality did not increase. Only the use of beta blocker and inhaled nitric oxide increased over the study period. Aspirin also increased over the study period as seen by the interval change all the way until the final year did.

One of the major limitations of these analyses is that the temporal relationship of medical interventions and pharmacologic therapies cannot be fully ascertained. However, of the four endpoints of interest, only cardiac arrest would be impacted by this. Billed charges and postoperative length of stay represent a culmination of the entire admission and thus these would be inclusive of all medical interventions and pharmacologic therapies. Inpatient mortality would occur after any of the medical interventions and pharmacologic therapies as well. Thus, only cardiac arrest is susceptible to

Table 5 Summary of effects

	Billed charges	Postoperative length of stay	Cardiac arrest	Inpatient mortality
Year	Increased		Decreased	Decreased
Heart failure	Increased	Increased		
Isomerism				
Syndrome	Increased	Increased		
Bradyarrhythmia	Increased	Increased	Increased	Increased
Tachyarrhythmia	Increased	Increased	Increased	Increased
Acute kidney injury	Increased	Increased		Increased
Pulmonary hypertension	Increased	Increased		Increased
Hypothyroidism				Decreased
Epinephrine	Decreased	Decreased		
Norepinephrine	Decreased	Decreased		Increased
Dopamine	Increased	Decreased		Increased
Dobutamine				
Milrinone	Increased			
Vasopressin			Increased	Increased
Sodium bicarbonate	Decreased	Decreased	Decreased	
Calcium gluconate	Decreased	Decreased		
Calcium chloride	Decreased	Decreased	Decreased	Decreased
Sildenafil	Decreased			
Inhaled nitric oxide	Increased			
Steroids	Decreased	Decreased	Decreased	Increased
ACE Inhibitor	Decreased	Decreased	Decreased	Decreased
Beta blocker				
Alpha blocker		Decreased	Decreased	
Nicardipine	Increased	Increased		Decreased
Sodium nitroprusside	Decreased	Decreased	Increased	
Aspirin	Increased	Increased	Decreased	Decreased
Warfarin				
RV-PA conduit	Increased		Decreased	
Peritoneal dialysis				Increased
CRRT	Decreased		Increased	Increased
Cardiac arrest	Increased	Increased	–	Increased
ECMO	Increased	Increased	–	Increased

temporal bias in the sense that a medication like vasopressin, which was found to be associated with increased odds of cardiac arrest, may have been started because of the cardiac arrest and thus would not have contributed to the cardiac arrest risk itself. Thus, the cardiac arrest may have been the trigger for the intervention and not the result of it. However, for medications such as sodium bicarbonate and calcium gluconate, often administered during cardiac arrest, the medications were found to be associated with cardiac arrest which must lead one to question whether administration of these medications may have actually helped prevent some cardiac arrest. Additionally, if a specific intervention or medication was associated with a significant increase or decrease in both cardiac arrest and inpatient mortality, the similar direction of effect on both endpoints raises the likelihood that intervention or medication is causative. Nonetheless, this is all subjective and causation cannot be truly determined from these analyses.

Using some of this logic a few factors deserve particular attention. The following were associated with significant decrease in both cardiac arrest and inpatient mortality: more recent year of surgery, calcium chloride, angiotensin converting enzyme inhibitor, and aspirin. The following were associated with a decrease in only inpatient mortality: nicardipine.

Calcium is essential to cardiovascular physiology as it is deeply related to myocardial contraction and its serum levels are known to decrease after cardiac surgery utilizing cardiopulmonary bypass in children [9]. Although calcium is often cited as having an impact in hemodynamics and

systemic oxygen delivery, to our knowledge there are five studies reporting these effects in pediatric cardiac patients, of which only one involves exclusively patients with single ventricle physiology. Savorgnan and colleagues found that calcium chloride boluses used in response to hypotensive episodes led to an improvement in mean blood pressure and pulmonary-to-systemic blood flow ratio without compromising systemic oxygen delivery in patients with single ventricle physiology that had undergone cardiac surgery [10]. Averin and colleagues reported that calcium chloride infusions in pediatric patients in the cardiac intensive care unit (CICU) significantly improved systemic oxygen delivery independently of baseline calcium level [11]. Particularly, neonates had the most improvement, supporting the evidence that extracellular calcium plays an important role in cardiovascular physiology [11, 12]. Additionally, Karki and colleagues demonstrated that the concurrent infusion of calcium chloride and vasopressin in pediatric patients with acute cardiocirculatory failure can improve the hemodynamic status, organ perfusion and overall organ function [13]. Contrarily, Dyke and colleagues suggested that higher calcium supplementation was associated with higher morbidity and mortality [14]. In this study calcium chloride was used to maintain ionized calcium levels above 1.2 mmol/L [14]. Meanwhile, Murray and colleagues did not find differences in hemodynamic status, vasoinotropic score, postoperative length of stay, time to enteral feeding, length of ventilation, or mortality in neonates who received calcium chloride infusions after cardiac surgery compared to those who did not receive the infusion [15]. The mechanism by which calcium chloride improves the hemodynamic status of the patient may be by its inotropic effect and secondary arterial vasoconstriction [11]. The finding of these analyses supports the use of calcium chloride in neonates that have undergone the Norwood procedure. Nevertheless, more studies are needed to further clarify the impact of calcium chloride in this population.

The Norwood procedure involves the creation of a shunt to reestablish the pulmonary circulation, mainly using an artificial shunt in both the MBTS and Sano conduit. This increases the risk of thrombosis due to blood flow alterations, hypercoagulable state, and foreign material exposure [16]. The reported incidence of thrombosis is as high as 40% [17] and is associated with increased length of stay and mortality [18, 19]. Some of the most important risk factors for thrombosis include small shunt size, small infant size, and high levels of perioperative hemoglobin[20]. Although aspirin is often used to reduce the incidence of thrombosis, current studies report conflicting results [21–23]. Its effect would be explained by its irreversible inhibition of cyclooxygenase-1 and -2 that leads to inhibition of platelet adhesion and aggregation, and decreased inflammation and infiltration at the thrombus site [24]. The current guidelines by the American College of Chest Physicians recommends patients undergoing Norwood procedure should receive either aspirin or no antithrombotic therapy as compared to prolonged low molecular weight heparin or vitamin K antagonists postoperatively [25]. It should be noted that there are different implications of utilizing aspirin in the setting of an MBTS versus a Sano conduit. As the MBTS has a smaller diameter than a Sano conduit, the risk of thrombosis is greater. But as frequency of MBTS or Sano conduit varies, the use of aspirin may also vary directly as a result.

The following were associated with significant increase in both cardiac arrest and inpatient mortality: bradyarrhythmia, tachyarrhythmia, vasopressin, and continuous renal replacement therapy. The following were associated with an increase in only inpatient mortality: acute kidney injury, pulmonary hypertension, norepinephrine, dopamine, peritoneal dialysis, cardiac arrest, and extracorporeal membrane oxygenation.

Acute kidney injury is common after cardiac surgery and is associated with poor outcomes [26, 27]. This analysis is in alignment with previous studies that demonstrate acute kidney injury after Norwood is associated with increased mortality. In a retrospective cohort by Wong and colleagues, 75% of their patients developed AKI with 21% developing severe AKI after stage 1 palliation [28]. Severe AKI in this cohort was significantly associated with continuous intravenous loop diuretic infusion, need for ECMO, and in-hospital death [28]. Additionally, AKI was found to be an independent risk factor for developing AKI after stage 2 palliation and with prolonged duration of mechanical ventilation after stage 3 palliation [28]. More studies are needed to further understand AKI in single ventricle patients after undergoing stage 1 palliation, particularly for assessing the long-term implications of AKI in this patient population [29].

Tachyarrhythmias are not an uncommon postoperative complication after the Norwood procedure[30]. Postoperative arrhythmias have been associated with higher risk of interstage death [5, 31]. Although mechanistically the cause of the arrhythmias in this patient population is difficult to identify, a prolonged use of vasoactive agents remains as a common risk factor [32]. A retrospective study performed by McFerson and colleagues in patients after Norwood procedure found that the total duration of epinephrine and the highest milrinone dose were both statistically associated with an occurrence of postoperative tachyarrhythmia [32]. Whether tachyarrhythmias themselves directly mediate mortality by reduction of cardiac output or happen to occur in sicker patients already at greater risk for adverse events cannot be elucidated by these current analyses.

In these analyses, the use of vasopressin was associated with increased risk of inpatient mortality and cardiac arrest. The use of vasopressin after cardiac surgery in pediatric patients has been shown in the past to increase

systolic and diastolic blood pressure, and to decrease heart rate in patients with biventricular circulation [33]. However, more recent data have challenged this, demonstrating no significant increase in blood pressure. Furthermore, this more recent data demonstrated that even if blood pressure increased with initiation of vasopressin, systemic oxygen delivery did not improve [34–36]. It is possible that vasopressin may be utilized in sicker patients or that vasopressin alters the physiology in a negative way. In the setting of parallel circulation, increasing systemic vascular resistance may promote more pulmonary blood flow at the expense of systemic blood flow. This may negatively impact systemic oxygen delivery while also increasing myocardial work required for the maintenance of a certain stroke volume. Additional studies are necessary to clarify the role of vasopressin after the Norwood procedure.

In this study the use of dopamine was associated with an increased risk of inpatient mortality. Dopamine is a precursor of norepinephrine and is commonly used in patients with low cardiac output to increase oxygen delivery (D_{O2}) [37]. With its activation of adrenergic receptors and its action on the central nervous system and the endogenous sympathetic drive, it also increases systemic oxygen consumption (V_{O2}), thus offsetting the improved D_{O2} [38, 39]. Li and colleagues performed a study in neonates after the Norwood procedure and demonstrated that dopamine negatively affects V_{O2}–D_{O2} balance and its early termination significantly decreases V_{O2}, thus improving the balance [39]. This analysis further supports that the use of dopamine after undergoing the Norwood procedure should be done with caution.

The evolving understanding of the physiologic state in which the saturation of the blood going to the pulmonary and systemic circulations is equal and the distribution of flow is dependent on the relative resistances of the two circuits has unveiled that, as in any critical illness, maintaining systemic oxygen delivery is the most vital factors. The balance of systemic oxygen delivery and systemic oxygen consumption is what ultimately modulates the risk for hemodynamic decompensation. The systemic venous saturation ultimately underpins the risk for cardiac arrest in patients. Modulating vital signs for the sake of maintaining arbitrarily normal values is likely not beneficial if systemic oxygen delivery is not maintained. The utilization of hypoxic gas admixture with nitrogen in those with this unique circulation is one such example of an intervention that was utilized to maintain what was perceived to be normal saturations in this circulatory state, without actually improving, and potentially even decreasing, systemic oxygen delivery [40–43].

Systemic oxygen delivery is a function of oxygen content and cardiac output. Thus, systemic oxygen delivery has multiple components which include, but are not limited to, hemoglobin, intravascular volume status, partial pressure of oxygen, blood pressure, and heart rate. Thus, changes in one of these parameters outside of accepted normal may not result in a change in systemic oxygen delivery if another one of these values changes concomitantly. This demonstrates the need for a global evaluation of patients that focuses on the ultimate endpoint of systemic oxygen delivery.

As this concept is better understood and more wholeheartedly adopted, one can understand that interventions and medications utilized to act on specific vital signs may actually not increase systemic oxygen delivery. In fact, increase in vasoactive support to help augment blood pressure may even lead to detrimental effects by increasing myocardial oxygen consumption. Thus, following systemic oxygen delivery by means of venous saturation, near infrared spectroscopy, lactate levels, and/or end organ function is likely to be more helpful than by following individual vital sign parameters in isolation. Targeting interventions based on optimizing systemic oxygen delivery and systemic oxygen consumption have already been demonstrated to improve short-term outcomes and have been demonstrated to improve some long-term outcomes as well [44–50]. These data offer some preliminary insights into general trends. These are not patient, nor event specific, however. These current data cannot be generalized into all clinical situations even in this specific patient population. But they do offer a starting point.

While these analyses offer valuable, novel insight, they are not without their limitations. Firstly, the temporal relationship of interventions is not known from the data provided in the database. But as pointed out before, three of the four endpoints (billed charges, postoperative length of stay, and inpatient mortality) modeled are reflective of the entirety of the admission. None of these things can occur before the culmination of the admission. Thus, the only endpoint which may be impacted by this limitation is cardiac arrest. Additionally, doses and duration of medications cannot be extracted from the database. Thus, these cannot be commented on. Regardless, the purpose of these analyses was not to establish causal relationships but simply characterize associations to provoke thought and help stimulate the development of hypothesis that can help guide future studies.

Another limitation of these analyses is that baseline demographics and clinical variables reflecting severity of illness and systemic oxygen delivery are not available from the database. Severity of illness can be gauged, to some degree, by the comorbidities included but this is by no means a complete surrogate.

Yet another limitation is the low frequency of use of some interventions or medications. This issue was present only for a few interventions such as warfarin or sildenafil. As this reflects clinical practice this may not even be a true limitation. The vast amount of data in the database allows for adequate power with respect to most of the interventions and medications included in these analyses. PHIS

data are based on administrative information and weights are not contained within; therefore, this information was not part of the analyses.

All statistical analyses are also with their limitations. Statistics, in and of themselves, are based on human construct such as an arbitrary selection of significance levels for *p* values. The statistical tests ran for these analyses are not without their limitations but were selected as being among the most appropriate tests to answer the questions being posed. The use of stepwise regressions versus more "contemporary" Bayesian methods is beyond the scope of this manuscript but warrants brief mention. Backward stepwise regression using likelihood ratios for selection have been demonstrated by some studies to offer equal, and in some cases, better model quality when compared to Bayesian models [51]. To further strengthen the stepwise approach, the variables of interest entered into the models were selected a priori with some previous, albeit, potentially anecdotal thought. This helps strengthen the reproducibility, stability, and interpretation of resulting models.

Despite the limitations, we feel these analyses offer a novel insight into the frequency and impact of comorbidities, interventions, and medications on characteristics of the Norwood admission for children with hypoplastic left heart syndrome. We stress, however, that these findings are limited due to their source from a national administrative database. The associations delineated here with specific outcomes should be utilized as pilot data to be used for hypothesis generation. The benefit being that future studies, retrospective or prospective, can be designed using some of the findings here. All the associations here warrant further, more specific delineation and all the associations here represent global phenomena and there may be patient or situation specific considerations for any intervention.

Conclusion

In Norwood admission for patients with hypoplastic left heart syndrome, the frequency of pharmacologic therapies and cardiac arrest has decreased over time. There are significant associations between acute kidney injury, arrythmias, and pulmonary hypertension with cardiac arrest and mortality.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interest to disclose.

Ethical Approval These analyses did not require institutional review board approval as they used previously published data that were deidentified. These analyses are in compliance with the Helsinki declaration of 1975 and its subsequent revisions.

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