Original Article

Survival and Neurocognitive Outcomes After Cardiac Extracorporeal Life Support in Children Less Than 5 Years of Age

A Ten-Year Cohort

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Background—Survival after pediatric cardiac extracorporeal life support (ECLS) is guarded, and neurological morbidity varies widely. Our objective is to report our 10-year experience with cardiac ECLS, including survival and kindergarten entry neurocognitive outcomes; to identify predictors of mortality or adverse neurocognitive outcomes; and to compare 2 eras, before and after 2005.

Methods and Results—From 2000 to 2009, 98 children had venoarterial cardiac ECLS. Sixty-four patients (65%) survived to hospital discharge, and 50 (51%) survived ≤5 years of age. Neurocognitive follow-up of survivors was completed at mean (SD) age of 52.9 (8) months using Wechsler Preschool and Primary Scale of Intelligence. Logistic regression analysis found the longer time (hours) for lactate to fall below 2 mmol/L on ECLS (hazard ratio, 1.39; 95% confidence interval, 1.05, 1.84; *P*=0.022), and the amount of platelets (mL/kg) given in the first 48 hours (hazard ratio, 1.18; 95% confidence interval, 1.06, 1.32; *P*=0.002) was independently associated with higher in-hospital mortality. Receiving ECLS after the year 2005 was independently associated with lower risk of in-hospital mortality (hazard ratio, 0.36; 95% confidence interval, 0.13, 0.99; *P*=0.048). Extracorporeal cardiopulmonary resuscitation was not independently associated with mortality or neurocognitive outcomes. Era was not independently associated with neurocognitive outcomes. The full-scale intelligence quotient of survivors without chromosomal abnormalities was 79.7 (16.6) with 25% below 2 SD of the population mean.

Conclusions—Mortality has improved over time; time for lactate to fall on ECLS and volume of platelets transfused are independent predictors of mortality. Extracorporeal cardiopulmonary resuscitation and era were not independently associated with neurocognitive outcomes. **(*Circ Heart Fail*. 2015;8:312-321. DOI: 10.1161/CIRCHEARTFAILURE.114.001503.)**

Key Words: extracorporeal circulation ■ follow-up studies ■ pediatrics

Extracorporeal life support (ECLS) was originally used for neonates with respiratory failure, and in recent years, there has been an increase in the use of ECLS for severe cardiac failure refractory to medical management. Common indications for pediatric cardiac ECLS include failure to separate from cardiopulmonary bypass after repair of congenital heart disease, low cardiac output syndrome either because of postoperative myocardial dysfunction or primary myocardial disease (myocarditis or cardiomyopathy), hypoxia which is typically secondary to cardiorespiratory failure in a patient with a cavopulmonary shunt or finally cardiac arrest refractory to medical cardiopulmonary resuscitation (ECPR).

Clinical Perspective on p 321

Reported survival to hospital discharge after cardiac ECLS in single-center pediatric studies varies from 32% to 59%[1–8] and most recently as high as 73%.[9] These international cardiac ECLS survival outcomes are encouraging; however, long-term neurocognitive and functional outcomes are less well reported. We have previously reported mental delay in 50%

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of survivors at 2 years of age.[4] Neurological morbidity post-ECLS varies widely depending on when and how the child is evaluated.[4,6,9–11] This high incidence of adverse neurological outcomes has translated to increasing attention to neuroprotection during ECLS.

Our objective is to report our 10-year experience with cardiac ECLS, including survival and kindergarten-entry neurocognitive outcomes; to identify predictors of mortality or adverse neurocognitive outcomes; and to compare 2 different eras, before and after 2005. In January 2005, our ECLS program switched from a Biomedicus centrifugal pump (Medtronic, Minneapolis) and Avecor silicone elastic oxygenator without circuit surface coating to a standard circuit including Maquet Rotaflow centrifugal pump (Maquet Inc, Hirrlingen, Germany), Maquet Quadrox-D oxygenator (Maquet Inc, Hirrlingen, Germany), and Bioline PVC (Maquet Inc, Hirrlingen, Germany) heparin-based coating. In 2005, a pediatric thrombosis team became formally involved in our ECLS program, and we started following heparin and antithrombin levels to guide anticoagulation. Previously, we monitored heparin anticoagulation solely via the activated clotting time. In 2005, we also developed formal ECPR protocols and a pediatric ventricular assist device program and began transitioning some cardiac ECLS patients to longer term support devices. We hypothesize that these programmatic changes would translate into improved outcomes. Hence, survival, neurocognitive, and functional outcomes between these two 5-year periods are compared.

Methods

This study uses data from an interprovincial inception cohort outcomes study conducted in 4 provinces in western Canada, the Complex Pediatric Therapies Follow-up Program. All patients under 5 years of age who received venoarterial cardiac related ECLS from January 2000 through December 2009 were identified and registered around the time of cannulation. We have previously reported the 2-year survival and neurodevelopmental follow-up of the first cohort of patients (2000–2009) in a separate publication.[4] ECLS was performed at Stollery Children's Hospital, Edmonton, Canada, for all patients.

Demographic and hospitalization variables that were previously agreed on were collected prospectively.[12] Other specific pre-ECLS, ECLS, and post-ECLS variables were collected from the medical chart retrospectively (Table SI in the Data Supplement). Our ECLS program's policy is to maintain platelets >100 000 for infants <3 months and >80 000 for infants ≥3 months. We maintain a hemoglobin >100 g/L in all patients. Long-term follow-up was discussed with the parents or guardians once survival was probable. With their consent, contact was made with their respective follow-up clinics at the tertiary site of origin.

All consecutive patients given venoarterial cardiac related ECLS at an age <5 years over the 10-year period were registered. For patients who had multiple ECLS runs, only the first run was included in the analysis. All survivors received multidisciplinary neurocognitive assessments through existing follow-up clinics in Edmonton and Calgary, Alberta; Regina and Saskatoon, Saskatchewan; Vancouver, British Columbia; and Winnipeg, Manitoba. Ethics approvals were obtained from each site before study onset. Neurocognitive follow-up of survivors was performed ≥6 months after ECLS and ≥4 years of age, and before the sixth birthday. All parents or guardians signed individual informed consent.

Neurocognitive follow-up of survivors was completed by multidisciplinary teams at 1 of the 6 centers in western Canada. At assessment, a clinic nurse recorded history of hospitalizations, illnesses, medication use, and need for supplemental oxygen. Physical measurements were obtained as has been described.[12] The family socioeconomic status (SES) was determined by the Blishen Index,[13] a formula considering the relative income, education level, and prestige factor of employment with a population mean and SD of 43 (13). Maternal education was indicated by years of schooling. Pediatricians experienced in neurodevelopmental follow-up examined each child for evidence of motor disability, defined as nonprogressive cerebral palsy should the insult occur under the age of 1 year,[14] or other nonprogressive motor disability, for example stroke, for older children, or visual impairment, defined as corrected visual acuity in the better eye of less than 20/60. Hearing was evaluated by experienced certified pediatric audiologists in soundproof environments, as has been described.[12] Permanent hearing impairment was defined as bilateral loss of >25 dB hearing level at any frequency from 250 to 4000 Hz. Disability includes both motor and sensory disability. Experienced pediatric psychologists or psychometrists assessed cognitive ability and visual–motor skills by using current age-appropriate standardized measures, including the Wechsler Preschool and Primary Scales of Intelligence—third edition[15] and the Beery–Buktenica Developmental Test of Visual–Motor Integration—fifth edition (VMI).[16] Variables included the United States normed full-scale intelligence quotient (FSIQ), verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), and VMI, each expressed as a standard score with a mean of 100 and SD of 15. The parent completed the Adaptive Behavior Assessment System, second edition,[17] for children before their sixth birthday. The General Adaptive Composite score (with a population mean of 100 and an SD of 15) from the Adaptive Behavior Assessment System, second edition was used to support the tested neurocognitive findings.

Statistics

Continuous variables are presented as median (Q1–Q3; min–max) and categorical variables are presented as counts (percentages). To compare pre- to post-2005 variables, we used t-tests for continuous variables not having a skewed distribution, and Fisher exact test for categorical variables. The primary outcomes of this study were mortality, and the neurocognitive (FSIQ, VIQ, PIQ, VMI) and functional (General Adaptive Composite) outcomes. To screen for variables associated with the primary outcomes we used univariate regression models and included all relevant variables from Table SI in the Data Supplement. Kaplan–Meier curve was used to describe survival since ECLS. The start of follow-up began at the time of ECLS. Stepwise multivariable logistic and Cox regression analysis were used to examine which variables significant at a P value of ≤0.1 on the univariate analysis or considered clinically relevant (ECLS era and receiving ECPR) were predictive of in-hospital and mortality ≤5 years of age, respectively. Results are presented as odds ratios (ORs) and hazard ratios (HRs) along with 95% confidence intervals (CIs) and 2-sided P values. ORs and HRs reported reflect changes per unit increase in the predictor variables. Stepwise multiple linear regression models were used to examine which variables significant at a P value of ≤0.10 on the univariate analysis or considered clinically relevant (ECLS era, receiving ECPR and SES) were predictive of the neurocognitive outcomes FSIQ, PIQ, VIQ, and VMI and functional outcome of General Adaptive Composite. The analysis of predictors of neurocognitive outcomes only includes those surviving children without chromosomal abnormalities (n=44). Results are presented as effect sizes along with 95% CIs and 2-sided P values. The proportion of variance explained by a model was calculated by dividing the model variance by the total variance in the outcome. Multiple comparison adjustments have not been made. Statistical analyses were performed using SAS version 9.3.

Results

Description of the Cohort

Ninety-eight patients had cardiac related venoarterial ECLS over 10 years: 39 and 59 patients from 2000 to 2004 and 2005 to 2009, respectively. The patients having cardiac surgery prior to ECLS were 68 (3.7%) of the total 1844 patients under 5 years of age having cardiac surgery with cardiopulmonary bypass at our institution during the study period. Descriptive demographic and peri-ECLS variables are listed in Table SI in the Data Supplement. The median (Q1–Q3; min–max) age at the time of ECLS was 2.1 (0.4–7.1; 0–56) months and median (Q1–Q3; min–max) weight 4.4 (3.3–6.8; 1.4–18) kg. Fifty-four children (55%) were male; 50 (51%) and 46 (47%) of the patients were cannulated through the neck and chest, respectively. Two patients required multiple cannulation sites. Fourteen patients had an additional cephalad cannula; they were all in the second time period cohort (2005–2009). Cardiac anatomy was biventricular in 65 (66%) and univentricular in 33 (34%); 9 patients (9.2%) had myocarditis or cardiomyopathy. Eighty-three patients (84%) required perioperative ECLS, defined as cannulation onto ECLS during the cardiac surgery hospital admission, either before, during, or after the cardiac surgery with cardiopulmonary bypass. Nine patients (9.1%) had a chromosomal abnormality, but only 6 of these children survived to hospital discharge. Over the 10-year period, indications for ECLS included failure to wean from cardiopulmonary bypass in the operating room in 27 (27%), progressive low cardiac output syndrome in 28 (29%), hypoxia in 6 (6%), and cardiac arrest requiring ECPR in 37 (38%). Four patients (all in the second cohort) had multiple (2) ECLS runs which were all provided within the same hospitalization for each patient. Hence, neurocognitive assessments used in the analysis were performed after both ECLS runs had occurred. Two of those patients survived to hospital discharge and neurocognitive assessment. Complete follow-up data were available for all patients.

Description of Outcomes

Sixty-four patients (65%) survived to hospital discharge, and 50 (51%) survived ≤5 years of age. Neurocognitive follow-up was performed in all survivors at a mean (SD) age of 52.9 (8) months, and outcomes for the 44 survivors without chromosomal abnormalities are shown in Table 1. Neurocognitive assessment was performed at a mean (SD) of 43.4 (14.5) months and median (Q1–Q3; min–max) of 48 (39.7–52.2; 8–70) months after ECLS decannulation. The mean (SD) FSIQ score in 44 survivors without chromosomal abnormalities was 79.7 (16.6) and was significantly skewed to the left compared with the normal population (Figure 1).

Table 1. Neurocognitive and Functional Outcomes of Survivors Without Chromosomal Abnormalities at 5 Years of Age (n=44)

Outcomes	Mean (SD)
FSIQ	79.7 (16.6)
PIQ	81.1 (16.1)
VIQ	81.6 (16.6)
VMI	80.5 (16.4)
GAC	79.2 (19.4)

FSIQ indicates full-scale intelligence quotient; GAC, General Adaptive Composite from the Adaptive Behavior Assessment System; PIQ, performance intelligence quotient; VIQ, verbal intelligence quotient; and VMI, visual-motor index.

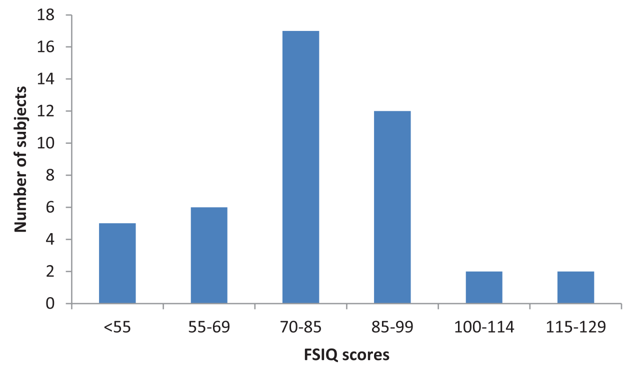

Figure 1. Distribution of full-scale intelligence quotient (FSIQ) scores in the 44 survivors without chromosomal abnormalities of cardiac related extracorporeal life support (ECLS) at kindergarten entry. In a normal population, the mean score is 100 and SD is 15. The ECLS survivor scores are skewed to the left.

FSIQ scores >2 SD below the population mean were present in 11 (25%) of the 44 survivors without chromosomal abnormalities. The 6 survivors with chromosomal abnormalities all had FSIQ scores >2 SD below the population mean. Six of the 50 surviving children (12%) had motor disability; 9 (18%) had microcephaly; 4 (8%) had bilateral sensorineural hearing loss; 2 (4%) had visual impairment; and 4 (8%) had a seizure disorder.

Comparison of 2 Time Period Cohorts

Table 2 describes the 2 different eras. ECPR was more common in the second cohort. Pre-ECLS inotrope scores, ventilator days, and arterial lactate within 2 hours of ECLS cannulation were significantly lower in the second cohort. Peak lactate on ECLS was also significantly lower in the second time period cohort. Total ECLS hours and hospital stay were longer in the second cohort.

Prediction of Survival

Kaplan–Meier curve of survival time since ECLS is displayed in Figure 2. Kaplan–Meier curve of survival time since birth is displayed in the Supplementary material (Figure SI in the Data Supplement). Table 3 details the univariate variables associated with higher hospital mortality at a P value of <0.1. Multiple logistic regression analysis found that the longer it takes (hours) for the plasma lactate level to fall below 2 mmol/L after starting ECLS (OR, 1.39; 95% CI, 1.05–1.84; P=0.022) and the amount of platelets (mL/kg) given in the first 48 hours (OR, 1.18; 95% CI, 1.06–1.32; P=0.002) were significantly independently associated with higher in-hospital mortality. Receiving ECLS after the year 2005 was associated with lower risk of in-hospital mortality (OR, 0.36; 95% CI, 0.13–0.99; P=0.048).

Table 4 describes the univariate analysis of mortality ≤5 years of age. Multivariate Cox regression analysis found that the longer time (hours) for lactate to fall below 2 mmol/L after starting ECLS (HR, 1.28; 95% CI, 1.09–1.51; P=0.003), the amount of platelets (mL/kg) given in the first 48 hours of ECLS (HR, 1.11; 95% CI, 1.05–1.18; P<0.0001), and a higher cumulative fluid balance 48 hours postinitiation of ECLS (HR, 1.50; 95% CI, 1.11–2.03; P=0.008) were significantly

Table 2. Comparison of 2 Time Period Cohorts

		Study Periods		Significance
Variable	Total (n=98)	2000–2004 (n=39)	2005–2009 (n=59)	*P* Value
Age, mo	8 (13.4)	6.9 (13.4)	8.8 (13.6)	0.55
Age<29 d	41 (42%)	22 (56%)	19 (32%)	0.02
Male sex	54 (55%)	20 (51%)	34 (58%)	0.68
Chromosomal abnormality*	9 (9%)	3 (8%)	6 (10%)	1.00
Weight, kg	5.6 (3.5)	5.3 (3.3)	5.9 (3.7)	0.41
Indication for ECLS				
Failed weaning of CBP	27 (28%)	13 (33%)	14 (24%)	0.36
LCOS	28 (29%)	14 (36%)	14 (24%)	0.25
Hypoxia	6 (6%)	3 (8%)	3 (5%)	0.68
ECPR	37 (38%)	9 (23%)	28 (48%)	0.02
Surgery in relation to ECLS				
None	12 (12%)	1 (3%)	11 (19%)	0.06
Before	68 (12%)	31 (80%)	37 (62%)	0.08
After	12 (12%)	5 (13%)	7 (12%)	0.89
During	3 (3%)	2 (5%)	1 (2%)	0.56
Previous admission	3 (3%)	0	3 (5%)	0.27
CPB time, min	174.8 (112.7)	181.6 (121.9)	168.2 (104.16)	0.61
	n=75	n=37	n=38	
Aorta cross-clamp time, min	61.1 (42.7)	57.1 (38.5)	65 (46.5)	0.45
	n=67	n=33	n=34	
Circulatory arrest time, min	24.3 (16.5)	25.5 (18.3)	23 (14.3)	0.66
	n=36	n=21	n=15	
Location where ECLS was initiated				
OR	33 (34%)	17 (44%)	16 (27%)	0.14
PICU	60 (61%)	22 (56%)	38 (64%)	0.43
Cardiac catheterization laboratory	2 (2%)	0	2 (3%)	0.25
Referral hospital	3 (3%)	0	3 (5%)	0.15
ECLS support type				
VA	84 (86%)	39 (100%)	45 (76%)	0.001
VA+V	14 (14%)	0	14 (24%)	0.001
Ventilator days pre-ECLS	6.9 (13)	11.2 (15.5)	5.9 (12.3)	0.18
	n=72	n=13	n=59	
Peak lactate within 2 h of ECLS cannulation, mmol/L	8.6 (6.5)	12.7 (6.8)	6.1 (4.5)	<0.001
	n=80	n=31	n=49	
Pre-ECLS inotrope score within 1 h of cannulation	25.0 (33.3)	34 (39.7)	19.0 (27.1)	0.03
Peak lactate on ECLS, mmol/L	9.5 (5.6)	11.1 (5.7)	8.5 (5.4)	0.02
Time for lactate to fall to ≤2 mmol/L, h	22.8 (17.6)	24.1 (20.5)	21.9 (156)	0.57
ECLS flow at 24 h, mL/kg/min	112.1 (42.8)	119.3 (61.6)	107.3 (22.8)	0.25
Inotrope score at 24 h of ECLS	9.8 (10.6)	10.4 (15.4)	9.4 (5.5)	0.70
Cumulative fluid balance at 48 h of ECLS, mL/kg	480.3 (942.8)	689.4 (610.2)	342.2 (1092.6)	0.07
First day of negative fluid balance	4.1 (1.6)	4.4 (1.8)	3.9 (1.5)	0.17
Cumulative PRBC at 48 h of ECLS, mL/kg	192.2 (158)	222.2 (181.8)	172.3 (138.2)	0.13
Cumulative platelets at 48 h of ECLS, mL/kg	59.4 (49.1)	63.3 (49.2)	56.9 (49.2)	0.54
PELOD at 48 h	16.9 (8.5)	15.4 (7.8)	17.9 (8.9)	0.16
CRRT on ECLS	54 (55%)	26 (67%)	29 (49%)	0.09
Peak plasma-free hemoglobin in first 120 h, mg/L	744.2 (1036.8)	933.6 (931.1)	619.1 (1090.5)	0.14

(*Continued*)

Table 2. continued

Variable	Total (n=98)	Study Periods 2000–2004 (n=39)	2005–2009 (n=59)	Significance *P* Value
Insertion of left atrial vent	35 (36%)	8 (21%)	27 (46%)	0.07
Total ECLS hours	161.1 (143.9)	118.9 (80.7)	188.9 (155.6)	0.01
Total ventilator days	31.9 (36.1)	30.1 (42.8)	33.1 (31.3)	0.77
Total hospital length of stay	67.9 (82.8)	43.3 (26)	84.3 (100.8)	0.004
Survival to hospital discharge	64 (65%)	21 (54%)	43 (73%)	0.05
Survival to <5 y of age	50 (51%)	16 (41%)	34 (58%)	0.11

Data presented as mean (SD) unless otherwise noted. CPB indicates cardiopulmonary bypass; CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support; ECPR, extracorporeal cardiopulmonary resuscitation; LCOS, low cardiac output syndrome; OR, operating room; PELOD, pediatric logistic organ dysfunction; PICU, pediatric intensive care unit; PRBC, packed red blood cells; VA, venoarterial; and VA+V, venoarterial and venovenous.

*Chromosomal abnormalities were Turner syndrome and 2 of chromosomal 22q11 microdeletions in the first cohort and 2 of each of Trisomy 21, chromosomal 22q11 microdeletion, and Noonan syndrome in the second cohort.

independently associated with higher mortality ≤5 years of age. Having perioperative ECLS (HR, 0.42; 95% CI, 0.20–0.87; P=0.021) and ECLS after the year 2005 (HR, 0.52; 95% CI, 0.27–0.99; P=0.047) were significantly associated with lower mortality at 5 years of age. Receiving ECPR (HR, 1.9; 95% CI, 0.98–3.69; P=0.058) was not independently significantly associated with mortality ≤5 years of age.

Prediction of Neurocognitive Outcomes

Univariate regression analysis found that the following variables were associated with lower FSIQ at a P value ≤0.1: weight, need for continuous renal replacement therapy (CRRT) prior to ECLS, higher inotrope score at 24 hours of ECLS, more days on mechanical ventilation, and longer hospital length of stay (LOS; Table 5–7). Similarly, for lower PIQ the following variables were associated at a P value ≤0.1: weight, higher inotrope score at 24 hours of ECLS, more days on mechanical ventilation, and longer hospital LOS (Table 5–7). For lower VIQ, age, weight, location where ECLS was started, higher inotrope score at 24 hours of ECLS, more days on mechanical ventilation, and longer hospital LOS were associated at a P value ≤0.10 (Table 5–7). Lower VMI was associated at a P value ≤0.1 with perioperative ECLS, more mechanical ventilation

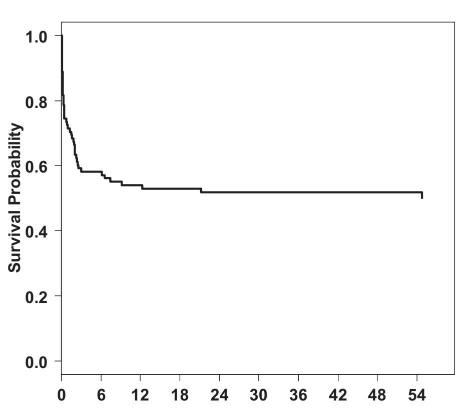

Figure 2. Kaplan–Meier estimates of survival time since extracorporeal life support (ECLS).

days, and longer hospital LOS (Table SII in the Data Supplement). Lower General Adaptive Composite was associated at a P value ≤0.1 with increased number of mechanical ventilation days, longer hospital LOS, and ECLS before the year 2005 (Table SII in the Data Supplement).

After adjusting for time era, ECPR and SES, multiple linear regression found that higher weight was significantly associated with higher FSIQ, PIQ, and VIQ scores (Table 5–7). For VIQ, higher SES was also independently associated with higher scores. Multiple regression models selected explained 15% variation in FSIQ scores, 15.2% variation in PIQ scores, and 18.3% variation in VIQ scores.

Discussion

Survival to hospital discharge was 64 of 98 (65%) over the 10-year cohort which is consistent with previous reports of cardiac ECLS patients.[1–8] The more recent era time cohort (2005–2009) demonstrated a significantly improved survival to hospital discharge (from 54% to 73%), similar to a recent report.[9] A shorter time for lactate to fall below 2 mmol/L on ECLS was significantly associated with improved survival to hospital discharge suggesting that aggressive ECLS support, often requiring additional venous access to achieve adequate flows, leads to better outcomes. In the second time period cohort, 52% of the patients with neck cannulation had an additional cephalad venous cannula. Lower platelet volumes (mL/kg) in the first 48 hours of ECLS were associated with improved survival to hospital discharge which may reflect an independent effect of platelets on outcome. There is increasing evidence for a specific role of platelets in the inflammatory cascade.[18]

As we have become more experienced with ECLS for cardiac patients, we may have been more aggressive in cannulating earlier in borderline patients in the second time period cohort, which may explain their improved outcomes. Pre-ECLS inotrope scores, ventilator days, and arterial lactate within 2 hours of ECLS cannulation were significantly lower in the second cohort (Table 2). Peak lactate on ECLS was also significantly lower in the second time period cohort, which may be because the peak lactate prior to cannulation was lower. There was no difference in ECLS flows at 24 hours,

Table 3. Univariate and Multiple Logistic Regression Analysis of Hospital Mortality in Cardiac ECLS Patients (n=98)

	Univariate		Multiple	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Hospital LOS, d	0.95 (0.93, 0.97)	<0.001		
Age<29 d	4.34 (1.79, 10.52)	0.001		
Platelets first 48 h, mL/kg	1.18 (1.06, 1.31)	0.002	1.18 (1.06, 1.32)	0.002
CRRT, yes	3.35 (1.35, 8.30)	0.009		
Time lactate<2 mmol/L	1.37 (1.06, 1.78)	0.015	1.39 (1.05, 1.84)	0.022
Total mechanical ventilation, d	0.97 (0.95, 1.00)	0.020		
PELOD in first 48 h	1.82 (1.08, 3.05)	0.023		
Single ventricle, yes	2.46 (1.03, 5.88)	0.043		
Highest urea pre-ECLS, mmol/L	1.10 (1.00, 1.21)	0.051		
ECLS after 2005, yes	0.43 (0.19, 1.02)	0.055	0.36 (0.13, 0.99)	0.048
Highest lactate pre-ECLS, mmol/L	1.01 (1.00, 1.01)	0.092		
Highest ECLS flow in first 24 h, mL/kg/min	1.11 (0.98, 1.26)	0.100		
ECPR, yes	1.03 (0.44, 2.43)	0.943	1.89 (0.68, 5.28)	0.223

ORs reported reflect changes per unit increase in the predictor variables. CI indicates confidence interval; CRRT, continuous renal replacement; ECLS, extracorporeal life support; ECPR, extracorporeal cardiopulmonary resuscitation; LOS, length of stay; OR, odds ratio; and PELOD, pediatric logistic organ dysfunction.

time for lactate to fall below 2 mmol/L or inotrope score at 24 hours of ECLS between the 2 eras.

It is notable that single-ventricle anatomy was not associated with increased mortality in our group which is different than some other published series.[9,11] Historically, single-ventricle patients, either with an aortopulmonary shunt or a cavopulmonary connection, have a lower rate of survival than other cardiac ECLS patients.[19,20] A recent

Table 4. Univariate and Multiple Cox Regression Analysis of Mortality ≤5 Years of Age in Cardiac ECLS Patients (n=98)

	Univariate		Multiple	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Platelets first 48 h	1.09 (1.04, 1.15)	<0.001	1.11 (1.05, 1.18)	<0.001
Age<29 d	2.61 (1.46, 4.65)	0.001		
Time lactate<2 mmol/L	1.27 (1.09, 1.48)	0.002	1.28 (1.09, 1.51)	0.003
Cumulative fluid balance first 48 h, mL/kg	1.45 (1.11, 1.90)	0.007	1.50 (1.11, 2.03)	0.008
CRRT, yes	2.24 (1.21, 4.13)	0.010		
PELOD in first 48 h	1.42 (1.07, 1.89)	0.014		
Highest plasma free hemoglobin	1.31 (1.05, 1.62)	0.015		
Inotrope score pre-ECLS	2.07 (1.10, 3.90)	0.025		
Highest ECLS flow in first 24 h, mL/kg/min	1.06 (1.01, 1.12)	0.028		
Hospital LOS, d	0.99 (0.98, 1.00)	0.039		
Perioperative ECLS, yes	0.50 (0.25, 0.97)	0.041	0.42 (0.20, 0.87)	0.021
Highest lactate pre-ECLS, mmol/L	1.01 (1.00, 1.01)	0.043		
Weight, kg	0.90 (0.81, 1.01)	0.062		
ECLS after 2005, yes	0.59 (0.33, 1.04)	0.069	0.52 (0.27, 0.99)	0.047
Single ventricle, yes	1.70 (0.96, 3.02)	0.071		
Seizures pre-ECLS, yes	2.48 (0.89, 6.92)	0.083		
ECPR, yes	1.32 (0.75, 2.33)	0.343	1.90 (0.98, 3.69)	0.058

HRs reported reflect changes per unit increase in the predictor variables. CI indicates confidence interval; CRRT, continuous renal replacement; ECLS, extracorporeal life support; ECPR, extracorporeal cardiopulmonary resuscitation; HR, hazard ratio; LOS, length of stay; and PELOD, pediatric logistic organ dysfunction.

Table 5. Univariate and Multiple Regression Analysis of Full-Scale Intelligence Quotient in Cardiac ECLS Patients Without Chromosomal Abnormalities (n=44)

	Univariate		Multiple	
	Effect Size (95% CI)	*P* Value	Effect Size (95% CI)	*P* Value
Hospital LOS, d	−0.09 (−0.15, −0.03)	0.003		
Total mechanical ventilation, d	−0.14 (−0.25, −0.04)	0.010		
CRRT prior to ECLS, yes	29.00 (−15.02, 73.02)	0.076		
Weight, kg	1.10 (−0.12, 2.31)	0.076	1.32 (0.07, 2.57)	0.039
Highest inotrope score first 24 h of ECLS	−0.84 (−1.85, 0.17)	0.100		
SES	0.30 (−0.14, 0.74)	0.177	0.39 (−0.05, 0.84)	0.081
ECPR	−0.50 (−11.67, 10.67)	0.929	−2.96 (−13.98, 0.07)	0.590
ECLS after 2005, yes	−1.68 (−13.06, 9.71)	0.768	−1.11 (−12.17, 9.96)	0.841

We did not consider hospital LOS, post-ECLS—days, or total mechanical ventilation—days in the multiple regression models, as these are in the direct pathway from exposure to outcome. Effect sizes reported are also known as slopes and reflect changes per unit increase in the predictor variables. CI indicates confidence interval; CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support; ECPR, extracorporeal cardiopulmonary resuscitation; LOS, length of stay; and SES, socioeconomic status.

review of outcomes after pediatric cardiac ECLS found that single-ventricle patients after the Norwood procedure have equivalent outcomes to biventricular patients; however, the limited available reports suggest that those with a cavopulmonary connection had a particularly poor outcome.[21] In our series, 2 and 8 patients had ECLS post-Glenn or -Fontan in the first and second era, respectively, with 50% and 63% survival. We deliberately run higher ECLS flows on single-ventricle patients to provide adequate systemic and pulmonary blood flow, which may contribute to their good survival. Our single-ventricle group had similar time for lactate to fall below 2 mmol/L while on ECLS and platelet transfusion requirements which may help explain their good survival.

Fourteen survivors to hospital discharge (14 of 65; 21.8%) died between hospital discharge and follow-up to 5 years of age. Other reports of neurodevelopmental follow-up post-ECLS[6,9,11] also demonstrate high mortality rates once discharged from hospital. Debrunner et al[22] compared midterm survival of infants requiring a Norwood procedure with and without postoperative ECLS support. Neonates who required ECLS after their Norwood procedure demonstrated significantly decreased survival to hospital discharge as well as to most recent follow-up.[22] In our study, mortality at 5 years of age was independently associated with longer time for lactate to fall below 2 mmol/L on ECLS, increased platelet requirements in the first 48 hours of ECLS, a higher cumulative fluid balance 48 hours after ECLS initiation, nonperioperative ECLS, and ECLS during the first time period cohort (2000–2004). It is notable that a higher cumulative fluid balance was not associated with in-hospital mortality, but was associated with 5-year mortality. This may indicate that early events during ECLS can influence long-term outcomes, even if they do not change hospital survival. Future work should aim to determine a mechanism for this finding. Fluid overload is associated with mortality in pediatric patients requiring CRRT[23–27]; however, no study to date has demonstrated causality. Selewski et al[27] demonstrated in

Table 6. Univariate and Multiple Regression Analysis of Performance Intelligence Quotient in Cardiac ECLS Patients Without Chromosomal Abnormalities (n=44)

	Univariate		Multiple	
	Effect Size (95% CI)	*P* Value	Effect Size (95% CI)	*P* Value
Hospital LOS post-ECLS, d	−0.10 (−0.15, −0.04)	0.001		
Total mechanical ventilation, d	−0.15 (−0.25, −0.05)	0.004		
Weight, kg	1.05 (−0.14, 2.24)	0.082	1.31 (0.09, 2.52)	0.036
Highest inotrope score first 24 h of ECLS	−0.80 (−1.79, 0.19)	0.109		
SES	0.26 (−0.17, 0.70)	0.228	0.36 (−0.07, 0.79)	0.099
ECPR	−3.00 (−13.85, 7.86)	0.580	−5.53 (−16.27, 5.21)	0.304
ECLS after 2005, yes	0.76 (−11.88, 10.36)	0.891	0.18 (−10.60, 10.97)	0.973

We did not consider hospital LOS, post-ECLS—days, or total mechanical ventilation—days in the multiple regression models, as these are in the direct pathway from exposure to outcome. Effect sizes reported are also known as slopes and reflect changes per unit increase in the predictor variables. CI indicates confidence interval; ECLS, extracorporeal life support; ECPR, extracorporeal cardiopulmonary resuscitation; LOS, length of stay; and SES, socioeconomic status.

Table 7. Univariate and Multiple Regression Analysis of Verbal Intelligence Quotient in Cardiac ECLS Patients Without Chromosomal Abnormalities (n=44)

	Univariate		Multiple	
	Effect Size (95% CI)	*P* Value	Effect Size (95% CI)	*P* Value
Hospital LOS post-ECLS, d	−0.09 (−0.14, −0.03)	0.004		
Total mechanical ventilation, d	−0.14 (−0.25, −0.04)	0.009		
Weight, kg	1.19 (−0.01, 2.40)	0.052	1.41 (0.18, 2.63)	0.026
Highest inotrope score first 24 h of ECLS	−0.98 (−1.98, 0.01)	0.053		
Age, d	0.01 (−0.00, 0.02)	0.055		
Location of ECLS started	7.47 (−0.75, 15.69)	0.074		
SES	0.35 (−0.09, 0.79)	0.112	0.44 (0.01, 0.88)	0.046
ECLS after 2005, yes	−2.31 (−13.66, 9.05)	0.684	−2.00 (−12.83, 8.83)	0.710
ECPR, yes	1.48 (−9.66, 12.62)	0.790	−1.09 (−11.88, 9.70)	0.839

We did not consider hospital LOS, post-ECLS—days, or total mechanical ventilation—days in the multiple regression models, as these are in the direct pathway from exposure to outcome. Effect sizes reported are also known as slopes and reflect changes per unit increase in the predictor variables. CI indicates confidence interval; ECLS, extracorporeal life support; ECPR, extracorporeal cardiopulmonary resuscitation; LOS, length of stay; and SES, socioeconomic status.

an observational study of patients on ECLS and CRRT that starting CRRT prior to excessive fluid overload was associated with improved outcomes.

There were a higher number of ECPR cases in the second era. This may reflect the implementation of formal ECPR protocols and their subsequent acceptance. The need for ECPR demonstrated no independent statistically significant association with mortality which is comparable to some other studies of ECPR in children with cardiac disease.[28,29] ECPR was not predictive of neurocognitive outcomes in our study, and this is consistent with a recent review of the literature which also found that ECPR was not associated with mortality or neurocognitive outcomes.[21]

Our most recent era patients have better survival and similar neurocognitive outcomes. The reasons are unclear, but likely involve improved care over the years, including earlier initiation of ECLS when it is indicated and better ECLS, perhaps secondary to improved circuit design, resulting in a faster drop in lactate and less positive fluid balance at 48 hours, which is associated with improved survival. Platelet transfusions may be associated with mortality; this requires further study. We were unable to confirm suggestions that early CRRT improves outcomes, or that ECPR is associated with worse outcomes in cardiac ECLS patients. In addition, our more comprehensive anticoagulation monitoring practice was not associated with any change in blood product utilization or plasma-free hemoglobin over time. Our improved survival over time, without worse neurocognitive outcomes, is encouraging as it suggests that we are not saving only children destined to have poor outcomes.

There is a paucity of studies examining long-term neurocognitive outcomes in survivors of cardiac ECLS.[4,6,9–11] Chow et al[11] report long-term neurological sequelae in 39% of survivors; long-term outcomes were evaluated by standardized questionnaire. Hamrick et al[6] report that 50% of their long-term infant survivors were neurologically intact using formal neuromotor and cognitive testing. Similarly, we have previously reported mental delay in 50% of survivors at 2 years of age.[4] Ibrahim et al[10] detail that 62% of their extracorporeal membrane oxygenation survivors have moderate–severe impairment as measured by attainment of gross motor and language milestones or school performance. Recently, Chrysostomou et al[9] describe that 89% of long-term survivors had normal function or mild neurodevelopmental disability at mean 1.9-year follow-up, when the neurological status was assessed by the Pediatric Overall Performance Category. Pediatric Cerebral Performance Category and Pediatric Overall Performance Category were developed to quantify short-term cognitive impairment and overall short-term functional morbidity, respectively.[30] A follow-up study demonstrated that Pediatric Cerebral Performance Category and Pediatric Overall Performance Category were associated with more comprehensive psychometric measures of function.[31] However, the longest follow-up was only ≤6 months and was evaluated by parental report of adaptive behavior. Hence, Pediatric Overall Performance Category and Pediatric Cerebral Performance Category do not provide detailed information on objective longer term neurofunctional outcomes. Our study details the largest group of pediatric cardiac ECLS survivors and their formally assessed neurocognitive outcomes at 5 years of age. Our findings are concerning with 25% of survivors having FSIQ below 2 SD of the population norms.

Strengths of our study are the length of follow-up, evaluation of all long-term survivors, and formal neurocognitive assessments. The survivors were followed prospectively to kindergarten entry, and therefore we still do not know what their school performance will be; however, the neurocognitive assessments done at this age are generally stable in relation to school-age intelligence.[15] Limitations of the present study include the relatively small number of subjects in each time period cohort, and the retrospective collection of some of the acute care variables during the ECLS run. Additionally, the study was conducted in a single center. Consequently, the results reflect the outcomes of a highly experienced referral ECLS center where high-risk children are supported.

Conclusions

Children <5 years of age who required cardiac ECLS had a 65% survival to hospital discharge and 51% survival ≤5 years of age. There was a statistically significant higher survival in the second time period cohort suggesting that improvements over time, likely including our ECLS circuit design and patient care protocols, have improved outcomes. Of concern, the FSIQ of survivors without chromosomal abnormalities was 79.7 (16.6) with 25% having a score below 2 SD of the population mean, which emphasizes the importance of early intervention programs for these children to optimize their ultimate long-term function.

Appendix

The Western Canadian Complex Pediatric Therapies Follow-up Group includes: Reginald Sauve, Calgary, Alberta; Diane Moddemann, Winnipeg, Manitoba; Patricia Blakley, Saskatoon, Saskatchewan; Anne Synnes, Vancouver, BC; and Jaya Bodani, Regina, Saskatchewan, Canada.

Disclosures

None.

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CLINICAL PERSPECTIVE

We report our 10-year experience with cardiac venoarterial extracorporeal life support (ECLS) in children <5 years of age. The 98 children were a prospective inception cohort enrolled in the Western Canadian Complex Pediatric Therapies Follow-up Program, and all 50 survivors had detailed neurocognitive assessment done ≥6 months after ECLS, at the age of 52.9 (SD, 8) months. We found a 65% (n=64) survival to hospital discharge and 51% (n=50) survival to 5 years of age. Higher volume of platelets transfused in the first 48 hours of and longer time for lactate to fall to ≤2 mmol/L on ECLS were independent predictors of higher mortality. Having surgery in the second era (after year 2005) was independently associated with lower mortality at hospital discharge and to the age of 5 years, without a difference in the neurocognitive outcomes. Of survivors without chromosomal abnormalities (n=44), 25% (n=11) had a full-scale intelligence quotient below 2 SD of the population mean; the mean (SD) full-scale intelligence quotient was 79.7 (16.6), significantly skewed to the left compared with population norms. We did not identify modifiable variables independently associated with neurocognitive outcomes. Of the 50 survivors, 6 (12%) had motor disability, 9 (18%) microcephaly, 4 (8%) bilateral sensorineural hearing loss, and 2 (4%) visual impairment. These findings emphasize the importance of early intervention programs for these children to optimize their ultimate long-term function, and early attention to optimal ECLS flows and technique to improve the survival after cardiac ECLS. The role of platelets in determining survival warrants further investigation.

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Survival and Neurocognitive Outcomes After Cardiac Extracorporeal Life Support in Children Less Than 5 Years of Age: A Ten-Year Cohort

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SUPPLEMENTAL MATERIAL

Table S1. Demographics, variables and outcomes for all cardiac related ECLS patients (n=98)

Demographic/Pre ECLS	**Median or n (Q1-Q3; min-max or %)**
Age (months)	2.1 (0.4-7.1; 0-56)
Weight (kg)	4.4 (3.3-6.8; 1.4-18)
Gender (male)	54 (55)
Single ventricle (yes)	33 (34)
Inotrope score pre-ECLS	19 (5-30;, 0-236)
Days on mechanical ventilation pre-ECLS	1 (0-10; 0-83)
Lactate level pre-ECLS (n=80)	7.1 (3.7-13.1; 0.2-28)
Time ECLS in relation to cardiac surgery	
No surgery	15 (15)
Before	12 (12)
After	71 (72)
CPB (yes)	74 (96)
CPB time (minutes)	150 (86-218; 30-546)
Aortic cross-clamp time (minutes)	59 (28-82; 0-172)
DHCA time (minutes)	23.5 (8.5-37;, 1-58)
Re-CPB in the OR (yes)	19 (26)
ECLS	**Median or n (Q1-Q3; min-max or %)**
Indication	
Failed to wean CPB	27 (27)
LCOS	28 (29)
Hypoxia	6 (6)
ECPR	37 (38)
ECLS start location	

OR	33 (34)
PICU	60 (61)
Other	5 (5)
Cannulation site	
Chest	50 (51)
Neck	46 (47)
Multiple	2 (2)
Left atrial vent (yes)	35 (36)
Time to lactate ≤ 2 mmol/L (hours)	18 (9-34; 0-102)
Highest plasma lactate on ECLS	8 (4.9-3.7; 0.9-26)
ECLS run (hours)	136 (84-171; 3-835)
ECLS flow at 24 hours (ml/kg/minute)	103 (92-121; 50-200)
Inotrope score first 24 hours	10 (5-12.5; 0-86)
PRBC transfusion first 48 hours (ml/kg)	141 (85-254; 0-800)
Cumulative fluid balance first 48 hours	209.2 (111-386.9; -131.5-989.2)
First day negative fluid balance	4 (3-6; 1-6)
Platelet transfusion first 48 hours (ml/kg)	46.5 (24-81; 0-283)
Highest plasma free hemoglobin	282 (170-438; 81-924)
Sternal exploration in the first 5 days (yes)	51 (52)
PELOD at 48 hrs	13 (12-22; 1-51)
Seizures while on ECLS (yes)	17 (17)
CRRT while on ECLS (yes)	54 (55)
Post ECLS	**Median or n (Q1-Q3; min-max or %)**
Total ventilation days	22 (11-38; 2-258)
Total PICU LOS	19.5 (12-43; 1-317)
Total Hospital LOS	50 (23-75; 3-564)

Survival to hospital discharge	64 (65)
Survival to <5 years of age	50 (51)

ECPR: extracorporeal cardiopulmonary rescucitation, ECLS: extracorporeal life support, PICU: pediatric intensive care unit, OR: operating room, ER: emergency room, MRI: magnetic resonance image, NICU: neonatal intensive care unit, ICU: intensive care unit, CPR: cardiopulmonary rescucitation, PRBC: packed red blood cells, CRRT: continuous renal replacement therapy.

Table S2. Univariate and multiple regression analysis of VMI and GAC in cardiac ECLS patients without chromosomal abnormalities (n=44)

Visual-Motor Index	**Univariate**		**Multiple**	
	Effect size (95% CI)	*P-value*	Effect size (95% CI)	*P-value*
Hospital LOS - Days	-0.10 (-0.16, -0.05)	*0.001*		
Total mechanical ventilation - Days	-0.16 (-0.26, -0.05)	*0.004*		
CPB - Yes	-41.94 (-70.93, -12.94)	*0.006*		
General Adaptive Composite from the Adaptive Behavior Assessment System	**Univariate**		**Multiple**	
	Effect size (95% CI)	*P-value*	Effect size (95% CI)	*P-value*
Hospital LOS - Days	-0.07 (-0.14, -0.00)	*0.083*		
Total mechanical ventilation - Days	-0.12 (-0.24, 0.01)	*0.075*		
ECLS after 2005 - Yes	-10.91 (-23.62, 1.80)	*0.091*		

VMI: Visual-Motor Index, GAC: General Adaptive Composite from the Adaptive Behavior Assessment System, ECLS: extracorporeal life support, LOS: length of stay, CPB:cardiopulmonary bypass

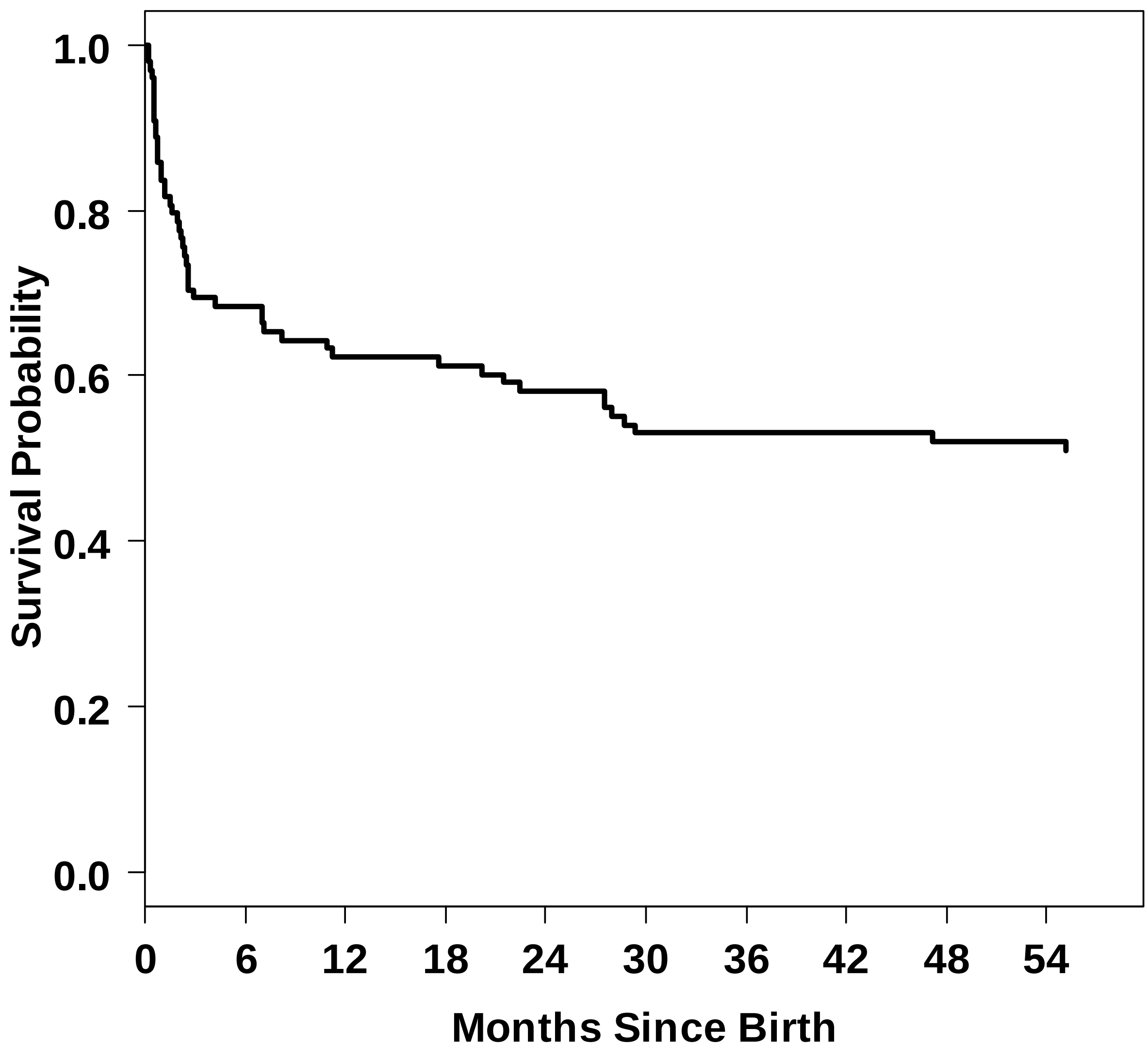

Figure S1. Kaplan Meier estimates of survival time since birth.