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Massive Transfusion as a Predictor of Survival in Pediatric Patients Receiving Extracorporeal Life Support

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Abstract
Massive Transfusion as a Predictor of Survival in Pediatric Patients Receiving Extracorporeal Life Support

By Anne Marie Winkler

Extracorporeal life support (ECLS) is a technique that has been shown to be effective in supporting patients of all ages with life-threatening cardio-respiratory failure of varying etiologies and has become the standard therapy for neonatal, pediatric and adult patients with acute cardiac or respiratory failure that is unresponsive to traditional management. As a result of added extracorporeal volume, acquired hemostatic changes, and occurrence of hematologic complications, transfusion requirements associated with ECLS are very high and patients are commonly massively transfused; however, associations between massive transfusion, complications, and all-cause mortality have not been formally investigated in ECLS patients. One prior study demonstrated a weak association between each packed red blood cell (RBC) transfusion volume of 10 ml/kg/day and in-hospital mortality (OR 1.024, CI 1.004-1.046, p=0.018) in ECLS patients(15). As a result, a cohort study of all ECLS patients less than 18 years of age was conducted at a single institution from 1/1/2009 - 12/31/2011 to examine the association between massive transfusion, defined as RBC transfusion of greater than one blood volume plus circuit volume based upon on patient weight, complications, and all-cause mortality. In this cohort, massive transfusion which occurred in 32.7% of the entire cohort and 36.3% of neonatal subjects was associated with increased all-cause mortality, and this effect was stronger for neonates (OR 6.45, CI 1.81-22.9, p=0.004). Kaplan–Meier estimates for the probability of death did significantly differ between subjects who were massively transfused versus those who were not (Log rank <0.0001) and the effect of massive transfusion was time-dependent. Subjects who were massively transfused with an ECLS duration greater than 4 hours had an increased hazard of death (HR 3.38, CI1.59-7.20, p=0.002) when controlling for ECLS mode. As a result, massive transfusion is independently associated with an increased risk for all-cause mortality, similar to investigations linking RBC transfusion to increased morbidity and mortality in non-ECLS critically ill patients.

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INTRODUCTION

Extracorporeal life support (ECLS) is a technique that has provided temporary cardio-respiratory support to over 48,000 critically ill patients with life threatening disease with an international overall survival of 73% (1). Traditionally, this technique has been utilized mainly for the treatment of life threatening acute neonatal respiratory failure; however, over the past decade, ECLS has been increasingly used in large numbers for a diverse group of indications, which includes but is not limited to cardiac failure, and pediatric and adult respiratory failure. ECLS has been shown to be effective in supporting patients of all ages with life-threatening cardio-respiratory failure of varying etiologies based on the results of randomized controlled trials in both the neonatal and adult populations, as well as clinical experience. Thus, ECLS has become the standard therapy for neonatal, pediatric and adult patients with acute cardiac or respiratory failure that is unresponsive to traditional management (2,3).

Since the inception of extended duration bedside extracorporeal cardio-respiratory support, hematologic complications, including both hemorrhage and thrombosis, have been major issues in providing ECLS safely; hematologic complications occur in approximately 10% of all ECLS patients and are associated with increased mortality(4). Moreover, if a patient develops hemorrhagic or thrombotic complications, transfusion and factor replacement therapy are critical to the management and survival of the ECLS patient. As a result, transfusion requirements associated with ECLS are very high and patients are commonly massively transfused. An association between massive transfusion and mortality has not been formally investigated in ECLS patients and no validated transfusion algorithms have been evaluated. As a result, this study was designed to determine the associations between massive transfusion, all-cause mortality, and complications in pediatric patients receiving ECLS support and is an important first step in understanding the transfusion management of ECLS patients.

BACKGROUND

Extracorporeal life support (ECLS) is a technique that has provided temporary cardio-respiratory support to over 48,000 critically ill patients with life threatening disease with an overall survival of 73% internationally (1). During ECLS, blood is removed via large bore cannulas and an external pump delivers the blood first to a gas exchanging membrane (oxygenator) to provide oxygenation and carbon dioxide clearance, and then returns the blood to the patient. The site of the returning blood (arterial or venous) determines the mode of ECLS, and whether solely respiratory support (venovenous or VV mode) or combined cardio-respiratory support (venoarterial or VA mode) is provided. Traditionally, this technique has been utilized mainly for the treatment of life threatening acute neonatal respiratory failure; however, over the past decade, ECLS has been increasingly used in large numbers for a diverse group of indications, which includes but is not limited to cardiac failure, and pediatric and adult respiratory failure (see table below).

Top indications for ECLS by Patient Age

Neonate (0-30 days)	**Pediatric (>30 days and <18 years)**	**Adult (18 years and older)**
Meconium Aspiration Syndrome Congenital Diaphragmatic Hernia Persistent Pulmonary Hypertension Sepsis Respiratory Distress Syndrome Pneumonia Air Leak Syndrome Congenital Heart Defect Cardiomyopathy Cardiac transplant	Viral Pneumonia Acute Respiratory Distress Syndrome Bacterial Pneumonia Aspiration Pneumonia Congenital Heart Defect Cardiomyopathy Cardiac transplant	Acute Respiratory Distress Syndrome Bacterial Pneumonia Viral Pneumonia Aspiration Pneumonia Congenital Heart Defect Cardiomyopathy Cardiac transplant

Additionally, the use of ECLS has expanded to transplant patients who are successfully being bridged to both cardiac and lung transplantation. Thus, ECLS is a technique that has been shown to be effective in supporting patients of all ages with life-threatening cardio-respiratory failure of varying etiologies and based on the results of randomized controlled trials in both neonatal and adult populations, as well as clinical experience, ECLS has become the standard therapy for

neonatal, pediatric and adult patients with acute cardiac or respiratory failure that is unresponsive to traditional management (2,3).

Since the inception of extended duration bedside extracorporeal cardio-respiratory support in 1971 with the Bramson lung, hematologic complications including both hemorrhage and thrombosis have been major issues in providing ECLS safely (4). In the first reported case, in only 75 hours of extracorporeal support, the patient received 34 units of blood products (4). While the technology has matured over the years, hematologic complications, including both thrombosis and hemorrhage, are common occurring in approximately 10% of all ECLS cases and are associated with increased mortality. From the 2012 Extracorporeal Life Support Organization (ELSO) registry report, 2-17% of ECLS patients suffered one or more hematologic complications (1).

In all patient populations, hematologic complications have a negative impact on survival. For example, in the neonatal respiratory ECLS population the survival percentages are 7-38% less if a patient experiences a hematologic complication (1). The development of hematologic complications has also been found to be a function of the duration of ECLS. An autopsy based study of cardiac surgery patients receiving ECLS demonstrated a positive linear correlation of risk of thromboembolism and duration (5). This is especially important to consider because the duration of neonatal respiratory ECLS runs, for example, have increased from 144 hours to 209 hours over the past decade (1). Thus, hematologic complications, being common and negatively impacting survival, make an attractive target for optimization. However, tempering that enthusiasm is the fact that the coagulation system is quite complex in the normal host and when taking into consideration the additional effects of the artificial surfaces on blood, it becomes much more difficult to assess.

Hemorrhagic and thrombotic complications during ECLS are multifactorial. As a result of direct exposure of the blood to the artificial surfaces of the tubing and oxygenators, there is significant activation of the coagulation system immediately following ECLS initiation (6,7). The hemostatic balance can also be altered during ECLS due to a number of factors including systemic heparinization, platelet dysfunction, hyperfibrinolysis, coagulation factor consumption, and disseminated intravascular coagulation (8).

Blood transfusion and factor replacement therapy during ECLS support typically occurs for three reasons. First, packed red blood cell (RBC) units, in addition to other solutions and heparin, are necessary to prime the circuit before a patient is cannulated. Secondly, blood components and coagulation factors are routinely administered to maintain the hemostatic balance that is disrupted as a result of the extensive coagulation activation that occurs during ECLS support (9). Platelet (PLT) products are also commonly transfused, in addition to RBC, fresh frozen plasma (FFP), and cryoprecipitate (Cryo). Lastly, if a patient develops hemorrhagic or thrombotic complications, transfusion and factor replacement therapy are critical to the management and survival of the ECLS patient. As a result, transfusion requirements associated with ECLS are very high and patients are commonly massively transfused. In an adult, massive transfusion is most common following trauma and defined as replacement of one blood volume within 24 hours or transfusion of 10 or more RBC within 24 hours. In pediatric patients, the definition of massive transfusion has not been well established; however, the definition has been extrapolated from adults (10,11).

Following trauma, there is a significant association between the number of RBCs transfused and mortality (12). However, this difference in mortality is diminished when high FFP to RBC ratios are obtained; transfusion ratios of 1RBC:1FFP were independently associated with improved survival to discharge primarily by decreasing death due to hemorrhage (13). As a result, massive transfusion protocols have been developed to improve transfusion management using preset ratios

of RBC, FFP, PLT and CRYO transfusions to recapitulate whole blood transfusion and have demonstrated decreased mortality compared to historical controls (14). However, a similar association between massive transfusion and mortality has not been formally investigated in ECLS patients and no validated transfusion algorithms have been evaluated in pediatric patients receiving ECLS support. Smith et al have been the only investigators to examine the association between RBC transfusion and mortality in ECLS; in a single center retrospective review, the authors demonstrated that RBC transfusion volumes of 10 ml/kg/day were associated with increased odds of in-hospital mortality (OR 1.024, CI 1.004-1.046, p=0.018) (15). This study was designed to determine the associations between massive transfusion, mortality, and hemorrhagic complications in pediatric patients receiving ECLS support and is an important first step in understanding the transfusion management of ECLS patients.

METHODS

Research Goal

Because of the known association between massive transfusion and increased mortality in trauma, the research goal was to determine if mortality differed amongst pediatric ECLS patients who were massively transfused compared to those who were not. The primary hypothesis was that pediatric patients on ECLS who experienced massive transfusion would have increased mortality than those who were not massively transfused. A secondary hypothesis was that pediatric ECLS patients who experienced massive transfusion would have increased mechanical and hemorrhagic complications than those were not massively transfused.

Study Design and Research Subjects

Each year at Children's Healthcare of Atlanta (CHOA) at Egleston, approximately 40 children receive ECLS. Like many other centers, CHOA reports all cases to an international registry maintained by ELSO and Egleston has contributed 859 of these cases from January 1991-December 2011. A cohort study was conducted of all ECLS patients less than 18 years of age at Egleston from 1/1/2009 - 12/31/2011. Data collection was limited to this time frame because ECLS circuitry, circuit components and volume were comparable, and complete electronic medical record documentation was available. Patients were excluded if 18 years of age or older and/or had incomplete electronic transfusion histories.

In accordance and compliance with federal guidelines for conducting research, review and approval for this study was obtained from the Institutional Review Boards at Emory University and CHOA. This study is in compliance with the Health Insurance Portability and Accountability Act (HIPAA). Data was collected from the medical records of pediatric patients at CHOA and deidentified.

Data Collection

Study data were collected and managed using REDCap electronic data capture tools hosted at Emory University (16). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Existing data from the ELSO registry was imported into REDCap.

The primary exposure of interest was massive transfusion, defined as replacement of one blood volume plus ECLS circuit volume in the first 24 hours of ECLS support. More specifically, patients weighing less than 10 kg were calculated using the formula [80 ml/kg x weight (kg)] + 450 ml, and patients weighing greater than 10 kg were calculating using [70 ml/kg x weight (kg)] + 750 ml; the difference in formulas by weight takes into consideration the differences in both patient blood volume and circuit volume. These formulas were modified from the definition of massive transfusion for adult trauma patients (10,11). The primary outcome was all-cause mortality, which was taken from the ELSO standardized reporting defined as survival to death, discharge or transfer. Secondary outcomes included occurrence of a mechanical complication, defined as a complication requiring a change of equipment, and/or hemorrhagic complication, defined as a hemorrhage requiring medical intervention; both of these complications are reported using standardized criteria to the ELSO registry. Additional data collected included: 1) patient demographics (gender, race, weight, age, estimated gestational age if applicable), 2) admission details including admission reason, patient location, date of intubation, type of surgery if applicable, 3) ECLS details including dates and times of ECLS, indication, mode (VA or VV), duration (hours and days), and addition of other treatment modalities including continuous renal replacement therapy or therapeutic plasma exchange, 4) transfusion histories including number

and volume (ml) of blood components (RBC, FFP, PLT, CRYO) transfused within 24 hours of ECLS cannulation including intraoperative transfusion and for the remainder of the ECLS episode, 5) patient vital signs (heart rate and systolic blood pressure), mode of mechanical ventilation, papillary response and Glasgow Coma Scale in the first 24 hours and 6 hours prior to ECLS cannulation, and 6) the following laboratory data in the first 24 hours as well as in 6 hours prior to ECLS cannulation: PaO2, PaCO2, white blood cell count, platelet count, aspartate aminotransferase (AST), prothrombin time/international normalized ratio (PT/INR), and creatinine (Cr). The pediatric logistic organ dysfunction (PELOD) score, which includes six organ dysfunctions and 12 variables, was calculated using an online calculator for the first 24 hours of admission and for the 6 hours prior to ECLS cannulation; when the variable was measured more than once, the most severe value was used in calculating the score (17-20). The PELOD score has been developed and prospectively validated to estimate disease severity and probability of death for intensive care unit pediatric patients.

Data Analysis

Continuous data are reported as means or medians, where appropriate, and categorical variables are reported as frequencies with percentages. Demographic and clinical data where compared using Students t-tests or Wilcoxon Signed Rank, where appropriate, for continuous variables and Chi-Square or Fisher's exact tests, where appropriate, for categorical variables. All-cause mortality comparisons were achieved with the use of multivariate logistic regression analysis, with all-cause mortality, the reciprocal of the ELSO reported outcome of survival to death, discharge or transfer, as the binary dependent variable. Only covariates with a univariate significance of $p<0.10$ were considered for inclusion within the multivariate model unless thought to be clinically

significant. Data from multivariate logistic regression analyses are reported as estimated odds ratios (OR) with 95% confidence intervals (CI). Confounding was assessed by comparison of the parameter estimate for massive transfusion (exposure) with and without the potential confounder as covariate in the model. Survival analysis including Kaplan Meier survival curves and extended Cox proportional hazards models were also performed; Log rank results as well as hazard ratios (HR) with 95% CIs are reported. All data were analyzed with SAS 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

From January 1, 2009 through December 31, 2011, 173 patients received ECLS support at Egleston. Of these, 8 subjects were excluded and one patient had two ECLS episodes in a single admission, only one of which was included in the analysis (Figure 1). As a result, 165 total ECLS subjects were included in the analysis (Figure 1), of which 77 (46%) were neonates (less than 30 days of age). The incidence of massive transfusion was 32.7% in the entire cohort. Baseline demographic characteristics of the entire cohort are summarized in Table 1. Subjects who were massively transfused (MT) were younger with a median age of 4 days (3-10.5) compared to 85 days (1-2207) for those who were not MT ($p<0.0001$). On the other hand, patients who were MT weighed more (4.76 kg, 3.2-23.9) than those who were not MT 3.8 kg (2.94-4.6) ($p<0.0001$). Between groups, there was no significant difference in illness severity as measured by PELOD either within the first 24 hours of admission or within 6 hours of ECLS initiation or with pre-ECLS intubation days, which has previously been shown to be a predictor of survival (Table 2) (21). In addition, there were no differences in pre-ECLS hemoglobin concentrations, platelet counts, or coagulation studies in patients who were MT as compared to those that were not MT, suggesting that the reasons for transfusion were not due to underlying anemia, thrombocytopenia, or coagulopathy (Table 2).

Of the subjects who were MT, ECLS was predominantly initiated for a cardiac indication (72.2%) and all were placed on VA ECMO ($p<0.0001$) (Table 3). Addition of other circuit components, namely continuous renal replacement therapy (CRRT) or therapeutic plasma exchange (TPE) was not different between groups (Table 3). By definition, subjects who were MT received transfusion of greater volumes of RBCs (305.5 ml/kg versus 150.6 ml/kg) (Table 4). Likewise, they also received greater volumes of FFP (83.0 versus 24.8 ml/kg); although for both groups the transfusion ratio of RBC: FFP was greater than 1.0 (Table 4). There was no difference in either mechanical or hemorrhagic complication rates between subjects who were MT versus those who

were not and no significant difference in ECLS duration although there was a trend toward longer duration in patients who were not MT (Table 4). In univariate analysis, subjects who were MT did have increased mortality as compared to those who were not MT (53.7% versus 27.9%, p=0.0012) (Table 4). A multivariate logistic regression analysis of all-cause mortality is detailed in Table 5; when controlling for age and MT, only VA ECLS mode remained a significant predictor of all cause mortality with an odds ratios of 2.46 (CI 1.17-5.20, p=0.018). Moreover, Kaplan–Meier estimates for the probability of death did significantly differ between patients who were MT versus those who were not MT (p<0.0001, Figure 2). From the Kaplan Meier curves, it is evident that the proportional hazards assumption is not satisfied and the two curves diverge after 4 hours of ECLS duration, which is the time dependent covariate. As a result, an extended Cox proportional hazards model was performed, which demonstrated an increased hazard for death (HR 3.38, CI1.59-7.20, p=0.002) in patients who were massively transfused with an ECLS duration greater than 4 hours when controlling for ECLS mode (Table 6).

Neonatal Subgroup Analysis

Of the 77 neonates, 28 (36.3%) were MT. Baseline demographic characteristics of the neonatal ECLS cohort are summarized in Table 7. Subjects who were not MT were younger with a median age of 3.4 days compared to 7.9 days in those who were not (p=0.001) similar to the results of the entire cohort. Between groups, there was no significant difference in weight, sex, or race. While there was a statistically difference in admission PELOD scores (19 versus 22, p=0.003), values of 19 and 22 provide comparable predicted death rates (Table 8). In addition, subjects who were MT had lower hemoglobin concentrations (13.3. g/dl versus 14.8 g/dl, p=0.01), and more prolonged APTTs (80.4 sec versus 49.5 sec) compared to those who were not; however, the differences in these parameters would not solely explain the need for MT (Table 8).

Of the neonatal subjects who were MT, ECLS was predominantly initiated for a cardiac indication (82.1%) and all were placed on VA ECMO ($p<0.0001$) (Table 9). Subjects who were MT were more likely to receive CRRT (46.4% versus 22.5%, $p=0.029$) (Table 9). By definition, subjects who were MT received transfusion of greater volumes of RBCs (385.6 ml/kg versus 174.1 ml/kg, $p<0.0001$) (Table 10). Likewise, they also received greater volumes of FFP (57.8 ml/kg versus 16.4 ml/kg, $p=0.003$), PLT (68.6 ml/kg versus 33.2 ml/kg, $p<0.0001$), and Cryo (2.6 units versus 0.04 units, $p<0.0001$) (Table 10). There was no difference in either mechanical or hemorrhagic complication rates between subjects who were MT versus those who were not and no significant difference in ECLS duration (Table 10). In univariate analysis, neonatal subjects who were MT did have increased mortality as compared to those who were not MT (60.7% versus 26.5%, $p=0.003$) (Table 10). A multivariate logistic regression analysis of all-cause mortality is detailed in Table 11; MT (OR 6.45, CI 1.81-22.9, $p=0.004$), admit PELOD (OR 1.19 for each one point increase in score), and addition of CRRT (OR 6.69, CI 2.11-22.19, $p=0.002$) were all significant predictors of mortality. Moreover, Kaplan–Meier estimates for the probability of death did significantly differ between patients who were MT versus those who were not MT (Figure 3). Similar to the entire ECLS cohort, the Kaplan-Meier curves overlap and diverge after 4 hours of ECLS duration, and an extended Cox proportional hazards model showed similar results to the entire cohort; neonates who were massively transfused with an ECLS duration greater than 4 hours had an increased hazard of death (HR 4.94; 1.91-12.78, $p=0.001$) when controlling for admit PELOD and CRRT (Table 12).

DISCUSSION

ECLS is a technique that has been shown to be effective in supporting patients of all ages with life-threatening cardio-respiratory failure of varying etiologies, and has become the standard therapy for neonatal, pediatric and adult patients with acute cardiac or respiratory failure that is unresponsive to traditional management (2,3). As a result of added extracorporeal volume of the ECLS circuit, acquired hemostatic changes, and occurrence of hematologic complications, transfusion requirements associated with ECLS are very high and patients are commonly massively transfused. The associations between massive transfusion, complications (mechanical and/or hemorrhagic), and all-cause mortality have not been formally investigated in ECLS patients. As a result, this cohort study was designed to determine these associations as an important first step in understanding the transfusion management of ECLS patients. The prevalence of massive transfusion, defined as RBC transfusion of greater than one blood volume plus circuit volume based upon on patient weight, was 32.7% in the entire ECLS cohort. From univariate analysis, massive transfusion was not associated with increased mechanical or hemorrhagic complications; however, patients who were massively transfused had increased all-cause mortality compared to those subjects who were not. However, this association was no longer significant and only venoarterial ECLS mode was a significant predictor of all-cause mortality (OR 2.46, CI 1.17-5.20, p=0.018) when controlling for age and massive transfusion in multivariate analysis. Due to the heterogeneity of the ages and weights of entire ECLS cohort, a subgroup analysis of neonates (subjects less than 30 days of age) who received ECLS support and represented approximately half of all ECLS patients was performed. Similarly, massive transfusion, which occurred in 36.6% of neonatal ECLS subjects, was not associated with an increase in reported mechanical or hemorrhagic complications, and patients who were massively transfused had increased all-cause mortality compared to those subjects who were not in univariate analysis. In multivariate analysis, the association of massive transfusion and all-cause

mortality remained significant (OR 6.45, CI 1.81-22.9, p=0.004) after controlling for illness severity represented by admit PELOD score and presence of CRRT. Using survival analysis, Kaplan–Meier estimates for the probability of death significantly differed between patients who were massively transfused versus those who were not massively transfused and the effect of massive transfusion (Log rank <0.0001 for entire cohort, Log rank 0.005 for neonates) was determined to be time-dependent. Patients who were massively transfused and whose ECLS duration was greater than 4 hours had an increased hazard for death (HR 3.38, CI 1.20-4.02, p=0.002) as compared to those subjects who were not massively transfused and whose ECLS duration was greater than 4 hours. In conclusion, massive transfusion in ECLS patients is independently associated with an increased risk of all-cause mortality.

Only one prior study has investigated the association between transfusion and mortality in ECLS patients. In this retrospective review of 203 ECLS episodes for non-cardiac indications, the authors demonstrated a similar, but weak association between each RBC transfusion volume of 10 ml/kg/day and in-hospital mortality (OR 1.024, CI 1.004-1.046, p=0.018) independent of weight, ECLS mode, presence of congenital diaphragmatic hernia, and complications including hemorrhage, neurologic injury, and renal insufficiency (15).

Interestingly, mortality did not correlate with the occurrence of mechanical or hemorrhagic complications and the mechanism linking massive transfusion and mortality remains elusive. Similarly, red cell transfusion has been associated with increased mortality and morbidity in critically ill adult patients; however, the exact cause remains unknown (22). Current investigations examining the effect of red cell age and other biologic markers on mortality are underway (23). Unfortunately, the effect of red cell storage is not applicable to this ECLS cohort as all subjects were transfused RBCs less than 5 days of age by protocol. As a result, research

needs to continue to investigate the mechanism by which transfusion contributes to morbidity and mortality in ECLS patients. In addition, similar to the success of massive transfusion outcomes and protocols in trauma, the relationship between blood product ratios and mortality needs to be further explored.

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Figure 1: ECLS Cohort Composition

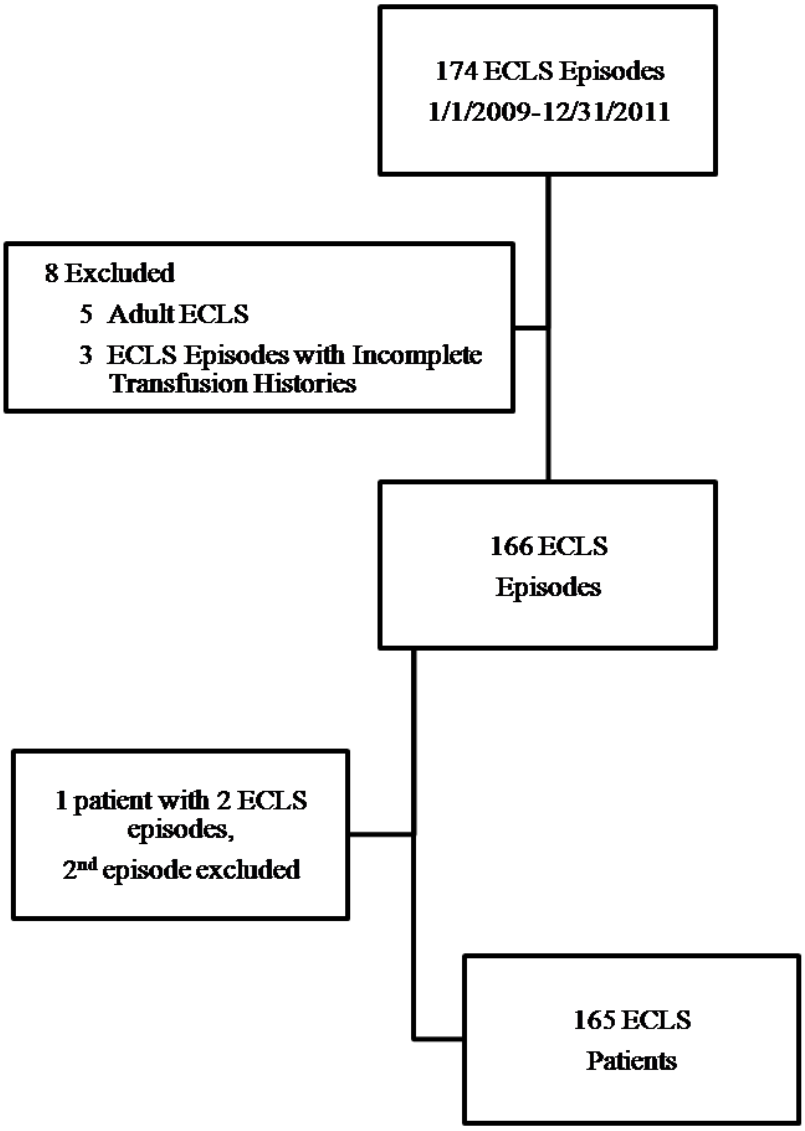


Table 1: Baseline demographic characteristic of ECLS cohort

	MT (n=54)	**Not-MT (n=111)**	**p-value**
Age (days)	4 (3-10.5)	85 (1-2207)	< 0.0001*
Weight (kg)	4.76 (3.2-23.9)	3.8 (2.94-4.6)	< 0.0001*
Male Sex (%)	34 (63%)	66 (59.5%)	0.666
Race			0.731
White	22 (42.3%)	37 (34.9%)	
Black	23 (44.2%)	47 (44.3%)	
Hispanic	3 (5.8%)	13 (12.3%)	
Asian	2 (3.9%)	5 (4.7%)	
Other	2 (3.9%)	4 (3.8%)	

For continuous variables, medians and interquartile ranges reported
*Wilcoxon Signed Rank
Other races included: Brazilian (2), Burmese (1), Multiracial (2)
ECLS= extracorporeal life support
MT=massive transfusion

Table 2: Admission and pre-ECLS illness severity and hematologic laboratory data of entire ECLS cohort

	MT (n=54)	**Not-MT (n=111)**	**p-value**
Admit PELOD	18.2 (5.78)	19.5 (7.63)	0.302
Pre-ECLS PELOD	20.3 (6.5)	21.2 (7.16)	0.438
Pre-ECLS Intubation Days	1 (0-6)	1 (0-4)	0.335
Pre-ECLS Hemoglobin (g/dl)	12.3 (2.7)	12.9 (2.8)	0.141
Pre-ECLS INR	1.6 (0.4)	1.6 (0.6)	0.724
Pre-ECLS APTT (sec)	74.7 (70.0)	52.3 (38.7)	0.034
Pre-ECLS Fibrinogen (mg/dl)	249 (129)	278 (174)	0.386
Pre-ECLS Platelets (per ml)	203 (133)	238 (178)	0.252

For continuous variables, means and standard deviations are reported
ECLS=extracorporeal life support
MT=massive transfusion
PELOD=pediatric logistic organ dysfunction score
INR=international normalized ration
APTT=activated partial thromboplastin time

Table 3: ECLS indications, mode, and additional circuit components of entire ECLS cohort

	MT (n=54)	**Not-MT (n=111)**	**p-value**
Patient Type			< 0.0001
Respiratory	15 (27.8%)	87 (78.4%)	
Cardiac / ECPR	39 (72.2%)	24 (21.6%)	
ECLS Mode			< 0.0001
VV	10 (18.5%)	71 (64%)	
VA	44 (81.5%)	40 (36%)	
CRRT	29 (53.7%)	59 (53.2%)	0.947
TPE	4 (7.4%)	5 (4.5%)	0.476*

* Fisher's Exact Test
ECLS= extracorporeal life support
MT=massive transfusion
VV=venovenous ECLS
VA=venoarterial ECLS
CRRT=continuous renal replacement therapy
TPE=therapeutic plasma exchange

Table 4: ECLS blood utilization and outcomes in the entire ECLS cohort

	MT (n=54)	**Not-MT (n=111)**	**p-value**
RBC (ml/kg)	305.5 (327.1)	150.6 (275.2)	0.002
FFP (ml/kg)	83.0 (147.9)	24.8 (51.7)	0.0003
PLT (ml/kg)	235.2 (390.7)	163.9 (227.6)	0.1413
Cryo (units)	1.7 (3.0)	1.0 (3.5)	0.226
Mechanical Complications	8 (14.8%)	28 (25.2%)	0.129
Hemorrhagic Complications	22 (40.7%)	48 (43.2%)	0.760
ECLS Duration (hours)	157 (106.6)	208 (183.5)	0.058
Mortality	29 (53.7%)	31 (27.9%)	0.0012

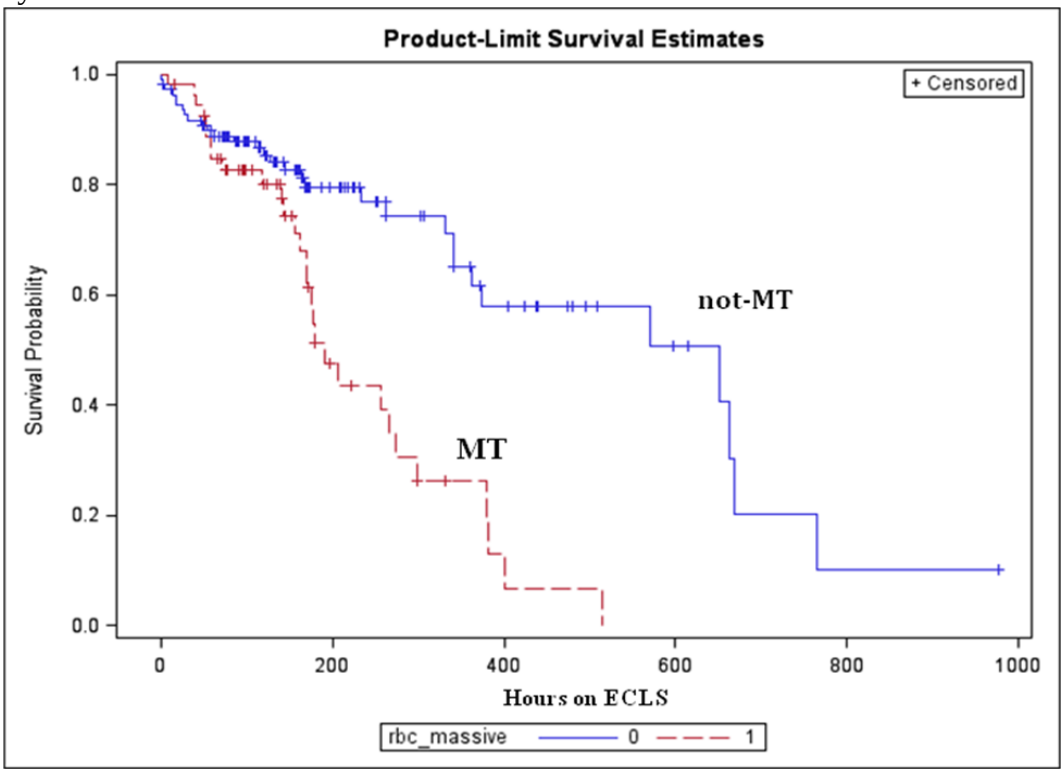
For continuous variables, means and standard deviations are reported
ECLS=extracorporeal life support
MT=massive transfusion
RBC=red blood cells
FFP = fresh frozen plasma
PLT = apheresis platelets
Cryo=cryoprecipitate

Table 5: Multivariate logistic regression analysis for all cause mortality among entire ECLS cohort

Variable	Odds Ratio	95% Confidence Interval	p-value
Massive Transfusion	2.05	0.93-4.52	0.074
ECLS Mode	2.47	1.17-5.20	0.018
Age (days)	1.00		0.634

Overall goodness of fit $\chi^2 = 153.397$, $p = 0.0015$
-2LnL = 215.402
ECLS=extracorporeal life support

Figure 2: Kaplan–Meier Survival Estimates for Probability of Death in all ECLS subjects by Massive Transfusion



Log Rank <0.0001
ECLS= extracorporeal life support
MT=massive transfusion

Table 6: Extended Cox proportional hazards model for all cause mortality among entire ECLS cohort

Variable	Hazard Ratio	95% Confidence Interval	p-value
MT and ECLS duration $\leq$ 4 hours	0.97	0.40-2.34	0.946
MT and ECLS duration > 4 hours	3.38	1.20-4.02	0.002
ECLS Mode	2.23	1.20-4.15	0.011

Overall goodness of fit χ^2 = 25.333, p = <0.0001
-2LnL = 466.033
ECLS=extracorporeal life support
MT=massive transfusion

Table 7: Baseline demographic characteristic of neonatal ECLS cohort

	MT (n=28)	**Not-MT (n=49)**	**p-value**
Age (days)	7.89 (6.2)	3.35 (5.36)	0.001
Weight (kg)	3.23 (0.69)	3.84 (4.44)	0.469
Male Sex (%)	19 (67.9)	33 (67.4)	0.963
Race			0.559
White	12 (42.9%)	15 (32.6%)	
Black	12 (42.9%)	17 (37%)	
Hispanic	3 (10.7%)	9 (19.6%)	
Asian	0	2 (4.6%)	
Other	1 (3.6%)	3 (6.5%)	

For continuous variables, means and standard deviations are reported
ECLS= extracorporeal life support
MT=massive transfusion

Table 8: Admission and pre-ECLS illness severity and hematologic laboratory data in neonatal ECLS cohort

	MT (n=28)	**Not-MT (n=49)**	**p-value**
Admit PELOD	19.0 (3.5)	22.1 (4.6)	0.003
Pre-ECLS PELOD	21.1 (5.6)	22.3 (4.8)	0.344
Pre-ECLS Intubation Days	3.61 (4.71)	2.12 (3.74)	0.132
Pre-ECLS Hemoglobin (g/dl)	13.3 (2.4)	14.8 (2.4)	0.01
Pre-ECLS INR	1.6 (0.3)	1.6 (0.6)	0.875
Pre-ECLS APTT (sec)	80.4 (79.8)	49.5 (29.9)	0.036
Pre-ECLS Fibrinogen (mg/dl)	270 (126)	239 (150)	0.49
Pre-ECLS Platelets (per ml)	230 (131)	225 (131)	0.872

For continuous variables, means and standard deviations are reported
ECLS=extracorporeal life support
MT=massive transfusion
PELOD=pediatric logistic organ dysfunction score
INR=international normalized ration
APTT=activated partial thromboplastin time

Table 9: Neonatal ECLS indications, mode, and additional circuit components

	MT (n=28)	**Not-MT (n=49)**	**p-value**
Patient Type			<0.0001
Respiratory	5 (17.9%)	44 (89.8%)	
Cardiac / ECPR	23 (82.1%)	5 (10.2%)	
ECLS Mode			<0.0001
VV	4 (14.3%)	38 (77.6%)	
VA	24 (85.7%)	11 (22.5%)	
CRRT	13 (46.4%)	11 (22.5%)	0.029

ECLS= extracorporeal life support
MT=massive transfusion
VV=venovenous ECLS
VA=venoarterial ECLS
CRRT=continuous renal replacement therapy

Table 10: Neonatal ECLS blood utilization and outcomes

	MT (n=28)	**Not-MT (n=49)**	**p-value**
RBC (ml/kg)	385.6 (176.5)	174.1 (51.3)	<0.0001
FFP (ml/kg)	57.8 (93.4)	16.4 (14.3)	0.003
PLT (ml/kg)	68.6 (36.9)	33.2 (15.6)	<0.0001
Cryo (units)	2.6 (3.1)	0.04 (0.2)	<0.0001
Mechanical Complications	4 (14.3%)	12 (24.5%)	0.288
Hemorrhagic Complications	10 (35.7%)	17 (34.7%)	0.928
ECLS Duration (hours)	166.8 (93.8)	179.3 (142.8)	0.681
Mortality	17 (60.7%)	13 (26.5%)	0.003

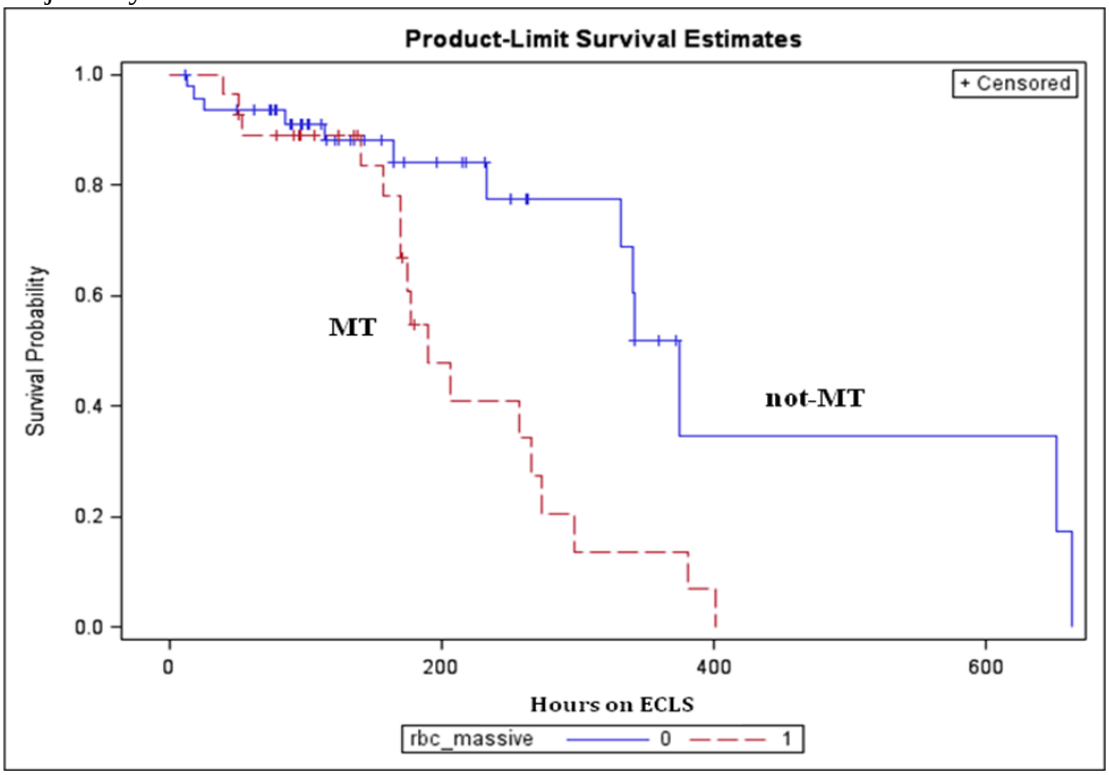
For continuous variables, means and standard deviations are reported
ECLS=extracorporeal life support
MT=massive transfusion
RBC=red blood cells
FFP = fresh frozen plasma
PLT = apheresis platelets
Cryo=cryoprecipitate

Table 11: Multivariate logistic regression analysis for all-cause mortality among neonatal ECLS cohort

Variable	Odds Ratio	95% Confidence Interval	p-value
Massive Transfusion	6.45	1.814-22.895	0.004
Admit PELOD	1.19	1.037-1.360	0.013
CRRT	6.69	2.106-22.183	0.002

Overall goodness of fit $\chi^2 = 17.1375$, $p = 0.0007$
-2LnL = 101.054
ECLS= extracorporeal life support
PELOD=pediatric logistic organ dysfunction score
CRRT=continuous renal replacement therapy

Figure 3: Kaplan–Meier Survival Estimates for Probability of Death in Neonatal ECLS subjects by Massive Transfusion



Log Rank = 0.005
ECLS= extracorporeal life support
MT=massive transfusion

Table 12: Extended Cox proportional hazards model for all-cause mortality among neonatal ECLS subjects

Variable	Hazard Ratio	95% Confidence Interval	p-value
MT and ECLS duration $\leq$ 4 hours	1.0	-	-
MT and ECLS duration > 4 hours	4.94	1.91-12.78	0.001
Admit PELOD	1.12	1.01-1.25	0.036
CRRT	0.49	0.21-1.16	0.105

Overall goodness of fit $\chi^2 = 12.223$, p = 0.007
-2LnL = 159.023
ECLS= extracorporeal life support
MT=massive transfusion
PELOD=pediatric logistic organ dysfunction score
CRRT=continuous renal replacement therapy