Supplementary Table S1: Univariable tests of association with daily intracranial hemorrhage

Variable	P-value	Missingness
Included in final model		
Daily fibrinogen	<.01	7%
Gestational age at birth	<.01	2%
Age at ECMO initiation	0.03	0%
Therapeutic hypothermia	0.03	0%
Mode of ECMO	0.04	0%
Excluded from final model		
Daily lactate concentration	<.01	12%
Daily pH in arterial blood	0.01	2%
Meconium aspiration syndrome	0.02	0%
Weight	0.06	0%
Clinical site	0.11	0%
Baseline VIS	0.13	0%
Congenital diaphragmatic hernia	0.44	0%
CPB in the 24 hours prior to ECMO initiation	0.44	0%
OI prior to ECMO initiation	0.50	37%
Persistent pulmonary hypertension of the newborn	0.54	0%
Daily Platelets	0.68	2%
Documented infection at prior to ECMO initiation	0.77	0%
Placed on ECMO directly from CPB	0.82	0%
Primary ECMO indication	0.84	0%
Primary Respiratory Diagnosis	0.86	0%
Daily activated clotting time (ACT)	0.97	1%

Abbreviations: ECMO, extracorporeal membrane oxygenation; VIS, vasoactive inotrope score; CPB, cardiopulmonary bypass; OI, oxygenation index; ACT, activated clotting time.

Table 1 Description of cohort by therapeutic hypothermia

	Therapeutic hypothermia		
	No (N = 247)	Yes (N = 20)	P-value
Gestational age at birth (weeks)	38.0 [37.0, 39.0]	38.0 [38.0, 39.0]	0.947[1]
Age at ECMO initiation (days)	3.0 [1.0, 7.0]	1.0 [1.0, 3.0]	0.115[1]
Weight (kg)	3.1 [2.8, 3.5]	3.2 [2.7, 3.4]	0.837[1]
Male	156 (63.2%)	8 (40.0%)	0.055[2]
Primary ECMO indication			0.266[2]
Respiratory	136 (55.1%)	15 (75.0%)	
Cardiac	88 (35.6%)	4 (20.0%)	
eCPR	23 (9.3%)	1 (5.0%)	
Primary Diagnosis			0.020[2, 3]
Respiratory			
Airway/tracheal	3 (1.2%)	0 (0.0%)	
Respiratory distress/failure	128 (51.8%)	16 (80.0%)	
Non-respiratory			
Cardiac arrest	4 (1.6%)	0 (0.0%)	
Cardiovascular disease - acquired	1 (0.4%)	0 (0.0%)	
Cardiovascular disease - arrhythmia	2 (0.8%)	0 (0.0%)	
Cardiovascular disease - congenital	105 (42.5%)	4 (20.0%)	
Congenital anomaly or chromosomal defect	1 (0.4%)	0 (0.0%)	
Hypoxic ischemic encephalopathy	1 (0.4%)	0 (0.0%)	
Sepsis/SIRS/septic shock	2 (0.8%)	0 (0.0%)	
Mode of ECMO			0.037[2]
VA	217 (87.9%)	14 (70.0%)	
VV	30 (12.1%)	6 (30.0%)	
CPB in the 24 hours prior to ECMO initiation	78 (31.6%)	2 (10.0%)	0.044[2]
Placed on ECMO directly from CPB	37 (15.0%)	1 (5.0%)	0.326[2]
Meconium aspiration syndrome	41 (16.6%)	6 (30.0%)	0.134[2]
Congenital diaphragmatic hernia	53 (21.5%)	3 (15.0%)	0.775[2]
Persistent pulmonary hypertension of the newborn	75 (30.4%)	13 (65.0%)	0.003[2]
Documented infection prior to ECMO initiation	11 (4.5%)	1 (5.0%)	1.000[2]
OI prior to ECMO initiation	29.4 [11.0, 50.2]	26.3 [16.0, 50.0]	0.817[1]
VIS prior to ECMO initiation			0.202[1]
None	62 (25.1%)	1 (5.0%)	

Table 1 Description of cohort by therapeutic hypothermia

	Therapeutic hypothermia		
	No (N = 247)	Yes (N = 20)	P-value
Low	77 (31.2%)	9 (45.0%)	
High	108 (43.7%)	10 (50.0%)	
Platelet count prior to ECMO initiation (10³/microliter)	179.0 [132.5, 241.5]	163.0 [124.0, 231.0]	0.544[1]
Clinical Site			0.021[2]
A	39 (15.8%)	4 (20.0%)	
B	59 (23.9%)	3 (15.0%)	
C	21 (8.5%)	1 (5.0%)	
D	28 (11.3%)	0 (0.0%)	
E	18 (7.3%)	1 (5.0%)	
F	26 (10.5%)	8 (40.0%)	
G	16 (6.5%)	2 (10.0%)	
H	40 (16.2%)	1 (5.0%)	

Abbreviations: ECMO, extracorporeal membrane oxygenation; eCPR, extracorporeal cardiopulmonary resuscitation; SIRS, systemic inflammatory response syndrome; VA, venoarterial; VV, venovenous; CPB, cardiopulmonary bypass; OI, oxygenation index; VIS, vasoactive inotrope score.

[1] P-values for ordinal variables are based on the Wilcoxon rank-sum test. Data are expressed as median and interquartile range.

[2] P-values for categorical variables are based on Fisher's exact test; for tables larger than 2X2, the p-value is estimated using Monte Carlo simulations. Data are expressed as counts and column percentages.

[3] The p-value for primary diagnosis is based on respiratory vs. non-respiratory and does not consider the subcategories.

Table 2 Complications and outcomes by therapeutic hypothermia

	Therapeutic hypothermia		
	No (N = 247)	Yes (N = 20)	P-value
In-hospital mortality	107 (43.3%)	6 (30.0%)	0.347[1]
Functional status at hospital discharge			0.143[2]
Good	46 (18.6%)	5 (25.0%)	
Mildly abnormal	62 (25.1%)	8 (40.0%)	
Moderately abnormal	27 (10.9%)	1 (5.0%)	
Severely abnormal	5 (2.0%)	0 (0.0%)	
Not applicable (dead)	107 (43.3%)	6 (30.0%)	
Duration of ECMO (days)	5.3 [2.8, 10.1]	6.7 [3.9, 9.1]	0.742[2]
Duration of ICU stay (days)	29.0 [15.3, 53.0]	30.0 [14.8, 53.0]	0.941[2]
Duration of hospital stay (days)	33.6 [16.4, 59.2]	40.5 [15.0, 65.8]	0.901[2]
Complications in the first seven days of ECMO			
New documented infection	19 (7.7%)	0 (0.0%)	0.376[1]
Bleeding event	144 (58.3%)	15 (75.0%)	0.163[1]
Thrombotic event	70 (28.3%)	5 (25.0%)	1.000[1]
Intracranial hemorrhage	39 (15.8%)	8 (40.0%)	0.012[1]
Neurologic event	82 (33.2%)	9 (45.0%)	0.329[1]
Renal failure	74 (30.0%)	9 (45.0%)	0.208[1]
Hepatic failure	78 (31.6%)	6 (30.0%)	1.000[1]
Mean daily RBC transfusion in first seven days of ECMO (mL/kg)	35.8 [27.3, 55.9]	45.0 [27.7, 70.4]	0.628[2]

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; RBC, red blood cell.

[1] P-values for categorical variables are based on Fisher's exact test. Data are expressed as counts and column percentages.
[2] P-values for ordinal variables are based on the Wilcoxon rank-sum test. Data are expressed as median and interquartile range.

Multivariate model for intracranial hemorrhage

Variable	Adjusted Relative Risk (95% CI)	P-value
Age at ECMO initiation (days)	0.91 (0.84, 0.98)	0.009
Gestational age at birth (weeks)	0.82 (0.71, 0.94)	0.006
Therapeutic hypothermia	2.97 (1.11, 7.91)	0.030
Daily fibrinogen concentration (10 mg/dl)	0.95 (0.92, 0.98)	<.001
Mode of ECMO		0.038
VA	Reference	
VV	0.25 (0.07, 0.93)	

Abbreviations: ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous.

Wald confidence intervals and p-values for the adjusted relative risk are based Poisson regression model with autoregressive covariance structure of order 1 within subjects and robust error estimates.

Table 4 Association between intracranial hemorrhage in the first seven days of ECMO and outcomes

	Intracranial hemorrhage in the first 7 days of ECMO		
	No (N = 220)	Yes (N = 47)	P-value
In-hospital mortality	84 (38.2%)	29 (61.7%)	0.004[1]
Functional status at hospital discharge (among survivors)			0.060[2]
Good	48 (35.3%)	3 (16.7%)	
Mildly abnormal	61 (44.9%)	9 (50.0%)	
Moderately abnormal	22 (16.2%)	6 (33.3%)	
Severely abnormal	5 (3.7%)	0 (0.0%)	
Duration of ECMO (days)	5.3 [2.8, 9.9]	5.0 [2.8, 11.3]	0.990[2]
Duration of hospital stay (days)	35.7 [18.7, 62.9]	22.2 [6.9, 50.0]	0.007[2]
Duration of ICU stay (days)	30.3 [16.1, 54.0]	20.1 [6.8, 48.9]	0.046[2]

Abbreviations: ECMO, extracorporeal membrane oxygenation.

[1] Fisher's exact test. Data are expressed as counts and column percentages.
[2] P-value is based on the Wilcoxon rank-sum test. Data are expressed as median and interquartile range.