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In-Hospital Outcomes Following Extracorporeal Membrane Oxygenation in a Retrospective Cohort of Infants

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Abstract

Objective—We sought to characterize associations between infant characteristics and extracorporeal membrane oxygenation (ECMO) survival using electronic health records data.

Study Design—We examined a cohort study of infants 32 weeks of gestational age and 1,800 g birth weight supported with ECMO in a Pediatric Medical Group neonatal intensive care unit from 1998 to 2013.

Results—We identified 268 infants, of which 45 (17%) were <37 weeks of gestational age. Survival to discharge was 87% but was lower in premature compared with term infants (76 vs. 89%, $p = 0.03$). In multivariable analysis, acute kidney injury (odds ratio [OR] = 4.00; 95% confidence interval [CI] = 1.05, 15.24), postnatal age at cannulation of 7 to 13 days (OR = 5.86; 95% CI = 1.21, 28.44), and venoarterial ECMO cannulation (OR = 4.33; 95% CI = 1.77, 10.60) were associated with lower survival.

Conclusion—ECMO cannulation type, postnatal age, and acute kidney injury were associated with lower ECMO survival, while prematurity was not. Future studies are needed to identify risk factors and strategies to improve outcomes.

Keywords

extracorporeal membrane oxygenation; infant; survival; temporal trends

Extracorporeal membrane oxygenation (ECMO) is a lifesaving intervention providing full cardiopulmonary support.^{1–3} Following its introduction into the neonatal intensive care unit (NICU) in the 1970s, adoption of ECMO permitted survival of infants with severe reversible respiratory failure and otherwise poor prognoses.^{1,3} Over time, however, survival in infants

supported with ECMO has decreased;^{4–7} this decrease may be due to the underlying illness severity of infants on ECMO.^{6–8} As NICUs have increasingly adopted less invasive interventions for respiratory failure, including high-frequency ventilation, inhaled nitric oxide, and surfactant administration, lower-risk infants are successfully supported through the critical phase of their illness, and only the highest-risk infants require ECMO support,^{6,9–11} including an increasing proportion of premature infants. ECMO is indisputably useful, but it is also expensive, resource-intensive, and associated with high morbidity.^{12–14} Given these risks, a continuous evaluation of ECMO outcomes in the face of changing infant characteristics is warranted.

The objective of our study was to characterize the associations between clinical characteristics and ECMO outcomes over time in a large multicenter cohort of hospitalized infants using electronic health records data. We hypothesized lower survival among premature infants, those requiring ECMO in later years, and those requiring a higher level of cardiopulmonary support at the time of ECMO initiation.

Material and Methods

Study Design and Sample

We performed a retrospective cohort study of all infants born at gestational age ≥ 32 weeks and birth weight $\geq 1,800$ g ($n = 724,783$) who received ECMO support ($n = 590$) and were discharged between 1998 and 2013 from NICUs in the United States managed by the Pediatrix Medical Group. This study was developed after all data were collected. Data were extracted from a clinical data warehouse that prospectively captures data from electronic health records, including daily progress notes and other documentation generated by clinicians using a computer-assisted tool. The method of data extraction was previously described in detail.¹⁵ We excluded infants with major congenital anomalies including congenital diaphragmatic hernia ($n = 274$) and those with missing survival status at discharge (transferred infants, $n = 48$). The Duke University Institutional Review Board approved the conduct of this study.

Study Measurements

We defined prematurity as gestational age < 37 weeks. We identified ECMO cannulation type as either venovenous (VV) or venoarterial (VA) cannulation. We defined early ECMO initiation as ECMO cannulation on day-of-life 0 or 1, and death on ECMO as death while on ECMO or the day after decannulation. We defined small for gestational age status according to Olsen's definition.¹⁶ The primary outcome was survival to NICU discharge. We documented the presence of diagnoses most commonly associated with ECMO support including meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn, respiratory distress syndrome, pneumonia, influenza or respiratory syncytial virus infection, and sepsis, defined as the presence of a positive blood, catheter urine, or cerebrospinal fluid culture with an organism not typically considered a contaminant.¹⁷ We allowed multiple diagnoses to be present in the same infant because diagnoses are not identified as primary or secondary in the data source. We also documented the presence of major morbidities including a diagnosis of intraventricular hemorrhage (IVH), necrotizing

enterocolitis (NEC), and bronchopulmonary dysplasia (BPD; defined as previously described).¹⁸ Infants were diagnosed with BPD if they received respiratory support or supplemental oxygen in the form of continuous mechanical ventilation, nasal cannula, or continuous positive airway pressure from postnatal age (PNA) of 28 to 34 days. We defined NEC as any diagnosis of medical or surgical NEC at any time during the NICU stay, and IVH as a diagnosis of grade III or IV IVH at any time during the NICU stay. We defined acute kidney injury (AKI) following the Kidney Disease: Improving Global Outcomes criteria as an increase in serum creatinine by 50% or 0.3 mg/dL while on ECMO.¹⁹

Statistical Methods

We used counts (percentages) and medians (interquartile ranges) to describe categorical and continuous study variables. To compare the distribution of variables between groups, we used chi-square, Fisher's exact, and Wilcoxon rank sum tests where appropriate. We used multivariable logistic regression to evaluate the possible association of death at NICU discharge with the following covariates selected a priori: prematurity, small for gestational age status, duration of ECMO, the presence of AKI, PNA at cannulation, ECMO cannulation type (VA vs. VV), and discharge year. Infants who were missing data for covariates were excluded from regression analyses. We considered the sample size to be adequate to perform the regression if >4 deaths per variable occurred in the cohort.²⁰ With seven covariates in the model, >28 deaths were required. We calculated yearly ECMO prevalence, survival, the proportion of premature infants, and prevalence of diagnoses and comorbidities for each discharge year and used a nonparametric trend test to assess for trend over time. Comorbidities were evaluated in both the entire cohort and among survivors only. We conducted all analyses in Stata 14.1 (College Station, TX), and considered *p* values <0.05 statistically significant.

Results

Infant Characteristics

We identified 268 infants that met inclusion criteria and were supported with ECMO, of whom 45 (17%) were premature, and 66 (25%) were inborn (►Table 1). Median gestational age was 39 weeks (interquartile range: 37, 40) and median birth weight was 3,203 g (interquartile range: 2,869, 3,610). Early ECMO was used in 48% of infants; the median PNA and weight on the day of ECMO cannulation were 2 days (interquartile range: 1, 2) and 3,200 g (interquartile range: 2,867, 3,605). The median duration of ECMO support was 6 days (interquartile range: 4, 8). The most common diagnoses associated with ECMO were persistent pulmonary hypertension of the newborn in 91% of infants, MAS in 40%, and pneumonia in 20%. VV cannulation was used in 61% of ECMO runs. Infants on VV ECMO had a similar median birth weight compared with those on VA, 3,250 g (interquartile range: 2,899, 3,665) versus 3,120 g (interquartile range: 2,785, 3,480) (*p* = 0.07), but were more likely to be diagnosed with MAS (48 vs. 25%, *p* < 0.001). ECMO use ranged from a peak of 0.63 per 1,000 infants in 1998 to 1999, to a low of 0.20 per 1,000 infants in 2012 to 2013 (*p* = 0.002) (►Fig. 1).

There was no difference in the median PNA at start of ECMO between premature and term infants (1 day [interquartile range: 1, 2] vs. 2 days [interquartile range: 1, 2], $p = 0.92$), but premature infants had a lower median birth weight (2,760 g [interquartile range: 2,460, 3,210] vs. 3,239 g [interquartile range: 2,930, 3,655], $p < 0.01$). For premature infants, PNA and weight at ECMO cannulation ranged from 0 to 15 days, and 2,000 to 5,190 g, respectively. Compared with full-term infants, premature infants were more likely to be diagnosed with respiratory distress syndrome (29 vs. 5%, $p < 0.01$), and less likely to be diagnosed with MAS (7 vs. 46%, $p < 0.01$). Premature infants were supported with VV ECMO at similar rates as full-term infants (50 vs. 64%, $p = 0.13$). There was no significant trend in the proportion of premature infants supported with ECMO over time, with a low of 12% (3/25) premature infants in 2000 to 2001 to a peak of 29% (6/21) premature infants in 1998 to 1999, $p = 0.77$.

Outcomes

Overall survival to discharge was 87%, with 92% of infants surviving to ECMO decannulation. The median birth weight was similar between survivors and nonsurvivors (3,219 g [interquartile range: 2,884, 3,615] vs. 3,005 g [interquartile range: 2,690, 3,500], $p = 0.15$). The median gestational age was higher among survivors compared with nonsurvivors (39 weeks [interquartile range: 38, 40] vs. 38 weeks [interquartile range: 36, 39], $p < 0.001$), though this difference in median gestational age is unlikely to be clinically significant. Premature infants had lower survival compared with full-term infants (76% [34/45] vs. 89% [199/223], $p = 0.02$). Survival varied by diagnosis was highest for MAS (96%, 102/106), and lowest in infants with sepsis (71%, 17/24) and respiratory syncytial virus or influenza infection (0%, 0/1) (►Table 1). Survival peaked at 95% in 2002 to 2003 but has since declined to a low of 71% in 2012 to 2013. There was no significant trend in the prevalence of diagnoses over this period (►Fig. 2).

Infants supported with VV ECMO had higher survival compared with those supported with VA ECMO (93 vs. 77%, $p < 0.001$). Early ECMO initiation was not associated with improved survival when compared with late ECMO (84 vs. 90%, $p = 0.15$). Age 2 to 6 days at cannulation was associated with the highest survival (95%), while ages 0 to 1 days, 7 to 13 days, and 14 days had lower survival (84, 55, and 57%, respectively; $p < 0.001$). The duration of ECMO support was significantly associated with survival, $p < 0.001$; infants on ECMO for 4 to 7 days had the highest survival of all groups (96%). In multivariable analysis, only VA (relative to VV) ECMO cannulation (odds ratio [OR] = 4.33; 95% confidence interval [CI] = 1.77, 10.60), PNA of 7 to 13 days at cannulation (OR = 5.86; 95% CI = 1.21, 28.44), and AKI (OR = 4.00; 95% CI = 1.05, 15.24) were associated with decreased survival (►Table 2).

The most common morbidities were BPD (17%) and IVH (6%). Survivors were less likely to suffer from any of the studied morbidities (16 vs. 46%, $p < 0.001$). IVH was associated with significantly lower survival, and as expected, survival among infants with BPD was high (►Table 3). There was no difference in the prevalence of BPD and NEC between premature and full-term infants (10 vs. 19% [$p = 0.18$] for BPD, and 0% vs. <1% [$p = 0.999$] for NEC). IVH was more common in preterm infants (13 vs. 5%, $p = 0.046$). There

were no temporal trends in the prevalence of any of the morbidities. Results were similar when morbidities were evaluated among survivors only. Both IVH and BPD were more common after VA cannulation compared with VV (13 vs. 2% [$p = 0.001$], and 24 vs. 12% [$p = 0.03$]).

Discussion

We described a cohort of infants supported with ECMO over a 17-year period. Overall survival in our cohort was 87% but was lower in premature infants. VA ECMO cannulation, PNA 7 to 13 days at ECMO cannulation, and AKI while on ECMO were associated with lower survival.

Survival of infants supported with ECMO has been reported to be declining over time, and our study is consistent with this finding.^{5,6,10,21,22} This negative trend may be due to the selection of sicker infants for ECMO support. In a single-center study of 799 infants with respiratory failure supported with ECMO, survival decreased from 88% between 1972 and 1998 to 72% between 1998 and 2010 ($p < 0.01$).⁵ In this study, mean duration of ECMO increased over time, likely indicating increasing complexity of each ECMO run. The authors also noted that infants treated in earlier years were more likely to have reversible causes of respiratory failure, while recent cases had diagnoses of higher severity, such as congenital diaphragmatic hernia. They hypothesized that decreased survival was a consequence of changes in infant characteristics and illness severity, and increased the willingness of providers to initiate ECMO in infants who formerly would have been considered too ill or immature. Our results are consistent with these findings; 17% of our entire cohort was premature. Nevertheless, we did observe a higher survival in our cohort, possibly due to higher prevalence of more reversible causes of respiratory failure and the exclusion of any congenital anomaly including congenital diaphragmatic hernias, which carry a higher mortality.²³

While prior studies characterizing trends in ECMO survival over time were based on the voluntary Extracorporeal Life Support Organization (ELSO) registry, our data are derived directly from the electronic health records of nearly one million NICU admissions over almost two decades,²⁴ which allows us to report yearly prevalence of ECMO use, rather than absolute numbers relied upon in ELSO reports. Despite this difference, we found a decline in ECMO use over time mostly consistent with a recent ELSO-based study.⁶ In this study, 26,583 infants with respiratory failure were supported with ECMO from the inception of the ELSO registry until the year 2013; of these, the highest number of ECMO cases was reported in 1992 (1,516 cases), followed by a steady decline to approximately 800 cases per year, which plateaued in 1998. While our study only reached back to data from 1998, we observed a similar early peak in ECMO use, followed by a decrease in prevalence. As observed in the ELSO registry, we did not yet, however, reach a plateau in our cohort. The ELSO study authors postulated that decreased ECMO use may be due to evolving infant selection, with most infants now successfully supported by less invasive means including high-frequency ventilation and inhaled nitric oxide, and only a smaller cohort of the sickest infants requiring ECMO. Since a large number of infants included in our cohort were referred from outside hospitals for ECMO support, we were unable to provide a complete

picture of the medical management received or fully characterize the severity of their illness. Nonetheless, our cohort does have a large proportion of infants with MAS or persistent pulmonary hypertension of the newborn, which are associated with better outcomes.⁶

After adjusting for several risk factors, prematurity was not independently associated with survival in our cohort. This finding differs from several earlier reports identifying poor survival among premature infants on ECMO,^{2,14,25} and is somewhat at odds with ELSO's published relative contraindication for ECMO in neonatal respiratory failure in infants with a postmenstrual age <34 weeks.²⁶ Importantly, this cutoff is based on early studies revealing that younger infants treated with ECMO have a high incidence of IVH.^{25,27} Premature infants are at high risk for IVH as a result of the fragility of their intracranial capillaries,^{28,29} and the systemic heparinization required for ECMO further increases the risk of bleeding. Our cohort included 3/45 premature infants with postmenstrual age <34 weeks at cannulation, with 100% survival and no cases of IVH. However, IVH was associated with worse survival and was more prevalent in the overall cohort of premature infants. Numerous factors may affect the risk of IVH including anticoagulation management, the pre-ECMO level of illness, and resuscitative measures. While our analysis was unable to account for all such factors, we did observe a relatively high use of VV ECMO in premature infants (50%, 22/44), which is known to be associated with a lower risk of thromboembolic complications due to the lack of arterial cannulation.¹³ Prior studies have suggested that premature infants are more moribund because providers delay ECMO initiation, due to the perceived contraindications or the technical difficulties associated with cannulation, effectively prolonging the disease course.³⁰ We did not observe a significant difference in PNA at ECMO initiation, suggesting that this may not be the case in our cohort, again potentially explaining the lack of significant difference in survival between premature and full-term infants in the adjusted analysis. We did note that the median gestational age was higher among survivors than nonsurvivors.

As anticipated, the absence of any major morbidity was correlated with survival. IVH is a known predictor of mortality on ECMO, and this association was again demonstrated in our study.^{13,14,31} Likewise, we observed decreased survival for infants with AKI. In our study, we defined AKI using the Kidney Disease: Improving Global Outcomes criteria, which are based on specific increases in serum creatinine, as opposed to ELSO studies that use creatinine cutoffs to define renal dysfunction.³² Past studies report a wide variation in incidence of renal insufficiency that is affected by patient population and definitions used, and ranges from 8% in a 10-year ELSO retrospective analysis³³ to 64% in a 14-year single-center study.³⁴ Using absolute creatinine levels, prior studies may have included infants with longer standing renal dysfunction, while our definition is less inclusive. In addition to AKI and prematurity, PNA at ECMO initiation was also associated with survival. A 2014 study of the ELSO registry found that infants cannulated before 7 days of age had better survival compared with those cannulated at ≥7 days of age; the authors posit that factors including longer duration of mechanical ventilation, differing pathophysiology, and greater infection rates are responsible for the difference in survival.¹³ Our study analogously found that infants cannulated after 7 days of age had lower survival, but the majority of nonsurvivors were cannulated in the first 2 days of life. The greater severity of illness in these infants was most likely the reason for more immediate ECMO cannulation. Therefore, we compared

survival of infants cannulated after day-of-life 2, but before day-of-life 7 to infants cannulated after day-of-life 7, and found an even higher discrepancy in survival (95 vs. 56%) than the ELSO report. Taken together, these findings may support the notion that ECMO cannulation should be considered before day-of-life 7 in infants with severe respiratory failure.

The strengths of our study include the use of a multicenter, electronic health record-derived database that encompasses all admissions to Pediatrix Medical Group NICUs. This data source allowed us to directly identify infants receiving ECMO support, rather than having to rely on self-reported registry data. Access to detailed hospital records allowed us to identify several infant characteristics associated with ECMO use and outcomes, and the longevity of the database provided us with an opportunity to demonstrate trends over time. Despite these strengths, the electronic health record-derived clinical data warehouse, while representative of daily clinical practice, has not undergone the scrutiny of a clinical trial database. Several important details about ECMO cannulation and conduct were not available for analysis, and the high proportion of referred infants limited our ability to provide a thorough description of the clinical course before ECMO cannulation.

In conclusion, we again demonstrated a decline in ECMO survival over time but found further evidence to the fact that acceptable outcomes are attainable in premature infants, and that survival may be affected by underlying diagnoses, comorbidities, and timing of ECMO cannulation. These findings support the development of ECMO guidelines incorporating the above and other factors, which would optimally be based on data from clinical trials comparing ECMO use to conventional medical therapies, as has been previously suggested.⁴ Our study findings may be considered in support of the design and conduct of such prospective clinical trials in the future.

Acknowledgments

Conflict of Interest

Dr. Greenberg receives salary support for research from the National Institutes of Health training (Grant nos: 5T32HD043728–10 and 5T32HD043029–13). Dr. Smith receives salary support for research from the NIH (Grant no: NIH-1R21HD080606–01A1) and the National Institute for Child Health and Human Development (NICHD) (Grant no: HHSN275201000003I). Dr. Laughon is supported by the U.S. government for his work in pediatric and neonatal clinical pharmacology (Grant no: HHSN267200700051C [Principal Investigator: Benjamin]), the NICHD (Grant no: K23 HD068497), and the National Heart, Lung, and Blood Institute (Grant no: R34 HL124038). Dr. Hornik receives salary support for research from the National Center for Advancing Translational Sciences of the NIH (Grant no: UL1TR001117).

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Fig. 1.
ECMO use and survival over time. ECMO, extracorporeal membrane oxygenation.

Fig. 2.

Diagnoses of infants supported with ECMO over time. ECMO, extracorporeal membrane oxygenation; MAS, meconium aspiration syndrome; PPHN, persistent pulmonary hypertension; RDS, respiratory distress syndrome; RSV, respiratory syncytial virus.

Table 1

Clinical characteristics and outcomes

	Survivors (<i>n</i> = 233)	Nonsurvivors (<i>n</i> = 35)	<i>p</i> Value
Gestational age (wk)			
32	1 (<1%)	0 (0%)	0.030
33–36	33 (14%)	11 (31%)	
37–40	168 (72%)	23 (66%)	
> 40	31 (13%)	1 (3%)	
Median (range)	39 (32–43)	38 (34–42)	
Birth weight (g)			
< 2,500	17 (7%)	6 (17%)	0.16
2,500–3,499	139 (60%)	20 (57%)	
3,500–4,499	69 (30%)	7 (20%)	
4,500	8 (3%)	2 (6%)	
Median (range)	3,219 (2,059–4,972)	3,005 (1,965–4,065)	
Small for gestational age	26 (11%)	1 (3%)	0.22
Female	98 (42%)	16 (46%)	0.72
Diagnoses			
PPHN	215 (92%)	29 (83%)	0.10
MAS	102 (44%)	4 (11%)	<0.001
Pneumonia	43 (18%)	11 (31%)	0.11
RDS	20 (9%)	5 (14%)	0.34
Sepsis	17 (7%)	7 (20%)	0.023
RSV or influenza	0 (0%)	1 (3%)	0.13
ECMO cannulation			
VA	79 (34%)	24 (69%)	<0.001
VV	152 (66%)	11 (31%)	
Antenatal steroids	6 (3%)	2 (6%)	0.28
5-minute Apgar score			
0–3	21 (9%)	5 (16%)	0.43

	Survivors (<i>n</i> = 233)	Nonsurvivors (<i>n</i> = 35)	<i>p</i> Value
4–6	50 (22%)	7 (23%)	
7–10	157 (69%)	19 (61%)	
C-section	135 (59%)	19 (61%)	0.85
HFV	147 (63%)	22 (63%)	>0.99
iNO	150 (64%)	19 (54%)	0.26
Surfactant	98 (42%)	15 (43%)	>0.99
PNA at cannulation (d)			
0–1	108 (46%)	21 (60%)	<0.001
2–6	115 (49%)	6 (17%)	
7–13	6 (3%)	5 (14%)	
14	4 (2%)	3 (9%)	
Median (range)	2 (0–17)	1 (0–29)	
Days of ECMO			
2–3	13 (6%)	18 (51%)	<0.001
4–7	153 (66%)	7 (20%)	
8–14	51 (22%)	6 (17%)	
> 14	15 (6%)	4 (11%)	
Median (range)	6 (2–49)	3 (2–34)	
Acute kidney injury	8 (3%)	7 (20%)	0.001

Abbreviations: ECMO, extracorporeal membrane oxygenation; HFV, high-frequency ventilation; iNO, inhaled nitric oxide; MAS, meconium aspiration syndrome; PNA, postnatal age; PPHN, persistent pulmonary hypertension; RDS, respiratory distress syndrome; RSV, respiratory syncytial virus; VA, venoarterial; VV, venovenous.

Note: Numbers in the table are counts (percentage) unless otherwise indicated.

Table 2

Risk factors for mortality in multivariable regression

Variable	OR (95% CI)
Acute kidney injury	4.00 (1.05–15.2)
Age at cannulation (d)	
0–1	Reference
2–6	0.29 (0.11–0.82)
7–13	5.86 (1.21–28.4)
14	5.95 (0.68–51.8)
VA ECMO cannulation	4.33 (1.77–10.6)

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; OR, odds ratio; VA, venoarterial.

Note: Adjusted for small for gestational age status, duration of ECMO support, and discharge year.

Table 3

Morbidities during NICU stay

	Survivors <i>n</i> = 233 (%)	Nonsurvivors <i>n</i> = 35 (%)	<i>p</i> Value
Any morbidity	37 (16)	16 (46)	<0.001
IVH	5 (2)	12 (34)	<0.001
NEC	0 (0)	1 (3)	0.131
BPD	34 (18)	4 (11)	0.464

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit.