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ARTICLE

National trends in neonatal extracorporeal membrane oxygenation in the United States

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Abstract

Objective To determine trends in neonatal extracorporeal membrane oxygenation (ECMO) utilization from 2002–2011.

Study design Using the Nationwide inpatient sample (NIS), we conducted a population-based retrospective cohort study to identify ECMO utilization among neonates. Incidence of ECMO utilization, length of stay (LOS), cost and mortality were estimated.

Result In all, 33,367,146 neonates were identified of which 7603 (18 per 100,000 live births) underwent ECMO. Neonatal ECMO increased from 12 to 23 runs per 100,000 live births. Mortality was 48.4%, decreasing from 47.5 to 41.9% between 2002 and 2011. On multivariate analysis, mortality was significantly higher for infectious indications (OR 4.1; CI 1.1–16.0), E-CPR (OR 3.8; CI 1.4–10.7) and cardiac indications (OR 2.0; CI 1.5–2.8). On hierarchical regression, LOS increased by 1.6 days each year ($p = 0.02$) and cost of hospitalization increased by $14,033 each year ($p < 0.0001$).

Conclusion Neonatal ECMO utilization increased, while mortality decreased during the study period. These findings suggest an improvement in neonatal ECMO care.

Introduction

Extracorporeal membrane oxygenation (ECMO) is a complex technique for providing life support to critically ill patients with life-threatening respiratory and/or cardiac failure refractory to conventional or standard therapy. The first successful use of ECMO in neonates was reported by Bartlett in 1976 in a cohort of neonates with post-operative cardiac failure, respiratory distress syndrome, meconium aspiration syndrome, and persistent fetal circulation [1]. Since then, use of ECMO as a life-saving procedure in neonates, infants, and young children has been extended to various congenital heart diseases as well as non-cardiac diseases such as congenital diaphragmatic hernia (CDH), sepsis, and congenital lung abnormalities. The growth in the utilization of ECMO is largely attributable to increased availability of the technology worldwide [2] as well as the recognition that neonatal ECMO is cost-effective at reducing death or disability at 7 years of age when compared to conventional management [3]. The deployment of veno-arterial (VA) ECMO to rescue patients with cardiac arrest refractory to cardiopulmonary resuscitation was first reported in 1976 [4] and evidence of measurable survival benefit over CPR alone has resulted in the increased use of extracorporeal cardiopulmonary resuscitation (E-CPR) [5]. The American Heart Association 2015 guidelines recommended the use of E-CPR in pediatric patients with cardiac diagnoses and in-hospital cardiac arrest. E-CPR is most commonly performed in older pediatric patients. More recently, E-CPR is being performed in neonates [5].

Since ECMO is one of the most resource-intense and costliest interventions in the pediatric as well as the adult population, several studies have been conducted looking at

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resource utilization and outcomes [6–9]. However, these studies did not focus solely on neonatal ECMO and moreover, most of these studies were limited to particular diagnostic categories [10–14]. There is currently limited data on the temporal variations in the incidence, mortality, and resource utilization associated with neonatal ECMO in the United States. The objective of our study was to determine the trends in ECMO utilization, mortality and its determinants, cost of hospitalization, and length of stay (LOS) among neonates undergoing ECMO between 2002 and 2011 using the nationwide inpatient sample (NIS).

Materials and methods

Data source

We extracted our study cohort from the NIS database provided by the Agency for Healthcare Research and Quality [15]. The NIS contains all-payer discharge data from inpatient hospitalization from 20% of all hospitals in 44 participating US states. The NIS utilizes data from roughly 1000 hospitals each year to create a sample representing > 95% of the US population [15]. Each individual hospitalization in this database is de-identified and maintained as a unique entry with one primary discharge diagnosis, < 24 secondary diagnoses along with < 15 procedural codes during that hospitalization. Weights provided by the NIS were used to generate national estimates.

Study population and design

Newborn infants were identified using the data element ''Neomat.'' To prevent duplication of data from the receiving hospital, we opted to limit admission age to ≤ 30 days and exclude all infants ≤ 30 days that were transferred out (Fig. 1) [16–18]. Neonates undergoing ECMO were identified using International Classification of Diseases, 9th Revision, and

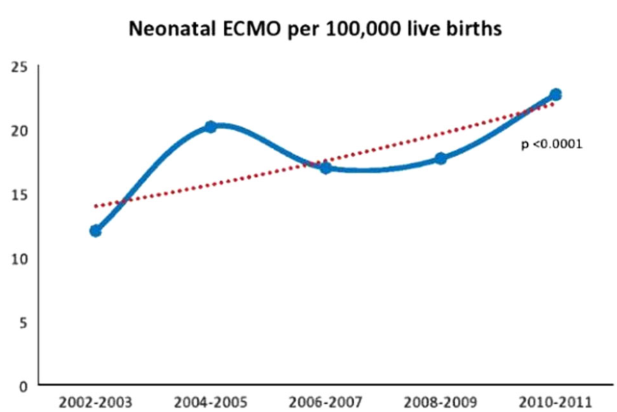

Fig. 1 Neonatal ECMO per 100,000 live births

Clinical Modification (ICD-9 CM) procedure code 39.65 in any procedure groups (PR1-PR15). Indications for ECMO categories were identified using ICD-9 CM diagnosis codes (Appendix-1). All indications for ECMO were considered mutually exclusive in order of precedence (extracorporeal cardiopulmonary resuscitation (E-CPR) > congenital diaphragmatic hernia (CDH) > meconium aspiration syndrome (MAS) > respiratory distress syndrome (RDS) > persistent pulmonary hypertension of the newborn (PPHN) > pneumonia > congenital heart defects (CHD) > cardiomyopathy > myocarditis > sepsis), where cases identified with E-CPR were placed in the first category, but excluded from the next. This process was continued for the remaining categories [7]. We divided indications for ECMO into four broad categories: E-CPR, respiratory indications (CDH, RDS, PPHN, MAS), cardiac indications (CHDs, cardiomyopathy, myocarditis), and infectious indications (sepsis, pneumonia) for ECMO. Procedure codes (e.g., CPR, ECMO) are identified by the hospital day on which the event occurred, whereas diagnosis codes are applied to the entire hospitalization (precluding temporal association between comorbidities and procedures). Because procedures are identified by hospital day and ICD-9 code in the database, the most specific definition possible consists of identifying CPR and ECMO events that occurred on the same hospital day [19].

Definition of variables

We studied baseline characteristics of the study population for potential confounding assessment. Patient level characteristics such as age, gender, race, median household income according to ZIP Code (< $36,000, $36,000 to $44,999, > $45,000), primary payer (Medicare/Medicaid, private insurance, self-pay, or no charge), admission day, admission type and hospital-level characteristics such as hospital location (urban/rural), hospital bed size (small, medium, and large), region (Northeast, Midwest, or North Central, South, and West), teaching status were studied. To calculate the estimated cost of hospitalization, the NIS data were merged with cost-to-charge ratios available from the Healthcare Cost and Utilization Project. We estimated the cost of each inpatient stay by multiplying the total hospital charge with the cost-to-charge ratio [20]. Adjusted cost for each year was calculated in terms of the 2012 cost after adjusting for inflation according to the latest consumer price index data released by US government [21]. This enabled us to standardize the costs over the study period. Length of stay and cost were calculated only for survivors.

Statistical analysis

Statistical analysis system (SAS®) 9.4 (SAS Institute Inc., Cary, North Carolina) was utilized for analyses. Survey

Table 1 Baseline characteristics of neonates undergoing ECMO

	2002–2003 (*n* = 1008)	2004–2005 (*n* = 1755)	2006–2007 (*n* = 1527)	2008–2009 (*n* = 1515)	2010–2011 (*n* = 1798)	Total (*n* = 7603)	*p*
Gender (%)							<0.0001
Male	53.9	64.2	60.6	58.4	53.4	58.4	
Female	46.1	35.8	39.4	41.6	46.6	41.6	
Race (%)							<0.0001
White	35.0	38.3	30.1	38.0	44.4	37.6	
Other	41.0	32.5	37.8	48.5	44.1	40.6	
Missing	24.0	29.2	32.1	13.5	11.6	21.9	
Zip code income (%)							<0.0001
0–25 percentile	17.1	32.2	32.7	34.0	34.7	31.1	
26–50 percentile	22.6	22.2	27.9	25.1	25.1	24.6	
51–75 percentile	21.2	26.1	18.6	22.4	21.8	22.2	
76–100 percentile	36.9	16.9	19.6	17.5	16.0	20.1	
Missing	2.3	2.5	1.3	1.0	2.5	1.9	
Insurance (%)							<0.0001
Private	47.9	42.2	37.8	35.6	31.4	38.3	
Other	52.1	57.2	61.9	64.0	68.3	61.4	
Missing	0.0	0.6	0.3	0.3	0.3	0.3	
Hospital bed size (%)							<0.0001
Small	24.0	15.3	27.9	3.6	4.1	14.2	
Medium	20.3	28.3	10.3	17.8	17.4	19.0	
Large	55.8	56.4	61.9	78.6	78.5	66.9	
Hospital location (%)							0.0005
Rural	0.5	0.0	0.0	0.0	0.3	0.1	
Urban	99.5	100.0	100.0	100.0	99.7	99.9	
Hospital region (%)							<0.0001
Northeast	12.4	10.3	9.0	14.2	9.6	10.9	
Midwest	17.1	28.9	19.6	17.5	17.1	20.4	
South	40.1	45.8	47.1	24.8	46.0	41.2	
West	17.5	15.0	10.3	31.4	14.3	17.4	
Missing	12.9	0.0	14.1	12.2	13.0	10.0	
Hospital teaching status (%)							<0.0001
Non-teaching	0.5	2.8	4.5	0.7	0.3	1.8	
Teaching	99.5	97.2	95.5	99.3	99.7	98.2	
Missing							
Indication for ECMO							<0.0001
ECPR	1.4	1.1	1.6	2.0	3.0	1.9	
CDH	29.5	20.8	22.1	20.5	20.9	22.3	
MAS	22.6	12.5	13.1	14.9	17.9	15.8	
RDS	21.7	32.8	37.2	34.7	37.7	33.6	
PPHN	1.4	5.6	2.9	3.0	7.2	4.3	
Pneumonia	1.4	1.7	1.0	1.7	1.1	1.4	
CHD	19.8	25.0	20.5	22.1	11.9	19.7	
Cardiomyopathy	0.5	0.0	0.3	0.3	0.3	0.3	
Myocarditis	0.0	0.3	0.3	0.0	0.0	0.1	
Sepsis	1.8	0.3	1.0	1.0	0.0	0.7	
Survivors							<0.0001
Yes	52.5	50.3	45.2	51.5	58.1	51.6	
No	47.5	49.7	54.8	48.5	41.9	48.4	
Length of stay (median days)	32	34	40	44	42	39	0.0007
Cost (median $)	120,363	146,942	151,487	169,362	191,987	160,830	<0.0001

procedures were used to account for the complex survey design and clustering of this data. Since NIS represents a 20% stratified random sample of US hospitals, analyses were performed using hospital-level discharge weights provided by the NIS, to obtain national estimates. The incidence of ECMO utilization was expressed as the number of neonates undergoing ECMO per 100,000 live births. The yearly number of births was obtained from the Wide-

Table 2 Trends in neonatal ECMO by indication

Indication	2002–2003 ($n = 1008$)	2004–2005 ($n = 1755$)	2006–2007 ($n = 1527$)	2008–2009 ($n = 1515$)	2010–2011 ($n = 1798$)	Total ($n =$ 7603)	p
Respiratory (%)	75.1	71.7	75.3	72.9	83.8	76.0	<0.0001
Cardiac (%)	20.3	25.3	21.2	22.4	12.1	20.1	<0.0001
Infectious (%)	3.2	1.9	1.9	2.6	1.1	2.1	0.1
ECPR (%)	1.4	1.1	1.6	2.0	3.0	1.9	<0.0001

ranging Online Data for Epidemiological Research (WONDER) program on the Centers for Disease Control and Prevention website [22]. We compared the baseline characteristics of neonates undergoing ECMO for years 2002–2011 to estimate differences utilizing chi-square test for categorical variables, Student's *t*-test for normally distributed continuous variables and Wilcoxon rank-sum test and survey regression for non-normally distributed continuous variables. For trend analysis, chi-square test of trend for proportions was used using the Cochrane Armitage test via the ''trend'' command in SAS®. Survey logistic regression was used to analyze the predictors of mortality. Hierarchical mixed effects logistic regression models to analyze multivariate predictors of LOS and cost of hospitalization. Hierarchical regression is designed to deal with clustered or grouped data in which analytic units are naturally nested or grouped within other units of interest and helps to account for "within-cluster" correlations at each level of the hierarchy and properly adjust estimates to account for them [23]. Weights provided by NIS were used to generate national estimates. p-value of <0.05 was considered significant for all analyses.

Results

Demographic characteristics of study cohort

We identified 7603 neonatal discharges in the NIS database who underwent ECMO from 2002 through 2011. The demographic characteristics of the study cohort are summarized in Table 1. Briefly, 58.4% were males, 37.6% were White and 61.4% had non-private insurance. Neonates who underwent ECMO were more likely to undergo the therapy at large (66.9%), urban (99.9%), teaching (98.2%) hospitals. The South geographic census region recorded the most (41.2%) ECMO runs while the Northeast had the least (10.9%).

Trends in ECMO utilization and mortality

During the study period, neonatal ECMO utilization averaged 18 ECMO runs per 100,000 live births, increasing from 12 to 23 per 100,000 live births ($p < 0.0001$) as shown in Figure 1. As shown in Table 2, of the 7603 neonates who underwent ECMO, 76.0% had a principal respiratory diagnosis. A principal cardiac indication was identified in 20.1% of neonates who underwent ECMO during the study period. Trends for respiratory indications increased from 75.1% to 83.8%, while cardiac indications decreased from 20.3 to 12.1% from 2002 to 2011 ($p < 0.0001$). Trends for E-CPR increased from 1.4% in 2002–03 to 3.0% in 2010–11 ($p < 0.0001$). Infectious indications comprised 2.1% of all neonatal ECMO cases. As shown in Table 1, the most common neonatal diagnosis requiring ECMO was RDS (33.6%), followed by CDH (22.3%), CHD (19.7%) and MAS (15.8%). Sepsis, cardiomyopathy, and myocarditis were the least common conditions for which ECMO was used.

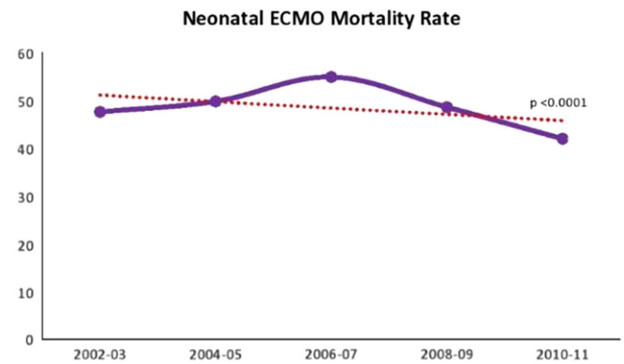

Fig. 2 Neonatal ECMO mortality rate

Mortality rate for neonates undergoing ECMO was 48.4% during the study period. It decreased significantly from 47.5 to 41.9% between 2002–03 and 2010–11 ($p <$ 0.0001) as shown in Figure 2. Table 3 shows mortality decreased significantly from 45.4 to 37.8% for neonates requiring ECMO for respiratory indications between 2002–03 and 2010–11 ($p < 0.0001$). Mortality among neonates who underwent ECMO due to a principal cardiac diagnosis increased from 52.3 to 61.4% ($p = 0.01$). On multivariate analysis, ECMO mortality risk was highest for infectious indications (OR 4.1; CI 1.1–16.0), followed by E-CPR (OR 3.8; CI 1.4–10.7) and cardiac indications (OR 2.0; CI 1.5–2.8) as compared to respiratory indications.

Table 3 Trends in neonatal ECMO mortality by indication

Indication	2002–2003	2004–2005	2006–2007	2008–2009	2010–2011	Total	*p*
Respiratory (%)	45.4	45.4	50.2	41.2	37.8	43.6	<0.0001
Cardiac (%)	52.3	60.4	65.2	66.2	61.4	61.7	0.01
Infectious (%)	57.1	57.1	83.3	87.5	50.0	68.8	0.18
ECPR (%)	66.7	75.0	100.0	66.7	72.7	75.9	0.68

Table 4 Trends in neonatal ECMO hospital LOS and cost by indication in survivors

Indication	LOS (days)/ Cost ($)	2002–2003	2004–2005	2006–2007	2008–2009	2010–2011	Total	*p*
Respiratory	LOS	33	32	40	42	41	38	0.006
	Cost	115,418	129,637	142,095	160,594	185,295	148,176	<0.0001
Cardiac	LOS	27	41	40	52	49	41	0.01
	Cost	106,695	199,261	187,663	220,178	281,302	193,976	0.003
Infectious	LOS	60	27	12	101	16	34	0.4
	Cost	523,726	255,593	80,275	487,762	103,015	202,721	0.4
ECPR	LOS	108	23	[a]	33	37	33	0.6
	Cost	248,866	[b]	[a]	160,095	175,889	204,480	0.8

[a] No survivors in 2006–2007

[b] For the survivors, cost was missing and so is not reported

Resource utilization

The median length of stay for ECMO increased significantly from 32 to 42 days ($p = 0.0007$) during the study period. Table 4 shows LOS and cost trends by indication. The median length of stay for respiratory indications increased from 33 to 41 days ($p = 0.006$). The median length of stay increased for cardiac indications (27 to 49 days; $p = 0.03$). On multivariate analysis, length of stay increased by 1.6 days per year (95% CI 0.3–2.9 days; $p = 0.02$). When compared to infants in the same diagnostic category, not requiring ECMO, those who received ECMO had significantly longer LOS (Supplementary Table 2).

The median cost of hospitalization for ECMO increased significantly from $120,363 to $191,987 ($p < 0.0001$). Median cost for respiratory indications increased from $115,418 to $185,295 ($p < 0.0001$). Median cost for cardiac indications increased from $106,695 to $281,302 ($p = 0.003$) as shown in Table 4. Table 5 shows on multivariate analysis, with yearly increments, the cost of hospitalization increased by $14,033 (95% CI $9508-$18558; $p < 0.0001$). Compared to other insurance types, cost of hospitalization for patients with private insurance was higher by $20,281 (95% CI $573–$39,989; $p = 0.05$). Compared to small hospitals, cost of hospitalization was significantly lower by $93,957 in large hospitals (95% CI $136,358–$51,556; $p < 0.0001$). Compared to respiratory indications, the cost of hospitalization for cardiac indications was significantly higher by $48,562 (95% CI $20,105–$77,019; $p = 0.001$). When compared to infants in the same diagnostic category, who did not require ECMO, infants who received ECMO had a significantly higher median hospital cost (Supplementary Table 2).

Discussion

Our study is one of the largest analysis of trends in neonatal ECMO and its outcomes in the United States. We highlight the progression and variation in incidence, mortality, LOS, and cost by indication of neonatal ECMO in 7603 patients from 2002–2011. We know of only one other study in the literature by Song et al. [24] that studied demographic and geographic factors in 5151 neonatal patients undergoing ECMO from the Kids' Inpatient Database (KID) years 1997, 2000, 2003, 2006, 2009, and 2012 . Our study extends the breadth of currently existing data on neonatal ECMO.

ECMO utilization in neonates has almost doubled during the 10-year study period. This is secondary to improved devices, catheters and a shared knowledge among ECMO centers working closely to improve care in this critically ill neonatal population [25, 26]. As ECMO experience has broadened, new indications have evolved [27]. ECMO is being offered to neonates that are younger and smaller in size [28]. Respiratory indications accounted for 76% of all neonatal ECMO. RDS was the most common (33.6%) indication for ECMO. This finding is consistent with Bokman et al. [7] who showed RDS as the leading cause for ECMO across all age groups in the pediatric population

Table 5 Predictors of neonatal ECMO mortality, hospital LOS, and cost

	Mortality		LOS (days)[a]		Cost ($)[a]	
Variable	Odds ratio (95% confidence interval)	*p*	Beta coefficient (95% confidence interval)	*p*	Beta coefficient (95% confidence interval)	*p*
Gender						
Male	Reference		Reference		Reference	
Female	1.1 (0.9–1.5)	0.3	2.4 (−3.8–8.6)	0.4	12,354 (−7000–31708)	0.2
Year	1.0 (0.9–1.0)	0.4	1.6 (0.3–2.9)	0.02	14,033 (9508–18558)	<0.0001
Insurance status						
Other	Reference		Reference		Reference	
Private	1.1 (0.8–1.4)	0.7	3.3 (−3–9.6)	0.3	20,281 (573–39,989)	0.05
Hospital bed size						
Small	Reference		Reference		Reference	
Medium	0.9 (0.5–1.5)	0.6	3.4 (−9.9–16.6)	0.6	−16,219 (−64,680–32,242)	0.5
Large	0.7 (0.4–1.2)	0.2	−1.7 (−13.1–9.7)	0.8	−93,957 (−136358–−51,556)	<0.0001
Indication for ECMO						
Respiratory	Reference		Reference		Reference	
Cardiac	2.0 (1.5–2.8)	<0.0001	5.2 (−3.5–13.9)	0.2	48,562 (20,105–77,019)	0.001
Infectious	4.1 (1.1–16.0)	0.04	−6.5 (−35.1–22.2)	0.7	42,179 (−56,144–140,502)	0.4
ECPR	3.8 (1.4–10.7)	0.01	−10.1 (−42–21.7)	0.5	−2208 (−100,631–96,216)	1.0

[a] LOS and cost calculated among survivors only

[29]. However, data presented by Extracorporeal Life Support Organization (ELSO) Registry shows a decline in neonates with RDS requiring ECMO [30]. This may be due to differences in how data are collected in ELSO, KID, and NIS. The ELSO is an international non-profit consortium of healthcare institutions who are dedicated to the development and evaluation of novel therapies for support of failing organ systems and to maintain a registry of patients receiving ECMO both in the United States and internationally. The KID is the largest publicly-available all-payer pediatric inpatient care database in the United States and it is released every 3 years. The KID sample contains 10% of normal newborns and 80% of other pediatric discharges. The NIS utilizes data from roughly 1000 hospitals each year to create a sample representing > 95% of the U.S. population [15]. Further, it is plausible that neonates with unclear etiology for severe respiratory failure at birth may get coded as RDS.

We showed a decrease in use of ECMO for cardiac indications from 2002 to 2011. The ELSO registry reported stable numbers of neonatal cardiac related ECMO and a significant increase in pediatric cardiac related ECMO. Use of E-CPR in neonates has increased significantly. In 2010–2011, 3% of all ECMO runs were E-CPR, which doubled during the study period (2002–2011). ELSO reported a 35% increase in neonatal E-CPR from 2009 to 2015 [30]. Our study is the first to report a rising trend in E-CPR for neonates from 2002.

We demonstrated a decreasing trend in mortality of neonates undergoing ECMO. This is likely due to many factors such as improved ECMO devices and techniques, earlier initiation of ECMO, neonatal intensive care practices, including changes in ventilatory strategies and nitric oxide use. Non-respiratory indications for initiation of ECMO in the neonatal population were associated with highest mortality. We showed increasing odds of mortality by indication: infectious > E-CPR > cardiac > respiratory. Song et al. [24] showed increasing odds of mortality in neonates with cardiac related primary diagnosis. However, they did not compare risk of mortality in neonates that underwent E-CPR or required ECMO for infectious causes.

Median hospital LOS for neonates on ECMO was 39 days. Other studies have reported median LOS varying from 23 to 32 days [7, 24]. This variation is likely because the populations studied were cross-sectional cohorts available every 3 years from the KID. Both LOS (1.6 days/year) and inflation adjusted hospital cost ($14,033/year) rose per year during the study period after adjusting for confounders such as gender, year, insurance status, and hospital size. Several factors may play a role in this. These include duration of ECMO, multiple ECMO runs, severity of illness requiring use of other life-saving medical therapies such as continuous renal replacement therapy, therapeutic hypothermia etc. We also did not evaluate the contribution of complications of ECMO towards LOS and cost. Neonates undergoing ECMO for cardiac indications generated significantly higher cost than neonates with respiratory indications for ECMO. These patients often undergo expensive procedures such as several cardiac surgeries and consequently end up with longer costly hospitalizations [31]. We also showed decreased hospital cost in larger hospitals. Faraoni et al. [31] showed similar results after controlling for diagnostic groups, LOS and ECMO complications in pediatric patients undergoing ECMO. This is likely due to streamlined processes and dedicated personnel established to care for neonates requiring ECMO, resulting in higher volume, improved outcomes, shorter LOS and subsequently decreased cost. Despite the increased cost of hospitalization, neonatal ECMO has been shown to cost-effective [3].

We found regional differences in the utilization of ECMO in the U.S. The reasons for these differences are not clear from available published literature on neonatal ECMO. A recent survey of 81 active neonatal respiratory ECMO centers (84% were in North America) found that there was significant variation and deviation from the published ELOS guidelines regarding patient eligibility and selection for ECMO based on these guidelines at different ECMO centers [28]. Such variation in patient selection could account for the regional differences. A review of the ELSO registry [32] shows that most of the ECMO centers are in the eastern half of the U.S. and it is possible that the differential distribution and access to neonatal ECMO centers may also account for such regional variation in ECMO use.

Our study has several limitations. NIS is an administrative database and all diagnoses codes are ICD-9 based. We could not assess the impact of race due to significant missing data. No clinical data such as arterial blood gas analysis, duration of CPR, illness severity, duration, and type of mechanical ventilation were available. We did not have information on ECMO related specifics such as veno-arterial vs. veno-venous ECMO, type of catheter used and difficulties with catheter placement, type of ECMO pump used, duration, and number of ECMO runs. All these factors can impact survival outcomes, LOS, and cost of hospitalization. The NIS database does not have information on admission location of neonatal patients (neonatal intensive care unit vs. pediatric intensive care unit). Since we included newborns < 30 days of age, it is logical to assume that the ECMO therapy was provided in both the NICU and PICU but were unable to delineate the differences between them.

Our study possesses several strengths. To our knowledge, this is the largest study to trend the outcomes and utilization of ECMO in the neonatal population over a 10-year period from 2002 through 2011. We utilized the NIS, which approximates a 20-percent stratified sample of all discharges from U.S. community hospitals, excluding rehabilitation and long-term acute care hospitals. The NIS contains information on all patients, regardless of payer, including individuals covered by Medicare, Medicaid, or private insurance, uninsured. Therefore, the data and the findings of our study are nationally representative.

In conclusion, there was an increase in the utilization of neonatal ECMO from 2002 through 2011. There was improved survival in male infants and a reduced risk of death in large, urban teaching hospitals but increased risk of death for ECMO performed for non-respiratory indications. LOS and hospital cost increased during the study period. Future studies looking at resource utilization and outcomes of neonatal ECMO after discharge from the hospital and the factors that would impact these are recommended to ascertain the cost-effectiveness of neonatal ECMO in the US.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Bartlett RH, Gazzaniga AB, Jefferies MR, Huxtable RF, Haiduc NJ, Fong SW. Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. Trans Am Soc Artif Intern Organs. 1976;22:80–93.
2. Barbaro RP, Paden ML, Guner YS, Raman L, Ryerson LM, Alexander P, et al. Pediatric Extracorporeal life support organization registry international report 2016. ASAIO J. 2017;63:456–63.
3. Petrou S, Bischof M, Bennett C, Elbourne D, Field D, McNally H, et al. Cost-effectiveness of neonatal extracorporeal membrane oxygenation based on 7-year results from the United Kingdom Collaborative ECMO Trial. Pediatrics. 2006;117:1640–9.
4. Mattox KL, Beall AC. Resuscitation of the moribund patient using portable cardiopulmonary bypass. Ann Thorac Surg. 1976;22:436–42.
5. McMullan DM, Thiagarajan RR, Smith KM, Rycus PT, Brogan TV. Extracorporeal cardiopulmonary resuscitation outcomes in term and premature neonates. Pediatr Crit Care Med. 2014;15:e9–16.
6. Barbaro RP, Odetola FO, Kidwell KM, Paden ML, Bartlett RH, Davis MM, et al. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. analysis of

the extracorporeal life support organization registry. Am J Respir Crit Care Med. 2015;191:894–901.
7. Bokman CL, Tashiro J, Perez EA, Lasko DS, Sola JE. Determinants of survival and resource utilization for pediatric extracorporeal membrane oxygenation in the United States 1997-2009. J Pediatr Surg. 2015;50:809–14.
8. Freeman CL, Bennett TD, Casper TC, Larsen GY, Hubbard A, Wilkes J, et al. Pediatric and neonatal extracorporeal membrane oxygenation. Crit Care Med. 2014;42:512–9.
9. Gray BW, Haft JW, Hirsch JC, Annich GM, Hirschl RB, Bartlett RH. Extracorporeal life support: experience with 2,000 patients. ASAIO J. 2015;61:2–7.
10. Davis JS, Ryan ML, Perez EA, Neville HL, Bronson SN, Sola JE. ECMO hospital volume and survival in congenital diaphragmatic hernia repair. J Surg Res. 2012;178:791–6.
11. Prodhan P, Bhutta AT, Gossett JM, Stroud MH, Rycus PT, Bratton SL, et al. Extracorporeal membrane oxygenation support among children with adenovirus infection: a review of the Extracorporeal Life Support Organization registry. ASAIO J. 2014;60:49–56.
12. Zabrocki LA, Brogan TV, Statler KD, Poss WB, Rollins MD, Bratton SL. Extracorporeal membrane oxygenation for pediatric respiratory failure: Survival and predictors of mortality. Crit Care Med. 2011;39:364–70.
13. Chan T, Thiagarajan RR, Frank D, Bratton SL. Survival after extracorporeal cardiopulmonary resuscitation in infants and children with heart disease. J Thorac Cardiovasc Surg. 2008;136:984–92.
14. Raymond TT, Cunnyngham CB, Thompson MT, Thomas JA, Dalton HJ, Nadkarni VM, et al. Outcomes among neonates, infants, and children after extracorporeal cardiopulmonary resuscitation for refractory in-hospital pediatric cardiac arrest: A report from the National Registry of CardioPulmonary Resuscitation*. Pediatr Crit Care Med. 2009;11:1.
15. Agency for Healthcare Research and Quality, Rockville M. HCUP National Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 2015. http://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp (accessed 3 Oct 2017).
16. Tashiro J, Wang B, Sola JE, Hogan AR, Neville HL, Perez EA. Patent ductus arteriosus ligation in premature infants in the United States. J Surg Res. 2014;190:613–22.
17. Burke BL, Robbins JM, Mac BT, Hobbs CA, Nesmith C, Tilford JM. Trends in hospitalizations for neonatal jaundice and kernicterus in the United States, 1988-2005. Pediatrics. 2009;123:524–32.
18. Westfall JM, McGloin J. Impact of double counting and transfer bias on estimated rates and outcomes of acute myocardial infarction. Med Care. 2001;39:459–68.
19. Lowry AW, Morales DLS, Graves DE, Knudson JD, Shamszad P, Mott AR, et al. Characterization of extracorporeal membrane oxygenation for pediatric cardiac arrest in the United States: Analysis of the kids' inpatient database. Pediatr Cardiol. 2013;34:1422–30.
20. Agency for Healthcare Research and Quality, Rockville M. HCUP Cost-to-Charge Ratio Files (CCR). Healthcare Cost and Utilization Project (HCUP). https://www.hcup-us.ahrq.gov/db/state/costtocharge.jsp.
21. U.S. Bureau of Labor Statistics. CPI Inflation Calculator. https://www.bls.gov/data/inflation_calculator.htm (accessed 22 Dec 2017).
22. Centers for Disease Control and Prevention (CDC). CDC WONDER. https://wonder.cdc.gov/ (accessed 7 Mar 2018).
23. Chu, B, Steiner, C, Houchens R. Hierarchical modeling using HCUP data report# 2007–01. HCUP Methods Ser. 2007. https://www.hcup-us.ahrq.gov/reports/methods/2007_01.pdf (accessed 22 Dec 2017).
24. Song AY, Chen H-HA, Chapman R, Govindarajan A, Upperman JS, Burke RV, et al. Utilization patterns of extracorporeal membrane oxygenation in neonates in the United States 1997-2012. J Pediatr Surg. 2017;52:1681–7.
25. Lawson S, Ellis C, Butler K, McRobb C, Mejak B. Neonatal extracorporeal membrane oxygenation devices, techniques and team roles: 2011 survey results of the United States' Extracorporeal Life Support Organization centers. J Extra Corpor Technol. 2011;43:236–44.
26. Extracorporeal Life Support Organization (ELSO). https://www.elso.org.
27. Di Nardo M, MacLaren G, Marano M, Cecchetti C, Bernaschi P, Amodeo A. ECLS in pediatric cardiac patients. Front Pediatr. 2016;4:109.
28. Chapman R, Peterec S, Bizzarro M, Mercurio M. Patient selection for neonatal extracorporeal membrane oxygenation: beyond severity of illness. J Perinatol. 2009;29:606–11.
29. Agency for Healthcare Research and Quality, Rockville M. HCUP Databases. Healthcare Cost and Utilization Project (HCUP). March 2017. https://www.hcup-us.ahrq.gov/kidoverview.jsp (accessed 2 Apr 2018).
30. Thiagarajan RR, Barbaro RP, Rycus PT, Mcmullan DM, Conrad SA, Fortenberry JD, et al. Extracorporeal life support organization registry international report 2016. ASAIO J. 2017;63:60–7.
31. Faraoni D, Nasr VG, DiNardo JA, Thiagarajan RR. Hospital costs for neonates and children supported with extracorporeal membrane oxygenation. J Pediatr. 2016;169:69–75.e1.
32. Extracorporeal Life Support Organization-ECMO and ECLS Membership and Center Map. https://www.elso.org/Membership/CenterMap.aspx (accessed 28 Mar 2018).