# Pediatric and Neonatal Extracorporeal Membrane Oxygenation: Does Center Volume Impact Mortality?*

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**Objective:** Extracorporeal membrane oxygenation, an accepted rescue therapy for refractory cardiopulmonary failure, requires a complex multidisciplinary approach and advanced technology. Little is known about the relationship between a center's case volume and patient mortality. The purpose of this study was to analyze the relationship between hospital extracorporeal membrane oxygenation annual volume and in-hospital mortality and assess if a minimum hospital volume could be recommended.

**Design:** Retrospective cohort study.

**Setting:** A retrospective cohort admitted to children's hospitals in the Pediatric Health Information System database from 2004 to 2011 supported with extracorporeal membrane oxygenation was identified. Indications were assigned based on patient age (neonatal vs pediatric), diagnosis, and procedure codes. Average hospital annual volume was defined as 0–19, 20–49, or greater than or equal to 50 cases per year. Maximum likelihood estimates were used to assess minimum annual case volume.

**Patients:** A total of 7,322 pediatric patients aged 0–18 were supported with extracorporeal membrane oxygenation and had an indication assigned.

**Interventions:** None.

**Measurements and Main Results:** Average hospital extracorporeal membrane oxygenation volume ranged from 1 to 58 cases per year. Overall mortality was 43% but differed significantly by indication. After adjustment for case-mix, complexity of cardiac surgery, and year of treatment, patients treated at medium-volume centers (odds ratio, 0.86; 95% CI, 0.75–0.98) and high-volume centers (odds ratio, 0.75; 95% CI, 0.63–0.89) had significantly lower odds of death compared with those treated at low-volume centers. The minimum annual case load most significantly associated with lower mortality was 22 (95% CI, 22–28).

**Conclusions:** Pediatric centers with low extracorporeal membrane oxygenation average annual case volume had significantly higher mortality and a minimum volume of 22 cases per year was associated with improved mortality. We suggest that this threshold should be evaluated by additional study. (*Crit Care Med* 2014; 42:512–519)

**Key Words:** cardiopulmonary resuscitation; critical care; extracorporeal membrane oxygenation; low-volume hospitals; pediatrics; risk adjustment

Extracorporeal membrane oxygenation (ECMO) provides prolonged partial cardiopulmonary bypass and has been used for infants and children with severe cardiopulmonary failure unresponsive to conventional therapy since 1975 (1–3). More recently, this complex technology has been successfully used emergently to rescue "failing" ECMO deployment during cardiopulmonary resuscitation (E-CPR) (4–6). Initial successful applications of ECMO were almost exclusively among term neonates with pulmonary hypertension; however, ECMO has increasingly been used to support older children and adults with both cardiorespiratory failure and cardiac arrest (6–8). Practice in the United Kingdom has

*See also p. 726.

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focused on regional ECMO referral centers while development in the United States has not been centralized (7, 9).

There are numerous reports regarding increasing surgical experience and center volume demonstrating lower mortality in many high-risk surgical procedures (10–13). These observations led to recommendations regarding minimum volume standards for some surgical procedures (12). The favorable relationship between increasing volume and improved outcome also exists for infants and children with some complex conditions (14, 15).

Given that pediatric and neonatal ECMO are highly complex medical-surgical endeavors, a reasonable hypothesis is that center experience and volume may be associated with mortality. There are no large multicenter reports addressing pediatric ECMO center volume and survival. We used a large administrative pediatric database to determine if after adjustment for case-mix, center volume was associated with mortality. Our hypothesis was that an inverse relationship existed between ECMO center volume and mortality. Because applications of ECMO are expanding among both children and adults, study of this high-cost rescue therapy is increasingly important.

## MATERIALS AND METHODS

### Data Source

The Pediatric Health Information System (PHIS) database, a multicenter administrative database with data from over 40 children's hospitals in the United States, was used. Participating hospitals provide data on demographics, outcomes, diagnoses, procedures, and charges using Clinical Transaction Classification (CTC) codes for billed services (16, 17). Data are de-identified centrally which qualified for exemption from human subjects review by the University of Utah Institutional Review Board.

### Patients

Patients admitted between January 1, 2004, and December 31, 2011, less than 18 years old, with an *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM), procedure code for ECMO (39.65) or CTC code for ECMO (521181) were evaluated for inclusion.

### Diagnosis Groups

Diagnostic categorization emulated categorizations used by the Extracorporeal Life Support Organization (ELSO) ECMO indications (**Fig. 1**). See details of the diagnostic categorization in **Appendix 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/A754). Seven diagnostic categories were defined: congenital diaphragmatic hernia (CDH), neonatal or pediatric respiratory failure, neonatal or pediatric cardiac disease, and neonatal or pediatric cardiac arrest. Available data could not distinguish a cardiac arrest prior to initiation of ECMO from an ongoing arrest when starting ECMO (i.e., E-CPR). All patients with a cardiac arrest were classified as neonatal or pediatric cardiac arrest regardless of other diagnosis codes except for CDH as cardiac arrest in this group is rarely the indication for ECMO (4).

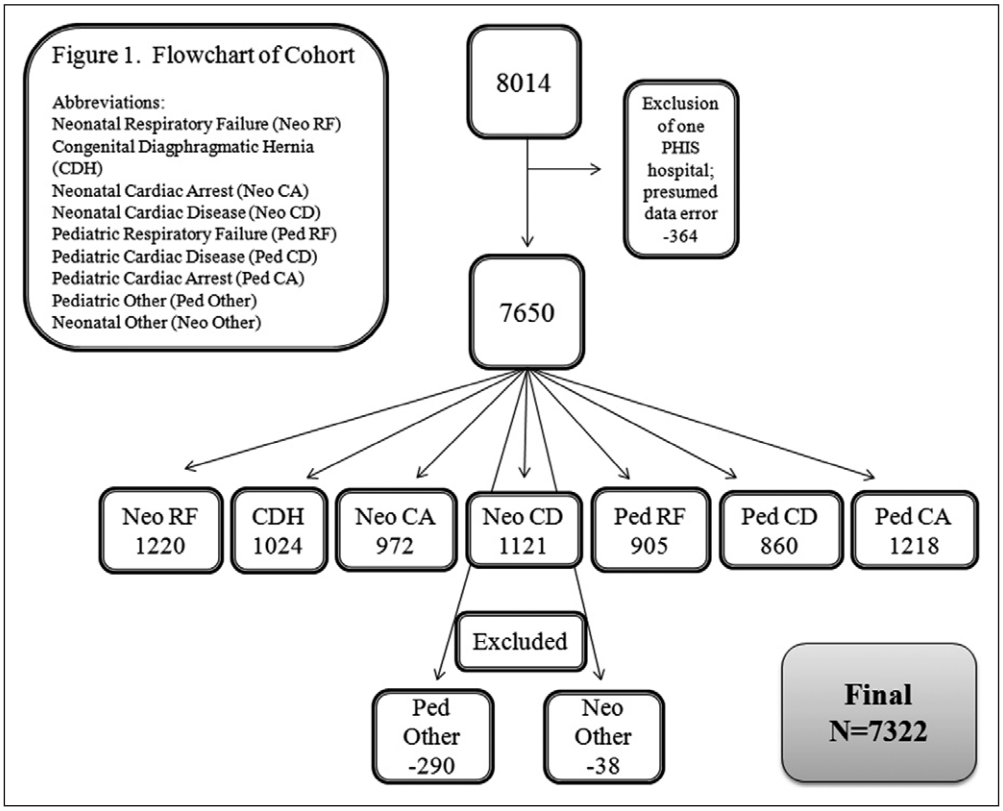


**Figure 1.** Flowchart of cohort inclusions, exclusions, and diagnostic categorization. PHIS = Pediatric Health Information System, Neo RF = neonatal respiratory failure, CDH = congenital diaphragmatic hernia, Neo CA = neonatal cardiac arrest, Neo CD = neonatal cardiac disease, Ped RF = pediatric respiratory failure, Ped CD = pediatric cardiac disease, Ped CA = pediatric cardiac arrest, Ped Other = pediatric other, Neo Other = neonatal other.

### Study Variables

The primary outcome was in-hospital mortality and primary exposure was annual hospital ECMO volume. Covariates included demographics, year of admission, and ECMO indication. Risk Adjustment for Congenital Heart Surgery (RACHS-1) was used to adjust for complexity of cardiac surgical repair as mortality is increased for patients with single ventricle physiology after both cardiac surgery and E-CPR (18–20).

### Hospital Variables

We created an average annual ECMO volume for each hospital over the study period using quarterly data and averaged to cases per year. Empirically, hospital volume was categorized as

low, medium, or high, that is, 0–19, 20–49, and greater than or equal to 50 average ECMO cases per year based on clinical assessment, respectively. Average annual ECMO volume was also evaluated continuously.

### Subgroup Analysis

Two additional diagnostic categories, respiratory syncytial virus (RSV) bronchiolitis and stage 1 palliation in hypoplastic left heart syndrome (HLHS), were created due to their consistent coding to evaluate homogenous groups (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A754).

### Statistical Analyses

Statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL) and the R Language and Environment (21). Categorical data were compared using the chi-square test and continuous data using the Wilcoxon rank sum test; *p* value less than 0.05 was considered significant. Multivariable logistic regression was used to evaluate ECMO volume and hospital mortality. Center case-mix was adjusted for indication for ECMO which included age, ECMO support year, and RACHS-1 scores for classified congenital cardiothoracic procedures.

We also sought to evaluate a potential "cut point" for minimal annual ECMO volume associated with improved survival using a maximum likelihood approach. This approach is based on the assumptions that such a cut point exists and patients at centers falling on the same side of the cut point have the same chance of survival. A likelihood was calculated for each possible cut point and the optimal point was chosen as the value providing the highest likelihood. To assess the precision of the cut point estimate, a CI was calculated using a nonparametric bootstrap method (22).

## RESULTS

Seven thousand three hundred twenty-two children meeting study criteria underwent ECMO support from 2004 to 2011. Children's hospitals within this cohort performed an average of 1 to 58 ECMO cases per year. Overall in-hospital mortality was 43%. Comparing patients who survived with those who died (**Table 1**), there were significant differences related to patient age, indication for ECMO, year of ECMO support, length of stay, and treating hospital ECMO volume. Fifteen hospitals were categorized as low-volume centers, 22 as medium-volume centers, and three as high-volume centers representing 16%, 69%, and 15% of the patient cohort, respectively.

**Table 2** describes patient characteristics by ECMO volume category. Overall mortality was significantly higher at low-volume centers (47%) compared with medium- and high-volume centers (42% and 41%) ($p = 0.01$). However, the indication for ECMO also differed significantly by center volume categories, with more cardiac disease patients in the low ECMO volume group and more cardiac arrest cases treated at high-volume centers, whereas neonatal respiratory cases were more common at low- and medium-volume centers. ECMO indications by patient age groups (neonatal vs older children) are highlighted in Table 2.

After adjusting for these potential confounders, significantly higher mortality persisted at low-volume centers compared with medium- (odds ratio [OR], 0.86; 95% CI, 0.75–0.98) and high-volume centers (OR, 0.75; 95% CI, 0.63–0.89) (**Table 3**). Age was included within indication for ECMO as neonatal versus older patients. A second logistic regression model including average center volume as a continuous variable found that for each additional 10 patients per year, the odds of mortality decreased 5% (OR, 0.95; 95% CI, 0.92–0.98).

### Subgroup Analysis

Because of concern regarding potential misclassification of ECMO indication, a subset of patients who had consistent ICD-9-CM procedure and diagnosis coding was evaluated. CDH ($n$ = 1,016), HLHS with stage 1 palliation surgery ($n$ = 522), and patients with RSV bronchiolitis ($n$ = 217) were identified using the ICD-9-CM procedure and diagnosis codes described in Appendix 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/A754). **Table 4** shows this subset and compares mortality by center volume. In-hospital mortality differed by indication and was 54% for CDH, 31% for RSV, and 62% for HLHS undergoing stage 1 palliation. A similar multivariable analysis of this subset adjusting for primary diagnosis as well as presence of a cardiac arrest and year of treatment found that patients treated at both medium and high ECMO volume centers had significantly lower odds of mortality (OR, 0.74; 95% CI, 0.56–0.98 and OR, 0.59; 95% CI, 0.42–0.83, respectively) compared with low-volume centers.

Finally, we evaluated center average annual ECMO volume and unadjusted mortality (**Fig. 2**). Evaluating death and the annual ECMO volume at each center, the maximum likelihood estimate of the optimal cutoff for volume was a minimum of 22 ECMO cases per year. An identical result was found when risk factors were included in logistic regression models. This was also the cutoff that produced the most significant difference between high- and low-volume centers ($p = 0.00001$). We found no evidence that the model assumptions were violated. The 95% bootstrap CI, from both univariate and multivariate models, was 22–28 average annual cases.

## DISCUSSION

In this large retrospective multicenter database, we found that ECMO centers caring for fewer than 20 ECMO cases annually had significantly higher case-mix adjusted mortality than centers with larger ECMO volume. Centers had wide variation in application of ECMO by indication as well as length of stay. However, when defining indications in a manner similar to ELSO and using a subgroup analysis, we continued to find a survival benefit for infants and children treated at medium to large ECMO volume centers compared with those treated at smaller centers. There was no significant difference in mortality between the medium- and high-volume centers. ECMO requires complex coordination of multiple providers to deliver care. Logically such care would appear sensitive to case volume;

**TABLE 1. Patient Demographics and Extracorporeal Membrane Oxygenation Center Volume Comparing Pediatric Survivors With Nonsurvivors**

| Variable | Survivors *n* = 4,191 *n* (%) | Nonsurvivors *n* = 3,131 *n* (%) | *p* |
|---|---|---|---|
| Age | | | < 0.001 |
| 0–7 d | 2,342 (56) | 1,760 (56) | |
| 8–30 d | 156 (4) | 156 (5) | |
| 31–365 d | 721 (17) | 494 (16) | |
| 1–10 yr | 663 (16) | 432 (14) | |
| > 10 yr | 309 (7) | 289 (9) | 0.83 |
| Male | 2,341 (56) | 1,741 (56) | |
| Race | | | < 0.001 |
| Black | 814 (19) | 453 (15) | |
| White | 1,988 (47) | 1,493 (43) | |
| Hispanic | 656 (16) | 479 (15) | |
| Asian | 91 (2) | 78 (3) | |
| Other | 518 (12) | 442 (14) | |
| Unknown | 124 (3) | 186 (6) | |
| Insurance | | | 0.15 |
| Public | 2,122 (51) | 1,579 (50) | |
| Private | 1,417 (34) | 1,120 (36) | |
| No insurance | 87 (2) | 63 (2) | |
| Other | 411 (10) | 259 (8) | |
| Unknown | 154 (4) | 110 (4) | |
| Length of stay (d)[a] | 38 (21, 66) | 19 (8, 19) | < 0.001 |
| Indication for ECMO | | | < 0.001 |
| Neonatal respiratory failure | 986 (24) | 236 (8) | |
| Congenital diaphragmatic hernia | 475 (11) | 549 (18) | |
| Neonatal cardiac arrest | 417 (10) | 555 (18) | |
| Neonatal cardiac disease | 590 (14) | 531 (17) | |
| Pediatric respiratory failure | 511 (12) | 394 (13) | |
| Pediatric cardiac arrest | 636 (15) | 582 (19) | |
| Pediatric cardiac disease | 576 (14) | 284 (9) | |
| Year of ECMO | | | 0.02 |
| 2004–2007 | 1,858 (44) | 1,473 (47) | |
| 2008–2011 | 2,333 (56) | 1,658 (53) | |
| Center volume (average ECMO cases/yr) | | | 0.01 |
| Low (0–19) (15 hospitals) | 619 (15) | 539 (17) | |
| Medium (20–49) (22 hospitals) | 2,909 (69) | 2,137 (68) | |
| High (≥ 50) (three hospitals) | 663 (16) | 455 (15) | |

ECMO = extracorporeal membrane oxygenation.
[a]Data presented as median (interquartile ranges).

**TABLE 2. Patient Characteristics by Center Extracorporeal Membrane Oxygenation Volume**

| Characteristic | Low *n* = 1,158 | Medium *n* = 5,046 | High *n* = 1,118 | *p* |
|---|---|---|---|---|
| Overall mortality | 539 (47) | 2,137 (42) | 455 (41) | 0.01 |
| Neonatal ECMO (< 31 d) | *n* = 682 (59) | *n* = 3,050 (60) | *n* = 607 (54) | |
| Indication for ECMO | *n* (%) | *n* (%) | *n* (%) | < 0.001 |
| Respiratory failure | 188 (28) | 885 (29) | 149 (25) | |
| Congenital diaphragmatic hernia | 153 (22) | 724 (24) | 147 (24) | |
| Cardiac disease | 202 (30) | 792 (26) | 127 (21) | |
| Cardiac arrest | 139 (20) | 649 (21) | 184 (30) | |
| Neonatal mortality | 320 (47) | 1,292 (42) | 259 (43) | 0.09 |
| ECMO year | | | | 0.001 |
| 2004–2007 | 370 (54) | 1,459 (48) | 268 (44) | |
| 2008–2011 | 312 (46) | 1,591 (52) | 339 (56) | |
| Length of stay (d)[a] | 32 (16, 62) | 31 (17, 58) | 31 (16, 60) | 0.67 |
| Pediatric ECMO | *n* = 476 (41) | *n* = 1,996 (40) | *n* = 511 (46) | |
| Indication for ECMO | *n* (%) | *n* (%) | *n* (%) | 0.11 |
| Respiratory failure | 159 (33) | 580 (29) | 166 (33) | |
| Cardiac disease | 120 (25) | 603 (30) | 137 (27) | |
| Cardiac arrest | 197 (41) | 813 (41) | 208 (41) | |
| Pediatric mortality | 219 (46) | 845 (42) | 196 (38) | 0.05 |
| ECMO year | | | | 0.08 |
| 2004–2007 | 211 (44) | 797 (40) | 226 (44) | |
| 2008–2011 | 265 (56) | 1,199 (60) | 285 (56) | |
| Length of stay (d)[a] | 23 (9, 47) | 28 (11, 56) | 26 (13, 47) | 0.04 |

ECMO = extracorporeal membrane oxygenation.

however, this is the first large evaluation of case-mix-adjusted pediatric ECMO volume and mortality.

Numerous studies have suggested an inverse relationship between surgical volume and mortality (12, 23). Bucher et al (14) describe the positive impact of volume on in-hospital mortality in infants with CDH also using the PHIS database. Several reports found an association between small surgical volume and increased mortality (15, 24, 25). In addition, recent reports have found an increasingly complex relationship with decreased mortality overall and the greatest difference in survival shown in the most complex conditions (26, 27). ELSO does suggest that ECMO centers perform a minimum of six ECMO cases annually (28); however, this is based on expert opinion.

For our study, ECMO indications were based on diagnosis codes and age as PHIS does not have data regarding specific indication for ECMO. Centers differed both in annual case volume and case-mix. Survival with ECMO support differs by indication for cardiorespiratory failure with the lowest mortality among neonates with respiratory failure and substantially higher mortality for patients with cardiac failure after surgery for congenital heart disease, cardiac arrest, and E-CPR (29–35). The recent 2012 ELSO international report of infants with CDH treated from 2004 to 2011 had an average annual survival of 46% mirroring our results (36). Likewise, patients with pediatric respiratory failure requiring ECMO had the same average annual survival, 56%, echoing the in-hospital mortality of our cohort with similar diagnoses (29). Sherwin et al (32) found a 69% mortality after stage 1 palliation in patients with HLHS supported by ECMO, which is similar to our subgroup analysis mortality (62%) that included cardiac arrest patients who may be classified as E-CPR cases in ELSO (19). Our neonatal cardiac arrest survival was 43% and pediatric cardiac arrest survival was 52%, which are similar to recent survival reported with E-CPR (44–47%) (33–35).

The post hoc analysis for an annual volume threshold of 22 cases is substantially greater than the ELSO recommendation of six cases per year. The PHIS hospitals are predominately large freestanding U.S. Children's Hospitals and likely are not representative of all ECMO centers. Furthermore, information

**TABLE 3. Center Volume and Mortality Risk Model**

| Factor | OR | 95% CI |
|---|---|---|
| Center volume | | |
| Low | 1 | Reference group |
| Medium | 0.86 | 0.75–0.98 |
| High | 0.75 | 0.63–0.89 |
| Indications for extracorporeal membrane oxygenation | | |
| Neonatal respiratory failure | 1 | Reference group |
| Congenital diaphragmatic hernia | 4.94 | 4.09–5.96 |
| Neonatal cardiac disease | 4.09 | 3.32–5.03 |
| Neonatal cardiac arrest | 6.21 | 4.97–7.76 |
| Pediatric respiratory failure | 3.28 | 2.70–3.99 |
| Pediatric cardiac disease | 2.54 | 2.04–3.16 |
| Pediatric cardiac arrest | 4.50 | 3.71–5.46 |
| Years treated | | |
| 2004–2007 | 1 | Reference group |
| 2008–2010 | 0.86 | 0.78–0.95 |

OR = odds ratio.

regarding the ECMO program structure at each hospital is not available. Some institutions have a centralized unit and medical supervision for patients on ECMO, whereas others offer ECMO in several different locations and medical supervision ranges from a core group to inclusion of all critical care physicians. Unfortunately, evaluation of whether survival is affected by only hospital volume versus provider volume and/or specific ICU (i.e., neonatal vs pediatric vs cardiac) volume was not possible. The consistent association of higher mortality at small volume centers should be validated by additional study. However, our findings lend support to the regionalized approach used in the United Kingdom although there is potential risk in transporting these critically ill ECMO patients.

Our study is limited by the retrospective and observational nature of the data and that many ECMO specific data were not prospectively collected. When using ICD-9-CM codes, many patients have overlapping codes and we chose to devise rules for diagnostic indications that mirrored definitions used in the ELSO registry to enable comparison. Our method certainly misclassifies some cases; however, our data regarding survival by indication are generally similar to other reports. For instance, neonates sometimes had respiratory codes appropriate for older ages; therefore, assumptions were necessary regarding age. However, analysis of a subset of pediatric patients with CDH, RSV, and HLHS (more clearly defined diagnoses), despite a smaller number in the cohort, found

**TABLE 4. Subgroup Analysis of Mortality and Center Volume**

| Variable | Congenital Diaphragmatic Hernia *n* = 1,016 *n* (%) | Respiratory Syncytial Virus *n* = 217 *n* (%) | Hypoplastic Left Heart Syndrome Stage 1 Palliation *n* = 522 *n* (%) | *p* |
|---|---|---|---|---|
| Age[a] (d) | 0 (0, 1) | 30 (1,654) | 0 (0, 1) | < 0.001 |
| Male | 596 (59) | 136 (63) | 305 (58) | 0.52 |
| Year of extracorporeal membrane oxygenation | | | | 0.01 |
| 2004–2007 | 500 (49) | 81 (37) | 245 (47) | |
| 2008–2011 | 516 (51) | 136 (63) | 277 (53) | |
| Cardiac arrest | 86 (9) | 71 (31) | 303 (58) | < 0.001 |
| Mortality | 544 (54) | 90 (42) | 321 (62) | < 0.001 |
| In-hospital mortality by center volume | *p* = 0.26 | *p* = 0.002 | *p* = 0.53 | |
| Low | *n* = 152 | *n* = 34 | *n* = 67 | |
| Number of deaths, *n* (%) | 87 (57) | 23 (68) | 45 (67) | |
| Medium | *n* = 718 | *n* = 132 | *n* = 366 | |
| Number of deaths, *n* (%) | 387 (54) | 48 (39) | 224 (61) | |
| High | *n* = 146 | *n* = 60 | *n* = 89 | |
| Number of deaths, *n* (%) | 70 (48) | 19 (32) | 52 (58) | |

[a]Data presented as median (interquartile ranges).

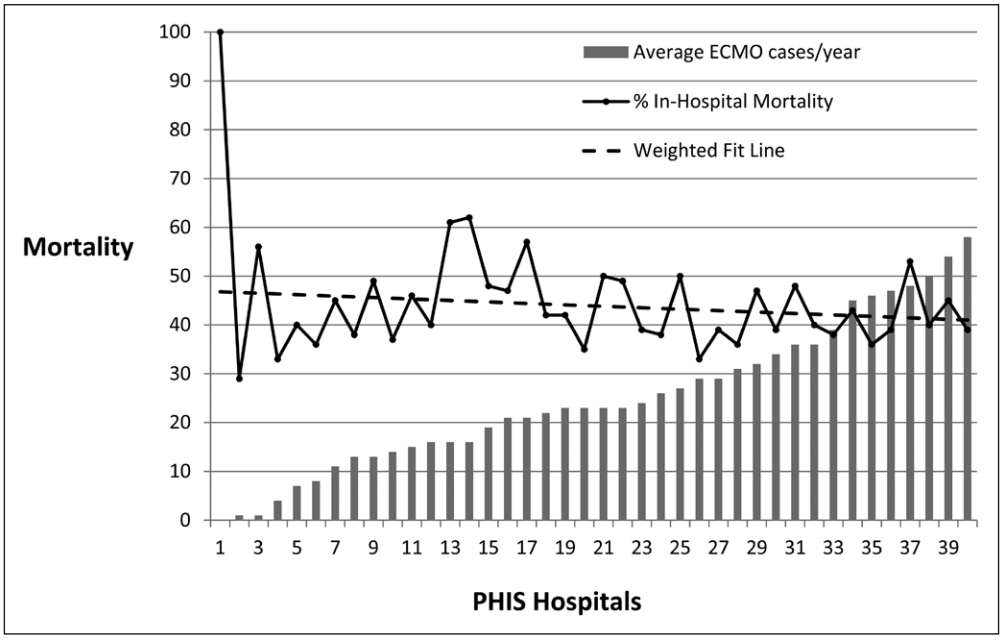


**Figure 2.** Average annual extracorporeal membrane oxygenation (ECMO) volume and mortality by center. Pediatric Health Information System (PHIS) centers are listed in the order of increasing average annual ECMO volume, shown by *bars*. The *solid line* represents overall in-hospital mortality by center. The *dashed line* is a weighted least squares regression line for the relationship between hospital ECMO volume ranking and in-hospital mortality. Each individual patient is weighted equally so the slope of the line is not disproportionately influenced by any single center. The downward slope shows decreasing mortality with increasing center volume.

consistently higher case-mix-adjusted mortality at the low-volume centers with an even stronger association.

Another limitation is in patients with cardiac arrest. This important diagnosis in the ECMO patient population could not be accurately placed in time relative to ECMO cannulation: prior to cannulation, during cannulation (E-CPR), or after going on ECMO. We were unable to more finely adjust for severity of illness with respect to progressive organ failure not captured by diagnosis coding. Finally, ECMO features such as mode of support, duration, and ECMO-related complications cannot be ascertained reliably with this data source. Severity of illness could not be fully adjusted for in this study, and therefore, our adjusted mortality evaluation has limitations. In addition, centers may have different thresholds for the application of ECMO support and inclusion and exclusion criteria likely vary. For example, some larger volume centers may have a lower threshold for institution of ECMO support due to experience and comfort with this advanced support. Additionally, larger centers may care for a higher complexity of patients and the estimated mortality benefit seen could have been underestimated. Clearly, these center differences could affect mortality, but we are unable to test for these potential differences with the data available.

Additionally, there are also reports that demonstrate patient-specific differences when comparing administrative databases and clinical databases (37). However, this imprecision is unlikely to substantially affect our primary analysis, which classified patients simply as having heart disease or cardiac surgery as an indication for ECMO rather than a specific anatomic diagnosis. The subset analysis did identify patients with HLHS palliated with a Norwood procedure. We used diagnosis and procedure codes that Pasquali et al (37) have shown to differ when comparing registry and administrative data for the Norwood procedure. When the Norwood procedure was identified in two databases, they found a 7% difference in patient number and an absolute mortality difference of 1.7%. We used the same codes to identify all patients in the PHIS database. When comparing mortality difference in Norwood patients supported by ECMO, we found a 9% mortality difference between high- (58%) and low- (67%) volume centers and expect that this relatively large mortality difference would likely persist even if some patients were misclassified by diagnosis/procedure because the mortality for all neonates with cardiac disease was 47%. Given these limitations, this is the first large multicenter report to describe this inverse relationship and many of our data did closely mirror those of other ECMO literature as well as the most recent ELSO July 2102 International Summary (36).

## CONCLUSIONS

These findings suggest that a minimum ECMO volume may be required to maximize ECMO program performance and achieve better survival. Regionalization of pediatric and neonatal ECMO centers when geographically possible may improve survival. Improved competence may enable centers to focus improvements and successfully care for higher risk cases. Additional investigation into a potential minimum volume for neonatal and pediatric ECMO is needed, and a minimum threshold of 20–22 cases per year may provide the framework for such continued evaluation. Merging information from complementary databases such as ELSO and PHIS would likely provide useful information to improve knowledge related to ECMO indications, complications, and survival.

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