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Extracorporeal membrane oxygenation in 61 neonates: Single-center experience

Running title: ECMO in neonates

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Conflict of Interest

The authors declare no conflict of interest.

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Abbreviations:

ARDS: acute respiratory distress syndrome

CDH: congenital diaphragmatic hernia

CHD: congenital heart disease

CPR: cardiopulmonary resuscitation

ECMO: extracorporeal membrane oxygenation

ELSO: Extracorporeal Life Support Organization

GA: gestational age

HIE: hypoxic ischemic encephalopathy

MAS: meconium aspiration syndrome

OI: oxygenation index

PPHN: persistent pulmonary hypertension of the newborn

SHD: survival to hospital discharge

VA: vein–artery cannulation

VV: vein–vein cannulation

Abstract

Background: There have been few reports regarding outcomes after extracorporeal membrane oxygenation (ECMO) in newborn Japanese infants.

Methods: A review of 61 neonates with ECMO through January 1995 at a single center was performed. ECMO was used in neonates with oxygenation index > 20 after conventional treatments. Background factors, such as etiology, vascular access mode (vein–vein [VV] or vein–artery [VA]), number of days with ECMO, and early ECMO (within 24 hours after birth), were analyzed in relation to outcome with respect to survival to hospital discharge (SHD).

Results: SHD was achieved in 35 (57%) infants, while the remaining 26 died during the hospital stay. Gestational age at birth was significantly higher and number of days with ECMO was significantly lower in SHD infants compared to those with adverse outcome (median, 4.0 vs. 5.5 days, respectively, $P = 0.008$). The SHD rate was significantly higher for those with VV than VA (78% [18/23] vs. 45% [17/38], respectively, $P = 0.016$), and for those with than without early ECMO (72% [28/39] vs. 32% [7/22], respectively, $P = 0.003$). The SHD rate was relatively high in neonates with meconium aspiration syndrome (MAS) (86% [12/14]), persistent pulmonary hypertension (PPHN) associated with hypoxic ischemic encephalopathy (HIE) (75% [6/8]), and emphysema (80% [4/5]). Stepwise logistic regression analysis identified two independent risk factors for SHD including early ECMO (OR [95%CI], 9.63 [2.47 – 37.6]) and ECMO length < 8 days (8.05 [1.94 – 33.5]).

Conclusions: Neonates having early ECMO and those with ECMO duration less than 8 days may have benefited from ECMO with respect to SHD.

Key words: extracorporeal life support, meconium aspiration syndrome, neonatal complications, respiratory failure, respiratory depression

Introduction

Extracorporeal membrane oxygenation (ECMO) can be used to provide temporary support during respiratory failure in newborns. This technique involves oxygenation of blood outside the body, thereby obviating the need for gas exchange in the lungs, and it can also aid cardiovascular circulation if necessary.[1] Significantly increased numbers of survivors were seen in two randomized trials of neonatal ECMO,[2,3] and active ECMO support was recommended for neonates with severe but potentially reversible respiratory failure. The United Kingdom Collaborative ECMO Trial incorporated an economic evaluation into its design from the outset and provided rigorous evidence of the cost-effectiveness of neonatal ECMO over a 7-year observation period.[5]

The Extracorporeal Life Support Organization (ELSO) was formed in 1989, as a group of centers using extracorporeal life support in the management of cardiopulmonary failure unresponsive to conventional medical and surgical therapies.[4] Until July 2011, nearly 51000 patients were registered at the ELSO and neonatal ECMO accounted for approximately 50% of all cases.[4] However, as no registry system has been available in Japan, reports on the outcomes of neonatal ECMO have been limited; to our knowledge, only one report is available in English addressing the outcomes of newborn Japanese infants treated with ECMO for congenital diaphragmatic hernia (CDH).[6] Accordingly, we retrospectively reviewed the outcomes of all newborn infants treated with ECMO over the past 21 years at a single center.

Methods

This study was conducted at Kagoshima City Hospital Neonatal Intensive Care Unit after receiving approval from the institutional review board of Kagoshima City Hospital.

Retrospective medical charts were reviewed for all newborn infants treated with ECMO during the 21-year study period between January 1995 and December 2015. ECMO was applied in newborn infants meeting all of following three criteria: (1) presence of severe respiratory failure defined as oxygenation index (OI) > 20 with lack of improvement despite > 12 hours of conventional treatments, including high frequency ventilation (since 1988), use of inhaled nitric oxide (since 1994), and use of catecholamine with or without volume loading; (2) etiologies of respiratory failure were considered to be treatable; and (3) a high mortality risk > 50% was anticipated without use of ECMO. Exclusion criteria included untreatable causes of respiratory failure (such as a congenital tracheal stenosis), bleeding diathesis associated with subgaleal hemorrhage, and severe congenital malformations. The OI was obtained from the following equation: $OI = FiO_2 \times \text{mean airway pressure (cm)} \times 100/\text{postductal } PaO_2$.

Information collected from medical charts included gestational age (GA, weeks) at birth, birthweight, Apgar scores at 1 and 5 minutes, underlying etiologies for respiratory failure, cannulation modes for ECMO (vein–vein [VV] or vein–artery [VA]), adverse

events associated with ECMO, and survival to hospital discharge (SHD). Early ECMO was defined as use of ECMO within 24 hours after birth.

ECMO Application

Vascular access was achieved by cannulation of the neck of neonates under open surgical procedure with general anesthesia. In cases with VV, single- and double-lumen catheters were inserted into the internal jugular vein cephalad and proximal (heart side) with catheter tip at the atrium, respectively, allowing drainage of blood from the both sides and blood return to the atrium. In cases with VA, two single lumen catheters were inserted into the internal jugular vein; one each cephalad and proximal (heart side), allowing drainage of blood from the both sides. Other single lumen catheter was inserted into the internal carotid artery proximal (heart side) with catheter tip at the aortic arch, allowing blood return to the aorta for the purpose of not only respiratory support but also circulatory support for infants with depressed cardiac function. Therefore, we preferred VA mode in patients with circulatory problems, such as hypotension and low cardiac motility on ultrasound study. VV blood flows of 60 – 80 mL/kg/min and VA blood flows rate of 80 – 100 mL/kg/min were used. Nafamostat mesilate was used for anticoagulation and activated clotting time of 200 – 250 s was maintained. Monitors were designed to measure circuit function and to alert the operator to abnormal conditions using four pressure sensors installed within the circuit.

Statistical analysis

Data are presented as the median (range). Statistical analyses were performed using the JMP10© statistical software package (SAS, Cary, NC). The Wilcoxon/Kruskal–Wallis method was used for comparison of medians. Fisher's exact probability test was used for comparison of categorical variables. Stepwise logistic regression analysis was performed to determine independent determinant factor for SHD. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

A total of 61 newborn infants underwent ECMO during the study period. No specific adverse events ascribed to ECMO occurred in the 61 infants. Of the 61 infants, 35 (57%) had SHD and the remaining 26 (43%) had adverse outcome, i.e., died before hospital discharge (Table 1). The GA at birth was significantly higher for SHD infants than those with adverse outcome (Table 1, Fig. 1), but birthweight and Apgar scores did not differ significantly between the two groups divided by outcome.

Underlying etiologies of respiratory failure included CDH (n = 16), meconium aspiration syndrome (MAS, n = 14), persistent pulmonary hypertension of the newborn (PPHN, n = 8) associated with hypoxic ischemic encephalopathy (HIE), sepsis (n = 7), emphysema (n = 5), and congenital heart disease (CHD, n = 4), and others (n = 7) (Table 1).

ECMO was used in 41 (67%) and 20 infants (37%) in 1995 – 2004 and 2005 – 2015, respectively. Vascular access was VV in 23 infants (38%) and VA in 38 infants (62%). Of the 61 infants with ECMO, 41 (67%) and 20 (33%) were born in years through 1995 – 2004 (period A) and 2005 – 2015 (period B), respectively (Table 1). Procedures for ECMO did not change over time. Although most background factors did not change significantly over time, the fraction of MAS infants appeared to decrease from 27% (11/41) in period A to 15% [3/20] in period B ($P = 0.353$) (data not shown). Experience of ECMO was considered as a determinant factor for SHD. However SHD rate did not differ significantly between the period A and period B (51% [21/41] vs. 70% [14/20], $P = 0.182$).

SHD rates according to etiologies were as follows; 31% (5/16) for CDH, 86% (12/14) for MAS, 75% (6/8) for PPHN and HIE, 43% (3/7) for sepsis, 80% (4/5) for emphysema, 25% (1/4) for CHD, and 57% (4/7) for others. Number of days with ECMO was significantly lower for infants with than without SHD (Table 1). The SHD rate was significantly higher for infants with than without early ECMO (72% [28/39] vs. 32% [7/22], respectively, $P = 0.003$), for those with than without VV mode (78% [18/23] vs. 45% [17/38], respectively, $P = 0.016$) (Table 1, Fig. 2). As many as 94% (15/16) of infants with both early ECMO and VV mode achieved SHD, while only 27% (4/15) of those with neither early ECMO nor VV mode did so ($P = 0.000$) (Fig. 2).

No optimal cut-off values were identified for differentiation of infants with and without SHD using the receiver operating characteristic curve in continuous variables of GA at birth, birthweight and number of days of ECMO. However, SHD rate was 61% [33/54] vs. 29% [2/7], $P = 0.030$ (with Fisher's exact test), for term (GA ≥ 37 weeks) and preterm infants, respectively, 64% [33/52] vs. 22% [2/9], $P = 0.125$, for those with birthweight ≥ 2500 g and < 2500 g, respectively, and 67% [29/43] vs. 33% [6/18], $P = 0.022$, for those with ECMO duration of < 8 days and ≥ 8 days, respectively. Then, stepwise logistic regression analysis (Wald) was performed after entering 7 factors including birthweight ≥ 2500 g (yes, no), GA at birth ≥ 37 weeks (yes, no), presence of CDH (yes, no), presence of MAS (yes, no), VV cannulation (yes, no), early ECMO (yes, no), and ECMO duration < 8 days (yes, no). The analysis identified two independent risk factors for SHD, giving early ECMO and ECMO duration of < 8 days OR (95%CI) of 9.63 (2.47 – 37.6) and OR of 8.05 (1.94 – 33.5), respectively.

Indeed, SHD rate was 88% (23/26) for infants with early ECMO and ECMO duration < 8 days. In two groups divided by the use of early ECMO, only frequency of birthweight ≥ 2500 g differed significantly between infants with vs. without early ECMO (95% [37/39] vs. 68% [15/22], respectively). In two groups divided by the ECMO duration of < 8 days, only frequency of CDH differed significantly between infants with vs. without ECMO duration of < 8 days (14% [6/43] vs. 56% [10/18], respectively). Although the birthweight ≥ 2500 g and CDH were confounding factors in this study, SHD rate was 91% (20/22) for infants without CDH, but with birth weight ≥ 2500 g, early ECMO, and ECMO duration < 8 days.

Discussion

This study demonstrated that among newborn infants treated with ECMO, SHD was likely to occur in those treated by ECMO within 24 hours after birth and in those with early weaning from ECMO (ECMO duration < 8 days).

Organ dysfunction score before ECMO is correlated with survival in adult patients with acute respiratory distress syndrome (ARDS).[10] Late ECMO application at and after age 7 days is a risk factor for adverse outcome of neonatal ECMO.[11] As it was considered that recovery from the disease became difficult with increasing time of hypoxemia, ECMO was initiated early (within 24 hours after birth) in 64% (39/61) of newborn infants when they were refractory to conventional treatments in this study. Although not in the field of neonatal intensive care, there are promising data for the early use of ECMO in acute hypoxemic respiratory failure, cardiac arrest, and cardiogenic shock.[8] For example, a literature review regarding the effects of ECMO on SHD rate in patients with influenza (H1N1) infection concluded that "ECMO is feasible and effective in patients with acute lung injuries due to H1N1 infection."[7] In a prospective observational study on the use of ECMO for patients aged 18 – 75 years with in-hospital cardiac arrest of cardiac origin undergoing cardiopulmonary resuscitation (CPR) of more than 10 minutes compared with patients receiving conventional CPR,[9] CPR with ECMO showed both short- and long-term survival benefits over conventional CPR. In a retrospective review of 65 patients with severe ARDS treated by ECMO,[10] 31 (48%) survivors had shorter durations of mechanical ventilation before ECMO (53 vs. 112 hours). In our population, early ECMO within 24 hours after birth was associated with higher SHD rate (72% [28/39] among early ECMO users vs. 32% [7/22] among non-early ECMO users) and was an independent risk factor for SHD; those with early ECMO had 9.6-fold higher chance of SHD independently of other factors. This supported our policy, i.e., the early use of ECMO when refractory to conventional treatments.

In our setting, VV and VA modes were used in 38% and 62% of 61 newborn infants, respectively and the SHD rate was significantly higher in the former than the latter (78% [18/23] vs. 45% [17/38], respectively), consistent with the 2012 ESLO registry report[4] in which VA was the predominant mode (72%) in neonatal ECMO with a higher survival rate in VV than VA mode of ECMO for respiratory failure (84% vs. 71%, respectively). However, the vascular access mode was a confounding factor and not an independent risk factor for SHD in this study.

In this study, the GA at birth was significantly higher for infants with than without SHD, consistent with a previous report by Ramachandrappa *et al.*[12] in which 2135 late preterm (GA at birth, 34-0/7 – 36-6/7), 3119 early-term (37-0/7 – 38-6/7), and 9274 full-term (39-0/7 – 42-6/7) infants registered at the ELSO from January 1986 to December 2006 were analyzed. GA at birth was a highly significant predictor of mortality, with mortality rates of 26%, 18%, and 11% for late preterm, early-term, and full-term, respectively.[12] In addition, they reported that late preterm infants had longer runs on ECMO, partly consistent with the results of the present study, although the

number of days with ECMO was not specified in their report.[12] In this study, the number of days with ECMO was significantly lower in SHD infants compared to those with adverse outcome (4.0 vs. 5.5 days, respectively). The average was reported as 7 days in a 2012 ELSO registry report.[4] Multivariate logistic regression analysis revealed that the short ECMO duration for less than 8 days, but not term delivery was an independent determinant for SHD in this study; those with ECMO duration for less than 8 days had 8.0-fold higher chance of SHD independently of other factors.

In our series of ECMO patients, overall SHD rate was 57% (35/61), which was somewhat poorer than that of 68% (21448/31327) in the neonatal ECMO registered at the ELSO through July 2012. This was mainly due to poorer outcome of CDH infants in this study compared to the 2012 ELSO registry report[4]; SHD rate was only 31% (5/16) for CDH in this study, while it was approximately 50% in the 2012 ELSO registry report. Among newborn Japanese CDH infants treated with ECMO, survival to more than 90 days after birth was reported in 37% (16/37) of isolated CDH infants without other anomalies,[6] consistent with the value of 36% (5/14) in the present study. These observations suggested that revision of indications for ECMO in CDH is required in Japan. Our SHD rates for MAS (86% [12/14]) and PPHN associated with HIE (75% [75%]) were comparable to those in the ELSO report (94% and 77%, respectively).[4] Despite having the best outcome, use of ECMO for MAS was shown to have decreased in the ELSO report[4] as well as in this study. This may have been due to improvements in ventilatory techniques, equipment, and therapeutics.[13,14]

We reported experience with ECMO in 61 newborn Japanese infants born during the 21-year period from January 1995. Overall SHD rate was unsatisfactory, 57% (35/61), which was mainly due to poorer outcome for CDH infants that had a low SHD rate of 31% (5/16). However, SHD rates of 86% (12/14) for MAS, 75% (6/8) for PPHN associated with HIE, and 80% (4/5) for emphysema were comparable to those in the 2012 ELSO registry report.[4] We emphasized that the early use of ECMO within 24 hours after birth was effective in leading to SHD independently of other factors and showed that infants requiring ECMO more than 7 days were less likely to have SHD independently of other factors.

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Conflict of Interest

The authors declare no conflict of interest.

Author contribution

E.H., S.I., and H.M. designed the study, T.T., Y.M., T.K., C.I., H.N., M.K., T.Y., T.K., and M.K. perforemd data collection, K.C. helped to perform data analysis, and H.M. helped to draft the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1 Association between gestational age at birth, duration of ECMO, and survival to hospital discharge (SHD)

Figure 2 Association between early ECMO, VV mode, and SHD rate

A, consisted of 5 cases of MAS, 4 of PPHN associated with HIE, 3 of emphysema, 1 of CHD, and 2 of other etiologies. B, consisted of 4 cases of CDH, 6 of MAS, 2 of sepsis, and 1 of other etiology. C, consisted of one case each of MAS, emphysema, and other etiology. D, consisted of one case of CDH, 2 of PPHN associated with HIE, and one of sepsis.

Fig.1

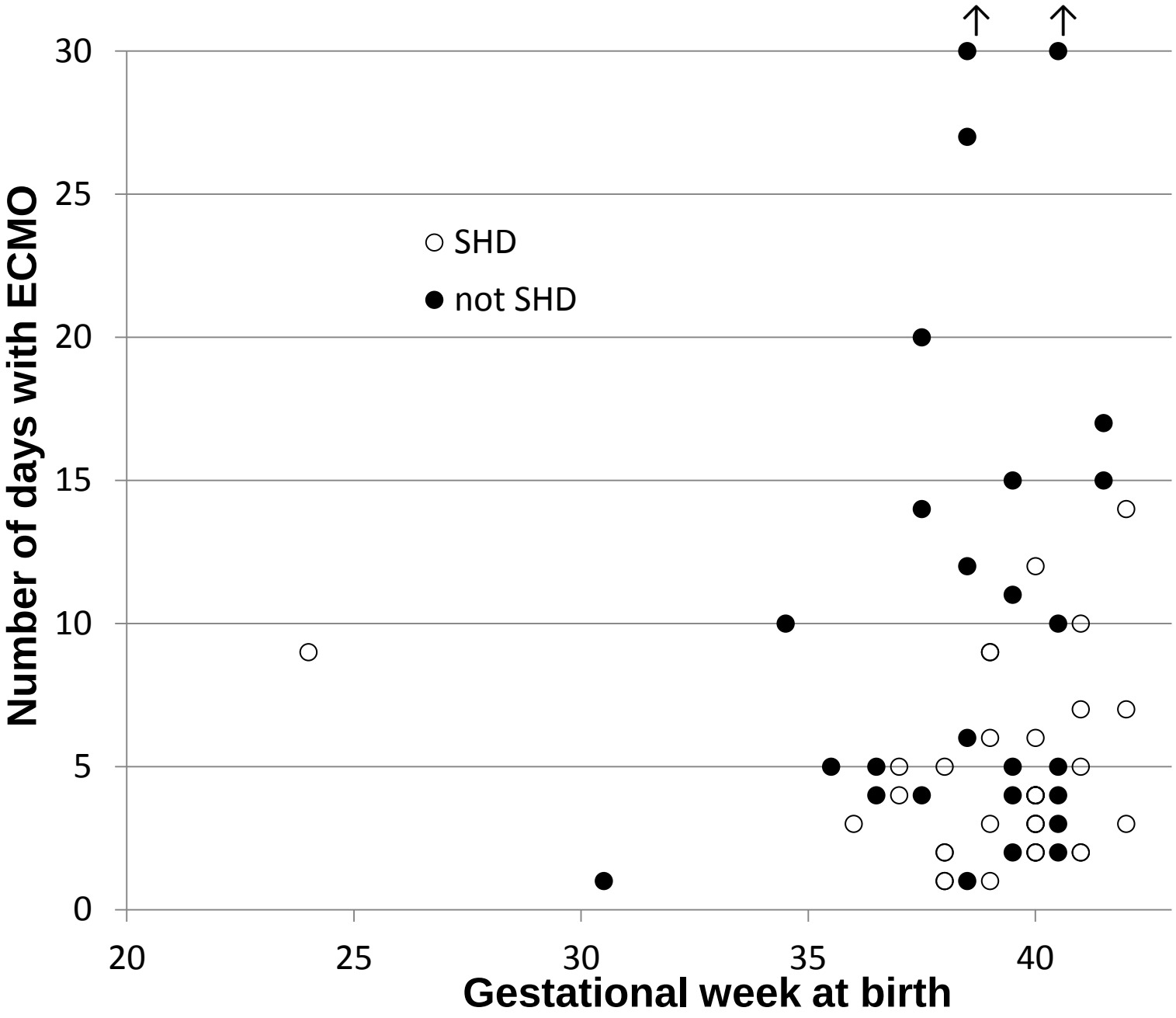

Number of days with ECMO
30
25
20
15
10
5
0
SHD
not SHD
20
25
30
35
40
Gestational week at birth

Fig. 2

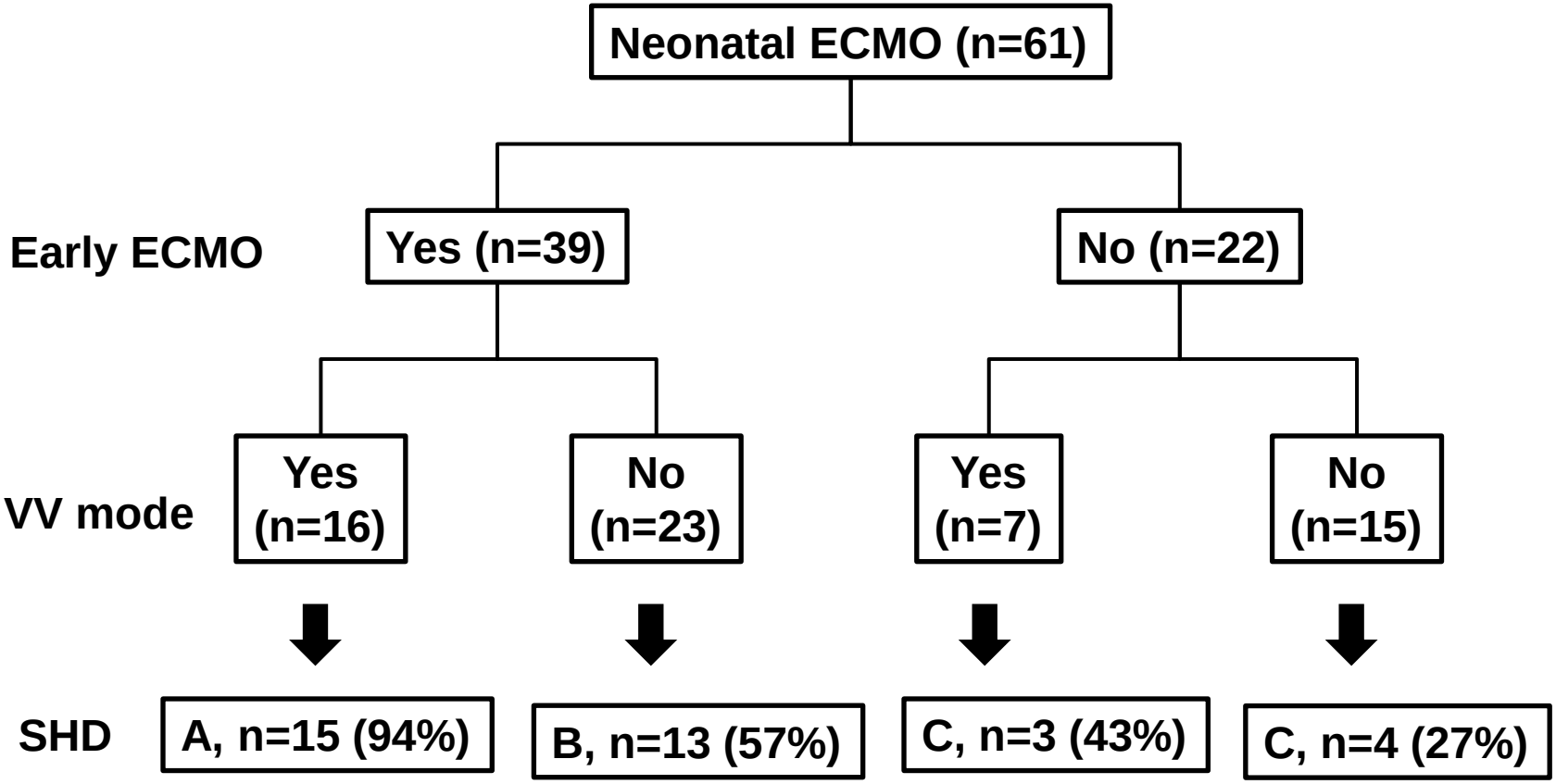

Neonatal ECMO (n=61)
Early ECMO
Yes (n=39)
No (n=22)
VV mode
Yes (n=16)
No (n=23)
Yes (n=7)
No (n=15)
SHD
A, n=15 (94%)
B, n=13 (57%)
C, n=3 (43%)
C, n=4 (27%)

Table 1 Factors associated with survival to hospital discharge (SHD)

	SHD		
	Yes (n=35)	No (n=26)	P-value
Background			
Gestational week at delivery	40 (24 - 42)	38.5 (30 - 41)	0.012
Birthweight (kg)	3.08 (0.63 – 4.33)	2.73 (2.03 – 4.45)	0.094
Apgar score at 1 min	4.5 (0 - 9)	6 (1 - 9)	0.471
Apgar score at 5 min	6 (0 - 10)	6 (1 - 10)	0.558
Underlying etiologies			
CDH (n=16)	5 (14%)	11 (42%)	0.014
MAS (n=14)	12 (34%)	2 (7.7%)	0.015
PPHN and HIE (n=8)	6 (17%)	2 (7.7%)	0.448
Sepsis (n=7)	3 (8.6%)	4 (15%)	0.446
Emphysema (n=5)	4 (11%)	1 (3.8%)	0.382
CHD (n=4)	1 (2.9%)	3 (12%)	0.303
Others (n=7)	4 (11%)	3 (12%)	1.000
ECMO application			
Year			
Period A (1995-2004, n=41)	21 (60%)	20 (77%)	0.164
Period B (2005-2015, n=20)	14 (40%)	6 (23%)	
Cannulation (vascular access)			
VV (n=23)	18 (51%)	5 (19%)	0.010
VA (n=38)	17 (49%)	21 (81%)	
Early ECMO			
Yes (n=39)	28 (80%)	11 (42%)	0.003
No (n=22)	7 (20%)	15 (58%)	
Duration (day)	4 (1 - 14)	5.5 (1 - 47)	0.008

Data are presented as median (range) or number of infants. MAS, meconium aspiration syndrome; CDH, congenital diaphragmatic hernia; CHD, congenital heart diseases; HIE, hypoxic ischemic encephalopathy; PPHN, persistent pulmonary hypertension of the newborn.