Characteristics of Neonates with Cardiopulmonary Disease Who Experience Seizures: A Multicenter Study

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Objective To compare key seizure and outcome characteristics between neonates with and without cardiopulmonary disease.

Study design The Neonatal Seizure Registry is a multicenter, prospectively acquired cohort of neonates with clinical or electroencephalographic (EEG)-confirmed seizures. Cardiopulmonary disease was defined as congenital heart disease, congenital diaphragmatic hernia, and exposure to extracorporeal membrane oxygenation. We assessed continuous EEG monitoring strategy, seizure characteristics, seizure management, and outcomes for neonates with and without cardiopulmonary disease.

Results We evaluated 83 neonates with cardiopulmonary disease and 271 neonates without cardiopulmonary disease. Neonates with cardiopulmonary disease were more likely to have EEG-only seizures (40% vs 21%, $P < .001$) and experience their first seizure later than those without cardiopulmonary disease (174 vs 21 hours of age, $P < .001$), but they had similar seizure exposure (many-recurrent electrographic seizures 39% vs 43%, $P = .27$). Phenobarbital was the primary initial antiseizure medication for both groups (90%), and both groups had similarly high rates of incomplete response to initial antiseizure medication administration (66% vs 68%, $P = .75$). Neonates with cardiopulmonary disease were discharged from the hospital later (hazard ratio 0.34, 95% CI 0.25-0.45, $P < .001$), although rates of in-hospital mortality were similar between the groups (hazard ratio 1.13, 95% CI 0.66-1.94, $P = .64$).

Conclusion Neonates with and without cardiopulmonary disease had a similarly high seizure exposure, but neonates with cardiopulmonary disease were more likely to experience EEG-only seizures and had seizure onset later in the clinical course. Phenobarbital was the most common seizure treatment, but seizures were often refractory to initial antiseizure medication. These data support guidelines recommending continuous EEG in neonates with cardiopulmonary disease and indicate a need for optimized therapeutic strategies. *(J Pediatr 2021;■:1-11).*

S eizures are a well-documented manifestation of neonatal brain dysfunction and injury, often resulting from hypoxic-ischemic injury (HIE), ischemic stroke, intracranial hemorrhage, and central nervous system infection.[1-3] Current management practices are based mostly upon data collected in neonates with acute symptomatic seizures because of these well-characterized primary neurologic disorders. Seizures also occur in neonates with cardiopulmonary diseases, defined herein as congenital heart disease (CHD), congenital diaphragmatic hernia (CDH), and exposure to extracorporeal membrane oxygenation (ECMO). Neonates with cardiopulmonary disease may have abnormal brain development, abnormal brain function because of

CDH	Congenital diaphragmatic hernia
cEEG	Continuous electroencephalography
CHD	Congenital heart disease
ECMO	Extracorporeal membrane oxygenation
EEG	Electroencephalographic
HIE	Hypoxic-ischemic encephalopathy
ICU	Intensive care unit
NSR-1	Neonatal Seizure Registry-1

cardiopulmonary pathophysiology, and complications associated with required life-sustaining technology.[4-9] These conditions may result in acute acquired brain injuries that manifest as seizures. Single-center studies of neonates with cardiopulmonary disease have reported clinical and electrographic seizure incidence ranging from 1% to 20%.[10-17] Thus, consensus-based guidelines recommend performing a minimum of 24 hours of continuous electro-encephalography (cEEG) monitoring for neonates with car-diopulmonary disease.[18] However, few data are available regarding distinct seizure presentation or treatment chal-lenges in neonates with cardiopulmonary disease. If seizure characteristics differ between neonates with and without cardiopulmonary disease, then more specific cEEG and seizure management strategies may be necessary to optimize outcomes.

In this study, we aimed to compare the clinical presenta-tion, seizure characteristics, cEEG strategies, seizure manage-ment, and outcomes in neonates with and without cardiopulmonary disease. We hypothesized that neonates with cardiopulmonary disease, compared with neonates without cardiopulmonary disease, would experience a comparably high incidence of electrographic seizures because of acute brain injury and that seizures would more often be refractory to first-line antiseizure medications.

Methods

The first cohort of the Neonatal Seizure Registry (NSR-1) was a prospective cohort of consecutive neonates (less than 44 weeks of postmenstrual age at the time of seizure onset) with clinical or electroencephalographic (EEG)-confirmed seizures enrolled at seven tertiary care pediatric hospitals from January 2013 to April 2015.[1,19-22] This cohort included neonates enrolled at 6 of the NSR-1 sites. These institutions adhere to the American Clinical Neurophysiology Society's guideline for cEEG in neonates,[18,23] which recommends cEEG for differential diagnosis of suspicious clinical events and screening for electrographic seizures for a minimum of 24 hours in high-risk neonatal populations. High-risk neonatal populations include those with acute etiologies such as encephalopathy, intracranial infection, and intracra-nial hemorrhage, and neonates with underlying cardiopul-monary diseases such as CHD requiring surgical repair with cardiopulmonary bypass or undergoing ECMO. Partici-pating sites received Institutional Review Board approval for the study, and a waiver of informed consent was granted.

Clinical and EEG data were abstracted from electronic medical records into a secure REDCap database.[24] Clinical data included (1) demographics; (2) cEEG characteristics (in-dications, age at onset, location); (3) seizure characteristics (exposure, semiology, timing); (4) seizure treatment (antisei-zure medication, dosing, therapeutic drug levels, seizure responsiveness); and (5) disposition (mortality, discharge on antiseizure medication). EEG data were acquired clinically according to American Clinical Neurophysiology Society guidelines[18,23] and analyzed by electroencephalographers at

each site. The clinical EEG reports were abstracted into the study database. All neonates had at least 1 EEG recorded. If multiple EEG studies were acquired during the study period, then data from subsequent EEG studies were also included in the database (EEG start and stop date/time, presence of elec-trographic seizures). EEG monitoring indication was re-corded only for the initial EEG performed on all neonates. Electrographic seizures were defined as a sudden and abnormal EEG event defined by a repetitive and evolving pattern with a minimum peak-to-peak voltage of 2 microvolts and duration of at least 10 seconds with (electroclinical) or without (EEG-only) concurrent clinical signs.[23] Electro-graphic seizure exposure was categorized as none, low (<7 sei-zures), many-recurrent (≥7 seizures), or status epilepticus (summed duration of seizures comprising ≥50% of any 1-hour epoch). EEG-only seizures were defined as seizures evident on EEG but without any identifiable clinical manifes-tation. The exact date and time of the initial clinical and/or electrographic seizure were recorded. The initial antiseizure medication loading dose was defined as the amount of medi-cation administered in mg/kg in the first bolus of the initial antiseizure medication, and the total loading dose was defined as the total amount of medication administered in mg/kg in the initial 72 hours of treatment with an antiseizure medica-tion. Incomplete response to initial antiseizure medication was defined as the occurrence of ≥1 electrographic seizure occurring >30 minutes after the initial loading dose of at least 20 mg/kg of phenobarbital, 15 mg/kg of phenytoin or fosphe-nytoin, or 40 mg/kg of levetiracetam.

Neonates were categorized as having or not having cardio-pulmonary disease. Neonates with cardiopulmonary disease were defined as those with CHD, CDH, or ECMO exposure. Neonates with cardiopulmonary disease were analyzed as those with CHD-only, CDH-only, ECMO-only, and multiple diagnoses (≥2 diagnoses of CHD, CDH, and/or ECMO). Pri-mary underlying seizure etiologies were not limited for neo-nates with cardiopulmonary disease to maximize the number of neonates included in the cohort, and included acute symp-tomatic etiologies such as HIE, ischemic stroke, intracranial hemorrhage, and intracranial infection. Neonates without cardiopulmonary disease were included if they had a primary seizure etiology of HIE, ischemic stroke, intracranial hemor-rhage, or intracranial infection without a comorbid cardio-pulmonary disease.

Statistical analyses were performed using Stata (StataCorp LLC) v 15.1. Standard descriptive statistics included fre-quencies and percentages to summarize categorical variables and median and IQRs to summarize continuous variables because of skewness in distribution. To compare cardiopul-monary disease and noncardiopulmonary disease cohorts or within the cardiopulmonary disease cohort across diag-nosis subgroups, the Pearson χ^2 or Fisher exact test (for vari-ables with ≤5 subjects per group) was used as appropriate to assess binary and nominal categorical variables, and the Kruskal Wallis test was used to assess continuous variables. For certain categorical variables (such as seizure etiology), individual tests of comparison were run between the

cardiopulmonary disease and non-cardiopulmonary disease groups for each response option. Cox proportional hazards model was used to assess the difference in time to death and time to hospital discharge between the 2 groups, with the estimated hazard ratio reported.

Results

Demographic and Clinical Characteristics

The cohort of 354 neonates included 83 neonates (23%) with cardiopulmonary disease and 271 neonates (77%) without cardiopulmonary disease. The cardiopulmonary disease cohort included 73 neonates (88%) with CHD, 5 neonates (6%) with CDH, and 26 neonates (31%) who received ECMO. Multiple cardiopulmonary disease diagnoses occurred in 20 neonates (24%), including 16 neonates (80%) with CHD and ECMO, 2 neonates (10%) with CDH and ECMO, 1 neonate (5%) with CHD and CDH, and 1 neonate (5%) with CHD, CDH, and ECMO. Table I provides clinical characteristics of the cardiopulmonary disease cohort.

Surgical intervention occurred in 48 out of 73 neonates (66%) with CHD at a median of 81 hours of age (IQR 35, 167). Among 48 neonates undergoing surgical repair, cardiopulmonary bypass was utilized in 29 neonates (60%) for a median duration of 95 minutes (IQR 76, 154), and deep hypothermic circulatory arrest was utilized in 12 neonates (25%) for a median duration of 38 minutes (IQR 35, 50). Among 5 neonates with CDH, 3 neonates (60%) underwent surgical intervention at a median of 58 hours of age (IQR 27, 94). Three neonates (60%) with CDH underwent ECMO, only 1 of whom underwent surgery. Among 26 neonates who received ECMO, 24 (92%) had veno-arterial ECMO, 1 (4%) had veno-venous ECMO, and 1 (4%) had unknown ECMO type. ECMO cannulation was in the neck for 14 out of 26 neonates (54%), chest for 11 out of 26 neonates (42%), and unknown for 1 out of 26 neonates (4%). ECMO cannulation occurred at a median of 176 hours of age (IQR 21, 507). The most common indication for ECMO use was CHD.

The cohort of 271 neonates without cardiopulmonary disease included 144 neonates (53%) with HIE, 55 neonates (20%) with ischemic stroke, 44 neonates (16%) with intracranial hemorrhage, and 28 neonates (10%) with intracranial infection. Table II compares the cardiopulmonary disease and noncardiopulmonary disease cohorts. Neonates with cardiopulmonary disease had a lower birthweight (3.1 vs 3.3 kg, $P = .06$), lower gestational age (38.6 vs 39.3 weeks, $P = .001$), and higher Apgar scores at 1 minute (7 vs 2, $P < .001$) and 5 minutes (8 vs 6, $P = .002$) compared with neonates without cardiopulmonary disease.

EEG Monitoring Characteristics

All neonates in both cohorts underwent cEEG monitoring because they were considered high-risk populations. Compared with neonates without cardiopulmonary disease, neonates with cardiopulmonary disease more often

Table I. Clinical characteristics of the cardiopulmonary disease cohort	
CHD cohort (n = 73)	
Prenatal diagnosis	36 (50%)
CHD defect	
Hypoplastic left heart syndrome	16 (22%)
Transposition of great arteries	7 (10%)
Other*	52 (71%)
Single ventricle pathology	30 (41%)
Surgical intervention completed	48 (66%)
Age at surgery (h of age)	81 [35, 167]
CPB utilized	29 (60%)
CPB duration (min)	95 [76, 154]
DHCA utilized	12 (25%)
DHCA duration (min)	38 [35, 50]
CDH cohort (n = 5)	
Prenatal diagnosis	5 (100%)
Surgical intervention completed†	3 (60%)
Age at surgery (h of age)	58 [27, 94]
Patch repair	2 (67%)
ECMO utilized	3 (60%)
ECMO cohort (n = 26)	
ECMO indications	
CHD	8 (31%)
CDH	3 (12%)
Intractable metabolic acidosis	2 (8%)
Inability to wean CPB	2 (8%)
PPHN	3 (12%)
Pulmonary hypoplasia	2 (8%)
Sepsis	2 (8%)
Other‡	15 (58%)
ECMO type	
Veno-arterial	24 (92%)
Veno-venous	1 (4%)
Unknown	1 (4%)
Cannulation site	
Chest	11 (42%)
Neck	14 (54%)
Unknown	1 (4%)
Age at surgery (h of age)	176 [21, 507]

CPB, cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest; *PPHN*, persistent pulmonary hypertension of the newborn.
Data are presented as n (%) or median [IQR].
*Individual neonates could have more than one diagnosis. Other CHD diagnoses included atrial septal defect, bicuspid aortic valve, cardiac rhabdomyomas, coarctation of the aorta with and without arch hypoplasia, congenital pulmonary airway malformation, double inlet left ventricle, Ebstein anomaly of the tricuspid valve, heterotaxy syndrome with a single ventricle, hypertrophic cardiomyopathy, levocardia, patent ductus arteriosus, patent foramen ovale, pulmonary atresia, pulmonary stenosis, small aortic and mitral anulus, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, truncus arteriosus, unbalanced atrioventricular septal defect, and ventricular septal defect.
†Two neonates with CDH died before undergoing repair of the defect.
‡Patients could have multiple indications. ECMO indications affecting only 1 patient per category are listed as 'Other' and included cardiac arrest, intractable shock, low cardiac output, lung mass, pneumothorax, respiratory failure, and meconium aspiration syndrome.

underwent cEEG in the cardiac intensive care unit (ICU) than the neonatal ICU (50% vs 0%; 47% vs 98%; $P < .001$) and had cEEG initiated later in their clinical course (141 vs 29 hours of age, $P < .001$). The cEEG indication varied between neonates with and without cardiopulmonary disease. Neonates with cardiopulmonary disease were less likely to be monitored for encephalopathy and/or suspicious clinical events, and they more likely to be monitored for "other" indications such as institutional cEEG protocols (clinical events with or without encephalopathy: 73% vs 98%; other: 24% vs 2%; $P < .001$). All neonates with and without cardiopulmonary disease had 1 EEG recorded. Of neonates with cardiopulmonary disease, 34 (41%) had a second EEG and

Table II. Comparison of demographic, EEG monitoring, seizure characteristics, seizure treatment, and outcomes between the cardiopulmonary disease and noncardiopulmonary disease cohorts

Variables	Cardiopulmonary disease cohort (n = 83)	Non-cardiopulmonary disease cohort (n = 271)	P value
Demographics			
Sex, female	36 (43%)	122 (45%)	.79
Gestational age (wk)	38.6 [37, 40]	39.3 [38, 40]	.001
Birth weight (kg)	3.1 [2.6, 3.5]	3.3 [2.8, 3.6]	.06
Apgar, 1 min	7 [3, 8]	2 [1, 7]	<.001
Apgar, 5 min	8 [6, 9]	6 [3, 9]	.002
EEG monitoring characteristics			
EEG location			<.001
Neonatal ICU	39 (47%)	265 (98%)	
Pediatric ICU	2 (2%)	5 (2%)	
Cardiac ICU	42 (50%)	0 (0%)	
Other	0 (0%)	1 (0.4%)	
EEG indication			<.001
Clinical events	40 (48%)	142 (52%)	
Encephalopathy	13 (16%)	72 (27%)	
Clinical events and encephalopathy	8 (10%)	53 (20%)	
Paralysis	2 (2%)	0 (0.0%)	
Other	20 (24%)	4 (2%)	
Age at start of EEG (h)	141 [53, 305]	29 [10, 68]	<.001
Seizure characteristics			
Primary seizure etiology			<.001
HIE	30 (36%)	144 (53%)	
Ischemic stroke	22 (26%)	55 (20%)	
Hemorrhage	12 (14%)	44 (16%)	
Infection	1 (1%)	28 (10%)	
Other*	18 (22%)	0 (0%)	
Clinical seizure prior to EEG monitoring	47 (57%)	188 (69%)	.03
Age at first seizure [clinical or EEG] (h)	173.7 [45.7, 339.1]	21.3 [9.7, 56.7]	<.001
EEG-only seizures present	33 (40%)	56 (21%)	<.001
EEG seizure exposure			.27
None	11 (13%)	40 (15%)	
Rare (<7)	15 (18%)	64 (24%)	
Many-recurrent (≥7)	32 (39%)	116 (43%)	
Status epilepticus	24 (29%)	48 (18%)	
Unknown	1 (1%)	3 (1%)	
Treatment characteristics			
Initial antiseizure medication			.03
Phenobarbital	69 (85%)	247 (92%)	
Phenytoin/fosphenytoin	2 (2%)	1 (0.4%)	
Levetiracetam	7 (9%)	7 (3%)	
Other	1 (1%)	1 (0.4%)	
N/A – no load given	2 (2%)	14 (5%)	
Antiseizure medication(s) administered[†]			
Benzodiazepine intermittent dose	10 (12%)	55 (20%)	.09
Benzodiazepine infusion	14 (17%)	26 (10%)	.07
Phenobarbital	76 (92%)	255 (94%)	.41
Phenytoin/fosphenytoin	28 (34%)	97 (36%)	.73
Levetiracetam	39 (47%)	81 (30%)	.004
Topiramate	3 (4%)	7 (3%)	.62
Vitamins[‡]	6 (7%)	7 (3%)	.08
Other antiseizure medication[§]	4 (5%)	3 (1%)	.03
Phenobarbital prior to EEG	20 (24%)	137 (51%)	<.001
Phenobarbital total loading dose (mg/kg)	40 [20, 50]	30 [20, 40]	.02
Highest phenobarbital level	45 [31, 59]	45 [35, 53]	.74
Phenytoin/fosphenytoin total loading dose (mg/kg)	20 [20, 30]	20 [20, 22]	.09
Levetiracetam total loading dose (mg/kg)	40 [20, 60]	40 [30, 60]	.48
Incomplete response to initial antiseizure medication loading dose	n = 77 51 (66%)	n = 261 178 (68%)	.75
Disposition			
Discharge or death on antiseizure medication	68 (82%)	183 (68%)	.01

(continued)

Table II. Continued

Variables	Cardiopulmonary disease cohort (n = 83)	Non-cardiopulmonary disease cohort (n = 271)	P value
Disposition			.01
Death	25 (30%)	37 (14%)	
Home	53 (64%)	193 (71%)	
Transfer	3 (4%)	25 (9%)	
Hospice	2 (2%)	12 (4%)	
Long-term care facility	0 (0%)	4 (2%)	
Age at death (d)	23 [12, 50]	5 [3, 18]	.001
Age at discharge (d)	37 [20, 63]	12 [9, 22]	<.001

N/A, not applicable.
Data are presented as n (%) or median [IQR].
*Other primary seizure etiologies include brain malformation (6 CHD, 1 CDH), inborn errors of metabolism (1 CHD), neonatal epilepsy (3 CHD), and other (5 CHD, 2 multi-diagnoses).
†Multiple antiseizure medications could be administered throughout the hospital course.
‡Vitamins include pyridoxine, folinic acid, and pyridoxal-5-phosphate.
§Other medications include acetazolamide, bumetanide, carbamazepine, lacosamide, lidocaine, oxcarbazepine, valproic acid, and other vitamins (calcitriol, calcium, magnesium, thiamine).

11 (13%) had a third EEG. Of neonates without cardiopulmonary disease, 71 (26%) had a second EEG and 20 (7%) had a third EEG.

Seizure Characteristics

The primary seizure etiology varied between the groups. Although HIE was the most common primary seizure etiology for neonates with and without cardiopulmonary disease, neonates with cardiopulmonary disease were more likely to have other etiologies as the primary seizure etiology (22% vs 0%, $P < .001$), including neonatal epilepsies (n = 3), brain malformations (n = 7), and metabolic disorders (n = 1). Neonates with cardiopulmonary disease were less likely to have clinical seizures prior to cEEG initiation (57% vs 69%, $P = .03$) and more likely to experience EEG-only seizures (40% vs 21%, $P < .001$). Further, neonates with cardiopulmonary disease experienced their first seizure, either clinical or electrographic seizures, later in their course (173.7 vs 21.3 hours of age, $P < .001$). Among neonates who experienced electrographic seizures, they were most often identified on the initial cEEG, including 64 out of 83 (77%) of neonates with cardiopulmonary disease and 220 out of 271 (81%) of neonates without cardiopulmonary disease. The yield of seizure detection on the second EEG was 32% (11 out of 34) for neonates with cardiopulmonary disease and 20% (14 out of 71) for neonates without cardiopulmonary disease. The yield of seizure detection on the third EEG was 27% (3 out of 11) for neonates with cardiopulmonary disease and 5% (1 out of 20) for neonates without cardiopulmonary disease. Electrographic seizure exposure did not vary significantly by the presence of cardiopulmonary disease, as neonates with and without cardiopulmonary disease had similarly high rates of many-recurrent electrographic seizures (39% vs 43%) and status epilepticus (29% vs 18%, $P = .27$). Notably, electrographic seizure exposure varied within the cardiopulmonary disease cohort ($P = .05$); neonates with ECMO and multiple cardiopulmonary disease diagnoses experienced higher rates of status epilepticus (43% and 45%, respectively). Neonates with CHD-only experienced many-recurrent seizures (42%) and the lone neonate with CDH-only did not experience any electrographic seizures

(0%). Table III provides within-group differences between the subgroups of neonates with cardiopulmonary disease (CHD, CDH, ECMO, and multiple diagnoses).

Seizure Treatment

Although phenobarbital was the most prescribed antiseizure medication in both cohorts, neonates with cardiopulmonary disease were more likely to receive levetiracetam as both the initial loading (9% vs 3%, $P = .03$) and as an administered antiseizure medication during the hospital course (47% vs. 30%, $P = .004$) compared with neonates without cardiopulmonary disease. Compared with neonates without cardiopulmonary disease, neonates with cardiopulmonary disease were less likely to receive phenobarbital prior to cEEG initiation (24% vs 51%, $P < .001$). Although neonates with cardiopulmonary disease ultimately received a higher total loading dose of phenobarbital (40 vs 30 mg/kg, $P = .02$), the 2 groups achieved comparable therapeutic drug levels (highest phenobarbital level of 45 mcg/mL for both groups, $P = .74$). Levetiracetam and (fos)phenytoin dosing was similar for both groups. Treatment response was similar for both groups, including high rates of incomplete response to initial loading antiseizure medication in neonates with and without cardiopulmonary disease (66% vs 68%, $P = .75$).

Short-Term Outcomes

Although the raw rates of in-hospital mortality varied between the cohorts (30% in cardiopulmonary disease cohort vs 14% in noncardiopulmonary disease cohort), neonates with and without cardiopulmonary disease had similar rates of in-hospital death per time when accounting for their differential hospitalization durations (hazard ratio 1.13, 95% CI 0.66-1.94, $P = .64$). Within the cardiopulmonary disease cohort, the high rates of in-hospital mortality were primarily driven by neonates who required ECMO (71% mortality) or had multiple cardiopulmonary disease diagnoses (65% mortality) (Table III). Overall, 13% of neonates with CHD died and no neonates with a sole diagnosis of CDH died. The rate of hospital discharge was about 70% lower for neonates with cardiopulmonary disease compared to neonates without cardiopulmonary disease (hazard ratio 0.34, 95% CI 0.25-

Table III. EEG monitoring, seizure characteristics, seizure treatment, and outcomes of the cardiopulmonary disease cohort

	CHD (n = 55)	CDH (n = 1)	ECMO (n = 7)	Multiple diagnoses* (n = 20)
Demographics				
Sex, female	24 (44%)	1 (100%)	5 (71%)	6 (30%)
Gestational age (wk)	39 [38, 40]	39 [n/a]	36.7 [27, 40]	38.2 [37, 39]
Birth weight (kg)	3.1 [2.6, 3.4]	2.62 [n/a]	2.7 [0.7, 3.2]	3.3 [2.9, 3.7]
Apgar score, 1 min	7 [4, 8]	1 [n/a]	2 [1, 8]	6 [4, 8]
Apgar score, 5 min	8 [7, 9]	5 [n/a]	5 [3, 9]	8 [6, 8]
EEG monitoring characteristics				
EEG location				
Cardiac ICU	27 (49%)	0 (0%)	1 (14%)	14 (70%)
Neonatal ICU	27 (49%)	1 (100%)	5 (71%)	6 (30%)
Pediatric ICU	1 (2%)	0 (0%)	1 (14%)	0 (0%)
EEG indication				
Clinical events	33 (60%)	1 (100%)	0 (0%)	6 (30%)
Encephalopathy	5 (9%)	0 (0%)	2 (29%)	6 (30%)
Clinical events and encephalopathy	6 (11%)	0 (0%)	2 (29%)	0 (0%)
Paralysis	7 (0%)	0 (0%)	1 (14%)	1 (5%)
Other	11 (20%)	0 (0%)	2 (29%)	7 (35%)
Age at EEG onset (h)	118 [52, 221]	260 [n/a]	87 [6, 2887]	209 [81, 376]
Seizure characteristics				
Primary seizure etiology				
HIE	15 (27%)	0 (0%)	6 (86%)	9 (45%)
Ischemic stroke	16 (29%)	0 (0%)	0 (0%)	6 (30%)
Hemorrhage	8 (15%)	0 (0%)	1 (14%)	3 (15%)
Infection	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Other[†]	15 (27%)	1 (100%)	0 (0%)	2 (10%)
Clinical seizure prior to EEG	36 (65%)	1 (100%)	3 (43%)	7 (35%)
Age at first seizure [clinical or EEG] (h)	120 [29, 240]	240 [n/a]	97 [6, 2887]	289 [208, 491]
EEG-only seizures present	19 (35%)	0 (0%)	4 (57%)	10 (50%)
EEG seizure exposure				
None	9 (16%)	1 (100%)	0 (0%)	1 (5%)
Rare (<7)	11 (20%)	0 (0%)	2 (29%)	2 (10%)
Many-recurrent (≥7)	23 (42%)	0 (0%)	1 (14%)	8 (40%)
Status epilepticus	12 (22%)	0 (0%)	3 (43%)	9 (45%)
Unknown	0 (0%)	0 (0%)	1 (14%)	0 (0%)
Treatment characteristics				
Initial loading antiseizure medication				
Phenobarbital	45 (82%)	1 (100%)	5 (71%)	18 (90%)
Phenytoin/fosphenytoin	1 (2%)	0 (0%)	0 (0%)	1 (5%)
Levetiracetam	6 (11%)	0 (0%)	1 (14%)	0 (0%)
Other	1 (2%)	0 (0%)	0 (0%)	0 (0%)
N/A – no load	2 (4%)	0 (0%)	1 (14%)	1 (5%)
Antiseizure medication(s) administered[‡]				
Benzodiazepine intermittent dose	6 (11%)	0 (0%)	0 (0%)	4 (20%)
Benzodiazepine infusion	7 (13%)	0 (0%)	1 (14%)	6 (30%)
Phenobarbital	50 (91%)	1 (100%)	6 (86%)	19 (95%)
Phenytoin/fosphenytoin	16 (29%)	0 (0%)	2 (29%)	10 (50%)
Levetiracetam	25 (45%)	0 (0%)	4 (57%)	10 (50%)
Topamax	3 (5%)	0 (0%)	0 (0%)	0 (0%)
Vitamins[§]	6 (11%)	0 (0%)	0 (0%)	0 (0%)
Other antiseizure medication[¶]	2 (4%)	0 (0%)	1 (14%)	1 (5%)
Phenobarbital prior to EEG	13 (24%)	1 (100%)	1 (14%)	5 (25%)
Phenobarbital total loading dose (mg/kg)[**]	40 [20, 50]	20 [n/a]	35 [20, 50]	40 [35, 60]
Highest phenobarbital level	51 [32, 64]	29 [n/a]	43 [42, 51]	31 [22, 58]
Phenytoin/fosphenytoin total loading dose (mg/kg or mg phenytoin equivalent /kg)	20 [20, 30]	n/a	29 [27, 30]	20 [20, 34]
Levetiracetam total loading dose (mg/kg)	25 [20, 50]	n/a	40 [30, 60]	60 [40, 60]
Incomplete response to initial antiseizure medication loading dose	31 (61%)	0 (0%)	4 (67%)	16 (84%)
Disposition				
Discharge or death on antiseizure medication	48 (87%)	1 (100%)	3 (43%)	16 (80%)
Disposition				
Death	7 (13%)	0 (0%)	5 (71%)	13 (65%)
Home	45 (82%)	1 (100%)	2 (29%)	5 (25%)
Transfer	1 (2%)	0 (0%)	0 (0%)	2 (10%)
Hospice	2 (7%)	0 (0%)	0 (0%)	0 (0%)
Long-term care facility	0 (0%)	0 (0%)	0 (0%)	0 (0%)

(continued)

Table III. Continued

	CHD (n = 55)	CDH (n = 1)	ECMO (n = 7)	Multiple diagnoses* (n = 20)
Age at death (d)	7 [5, 60]	n/a	60 [21, 125]	23 [13, 35]
Age at discharge (d)	33 [19, 57]	107 [n/a]	62 [40, 84]	61 [37, 63]

N/A, not applicable.

Data are presented as n (%) or median [IQR].

*Multiple diagnoses include 16 CHD + ECMO, 2 CDH + ECMO, 1 CHD + CDH, 1 CHD + CDH + ECMO.

†Other primary seizure etiologies include brain malformation (6 CHD, 1 CDH), inborn errors of metabolism (1 CHD), neonatal epilepsy (3 CHD), and other (5 CHD, 2 multi-diagnoses).

‡Multiple antiseizure medications could be administered throughout the hospital course.

§Vitamins include pyridoxine, folinic acid, and pyridoxal-5-phosphate.

¶Other medications/vitamins include acetazolamide, bumetanide, carbamazepine, lacosamide, lidocaine, oxcarbazepine, valproic acid, and other vitamins (calcitriol, calcium, magnesium, thiamine).

**Total loading dose is the total amount of medication administered in mg/kg in initial 72 hours of treatment.

0.45, $P < .001$). The **Figure** demonstrates the time-to-event analysis for in-hospital mortality and hospital discharge for both cohorts. Neonates with cardiopulmonary disease were more likely to be discharged or die while maintained on an antiseizure medication (82% vs. 68%, $P = .01$).

Discussion

In this large, multicenter cohort of children with neonatal seizures with and without cardiopulmonary disease, we found high rates of seizures, particularly EEG-only seizures, which were often resistant to initial antiseizure medication administration. These findings provide additional evidence for neonatal guidelines that recommend cEEG monitoring of high risk neonatal populations,[18] such as those with cardiopulmonary disease, and they also highlight the need for more effective antiseizure medication management strategies.

Seizures have been well-characterized for neonates with acute brain injuries such as perinatal asphyxia, ischemic stroke, intracranial hemorrhage, and central nervous system infection.[1,3,25,26] Less is known about neonates with seizures in the setting of underlying cardiopulmonary disease (including CHD, CDH, or ECMO) because prior studies of neonates with cardiopulmonary disease are limited to single-center cohorts.[10,11,13,15,16] Thus, this study provides multicenter data regarding seizure incidence, characteristics, and outcomes in a contemporary cohort of neonates with multiple types of cardiopulmonary disease and guideline-directed use of cEEG. Our data indicate there are several important differences in seizure presentation between neonates with and without cardiopulmonary disease. Neonates with cardiopulmonary disease are less likely to present with clinically evident seizures, are more likely to experience EEG-only (subclinical) seizures, which would not be detected by clinical observation alone; are more often well-appearing at the time of birth (higher Apgar scores) and then experience seizures later in their clinical course; have a comparably high seizure exposure; and experience an equally low response rate to antiseizure medications in comparison to neonates without cardiopulmonary disease. Overall, these findings indicate that neonates with cardiopulmonary disease are a high-risk group for EEG-only seizures near the time of cardiopulmonary disease reparative procedures and that seizures are often refractory to initial treatment.
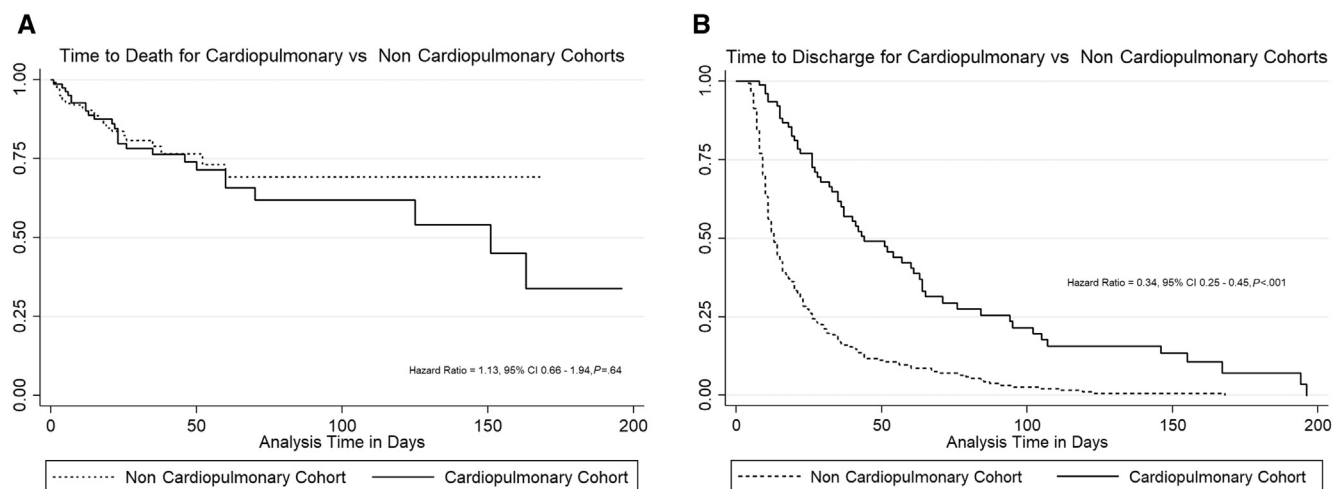
Figure. A, Time-to-death and **B,** time-to-discharge curves for cardiopulmonary disease and non-cardiopulmonary disease cohorts.

It is established that neonates with cardiopulmonary diseases often have abnormal, immature brain structure preoperatively.[4-7] However, in our cohort, they tended to appear well at birth and subsequently experienced decompensation with seizures detected later in their clinical course, presumably in the postoperative period because the median clinical and EEG seizure onset in cardiopulmonary disease group was after the median surgical time. In addition, neonates with cardiopulmonary diseases were often sedated and paralyzed in the postoperative period, limiting the utility of neurologic examination to assess encephalopathy and the ability to observe for clinical events concerning for seizure. Without cEEG monitoring in the high-risk, postoperative period, electrographic seizures would not be detected and seizure burden would not be accurately assessed. Thus, protocol-driven cEEG in this period is necessary to accurately detect and manage seizures in neonates with cardiopulmonary disease.[18]

Our data also demonstrate that phenobarbital is the most frequently administered first-line antiseizure medication for neonates with and without cardiopulmonary disease, but neonates with cardiopulmonary disease are more likely than neonates without cardiopulmonary disease to receive levetiracetam during their hospital course. Clinicians may be concerned about potential systemic side effects in neonates with cardiopulmonary disease and, thus, administer levetiracetam in place of phenobarbital in some patients.[27-30] However, data from the NEOLEV2 trial (Efficacy of Intravenous Levetiracetam in Neonatal Seizures), a randomized controlled trial assessing the efficacy of phenobarbital vs levetiracetam as first-line treatment for neonatal seizures indicated that phenobarbital was significantly more efficacious than levetiracetam for seizure cessation in a heterogenous group of neonates.[31] The optimal balance between safety and seizure efficacy in neonates with cardiopulmonary disease requires further evaluation.

In our study, although neonates with and without cardiopulmonary disease received similar initial antiseizure medications to treat seizures, neonates with cardiopulmonary disease received higher doses of phenobarbital compared with neonates without cardiopulmonary disease, although both groups ultimately achieved similar therapeutic antiseizure medication levels. This finding suggests that neonates with cardiopulmonary disease may require larger antiseizure medication doses compared with neonates without cardiopulmonary disease to achieve expected antiseizure medication levels, potentially related to higher volumes of distribution and blood loss related to surgical procedures,[32,33] and that seizures are often refractory even with appropriate antiseizure medication levels, as demonstrated in prior studies.[34] We did not collect data regarding antiseizure medication administration and serum level timing, thereby limiting our ability to evaluate the role of antiseizure medication administration timeliness on seizure responsiveness. More detailed data regarding antiseizure medication management would be beneficial in future studies of seizures in neonates with cardiopulmonary disease.

Although the majority (78%) of neonates with cardiopulmonary disease experienced seizures in the context of acute brain injury (HIE, stroke, hemorrhage, or intracranial infection), 22% of neonates with cardiopulmonary disease had early-onset epilepsies because of genetic syndromes, brain malformations, or inborn errors of metabolism. Given that many cardiac anomalies occur in the context of genetic conditions and/or concurrent brain malformations, it may be challenging to assess whether neonatal seizures in this population arise from an acute symptomatic cause, an endogenous congenital cause that predisposes to epilepsy, or both.[21,35] An additional important consideration in this discussion of etiology is the role of the maternal-fetal-placental environment and its interplay with underlying genetic predispositions.[36-38] Ongoing research has unveiled how time-dependent destructive processes in the fetal environment can predict acute and chronic outcomes following birth, as well as elucidate the time-course of clinical symptoms in neonates and infants presenting with seizures or other neurologic impairments.[39,40] For example, prenatal insults sustained in the first 2 trimesters may present with delayed neurologic complications, similar to the time-course noted in our patients with cardiopulmonary disease. The first cohort of the NSR-1 did not collect prenatal data such as placental pathology and markers of maternal health to assess the impact of the maternal-fetal-placental environment on our patients. We cannot assess brain lesions, which may include anomalous brain development, destructive brain lesions, or both. Patients with cardiopulmonary diseases may be at risk for both forms of brain lesions, and the underlying brain lesion characteristics determine epileptogenic network development that ultimately informs acute and chronic seizure responsiveness to treatment. Neuroimaging data are not available to delineate further this information in our cohort, but understanding these differences may help clinicians tailor seizure management, as the duration of antiseizure medication treatment may differ by etiology. Early antiseizure medication discontinuation may be appropriate with acute symptomatic etiologies,[41,42] and prolonged antiseizure medication treatment may be appropriate with epilepsy. In our cohort, neonates with cardiopulmonary disease were more likely to die or be discharged home on an antiseizure medication than neonates without cardiopulmonary disease. Discharge on an antiseizure medication, especially despite the longer hospital course for neonates with cardiopulmonary disease, may reflect that clinicians were concerned about a higher risk for future epilepsy and/or concerned about the potential risk of recurrent convulsive seizures in these medically complex patients. Further, early diagnosis of genetic syndromes or structural brain malformations may impact epilepsy management over the lifespan with the introduction of precision based therapies for genetic epilepsies and more widespread use of epilepsy surgery for lesional epilepsy.[43]

We defined cardiopulmonary diseases as the presence of CHD, CDH, or the need for ECMO. Among neonates with cardiopulmonary disease, seizures have been best characterized in those with CHD. Among neonates with CHD, the

reported seizure incidence has varied over time as earlier studies described clinical seizures without EEG assessment. Single-center studies of neonates with CHD undergoing cEEG demonstrated an incidence of 0%-6% for clinical seizures and 1%-20% for electrographic seizures.[11,13,14,16] Neonates with CHD have seizure onset at a median of 21-22 hours after surgery,[14] have a high seizure burden,[10,16,44] and have a high incidence of EEG-only seizures.[11]

The incidence of seizures in neonates who require ECMO has also been previously described in single-center studies. In a single-center study of 99 neonatal and pediatric patients on ECMO, the incidence of electrographic seizures was 9% in the neonatal ICU cohort, 27% in the cardiac ICU cohort, and 8% in the pediatric ICU cohort, with pre-ECMO low cardiac output as the only significant risk factor for seizure occurrence ($P = .03$).[15] There was also a trend toward higher seizure occurrence in patients with veno-arterial ECMO, persistent pulmonary hypertension, an abnormal EEG background, and a history of CHD surgery. A separate single-center study evaluated 70 neonatal and pediatric patients who underwent cEEG for a minimum of 24 hours after ECMO initiation.[17] Electrographic seizures occurred in 23% of the cohort, with status epilepticus in 7%. Subclinical seizures were present in 56% of patients with seizures, and seizures began within 24 hours of ECMO initiation in 50% of patients. Patients with electrographic seizures were younger (0.6 months vs 6.7 months, $P = .03$). A more recent single-center study of seizures in pediatric patients exposed to ECMO evaluated 201 patients, including 92 neonates.[45] Seventeen neonates (18%) experienced ES, occurring at a median of 2.8 hours after cEEG monitoring was initiated. Neonates experienced a median of 21 seizures in the first 24 hours of cEEG monitoring, and the presence of electrographic seizures was associated with ipsilateral brain injury.

CDH can occur in isolation or as a part of a genetic syndrome with associated brain malformations that can increase the risk of neonatal-onset epilepsy. As a result of CDH with or without an underlying genetic association, patients often have an impact on lung size and function and cardiac output, with common symptoms requiring ECMO support. As previously noted, ECMO use is associated with a risk of brain injury which commonly manifests as seizure in neonates. The incidence of acute seizures in the CDH population with and without ECMO exposure has not been well characterized, but seizures are a documented complication.[46,47]

Our work has several limitations. First, specific pathways or protocols for seizure management were not implemented across the NSR-1 centers and care was determined by treating clinicians, thereby yielding variability in how and when seizures were managed. However, this variability across clinicians and hospitals inherently adds to the generalizability of the conclusions. Similarly, paralytic and sedative uses were not standardized across NSR-1 sites, but varying use of these medications in the postoperative period could affect seizure identification and seizure exposure. Second, our cohort includes a small number of neonates with CDH, thereby reducing the generalizability of our results to this population, especially given that we are only evaluating neonates with CDH who experienced seizures and some had additional cardiopulmonary disease diagnoses. However, as noted above, only a few prior studies have evaluated neonatal seizures in CDH, and, thus, our data help to better understand the seizure profiles for these patients. Lastly, the data available for review for the cohort were limited by the scope of the initial NSR-1 goals. Although we report antiseizure medication dosing and serum antiseizure medication levels, data were not collected regarding the timing of these doses and levels. This precludes conclusions regarding antiseizure medication efficacy and pharmacokinetics which may differ among neonates with cardiopulmonary disease given their concurrent use of technology which impacts fluid status, volume of distribution, and hepatic metabolism.[33] In addition, the NSR-1 did not collect data regarding antiseizure medication adverse events. Given that some commonly used antiseizure medications may cause bradycardia, hypotension, and respiratory depression, the underlying pathophysiology of the cardiopulmonary diseases may impact the acceptability of these adverse effects. In our cohort, neonates with cardiopulmonary disease were more likely to receive levetiracetam compared with neonates without cardiopulmonary disease. We hypothesize that the side effect profile of levetiracetam may have been preferred for neonates with cardiopulmonary disease, leading to increased use in this group, although providers were not questioned about the rationale for their antiseizure medication choices. Future studies are needed to evaluate the adverse events associated with antiseizure medication administration in neonates with cardiopulmonary disease to ensure our efforts to treat seizures are not causing harm. Further, NSR-1 did not collect genetic, prenatal/fetal, or placental data, limiting our ability to assess the potential impact of specific genetic variations and prenatal exposures on our neonates with cardiopulmonary disease, and perhaps limiting our explanation of some of the key differences noted between neonates with and without cardiopulmonary disease. Finally, this cohort does not include neuroimaging data or long-term outcome data, limiting our ability to correlate seizure exposure with neuroimaging assessments of brain injury severity or long-term patient outcomes. Clinicians must consider that neonates with cardiopulmonary disease are certainly at risk for developmental as well as acquired brain lesions, both of which may be small and below the resolution threshold of clinically available neuroimaging technology, but undoubtedly influence epileptogenesis, response to antiseizure treatment, and neurodevelopmental outcomes.

Our data reinforce that neonates with cardiopulmonary disease are at high risk for seizures from brain injury following surgical repairs, co-existing neonatal epilepsies, or a combination of both, and therefore support guidelines that recommend cEEG in neonates with cardiopulmonary disease, particularly following surgical intervention. Consideration of seizure etiology is important, as some neonates with cardiopulmonary disease experience seizures due to a nonacute

etiology, and this may inform decisions regarding antiseizure medication administration duration. Given the occurrence and persistence of seizures in this population, future studies are needed regarding antiseizure medication efficacy and adverse events in neonates with cardiopulmonary disease to develop optimized seizure management approaches. Future work should also be directed at exploring the impact of the maternal-fetal-placental environment and genetics on the neurologic presentations and long-term outcomes of neonates with cardiopulmonary diseases. ■

Data Statement

Data sharing statement available at www.jpeds.com.

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